Insights from an individual-level model of HIV programmes in southern Africa: HIV testing, ART and resistance

THESIS

presented for the

DEGREE

of

DOCTOR OF PHILOSOPHY

in the Faculty of Population Health Sciences

(Field of study – epidemiology)

VALENTINA CAMBIANO

Research Department of Infection and Population Health,

UCL

April 2014

Declaration

I, Valentina Cambiano, confirm that the work presented in this thesis is my own. Where information is derived from other sources, I confirm that this has been indicated in the thesis. The only exception is the part of the section "4.3. Cost-effectiveness of different adult ART eligibility criteria and coverage scenarios in South Africa": I programmed within the Synthesis model the interventions agreed by the Modelling consortium and I provided them the outcomes from the model necessary to conduct the cost-effectiveness analysis, but other members of the Modelling Consortium summarized the results of the different models and applied the costs.

Abstract

Antiretroviral therapy (ART) has transformed HIV infection from a death sentence into a chronic condition. In sub-Saharan Africa, the area most affected by this disease, availability of ART has increased dramatically over the last few years. Nevertheless, many people are still not receiving ART either because they are not aware of being HIV-positive or because they struggle to access ART or to engage in HIV care. It is fundamental to take decisions which maximise the health benefits with the limited resources available.

When I was writing this thesis, there were countless discussions regarding whether the recommendation on when to start ART had to be modified to a CD4 count threshold higher than 350 cells/μL, given the compelling evidence that ART reduces substantially the risk of transmission in heterosexual serodifferent couples. In this thesis I evaluated the effectiveness and cost-effectiveness of alternative ways of increasing the number of adults receiving ART in South Africa: increasing the CD4 count threshold at which a person is eligible to be initiated on ART, or maintaining the eligibility criteria to CD4 count below 350 cells/μL but expanding the number of people who are diagnosed and engaged in care. In particular, I focused on the impact these two alternatives would have on the development and transmission of resistance. To inform the model on the extent to which NNRTI resistance mutations are present in people who have interrupted NNRTI, I conducted an analysis using data from the UK resistance database. In addition, since I found that the most cost-effective strategy was to expand the number of people engaged in HIV care without modifying the CD4 threshold at which a person is eligible to receive ART, I evaluated at which steps in the current leaky cascade of HIV care it was most cost-effective to intervene.

Finally, as new evidence regarding the accuracy and acceptability of HIV self-testing came up, I decided to evaluate the cost-effectiveness of introducing HIV self-testing in a setting such as Zimbabwe.

Acknowledgements

There are many people I would like to acknowledge. First of all, I would like to thank my principal supervisor Andrew Phillips for all his support and encouragement throughout the preparation of the thesis. I will never forget one of his reassuring sentences: “Vale, I know it’s all in your brain, it’s just matter of putting it on paper”, when not much was still on paper. Secondly, I would like to acknowledge my secondary supervisor, Alison Rodger, who had a more realistic vision and made sure I finished this dissertation on time. I really appreciated all the time and effort they put into reading the drafts, giving me constructive feedback as well as answering my numerous questions.

Special thanks go to my colleagues Fumiyo Nakagawa, Loveleen Bansi and Colette Smith for devoting the time to read and provide helpful comments on specific chapters and to Paul Revill and Alec Miners for introducing me to the world of health economics.

I would like to thank the Principal Investigators from the UK Drug Resistance Database and UK CHIC, who gave me the opportunity to use their databases. I feel very privileged to have had access to so much resistance data and I really appreciate the hard work of everyone involved.

In addition I would like to acknowledge my other colleagues from the Royal Free for encouraging me to continue writing and not to panic, In particular Leah Shepard, Colette Smith, Fiona Lampe and Debbie Ford.

Finally I would like to thank my friends and family for their continued support and encouragement and to Christian for his patience, emotional support and for cooking my meals for the last months. I am very grateful for all the support I have received from everyone.

Contents

Tables

Figures

List of abbreviations

3TC:	Lamivudine
ABC:	Abacavir
ADC:	Acquired Immune Deficiency Syndrome defining condition
AIDS:	Acquired Immune Deficiency Syndrome
ALT:	Alanine aminotransferase
ANC:	Antenatal clinic
aRR:	Adjusted relative risk
ART:	Antiretroviral therapy
ARV:	Antiretroviral drug
AST:	Aspartate transaminase
ATV:	Atazanavir
AZT:	Zidovudine
BMD:	Bone mineral density
BMI:	Body mass index
CBART:	Community-based ART programs
CDC:	Centers for Disease Control and Prevention
CET:	Cost-effectiveness threshold
CHIC:	Collaborative HIV Cohort Study
CI:	Confidence interval
CIA:	Central Intelligence Agency
CLIAI:	Condom-less insertive anal intercourse
CLLT:	Condom-less long-term

CLRAI: Condom-less receptive anal intercourse

CLST: Condom-less short-term

CKD: Chronic kidney disease

CNS: Central nervous system

CTX: Co-trimoxazole

CVD: Cardiovascular disease

d4T: Stavudine

DALY: Disability-adjusted life-year

ddC: Zalcitabine

ddI: Didanosine

DHS: Demographic and Health Survey

DNA: Deoxyribonucleic acid

DOT: Directly observed therapy

DRM: Drug resistance mutation

DRV: Darunavir

EFV: Efavirenz

eGFR: Estimated glomerular filtration rate

F-to-M: Female-to-male

FBC: Full blood count

FDA: U.S. Food and Drug Administration

FDC: Fixed-dose combination

FTC: Emtricitabine

GDP: Per capita gross domestic product

GUD: Genital ulcer disease

Hb: Haemoglobin

HBT: Home-Based Voluntary HIV Testing

HBV: Hepatitis B virus

HCV: Hepatitis C virus

HIV: Human Immunodeficiency Virus

HR: Hazard ratio

HSRC: Human Sciences Research Council

HT: Hepatotoxicity

HTC: (Provider-delivered) HIV testing and counselling

HSV-2: Herpes simplex virus-2

IAS-USA: International Antiviral Society -USA

ICER: Incremental cost-effectiveness ratio

IQR: Interquartile range

LPV/r: Lopinavir boosted with ritonavir

LMIC: Low and middle income countries

LTFU: Lost to follow-up

M-to-F: Male-to-female

MIM: Multiple indicator monitoring

MSM: Men who have sex with men

MTCT: Mother-to-child transmission

NGO: Non-governmental organization

NNRTI: Non-nucleoside reverse transcriptase inhibitor

NRMV: Non-nucleoside reverse transcriptase inhibitor resistant virus in majority virus

NRTI: Nucleoside reverse transcriptase inhibitor

NSP: National Strategic Plan [South Africa]

NVP: Nevirapine

OI: Opportunistic infection

OR: Odds ratio

PCP: Pneumocystis cariniii Pneumonia

PEPFAR: President's Emergency Plan for AIDS Relief

PHI: Primary HIV infection

PI: Protease inhibitor

PITC: Provider-initiated testing and counselling

PMN: Polymorphonuclear leukocytes

PMTCT: Prevention of mother-to-child transmission

POC: Point-of-care

PrEP: Pre-Exposure Prophylaxis

PSI: Population Services International

PY: Person-year

QALY: Quality-adjusted life-year

RBM: Risk behavioural model

RCT: Randomized controlled trial

RLS: Resource limited settings

RNA: Ribonucleic Acid

RR: Relative risk

RT: Reverse transcriptase

RTV: Ritonavir

SC: Seroconversion

ST: HIV self-testing

STI: Sexually transmitted infection

TAMs: Thymidine analogue mutations

TB: Tuberculosis

TDF: Tenofovir disoproxil fumarate

TDR: Transmitted drug resistance

TI: Treatment interruption

ULN: Upper limit of normal

UN: United Nations

UNAIDS: Joint United Nations Programme on HIV/AIDS

UNICEF: United Nations Children's Fund

UR: Uncertainty range

VCT: Voluntary counselling and testing

VF: Virological failure

VL: HIV-RNA viral load

VMC: Voluntary medical circumcision

WHO: World Health Organization

YAS: Zimbabwe Young Adult survey

1. Introduction

1.1. Aim of the thesis

The aim of this thesis is to evaluate the impact on human immunodeficiency virus (HIV) incidence and on patterns of resistance of different public health actions involving HIV testing and antiretroviral therapy (ART) in the South Africa and Zimbabwe adult epidemic, using a development of the Synthesis model, which is an individual based-stochastic model of the transmission and progression of HIV.

The interventions that will be assessed are:

- expansion of access to HIV treatment and care
- modification of the eligibility criteria for ART initiation
- improvement in different steps of the cascade of care
- introduction of HIV self-testing (ST)

Other mathematical models have addressed some of these questions, but most have not taking into account the role played by adherence to ART and the acquisition and transmission of drug resistant mutations. Particular focus will be given in this thesis to the impact on development of viral resistance through use of interventions, because there is growing concern that expansion of ART could lead to the spread of drug resistant virus.

In addition, I aim to estimate the persistence of non-nucleoside reverse transcriptase inhibitors (NNRTIs) resistance mutations after interrupting or stopping ART which contained an NNRTI. This parameter is particular important in settings with a high number of people lost to follow-up (LTFU), such as South Africa (1;2). To address this question, data from the UK CHIC and UK resistance database will be used. Although these data are from the UK and not from Southern Africa there is no reason to believe that this parameter should be different and there is paucity of resistance data from South Africa.

1.2. Overview of the thesis

Chapter 1 provides a background on HIV natural history and virology and the effects of ART. The reason to review and describe all these aspects of HIV is that there is lots of understanding of the processes regarding the transmission and progression of HIV and the impact of ART on the progression and where possible they are included in the Synthesis model.

In Chapter 2 the HIV epidemics in South Africa and Zimbabwe are described.

Chapter 3 presents the Synthesis transmission model in detail and the method used to calibrate it to the HIV epidemic in South Africa and Zimbabwe.

In Chapter 4 I discuss the evidence and current recommendations for initiating ART and present the findings from the assessment of the impact on HIV incidence of expanding access to care and eligibility criteria for ART initiation in South Africa. In addition, the impact on HIV incidence and cost-effectiveness data are compared to results from other mathematical models which addressed the same question.

Chapter 5 focuses on evaluating the impact on the levels of drug-resistance of expanding diagnosis, retention in care and modifying the eligibility criteria for ART initiation in South Africa.

In Chapter 6 I estimate the persistence of NNRTI resistance mutations after interrupting or stopping ART which contained an NNRTI, using data from the UK CHIC and UK resistance database.

In Chapter 7 I evaluate the cost-effectiveness of improvements in different steps in the cascade of care in South Africa. This chapter focuses on understanding which steps in the cascade of care among HIV testing, linkage to care, retention in pre-ART care, retention on ART and switch to second-line, have most influence on HIV incidence, deaths and costs, and hence which is more cost-effective to improve.

Chapter 8 contains analysis of the effectiveness and cost-effectiveness of introducing ST in another sub-Saharan African setting, Zimbabwe.

Chapter 9 summarizes the findings and conclusions from each of the chapters and discusses the overall limitations and implications of these results.

1.3. Description and mechanism of HIV virus

HIV is a *lenti-virus* (in Latin "*lenti*" means slow) because of the long interval between initial infection and the onset of serious symptoms. It belongs to a larger group of viruses known as *retroviruses* (3-5), which are composed of ribonucleic acid (RNA) instead of deoxyribonucleic acid (DNA) (6). These viruses have an enzyme, called reverse transcriptase (RT), which confers to them the unique property of transcribing viral RNA into DNA after entering a cell. The retroviral DNA can then integrate into the chromosomal DNA of the host cell, where it cannot be eradicated without killing the host cell (6).

There are two different strains of HIV: HIV-1 and HIV-2 (7). They are not closely related to each other and within these two types there are a variety of subgroups, some of which have considerable genetic diversity (3). HIV-1, characterized by higher rates of infectiousness (8) and faster progression, is the predominant form of the virus worldwide while HIV-2 is confined to areas in West-central Africa and India (7;9;10), for this reason I will focus only on HIV-1 and I will use the term HIV to refer to HIV-1. HIV-1 can be classified into four groups: the "major" group M, the "outlier" group O and two new groups, N and P (9;11;12). Group M is the most common and widely spread accounting for more than 90% of cases globally (9). Within group M there are at least eleven genetically distinct subtypes of HIV-1 circulating in the world: A1, A2, B, C, D, F1, F2, G, H, J and K (13). The main HIV-1 subtypes circulating among heterosexual population in southern Africa and India is subtype C accounting for over 48% of worldwide infections, while in the Americas, Australia, Japan and Western Europe the predominant subtype is B (7;14;15) (see Figure 1.1).

Figure 1.1. Global distribution of HIV-1 subtypes and recombinants [12].

In order for the virus to enter the cell, the presence on the cell surface of CD4 receptors and certain co-receptors is required (16). CD4 receptors are molecules expressed predominantly on the surface of helper T cell lymphocytes and macrophages, which are particular types of white blood cells. The main HIV co-receptors, CCR5 and CXCR4 (17), are differentially expressed in subpopulations of CD4-expressing cells and are highly expressed in T lymphocytes, thymocytes, macrophages and dendritic cells. For these reasons the main target cells of the HIV virus are CD4+ T cell and macrophages (7;17;18). Some HIV-1 strains have a preference for T-cells (T cell tropic strain): they use the CXCR4 co-receptor and fail to replicate in macrophages. While others replicate in macrophages and primary T cells (Macrophage (M)-tropic strain), using the CCR5 co-receptor (7). Although CXCR4-using viruses are generally more pathogenic than CCR5-using viruses, most viruses transmitted from one person to another use CCR5, even when infected persons have both viral types circulating in the blood.

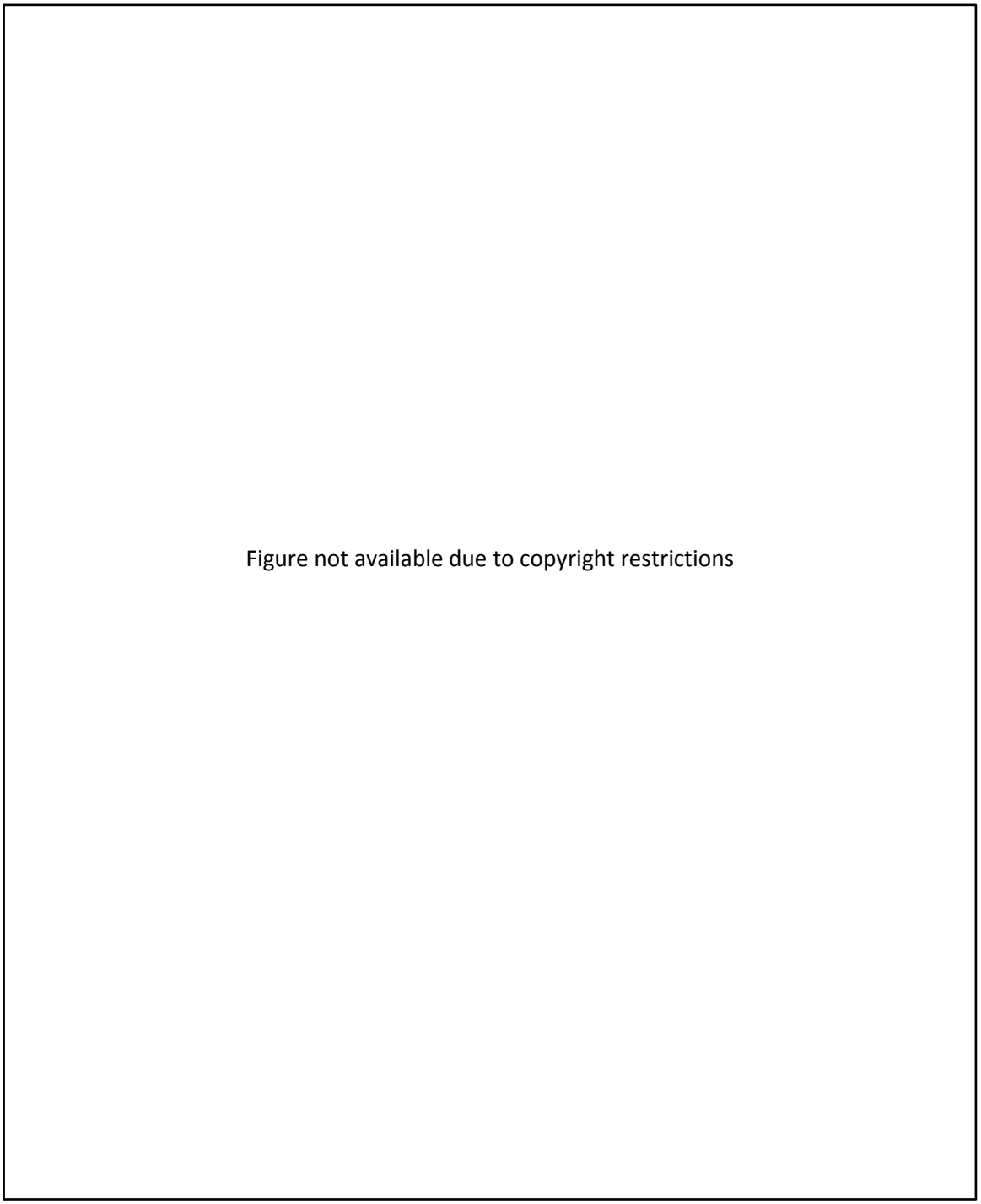
The replication of HIV-1 is a multistage process (18) (see Figure 1.2 at page 32 (19)). The first step in the process of viral replication is “attachment”. When an HIV virion approaches a target cell, the surface glycoprotein gp120 binds to the CD4 receptor of the host cell (18). The binding between the CD4 receptor and gp120 promotes further binding between the virion and co-receptor, which leads to a conformational change in gp120. At this point,

transmembrane molecules gp41 facilitate the fusion between the viral envelope and the membrane of the target cell. This second step is usually referred to as “fusion”. The viral core enters the host cell and breaks open (“uncoating”) releasing in the cytoplasm two copies of single-stranded RNA and three essential replication enzymes: integrase, protease and reverse transcriptase. Once the enzyme RT enters the cell it begins transcribing single strands of viral RNA into double-stranded DNA using endogenous cellular nucleotides (“reverse transcription”). The resulting DNA is transferred into the cell nucleus, where the enzyme integrase facilitates its “integration” into the host cell genome (7). The host cell genome now contains the genetic information of HIV. Once viral DNA has integrated into the cell it can remain dormant and may go undetected by the immune system for many years (20;21). Major reservoirs of infection are formed in compartments outside of the blood: lymphoreticular tissues (gut associated lymphoid tissues), central nervous system (CNS) and genital tract. These immune cells are latently infected, so they do not produce virus but if these cells are activated, they can start producing virus. This has complicated attempts to eradicate HIV (22). This activation of the cell induces “transcription” of the proviral DNA (division of the two strands of DNA) into a new strand of viral RNA called messenger RNA. The messenger RNA migrates into the cytoplasm (“nuclear export”) where building blocks for a new virus are synthetized by translation of the information contained in the messenger RNA. Some of the protein building blocks need to be processed into functional form by the enzyme protease. These core proteins assemble with the two viral RNA strands to form the capsid (“assembly”). These immature virus particles bud from the surface of infected cells acquiring a new envelope of host cell membrane proteins (“budding”) and float off into the bloodstream.

To become infectious these viral particles need to undergo “maturation”, a process involving systematic cleavage of Gag polyproteins by the activity of the protease. After maturation, the virus is ready to infect other cells. It is estimated that a single cell can produce thousands of infectious HIV particles every day (5).

CD4+ T cells are of particular importance because they are involved in activating and coordinating other white blood cells (macrophages and dendritic cells) when some pathogens are present. By doing this, HIV damages the whole immune system: decreases the number of macrophages and of natural killer cell and leads to malfunctioning of CD8 cells, which are designed to find infected cells and destroy them, and also of B cells, whose function is to identify which cells are infected and which ones are not and to produce antibodies.

Figure 1.2. HIV-1 viral life cycle (23)

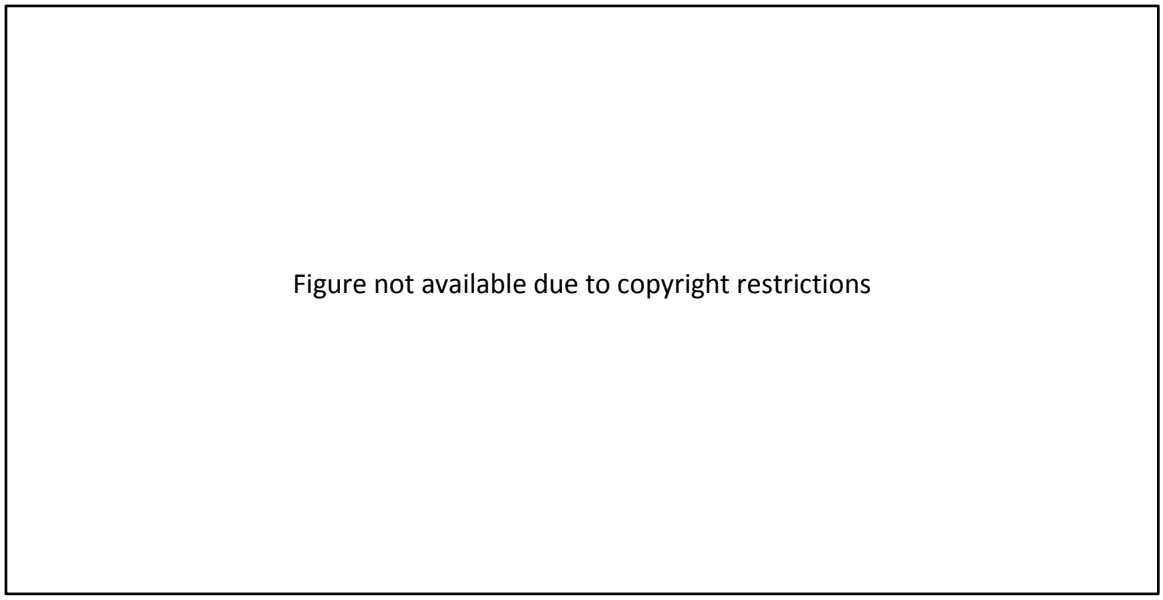


1.4. HIV transmission

HIV can be transmitted through blood, semen, cervico-vaginal and anal secretions and breast milk (24;25). The rate of transmission differs significantly by route of exposure.

The routes through which infection can take place are: via sexual intercourse (either vaginal, anal or potentially oral (26)), via blood, through the sharing of contaminated needles or syringes (27) or transfusions of contaminated blood (28) and from a mother to her baby during pregnancy, childbirth or through breastfeeding (24). The risk of an individual becoming infected with HIV is largely dependent on the levels of the virus present in the infected individual (29-31). Figure 1.3 illustrates the variation in the risk of transmission across the different types of exposure, which are described in more detail in the following sections.

Figure 1.3. Per contact probability of HIV transmission (32)



1.4.1. Sexual transmission

Worldwide, the most common route of HIV transmission is by sexual intercourse (29). The risk of HIV infection through this route is dependent on many factors (26;33;34) such as the sexual partner's gender, the type of sex act, HIV-RNA viral load (VL) levels, the stage of infection, genetic susceptibility such as having a delta-32 mutation in the CCR5 gene so that this receptor is either not expressed (if homozygous) or expressed at lower density (if heterozygous), the presence of ulcerative sexually transmitted infections (STIs) (i.e. Herpes simplex virus-2, HSV-

2), sexual practices which breach mucosal integrity and of course use of preventive methods such as condoms and circumcision, which will be discussed in section 1.10.

1.4.1.1. Role of HIV-RNA levels on risk of transmission

The strongest factor associated with the risk of sexual transmission of HIV is the VL of the infected partner, which reflects the volume of virus circulating in the body. The first large epidemiological study to estimate the risk of transmission by VL levels in the source partner was the Rakai study, published in 2000 by Quinn et al. (31). They found that the mean serum VL level was significantly higher among HIV-positive subjects whose partners became infected with HIV than among those whose partners remained HIV uninfected. There was a significant dose response effect between risk of transmission and the serum VL of the index case: the rate of transmissions ranged from 0 in the 51 couples where the index partner had VL of 1500 copies/mL or below up to 23/100 person-years (PYs) among couples where the HIV-positive partner had VL of 50,000 copies/mL or more. Subsequently other studies have confirmed this finding (35;36). Fraser and colleagues re-analysed the data from the Zambian cohort (35) and estimated the rate of transmission per 100 PYs within a stable long-term serodifferent relationship by set-point VL (see section 1.5.1) (37). These estimates are respectively 2/100 PYs for VL of 1,000 copies/mL, 13.2 for a VL of 10,000 copies/mL, 27.9 for a VL of 100,000 copies/mL up to 31.3 for a VL of 1,000,000 copies/mL. It has been established that this effect is independent of other recognized predictors of HIV transmission, such as history of any unprotected sex, sex, HSV-2 seropositivity and circumcision of the HIV uninfected partner (38).

1.4.1.2. Role of stage of infection on risk of transmission

Another factor that has a major effect on the risk of transmission is stage of infection (described in section 1.5). Since the early days of HIV research, models and longitudinal studies suggested that the rate of heterosexual HIV transmission per coital act was higher during the first months since infection (referred to as primary HIV infection [PHI]), lower during the asymptomatic period and higher again in the last years before death. This is likely to be mainly due to the high VL observed in the earliest and latest period of HIV infection (39-41). Using the data from the Rakai study, Wawer et al. estimated the rate of HIV transmission per coital-act by stage of infection (42). During the first 5 months since seroconversion (SC, see section 1.5.1) is 0.0082/coital act, corresponding to 1 transmission in 122 sexual acts, 8-10 times higher than during the asymptomatic infection (between 6-15 months it is 0.0015, corresponding to 1

transmission in 667 acts) and then it increases again during the two years before death of the HIV-infected partner: 0.0028/coital act, corresponding to 1 in 357. The data on the primary and asymptomatic phase were based on a small number of serodifferent couples (n=23), and individuals were tested only every 10 months, therefore the date of SC and death were approximated as halfway through the interval. In 2008 Hollingsworth et al. (43) re-analysed these data, attempting to discount coital acts that happened after transmission occurred and assessing the rate of transmission as a function of time since the partnership was first observed, rather than per coital act. They estimated that the transmission rate per 100 PYs was: 276 in the first 3 months since infection, 10.6 during the asymptomatic phase and during the last years before death respectively, 76 (95% CI: 41.3, 128) between 19 and 10 months before deaths and 0 during the last 10 months before death, due to the limited sexual contact because of unhealthy condition of the infected partner. Mathematical models have estimated that PHI could contribute between 9 and 39% of HIV infections (33;43), while the late stage between 20 to 27% of HIV infections (43). Evidence of the crucial role of the acute infection also comes from phylogenetic studies, which estimated comparable contributions (44).

It seems that VL may not explain all of the increased risk of transmission seen during the first months since SC (37;43;45). Additional factors include presence of other STIs, which will be discussed in more detail in section 1.4.1.3, potentially higher susceptibility in newly exposed HIV-negative partners and more infectious virus present during PHI (46). The high variability in susceptibility across individuals means that the most susceptible individuals are likely to get infected during the first exposure period, while other less susceptible partners are unlikely to get infected at all. The latter factor relates to the fact that there is some evidence that patterns of amino acids in the viral envelope could be favoured at transmission and be present during PHI but waning over time (46). In addition to the highest rate of HIV transmission per sex act, during PHI people are less likely to know their HIV status and are therefore less likely to use condoms (47;48). The important role that acute infection plays is generally agreed, although the relative contribution of PHI varies considerably according to the stage of the epidemic and the structure of sexual contact networks.

The advanced stage of the disease is also characterized by a high rate of transmission per sexual contact due to the rising VL, but the contribution of this phase is believed to be smaller. This is likely because individuals in the late stage of HIV infection report less sexual intercourse and have fewer partners, and only a minority of HIV-infected partners remain serodifferent by this stage. It is not clear that the advanced stage is a risk factor for transmission independently of VL.

1.4.1.3. Role of STIs on risk of transmission

An increased risk of HIV transmission can also be seen with increased levels of VL in genital secretions (49). Concentration of HIV in semen and in the genital and rectal compartments is likely to be the most important determinant of sexual HIV transmission; nevertheless most of the studies considered levels of VL in plasma. Inter-current symptomatic and asymptomatic STIs can lead to a transient increase in VL in the genital compartment, especially those causing genital ulcer disease (GUD) (50) and this increases the risk of HIV transmission (51). HSV-2 represents the most frequent cause of genital ulceration worldwide, with an estimated prevalence between 60% and 90% among people living with HIV (52). In people co-infected with HIV and HSV-2, reactivation of HSV-2 has been associated with raised levels of VL in blood and genital tracts (53-55). In particular in a meta-analysis of observation studies the risk of HIV transmission was estimated to be 5.3 times higher in people with history of GUD, compared to couples where both members never had STIs (56). A previous meta-analysis had estimated this factor would increase susceptibility by 2.8 times for females and by 4.4 in men (57), while a study on high risk group had estimated a much bigger effect: an increase in the risk of transmission per act of 10-50 times for male-to-female (M-to-F) and between 50 and 300 times for female-to-male (F-to-M) (58). For these reasons it is thought to contribute significantly to the on-going HIV epidemic (53;59).

1.4.1.4. Role of sex route and gender on risk of transmission

Risk of transmission following exposure differs also by sex route and sex. A meta-analysis of observational studies estimated the heterosexual risk of HIV infection per sexual act in high and low income countries (56). In high income countries it was 0.0004 (1 in 2500) for F-to-M and 0.0008 (1 in 1250) for M-to-F, while in low income countries, in the absence of commercial sex exposure it was 0.0038 for F-to-M and 0.0030 for M-to-F (56). In multivariate analysis in high income countries, the M-to-F risk of transmission was 80% higher than F-to-M (although not statistically significant), while the relative risk (RR) for the same comparison in low income countries was close to 1, indicating no difference. In addition, the risk of transmission for F-to-M in low income countries was significantly higher (3.3 times) that in high income countries. It is worth mentioning that estimates from low income countries were much more heterogeneous than from high income countries, likely indicative of poorer quality studies, higher heterogeneity of risk factors or underreporting of number of condom-less sex acts, which is more common among women than men (60). In Fideli et al. where it was assessed

whether the transmissions were epidemiologically linked (35) the association between VL and risk of transmission was much stronger for F-to-M than for M-to-F. In addition, when restricting to transmissions which occurred in couples who did not report receptive anal intercourse, GUD and commercial sex or to the asymptomatic phase the risk of M-to-F and combined transmission (0.0007 per act) was similar to the risk of M-to-F transmission in high income countries. This seems to suggest that this is the average per-vaginal-sex-act transmission risk in absence of cofactors, during the asymptomatic phase.

The risk of transmission per M-to-F condom-less receptive anal intercourse (CLRAI) act is estimated to be much higher: 0.017 per sex act (1 transmission in 59 sex acts) (56), but this is based on very few studies (41;61). A meta-analysis focusing on HIV transmission risk through anal intercourse (62) found a similar estimate for CLRAI (0.014 per sex act) and no significant difference between the risk for male-to-male and M-to-F. Per-act estimates for condom-less insertive anal intercourse (CLIAI) on treatment are not available. The risk of transmission per partner per CLIAI is 0.217, compared to 0.404 for CLRAI (62). The PARTNER study following heterosexual and same sex serodifferent couples who reported condom-less sex, has so far observed zero linked HIV transmissions among couples where the HIV-positive was on ART with suppressed VL (63). However the upper limit of the confidence interval (CI) for the rate of HIV transmission per 100 PYs was up to a maximum of 4, for the practice of CLRAI in men who have sex with men (MSM), due to the lower number of PYs accumulated so far.

In sub-Saharan Africa most of HIV transmissions are attributable to heterosexual sex, but epidemics among MSM have also been identified (64;65).

1.4.2. Role of genetic mutation (delta-32) on risk of transmission

Certain genetic mutations can also reduce the risk for acquisition of HIV infection, even within the context of on-going high sexual risk behaviours with HIV-positive partners. CCR5 (chemokine receptor 5) is a chemokine receptor which is used by the HIV virus to enter the cell (see section 1.3). Individuals who are homozygous (and to a lesser extent heterozygous) for a 32-base-pair deletion (delta-32 mutation) in the CCR5 reading frame are highly protected from HIV infection (34;66), because of the lower level of expression of this receptor on the cell surface, making cell infection and hence HIV acquisition risk lower. This mutation is more prevalent in caucasian populations, with prevalence around 10% (67).

1.4.3. Transmission via blood contact

HIV can also be transmitted via blood and blood products, either through blood transfusion (28), re-using and sharing of syringes and needles (68) or by contact with infected blood (often referred to as occupational exposure) (69). Transmission via blood is the most efficient mode of transmission. For blood transfusion recipients, the transmission probability per exposure event is estimated to be between 90 and 100% (28;70). While the HIV acquisition risk for occupational exposures in terms of needle stick injury is estimated at 1 in 300 per exposure (69;71) and at 1 in 900 after mucus membrane exposure (72).

The most common source of transmission via blood is through the reusing or sharing of syringes and needles among people who inject drugs (68). Incidence rates of transmission have been estimated up to levels between 10 and 50/100 PYs in people who inject drugs in many populations around the world (73).

In the early stages of the epidemic when blood products were not screened for HIV, a number of people, patients needing organ or tissue replacement and people with haemophilia requiring Factor VIII replacement, a blood coagulant, became infected through exposure to infected blood products (74). Since 1985, blood products have been routinely screened for HIV in the USA, Canada, Europe and other high income countries (5). In most recent years some low and middle-income countries (LMIC) including South Africa, Botswana, Zimbabwe and Zambia have reported screening in a quality assured manner 100% of donated blood units (75).

1.4.4. Mother-to-child transmission

HIV can also be transmitted from mother to child (vertical transmission) either in utero during pregnancy, at birth or through breastfeeding (24;76-79). From the start of the HIV epidemic, it was clear that vertical transmission from mother to child was a major source of new HIV infections and still, in 2011, 330,000 new HIV infections occurred in children (80), mainly due to mother-to-child transmission (MTCT). The rate of MTCT, in the absence of any interventions, is around 15-45% (81-83), with higher rates seen amongst mothers who become HIV-positive during their pregnancy (84).

1.5. Pathogenesis of HIV infection

The HIV disease progression can be classified in different stages. Both, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), have developed classification systems for the stages of HIV disease and its progression to AIDS. Table 1.1 summarizes the details of the two classification systems. The main difference is that the CDC system assesses the severity of HIV disease progression by CD4 count and HIV-specific conditions, while the WHO system does not require CD4 count measurements and allows healthcare workers with varying levels of expertise and training to diagnose Acquired Immune Deficiency Syndrome (AIDS) (85). This is especially useful in resource constrained settings, where CD4 count measurements are not always routinely available.

Table 1.1. Stages of HIV infection for adolescents and adults

WHO classification (86)	CDC stage classifications (87)	Clinical symptoms
1. Asymptomatic (HIV infection)	A. Asymptomatic (HIV infection)	No AIDS-defining condition (ADC) and either CD4+ T-lymphocyte count of >500 cells/µL or CD4+ T-lymphocyte percentage of total lymphocytes of >29
2. Mild (HIV infection)	B. Symptomatic	No ADC and either CD4+ T-lymphocyte count of 200-499 cells/µL or CD4+ T-lymphocyte percentage of total lymphocytes of 14-28.
3. Advanced (advanced HIV disease)		
4. Severe AIDS	C. AIDS	ADC or CD4+ T-lymphocyte count < 200 cells/µL

ADC: Acquired Immune Deficiency Syndrome defining condition; AIDS: Acquired Immune Deficiency Syndrome; CDC: Centers for Disease Control and Prevention; WHO: World Health Organization;

1.5.1. Primary HIV infection

The first phase of HIV infection which lasts between 9 to 12 weeks since infection (43;88) is usually called primary HIV infection or acute infection. It is characterized by high levels of VL in the blood stream (89-91) up to > 6 log copies/mL (5).

During this period, within a few weeks of HIV infection, HIV antibodies develop and become detectable using standard antibody tests (see section 1.7). This is called seroconversion. At this point in time VL levels are on average 4.7 log copies/mL (92) and the CD4 cell count between 500 and 700 cells/µL (92;93). CD4 levels at SC tend to be 30 to 50 cells higher in women than in

men (93;94), and this reflects the fact that in HIV-uninfected people it has been observed that women tend to have between 60 and 100 CD4 cells/μL more than men (95).

SC is accompanied in most individuals (70-80%) by mild flu-like symptoms for 7-10 days (25), which can include fever, sweats, malaise, lethargy, nausea, headache, sore throat, skin rash, lymphadenopathy, splenomegaly, myalgia, arthritis, diarrhoea or thrombocytopenia (89;96). Some more severe symptoms can occur rarely such as gastrointestinal haemorrhage, encephalopathy, pneumonitis, or rhabdomyolysis linked to acute renal failure.

During this phase and for the first 6-10 months after SC, VL levels decline relatively sharp (0.53 log copies/mL per year) (92) to achieve what is referred to as VL set-point (97) (see Figure 1.4). This is accompanied by a gradual decline in CD4 cell count; although an initial dramatic depletion of $CD4^+$ T cells (25) (See Figure 1.4) occasionally occurs followed by an increase to levels below the pre-infection level (25). Most individuals enter a relatively asymptomatic stage (91;96).

Figure 1.4 Typical course of HIV infection

1.5.2. Clinical latency and advanced HIV infection

The phase called “clinical latency” or “chronic HIV infection” includes two stages: the “asymptomatic” and the “symptomatic” phase (see Table 1.2). Based on the CDC classification, people are considered in the asymptomatic stage if their CD4 is above 500 cells/μL and they do not have an ADC and in the symptomatic stage if their CD4 is between 200 and 500 cells/μL,

they have not experienced an ADC, but they present with symptoms that either are attributable to HIV infection or indicate a defect in cell-mediated immunity or are considered to have a clinical course or management complicated by HIV infection. The "symptomatic" phase in the WHO classification is divided into "Mild" (clinical stage 2) and "Advanced" (clinical stage 3) and the conditions which characterize these two stages are listed in Table 1.2.

Table 1.2. WHO Clinical Staging of HIV/AIDS for Adults and Adolescents (86)

Figure not available due to copyright restrictions

There is a sharp decline in VL in the first months from SC, after the initial peak, with the level falling to an average of around 4 log copies/mL, but with a high level of variation between individuals, from below 50 copies/mL to above 100,000 copies/mL. Thereafter VL slowly increases on average with a rate of increase between 0.08 and 0.11 log copies/mL per year (92;98;99), so that at two, five, and ten years following SC VL levels are on average 4.0, 4.3 and 4.8 log copies/mL (92). The VL is very variable, not only within a person over time but also between persons, of the magnitude of thousands of times (100).

This persistent viral replication leads to a progressive deterioration of the immune system: the CD4+ T cell count in the asymptomatic phase on average decreases moderately (see Figure 1.4 at page 40): between -1.2 (93) (in MSM, 25 years old at SC in the post-1996 era) and -1.7 cells/µL per year on the square root scale) (92), but the rate of decline is highly variable between individuals and dependent among other things on the current VL. This translates into median times to respectively CD4 below 500, 350 and 200 cells/µL of 1.2 years, between 4 and 4.2 years and between 7.6 and 7.9 years (93;101). Once the CD4 count drops below 500 cells/µL half the immune reserve has been severely depleted (5).

As VL increases and CD4 cell count falls, the risk of developing AIDS related illness and of dying increases. An AIDS diagnosis, also referred to as WHO clinical stage 4, is defined as the occurrence of one of a number of different opportunistic infections (OIs) listed in Table 1.2 (86) (see Table 1.1 at page 39). Most AIDS events occur when CD4 cell count reaches levels below 200 cells/µL. Nevertheless, some events, such as tuberculosis (TB) and severe bacterial disease, which are the most frequent causes of HIV-related morbidity in Africa, can occur in individuals at any CD4 cell count. In adults, the average time between infection and development of AIDS is between 7.7 and 11 years (102;103). Among people infected at a young age (25-29 years) between 13% and 20% develops AIDS (excluding Kaposi's sarcoma) by 5 years (103;104), 46% by 10 years (103;104) and 88% by 20 years (104). In cohorts from sub-Saharan Africa faster progression to AIDS has been observed compared to cohorts of non-African Europeans, nevertheless this was mainly due to pulmonary and disseminated TB (105).

The average survival time after an AIDS diagnosis has been estimated to be between 15 (100) and 19 months (43), but it is very variable depending on the population studied, on the AIDS-defining events and on the number of ADCs. In the absence of ART, it ranges from 3 months to

2 years in South Africa (106) and Europe (107), 7 months in Thailand (108) and 9.2 months in Uganda (109). In Europe, the ADCs with the shortest survival from diagnosis are progressive multifocal leukoencephalopathy (2 months) and malignant lymphoma (5 months), while those with the longest median survival are Kaposi's sarcoma and extra-pulmonary TB (17 and 22 months respectively) (107). In South Africa survival from AIDS diagnosis varies from less than 3 months from a diagnosis of encephalopathy and wasting to more than 2 years from a diagnosis of extra-pulmonary TB and herpes simplex virus infection (106). This relationship between type of ADC and survival is most marked in patients with CD4 above 50 cells/µL (106) and having a second ADC diagnosed decreases survival time by between 1.5 and 2-fold (110). The type of ADC differs by setting, in particular in sub-Saharan Africa the most common are TB (around 30%) and HIV wasting syndrome (around 15%), while in Europe among person of non-African origin, Pneumocystis pneumonia (PCP) and Kaposi's sarcoma (around 15-20% each) are most common (105). On the contrary, in people living in Europe of African origin the most prevalent ADC is TB with over 60% of case of which almost two thirds are extra-pulmonary TB (105).

Overall, survival of people infected with HIV from SC who are untreated varies between 7.9 and 12.5 years, depending on age at infection, in Europe, North America and Australia (103). Among people aged 25-29 years at SC, respectively 90% and 60% survived at 5 and 10 years (103). Similar estimates have been found in developing countries: an analysis including people from community-based studies in East Africa, South Africa (miners), Thailand and Haiti found median survival among people aged 25 to 29 years ranging from 7.5 years in Thailand to 11.6 years among miners in South Africa (111). Studies in Uganda estimated median survival between 8.7 and 9.7 years (112;113), while studies in workers in Ethiopia and Tanzania estimated median survival between 9.1 and 13.7 years (114;115). The specific causes of mortality among HIV-infected patients also vary by country. In South Africa, the causes of death for HIV-infected patients have been examined among a group of HIV-infected miners. In this population TB was the leading cause of death in both HIV-positive (47%) and negative men (26%) who died from natural causes. Despite a great increase in the mortality rate from natural causes with duration of HIV infection, the pattern of disease changed minimally, suggesting that the speed of progression does not affect which type of disease can affect these people (116).

1.6. Predictors of disease progression

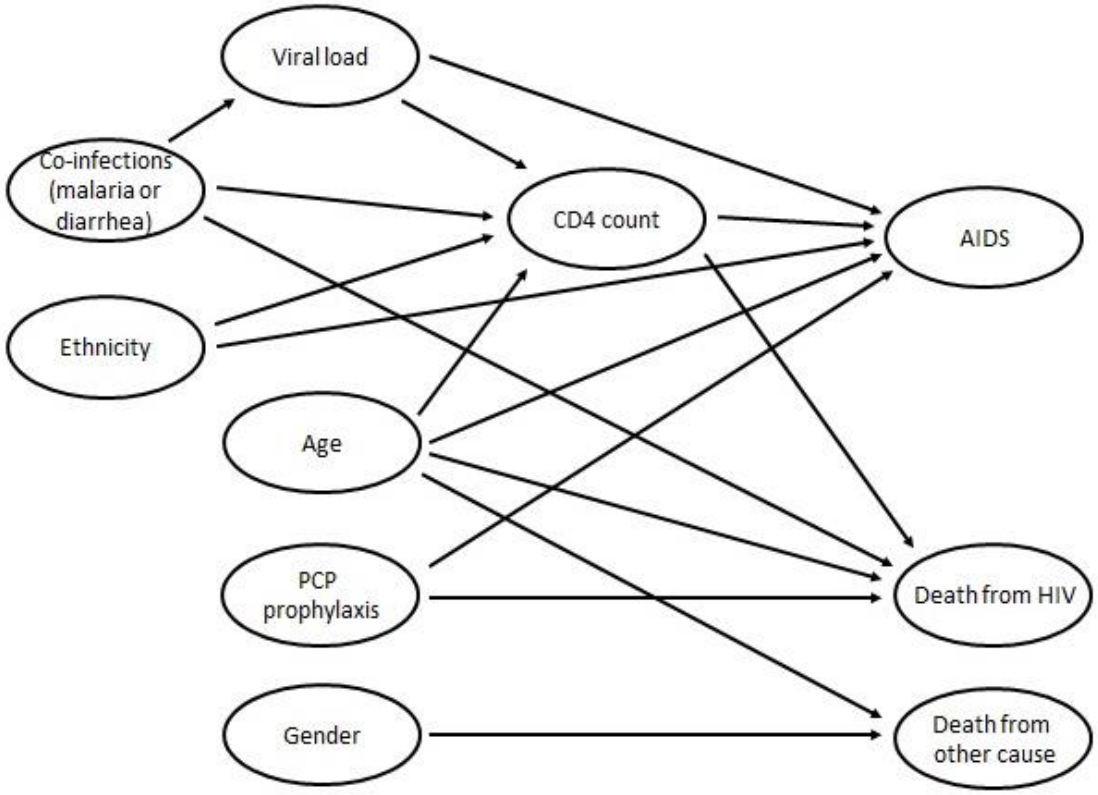
In the absence of ART, the main predictors of progression to AIDS and death are VL, CD4 cell count, age and PCP prophylaxis, although many others have been investigated with conflicting evidence. Figure 1.5 illustrates the relationship between these factors.

1.6.1. Role of viral load and CD4 in predicting disease progression

The single best predictor of long-term progression to AIDS (117;118) and death is the amount of VL circulating in the plasma, as it predicts the rate of decline in CD4 cell count (117). In fact, higher VL is associated with a faster rate of CD4 cell count decline (119;120) and disease progression (117;121;122). In particular, the CD4 slopes are estimated to be between 1.5 and 1.9 steeper for people with the highest compared with the lowest VL quartile (123).

One of the first studies to evaluate the capacity of plasma VL to predict progression found that the percentage of patients who progressed to AIDS within 6 years varied from 5.4% if their VL was 500 copies/mL or less, to 80% if the VL was more than 30,000 copies/mL; the percentage who died of AIDS ranged from 0.9 in those with VL of 500 copies/mL or less up to 69.5% in those with VL above 30,000 copies/mL. Nevertheless the use of CD4 measurements, in addition to VL, improves the capacity of predicting these outcomes (117;118). VL is usually considered a good long-term (5-10 years) marker of risk of clinical progression (117;124-127), while CD4 cell count is a much better predictor of short-term risk of disease progression (126;128-131).

Figure 1.5. Main factors determining progression of HIV in absence of antiretroviral treatment



AIDS: Acquired Immune Deficiency Syndrome; PCP: Pneumocystis cariniii Pneumonia;

1.6.2. Factors affecting CD4 cell counts

Even in healthy individuals, several factors can influence CD4 cell count levels, including sex and age, genetic factors, such as HLA type, factors such as parasitic, respiratory, gastrointestinal co-morbidities and acute infections (132), conditions such as fatigue, stress and exercise, drug use and even time of the day (133-135). In HIV uninfected individuals CD4 count can vary between 500 and 1600 cells/μL (7;95;136) and natural daily variability is large (134;137).

Among HIV-infected populations, few studies have assessed the depletion of CD4 cells in African countries (138-140) and very few have directly compared estimates from low and high income countries (105;114;141-143). Some have found a lower CD4 cell count at SC (105;114;141;143) in African populations and slower CD4 decline over time (105;114;142;144;145). This does not seem to depend on income level of country of residence because studies that have compared people living in high income countries of African origin and not found a significantly lower CD4 decline in those of African-descent (on the square root scale -0.04/year) compared to people of non-African origin (-0.07/year) (105;142;146). Part of this effect seems to be explained by HIV subtype, with subtype C being characterized by a slower decline compared to B (142;146). Nevertheless, this ethnicity effect remains even when adjusting for subtype (146;147), therefore the most likely explanation is a genetic cause. Although, the CD4 cell count is significantly lower at SC in people of black ethnicity, due to slower CD4 cell loss, by approximately 2.5 years since SC the CD4 levels are the same as those of caucasian ethnicity (105).

Older age at SC is associated with steeper CD4 count slopes (93;94;123;138;148), although some smaller studies failed to find this effect (149;150).

Other factors seem to be associated with CD4 cell count decline, but the evidence is less clear. Presence of a clinically recognized SC illness is associated with steeper slope (94). Risk group (93) also seems to be related to CD4 depletion, with people infected through heterosexual sex and people who inject drugs experiencing a slower CD4 count decline compared to individuals infected through homosexual sex (93;94;151). Some studies found a faster CD4 decline for women (152;153), but studies with a bigger sample size and a more accurate date of SC did not find any evidence of this (93;94;154). In addition, several studies have attempted to determine whether the virulence of HIV-1 has increased over the course of the epidemic, but

the results are conflicting with some suggesting that HIV-1 virulence is decreasing (155-158), stable (159-164) and some that it is increasing (165)(166-169) over time and more recently a study hypothesised virulence increased and then reached a plateau (170).

1.6.3. Effect of demographic factors on risk of AIDS and death

In the absence of ART, age at SC is the major predictor of development of AIDS (148;171) and death (172) after time since SC and therefore VL and CD4 count. In developed countries it has been estimated that the median time to developing AIDS in the absence of ART ranges from 7.7 years for people aged 45-54 years at SC up to 11 years for those aged 15-24 years and the survival time from around 8 years in the older group up to 12.5 years for those aged 15-24 years (103). An almost linear increase in mortality rate as age increases has been found as well in studies from South Africa (173;174) and Uganda (112;113). In South Africa, death rates in HIV-infected people vary from below 50/1,000 PYs in people aged less than 20 years up to 150/1,000 PYs in people aged 50 years or more (174).

Many studies investigated whether there was a difference in survival between sexes, given the lower CD4 cell counts in women, but no significant difference has been found between sex (112;174;175) nor among exposure categories (103). The only exception is Kaposi's sarcoma with higher incidence in those infected through sex between men (103) and cervical cancer, an ADC that can only occur in women.

Despite the slower rate of CD4 depletion observed in African people, the risk of developing AIDS is higher in people of African origin, especially if living in sub-Saharan Africa (105). Shorter survival has been observed in people with subtypes D, and AD recombinant or multiple infections compared with subtype A. Non-A subtypes had a median survival time of 7.5 years, whereas over 90% of those infected with subtype A survive more than 7 years from SC (112).

1.6.4. Effect of co-infections on AIDS and mortality

Co-infections, such as with hepatitis C virus (HCV), hepatitis B virus (HBV), which share transmission routes with HIV and endemic illnesses, including malaria and diarrheal diseases, which HIV people are more susceptible to (176-180), could potentially have an impact on HIV progression.

Findings are conflicting regarding the role of HBV and HCV on the course of HIV disease. Early studies found faster progression to AIDS among HBV-antibody-positive people (181), but this has not been confirmed by studies conducted in the early ART era (182) or more recently (183). On the contrary for HCV, early studies failed to detect any relationship between HCV infection and HIV progression (184-188), but some studies have observed faster HIV progression in people co-infected with HCV (189;189-191). A meta-analysis published in 2009 (192) concluded that HCV co-infection did not increase mortality among patients with HIV infection before the introduction of ART, but that since the introduction of ART, people co-infected with HIV and HCV, compared with HIV infection alone, have increased risk of mortality, but not of developing AIDS. A more recent study from China has even found that HCV co-infection seems to be associated with slower disease progression in the absence of ART (193). Co-infection with GB virus C (GBV-C, or hepatitis G virus) was associated with improved survival in the pre-ART era but modern ART has eradicated this advantage (194).

People co-infected with malaria and diarrheal diseases tend to have higher HIV viral loads, of the order of 0.25 log higher copies/mL (195-197) and more rapid disease progression than people infected only with HIV (198;199). A recent randomized controlled trial (RCT) demonstrated that providing people with water filters and insecticide-treated bed nets significantly reduce the likelihood of diarrhoea and malaria and is associated with a slower HIV progression (200).

1.6.5. Effect of co-trimoxazole on AIDS and mortality

Prophylaxis with co-trimoxazole (CTX), a combination of two antibiotics (Trimethoprim and sulfamethoxazole), is recommended in adults with HIV and WHO clinical stage 2, 3 and 4 and if CD4 measurements are available in all those with CD4<350 cells/μL (201). Irrespective of CD4 cell counts, in patients with clinical stage 2 or 3 of the WHO classification (202) or with pulmonary TB at any CD4 level (203) it reduces the rates of mortality, up to half (203), and substantially those of severe events (202). Even in areas with high rates of bacterial resistance to CTX, CTX prophylaxis is effective in reducing mortality by around 50%, rates of malaria by around 70% and diarrhoea by 35%.

1.7. Tests to detect HIV

1.7.1. HIV testing

A reproducible laboratory test able to detect HIV antibody was developed in 1984 (204). It became available in 1985, but it was mainly used to confirm the diagnosis of symptomatic people and to screen blood products (see section 1.4.3). The first type of HIV test widely employed to screen for HIV is the *enzyme-linked immunosorbent assay*. This test is characterized by high sensitivity but has to be conducted in a laboratory; it takes at least few hours to be processed and is quite expensive. Rapid, point-of-care (POC) tests, which do not require laboratory equipment nor specialized laboratory staff and produce a result usually in less than 40 minutes became available in the late 1990s (205).

These tests are all antibody tests and therefore are unable to detect HIV infection if the HIV infection is recent, because the antibodies take some time to develop (usually up to around 3 months or more). The time from infection to when the test is able to detect the HIV infection is usually referred to as the "window-period".

Fourth generation tests, able to detect antibodies and p24 antigens with a much shorter window period (11 days-1 month) are now available, mainly in high income countries. They are generally extremely sensitive, 99.8% or more (206), but there is only one POC which has been approved by U.S. Food and Drug Administration (FDA), Determine HIV 1/2 Ag/Ab Combo (207).

1.7.2. Viral load testing

Viral load testing allows measuring VL (see section 1.4.1.1), in terms of number of copies of HIV-RNA per millilitre of blood. These assays were firstly used in the 1990s, as a research tool and they were crucial to help understanding the natural history of HIV and to evaluate more timely (compared to the use of CD4 count) the response to treatment in patients. In 1995 the minimum amount they could measure was 10,000 copies/mL, but this threshold has been decreasing over years, with the introduction of new generation assays: 400 or 500 copies/mL by 1996-97, 40 or 50 copies by 1998 and nowadays tests used for research can detect five or even one copy/mL.

In high income countries, VL tests, whether commercially available (employing molecular technique) or for research purpose, are conducted in laboratory and they are widely available. In resource limited settings (RLS), standard VL testing is very rarely available, because of the necessity of expensive equipment, laboratory space and highly trained personnel (208). The

use of dried blood spots, which consist of individual spotting whole blood onto filter paper after a finger or heel prick and leaving it to dry at room temperature, is an encouraging option and has allowed reaching more remote areas (209). However, it requires shipping the dried blood spots stored with desiccant to central laboratories, with potential logistic issues. For this reasons researchers are working on developing a reliable point-of-care VL testing, which could be more feasible to use and affordable (210).

1.8. HIV treatment

The first drug found to be effective in significantly reducing death rates in people with AIDS was zidovudine (AZT), in 1986. Since then many more antiretroviral drugs (ARVs) have been developed and licensed. At the moment 36 ARVs are currently approved for the treatment of HIV by the FDA (211), including fixed-dose combinations (FDCs) (single pill containing multiple ARVs). They belong to six different classes of drugs, each of which attack different stages of the HIV life cycle (see section 1.3). The classes are nucleoside reverse transcriptase inhibitors, NNRTIs, protease inhibitors (PI), fusion inhibitors, entry inhibitors (CCR5 co-receptor antagonist) and HIV integrase strand transfer inhibitors.

1.8.1. Nucleoside Reverse Transcriptase Inhibitors

AZT is a nucleoside reverse transcriptase inhibitor (NRTI). It was initially developed as an anticancer agent (212), but in 1986 it was found to be efficacious in reducing mortality in people with AIDS (1 death in the AZT arm versus 16 deaths in the placebo arms out of 282 patients in total), after only 6 months since the RCT was started (213). AZT was approved for the market in the US in March 1987 (211).

ARVs belonging to this class interfere with the HIV life cycle phase called reverse transcription, during which the HIV enzyme RT converts HIV RNA into DNA. Nucleoside analogues are faulty versions of the building blocks necessary for HIV reproduction. When HIV RT enzyme uses a nucleoside analogue instead of a normal nucleoside, the DNA chain cannot be completed and so HIV cannot replicate in a cell (214).

The first RCT evaluating the efficacy of AZT found that AZT could significantly decrease mortality and the frequency of OIs (215) over 24 weeks, but a higher frequency of serious adverse reactions were found in patients receiving AZT (216). Unfortunately the benefits of monotherapy treatment with AZT were found to be transient (217;218): the life of patients was prolonged only by 6 to 18 months (219) and resistance mutations in patients taking AZT for more than 6 months were reported (220-222). In an attempt to overcome the issue related to the development of resistance, some studies were conducted evaluating combinations of the drugs available: AZT, didanosine (ddI) and zalcitabine (ddC). Dual therapy using ddI or ddC in combination with AZT was found to delay death, and the development of new AIDS defining illnesses compared to AZT monotherapy (223) and dual-therapy with ddI was found to be more effective than with ddC (223). Nevertheless, in studies using the combination of the three drugs it was found that ddI and ddC had similar toxicities and cross resistance profile (224) and therefore they did not overcome the resistance issue.

In the following years many other NRTIs have been developed and currently nine are approved in the US, Zimbabwe and South Africa (see Appendix I). Among NRTIs, use of ddC and ddI is very rare both in South Africa and Zimbabwe because since ART has been rolled out, they have never been recommended as first-line regimens. Stavudine (D4T), part of the first-line regimen when ART was rolled out in these two countries, is not recommended anymore as a 1st line regimen, because of its side effects, while AZT, lamivudine (3TC), emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) are most commonly used (225-230).

1.8.2. Protease Inhibitors

PIs were introduced in 1995. Their availability changed HIV treatment dramatically, because it allowed a combination of three ARVs to be used which belonged to two different classes, (from this point onward I will refer to combination antiretroviral therapy when using the acronym ART).

PIs work by restricting the function of the protease enzyme, which the HIV virus uses to produce infectious viral particles, so although the HIV virus is created, it is unable to go on and infect other cells (214).

One of the first RCTs comparing combination ART with dual therapy was the ACTG 229 trial (128). They compared saquinavir in combination with AZT and ddC, to the dual therapy of AZT and ddC alone and found that the triple combination was well tolerated, reduced VL, increased CD4 count to a greater extent than those on dual therapy (128) and reduced the risk of AIDS and death (128;231;232). Part of the reason why dual therapy was found to be better than monotherapy, and triple therapy better than dual, is that drug resistance mutants pre-exist within the viral quasi-species (i.e. strains of HIV which are resistant to certain ARVs – discussed in more detail in section 1.9). Mutants resistant to a single ARV are fairly common, while mutants resistant to two or three ARVs are far less common, if not rare, especially if the three ARVs belong to two different classes. By using three ARVs which target two different phases of the replication, a mutant which is resistant to one of the three drugs will still be suppressed by the other two active ARVs. In addition, the regimen composed by more than one drug was more potent at suppressing VL.

In the following year two other PIs were approved in the US: Indinavir and Ritonavir (RTV) (211). The first used in combination with two NRTIs, was found to be superior to dual therapy composed of two NRTIs (233;234). It quickly became the most frequently prescribed PI in the developed world, but its intake regulation was quite strict, the pill burden high (three two-pills doses per day preferably on an empty stomach and with the necessity of a high intake of fluid) and renal toxicities were associated with it (235). RTV was found to be very potent against HIV (236;237), but it was poorly tolerated due to several toxicities, including severe gastrointestinal symptoms (238-241) and so its use as an ARV in its own right was abandoned (235). A few years later it was demonstrated in RCTs that, in low doses, RTV was effective and better tolerated in boosting the activity of other PIs, due to the fact that RTV inhibits the elimination of the PI by the liver. RCTs comparing regimens containing PIs boosted with RTV

found that they were superior to a non-boosted PI regimen and generally safe (242;243). In 2000, the introduction of lopinavir boosted with RTV (LPV/r) was demonstrated to be superior to nelfinavir (244), another PI, and saquinavir (245). In addition, it was demonstrated that patients on LPV/r had sustained efficacy even after 7 years of follow-up (246).

Regimens based on atazanavir (ATV), developed a few years later, have shown non-inferiority compared to regimens based on LPV or fosamprenavir in drug-naïve subjects, generally with improved tolerance (247). From current evidence, tipranavir (241) and darunavir (DRV) (248), two new generations PIs are regarded as very potent ARVs. Tipranavir has been shown to be effective in people with multi-PI resistant HIV-1 (249). DRV, a PI designed to be active against HIV resistant to then-current 'first-generation' PIs, was found to be effective in reducing VL (61% vs 15% on a control PI had a reduction in VL of 1 log) in patients with experience of all three classes of ARVs available at the time the study began in 2004 and with relatively high levels of PI resistance (250). In treatment naïve patients, the ARTEMIS study demonstrated that once daily DRV/r was non-inferior compared to LPV/r and also had a more favourable safety profile (251).

Currently there are eleven PIs approved for the market by FDA, but they are not all approved in South Africa and Zimbabwe (see Appendix I). The only PIs recommended in the Zimbabwean and South African guidelines are LPV/r and ATV/r as part of the second-line regimens (226-230) and DRV as part of the third line regimen in South Africa (226).

1.8.3. Non-nucleosides reverse transcriptase inhibitors

Shortly after the first PIs were approved, NNRTIs were introduced (219), leading to a choice of combination ART options. Similarly to NRTIs, NNRTIs affect reverse transcription, in particular, NNRTIs bind to the RT enzyme, obstructing its ability to convert the HIV RNA into HIV DNA (214).

The first NNRTI licensed was nevirapine (NVP) in 1996 (211). As with PIs, several RCTs demonstrated the superiority in suppressing VL using a combination of three ARVs belonging to two different classes, in this case one NNRTI in combination with two NRTIs, over dual therapy (252-254). In addition, NVP-based ART regimens were demonstrated to be at least as effective as nelfinavir-based ART regimens (255). Several studies evaluated the effect of switching from a PI-based ART regimen to NVP-based ART regimen (256-258), and found that patients could maintain a suppressed VL and that some could benefit from the improved quality of life and reduced toxicity.

Efavirenz (EFV) was licensed a couple of years later (211) and was also found to be a viable treatment option (259-261). In observational studies, EFV showed better virological outcomes than NVP (262-264) but when compared in RCTs they showed similar efficacy, but with differences in the safety profile (264), although both shared side effects such as hepatotoxicity, and severe rash (219). NVP, EFV and delavirdine are all classed as first generation NNRTIs and were approved by the FDA in the late 1990s (211). NVP was initially recommended for first-line therapy in both South Africa (225) and Zimbabwe (227). Current guidelines, both in western countries (265;266), South Africa (226) and Zimbabwe (229) now recommend EFV in first-line treatment regimen, even for pregnant and breastfeeding women, with the exception of the EACS guidelines who recommend replacing EFV with rilpivirine (267). Appendix I shows the five drugs in this class that have been approved for treatment of HIV (211).

Etravirine and Rilpivirine are considered 2nd generation NNRTIs. Etravirine, which is recommended to be considered as part of third line regimen in South Africa (226), but not in Zimbabwe, was approved in 2007 after two RCTs, DUET-1 (268) and DUET-2 (269). They demonstrated that etravirine was effective in patients with resistance to NNRTI and PIs. Rilpivirine is currently not recommended in any of these two countries (226;229).

1.8.4. Entry inhibitors, fusion inhibitors and integrase inhibitors

Enfuvirtide the only approved fusion inhibitor (211) and Maraviroc, the only approved entry inhibitor were approved respectively in 2003 and 2007 by FDA (211), but they are not currently recommended in South Africa (226) or Zimbabwe (229).

The class of Integrase inhibitors has been developed more recently and it includes: raltegravir , dolutegravir and elvitegravir (211). Integrase inhibitors block the enzyme integrase, which HIV uses to integrate genetic viral material into its target host cell DNA (214;270). Raltegravir has been recommended to be used by treatment experienced patients (265;266) and it is recommended as a third line option in South Africa (226), while dolutegravir and elvitegravir are not recommended. In ART-naïve patients, raltegravir (given in combination with TDF and FTC) was shown to be non-inferior to EFV-based regimen in terms of sustained viral suppression (271;272) and was associated with fewer drug-related clinical adverse events and smaller elevations in lipid levels (272). In addition it has been recently found to be safe and effective for pregnant women and babies (273).

1.8.5. Toxicities of ARV

Although the availability of combination ART has transformed HIV from a terminal to a chronic disease (274), ART remains a life-long treatment. Drug toxicities, together with poor adherence and development of drug resistance, are the main causes of treatment failure (amongst people who have managed to access and pick up their ARVs) and these three factors are very closely interlinked. In South Africa, the main barriers to remaining on ART are transport costs and the necessity to take time off work to attend the clinic (275) (see section 7.2.5), although ARV toxicities do play a role and in Europe, for example, they are the most frequent reason for discontinuation of a first-line regimen (276)

Toxicities may be specific to a particular ARV or to the class of ARVs, and adverse events can vary in severity from mild to fatal (see grades in Table 1.3). Regardless of the severity of the toxicity experienced, it may have an impact on adherence. Therefore, discussing potential side effects before patient and clinician decide on the ART is important. Patients also need to learn how to recognise the symptoms and signs of severe toxicities.

Table 1.3. Severity of toxicity (277)

Grade	Condition
1: Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
2: Moderate	Limitation in activity- some assistance may be needed; no or minimal medical intervention/therapy required
3: Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required hospitalization possible.
4: Severe life threatening	Extreme limitation in activity, significant assistance required; significant medical intervention/therapy required; hospitalization or hospice care

Table 1.4 summarizes the toxicities of the ARVs most widely used in South Africa and Zimbabwe, whether included in the Synthesis model (indicated by ✓✓), those for which the evidence is more clear, or not (indicated by ✓). Appendix II contains a thorough description of all the toxicities indicated in Table 1.4.

Table 1.4. Toxicities of most commonly used ARVs in South Africa and/or Zimbabwe

	NRTIs					NNRTIs		PIs	
	D4T	AZT	ddI	3TC/FTC	TDF	EFV	NVP	LPV/r	ATV/r
Nausea	✓	✓✓	✓✓	✓				✓✓	✓✓
Diarrhoea			✓✓	✓				✓✓	✓✓
Rash				✓		✓✓	✓✓		
Decreased appetite				✓					
Headache	✓	✓✓		✓					
Asthaenia (i.e. weakness)		✓		✓				✓	
Nail pigmentation		✓							
Lipoatrophy	✓✓	✓✓							
Peripheral neuropathy	✓✓		✓✓						
Pancreatitis	✓✓		✓✓						
Steatohepatitis	✓		✓						
Hepatotoxicity						✓	✓✓	✓	
Lactic acidosis	✓✓	✓✓	✓✓						
Anaemia		✓✓							
Neutropaenia		✓							
Nephrotoxicity					✓✓			✓	✓
Osteopaenia					✓				
Exacerbation of hepatitis B at withdrawal				✓	✓				
CNS						✓✓			
Steven's Johnson syndrome						✓	✓		
Fetal CNS malformation						✓			
Hypersensitivity reaction							✓		
Hypertriglyceridaemia, hypercholesterolaemia and risk of myocardial infarction								✓	

3TC: lamivudine; ARV: antiretroviral drug; ATV: atazanavir; AZT: zidovudine; CNS: central nervous system; d4T: stavudine; ddI: didanosine; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir boosted with ritonavir; NVP: nevirapine; TDF: tenofovir; ✓✓ ARV toxicity included in the Synthesis model; ✓ ARV toxicity reported in the literature but currently not included in the Synthesis model;

Among the drugs approved by the FDA, ddC and D4T are amongst those which cause the most serious adverse events. ddC was withdrawn from the market for adverse event concern at the end of 2006 and d4T is not recommended by WHO from 2009 due to the long-term irreversible side effects (278), although it has not been yet completely phased out.

1.8.6. When to initiate ART

Recommendations for the initiation of ART are based on CD4 T lymphocyte counts and plasma VL levels (279).

The WHO released new guidelines in July 2013 recommending initiating people on ART when CD4 count falls below 500 cells/µL (280) rather than at 350 cells/µL as recommended in the guidelines published in 2010 (277). Current South African guidelines recommend ART initiation when CD4 count is around 350 cells/µL (226) as do the European guidelines (266), while Zimbabwe revised the guidelines (229) following the new WHO recommendations. In the US, both the International Antiviral Society-USA (IAS-USA) guidelines (265) and the Department of Health and Human Services guidelines (281) recommend ART initiation for all adults with HIV, regardless of CD4 cell count.

As illustrated by different guidelines in different settings, there is currently debate over the optimum time to initiate ART. VL levels tend to change only moderately over time in untreated individuals, with most at approximately 0.1 log copies/mL increase per year (99). Early therapy has the advantage of reducing viral replication early on, decreasing the risk of early CD4 cell depletion and the risk of HIV transmission to other people. Delayed therapy on the other hand, means avoiding the risk of toxic drug effects and relying on more potent and tolerable drugs becoming available by the time treatment begins. In a few observational studies, they assessed the impact of initiating at a higher CD4 cell count, generally supporting earlier ART initiation (282;283), however confounding cannot be excluded. The Strategic Timing of Antiretroviral Therapy trial ("START") (284) is currently on-going aiming to answer this exact question: in people with CD4 above 500 cells/µL is it better to start ART or defer until the CD4 count reaches 350 cells/µL. The entire study is expected to take about 6 years, with follow-up ending in December 2015. Similarly the TEMPRANO study is aiming to evaluate the impact on mortality and severe HIV related disease of ART initiation at diagnosis (with CD4 count between 350 and 800 cells/µL) compared to deferral until CD4 falls below 350 cells/µL in Cote d'Ivoire (285) (see section 4.2.7 for more details).

1.8.7. Effectiveness and durability of ART regimens

The benefit of ART regimens in reducing the development of AIDS-defining illnesses and the risk of death is indisputable. Since the introduction of these combination ART regimens a dramatic reduction in AIDS and death rates have been observed in Europe (286;287) and the US (288;288). In Europe, the estimated death rates among people living with HIV on

combination ART decreased from 23.3/100 PYs in the period between March to September 1995, to 4.1/100 PYs of follow-up in the period between September 1997 and March 1998 (287) and in 2013 the death rate among people diagnosed with HIV in the UK was estimated to be 0.34/100 PYs (289). Overall, the risk of death for an HIV-positive patient in the combination ART era has been estimated to be >85% lower than in the pre-combination ART era (287). A study on HIV patients living in Europe and North America found that life expectancy in HIV-positive patients treated with combination ART increased between 1996 and 2005, and the average number of years remaining to be lived at age 20 years was about two-thirds of that in the general population in these countries (290). Similar improvements in patients living with HIV on combination ART have been observed in South Africa (291-295) and more generally in East, West and Southern Africa (296).

The main aim of using ART regimens is to suppress viral replication, which leads to increases of CD4 cell count and reduced risk of developing AIDS and death. It has been demonstrated that patients who receive ART have a lower risk of clinical progression for a given CD4 cell count and VL level compared to patients off ART (297;298). This demonstrates that ART may be protective against clinical progression beyond the protection conferred by lowering VL and increasing CD4 cell count. This could be due to an improvement in the overall immunodysfunction, beyond that captured by the measurement of CD4 cell count (299;300).

Patients experience different immunological and virological responses after initiating ART (301;302). In clinical practice, 70-90% of patients starting combination ART achieve undetectable VL by 1 year since ART initiation. In people initiating combination ART between 2000 and 2004 in Europe, 69% achieved virological suppression (VL<500 copies/mL) at the first measurement between 6 and 12 months, 86%, if patients with missing VL measurements at 6 to 12 months are excluded (303). Similar levels have been observed in sub-Saharan Africa. In a systematic review by Barth et al (304) virological suppression was 78% at 6 months since ART initiation, 76% at 12 months and 67% at 24 months. The same proportion (76%) of patients achieving virological suppression at 12 months (VL<1000 copies/mL) was observed in the WHO resistance survey (305). When restricting to living patients still receiving ART at 12 months, 90% had VL suppression. Among studies specifically in South Africa between 70% (306) and 85% (307) of those on treatment at 12 months achieved virological suppression.

The reason why some patients do not achieve virological suppression could relate to the presence of drug resistance mutations (DRMs) in their viral population or to low levels of adherence or both (308;309).

If viral replication is not fully controlled, emergence of resistance is likely to occur and this has been shown to limit the duration of virological suppression (308). People who experience rebound on the first-line of treatment have a lower chance of achieving viral suppression on a second or subsequent line of treatment because mutations to some of the drugs may already be present in the viral sub-species and because those who fail first-line are likely to have issues with adherence and thus more likely to fail second-line as well. For this reason guidelines tend to recommend a combination of three drugs, not only belonging to two different classes, but without any overlapping resistance mutations, to minimize the risk of resistance emergence (280).

1.9. Antiretroviral drug resistance

1.9.1. Genetic sequencing

The HIV genome is composed of 9,749 nucleotides (base-pairs) (310) and the order of the nucleotides within the DNA or RNA defines the genetic sequence. There are four different nucleotide bases in the RNA: two purine bases, adenine and guanine and two pyrimidine bases, cytosine and uracil. The adenine, cytosine and guanine bases are the same as those found in the DNA, but instead of the uracil base there is a pyrimidine base similar to uracil called thymine. When more than one kind of nucleotide can occur at a certain position, it is convention to use a single letter to represent a variety of possible nucleotides, for example the letters R and Y designate respectively the purines (adenine or guanine) and the pyrimidine (cytosine or thymine).

Genes that code for proteins are composed of triplets of nucleotides called codons, which specify one of the twenty existing amino acids (see Appendix III).

1.9.2. The HIV genome

The HIV genome varies a lot, even within each infected individual (311). As mentioned in section 1.3, several enzymes are involved in replication of the HIV-1 genome, each with their own error rate. Reverse transcriptase, in particular, is very error-prone (error rate 1.4×10^{5} per

base pair per cycle of replication (311), which is nearly one nucleotide mutation per replication cycle). The virus does not have a system to check and repair any error that occurs and therefore genetic mutations (alteration or mistake in the genetic code) occur during viral replication.

Although people are usually infected with only a single or few original clones of HIV, the replication cycle is very fast, each day between 1 and 10 billion viral particles are produced and destroyed (312). These two processes combined generate this high diversity (313;314). For this reason the HIV virus is considered a quasi-species of a virus, because there are different versions of the virus which have related but non-identical mutant and recombinant viral genomes (312).

The mutations are conventionally described by a combination of letters and numbers. The number relates to the position of the codon, the initial letter refers to the amino acid that is expected and the final letter to the amino acid that was found at that position (see Appendix III). For example the mutation M184V, which is one of the most common mutations associated with resistance to 3TC, occurs at codon 184, the expected amino acid is methionine (M) but the amino acid which is found is valine (V).

1.9.3. Emergence of antiretroviral drug resistance

The emergence of DRMs which inhibit the activity of ARVs represents a major barrier to the success of ART (312) and this has been observed in all settings where ARVs have been used (235). In absence of treatment, a particular viral species will dominate and this is generally referred to as “wild-type” virus. These viruses are susceptible to all ARVs and usually are present at infection, although, transmission of drug resistant strain can occur and so people can have a non “wild-type” virus even at infection (315) (see 1.9.7). Throughout this thesis this term will be used to indicate viruses that do not contain any DRMs.

As mentioned in section 1.9.2, many nucleotide changes can occur along the genetic sequences, generating a wide heterogeneity within the viral population of a person infected with HIV. A genetic mutation may result in a change in the amino acid that is present at a particular position. Some of these mutations impact the susceptibility of the virus to ARVs and therefore the activity of ARVs (235). When this occurs we say that a DRM has been acquired. These are usually distinguished in: “major” or “primary” DRMs which directly decrease the susceptibility of a certain ARV and may contribute to reduce the fitness of the virus (316) and “minor” or “accessory” DRMs which have a minor impact on reducing susceptibility or do so

only in presence of a major resistance mutation. The two main ways by which resistance mutations may arise in the dominant viral population of an individual are: as a result of a viral drift (i.e. a nucleotide change in the predominant virus) or more realistically, as a result of a viral shift (i.e. a change in the dominant virus to a virus from a different viral quasi-species). The time for resistance to emerge, under drug selection pressure, differs across individuals. Factors that influence the mechanism and the speed of emergence of resistance mutations include (312;317):

- number and type of DRMs before treatment is initiated
- level of viral replication
- the fitness of the mutants, which is the ability of the virus to replicate itself and infect new cells (fitness refers to a given environment – in the absence of drug virus with resistance mutations is usually slightly less fit than virus without mutations but in presence of drug it is more fit)
- viral fidelity, a decreased probability of new mutations emerging per replication round
- magnitude of drug selection pressure which depends on the drug potency (i.e. the magnitude of decrease in plasma VL)
- adherence to treatment
- ARV genetic barrier (i.e. the number of mutations required to confer resistance to this particular ARV)

1.9.3.1. Viral replication and emergence of resistance

In the presence of an ARV and ongoing viral replication, a pre-existent resistance mutation can be selected by the drug. If replication under drug pressure continues the mutant will acquire further mutations that increase resistance or alter fitness, the ability of virus to replicate and infect new cells (in a given set of conditions, including presence of ARVs) (318;319). Patients on a failing ART regimen with high levels of viral replication are those who experience the highest risk for DRMs to emerge in their dominant virus population. In fact, if the rates of replication are high, there is a greater chance of an error occurring and, if these patients are also receiving ART, it is likely that mutations will emerge that allow the virus to prosper in the presence of that specific ARV. In the presence of ART, viruses with DRMs tend to be fitter than viruses without those mutations so they tend to out-grow the less fit wild-type population and to become the dominant species.

Resistance to a particular ARV is more likely to emerge when both the potency of the ARV and the genetic barrier to resistance (i.e. the number of mutations required to confer resistance (312)) of the ARV are low. In fact if the potency is low, it fails to fully suppress the viral replication and if the genetic barrier is low the drug activity is reduced as soon as one or a few DRMs are acquired. The genetic barrier depends on a number of factors, including the level of pre-existent resistance, the replication rate of the pre-existent resistant viral strain and the number of DRMs that are required for loss of activity of an ARV.

Patients who are receiving a sub-optimal antiretroviral regimen (not combination ART) experience a rapid increase in VL and high chance of acquiring DRMs. Studies in people receiving monotherapy have shown that resistance emerges easily and rapidly to the ARV received (220). This is due to the fact that monotherapy inhibits replication initially, however once resistance emerges to the single ARV the patient is taking, the drug will not be effective anymore at suppressing the VL. Therefore, replication rates will increase with a consequent elevation in viral strains containing mutations that are resistant to the drug. The genetic barrier of dual therapy is higher than that of monotherapy because for replication to occur, the virus needs to develop resistance mutations to both drugs in the regimen. Because more mutations are generally necessary to confer resistance to two drugs rather than one, it generally takes longer for the VL to rise (320). Triple combination of ARVs is used to maximise antiretroviral activity and to inhibit viral replication. In order to maintain high the potency of the regimen and to avoid the emergence of resistance, adherence has to be good.

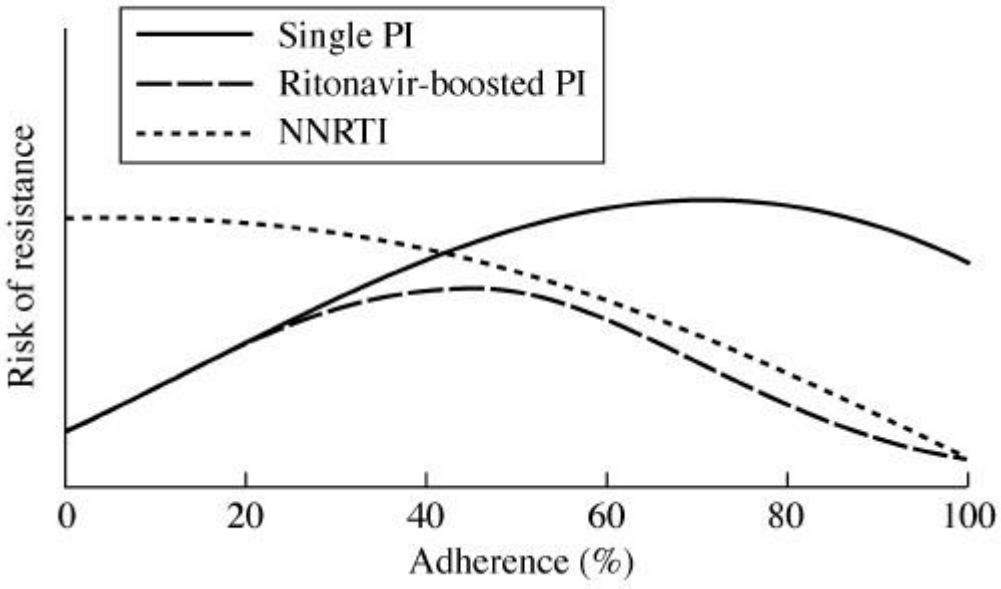
1.9.3.2. Adherence and emergence of resistance

Adherence to ART (i.e. taking the regimen as prescribed) is one of the main determinants of resistance emergence and long-term therapy success (321-324;324;325). In patients who received ART and had directly observed therapy (DOT) virological suppression rates up to 100% have been observed (326;327). Nevertheless it is not feasible to provide ART with DOT to all patients on ART. Different methods to assess adherence exist, such as self-report, self-administered questionnaire, physician perception, drug prescription, pharmacy refills, plasma pharmacokinetics drug levels, medication event monitoring system and DOT. Nevertheless none of them have been proved to be completely reliable (328).

The relationship between adherence and rates of emergence of resistance is an inverse U-shape. If the adherence is optimal the ART regimen prevents replication from occurring and

therefore it is very unlikely to accumulate DRMs. At the other extreme, if the adherence is very low, there is insufficient potency to prevent replication but there is minimal selection pressure and thus the rates of mutation accumulation are low (329). The higher rates of resistance mutation accumulation occurs when the adherence is intermediate, although the level of adherence with the higher risk of accumulating resistance mutations and the magnitude does vary by drug-class (see Figure 1.6 (330;331)) and to some extent by specific drug (332).

Figure 1.6. Relationship between medication adherence and the risk of developing drug resistance by drug class (330)



NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor;

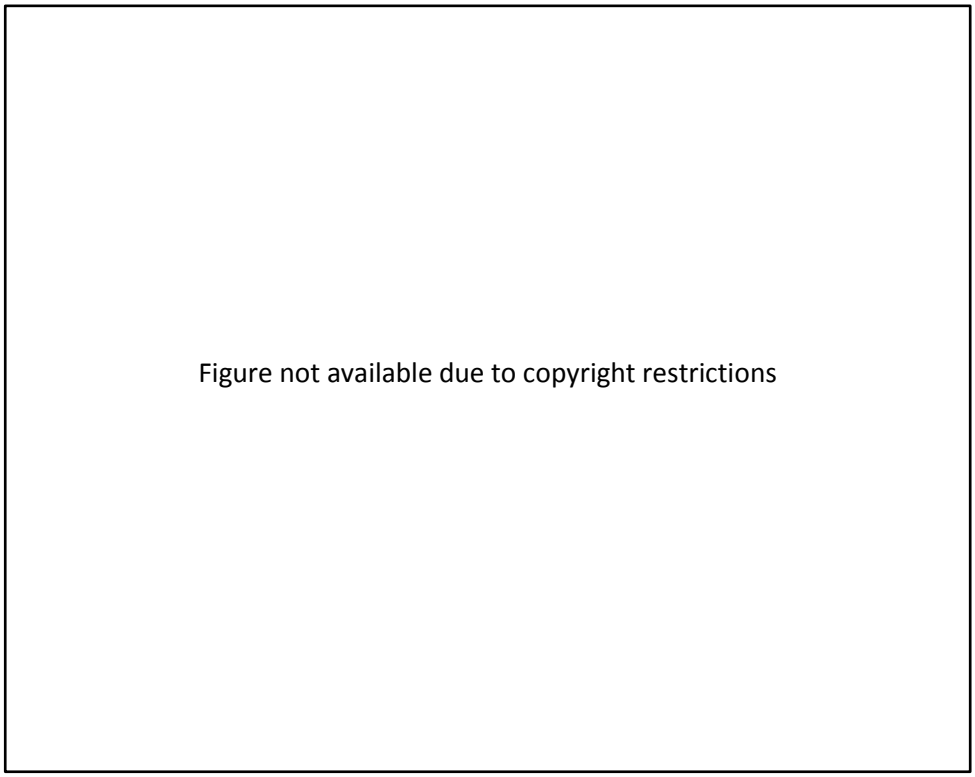
The level of resistance conferred by different mutations varies. Virus with DRMs located at, or near, the active sites of the enzymes targeted by an ARV, tend to have a higher ability to replicate in the presence of that ARV. These mutations are typically along the reverse transcriptase or protease section of the *pol* gene.

Some mutations cause resistance to a particular ARV but re-sensitize others (333-336), such as for example AZT and TDF in presence of M184V and thymidine analogue mutations (TAMS) (337;338), others improve the fitness of the virus under selective pressure from ARVs (339;340) and some lie along the pathway for developing major resistance mutations (341).

1.9.3.3. Classes of ARVs and emergence of resistance

Because the genetic barrier, potency, half-life and the mutations which confer resistance to an ARV are specific to each drug, the rate of emergence of resistance mutations differs by drug class and to some extent by individual drugs (330). Figure 1.7 shows the genetic barrier and the potency of the most common ARVs: NRTIs in black, NNRTI in green and PIs in red, integrase inhibitors in blue and entry inhibitors in purple.

Figure 1.7. Scheme summarizing the genetic barrier to resistance and the potency of the main ARVs (312)



3TC: lamivudine; ABC: abacavir; ARV: antiretroviral drug; ATV/r: atazanavir boosted with ritonavir; AZT: zidovudine; d4T: stavudine; ddI: didanosine; DRV: darunavir; ENF: enfuvirtide; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir boosted with ritonavir; MVC: maraviroc; NVP: nevirapine; RAL: raltegravir; TDF: tenofovir; VL: viral load;

When used in monotherapy, NNRTI resistant mutations are the quickest to occur, in a matter of weeks, followed by DRMs which develop while on an unboosted PI (within months), while NRTI DRMs are generally those which take longer to develop, often a matter of years (see **Error! Reference source not found.**). Nevertheless there is variability even within class. An example is the mutation M184I/V which emerges in patients failing 3TC monotherapy in a couple of weeks, while K65R, along the RT gene, emerging on a failing ddI, abacavir (ABC) or TDF containing regimen, takes much longer, as do most of the other NRTI mutations.

Table 1.5. Efficacy and time to resistance emergence in people receiving monotherapy with specific ARVs (342)

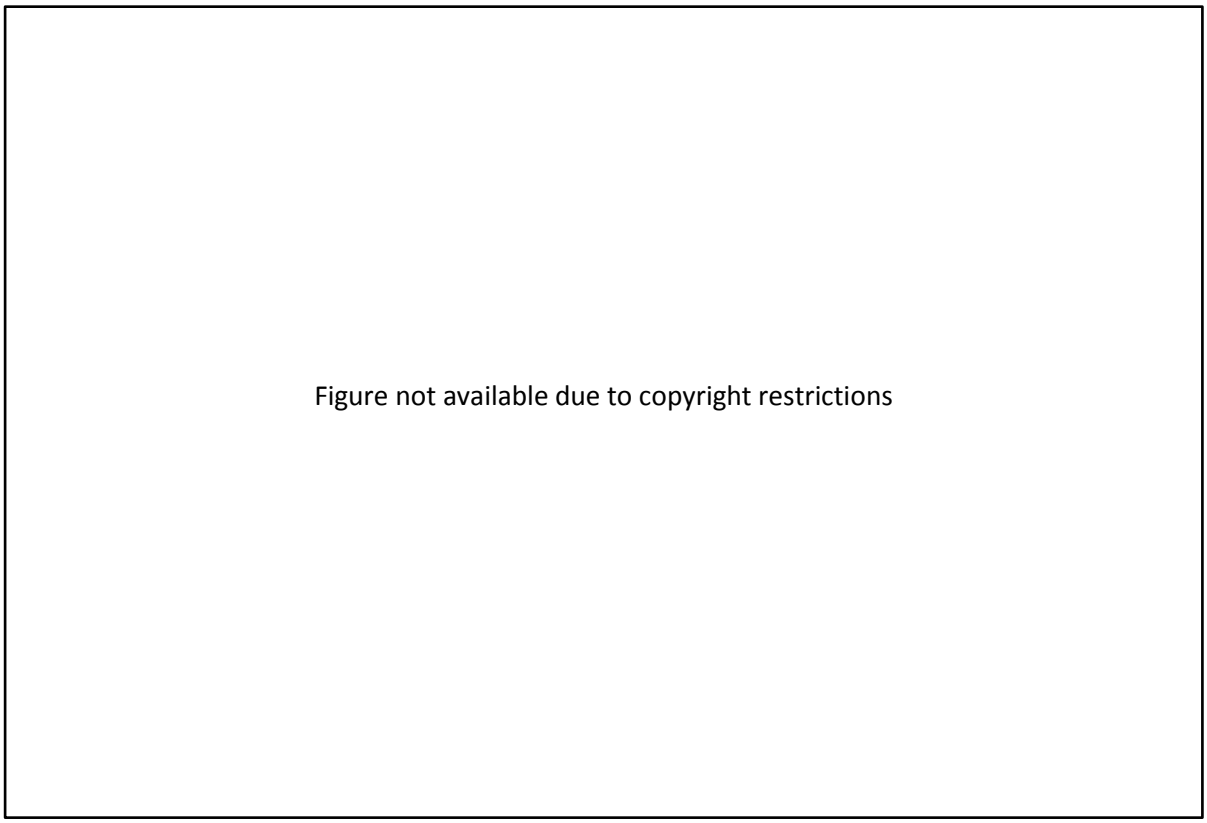
Figure not available due to copyright restrictions

As shown in Figure 1.6 (page 63) people on NNRTI-based ART rarely develop resistance at high levels of adherence due to the virological effectiveness of these regimens. While when adherence drops at intermediate or lower levels, NNRTI resistance develops rapidly. In general, resistance to NNRTIs emerges quickly if VL is not kept below 50 copies/mL. Nevertheless new generation NNRTIs, such as etravirine, have a better resistance profile (219).

Resistance to PIs is usually uncommon at low levels of adherence because of the significant fitness costs associated with these mutations (virus with these mutations remains less fit than wild-type). At high levels of adherence, people receiving ART regimens based on single PIs may develop resistance because residual viral replication is often seen on these regimens (332). On the contrary, if the regimen is based on RTV-boosted PI, the chances of accumulating DRM are

very low (see dashed lines in grey in **Error! Reference source not found.**) because this is possible only in a narrow range of drug levels (as the half-life of PI is short, the drug level at which DRMs can emerge is brief) and of adherence where there is sufficient drug around to select for mutations that reduce 'fitness', while still allowing residual viral replication so that new mutations can arise (330). Both tipranavir and DRV, new generation PIs, have a high genetic barrier to resistance and have activity against other PI-resistant strains (248).

Figure 1.8. Relationship between adherence and resistance in patients receiving a nelfinavir or lopinavir/r containing regimen (332)



PI: protease inhibitor;

1.9.4. Cross-resistance

Mutations acquired on a certain drug reduce susceptibility to that particular ARV. In addition, some mutations can confer resistance to other ARVs, including drugs the patient has never taken before. This phenomenon is called cross-resistance. This is a very problematic issue, because although many ARVs are available, the emergence of mutation to a particular ARV could reduce susceptibility to other ARVs. This is more likely for NNRTIs than for either NRTIs or PIs, especially for first generation NNRTI.

Y318F mutation, located next to the connection domain, is associated with resistance to delavirdine, EFV and NVP and is part of the NNRTI binding pocket (343). The connection domain in the reverse transcriptase joins the polymerase and RNase H domains and plays a structural role in the protein (344). Recent studies have reported that mutations in the connection domains can be acquired when receiving ART but their impact on NRTI susceptibility and therefore on response to ART does not seem to be large (345).

Mutations which confer resistance to more than one PI are likely to be associated with amino acid substitutions at one of six different positions along the protease section of the pol gene: 10, 46, 54, 82, 84 and 90. Other PI mutations, such as D30N, L33F, and G48V are relatively specific to certain PIs and are less likely to produce cross-resistance (346).

Between drug classes, there is almost no cross-resistance at all (312), although mutations in or near the connection subdomain of HIV-1 RT (codon 322 to 440) can confer resistance to NRTI and NNRTI (347;348) (evidence is available for the mutations N348I, A376S and Q509L (349)). Although there is some overlap among mutations for NRTI and PI drugs, PIs tend to require several mutations for their efficacy to be compromised. Therefore, the emergence of resistance of a single mutation is likely to result in reduced activity for some other ARVs from the same class but it should not compromise the use of ARVs from other classes.

1.9.5. Benefits associated with the emergence of resistance

The emergence of mutations, at least over the short term, may have some beneficial effect. Some mutations, for example, have been associated with hypersensitivity to other ARVs within the same class (350). Other mutations may affect the fitness of the virus. *In vitro* experiments, for example suggest that virus containing the M184V mutation have a lower fitness and higher fidelity compared to wild-type virus (351-358).

These findings have been confirmed by *in vivo* studies. The E-184V study conducted on patients with limited treatment options found that people who had failed a 3TC containing ART regimen with M184V had better outcomes if they switched to 3TC monotherapy, and therefore M184V mutation was continuously detected, rather than interrupting treatment completely (359). By lowering the viral replication capacity and increasing the fidelity of the dominant virus, other mutations may emerge at a slower rate and so the activity of other ARVs in the regimen may be preserved for longer (360). Nevertheless a RCT comparing patients failing a 3TC-containing regimen randomized to continue the same regimen (On-3TC) or

discontinue 3TC (Off-3TC) whilst receiving ART combination, found no additional virological or immunological benefit of continuing 3TC in patients harbouring M1841/V (360).

A reduction in viral fitness has been found in a few studies on people with DRMs (361-366). This could impact the ability of the virus to infect the T lymphocyte as efficiently (363) and therefore it may reduce the capacity of the virus to induce CD4 cell count decline. Nevertheless it is quite possible that this is not the case (367). A study evaluating the impact on CD4 count slope for a given VL level, in patients with VL above 500 copies/mL, did not find any difference according to the presence of specific DRMs or class of mutations (368).

1.9.6. ART interruptions

In the absence of ART, wild-type virus has the highest ability to replicate. Hence, if resistance mutations are present in majority virus (see 1.9.10), once ART is stopped wild-type strains are likely to become dominant again (369), because they are the fittest viruses (318). For some ARVs, the reversion to predominantly wild-type virus can happen in the first 4 to 6 weeks after the drugs are discontinued. This does not mean that DRMs disappear completely. In fact they are likely to remain present in plasma as low frequency mutants (not detected by commercially available resistance test, see 1.9.10) and also hidden in archived reservoirs of HIV proviral DNA.

Once ART is restarted (see Figure 1.9), VL declines, as the replication of wild-type strain is constrained, but if they harbour strains of HIV resistant to the ARV the patient is receiving (as it is the case in Figure 1.9), DRMs will become dominant again under selective pressure, compromising the effectiveness of the treatment.

Figure 1.9. Relationship between viral load and resistance (370)

1.9.7. Transmitted drug resistance

There is clear evidence that transmission of drug-resistant HIV strains can occur and may be associated with suboptimal virological response to 1st line regimens (371-374). The probability that a patient is infected with drug-resistant virus is linked to the prevalence of drug resistance in the HIV-infected population sexually active. The prevalence of transmitted drug resistance (TDR) mutations in people recently infected with HIV from East and Southern Africa has been estimated to be respectively 5.0% (375) and 5.6% (376). Among patients initiating ART in Lusaka Zambia a prevalence of 6% was found (377), while in Uganda the prevalence of TDR mutations was up to 8.6% (378). Up to 8%, but usually less than 5%, of transmitted viruses will exhibit resistance to drugs from more than one class (379-382).

In the absence of therapy, in people infected with ARV resistant virus, TDR mutations tend to revert to wild-type. Nevertheless, resistance-associated mutations can often be detected in viruses that were transmitted several years earlier (383-385) and seem to be more stable than those selected under drug pressure. The rate of persistence seems to vary by specific mutations: most TAMs, which affect all NRTIs, and T215 revertants (but not T215F/Y) seem to be highly stable, while NNRTI and PI mutations have been found to be relatively less persistent (386).

Standard resistance testing detects only mutations that are present in 15-20% of the viral population (this is described in more detail in section 1.9.10.1), therefore, even if resistant mutations are not detected, it is possible that resistant viruses are still present at low levels. Therefore the presence of resistant viruses, even at a low level, may still increase the risk of treatment failure (387-389). No prospective trial has so far assessed whether drug-resistance testing before initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest that virological responses in persons with baseline resistance mutations are suboptimal (371-374;390-392).

1.9.8. Super-infection

There is evidence that people infected with HIV can be re-infected, even after established immune response to the first infection (393-395). The incidence of this phenomenon is unclear, because it is inevitably very difficult to measure. Some suggest it could be similar to the incidence of the first infection (396) while others consider it to be a very rare

phenomenon (397). Its relevance is due to the fact that people originally infected with wild-type virus could be super-infected with a resistant virus, which could reduce their future treatment options.

1.9.9. Virological failure and switching to second-line regimens

Accumulation of DRMs is the underlying cause of most virological failures (VFs) in patients who have moderate to high adherence and optimal drug pharmacokinetics levels. The great majority of patients who initiate a first-line ART regimen and who are infected with wild-type virus have no DRMs present in their viral quasis-species at a level above 0.1%. Therefore their virus population is susceptible to all initiated ARVs.

Patients who experience VF (an increase in VL above a certain threshold, usually defined as two consecutive VLs above 1,000 copies/mL while on ART, although lower thresholds such as 50, 200, 400 and 500 are often used in high income countries) are very likely to have DRMs in their predominant virus population, to some, or all of the drugs in their regimen. Among people failing first-line ART (see section 5.1), the prevalence of resistance (at least one DRM detected in their viral quasi-species) ranges between 70 and 90% (305;398-401). WHO surveys to monitor emergence of resistance in countries where resistance testing is not routinely available found that 72% of patients failing first-line at 12 months since ART initiation had resistance in the dominant virus (305) and 70% in the PASER study, which included 13 cohorts from six countries in Africa (398). Levels around 85% have been found in Europe (399) and similar levels have been found in the South African public sector (82% (401), 87% (400)). Among patients on ART with detectable VL, in whom resistance was detected, the incidence of acquiring new DRMs per PY of follow-up has been estimated to be 1.61 (95% CI: 1.36, 1.91) (399). In patients who are starting ART the rate of new DRM acquisition, in the regions routinely sequenced at least, is likely to be slow at the beginning, because the selection of initial mutations may be difficult. But once initial mutations have emerged, the virus becomes more susceptible to the emergence of additional mutations so the rate of emergence is probably faster. Nevertheless, once the virus has become highly mutated, resistance accumulation rates slow down again, because only a finite number of mutations can emerge. In a study of patients kept on the same virological failing regimen for a median of six months (92% on a failing PI-containing regimen) considerable accumulation of DRMs was found,

especially in patients who had low levels of resistance to the failing regimen initially: in 25% of patients TAMs emerged, in 12% NNRTI DRMs and in 46% PI DRMs (402).

To maximise the chances that people who failed first-line, achieve virological suppression, the best option is to switch them to ARVs that are active against the ARV resistant viruses acquired. Therefore it helps, if possible, to identify which mutations are present in the viral population, by using a resistance test. In sub-Saharan Africa, including South Africa, where resistance tests are not routinely available, people who fail first-line, typically including two NRTIs and one NNRTI, are switched to a PI-based regimen (226), because there is no cross resistance between mutations acquired while on NNRTI and on PIs.

The degree of susceptibility that the virus has to an ART regimen can be assessed by using a resistance test.

1.9.10. Resistance testing

Resistance tests allow assessment of the presence of expected resistance to each ARV individually and to the regimen as a whole. There are two types of resistance test: genotypic and phenotypic (403). However, as genotypic test is the preferred one I will present only this type of resistance test (281).

1.9.10.1. Genotypic resistance testing

The genotypic resistance test produces a list of the type and position of each mutation, comparing the genetic code of the sampled virus to that of a consensus sequence (404-407). While it always involves sequencing the RT, protease sections of the *pol* gene, which are the areas target by NRTI, NNRTI and PI (408), the sequencing of integrase and the envelope genes (gp41 for enfuvirtide and V3 for maraviroc) is not part of the standard test even in resource rich settings (281). The genotypic resistance test looks specifically for mutations which are known to confer phenotypic drug resistance (mutations which require a high amount of drug to inhibit replication of a viral isolate *in vitro*) or to compromise treatment response (407;409). In fact, phenotypic changes are always caused by genotypic changes (317).

Since the relationship between presence of certain mutations and ARV activity is complex, there is disagreement on the impact of certain mutations on ARV predicted activity. Over

twenty different genotypic interpretation systems have been proposed. Most of them rely on data derived from *in vivo* (clinical outcome data) or *in vitro* (phenotypic testing of subtype B virus) (410). The most commonly used is probably the one provided by Stanford University, freely available, called "HIVdb" (411). The Stanford University also maintains the Stanford University HIV Drug Resistance Database (http://hivdb.stanford.edu). The IAS-USA publishes a list of all significant resistance-associated mutations in the RT, PR, integrase, and envelope genes that are considered to indicate some level of resistance to the licensed ARVs (412). Resistance mutations are generally classified as primary and secondary mutations. The former are those that occur during therapy with a non-suppressive regimen and lead to a decrease in the sensitivity of the virus to the single ARV. Secondary mutations are those that occur over time if people remain on a failing regimen with ongoing viral replication and in general have less impact on drug efficacy than primary mutations.

The HIVdb genotypic interpretation system (411) consists of:

a. a list of penalty scores for each ARV DRM in a sequence
b. estimates of decreased susceptibility for NRTIs, NNRTIs, PIs and integrase inhibitors
c. comments about each ARV resistance mutation

First of all, a list of differences in mutations between the submitted sequence and a consensus B sequence is generated. RT mutations are then classified into three groups: NRTI mutations (which reduce susceptibility to one or more NRTIs), NNRTI mutations (which reduce susceptibility to one or more NNRTIs) and other, which include mutations not associated or weakly associated with drug resistance and rare mutations whom effect on drug susceptibility has not been studied yet. Protease and integrase mutations are categorized as well in three groups: major (non-polymorphic mutations that by themselves reduce susceptibility to one or more inhibitors that usually occur during VF), minor (non-polymorphic or minimally polymorphic mutations that contribute to reducing the susceptibility in combination with major DRMs) and other (as for the RT category other but including rare non-polymorphic mutations).

The mutation penalty scores have been assigned, trying to reflect the effect of individual mutations on drug susceptibility and how mutation penalties are combined to return reliable estimates of ARV susceptibility for the most common combination of ARV DRMs. The sum of the mutation penalty scores for each of the mutations present within a subsequent sequence gives the estimate of decreased ARV susceptibility, which is categorized into five groups:

1) Susceptible: no evidence of reduced susceptibility to ARV compared to wild-type (total score of 0-9)
2) Potential low-level resistance: the virus is likely to be fully susceptible but there are mutations that may indicate previous ART exposure (total score of 10-14)
3) Low-level resistance: possible reduction in in vitro ARV susceptibility and/or patients with these mutations may have suboptimal virological response (total score of 15-30)
4) Intermediate Resistance: if the virus has intermediate resistance to a certain ARV (total score of 30-59), this ARV should in general only be used if the ARV has a high genetic barrier to resistance, such as some RTV-boosted inhibitors or if few other drugs are available
5) High level resistance (total score > 60) is the highest in vitro drug resistance. Patients with this level of resistance will have little or no virological response to treatment with that ARV.

To interpret genotypic test results it is necessary to know which mutations are selected by different ARVs and the potential for cross resistance to other drugs conferred by certain mutations. Clinical trials have demonstrated that consultation with specialists in HIV drug resistance improves virological outcomes (413).

1.10. Prevention methods

Several interventions have proven to be effective in reducing the risk of HIV transmission. This section summarizes the evidence for the prevention interventions which have been implemented in RLS and which are part of the analysis conducted in this PhD: condom use, voluntary medical circumcision (VMC) and earlier initiation of ART in HIV-positive people.

This section does not cover prevention of mother-to-child transmission (PMTCT) by use of ART during pregnancy, caesarean section at delivery and avoidance of breastfeeding, because the focus of this thesis is on adults.

1.10.1. Condom use

Condom use is the prevention method which confers the highest level of protection against sexual transmission of HIV and confers protection not only against HIV but also against other STIs, which are known to enhance the risk of HIV acquisition. The efficacy of male condoms in reducing transmission has been estimated to be at least 80% in heterosexual transmission and to confer 64% protection in anal sex among MSM, if used consistently and correctly (414). Nevertheless these estimates do not come from RCTs and it is likely that the effectiveness when used consistently and correctly is much higher. A study by Varghese et al found that the use of male condoms was associated with a 20-fold reduced risk (26). Even fewer data are available for the efficacy of female condoms in protecting from HIV transmission, but evidence suggests they can have similar efficacy in preventing HIV (415). Nevertheless their availability is not nearly as widespread as male condom use.

1.10.2. Circumcision

The practice of circumcision is common in some countries for religious and cultural reasons. The hypothesis that circumcision could reduce the risk of HIV transmission came from the observation that the risk of HIV transmission was higher among uncircumcised men (18·5% per act [95% CI: 2.3, 34.8]) than among circumcised men (2·2% per act [95% CI: 0.0, 6.4]) (416). Among those with GUD, estimates of HIV transmission were six times higher among uncircumcised men (42.8% per act [95% CI: 1.26, 73.0]) than among circumcised men (6.7% per act [95% CI: 0.0, 19.2]), while in the absence of GUD, no HIV transmission occurred in circumcised or uncircumcised men (416). A more recent study estimated the F-to-M transmission among uncircumcised men to be approximately 2.6 times higher compared to circumcised men (1.3% per act [95% CI: 0.5, 2.0] compared to 0.5% per act [95% CI: 0.3, 0.7]) and 4.5 times larger in non-circumcised than circumcised men in the presence of GUD (1.8% per act [95% CI: 0.0, 3.7] compared to 0.4% per act [95% CI: 0.0, 0.9]) (417). These results are consistent, yet somewhat higher, with the results of two previous meta-analyses (418;419).

To evaluate whether the reduction in the risk of HIV transmission observed in people circumcised was due to the circumcision itself or to other factors, three RCTs of VMC were conducted among heterosexual sero-different couples (420-422).

They found an efficacy of VMC in reducing the risk of HIV acquisition for men who have sex with women between 50 and 60% for men. This led WHO to recommend VMC as an intervention to reduce HIV transmission (423). Although this intervention does not directly

reduce the risk of transmission from M-to-F (45), it can reduce the risk indirectly by reducing the risk of heterosexual men becoming infected with HIV (419).

The potential role of VMC among MSM has not been fully investigated, and so far no RCT have been conducted to evaluate the efficacy of VMC in this population (424). A meta-analysis published in 2008 (425) found that the rate of HIV infection was non-significantly lower (14% decreased risk of HIV acquisition) among men who were circumcised compared with those who were not circumcised. Among those primarily engaging in insertive sex a bigger reduction in risk was found (30%), but still not statistically significant. A few studies (426;427), published more recently, found an association between circumcision and a reduction in HIV incidence, in participants who reported a preference for the insertive role in anal intercourse. The first followed a cohort of almost 1,500 HIV-negative homosexual men in Sydney (427), the second 1,824 HIV sero-negative MSM from Peru and the US, who participated in a placebo RCT of HSV-2 suppression for HIV prevention (HPTN 039) (426).

1.10.3. Antiretroviral therapy

As mentioned in section 1.4.1.1, early studies identified the VL level of the infected partner as the strongest predictor of sexual transmission in heterosexual serodifferent people who were not receiving ART (31;35;36). The ability of ART to suppress VL, led some researchers (428) to suggest that earlier initiation of ART, regardless of CD4 cell count, in HIV-positive people not eligible yet for ART according to guidelines, could prevent sexual transmission of HIV by reducing the infectiousness of HIV-positive people. Several observational studies of HIV serodifferent heterosexual couples (429-431) reported that transmission was rare in patients on ART, particularly in those with low VL concentrations. The definitive answer came in 2011 when the RCT trial HPTN 052 (432) reported the final results. This RCT was designed to compare the effect of early versus delayed ART on transmission of HIV. Overall, 1,763 heterosexual serodifferent couples in which the HIV-positive person was ART naive and had a CD4 count between 350 and 550 cells/μL were recruited from nine countries. Couples were randomized to either the early therapy arm, in which ART was initiated at study entry, or the delayed therapy arm, in which ART was initiated after two consecutive CD4 counts of 250 cells/μL or less. The primary endpoint was HIV infection in HIV-negative partners, with evidence based on genotyping that the infecting virus was likely to be from the partner. Three months after baseline, 89% of participants in the early therapy group had achieved viral suppression (<400 copies/mL) compared with 9% of the delayed therapy group. A total of 28 virologically linked transmissions were observed; of these 28 transmissions, only one was in

the early therapy group. This represents a 96% relative reduction in linked HIV transmissions as a result of initiating ART compared with deferral. These findings provide support for the use of ART in the prevention of HIV among heterosexuals and are believed to be a result of sustained suppression of VL in genital secretions. Further details are discussed in section 4.2.5.

The cost-effectiveness of changing the eligibility criteria to initiate ART in the context of South Africa is evaluated in Chapter 4, while its impact on the levels of resistance is evaluated in Chapter 5.

2. The HIV epidemic in South Africa and Zimbabwe

2.1. South Africa

2.1.1. Brief demographic introduction

2.1.1.1. Population size and age distribution

Since South Africa's first democratic election in 1994 three official censuses have been conducted, respectively in 1996, 2001 and 2011. They documented an increase in the total population from 41 million in 1996 up to almost 52 million in 2011 (see Table 2.1). The rate of growth for the South African population has increased slightly from 2002 to 2013: from 1.30% between 2002 and 2003 up to 1.34% between 2012 and 2013 (433) and in 2012 United Nations (UN) revised its estimate for South Africa, estimating it would reach 59.5 million by 2035.

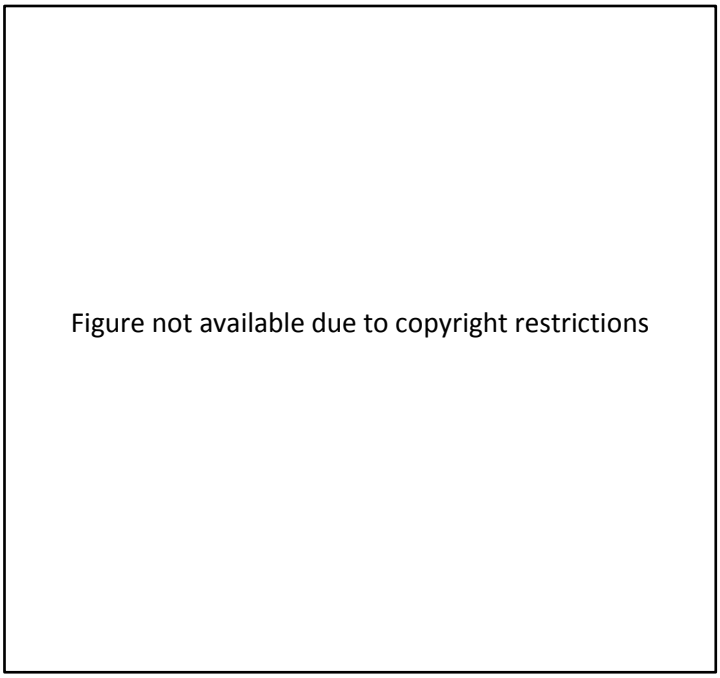
Table 2.1. South Africa population estimates and projections

Source	Year	All population (in million)	15-65 years old (in million)
South Africa censuses (434)	1996	40.58	24.7
	2001	44.82	28.2
	2011	51.77	-
Central intelligence agency (CIA) (435)	2011	49.00	32.26
	2013	48.60	31.88
Statistics South Africa (433)	2011	50.59	32.24
	2013	52.98	34.79
UN Secretariat (436)	2010	51.45	-
	2015	53.49 (+4.0% from 2010)	-
	2020	55.13 (+3.1% from 2015)	-
	2025	56.67 (+2.8% from 2020)	-
	2030	58.10 (+2.5% from 2025)	-
	2035	59.53 (+2.5% from 2030)	-

UN: United Nations;

Figure 2.1 shows the age and gender distribution in South Africa in 1996 (the first census with all information on all South Africa), before HIV impacted markedly on it. The graph shows that over 30% of the population is younger than 15 years old and the percentage of women with an age above 45 years old is higher than in men.

Figure 2.1. Population Structure Census 1996 (434)



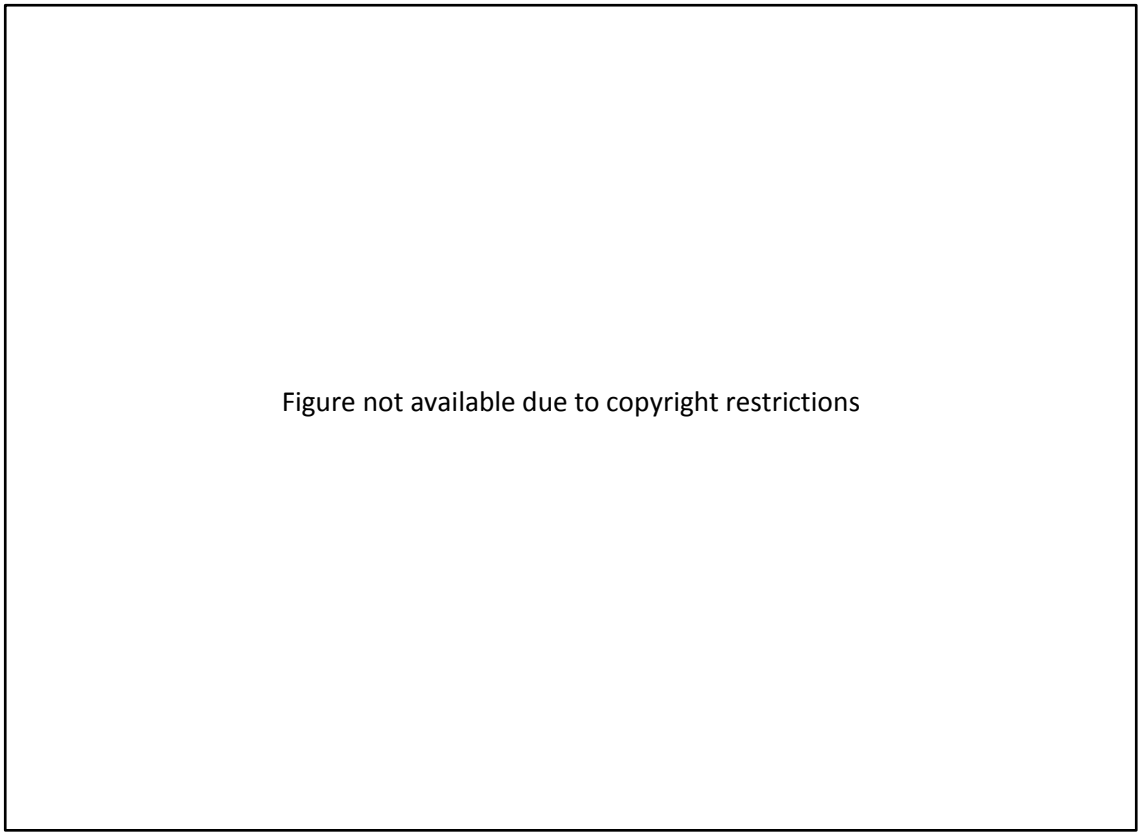
2.1.1.2. Mortality

The South African civil registration system of vital events is maintained by the Department of Home Affairs and regulated by an Act stipulated in 1992. Nevertheless in 1994 this system was still not representative at all (437). In 1996 it was estimated that only 67% of all deaths were registered, while in 1997 this had increased up to 80% for men and 78% for women and in the period between 2001 and 2007 it went up to 93% (438).

Statistics South Africa released data on numbers of deaths and causes of deaths, reported in the South African civil registration system starting from 1997. The cause of death comes from the death notification forms filled by medical practitioners and other certifying officials. This is the only national source of information regarding mortality in South Africa (438). When a death is registered, the Department of Home Affairs issues a death certificate and updates the National Population Register, but only if the person who died was a South African citizen or permanent resident and his/her birth was already registered at the time of death. Therefore the number of deaths reported by the Statistics South Africa is always higher than that reported by National Population Register (see Figure 2.2). Figure 2.2 illustrates the number of registered deaths over calendar year from 1997 until 2010. The number of deaths increased from just over 300,000 in 1997, it peaked in 2006 at around 600,000 deaths, and then it started declining again. The number of deaths in the group considered in the Synthesis model

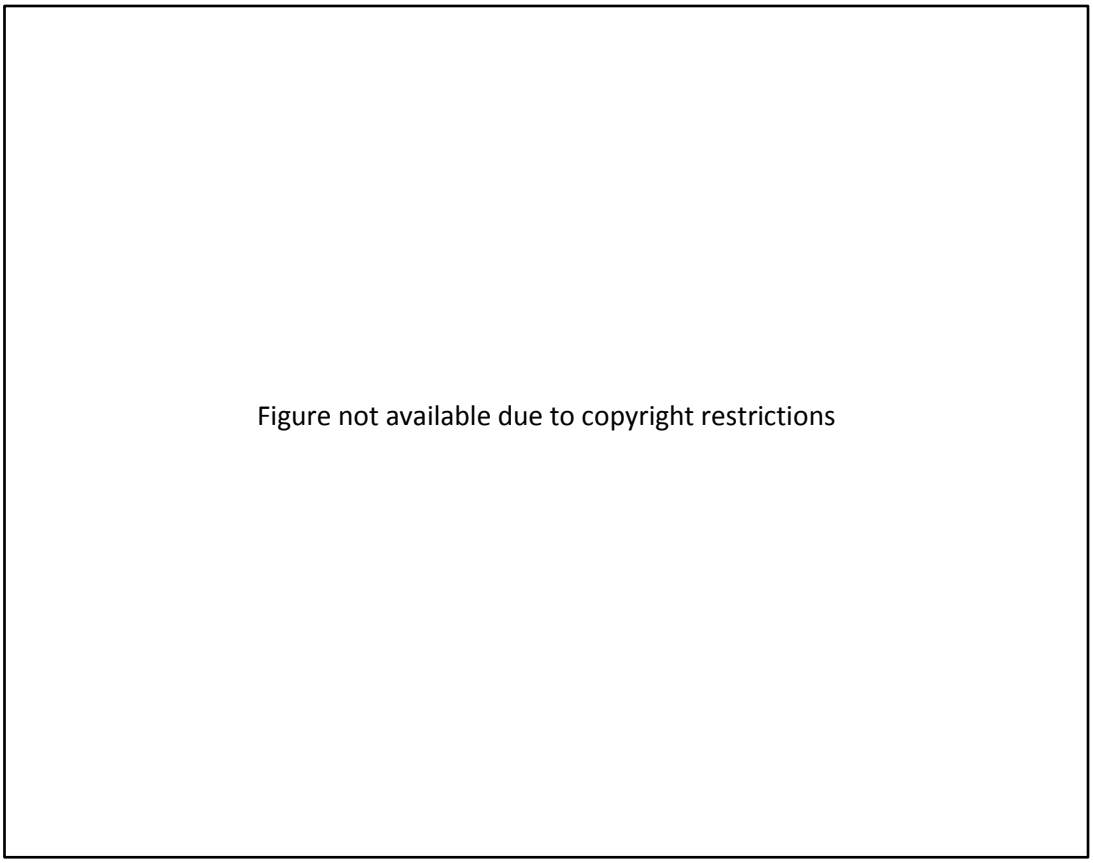
(15-64 years old) in 2010 was 337,846, 62% of the total number of deaths in the entire population, 543,856 (calculated from Table 2.2).

Figure 2.2. Number of registered deaths in South Africa (438)



Stats SA: Statistics South Africa; DHA: Department of Home Affairs; NPR: National Population Register;

Table 2.2. Number of deaths by gender and age in 1997 and 2010 in South Africa (438)

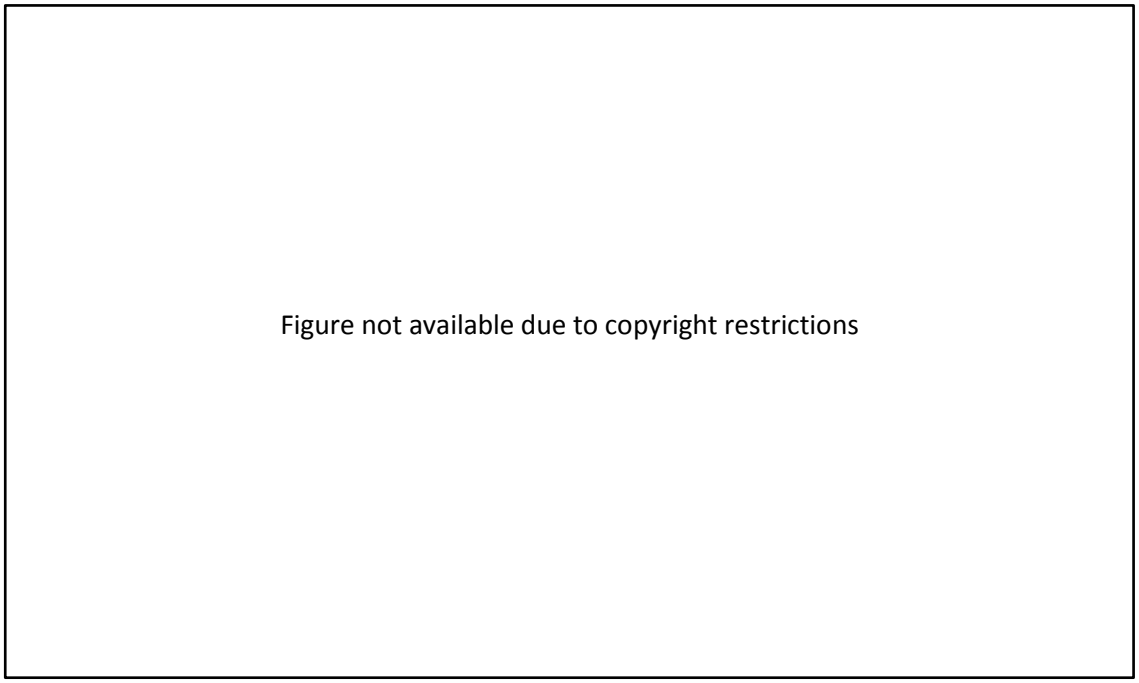


Unsp: unspecified;

Figure 2.3 shows the death rates in South Africa by gender for the calendar year 1997 and 2004 and overall for the period 2006-2010, in different age groups. In 1997 and 2004, men aged 15 to 64 years have higher death rates than women, for example in 1997 in the age group 15 to 19 years old the death rate for women was 165/100,000 compared to 235/100,000 in men. However a different pattern of death rates can be observed in 1997 (indicated by filled squares) compared to 2004 (indicated by empty squares) or the years to follow. The former being characterized by an increase in death rates as age increases, steeper in men than in women: in the age group 60 to 64 years old the death rate in men is estimated to be 3,614/100,000 compared to 2,201/100,000 in women. In 2004 the pattern is dramatically different with very high death rates in women aged 30 to 34 years (2,267/100,000), more than 4 times higher than in 1997 in the same age group and similar to the level in the age group 60 to 64 years old in 2004. In men aged 30 to 44 years the death rates more than doubled compared to 1997. The pattern of death rates observed from 2006 onwards is similar to that in 2004, although it is possible to observe an increasing decline in death rates across all age groups as calendar year increases. For example the death rate for the age group 30 to 34 years old has been declining gradually from around 2,200 per 100,000 in 2004 down to 1,100 in

2010. The increase in death rate observed between 1997 and 2004, more in young women, more pronounced in young women, was attributed mainly to TB and AIDS and the slow decline afterwards to the introduction and scale up of ART since 2004 (see section 2.1.8) and to the more intensive interventions to provide TB treatment, after a national emergency was declared in 2005.

Figure 2.3. Age and gender specific death rates (per 100,000) in 1997 and 2004 and from 2006 to 2010 in South Africa (437;438)



Overall, in 2013 the World Bank estimated a death rate for South Africa of 17.36 per 1,000 (439).

2.1.2. Sexual behaviour in South Africa

Data on sexual behaviour for South Africa have been collected in population–based HIV sero-prevalence surveys, conducted in 2002, 2005, 2008 and 2012 by Human Sciences Research Council (HSRC) (440). Nevertheless surveys on sexual behaviour are often affected by social desirability bias and recall bias (441).

2.1.2.1. Sexual debut

Given the high prevalence of HIV in younger age groups, especially for women (see section 2.1.3.1), it is important to understand at which age people start being at risk of contracting HIV. Information on age of sexual debut was collected among young people aged 15-24 years

in all four HSRC surveys. Figure 2.4 shows the proportion of men and women who reported sexual debut before the age of 15 years. At the last survey 10.7% reported sex before the age of 15, but this was more than three times in men compared to women (see Figure 2.4). It is not clear whether this difference is due to underreporting of sexual behaviour by females or over reporting by males or whether it is a true phenomenon that males tend to have earlier sexual debut than females.

Figure 2.4. Age of sexual debut by gender of respondents in the 15–24 years old in South Africa (440)

2.1.2.2. Condom use

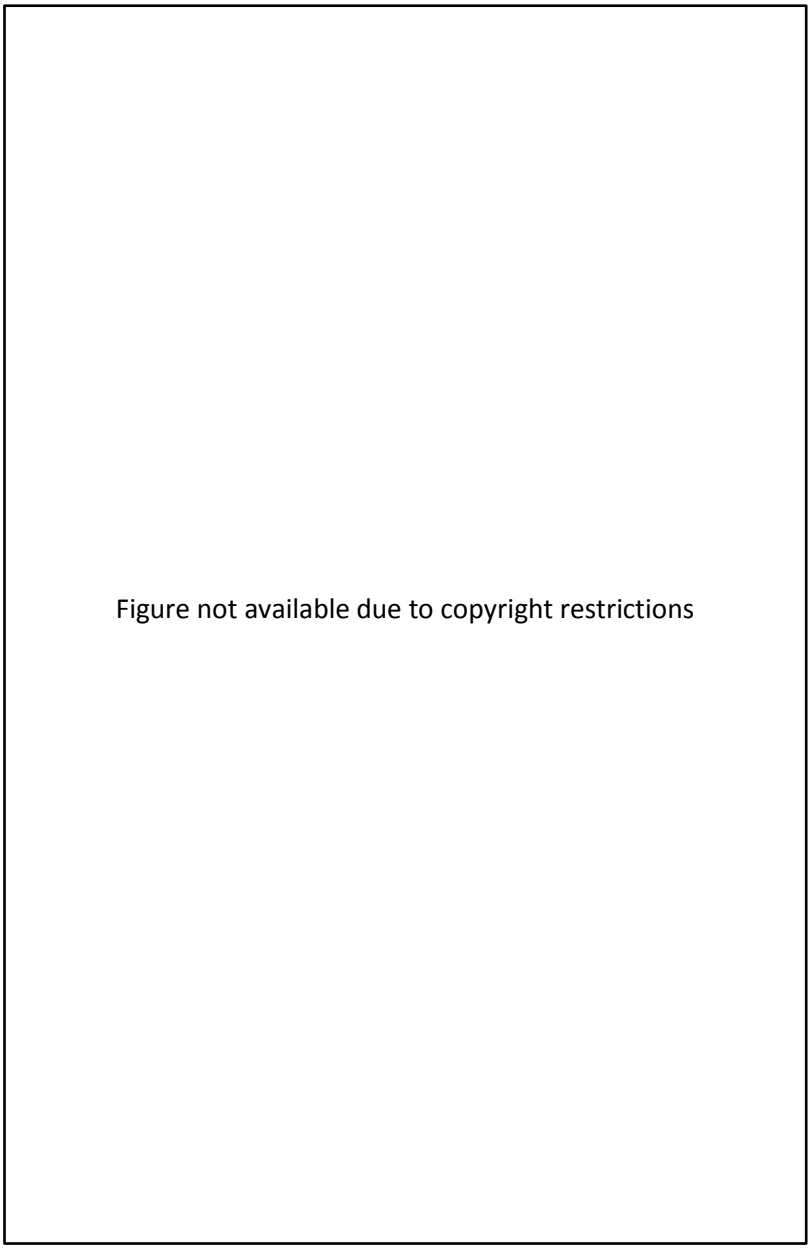
The South Africa Demographic and Health Survey (DHS) conducted in 2003 (442) highlighted that although condoms were available in South Africa, in people with multiple partners they were mainly used with non-primary partners (46.5%), while the use with primary partners was quite low (15.4%).

From 2002 the percentages of adults who reported condom use at last sex increased significantly from 2002 to 2008 and then decreased from 2008 to 2012 for all three age-sex groups considered: 15-24 years, 25-49 years and over 50 years (see Figure 2.5).

In people aged 15-24 years in men it was 57.1% in 2002, it peaked at 85.2% in 2008 and it declined to 67.5% at the last survey. In women of the same age group the pattern is similar,

but the peak reached in 2008 was 66.5% and in 2012 only 49.8% report condom use at last sex. As age increases, the use of condoms decreases, with levels in 2012 of 36.1% and 32.7% in men and women respectively aged 25 to 49 years. In the oldest group considered, 50 years old and above: 14.5% of men reported condom use at last sex compared to 8.2% in 2002 and in women the peak was reached in 2012 with 9.4% of women reporting condom use.

Figure 2.5. Condom use at last sex by age group and gender in 2002, 2005, 2008 and 2012 in South Africa (440)



2.1.2.3. Intergenerational sex: partners age differences

The practice of having sex with partners with a substantially different age (usually defined as 5 or more years of difference), especially young women having sex with older men, has been identified as a risk factor for contracting HIV (443).

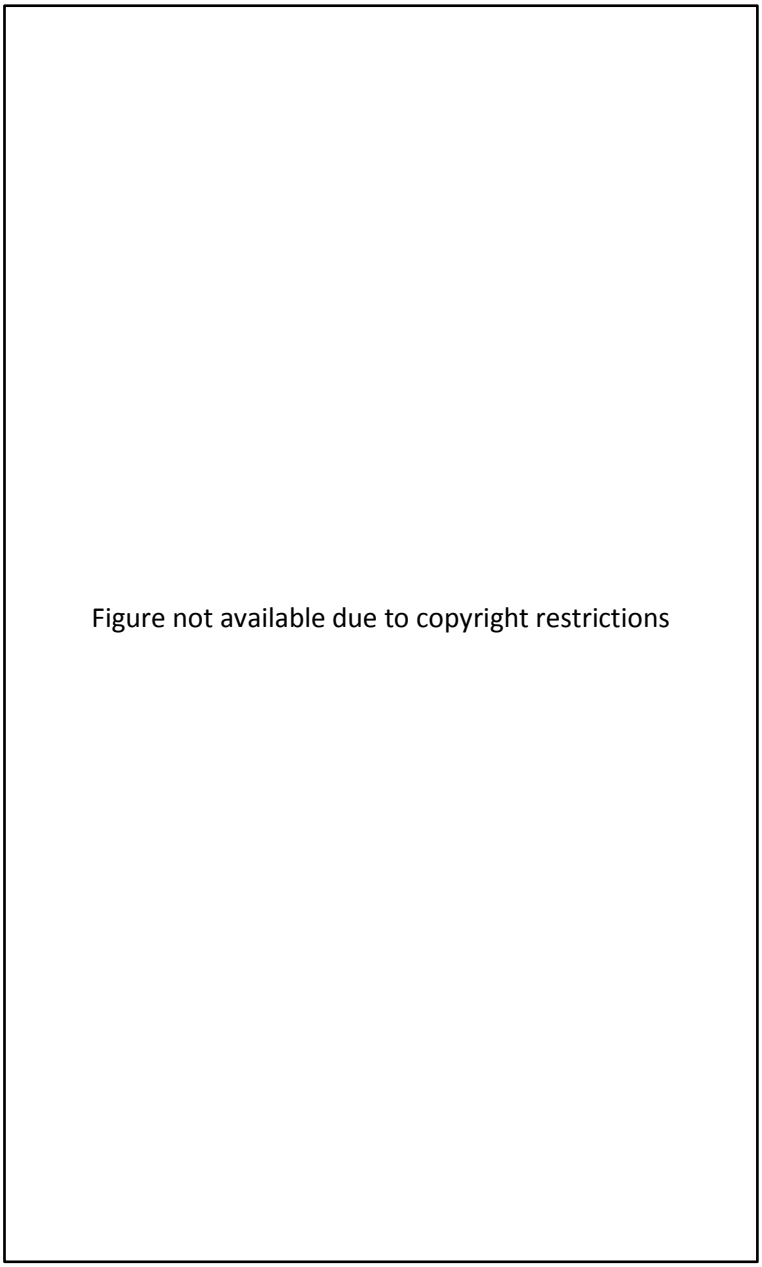
In all HSRC surveys, data on the age difference between sexual partners in people aged 15 to 19 years were collected. In all surveys almost 95% of men had a partner within 5 years of their own age, while among women 70% of them (with the exception in 2005 were it was 81%) had

a sexual partner within 5 years of their age. Overall a substantial increase was observed in the percentage of people reporting sex with a person with more than 5 year difference from 9.6% in 2005 to 19.8% in 2012 (440).

2.1.2.4. Multiple sexual partners

Concurrency, or in other words having multiple sexual partnerships overlapping in time, represents a major risk factor for contracting HIV. This information is quite difficult to capture but what is usually collected is the number of partners in the last 12 months. Figure 2.6 shows clearly that the group with the highest proportion of people reporting multiple partners in the last year is the age group 15 to 24 years. In this age group the proportion reporting more than one partner increased from 23% in 2002 to 37% in 2012 in men, while in women it remained quite stable between 6% and 9% (440). The older risk groups are characterized as well by a much lower proportion of women reporting multiple partners compared to men at much lower levels compared to those aged 15-24 years.

Figure 2.6. Percentage of adults reporting more than one sexual partner in the last year in South Africa (440)



2.1.3. The HIV epidemic

The first reported AIDS cases in South Africa were in two white homosexual men, who were diagnosed with AIDS in 1982 with HIV subtype B (444); five years afterwards, in 1987 the first black South African was diagnosed with AIDS (445).

2.1.3.1. HIV prevalence

South Africa is now the country with the largest HIV epidemic worldwide, with an estimated number of people living with HIV in 2012 of 6.4 million and an HIV prevalence of 12.2% (95% CI: 11.4, 13.1) (440). When restricting to the population aged 15-49 years, the HIV prevalence was estimated to be 18.8% (95% CI: 17.5, 20.3) (440), similar to the estimate of 18% from Joint United Nations Programme on HIV/AIDS (UNAIDS) corresponding to 6.1 million adults aged 15-49 years living with HIV (446). UNAIDS estimates that worldwide 35.3 million people (95% CI: 32.2 million, 38.8 million) were living with HIV in 2012 and 2.3 million new HIV infections occurred in the same year, the lowest number since mid-1990s when it was around 3.5 million (447). At the same time, the number of deaths due to AIDS-related causes has been decreasing, from 2.3 million (2.1 million, 2.6 million) in 2005 to 1.6 million (1.4 million, 1.9 million) in 2012. Of the 2.3 million new infections, 1.6 million, almost 70% occurred in sub-Saharan Africa and 75% of AIDS-related deaths (1.2 million).

Since 1990, annual anonymous surveys have been conducted in sentinel antenatal clinics (ANCs) to estimate HIV prevalence among women attending public ANCs (448) (See Figure 2.7). These sentinel surveys document a very rapid increase in HIV prevalence from less than 1% in 1990 up to 25% 10 years after and since 2004 the level has been relatively stable at round 30%.

These data have been extremely important to inform policy makers regarding the magnitude of the HIV epidemic among the sexually active population, but they could be biased estimations of the HIV prevalence in the general population. On one side they could be over estimations because only pregnant women, that by definition had condom-less sex, are included in these surveys; on the other side, they could be biased upwards because of the lower fertility observed in women with HIV (449).

Figure 2.7. HIV Prevalence among women attending sentinel ANC in South Africa (448)

The HSRC surveys, which are nationally representative, documented a slow increase in HIV prevalence between 2002 and 2008, from 15.6% to 16.9%, followed by a more rapid increase up to 18.8% in 2012 (see Table 2.3). Given the South African population is increasing (see section 2.1.1.1) with a stable HIV prevalence the total number of people living with HIV would still increase by approximately 100,000 people every year, according to the Spectrum model (450) [This was based on estimates before the 2012 HSRC were published in April 2014].

Table 2.3. HIV prevalence and number of people living with HIV in South Africa

Source	Age group	Year	HIV prevalence (95% CI)	Number of people living with HIV (in million)
HSRC surveys (440)	2+ years old	2002	11.4 (10.0, 12.7)	-
		2005	10.8 (9.9, 11.8)	-
		2008	10.9 (10.0, 11.9)	-
		2012	12.6 (11.7, 13.5)	
	15-49 years old	2002	15.6 (13.9, 17.6)	-
		2005	16.2 (14.9, 17.7)	-
		2008	16.9 (15.5, 18.4)	-
		2012	18.8 (17.5-20.3)	
	15-24 years old	2002	9.3 (7.5, 11.4)	-
		2005	10.3 (8.7, 12.0)	-
		2008	8.7 (7.2, 10.4)	-
		2012	7.1 (6.2, 8.1)	
ASSA2008 (page 51 in (450))	0+ years old	2010	10.9	5.5
Spectrum (page 51 in (450))		2009	-	5.63
UNAIDS (446)	0+ years old	2012	-	6.1 (5.8, 6.4)
	15+ years old		-	5.7 (5.5, 6.0)
	Females 15+ years old		-	3.4 (3.2, 3.6)
	15-49 years old		17.9 (17.3, 18.4)	-
Johnson (451)	15+ years old	2011	-	5.6

CI: confidence interval; HSRC: Human Sciences Research Council; UNAIDS: Joint United Nations Programme on HIV/AIDS

In South Africa, as in most countries with generalized HIV epidemics, the HIV prevalence remains higher for female than for males (see Figure 2.8). In females, the peak in HIV prevalence was in the 30-34 year age group, when over a third of them (36.0% in 2012) were HIV-positive (440). In the previous three surveys the 25-29 year age group was the most affected with a prevalence around 30% (452). In men, the higher HIV prevalence was observed in those aged 35 to 39 years, where over one in four men (28.8% in 2012) was estimated to be HIV-positive. Potential explanations for the higher prevalence of HIV in women than in men are the higher susceptibility to the HIV virus and social factors making women more vulnerable to HIV. The higher susceptibility (more pronounced during adolescence, pregnancy and early post-partum period) seems to be related to vaginal microbial ecology and physiology, hormonal changes, higher prevalence of sexually transmitted diseases (453) and possibly the use of hormonal contraceptive (although the evidence is mixed) (454). The social determinants include gender disparities, poverty, cultural and sexual norms, lack of education, violence and some intravaginal practices (i.e. using cloth or paper to clean the vagina, insertion of products

to dry or tighten the vagina and intravaginal cleaning with soap). This last behaviour has been associated with the development of bacterial vaginosis, which in turn, together with disrupted vaginal flora is associated with an increased risk of HIV acquisition. However a direct causal link between intravaginal cleaning with soap, disruption of vaginal flora, and HIV acquisition has not been demonstrated (455).

Figure 2.8. Age and gender specific HIV prevalence in 2012 in South Africa (440)

2.1.3.2. HIV incidence

Knowing the HIV prevalence is fundamental. This is the result of the HIV incidence (i.e. the rate of new HIV infections) and of mortality among the HIV-positive population and it is important to know how these two components are varying over time and result in the HIV prevalence observed.

Figure 2.9 shows the estimated number of people living with HIV, the number of new HIV infections and AIDS related deaths in South Africa estimated by the Spectrum model, used by UNAIDS to estimate HIV prevalence in countries with generalized epidemics. According to this model, the reason why HIV prevalence is not declining despite the decrease in HIV incidence is due to the fact that the number of new HIV infections (in green) is higher than the number of AIDS related deaths, due to the beneficial effect of ART in increasing survival.

Figure 2.9. Total number of people living in South Africa, number of people living with HIV, number of new HIV infections and number of AIDS related deaths estimated by the Spectrum model (456)

AIDS: Acquired Immune Deficiency Syndrome; PCP: Pneumocystis cariniii Pneumonia;

In the HSRC conducted in 2012, HIV incidence was measured using two methods: directly, using newly available assays able to identify recent infections (Limiting-Antigen Avidity EIA) and using a mathematical model (440). Using the first method the HIV incidence in the population 15 to 49 years old was estimated to be 1.72 (95% CI: 1.38, 2.06), almost double in females compared to men: 2.28 (95% CI: 1.84, 2.74) vs 1.21 (95% CI: 0.97, 1.45) (440). This corresponds to almost 400 thousand new HIV infections in the population 15 to 49 years old in 2012 (396000; 95% CI: 318000, 474000). Using the second method (457), they estimated an HIV incidence in the period 2008 to 2012 in the population 15 to 49 years old of 1.9 (95% CI: 0.8, 3.1) and higher in women compared to men: 2.1 (95% CI: 1.0, 3.4) vs 1.6 (95% CI: 0.6, 2.7).

In the previous HSRC survey (2008) (452), HIV incidence was estimated using two different methods: a direct method using the assays available at the time to detect recent infections (BED-CEIA) and an indirect method to estimated HIV incidence in people aged 15 to 20 years using data from HIV prevalence in this age group. Basically this second method calculates HIV incidence using single calendar year estimates of HIV prevalence for each age and assuming that the difference in HIV prevalence between age group represent incident HIV infections. This method is appropriate for young people where AIDS related mortality is likely to have a minor impact because it is unlikely they have been infected for HIV for long enough to develop AIDS (458).

Using this second method the HIV incidence in the population aged 15 to 20 years was calculated as well for the previous HSRC surveys, 2002 and 2005 (See Figure 2.10). They show

an increase in HIV incidence between 2002 and 2005 in people aged 15 to 20 years from level varying from 0.8% to 2.0% to levels between 1.0% and 2.2%, while a drop in HIV incidence has been observed in 2008 to levels around 0.5%-0.6% in people aged between 15 and 17 years up to a maximum of 1.7% in people aged 20 years in 2008.

The best way to estimate HIV incidence in a population is to follow a cohort of people over time and test them routinely for HIV (as often as possible), in order to observe the proportion of people who acquire HIV in a certain time frame. This method is referred to as "direct measurement of HIV incidence" and has been used in some circumstances (for example see section 2.2.3.2), but it is very laborious, expensive and not feasible at national level. Laboratory-based algorithms using assays able to distinguish between recent (usually within four to twelve months) and non-recent infection are a promising alternative to measure HIV incidence. They have been used in the last two HSRC surveys conducted in South Africa; however their accuracy is still matter of debate (459).

In addition, there are at least two indirect ways of estimating HIV incidence: (a) indirect estimation from HIV prevalence in young, recently exposed populations, and (b) by using a mathematical model either using HIV prevalence estimates from surveys repeated in series or using assumptions on risk behaviour and risk of HIV transmission. The former has been used in the HSRC surveys in 2002 and 2055 and has been described above. The second has been performed in the HSRC survey conducted in 2012. This latter method is used by UNAIDS to provide national estimates of HIV incidence around the globe, but its estimates clearly depend on the robustness of the assumptions underlying the model (risk behaviour, prevalence and transmission rates).

Figure 2.10. HIV incidence in South Africa (452)

2.1.3.3. Mortality in HIV-positive people

As mentioned in section 2.1.1.2, the difficulty in knowing the number of AIDS deaths is due to the fact that the vital registration is often not complete and the cause of death could be misclassified or missing. A study published in 2005 (460) reported that a large proportion of deaths caused by HIV in the period between 1996 and 2001 were classified as several different AIDS related conditions, without reference to HIV and these contributed to around 60% of the total HIV linked adult deaths.

As shown in Figure 2.9 (page 92) and in Table 2.4, the number of AIDS related deaths has been estimated to gradually increase up to a peak in 2005 of 345,000 deaths, representing almost half of all deaths occurring in that year to then decline to levels of almost half in 2013 with 178,000 deaths estimated.

UNAIDS updated the estimates regarding the HIV epidemic in South Africa using the Spectrum model and estimated that in 2012 240,000 [220,000-270,000] AIDS related deaths occurred.

The leading cause of death in South Africa and in people living with HIV in this country is TB. It was estimated that 65% of people living with active TB in 2012 were co-infected with HIV (461).

Table 2.4. Number of AIDS deaths and with HIV as specific cause in South Africa

Source	Year	Age-group	Number of AIDS related deaths (% of AIDS deaths)	Number of registered deaths with cause HIV
Groenewald (460)	2000-01	Males 15 to 59 years old	-	53,185
		Females 15 to 59 years old	-	59,445
Statistics South Africa "SA Statistics" (462)	2006	0+ years old	-	14,948
	2007		-	13,571
	2008		-	15,172
	2009		-	17,570
Statistics South Africa "Findings from death notification" (438)[a]	2008	0+ years old	-	15,179
	2009		-	17,785
	2010		-	18,325
		15 to 49 years old	-	14,493
		15 to 24 years old	-	1,126
Republic of South Africa – ASSA 2011 (450)	2005	0+ years old	257,000	-
	2010		194,000	-
UNAIDS HIV and AIDS estimates (463)	2012	0+ years old	240,000 (95% CI: 220,000, 270,000)	-

a: HIV underlying cause of death; CI: confidence interval; UNAIDS: Joint United Nations Programme on HIV/AIDS;

2.1.4. Response to HIV: history

Some steps to respond to the HIV epidemic when it was still below 1% were taken, such as for example the formation of the National AIDS Coordinating Committee of South Africa in 1992 to develop the first national strategic plan (NSP) on HIV and AIDS (464). However, it was only in 1994 that the NSP was adopted and these steps did not prove to be sufficient to avoid the rapid spread of HIV in South Africa.

In 1996 and 1997 it became clear that the government was not tackling HIV and the major crisis this disease was creating appropriately and was actually obstructing the conduct of clinical trials to test ARVs.

In 1998 activists and researchers started campaigning asking the South African Government for the provision of AZT to pregnant women to prevent vertical transmission and later for the provision of ARVs for people living with HIV.

In 1999 a new President of South Africa was elected, Thabo Mbeki. He openly declared that HIV did not cause AIDS and continued to deny this causal link for many years. In 2000 the National AIDS Council was created and it launched two major programmes:

- The National Integrated Plan for children infected and affected by HIV and AIDS (465)

- HIV/AIDS/STD NSP for South Africa 2000-2005 (466)

It was only in 2003 that the Government finally approved a plan for scaling up universal ART and this was started in 2004.

In 2006 a new NSP was released, the "HIV & AIDS and STI Strategic Plan for South Africa 2007-2011" (467), with the primary aims to:

"

- *reduce the rate of new HIV infections by 50% by 2011*
- *reduce the impact of HIV and AIDS on individuals, families, communities and society by expanding access to appropriate treatment, care and support to 80% of all HIV-positive people and their families by 2011."*

In 2009, when Jacob Zuma was elected as new president of South Africa, HIV and AIDS were finally recognized as major challenges and the government acknowledged the importance of knowing the HIV status. In 2010, his government launched a media campaign of HIV testing and counselling (HTC) (468), including several prevention initiatives such as the provision of 100 condoms to each person receiving HTC, information on HIV prevention, education and mass mobilisation.

In June 2011 in New York, South Africa signed the UN General Assembly 2011 Political Declaration on HIV and AIDS. This declaration states ten targets to be achieved by 2015:

"

1. *To reduce sexual transmission of HIV by 50%;*
2. *To reduce transmission of HIV among people who inject drugs by 50%;*
3. *To eliminate new HIV infections among children by 2015 and substantially reduce AIDS-related maternal deaths;*
4. *To reach 15 million people living with HIV with lifesaving antiretroviral treatment;*
5. *To reduce tuberculosis deaths in people living with HIV by 50%;*
6. *To close the resource gap;*
7. *To eliminate gender inequalities, gender-based abuse and violence and increase the capacity of women and girls to protect themselves from HIV infection;*
8. *To eliminate stigma and discrimination against people living with HIV;*
9. *To eliminate HIV-related restrictions on entry, stay and residence; and*

10. *To eliminate parallel systems for HIV-related services to strengthen integration of the AIDS response in health and development efforts. "*

In 2010 and 2011 several achievements were finally reached (450):

- 95% of HIV-positive pregnant women received PMTCT in 2010 (see Appendix IV)
- MTCT was reduced to 3.5%
- 55% of people in need (CD4<350 cells/μL or co-infected with TB) of treatment were receiving it (the target was 80%)
- 13 million were reached by the national HTC campaign by June 2011 (the target was 15 million)

At the end of 2011 a third NSP on HIV, sexually transmitted diseases and TB for the period 2012-2016 was launched (469), with five main goals, reflecting the targets set in the UN General Assembly 2011 Political Declaration on HIV and AIDS:

"

(1) Reduce new HIV infections by at least 50%
(2) Initiate at least 80% of eligible patients on antiretroviral treatment (ART), with 70% alive and on treatment five years after initiation
(3) Reduce the number of new TB infections as well as deaths from TB by 50%
(4) Ensure an enabling and accessible legal framework that protects and promotes human rights in order to support implementation of the NSP
(5) Reduce self-reported stigma related to HIV and TB by at least 50%"

2.1.5. Awareness of HIV status

In South Africa, client-initiated voluntary counselling and testing (VCT) was introduced in the early 1990s (470). However, by 2002 only around 20% of the population aged 15 years or more had ever tested for HIV and by 2005 still only 27.6% of men and 32.9% of women had tested (443). To address the issue of low uptake of HTC, since 2007 WHO has recommended provider-initiated testing and counselling (i.e. offer of HTC to anyone presenting at healthcare institutions, PITC) for countries with generalized epidemics (471) and South African guidelines for HTC released in 2010 emphasize this approach (472).

The last two HSRC surveys reported that 43.0% of men and 56.7% of women had ever tested for HIV in 2008 and in 2012 59% of men and 71.5% of women in 2012 (440).

Ever having had a test for HIV does not mean being aware of their current HIV status, especially given the high HIV incidence observed in South Africa. For this reason the proportion of people tested in the last 12 months has been collected in HSRC surveys conducted in 2005 and 2008 (see Figure 2.11). This increased overall from 11.9% to 24.7% and more markedly in women than men. Of those who ever tested for HIV at the HSRC survey conducted in 2008, 49.1% tested in the last 12 months compared to 66.2% in 2012, underlying how the uptake and frequency of testing is increasing over time.

Figure 2.11. Proportion tested in the last 12 months in South Africa (452)

In February 2010 the "National HIV Counselling and Testing Policy Guidelines" were published (472) recommending all health facilities to offer PITC. As mentioned, in April 2010, the largest HTC campaign in the world was initiated in South Africa aiming to test 15 million South Africans by 2011 (in 15 months). They estimated that in 20 months more than 20 million were tested for HIV within the campaign (473) and in addition the private sector provide HTC for some businesses employees (290,000 tested in 2011) (450). In occasion of the World AIDS day on 1st December 2013, the National AIDS Council re-launched the campaign (440).

2.1.6. Pre-ART care

Since 2004 national guidelines on how to deliver ART to eligible patients have been released (225). The first contained no information regarding how often to monitor people who were not yet eligible for ART. The 2nd national ART guidelines, released in 2010 (230), indicated clearly the actions to take on the day of diagnosis:

- Check HIV result
- Clinical staging and CD4 count measurement if HIV-positive
- Ask if pregnant or planning to conceive
- Screen for TB symptoms
- Haemoglobin (Hb) or full blood count (FBC) if available, to detect anaemia or neutropenia

In addition they indicated that patients not yet eligible for ART according to the current guidelines should be advised to visit the programme regularly for follow-up and their CD4 count should be tested every 6 months. During these follow-up visits they should receive information on how to avoid HIV transmission to sexual partner and children, if asymptomatic for TB isoniazid prophylaxis and counselling on nutrition and contraceptive and an annual cervical smear (230).

The national guidelines released in 2013 (226) are very similar to the previous one: they point out the need to confirm the HTC result with a rapid antibody test, ensuring that national testing algorithm has been followed, to actively screen for pregnancy and TB symptoms (using the WHO questionnaire) and to make sure the CD4 count measurement is conducted on the same day.

They all contain limited recommendation regarding the care of patients who are not eligible for ART and how programmes should organize themselves to care for these patients. To my knowledge there are no national data regarding how many people have been diagnosed for HIV, how many have been linked to care (received ART eligibility assessment) and how many are currently in pre-ART care. Programmes providing care for HIV-positive people have published data on their specific programme. The linkage to care and the retention in pre-ART care is generally poor; these are discussed in detail in sections 7.3.2 and 7.3.3.

2.1.7. ART initiation and procedures to monitor people on ART

The eligibility criteria for ART initiation in the public sector are indicated in the national guidelines. Those published in 2004 (225) follow the 2003 WHO guidelines for RLS (CD4 count <200 cells/µL or WHO stage 4 disease) (474). These were updated in 2010 (230), when people were considered eligible if they fulfilled one of the following criteria:

- CD4 count <200 cells/µL irrespective of clinical stage
- CD4 count <350 cells/µL for patients with TB/HIV or pregnant women
- WHO stage 4 irrespective of CD4 count

In 2013 they were revised (226) to consider eligible for ART, people with:

- CD4 count <350 cells/µL irrespective of WHO clinical stage
- All types of TB (In patients with TB/HIV drug resistant or sensitive TB, including extra pulmonary TB), HIV-positive women who are pregnant or breast feeding and patients with Cryptococcus meningitis or TB meningitis (defer ART for 4-6 weeks). All these patients are eligible irrespective of CD4 count.
- WHO stage 3 or 4 irrespective of CD4 count

In the first guidelines released in South Africa (225), lots of attention was paid to make sure only patients who expressed willingness and readiness to take ART adherently were initiated on ART. In particular, once patients were identified as clinically eligible, they needed to demonstrate the ability to attend the clinic regularly (usually they are asked to attend the clinic for 3 or more visits before being initiated). During these preparatory visits they receive ART and adherence education and counselling and they discuss issues related to disclosure of their own HIV status to friends and family.

The ART regimens recommended in the South African guidelines are summarized in the Table 2.5.

Table 2.5. ART regimen lines recommended in South Africa

Source	Line	Drugs	Notes
2004 (225)	1	d4T+3TC+EFV/NVP	For women of child bearing age, not on reliable contraception, NVP is preferred.
	2	AZT+ddI+LPV/r	-
2010 (230)	1a	TDF+3TC/FTC+EFV/ NVP	For TB co-infection EFV is preferred. For women of child bearing age, not on reliable contraception, NVP is preferred.
	1b	d4T+3TC+EFV	Only if currently on d4T based regimen with no side-effects. Substitute d4T with TDF if at high risk of toxicity (high BMI, low Hb, older female)
	1c	AZT+3TC+EFV/NVP	If TDF is contraindicated (renal disease)
	2a	TDF+3TC/FTC+LPV/r	Failing on a d4T or AZT-based 1st line regimen
	2b	AZT+3TC+LPV/r	Failing on a TDF-based 1st line regimen
	3	Specialist referral	-
2013 (475)	1a	TDF+FTC/3TC+EFV FDC preferred	First choice. This regimen is mandatory for people currently on d4T-based regimen experiencing toxicity or at high risk of toxicity (high BMI or pregnant). Switch to TDF if virally suppressed and the patient has normal creatinine clearance, even if well tolerated.
	1b	TDF+FTC/3TC+NVP	If EFV is contraindicated (patients with significant psychiatric co-morbidity or intolerance to EFV or where the neuropsychiatric toxicity of EFV may impair daily functioning, e.g. shift workers.)
	1c	AZT+3TC+EFV/NVP	If TDF is contraindicated (renal disease or the use of other nephrotoxic drugs e.g. aminoglycosides)
	1d	d4T+3TC+EFV/NVP	If TDF and AZT are contraindicated (Renal disease and anaemia or the use of other nephrotoxic drugs, aminoglycosides)
	1e	ABC+3TC+EFV/NVP	If TDF, AZT and d4T are contraindicated (Renal disease, anaemia, peripheral neuropathy, or the use of other nephrotoxic drugs, aminoglycosides)
	2a	AZT+3TC+LPV/r	Failing on a TDF-based 1st line regimen. Patients with anaemia and renal failure switch to ABC.
	2b	TDF+3TC/FTC+LPV/r	Failing on a d4T-based 1st line regimen
	2c	Switch LPV/r to ATV/r	Dyslipidaemia or diarrhoea associated with LPV/r
	3	Specialist referral (Most likely regimen: Raltegravir/ DRV/ Etravirine adjusted according to genotype Interpretation)	Should be expert and genotype resistance testing based decision and supervised care. The drugs for third line will be managed centrally.

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir boosted with ritonavir; AZT: zidovudine; BMI: body mass index; d4T: stavudine; ddI: didanosine; DRV: darunavir; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; Hb: Haemoglobin; LPV/r: lopinavir boosted with ritonavir; NVP: nevirapine; TB: tuberculosis; TDF: tenofovir; /: or, except for when is "LPV/r" or "ATV/r", where it indicates that those antiretrovirals are boosted with ritonavir;

Once initiated on ART, it is indicated in the guidelines released in 2004 (225) that patients need to visit the clinic as follows:

- monthly to collect ART medication.
- at 4, 8 and 12 weeks and 3-monthly afterwards to be monitor for drug tolerability, adverse events and adherence (pill count should be conducted at each visit)
- patients on NVP should be seen by the nurse at 2 weeks in addition to check:
    - for adverse events
    - do more blood tests (alanine aminotransferase [ALT])
    - ensure the correct dosing
- to measure CD4 count and VL 6-monthly while patients on the 1st line.

In 2010 (230) the frequency for CD4 and VL measurement has been reduced to month 6, 12 and then annually. In addition specific tests have been indicated to identify toxicities to specific drugs: ALT if on NVP and develops rash or symptoms of hepatitis , FBC at month 1, 2, 3 and 6 if on AZT, creatinine at month 3 and 6 and then annually if on TDF and fasting cholesterol and triglycerides at month 3 if on LPV/r.

The guidelines published in 2013 (226) recommend the same frequency of monitoring as the 2010 guidelines, except for a few details specified below: CD4 is recommended to be measured only at 1 year since ART initiation, for patients on AZT, FBC is recommended only at month 3 and 6 and finally for patients on TDF creatinine monitoring is recommended at month 3, 6, 12 months and then annually.

2.1.8. Roll out of antiretroviral therapy

The roll out of ART in public clinics started in April 2004 (476). However demonstration projects have been conducted since 2001 providing ART to patients with advanced disease in Khayelitsha in the Western Cape (477) and in Gugulethu (initiated in September 2002) (293;307;478). The scale up was relatively slow in these first years, but from 2010 the uptake (up to 30,000 initiations per month) increased dramatically (see Table 2.6). This was due to several contributions: the revision of the ART guidelines which increased the number of people who are considered eligible, the fact that regimens available have become safer and more effective, the shifting of tasks from doctors to nurses and counsellors in the management of HIV patients (this has been referred to as nurse-initiated management of patients on ART) and

the increase in the number of facilities providing ART, most of them primary healthcare clinics (described in section 7.2.8) and to the reduction in the price of ARVs (450).

Currently, the South Africa HIV treatment programme is the largest in the world, with over 2 million people on ART in 2013 (479). In November 2012 the South African Department of Health managed to get a tender awarded for a FDC for the first-line of ART (TDF+FTC+EFV), so these were available for patients from 1st April 2013. This allowed not only to reduce the pill burden for patients but also to reduce the cost of the first-line by 38%.

Table 2.6. Number of people on ART in South Africa

Source	Year	Age Group	Number on ART			ART coverage	
			All	Males	Females	2010 eligibility	2004 eligibility
Johnson (451)	2004	15+ years old	43,300	17,700	25,600	-	-
	2005		101,100	37,500	63,600	-	-
	2006		213,000	75,000	138,000	-	-
	2007		347,000	120,000	228,000	-	-
	2008		537,000	183,000	354,000	-	-
	2009		836,000	283,000	553,000	-	-
	2010		1,174,000	396,000	777,000	-	-
	2011		1,641,000	551,000	1,090,000	52%-	79%
DoH (480) (not available online, referenced by Statistic South Africa (481))	2005	15+ years old	101,416	-	-	-	-
	2006		215,875	-	-	-	-
	2007		386,315	-	-	-	-
	2008		609,762	-	-		44%
	2009		839,519	-	-	37%	56%
	2010		1,058,399	-	-	-	-
Republic of South Africa (450)	2010	0+ years old	-	-	-	-	58.3%
	2011		1,600,000	-	-	-	75.2%
SANAC (473)	2013	0+ years old	2,150,880	-	-	-	-
UNAIDS (479)	2013	0+ years old	2,200,000	-	-	-	-

DoH: Department of Health; SANAC: South African National AIDS Council; UNAIDS: Joint United Nations Programme on HIV/AIDS;

2.1.9. Retention on antiretroviral treatment and adherence

Once initiated on ART, in order to gain the maximum health benefit, people should not interrupt treatment. Especially in the first years of ART roll-out, lots of people died in the first year of ART mainly due to the very late diagnosis and therefore initiation of ART at low CD4 cell

count (477;482). Among those who remain alive by the 1st years of ART, a consistent proportion interrupt ART for various reasons and some of them are LTFU.

Data at a national level regarding how many people are in care and how many have interrupted or are LTFU are not available. Several studies have assessed how many people are LTFU in different ART programmes in South Africa (see section 7.3.5), nevertheless only a couple of studies (483;484) have distinguished between people who interrupted ART (i.e. come back to care after interruption) and those who are LTFU.

One of these studies (483), estimated that in the first year since ART initiation, among over 11,000 patients initiating ART between 2004 and 2008, 30% missed laboratory visits, and of these 40% of them returned back to care by 12 months since initiation. These people, who interrupted ART during the first year were estimated to have a 30% increase in detectable viraemia compared to those who remained continuously in care. The other study (484) estimated the rate of defaulting treatment (having stopped all ARVs for more than 30 days) and the rate of resuming ART in those who had interrupted in a cohort of over 1,000 people who initiated ART between 2004 and 2009. They estimated the rate of defaulting treatment to be 12.8/100 PYs (95% CI: 11.4, 14.4) and the rate of restarting ART 21.4/100 PYs (the probability within 3 years of defaulting therapy was 42%). Both these studies highlighted the fact that not all those who are reported in the literature as LTFU are actually permanently lost and there is a good chance of them coming back to care at a later point.

Not only do patients need to be on ART, but they need to take the ARVs daily and as prescribed. Adherence to ART is difficult to measure: self-reported measures are affected by desirability bias and more objective measures are often very expensive and can represent an actual intervention in themselves, making the results non generalizable to settings where these are not available. Self-reported adherence is generally the only way adherence is routinely monitored in South Africa. A systematic review in 2006 (485) estimated a pooled average adherence of 77% in Africa (95% CI: 68%, 85%) compared to 55% (95% CI: 49%, 62%) in North America. In South Africa the studies which reported the proportion of people with >95% adherence found levels from 57.2% (referring to doses in the previous 7 days) (486) to 88% (referring to doses in the previous 30 days) (487) and similar levels were reported by Darder and colleagues (488). Based on pharmacy-refill and pill count, Orrell estimated that over 48 weeks 63% of the population took 90% of their pills or more (489). Others, such as Dahab (490) looked at a more objective indication of low adherence, such as having a drop in VL of less than 1 log by 6 weeks. They estimated, based on this virological measure, that 85%

of the patients were adherent. More recently a study conducted in KwaZulu-Natal reported very good adherence in the first 6 months since ART initiation with 83% reporting being adherent using a visual analogue scale and 71% using a scale specific to the study (Adult AIDS Clinical Trials Group) (491). Nevertheless, it is not clear whether people in Africa, and more specifically in South Africa, have optimal adherence or whether the tools used to measure adherence are inappropriate to detect suboptimal adherence. A small study (n=165) in KwaZulu-Natal evaluated the sensitivity and specificity of five different adherence questions (492). None of them performed well, the best measure was the Likert scale. Using this scale when defining non-adherence as self-reported adherence less than ''excellent'', the sensitivity for detecting virological or immunologic failure was 100% and the specificity 5%, when defining non-adherence as self-reported adherence less than "very good'' the sensitivity was 42% and the specificity 55% and finally when defining it as less than ''good'' the sensitivity was 25% and the specificity 95%.

2.1.10. Virological outcome and development of resistance on first-line regimen

The outcome of people initiating ART regarding whether they are still in the same clinic, transferred to another one, lost or died is summarized in section 7.3.5 and Appendix XX, since Chapter 7 is focused on evaluating the impact of improvements at different steps of the cascade of care. In summary, it has been found that retention on ART varies between 63% at 13 months (483) up to 92% at 12 months since ART initiation (493). There was initially lots of concern regarding the high proportion of people not retained in care. Afterwards, it was found that actually lots of people not coming back to care were dead and misclassified as LTFU and as many were transferred to other clinics and were therefore still on ART (494).

In this section I summarize the evidence concerning the virological outcome of people initiating ART in South Africa. The risk of developing drug resistance among those who fail ART in South Africa is described in detail in section 5.1.

Virological response among people on ART has been found to be relatively good (see Appendix V). Studies estimated that among people retained in care at 12 months between 66% (304) and 96% (307) had VL<400 copies/mL. Fewer studies reported these outcomes at 24 or 36 months, but a similar proportion of people suppressed were reported: at 24 months ranging from 60% (495) to 96% (307) and at 36 months between 61% (495) and 88% (292). This same study (292) reported that at 5 years 84% were still virologically suppressed. When looking at a

lower limit of detection (the assays available when the studies were conducted were not always capable of detecting lower level of viraemia), around 65% (304) and 85% (307) achieved a VL <50 copies/mL at 12 and 24 months.

When looking at the virological outcome using as a denominator those initiated on ART a certain length of time ago, so taking into account the fact that some people are not in care anymore in the same clinic, these outcomes are obviously lower: at 12 months it varies from 55% (46% if VL<50 copies/mL) (496) to 77% (VL<25 copies/mL) (497) and at 24 months: from 18% (VL<50 copies/mL) (496) to 75% (304). While at 36 months 63% had VL below 50 copies/mL in the only study reporting this outcome, 80% if only those with more than 3-month follow-up were included (498).

Several studies also investigated the occurrence of VF after having achieved initial virological suppression (see Appendix VI). The definition of VF within the ART national guidelines has changed over time. In 2004 the requirement for VF was a VL above 5000 copies/mL preceded by a VL above 400 copies/mL, despite an adherence intervention conducted after the first VL above 400 copies/mL after at least 6 months on ART (225). They recommended a confirmatory VL in 3 months if a VL above 5000 copies/mL was measured and in 6 months if the initial raised VL was between 200 and 5,000 copies/mL. In addition it was indicated to switch people to second-line only if their adherence was above 80%. In 2010 the threshold for the confirmatory VL has been reduced from 5,000 to 1,000 copies/mL, with the indication of repeat VL within 6 months if the initial VL is between 400 and 1,000 copies/mL and within 3 months if above 1,000 copies/mL and finally in 2013 this has been newly revised to two consecutive VL>1,000 copies/mL, with the 2nd VL conducted two months after the first raised VL (226).

When asking for two consecutive raised VL the proportion of people on ART at 12 months who virologically fail is around 3% regardless of the exact definition of VF: 2 consecutive VL>1,000 copies/mL (VL measured every 4 months and adherence intervention in patients with a VL>1,000 copies/mL) (307) or 2 consecutive VL the first above 400 or 1000 copies/mL and the 2nd above 5,000 copies/mL (VL measured 6 monthly) (499). At 24 months the proportion experiencing VF varies between 5% (2 consecutive VL>1,000 copies/mL) (307) and 8% (2 consecutive VL the first above 400 or 1000 copies/mL and the 2nd above 5,000 copies/mL) (499). Only one study reported this outcome at 3 years with a level of 15% if the first VL is above 1,000 copies/mL followed by a consecutive VL above 5,000 or 16.9% if the first raised VL is above 400 copies/mL (499). Similar levels were observed in a study of patients enrolled in a workplace programme (17.9% experienced VF over a median follow-up of 2.6 years) (500).

Finally, Boulle and colleagues found that at 5 years (292) 14% (95% CI: 12%, 16%) had experienced VF (2 consecutive VL>5,000 copies/mL, despite enhanced adherence promotion after the first VL>5,000 copies/mL).

2.1.11. Switch to second-line and outcome on second-line regimen

Despite people failing the 1st line regimen, there is evidence that not many people are switched to a second-line regimen, from as low as 17% at 12 months since VF (500) up to 74% for those with at least 6 months of follow-up (499) and if they do usually not in a timely manner (292;499;501). This issue is further discussed in section 7.3.6 and Appendix XXI.

Once switched to a second-line regimen, people tend to have a slightly less optimal virological outcome than on 1st line (see Appendix VII). The proportion who achieved virological suppression by 12 months varies from around 60% using as cut off either 500 copies/mL (502) or 50 copies/mL (503) up to 86% (VL<400 copies/mL) (292). Very similar levels were found at 24 months, where it varies from around 65% (VL<50 copies/mL (503), VL<400 copies/mL (504)) up to 75% (VL<400 copies/mL (503); VL<1000 copies/mL (505)). Nevertheless it is not obvious whether this is due to having spent a long time on a failing regimen or to the fact that people who are switched to second-line are less likely to be adherent than those who did not fail the first-line regimen.

2.1.12. Circumcision

In 2007 WHO and UNAIDS recommended scaling up VMC in thirteen priority countries with generalized epidemics and low prevalence of circumcision (506). At the end of 2011, UNAIDS in collaboration with WHO published the *"Joint Strategic Action Framework to Accelerate the Scale-Up of Voluntary Medical Male Circumcision for HIV Prevention in Eastern and Southern Africa: 2012–2016"* (507) with the following goals:

"

- *Voluntary medical male circumcision prevalence of at least 80 percent among 15–49 year old males,*
- *Established a sustainable national programme that provides VMMC services to all infants up to two months old and at least 80 percent of male adolescents."*

In 2009, the prevalence of circumcision in South Africa was 42% (508) and they estimated that in order to achieve 80% circumcision coverage, 4.3 million men had to be circumcised (509). By the end of 2011 over 442,000 VMCs, 10.2% of the target, were performed (5190 in 2008, 9168 in 2009, 131117 in 2010 and 296726 in 2011). In the NSP for the period 2012–2016 the scaling up of VMC was outlined (469). In 2012 alone, 422,000 VMCs were performed, allowing the circumcision coverage to increase up to 55%. The plan now is for 900,000 men per year to be circumcised in order to achieve the target (473).

2.2. Zimbabwe

2.2.1. Brief demographic introduction

2.2.1.1. Population size and age distribution

Population censuses have been conducted in Zimbabwe since 1931. I am going to focus on the three censuses which have been performed since the first cases of HIV were observed, respectively in 1992, 2002 and 2012 (510;511). An increase in the total number of people living in Zimbabwe has been observed: from 10 million people in 1992 up to 13 million at the last census in 2012 (see Table 2.7). In the future it is projected that the Zimbabwe population is going to reach 20.3 million by 2030, with a decreasing rate of population change over time.

Table 2.7. Zimbabwe population estimates and projections

Source	Year	Age group	Population size (in million)		
			All	Males	Females
1992 Population Census cited in (511)	1992	0+ years old	10.41	-	-
2002 Population Census (511)	2002		11.63	5.6	6.0
2012 Population Census (510)	2012		13.06	6.28	6.78
UN Population Fund (512)	2011	0+ years old	12.8	-	-
CIA (513)	2013	0+ years old	13.77	6.87	6.90
		15-64 years old	8.00	4.00	4.00
		15-24 years old	3.05	1.53	1.52
		25-54 years old	4.45	2.30	2.15
		55-64 years old	0.50	0.18	0.32
UN Secretariat (436)	2010	0+	13.08	-	-
	2015		15.05 (+2.8[a])	-	-
	2020		17.12 (+2.6[a])	-	-
	2030		20.29 (+1.6[a])	-	-

CIA: Central Intelligence Agency; UN: United Nations; a – annual rate of population change in the previous five years;

Figure 2.12 shows the age and gender distribution estimated by the Census in 2002. The Zimbabwean population is very young with 41% of the population being below 15 years old and only 4% above 65 years old.

Figure 2.12. Population pyramid (%) in Zimbabwe in 2002 (511)

2.2.1.2. Mortality

The best way of estimating mortality is through vital registry, however the vital registry in Zimbabwe is not complete and this was still the case when the results from the census conducted in 2012 were published (510). Therefore the two main sources on mortality at a national level are the DHSs, which collected data on sibling survival and the censuses. Gregson and colleagues (514) conducted a thorough review of the epidemiological data for Zimbabwe on HIV prevalence, HIV incidence, mortality and sexual risk behaviour in an attempt to determine whether HIV prevalence was declining and to identify the determinants. Historical data on the mortality rate in Zimbabwe from the 1990s are summarized in Table 2.8.

Gregson et al. reported that in Zimbabwe the mortality rate started increasing in the late 1980s in urban areas and a few years later, at the beginning of 1990s in the rural areas (515). Both main sources of mortality data, although with different absolute estimates, documented an increased death rate; in particular, for example, in Harare the death rate was estimated to be around 6 per 1,000 in 1992 and it was estimated to be 10.6 ten years later. The DHS in 1994 estimated a death rate for women 15-49 years around 3/1,000 and around 4/1,000 for men and these death rates were more than double at the subsequent survey in 1999 (see Table 2.8). The peak in death rate was reached in the survey conducted in 2005-06 and at the last survey a slight reduction was observed: in men 11.5/1,000 compared to 13.3/1,000 in 2005-06 and in women 11.4/1,000 from 12.7/1,000 in 2005-06.

Table 2.8. Death rate estimates for Zimbabwe at national level

Source		Year	Age-group and area (if not national)	Crude death rate (Death/1000 people)			Average Life expectancy at birth
				All	Males	Females	
Population Census	cited by Gregson (514)	1992	Harare Bulawayo	6.2 6	- -	- -	- -
	(511)	2002	National Harare Bulawayo	17.22 10.60 13.89	- - -	- - -	- - -
	(510)	2012	National Harare Bulawayo	10.2 7.7 9.3	- - -	- - -	38 - -
DHS	(516)	1994	15-49 years old	-	4.17	3.34	-
	(517)	1999	15-49 years old	-	11.35	9.14	-
	(518)	2005-06	15-49 years old	-	13.30[a]	12.66[a]	-
	(519)	2011	15-49 years old 15-19 years old 20-24 years old 25-29 years old 30-34 years old 35-39 years old 40-44 years old 45-49 years old	- - - - - - - -	11.5[a] 2.3 3.4 6.4 14.0 23.1 30.0 32.0	11.4[a] 2.5 5.2 9.6 16.4 20.7 23.3 22.6	- - - - - - - -

DHS: Demographic and Health Survey; a: age standardized;

Figure 2.13 and Figure 2.14 illustrate the age specific death rates in Zimbabwe estimated in the DHS conducted in 1994, 1999 and 2005-06, respectively for women and men. To note is the dramatic increase especially in the age group 30 to 39 years old which increased by 2 fold from 1994 to 1999, while from 1999 to 2005-06 the increase in mortality was in the older age group. The last DHS survey conducted in 2010-11 (519) found a similar pattern of age and gender specific mortality to that observed in 2005-06.

Figure 2.13. Age specific mortality among women aged 15-49 years (Rates per 1,000 person-years), Zimbabwe, 1994-2006 (518)

ZDHS: Zimbabwe Demographic and Health Survey;

Figure 2.14. Age specific mortality among men aged 15-49 years (Rates per 1,000 person-years), Zimbabwe, 1994-2006 (518)

ZDHS: Zimbabwe Demographic and Health Survey;

2.2.2. Sexual behaviour

Data on sexual behaviour for Zimbabwe have been collected in several national population–surveys:

- The DHSs conducted in 1988, 1994, 1999, 2005-06 and 2011 (516-520)

- Knowledge, attitudes, practices and beliefs surveys commissioned by Population Services International (PSI) surveys conducted in 1997, 1999, 2001, 2003, 2005, 2006, 2007 referenced by Gregson et al. (514)
- National Youth Reproductive Health Survey conducted in 1997 (521)
- Zimbabwe Young Adult survey (YAS) in 2001 (522)
- National youth survey conducted by United Nations Children's Fund in 2004 referenced by Gregson et al.(514)
- Survey to evaluate the of Zimbabwe's National Behaviour Change Programme (523)

2.2.2.1. Sexual debut

Gregson et al. summarised all the estimates available regarding age at sexual debut from national surveys conducted in Zimbabwe (see Figure 2.15). The median age at sexual debut has been relatively stable, between 17 and 20 years in both males and females. The most recent DHS conducted in 2010-11 (519) found that among people aged 15-24 years, less than 50% had had sexual intercourse before entering in this age group. For this reason the median age at first sex for age group 15-24 years was not reported, nevertheless in the older age groups the age at sexual debut was between 18 and 19 years in women and 20-21 years in men.

Figure 2.15. Median age at sexual debut for respondents aged 15-24 years in Zimbabwe (514)

DHS: Demographic and Health Survey; IQR: interquartile range; PSI: Population Services International; UNICEF: United Nations Children's Fund; YAS: Zimbabwe Young Adult survey;

In the DHS the percentage of men 15 to 19 years reporting having ever had sex fell from 33% in 1994 to 24.7% in 2011, while in women it increased from 29.7% to 34.0%. The percentage

of men aged 15-19 years who reported having had sex before the age of 15 was 7.9% in 1994 and it decreased to 3.6% in 2011; similarly in women it was 5.2% in 1994 and 3.9% in 2011 (519).

2.2.2.2. Multiple sexual partners

Most of the surveys attempted to capture the information regarding faithfulness by asking whether they had one or more non-regular partner (usually defined as non-marital non–cohabiting) in the last 12 months.

Figure 2.16 shows the proportion reporting a non–regular sexual partner in the last 12 months (in grey data from DHS and in white PSI surveys). Similarly to what has been described for South Africa, in Zimbabwe a much lower proportion of women (maximum 20%) reported a non-regular sexual partner in the last year compared to men, where it ranges from around 20 to 35% in the PSI surveys and between 45% and 60% in the DHS surveys. The data suggest a reduction in the proportion reporting a non–regular sexual partner for men, but this is less clear for women.

Figure 2.16. Percentage of people aged 15–29 years reporting a non-regular sexual partner in past 12 months in Zimbabwe (514)

a. Males b. Females

The concept of concurrency, defined as more than one partner during the same period of time, was newly introduced in the last DHS survey (519). They reported that among women 15-24 years old only 0.6% had concurrent relationship in the last 12 months and 4.8% of men.

A representative household surveys of people aged 18 to 44 years in 16 districts found that the proportion of men with 2 partners or more in the last 12 months declined from 29.1% to 24.4% from 2007 to 2011 and in women from 7.4% to 5.1% (523).

2.2.2.3. Paid sex

In sexual intercourse where one of the two partners pays for sex it may often be difficult to negotiate condom use. For this reason and due to the high number of partners a person who is paid to have sex usually has, it is more likely this person is HIV-positive (524). Therefore it is very important to monitor which proportion of men report paying for sex and whether they use condoms during such sex. Table 2.9 shows that the percentage of men who paid for sexual intercourse in the past 12 months decreased over time from 7% in 1994 to 3% in 2011, in addition the proportion of men who reported using a condom at the last paid sexual intercourse increased from 82% up to 90%.

Table 2.9. Percentage of men reporting paying for sex and using condom at last paid sexual intercourse in Zimbabwe

Source		Year	Age	% of men who paid for sexual intercourse in the past 12 months	% reporting condom use at last paid sexual intercourse
DHS	(516)	1994	15-54	6.9	-
			15-19	7.6	-
	(517)	1999	15-54	7.0	81.5
			15-19	3.0	74.5
	(518)	2005-06	15-54	3.9	73.6
			15-19	1.1	76.6
	(519)	2010-11	15-54	3.0	87.8
			15-19	1.2	NA
			15-24	2.5	90.4

DHS: Demographic and Health Survey; NA: Not available, because sample size considered too small;

2.2.2.4. Condom use

Since the late 1990s when the first surveys were conducted the proportion of males aged 15-29 years reporting condom use at last sex with a non-regular partner varied between just above 60% up to around 90% (See Figure 2.17: in grey data from DHS, in black YAS and in white PSI survey). In women there is even more variability: from 40% up to just above 80%. At the last DHS survey this information was collected among people aged 15-24 years and it was 73.7% in men and 48% in women. Nevertheless, condom use at last sex among all those who

have at least 2 partners in the last 12 months was only 33% in men and 48% in women. The relationship between age and condom use is different in men and women, while younger men are more likely to report condom use at last sex (15-24 years, 50.5%), young women are less likely to use condom (15-24 years, 38.5%).

The evaluation of Zimbabwe's National Behaviour Change Programme reported that condom use at last sex with all non-regular partners in the last 12 months, increased from 23.5% in 2007 to 39.9% in 2011 (523).

Figure 2.17. Condom use at last sex with a non-regular sexual partner in people aged 15-29 years in Zimbabwe (514)

b. Males b. Females

2.2.2.5. Intergenerational sex: partners age differences

The DHS surveys started collecting data on intergenerational sex among people aged 15 to 19 years who had sex in the last 12 months from 2005. They found that 5% of women in 2005-06 had sexual intercourse with a man 10 years or older and this increased to 15.3% in 2010-2011, while it was 0.3% in men in the same year.

2.2.3. The HIV epidemic

2.2.3.1. HIV prevalence

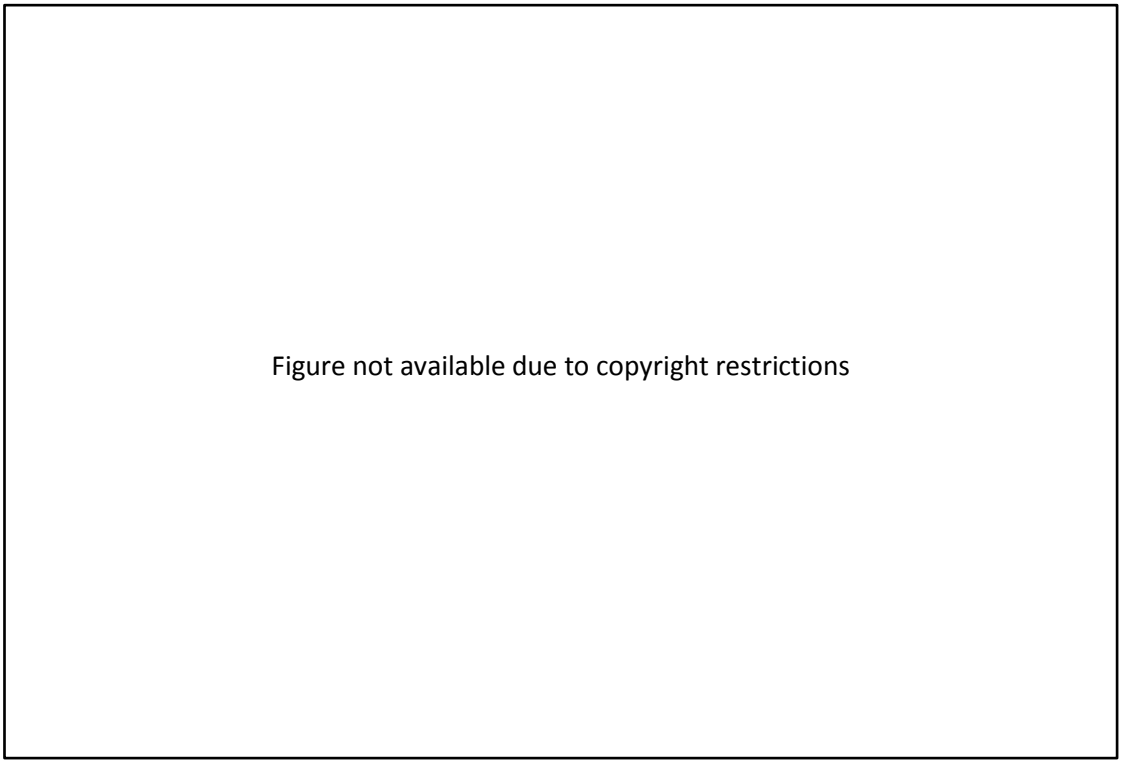
The first documented case of AIDS in Zimbabwe was reported in 1985 (525). By 1990, when they started conducting HIV sero-prevalence surveys in the ANCs, the HIV prevalence was

already more than 10%. Zimbabwe is currently 5th highest globally in terms of HIV prevalence, with an HIV prevalence in the adult population aged 15 to 49 years of 14.7% (95% CI: 13.8, 15.6) (526), preceded by South Africa on 4th place (446).

The number of adults (above the age of 15 years old) living with HIV was estimated to be 1.2 million in 2012 (95% CI: 1.1, 1.3) and in the same year 39,000 (95% CI: 34000, 45000] people were estimated to have died because of AIDS.

The sentinel ANCs where HIV prevalence surveys were conducted initially varied from year to year and large differences were observed within the same clinics (see Figure 2.18), questioning the validity of these surveys. They suggested that HIV prevalence increased between 1990 and around 1995 and then reached a plateau. In 2000 the HIV surveillance in sentinel ANCs was improved by selecting a higher number of clinics, especially in the rural areas and by documenting more thoroughly the procedures (527). In 2000, the Genscreen test was used for HIV testing. This test was subsequently found to be not very specific, for this reason from 2002 a combined test algorithm was used (527). Afterwards (not shown in the graph) the HIV prevalence in the sentinel clinics declined from 26% in 2002 to 16% in 2009.

Figure 2.18. HIV Prevalence estimates for individual ANC sites and from The Zimbabwe Young Survey and trends in HIV prevalence in adults 15-49 years as estimated by Estimation and Projection Package (EPP) (528)



The last two DHS surveys, conducted in 2005-6 and in 2010-11 have collected data on HIV prevalence documenting a decline in the population aged 15-49 years (see Table 2.10) from 18.1 (95% CI: 16.9, 19.3) to 15.2 (95% CI: 14.3, 16.1), more dramatic in women, where it declined from 21.1 to 17.7 than in men, where it declined from 14.5 to 12.3 (519).

Table 2.10. HIV prevalence and number of people living with HIV in Zimbabwe

Source	Age group	Year	HIV prevalence (95% CI)			Number of people living with HIV (million)
			All	Males	Females	
Mahomwa (527) and Zimbabwe Ministry of Health and Child Welfare (529) (not found online, cited by (514;530))	15-49 years old	2000	-	-	32[a]	-
		2001	-	-	30[a]	-
		2002	-	-	30[a], 25.8[b]	-
		2004	-	-	21.3[b]	-
		2006	-	-	17.7[b]	-
		2009	-	-	16.1[b]	-
	15-24 years old	2002	-	-	20.8	-
		2004	-	-	17.4	-
		2006	-	-	12.5	-
		2009	-	-	11.6	-
Zimbabwe Ministry of Health and Child Welfare (531), (not found online, cited by (530;532))	15-49 years old	1990	10.0	-	-	-
		1992	18.0	-	-	-
		1994	23.0	-	-	-
		1996	28.0	-	-	-
		1998	28.0	-	-	-
		2000	25.0	-	-	-
		2002	22.0	-	-	-
		2004	20.0	-	-	-
		2006	18.0	-	-	-
		2008	15.0	-	-	-
		2009	14.3	-	-	-
		2010	13.6	-	-	-
		2011	13.1	-	-	-
	15+ years old	1997	26.5	-	-	-
		2001	23.7	-	-	-
		2005	18.4	-	-	-
		2009	14.3 (13.4-15.3)	-	-	1.04 (0.9-1.2)
		2010	13.6 (12.7-14.7)	-	-	1.02 (0.9-1.1)
		2011	13.1 (12.1-14.3)	-	-	1.02 (0.9-1.1)
YAS (522)	15-29	2001-02	-	10	22	-
	15-24		-	5	17	-

Source		Age group	Year	HIV prevalence (95% CI)			Number of people living with HIV (million)
				All	Males	Females	
DHS	(518)	15-49	2005-06	18.1	14.5	21.1	-
		15-54		-	14.8	-	-
		15-19		4.6	3.1	6.2	-
		20-24		11.6	5.8	16.3	-
		25-29		21.8	13.1	28.8	-
		30-34		32.9	29.5	35.5	-
		35-39		33.4	32.1	34.5	-
		40-44		28.9	32.9	25.7	-
		45-49		21.4	26.0	18.0	-
		50-54		-	20.0	-	-
DHS	(519)	15-49	2010-11	15.2	12.3	17.7	-
		15-54		-	12.7	-	-
		15-19		3.8	3.4	4.2	-
		20-24		7.5	3.8	10.6	-
		25-29		15.8	10.3	20.1	-
		30-34		23.7	17.3	29.0	-
		35-39		27.3	25.2	29.1	-
		40-44		25.9	26.2	25.7	-
		45-49		25.5	29.9	22.5	-
		50-54		-	19.5	-	-

a: Genscreen HIV result; b: combined HIV test result; CI: confidence interval; DHS: Demographic and Health Survey; YAS: Zimbabwe Young Adult survey;

2.2.3.2. HIV incidence

At least two studies estimated HIV incidence in Zimbabwe, respectively in a cohort of pregnant women and in a cohort of male workers in Harare. The first reported an HIV incidence of 4.8/100 PYs (95% CI: 3.1, 6.5) in 1992 (533) declining to 3.4/100 PYs in 1999 (534), while in the cohort of male workers it declined from 3.0/100 PYs (95% CI: 2.5, 3.5) in 1994-95 (535) to 1.3/100 (95% CI: 1.0, 1.8%) in 2002-03 (536).

At the last DHS survey (see Table 2.10) the HIV prevalence in women aged 15 to 19 years was 4% compared to 6% in 2005-06, while in men aged 15-19 years it remained stable at 3% and this is an indication that the HIV incidence in this group is declining.

UNAIDS, using the Spectrum model, estimated that the HIV incidence in the adult population (15-49 years) peaked in the early 1990s at around 6/100 PYs and it has been declining since then to levels below 1 in 2009 (532). In terms of new HIV infections, in the entire population this corresponds to around 260,000 new HIV infections per year at its peak down to around 74,000 in 2009 (532) and 46,000 in 2011 (530).

2.2.3.3. Mortality in HIV-positive people

The sources of data available to estimate the mortality since the start of the HIV epidemic in this country are:

- Census, which collected information regarding death in the household of siblings
- Vital registration
- Population cohort data, which are not at national level

All these sources of data are characterized by incomplete recording and misreporting.

The vital registration data capture the cause of death but as mentioned is characterized by very low reporting rate; in 1995 for example the number of registered deaths was less than half the number of deaths estimated from the census conducted in 1997 (537). In an attempt to estimate the burden of disease in Zimbabwe, Chapman and colleagues explored the pattern of causes of deaths reported in the vital registration in 1995 and compared it to previous age specific death rates in Zimbabwe. They observed a significantly higher death rate in the population aged between 20 and 60 years and they noticed that initially only 14% of deaths were attributed to HIV, but that an increased death rate in the same age group was observed for common diseases including lower respiratory infections, TB, diarrhoeal diseases and meningitis, which are all associated with HIV infection.

Zimbabwe experts suggested that this could be due to wrong assignment of the underlying cause and that more deaths would have been expected to have HIV as underlying cause. For this reason they reassigned the underlying cause of death assuming that 95% of the difference between the age specific death rate between 1995 and 1984 was due to HIV, this meant reallocating 29% of all deaths. They concluded that of the 167,808 deaths in 1997, 54% were considered to be attributable to HIV.

Such a burden of deaths translates into a life expectancy at birth of 51.1 years in males and 47.0 in females.

UNAIDS estimate the number of AIDS deaths using the Spectrum model (see Figure 2.19). They estimated the number of AIDS deaths peaked in early 2000s and it has been declining since, with 39,000 (34,000-45,000) AIDS deaths estimated in 2012 (526).

Figure 2.19. Annual number of AIDS deaths in Zimbabwe (526)

2.2.4. Response to HIV: history

As happened in other countries, the first cases of HIV were met with some denial by the government and it was only in 1990 that HIV/AIDS issues were discussed publicly (538).

Several policies and strategic plan were developed since then:

- 1987: Emergency Short Term Plan
- 1993: Mid Term Plan 1
- 1994-99: Mid Term Plan2
- 1999: National Policy on HIV and AIDS
- 2000-04: National HIV and AIDS Strategic Framework
- 2006-10: Zimbabwe National HIV and AIDS Strategic Plan
- 2011-15: Zimbabwe National HIV and AIDS Strategic Plan

In 1985, as the first case of HIV was identified, universal screening of blood for HIV before transfusion was introduced and in 1987 a one year Emergency Short Term Plan was developed to train health personnel on the prevention and containment of HIV and AIDS and to make the population more aware of this issue.

Nevertheless it took six years, until 1993 to release the Mid Term Plan 1 aimed at promoting behavioural change especially in target groups, prevention, treatment of STIs and support for people living with HIV. The 2nd part of this plan, 5 years long was published in 1994, it concentrated on mobilizing non-health sectors to integrate HIV and AIDS issues.

Finally in December 1999 a national policy on HIV and AIDS was announced by the Government (539), this represented a major change. It sets five precise strategies:

“

1. *Establish a multi-sectorial National AIDS Council (NAC) with a clear mandate to ensure overall management and co-ordination of the National response to HIV/AIDS*
2. *Ensure that HIV/AIDS is recognised and treated as a major priority for political support and social and resource mobilization*
3. *Ensure that all sectors and organisations integrate HIV/AIDS into their planning and programming*
4. *Mobilise resources to support the national response to HIV/AIDS/STI*
5. *Promote effective monitoring and evaluation of all programmes/projects on HIV/AIDS/STI”*

Shortly after, the National AIDS Council was created through an Act of Parliament. In 2000 it was functioning and developed the National HIV and AIDS Strategic Framework 2000-2004, in line with the National Policy, with three main components:

- Prevention of new HIV infections, through PMTCT (see Appendix VIII), VCT, condom distribution, HIV awareness, STIs treatment and maintenance of blood safety.
- Treatment and care provided for OIs mainly through home-based care
- Mitigation and support in particular for orphans and vulnerable children in terms of food and nutrition, livelihoods, educational and stigma and discrimination control

As part of the mitigation strategy, in order to partly face the cost of responding to the HIV epidemic, the National AIDS Trust Fund (AIDS Levy) was set up: it consisted of a 3% tax on employed people and corporate earnings (538).

In May 2002 the Government declared HIV/AIDS a national emergency, with the long term aim of being able to use generic ARVs and in 2004 the national ART programme was launched.

By 2005, it was evident that the HIV prevalence was declining, although still high, and a new Zimbabwe National HIV and AIDS Strategic Plan was developed for the period 2006-2010 (540) after a thorough review of the achievements and challenges experienced. At that time only 7% of those in need of ART were receiving it, only about 20-30% from orphans and vulnerable children were benefiting from some form of assistance and 3,000 people were dying every

week because of HIV (540). The Zimbabwe National HIV and AIDS Strategic Plan 2006-10 was inspired by the principles of considering HIV as an emergency, the importance of tackling gender inequality and stigma, the necessity for all stakeholders to collaborate in a multi-sectorial response, the need for adequate resources, the fundamental of respecting commitment to international goals and the requisite to adopt evidence based strategies to address the epidemic. In 2006 the Behaviour Change Communication programme (541) was launched with the goal of reducing HIV incidence by:

1. *"enabling environment for behavioural change created including through increased leadership and gender-equality as well as reduced stigma associated with PLWHA [people living with HIV and AIDS]*
2. *Increased adoption of safer sexual behaviour and reduction in risk behaviour*
3. *Increased utilization of HIV prevention services (T&C [testing and counselling] including post-test support, PMTCT, PEP [post-exposure prophylaxis])*
4. *Improved national and sub-national institutional frameworks to address behavioural change "*

The programme covered 26 districts (out of 62) until 2009, but since then it has been expanded to cover the entire country.

Zimbabwe, as South Africa, participated at the UN General Assembly in June 2011 to assess progress made in the HIV and AIDS response since 2001 and signed the "Political Declaration on HIV and AIDS: Intensifying our Efforts to Eliminate HIV and AIDS", with concrete goals to reach by 2015 (see section 2.1.4).

These were included in the Zimbabwe National HIV and AIDS Strategic Plan 2011-2015:

- Reduction of HIV incidence by 50% in adults: from 0.85% (48, 168) in 2009 to 0.435% (24,084)
- Reduction in HIV incidence among children from 30% in 2010 to less than 5% by 2015
- Reduction in HIV and AIDS related mortality by 38%: from 71,299 (2010) for adults and 13,393 for children (2009) to 44,205 for adults and 8,304 for children
- Improvement in efficiency and effectiveness of the national multi-sectorial response: improvement in the National Commitments and Policy Instruments rating (not described here) from 6.2 in 2010 to 9.0.

2.2.5. Awareness of HIV status

HIV testing in Zimbabwe was initially introduced in 1985 to screen blood for transfusion and from 1986 it was used to diagnose hospitalized clinical cases, but in 1999 VCT was still available only in Harare (542). Since 1999 the DHSs collected information on whether people ever tested for HIV and more recently whether they tested in the last 12 months (see Table 2.11). In 1999, only 9% of men and 11% of women had ever tested for HIV and this increased to respectively 16% of men and 22% of women by 2005-06, still only 7% were tested in the last 12 months.

The Zimbabwe National HIV and AIDS Strategic Plan 2006-2010 (540) recognized HTC as a crucial part of the HIV national response and in 2008 the Zimbabwe National HTC Strategic Plan 2008-2010 was adopted, with a clear target: increase the percentage of the Zimbabwean population who know their HIV status, from 20% to 85% by 2010. To this purpose the number of services offering HTC increased and diversified: HTC were offered in VCT centres, outpatients wards and as well in PMTC, STI, TB, family planning community and home-based care, etc. (530). In addition, PITC was implemented in 2007 (543)(This reference is not available on line, but referenced by (544)) and recommended on top of the previously available VCT, campaigns and outreach activities were conducted at provincial level (530) and, starting from April 2011, primary counsellors were allowed to perform HIV testing (545). This allowed offering HTC to over 1.7 million people in 2010 and 1.8 in 2011 (530). This substantial uptake of HTC was captured as well by the DHS, which reported that 36% of adult men and 57% of women had ever tested for HIV of which respectively 20% and 34% in the last 12 months. Similarly the mid-term evaluation of the National Behaviour Change Programme (546) reported that 50% of the participants (aged 15 to 44 years) tested for HIV. In 2013 96% of the primary healthcare clinics were offering PITC (547).

Table 2.11. Levels of HIV testing in Zimbabwe

Source		Year	Age	% ever tested (and received results from 2005-06)		% tested in the last 12 months		Number of people tested for HIV (in million)
				Males	Females	Males	Females	
DHS	(517)	1999	15- 49(f), 54(m) years old	9.2	11.8	-	-	-
			15-19 years old	2.8	6.1	-	-	-
	(518)	2005-06	15- 49(f), 54(m) years old	16.4	21.7	6.6	6.6	-
			15-19 years old	6.9	12.0	2.9	4.8	-
	(519)	2010-11	15- 49(f), 54(m) years old	36.2	57.4	20.4	33.6	-
			15-19 years old	10.3	24.7	7.0	18.4	-
MIM survey (548)		2009	15-49 years old	-	44.9	-	-	-
Republic of Zimbabwe (530)		2010	0+ years old	-	-	-	-	1.7
		2011	0+ years old	-	-	-	-	1.8
Langhaug (546)		2010	18-44 years old	50 (district with NBCP programme), 36% (comparison)		-	-	-
Cowan (549)		2011	-	50	75	-	-	-
Mabugu (545)		2010	0+ years old	-	-	-	-	1.4
		2011	-	-	-	-	-	1.9
		2012	-	-	-	-	-	1.1
		2013 (Jan-Mar)		-	-	-	-	1.6

DHS: Demographic and Health Survey; f: female; m: male; MIM: Multiple indicator monitoring; NBCP: National behavioural change programme;

2.2.6. Pre-ART care

Despite the fact that the national guidelines on HTC published in 2005 (550) stressed the need to discuss linkage to care following the HIV diagnosis and pointed out that all sites providing HTC should have worked out all the possible linkages in the community to help in the referral, in 2013 linkage to HIV care was still considered poor and a major challenge to tackle (547). The ART programme manager in Zimbabwe pointed out that the major challenges were the fact that the clinics are congested, the distance to the clinic and consequently the high transport cost, competing priorities, insufficient referral information and limited capacity in term of CD4 machines (547).

To the best of my knowledge there are no data at a national level or from single programmes regarding linkage to care in Zimbabwe; three recent systematic reviews did not find any such studies (551-553).

2.2.7. ART initiation and procedures to monitor people on ART

Zimbabwe has released national guidelines on ART since 2005 (227). Those, in line with the 2003 WHO guidelines for RLS (474), were recommending ART for people with CD4 count <200 cells/μL or WHO stage 4 disease or CD4 count <350 cells/μL and WHO stage 3 disease and provision of CTX for all symptomatic people (WHO stage 2, 3 and 4) and/or CD4 count<200 cells/μL.

These were revised in 2010 (228), when the eligibility criteria were modified as follows:

- CD4 count <350 cells/μL, if CD4 count available, otherwise if WHO stage 3 or 4 are present
- all HIV-positive pregnant women with WHO stage 3 or 4 or CD4 count <350 cells/μL
- all TB patients irrespective of CD4 count

In November 2013 the Ministry of Health and Child Care launched new guidelines (229) following the WHO guidelines published in 2013 (280) recommending ART for people with:

- CD4 count <500 cells/μL irrespective of WHO clinical stage, with priority to people with CD4<350 cells/μL
- TB patients co-infected with HIV, HIV-positive pregnant and breastfeeding women (Option B+), patients co-infected with HBV and in serodifferent relationship; all irrespective of CD4 count.

The ART regimens recommended in the Zimbabwe guidelines are summarized in Table 2.12. As in many other developing countries, when ART was rolled-out D4T was part of the first-line, due to its very low cost. Since April 2011, following WHO recommendation in 2010 (277), clinicians in Zimbabwe have been allowed to replace D4T with less toxic drugs, such as TDF in adults. By December 2011, 9.5% of adults and adolescents were switched away from D4T (the target by 2011 was 20%) (530). The preferred first-line regimen is now composed of TDF, 3TC and EFV.

Table 2.12. ART regimen lines recommended in Zimbabwe

Source	Line	Drugs	Notes
2005 (227)	1a	D4T+3TC+NVP	-
	1b	AZT+3TC+NVP	-
	1c	D4T+3TC+EFV	-
	2a	TDF+3TC+LPV-r	-
2010 (228)	1a	TDF+3TC+NVP	Patients on D4T should be moved to this regimen
	1b	AZT+3TC+NVP	Monitor patients for anaemia
	2a	TDF+3TC*+LPV/r	Failing on a AZT-based 1st line regimen *Can be replaced with FTC
	2b	AZT+3TC+LPV/r	on a TDF-based 1st line regimen
	2c	ABC+ddI+LPV/r or ATZ/r	-
	2d	TDF+3TC+AZT+LPV/r or ATZ/r	-
2013 (229)	1a	TDF+3TC+EFV FDC preferred	First choice. If FDC not available dual TDF/3TC and EFV separately
	1b	TDF+3TC+NVP	Pregnant or breastfeeding women already on ART and stable should be continued on current ART regimen. Patients stable on this regimen should continue until national stock up runs out

3TC: lamivudine; ABC: abacavir; ATV/r: atazanavir boosted with ritonavir; AZT: zidovudine; d4T: stavudine; ddI: didanosine; EFV: efavirenz; FDC: fixed-dose combination; FTC: emtricitabine; LPV/r: lopinavir boosted with ritonavir; NVP: nevirapine; TDF: tenofovir;

Once initiated on ART, the patient is seen in the clinic to monitor for ART efficacy and toxicities at 2 and 4 weeks since ART initiation and monthly thereafter for another 3 months and afterwards, if stable, every 3 months. It is recommended that at these follow-up visits the following parameters are monitored: patient weight, WHO clinical stage, development of OIs, FBC (every 6 months), ALT (every 12 months), serum creatinine (every 12 months), and if available CD4 counts (every 6 months). In practice access to CD4 testing, at least between 2007 and 2009, was available mainly in district hospitals or higher level facilities and at other sites which were initiating people on ART (554).

Although the national guidelines mention that the ideal would be to monitor the efficacy of ART by measuring both CD4 count and VL 6 monthly, in practice the access to VL testing is very limited and a study of patients initiating ART between 2007 and 2009 found that more than half of the patients did not have a documented CD4 count at ART initiation (554). The guidelines reference the DART trial, which took place in Uganda and Zimbabwe (555), where it was found that it is safe to clinically monitor people on first-line regimen for toxicities without

routine laboratory monitoring (although it is useful when clinically indicated). Regarding the efficacy monitoring (CD4 count monitoring in this study), they found that it did provide a significant, although small, benefit in terms of disease progression and survival, likely due to the earlier identification of treatment failure and thus more timely switch to second-line. They reported that these benefits on progression, provided by CD4 monitoring, were seen only from the third year on ART, underlining that at least in the first years this is not indispensable. However, they found that in the arm receiving CD4 monitoring only 12% switched with a VL<400 copies/ml compared to 27% in the arm clinically monitored. They determined that a confirmatory CD4 measurement when clinical failure is identified, with confirmed treatment failure only if the CD4 is below 250 cells/μL, could identify 80% of those with VL<400 copies/mL, that therefore are less likely to benefit from switching to second line (556).

While ART is provided for free to patients, the consultation fee and lab-associated cost, like CD4 count, FBC are expected to be paid by the patients (554).

The guidelines defined treatment failure as either:

- clinical failure: new or recurrent WHO stage 3 or 4 after at least 6 months on ART
- immunological: either reduction in CD4 count to pre-ART levels or 80% reduction from the on-ART peak or persistent CD4 count <100 cells/μL (in 2005) or <200 cells/μL (in 2010)
- virological: VL>5,000 copies/mL

It is stressed that efforts to understand whether the patient is adherent should be made and the decision to switch a person to second-line should not be taken lightly.

2.2.8. Roll out of antiretroviral therapy

The ART programme was launched in Zimbabwe in 2004 (530), during a socio-economic crisis which lasted at least until 2009, with very high levels of recession and hyperinflation. At the start, in April 2004, only five sites in the entire country were providing ART and there were shortages of health workers and medical supplies due to the crisis (557). Since 2008 both ART initiation and follow-up of people on ART have been decentralized to lower level facilities (554) and by 2011, 590 sites were providing ART, of which 141 initiating people on ART (530). This corresponded with a massive increase in the number of people who could receive ART, (see Table 2.13), in particular by 2011 Zimbabwe achieved 80% of ART coverage with 476,000 people receiving ART (530).

Table 2.13. Number of people on ART in Zimbabwe

Source	Year	Number of people on ART (thousands)		ART coverage; Eligibility if CD4:	
		All (0+)	Adults	<350 cells/µL	<200cells/µL
Global AIDS Response (530)	2004	8	-	-	-
	2005	24.5	-	-	-
	2006	66.9	-	-	11%
	2007	97.7	-	-	26.5%
	2008	148.1	-	-	-
	2009	219.4	-	-	56.1%
	2010	326.2	298.0	-	-
	2011	476.3	436.2	79.7%	-
Global fund reports (545)	2010	326.2	-	-	-
	2011	401.4	440.0	77%	-
	2012	558.5	514.7	-	-
	2013	593.2	544.2	84%	-

2.2.9. Retention on antiretroviral treatment and adherence

Very limited data are available regarding retention and outcome of patients receiving ART in Zimbabwe. Systematic reviews conducted a few years ago evaluating retention on ART (1;2) did not find any studies conducted in Zimbabwe; more recently a few studies have been conducted, to my knowledge three within ART programmes run by non-governmental organizations (NGOs) (558-560) and one is a nationally representative multi-stage retrospective cohort study of the national ART programme (554) (see Appendix IX). They all reported around 90% retention on ART at 6 months, between 78% (554) and 97% (560) retention at 12 months and between 64% (554) and 75% (559) at 3 years. These results are in line with the estimates on retention in sub-Saharan Africa (1).

The Global AIDS progress report for Zimbabwe published in 2012 reported that in 1997 93.1% were retained on ART at 1 year since ART initiation, 75% in 2009 and 85.7% in 2010 (530). Interestingly the MSF programme in Buhera (560) found that the retention was significantly better in the patients initiated on ART in the health centres and among those referred to the health centres for follow-up on ART compared to the patients in the hospital, highlighting the fact that decentralization could improve retention on ART. Nevertheless it must be borne in mind that those who were referred to the health centres were more likely to be stable than those still in care at the hospital.

Dzangare and colleagues assessed whether clinics in Zimbabwe (17 clinics in 2007, 40 in 2008 and 24 in 2009) were meeting the minimum target of maximum of 20% being LTFU at 1 year since ART initiation, as part of monitoring WHO early warning indicators (561). They found that

in the 8 clinics with information for all three years the proportion of clinics not meeting this target decreased from 70% in 2007 to 33.3% in 2009. The report on drug resistance early warning indicators for 2013, including 74 clinics located across all 10 provinces reported that 23% of the clinics still had levels of retention below 75% and one of them (1.4%) did not collect this information (562).

Adherence to ART in adults living with HIV in Zimbabwe, to my knowledge, has been investigated only by the DART trial (563-565). Systematic reviews on adherence conducted a few years ago (485;566;567) have not found any studies from Zimbabwe. Within the DART trial they initially described the pattern of adherence, using drug possession rate (% of drugs taken between visit based on pill count) categorized as complete (if 100%) or good (≥95%) for monthly intervals (length of time between pharmacy refills) in almost 3,000 participants either in Zimbabwe or Uganda (565). They reported that 90% of the patients had pill counts performed at every visit and that the proportion with good adherence increased over time from 87% at 4 weeks to 94% at 48 weeks, nevertheless only 49% had good adherence at all visits in the first year of ART highlighting the variability of this phenomenon over time.

2.2.10. Virological outcome and development of resistance on first-line regimen

The only source of data which reported on virological outcome in patients receiving ART in Zimbabwe comes from routine cohort monitoring at sentinel sites. This is not surprising given that VL is generally not available. Between 2009 and 2011 these sentinel clinics reported that 10.4% of around 1,000 patients had a VL above 1000 copies/mL at 12 months after ART initiation. They found that after excluding those who had resistance at baseline the proportion that had acquired HIV drug resistance was 8.9% (reported in the "Report on the National HIV Drug Resistance Monitoring at Sentinel sites (2009–2011)" cited by (554)). The nationally representative retrospective study conducted by Mutasa-Apollo and colleagues reported that only 0.2% of patients (over a median follow-up of 1.4 years) had documented treatment failure, based on clinical or immunological monitoring, and were switched to second-line ART regimens (554). This is lower than the treatment failure rate of 2.64/100 PYs (95% CI: 1.73, 3.56) reported by a systematic review for Africa (568) using clinical/immunologic criteria to identify people with treatment failure. A few studies evaluating VF and risk of resistance have included patients from Zimbabwe, but without presenting the analysis by country (398;569).

I could not find any studies which evaluated the outcomes of people on second-line regimens; this is probably due to the fact that not many people have been switched to second-line so far.

2.2.11. Circumcision

As for South Africa, Zimbabwe is one of the priority countries indicated by UNAIDS for scaling up VMC (506), with only 10% of the male population circumcised in 2007 (518). It was estimated that in order to achieve 80% coverage of VMC, Zimbabwe had to conduct around 1.9 million VMCs.

In 2009, a policy on VMC was launched ("Zimbabwe Policy Guidelines on Safe and Voluntary Male Circumcision" cited by (530)) and a pilot programme was rolled out in five sites which were able to circumcise 2801 males (530). Since then VMC has been available for adolescent and adult men through a collaboration between the government and other agencies ("Strategy for safe medical male circumcision scale up to support comprehensive HIV prevention in Zimbabwe." cited by (538)) and in 2010 a five-year strategy for VMC was adopted, involving traditional circumcisers and by conductive community mobilization. This allowed a dramatic increase in the number of men circumcised in 2010 and 2011, but the target is still out of sight. By the end of 2011 only 50,580 VMC (2.6% of the target) were performed (None in 2008, 2801 in 2009, 11176 in 2010 and 36603 in 2011) (509).

A further communication strategy for VMC was developed in 2011 and hopefully it will be able to mobilize the target population for circumcision (530).

2.3. Brief comparison of the HIV epidemic in South Africa and Zimbabwe

South Africa, with an estimated population at the last census (2011) of almost 52 million (434) is four times the size of Zimbabwe (510). Both these countries experienced a dramatic increase in mortality, especially in people aged between 25 and 39 years, mainly caused by the spread of HIV. In Zimbabwe it started in the late 1980 in the rural areas and a decade later in the urban areas (515), while in South Africa it is documented since the end of 1990s (438) and in both countries the peak in mortality was reached in 2005-2006 (438;519).

National household surveys have been conducted in South Africa and Zimbabwe collecting data on self-reported sexual behaviour. The two countries present quite a different profile, however it is not clear whether they do reflect real differences in sexual habits or whether different attitudes in reporting sexual behaviour. In terms of percentage of people who

reported sex before the age of 15: in South Africa among females it remained stable at 5% from 2002 to 2012, while among males it was between 11 and 13% between 2002 and 2008 and it peaked at 17% in 2012 (440); in Zimbabwe, this information was asked to people age 15 to 19 years old and among males it halved from 7.9% in 1994 to 3.6% in 2011, while among females it declined from 5.2% in 1994 to 3.9% in 2011 (519). The condom use at last sex increased markedly in South Africa from 2002 to 2008 especially in young people, where it reached levels of 85% in men, but it then declined in 2012 (440). In Zimbabwe this information was collected only among people 15 to 29 years old and for contacts with non-regular partner, so these two pieces of information are not directly comparable. Here, levels between 60 and 90% were observed among males and between 40 and 90% among females (514). Data on intergeneration sex have been collected in people aged 15-19 years old. This has been found to double in South Africa from 9.6% in 2005 to 19.8% in 2012, due to an increase in intergenerational sex among females (440). Similar pattern was observed in Zimbabwe where it increased by 2-fold from 5% in 2005-06 to 15% five years later (519). In an attempt to assess the level of concurrency, the number of partners in the last year was collected in South Africa and the number of non-regular partners in Zimbabwe. In South Africa, the age group characterized by the higher percentage of people reporting more than one partner is the group aged 15 to 24 years: an increase from 23% in 2002 to 37% a decade later was observed among males while among females it increase from 6% to 9% in the same time frame (440). On the contrary, in Zimbabwe in people age 15 to 29 years old a decline seems to have occurred between the end of '90s and mid-2000 but similarly to South Africa the level reported by males was much higher than that reported by females (20%-60% vs 0-20%) (523).

The HIV epidemics in both Zimbabwe and South Africa are amongst the worst worldwide with an estimated prevalence in people aged 15-49 of 18.8% in South Africa in 2012 (440) and of 14.7% in Zimbabwe in 2011 (526) and 240,000 and 39,000 AIDS deaths in 2012 respectively in South Africa (463) and Zimbabwe (526). This epidemic hit Zimbabwe much earlier than in South Africa: by 1990 the HIV prevalence in ANC was above 10% in Zimbabwe (528) while in South Africa it was still less than 1% (448). In Zimbabwe a decline in HIV prevalence has been observed since mid-1990s both in ANCs and household surveys (519), on the other hand in South Africa HIV prevalence is still increasing (440). This difference in profile is likely to be due to the fact that HIV spread later in South Africa, to the fact that ART, which increases markedly life expectancy of people living with HIV, became largely available when the HIV prevalence has already peaked in Zimbabwe and to the fact that a reduction in sexual behaviour seems to have occurred.

The response to this terrible epidemic came quite late in South Africa, only in 2009 the government finally recognized this as a major plague and finally in 2010-11 the first major achievements were obtained: 95% of women receiving PMTCT, 55% of people in need of ART were receiving it(450). In Zimbabwe there was some initial response, such as the introduction of universal screening for blood and training for health personnel and the introduction of a tax to face the cost of addressing this issue. Unfortunately, a terrible economic crisis hit this country and it was only at the UN General Assembly in 2011 that concrete goals were established.

In order to be able to reach HIV care, first of all people need to be aware of their HIV status. Over the last few years, HIV testing has increased massively: at the last household survey conducted in South Africa in 2012, 65% of the population reported ever testing for HIV and 43% testing in the last year (440), in Zimbabwe at the last DHS conducted in 2011, 36% and 57% respectively of male and female reported ever testing, of which 20% and 34% in the last year (519). However linkage to care remains poor in South Africa and in Zimbabwe no data are available. The eligibility criteria to be eligible for ART differ between the two countries: a threshold of CD4<350 cells/µL is currently used in South Africa (226) while in Zimbabwe this has been moved to 500 cells/µL (229). The coverage of ART was estimated to be 79% in 2011 in South Africa, when considering people with CD4<200 cells/µL as eligible, but only 52% when considering a threshold of 350 cells/µL, while in Zimbabwe using this latter threshold the coverage has been estimated to 80% in 2011 (530). In both countries, programmes reported level of retention around 90% at one year, but the data are not available at national level and very few studies are available for Zimbabwe. Self-reported adherence to the therapy has been observed to be very high in the few programmes which collected this information; however there is evidence that this measure of adherence is biased. Virological response has been reported to be relatively good in South Africa with proportion of the population suppressed at one year since ART initiation up to 96% (307), although levels as low as 66% have been observed (304). At five years levels of suppression as high as 84% were reported (292). As VL monitoring is not available in Zimbabwe data on this piece of information are very rare.

Finally, both countries committed to reach 80% circumcision coverage (507), but by the end of 2011 only 10.2% and 2.6% of the target was reached respectively in South Africa and Zimbabwe (509). Since then VMC campaigns have been launched and in South Africa there is evidence that a large number of men have been circumcised (423).

3. HIV Synthesis heterosexual transmission model

3.1. Introduction

This chapter aims to present in detail the HIV Synthesis transmission model and the method use to calibrate the model to the South African and Zimbabwean HIV epidemics, but first of all it is worth considering which other approaches could have been used to address this PhD research question and what are the main types of mathematical models for infectious diseases. The goal of this thesis is to assess the long term effect on HIV incidence, mortality and spread of resistance of different public health actions to curb the HIV epidemic in South Africa and Zimbabwe. The gold standard type of study to address this question is a randomized controlled trial, but it is not feasible or ethical to conduct trials involving such a large number of people (we evaluated the impact at national level), for such a long length of time and at a very high cost. For this reason, mathematical models are used. They combine epidemiological data with infectious disease theory and assumptions about future circumstances to make projections on the HIV epidemic.

Mathematical models for infectious diseases can be divided in two main categories: deterministic and stochastic models. The former determine what happens on average in a population; therefore, given a set of input parameters, the results are going to be exactly the same, each time the model is run. On the contrary, in the stochastic model chance is incorporated and for each agent (in this case person) in the model there is a certain probability that a person becomes infected and/or move through different stages of the disease, thus given a certain set of parameters the model will provide the range in which an outcome can occur.

Deterministic models are usually compartmental models, which means that the population is divided in subgroups based on whether they are infected with the disease or not, their disease stage, sometimes whether they belong to different risk groups, etc. To determine the dynamic of such models difference or differential equations can be used, the former illustrate the transitions between different compartments, by determining the number of people in a certain compartment at time t, based on the number in that compartment at time t-1. Stochastic models are usually individual-based models, as it is the case for the Synthesis model, which means that the model tracks the infection process for each individual.

Mathematical models can be divided as well in dynamic transmission models, if they include the process of people having contact between each other's (and thus risk of transmitting the disease) and static models, if they do not model contacts and the force of infection is predetermined. In addition, there are network models which explicitly model the network of contacts.

The HIV Synthesis heterosexual transmission model is an individual-based stochastic model of heterosexual transmission, progression and treatment of HIV infection. The progression part of the model was originally created by Phillips and colleagues to reconstruct the HIV-infected population in the UK (570) and it was then developed further to include the dynamic process of HIV transmission and to be able to simulate a generalised heterosexual HIV epidemic (571). The aim of this model is to capture all the elements (e.g. sexual risk behaviour, HIV testing, PHI, VL, CD4 cell count, use of ART, adherence, resistance, drug failure, drug interruption, LTFU, occurrence of AIDS, non-AIDS death, etc.) for which we have a reasonable understanding of the underlying processes, based on data from clinical trials and observational studies, although not always from a sub-Saharan African setting.

When I started working on the Synthesis model, it was already a dynamic model simulating a generalized heterosexual HIV epidemic. However, both the progression and the transmission components have been developed further since the first publication, with my input, due to a complete re-evaluation of every parameter value and also some small additions to the model structure. In particular, I calibrated the model to specific settings such as South Africa and Zimbabwe and I developed sections of the model needed to address the questions of my research interest. I introduced the process of HIV testing in women attending ANC and for the general population; for the version of the model calibrated to Zimbabwe an age and gender-specific HIV testing process has been included, with the possibility of testing using ST. Regarding the pathway of care, I amended the model to capture all the steps HIV patients needs to go through and to be able to prepare outputs in the metrics agreed by the HIV Modelling Consortium. In addition, I added circumcision in the model, as VMC was demonstrated to be an effective prevention tool and both South African and Zimbabwe are now rolling it out. Finally I included in the Synthesis model the possibility of using PrEP, its efficacy in reducing the risk of HIV acquisition and also the risk of acquiring resistance in people who are infected with HIV while on PrEP. Because I contributed in developing the full model and I contributed to manuscripts published in peer-reviewed journals, sections of this chapter are part of the supplementary material of papers published in the literature on the Synthesis heterosexual transmission model (571-573).

In brief, the HIV Synthesis transmission model generates the life course of a random sample of all adult individuals in a population, for whom data are updated in 3 month periods. Most of the mathematical models are updated daily, in order to better capture concurrency and thus the instantaneous risk of transmission. Unfortunately, I could not reduce the time step, because of the time length the model takes to produce simulations. This certainly represents a limitation, however especially once the epidemic is established the model has been demonstrated to provide reasonable estimates. Each person in the model is simulated from the age of 15 years (before this age the only variable updated is age), when they are assumed to be potentially sexually active and they are followed until either death, or to any given calendar year of interest. For each simulated person, the model generates variables such as age, gender, calendar date, circumcision, whether they had an HIV test and variables characterizing the sexual behaviour: number of condom-less sex short-term (e.g. casual) partners and presence of a condom-less long-term (e.g. primary) partner. For HIV-infected people the main variables modelled are: PHI (a period of raised infectivity of 3 months duration), VL, CD4 cell count, presence of specific DRMs, HIV diagnosis, whether the person has been linked to care and retained in pre-ART care and after initiating ART, the antiretroviral regimen the person is currently on, adherence to ART and risk of AIDS and death. The progression model has been shown to provide a generally close fit to observed data relating to the natural progression and therapy outcomes (570;574;575). Given the richness of data in the literature on the progression of the disease in absence of ART and the impact of treatment on the progression and the use of objective measures to measure these phenomenons, I am quite confident about the parameters related to it. On the contrary, data on sexual behaviour are less often collected and although national survey are now asking information on this regard, there is evidence that they are heavily affected by desirability bias. Therefore I feel more uncertain about the parameters on sexual behaviour included in the Synthesis model.

3.2. Demographic model

Heterosexual transmission is the predominant mode of HIV transmission in both South Africa (452) and Zimbabwe (530). The epidemic is assumed to have started in 1989, close to when the first heterosexual AIDS cases were reported in South Africa (1987)(445) and Zimbabwe (1985)(525). The model runs for 45 years, with variables updated every 3 months. Each run of

the model simulates a cohort of 100,000 individuals, of which approximately 34,000 alive and aged between 15 and 65 years in 1989.

3.2.1. Determination of age in 1989 and general population death rates

The initial age and gender distribution for South Africa (see Table 3.1) is determined on the basis of the South African Census conducted in 1996 (576), because this is the first South Africa census where information was collected for all of South Africa. 48.2% of the South African population is assumed to be male. For Zimbabwe the distribution has been chosen so that it reflects the age distribution in 2015, when I want to evaluate the introduction of ST (see Chapter 8). The age distribution when the HIV epidemic is assumed started does not perfectly match with the age distribution reported for 1995 (577)(The closest in time age distribution I could find). I will modify this for future work on the Zimbabwe model.

The table below shows the age distribution of people within gender. The actual age of a person in a given a 10 year age group in 1989 is determined by sampling from a Uniform distribution. This means that, although it is taken into account the fact that the younger 10-year age groups represent a greater proportion of the population than the older age groups, due to increasing death rate as age increases (when not considering infant mortality), the model does not take into account the fact that the cohort of people aged 15 years old is going to be slightly bigger than the cohort of 16 years old, etc.. This is clearly an approximation; however it allows capturing the gender-specific age group distribution.

Table 3.1. Model assumptions on population age distribution

Age group	South Africa		Zimbabwe	
	Probability of being in age group in 1989	Distribution of people aged 15-65 years	Probability of being in age group in 1989	Distribution of people aged 15-65 years
Males				
(-35 - -24)	-	-	0.16075	-
(-25 - -14)	-	-	0.14725	-
(-15 - -4)	-	-	0.13375	-
(-5 – 4)	-	-	0.12025	-
(5 - 14)	-	-	0.10675	-
(-30 - 14)	0.733	-	-	-
(15 - 24)	0.091	0.34	0.09325	0.28
(25 - 34)	0.072	0.27	0.07975	0.24
(35 - 44)	0.067	0.20	0.0625	0.19
(45 - 54)	0.053	0.12	0.05275	0.16
(55 - 64)	0.019	0.07	0.03925	0.12
Females				
(-35 - -24)	-	-	0.16075	-
(-25 - -14)	-	-	0.14725	-
(-15 - -4)	-	-	0.13375	-
(-5 - 4)	-	-	0.12025	-
(5 - 14)	-	-	0.10675	-
(-30 - 14)	0.716		-	-
(15 - 24)	0.094	0.33	0.09325	0.28
(25 - 34)	0.077	0.27	0.07975	0.24
(35 - 44)	0.054	0.19	0.0625	0.19
(45 - 54)	0.034	0.12	0.05275	0.16
(55 – 64)	0.025	0.09	0.03925	0.12

Those distributions are chosen to reflect the growth in population seen in both countries, more dramatic in Zimbabwe than in South Africa (433;510;576;578). In the table above it is indicated that for Zimbabwe the cohort of people entering the age group 15-24 is increasing over time (for example the probability of being in the group of age indicated as minus 35 to minus 24, which are going to be age 15-24 in 2039, is higher than those age minus 25 to minus 14) (see Appendix VIII). This is not the case for South Africa, where it is assumed the number of people entering the age group 15 to 24 is constant, likely due mainly to an improvement in survival to 15 years of age, rather than increase in fertility (See Appendix IV).

However the ART availability and other health intervention are prolonging life expectancy in South Africa increasing the population size.

The only variable that is modelled and updated up to reaching the age of 15 is age itself. The "youngest" person in 1989 is age -30 for South Africa (i.e. will be born in 2019 and reach age 15 in 2034, when the modelled period ends) and -35 for Zimbabwe. This is due to the fact that the introduction of ST in Zimbabwe is assumed to occur in 2015, while the interventions began in South Africa in 2013.

In each point in time, each individual (whether HIV-positive or not) has an underlying age and gender specific probability of dying (see Table 3.2).

Table 3.2. Assumptions regarding age and gender specific death rates (per 1,000 person-years) in people without HIV based on (437;516)

Age group	Death rates (per 1,000 person-years)	
	Males	Females
15-19	2	1.5
20-24	3.2	2.8
25-29	5.8	4.0
30-34	7.5	4.0
35-39	8.0	4.2
40-44	10.0	5.5
45-49	12.0	7.5
50-54	19.0	11.0
55-59	25.0	15.0
60-64	35.0	21.0
65-69	45.0	30.0
70-74	55.0	38.0
74-79	65.0	50.0
80-84	100.0	70.0
85 or more	400.0	150.0

These underlying age and gender specific death rates reflect broadly those estimated in South Africa in 1997 (437) (see 2.1.1.3) and in Zimbabwe in 1994 (516) (see 2.2.1.3), before the significant impact of HIV-related deaths. HIV-infected people will have an additional probability of dying from HIV related causes, as described in section 3.12.3.

3.3. Model of sexual behaviour and risk of HIV acquisition

In this model, the sexual behaviour is characterized by two variables representing, respectively, the number of "short-term" or "casual" partners a person has sex with in the 3 month period without using condom, from this point onwards called condom-less short-term (CLST) partners and whether the person has a current "long-term" or "main" partner the person has sex with without condom in each 3 month period, referred to as condom-less long-term (CLLT) partner. The status of CLLT partners is tracked over time (i.e. if they are infected, diagnosed, on ART, etc.). CLST partners are not tracked over time, in that if a person has a CLST partner in time period *t* who is infected with HIV, this is independent of the probability that any short-term partner in time *t+1* is infected with HIV.

This model does not distinguish between whether a person had sex with a person using condom effectively or did not have sex, because it assumes that if correctly used condoms are 100% effective in preventing HIV transmission. Condom break can be treated as no condom use. It is assumed that HIV transmission only takes place via condom-less sex, therefore only partners with whom subjects have sex without using a condom are taken into account.

The risk behaviour is mainly determined by the level of condom-less sexual contacts required to produce an epidemic as described. Although some data on sexual behaviour for both countries are available (452;516-520;579), these data are often affected by social desirability bias and recall bias. Sexual risk behaviour tends to be under-reported particularly in women and higher levels of behaviour have to be assumed to generate epidemic of the proportions observed (443;452;518;519). In addition, even if these data were not biased, it would be impossible to directly calibrate the Synthesis model (i.e. simply use values from the data as parameter values in the model) to these data because the number of sexual partners people have condom-less sex with is not usually collected.

Both, the HSRC surveys for South Africa and the DHSs for Zimbabwe collect information on age of sexual debut among people aged 15-24 years and they reported that maximum around 10% had sex before the age of 15 years (see sections 2.1.2.1 and 2.2.2.1.) and no data are available on the age of first condom-less sex act. For simplicity the model assumes the minimum age of sexual debut is 15 years old. Since 2005 both HSRC surveys in South Africa and DHSs in Zimbabwe have collected data on age difference between sexual partners in people aged 15 to 19 years (see sections 2.1.2.3 and 2.2.2.5). In this model the CLLT partner is assumed to be in

the same 10 year age-category, while CLST partners can belong to different age groups, as illustrated in the age-mixing matrix (see Table 3.6 at page 154).

The parameter values relating to sexual behaviour are therefore derived by running the model several times sampling the parameters for the sexual behaviour and transmission rate from distributions (see Appendix XI), compare the model outputs to observed data, including HIV prevalence (see section 3.13), and select the set of parameters which minimize the distance between the simulations produced by the Synthesis model and the data from the literature.

In this model five parameters determine the sexual behaviour:

- the relative average sexual behaviour (*newp_factor*)
- the skewness in the distribution of number of condom-less partners (determined by *swn* and *highsa*)
- the rate with which new CLLT partnerships are formed (*eprate)*,
- the proportions of people who have a lifetime reduced likelihood of CLST partners (the proportion who experience very low sexual behaviour, *p_rred_p*)

Several structures for the risk behavioural model (RBM) (combination of distribution of parameters) have been identified and the distributions indicated in Appendix X.

3.3.1. Determination of number of condom-less short-term partners at period t

The numbers of CLST partners is assumed to depend on gender, age, propensity to be sexually active, experiencing an AIDS defining condition, being diagnosed with HIV and change in risk behaviour in the general population.

In a given 3-month period, the number of CLST partners is generated at random, according to which of four risk behaviour groups the person was in for the previous period. The four groups are:

- zero CLST partners,
- one CLST partner,
- Medium: 2-10 CLST partners,
- High: 10 or more CLST partners

The initial distribution is sampled among the distributions indicated in Appendix X Table A4 (page 390). Each individual can transit from one of these categories, i.e. partner group i at time $t-1$, to partner group j based on transition probabilities p_{gija}, given by:

$$p_{gija} = \frac{f_{g,i,j} \times r_{g,a}}{\left(f_{g,i,1} + \sum_{j=2}^{4}\left(f_{g,i,j} \cdot r_{g,a}\right)\right)}$$

Where:

- g = 0, 1 for males, females, respectively,
- a = 1-10 for age groups 15-, 20-, 25-, 30-, 35-, 40-, 45-, 50-, 55-, 60-, respectively.
- i=1-4 for the risk behaviour group 0, 1, 2-10, ≥10 CLST partner at time $t-1$,
- j= 1-4 for the risk behaviour group 0, 1, 2-10, ≥10 CLST partner at time t

Values of r_{ga} , determining relative level of sexual risk activity with CLST partners and f_{gij}, the values determining probability of transitioning between CLST partner risk behaviour groups are given respectively in Table 3.4 at page 153 (table A4 at page 390 in Appendix X for alternative RBMs) and Table 3.5 at page 153 (table A5 at page 391 in Appendix X for alternative RBMs), respectively, and if j=1 then r_{ga}=1.

Values of r_{ga} are modified at time *t* by the following factors:

- 0.01 if the subject belongs to that subset of people who experience only very low sexual risk activity (i.e. with CLST partners) in their life (Random 35% of men and 50% of women, *p_rred_p;* See table A6 at page 393 in Appendix X for values of alternative RBMs)
- 0.2 if the subject has a current AIDS defining disease
- *0.*83 (the actual value is *ch_risk_diag_newp*, sampled from the distribution indicated in the Appendix X) if the subject has been diagnosed with HIV in the last 6 months and by its square root afterwards.
- The change in risk behaviour in the general population, which has been observed in both South Africa and Zimbabwe (and needs to be invoked in order to explain stabilisation and decline in incidence), is parameterized slightly differently for the two countries (this does not reflect a perceived difference in the two epidemics but rather choice between two alternative parameterization approaches):
  - In South Africa it is assumed it occurred in two phases: the first started between 1992 and end of 1998 (*date_ch_risk_beh*, the value is sampled from a Uniform distribution) and finishes between 1999 and end of 2005 (*date_ch_risk_beh_2*,

the value is sampled from a Uniform distribution), the second phase finished between 2006 and end of 2009 (*date_ch_risk_beh_3*, the value is sampled from a Uniform distribution). The rate of annual decrease in risk behaviour for the first (*rate_ch_risk_beh*) and the second phase (*rate_ch_risk_beh_2*) are sampled from the distribution indicated in the Appendix XI, up to a maximum reduction of 0.95. Afterwards no change in risk behaviour is assumed (apart from changes as indicated above due to HIV diagnosis, etc.).

  - In Zimbabwe a certain threshold high HIV prevalence triggers the change in sexual behaviour (See section 3.3.2).

- factor which is sampled in each simulation and changes the overall average level of condom-less sex with CLST partners (*newp_factor*)

Actual transition probabilities between risk behaviour groups for each individual were determined by random sampling. For the first two groups the number of partners in the period is given (i.e. no CLST partners, 1 CLST partner, respectively). When a person was in the medium CLST partners group (2-9 CLST partners in a 3 month period), the number of partners is determined by sampling from a Poisson distribution with mean 1.5 for South Africa and 4.5 for Zimbabwe (parameter called *highsa*). When the transition is to > 10 CLST partners the number of partners is determined by sampling from a Poisson distribution with mean 2 and multiplied by the parameter *swn* (the value is sampled from the distribution indicated in the Appendix XI) that determine the skewness of this distribution.

3.3.2. Determination of having a condom-less long-term partner at period t

As for short-term partners, only condom-less sex long-term partnerships are modelled. Thus if a person has a long-term partner but condoms are used on all occasions of sexual intercourse in a specific 3-month period then this is not counted as having a CLLT partner for that period.

In 1989, before any population level reductions in risk behaviour and without widespread availability of condoms, around 60% of the population is assumed to have a CLLT partner (See Appendix X Table A8 at page 394 for details). Data from the South African census in 2001(580) report that around 40% of the adult population was married and 5% cohabiting but not married, while in Zimbabwe in 1989, 63% of the population was considered married (520).

At each period, people with no current CLLT partner have age-dependent probabilities of starting having sex without using condom with a long-term partner as indicated in Table 3.8 at page 154 (Appendix X table A8 at page 394 for alternative RBMs). This can be due to (re-)starting having condom-less with an existing long-term partner or starting a new partnership which involves condom-less sex.

At the time a CLLT partnership is started, it is classified into 3 duration groups, each with a different tendency to endure. The percent of people in each group is dependent on age and is shown in

Table 3.7 (page 154); all the age groups have a 30% chance of having a CLST partnership of the shortest duration considered, but the older they are the less likely they are to have the highest probability of continuing the relationship (category 3).

The status of the partner is not directly simulated. If the subject in the cohort simulated dis the relationship end and if the partner dies, this will be taken care by the length of relationship and by the fact that that the proportion of partnership formed by partners is balanced to the proportion of partnerships formed and ending by the subjects in the cohort simulated.

At time period *t*, for people with a CLLT partner, the probability of the partnership continuing is:

- $1-(0.25/ch\_risk\_beh\_ep)$ if duration category is 1,
- $1-(0.05/ch\_risk\_beh\_ep)$ if duration category is 2,
- $1-(0.02/ch\_risk\_beh\_ep)$ if duration category is 3

Where *ch_risk_beh_ep* is a parameter conveying the population level change in sexual behaviour with long-term partners that can occur (distribution indicated in the Appendix XI).

In the South African epidemic, the date at which it is assumed a change in sexual behaviour in the population initiated (condom became more widely available) is indicated by the parameter *date_ch_risk_beh.* Before this date the parameter *ch_risk_beh_ep* assumes value of 1. After *date_ch_risk_beh,* the duration of these condom-less sex relationships is reduced, if *ch_risk_beh_ep* assumes value <1 (see distribution in Appendix XI).

In the Zimbabwean model, the change in sexual behaviour occurs at a certain date, triggered by an HIV prevalence above a certain threshold (sample from a Uniform distribution between 0.1 and 0.4, the parameter is called *prev_threshold_rb_change*).

Further, the probability of having a CLLT partner is reduced by a factor *ch_risk_diag* in the 3 month period after a CLLT partner's diagnosis, if a CLLT partner has HIV and is diagnosed (see distribution in Appendix XI).

3.3.3. Determination of number of condom-less short-term partners who are HIV-infected at time t

For each CLST partner that a subject has at time *t*, the probability that the partner is infected is calculated. This is dependent on the prevalence of HIV in those of the opposite gender, taking consideration of age mixing. If the subject is of gender *g* and age group *a*, then for each CLST partner the first step is to determining by random sampling the age group of each given CLST partner, $\tilde{a}$ (in fact, for simplicity, all CLST partners at time *t* are assumed to be in this same age group). The gender and age mixing probabilities (i.e. the proportion of CLST partnerships formed by men in age group a_m which are with females of age group a_f ($z_{am,af}$) and the proportion of CLST partnerships formed by females in age group a_f which are with men of age group a_m ($z_{af,am}$)) used to determine this are given by values in Table 3.6 (page 154).

Then, for the given partner (of gender *1-g* and age group ,$\tilde{a}$), the probability that the partner is infected is then given by:

$$b = P\left(h_{g,a,t} = 1 \middle| x = 1 - g, agep = \tilde{a}\right) = \frac{\sum_i S_i L_{\tilde{a},1-g,t-1,i}}{\sum_i L_{\tilde{a},1-g,t-1,i}}$$

Where $\begin{cases} S_i = 1 \; if \; subject \; is \; HIV \; positive \\ S_i = 0 \; if \; subject \; is \; HIV \; negative \end{cases}$

and:

- $h_{g,a,t}$ is the HIV status (1=yes, 0=no) of the CLST partner of a subject of gender *g* and age *a* at time t
- *x* is the gender of the CLST partner, which is always the opposite, given the Synthesis model include only heterosexual relationships
- $\tilde{a}$ is the age group of the CLST partner

- $L_{\tilde{a},1-g,t-1,i}$is the number of CLST partnerships had by person *i*, of age group $\tilde{a}$ and gender *1-g* in time period *t-1*
- *i* is summed over all people of gender 1-g and age strata $\tilde{a}$

The numerator is the total number of CLST partnerships had by people HIV-positive of the opposite gender in age group $\tilde{a}$ at time *t-1*, while the denominator is the total number of CLST partnerships had by people of the opposite gender in age group $\tilde{a}$ at time *t-1* (regardless of HIV status).

Since I assume that all CLST partners at time *t* are from this same age group, the total number of infected CLST partners that the subject *i* has at time *t*, $L_{i,t,h=1}$, is then given by:

$$L_{i,t,h=1} = Min\big(Poisson\big(b_t * L_{i,t}\big), L_{i,t}\big)$$

The distribution of numbers of partners by age and gender, before introduction of HIV, is illustrated for one example epidemic in Table 3.10 (page 156) and Table 3.11 (page 156).

Apart from the age mixing, the sexual contacts are assumed to be practicly random mixing because there is not a higher likelihood of people with a higher number of short-term partners to have relationships with people with a higher level of partnerships and therefore more likely to have HIV.

3.3.4. Determination of probability that a condom-less long-term partner is HIV-infected at time t

E_t indicates whether the subject has a CLLT partner at time *t* ($E_t = 1$ means that the subject has 1 CLLT partnership at time *t*, $E_t = 0$ that the subject does not have CLLT partnership at time *t*).

H_t indicates whether the subject has a CLLT partner at time *t* who is infected with HIV ($H_t = 1$ if infected with HIV, else H_t = 0). A long-term partner at time *t* can be infected either because:

i. a new CLLT partnership has been formed and the partner was already infected with HIV,
ii. because a CLLT partner at *t-1*, which has remained a CLLT partner at time *t*, has become infected with HIV, or

iii. because a CLLT infected partner has remained as a CLLT partner.

For (i): $H_t = 1$ if $L_{i,t-1,h=1} \geq 1$ (i.e. if the subject had at least one CLST partner at time *t-1* who was infected with HIV, then it is assumed that the new CLLT partner at time *t* is infected)

For (ii): The probability that a CLLT partner of a subject of age group *a* and gender *g* becomes infected is dependent first of all on whether the long-term partner is "monogamous" (i.e. this is the only condomless relationship, long-term or short-term, the long-term partner has) or not. Based on the age and gender of the partner, it is determined whether the long-term partner is monogamous by sampling from a Binomial distributions with probability the proportion of people with monogamous relationships (only one long-term partner and no short term partners at time t).

If the long-term partner is not monogamous, the probability of becoming infected with HIV is derived from the HIV incidence at *t-1* for age group *a* (it is assumed the CLLT partner belong to the same 10 year age group) and gender 1-g among the sexually active population, either with a CLLT partner or at least one CLST partner, indicated as $i_{a,(1-g),(t-1)}$ (which is given by the number of subjects newly infected in age group at time *t-1* divided by the number of HIV-uninfected subjects in age group at *t-1*, who had condom-less relationships, either CLLT or CLST)

$$\begin{cases} H_t = 1, & U < i_{a,(1-g),(t-1)} \text{ where } U \text{ randomly sampled from } Uniform(0,1) \\ H_t = 0, & \text{otherwise} \end{cases}$$

If the long-term partner is monogamous, (s)he can be infected only from the subject the relationship is with and this is determined by taking into account the VL of the subject and applying the probability of transmission listed in section 3.3.5.

In order to maintain the balance, for each gender, between the number of uninfected people with a CLLT partner who is infected, and the number of infected people with a CLLT partner who is uninfected, this incidence $i_{a(1-g)(t-1)}$ is modified at time *t* depending on the degree of balance at time *t-1*.

For (iii): If $H_{t-1} = 1$ and $E_t \geq 1$ then assign $H_t = 1$

3.3.5. Determination of the risk of infection from a condom-less short-term partner

For each HIV-infected CLST partner of a subject of gender *g* and age group *a*, the VL group *v* of the partner is obtained by sampling from the VL distribution of those of the opposite gender. Thus I sample from Uniform(0,1), where the probability of the partner having VL in group *v* is given by:

$$\frac{\sum_i S_i L_{1-g,t-1,i,v}}{\sum_{v,i} S_i L_{1-g,t-1,i,v}}$$

where the numerator is the total number of CLST partnerships had by HIV-infected subjects in VL group *v* and the denominator is the total number of CLST partnerships had by HIV-infected subjects (in any VL group).

Table 3.3 shows the rate of transmission per 3 months, t_v, by VL group of the infected partner, *v*.

Table 3.3. Probability of transmission per 3 month period assumed in the model (43)

Viral load group of the partner (v)	**t_v**
< 2.7 log copies/mL	Normal (*tr_rate_undetec_vl*,0.000025)
2.7-3.7 log copies/mL	Normal (0.01,0.0025)
3.7-4.7 log copies/mL	Normal (0.03,0.0075)
4.7-5.7 log copies/mL	Normal (0.06,0.015)
≥5.7 log copies/mL	Normal (0.1,0.025)
Primary infection	Normal (*tr_rate_primary*,0.075)

The probabilities of transmission indicated in Table 3.3 are based on the estimates by Hollingsworth et al. (43) and are the rate of transmission per 3 months from a CLLT partner. Realization of whether the subject is infected by each CLST partner is determined by sampling from Uniform(0,1). These probabilities are increased by:

- *fold_tr_newp* fold, if it is a CLST partnership due to the assumed lower number of sex acts
- *fold_change_w* fold for female subjects aged ≥ 20 years
- *fold_change_yw* fold for women aged < 20 years
- *fold_circ* fold, if the subject is a man who is circumcised (420-422).

- *fold_change_sti* fold, if the person has an existing STI. The risk of a new STI in any one three month period is given by the number of CLST partners divided by 20 (or 1 if > 20 CLST partners)) (581-583).

See distribution of the parameters mentioned in Appendix XI.

Prevalence of circumcision in men (parameter *prev_circ*) is assumed to be 42% in South African (508) and 10% in Zimbabwe (518), and it is assumed VMC is rolled out between 2008 (this parameter is indicated as *mc_int*) and the end of 2012, with an annual increase in the probability of having VMC of *incr_anprob_circ*, in men not diagnosed with HIV, to give a number of men with VMC which reflects its roll-out (509).

Uncertainty in the transmission rate for different VL groups (except for the rate of transmission in PHI, and the rate of transmission when plasma VL is < 500 copies/mL) is incorporated by sampling for each epidemic (run of the model program) the parameter *fold_tr* (See distribution in Appendix XI), by which the transmission rate is multiplied. Uncertainty in the rate of transmission during PHI and when plasma VL < 500 copies/mL is incorporated by sampling respectively a value of the parameter *tr_rate_primary* and *tr_rate_undetec_vl* for each epidemic (See distribution in Appendix XI).

I assume that super-infection can occur (i.e. a person can be re-infected with HIV with consequent risk of acquiring new mutations) (396), in the same way as HIV infection occurs in the first place.

3.3.6. Determination of the risk of infection from a condom-less long-term partner

Infected CLLT partners at time *t* are classified by whether they are in PHI (if infection occurred at time *t-1*), whether they are diagnosed with HIV, whether they are on ART, and whether their current VL is < 2.7 log copies/mL.

The proportion of CLLT partners with HIV who have HIV diagnosed at time t, δ_t is determined with reference to the difference,d_{t-1}, in the proportion of subjects with HIV who are diagnosed with HIV, $\frac{\sum_i D_{i,t-1} T_{i,t-1}}{\sum_i T_{i,t-1}}$ and δ_{t-1};

$$d_{t-1} = \frac{\sum_i D_{i,t-1} T_{i,t-1}}{\sum_i T_{i,t-1}} - \delta_{t-1}$$

Where, $\sum_i D_{i,t-1} T_{i,t-1}$ is the total number of subjects diagnosed with HIV at time *t-1* and $\sum_i T_{i,t-1}$ is the total number of subjects with HIV (diagnosed and undiagnosed) at time *t-1*.

For the model calibrated to Zimbabwe

$$\begin{cases} \text{if } 0 < d_{t-1} \leq 0.05 \text{ then } \delta_t = 0.4 \\ \text{if } 0.05 < d_{t-1} \leq 0.10 \text{ then } \delta_t = 0.5 \\ \text{if } 0.10 < d_{t-1} \leq 0.15 \text{ then } \delta_t = 0.9 \\ \text{if } 0.15 < d_{t-1} \text{ then } \delta_t = 0.95 \end{cases}$$

For the model calibrated to South Africa $\{\text{if } d_{t-1} > 0 \text{ then } \delta_t = d_{t-1}$

The proportion of those diagnosed who are on ART and the proportion of those on ART who have VL<2.7 log copies/mL are determined in a similar manner. In this way the proportions diagnosed with HIV, on ART, and with current VL<2.7 log copies/mL are kept similar for the CLLT partners as in the simulated subjects themselves.

Risk of infection from a CLLT infected partner is determined by sampling from a Normal(tr_rate_primary, 0.0752) if the CLLT partner is in PHI (i.e. infected at t-1), Normal(tr_rate_undetec_vl, 0.0000252) if the CLLT partner has VL <2.7 log copies/mL, and Normal (0.05, 0.01252) otherwise (See values and distributions of the parameters in Appendix XI).

3.3.7. Transmitted resistance

Distinction is made for each mutation as to whether it is only present in minority virus, and thus assumed non-transmissible, even if VL is high, or if it is present in majority virus (584;585). The presence or absence of resistant mutations does not influence the infectivity of a person, for a given VL. For a newly infected person, the probability that the source partner has resistant virus in the majority circulating virus is determined by the prevalence of resistance among those (stratified by type of partnership) at that VL level, taking into account number of partnerships formed.

In other words, for a subject infected by a person in VL group *v* the probability of a resistance mutation being present in the infected person is given by:

$$\frac{\sum_i V_{i,t-1} R_{i,t-1}}{\sum_i V_{i,t-1}}$$

$R_i = 1$ if the person has at least one DRM present in majority virus, 0 otherwise, and V_i assumes value of 1 if the person belongs to VL group *v*.

The numerator is the total number of HIV-infected people with VL group *v* and with at least one DRM present in majority virus and the denominator is the sum over all HIV-infected subjects in VL group *v*. Again, realization of whether the subject is infected by a person with at least one DRM in majority virus is determined by sampling from Uniform(0,1).

For subjects infected from a source partner with a DRM, the probability that a specific mutation, *m*, is present in the source is given by:

$$\frac{\sum_i M_{i,t-1}}{\sum_i R_{i,t-1}}$$

Where M_i assume value 1 if the patient has a specific DRM *m* (if M_i =1, by definition R_i=1).

The numerator is the total number of HIV-infected subjects with DRM *m* present in majority virus and the denominator is the total number of HIV-infected subjects with at least one DRM in majority virus.

It is not assumed that all DRMs present in majority virus in the source partner are established in the circulating virus of the newly infected person. If a given DRM, *m*, is present in the source partner, the probability that the mutation is both transmitted and survives in the subject (i.e. that its presence will affect future response to drugs for which the mutation confers reduced sensitivity) is mutation specific, as shown in Table 3.9 (page 155).

We consider uncertainty in the extent to which TDR mutations are effectively immediately lost (even from minority virus) by sampling from a distribution for parameter *res_trans_factor* (See distribution in Appendix XI).

3.3.7.1. Loss from majority virus of transmitted mutations

Once the mutation is transmitted and established in the new host, there is a probability per 3 months of loss of persistence of TDR mutations from majority virus to minority virus (same for

each mutation) *rate_loss_persistence* (See distribution in Appendix XI). This assumption is based on the estimate by Castro and colleagues (386).

Table 3.4. Values of r_{ga} (age and gender-specific factor determining relative level of sexual risk activity)

Age group	Males (g=0)	Females (g=1)
15-	0.65 (0.6 in Zimbabwe)	1.50 (1.60 in Zimbabwe)
20-	0.65 (0.6 in Zimbabwe)	1.50 (1.60 in Zimbabwe)
25-	1.00	1.00
30-	0.80	0.80
35-	0.65	0.50
40-	0.50	0.35
45-	0.40	0.10
50-	0.35	0.05
55-	0.25	0.04
60-	0.15	0.02

Table 3.5. Values of f_{gij} (values determining probability of transitioning between condom-less short-term partner risk behaviour groups)

CLST partners group in period t-1 (i)	CLST partners group in period t (*j*)			
	0 (j=1)	1 (j=2)	Medium (2-9) (j=3)	High (≥10) (j=4)
			Poisson*	Poisson (mean of 2*swn)
Males (g=0)				
0	0.89	0.08	0.03	0.00
1	0.80	0.15	0.05	0.00
Medium (2-9)	0.35	0.27	0.38	0.00
High (≥10)	-	-	-	-
Females (g=1)				
0	0.93	0.05	0.02	0.00025
1	0.86	0.11	0.03	0.0005
Medium (2-9)	0.54	0.08	0.38	0.001
High (≥10)	0.05	0.05	0.10	0.80

CLST: condom-less short-term; *mean of 1.5 for South Africa, 4.5 for Zimbabwe;
The values reported in the table above refer to the risk behavioural model more often used. Different risk behavioural model have been considered (see Appendix X, table A5 391)

Table 3.6. Sexual mixing by age and gender.

The proportion of condom-less short-term partnerships formed by men in age group am which are with females of age group af ($\mathbf{z}_{\mathbf{a_m},\mathbf{a_f}}$) and the proportion of condom-less short-term partnerships formed by females in age group af which are with men of age group am ($\mathbf{z}_{\mathbf{a_f},\mathbf{a_m}}$)).

		Females				
		Age group (a_f)				
Males	**Age group (a_m)**	15-24	25-34	35-44	45-54	55-64
	15-24	0.865	0.11	0.025	0.00	0.00
	25-34	0.47	0.43	0.10	0.00	0.00
	35-44	0.30	0.50	0.20	0.00	0.00
	45-54	0.43	0.30	0.23	0.03	0.01
	55-64	0.18	0.18	0.27	0.27	0.10
		Males				
		Age group (a_m)				
Females	**Age group (a_f)**	15-24	25-34	35-44	45-54	55-64
	15-24	0.43	0.34	0.12	0.10	0.01
	25-34	0.09	0.49	0.30	0.10	0.02
	35-44	0.03	0.25	0.34	0.25	0.13
	45-54	0.00	0.00	0.05	0.25	0.70
	55-64	0.00	0.00	0.00	0.10	0.90

Table 3.7. Percent of newly formed condom-less long-term partnerships.

These are classified into each of three duration groups, each of which has a different tendency to endure (higher class, more durable).

	Duration group		
Age	**1**	**2**	**3**
15-44	30%	30%	40%
45-54	30%	50%	20%
55-64	30%	70%	0%

Table 3.8. Probability of starting a condom-less long-term partnership per 3 months

		South Africa	**Zimbabwe**
Age group partners	15-	0.07	0.1
	25-	0.09	0.1
	35-	0.035	0.1/2
	45-	0.035	0.1/3
	55-	0.02	0.1/5

Alternative sexual behaviour model.

In addition, alternative sexual behaviour structures have been developed (see Appendix X), including one where no woman or man has more than 10 CLST partners in a 3 month period; (so this means that I am then considering an epidemic in which there are essentially no sex workers). In the main sexual behaviour model a small number of women have very high number of CLST (≥10), while this is assumed to be very rare for men (See Table 3.10 at page 156).

Table 3.9. Table of probabilities that for a given mutation present in the source partner the mutation is both transmitted and survives in the subject.

They are based on evidence from studies comparing distribution of resistance mutations between treated and antiretroviral naïve populations; e.g. (346;586).

	Probability that for a given mutation the source partner the mutation is both transmitted and survives in the subject	
Mutation present	**South Africa**	**Zimbabwe**
M184V	0.2	0.2
K65R	0.2	0.2
L74V	0.5	0.5
Q151M	0.5	0.5
TAMS	0.5	0.5
NNRTI mutation	0.6	0.8
PI (LPV) mutations (30,32,33, 46,47,48,50L,50V,54,76,82,84,90)	0.5	0.5

LPV: lopinavir; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitor; TAMS: Thymidine analogue mutations;

3.3.8. Example results from epidemics simulated using modal values of parameter distributions

To illustrate some features of the epidemics generated, Table 3.10 shows the proportion of people with at least one, two, five, ten condom-less partners (as a total of CLST partner in addition to whether they have or not one CLLT partner) and shows the proportion of people with at least one (at least two) condom-less partners in the past year by HIV status and year using modal values for parameters. Table 3.13 shows the proportion of new infections that have been acquired from a person in PHI by year, and the proportion of new infections that have been acquired from a CLLT partner by year. Table 3.14 (page 158) shows HIV prevalence by age and gender and calendar year.

Table 3.10. Proportion of people with at least one, two, five, ten condom-less short-term partners before introduction of HIV for one example epidemic using modal values for parameters (mean over 30 runs).

	% with condom-less sex partners (short- or long-term) in past year							
Age group	**≥1**	**≥2**	**≥5**	**≥10**	**≥1**	**≥2**	**≥5**	**≥10**
	Male				**Females**			
15-	71%	29%	1.2%	0.02%	75%	41%	2.6%	2.5%
25-	85%	46%	2.0%	0.02%	82%	36%	1.8%	1.8%
35-	74%	31%	1.2%	0.01%	67%	17%	0.8%	0.8%
45-	65%	21%	0.8%	0.01%	54%	4%	0.1%	0.1%
55-	53%	10%	0.4%	0.00%	45%	2%	0.1%	0.1%

Table 3.11. Proportion of people with a condom-less long-term partner before introduction of HIV for one example epidemic using modal values for parameters (mean over 30 runs).

	% with condom-less long-term partner	
Age group	**Males**	**Females**
15-	48%	48%
25-	57%	57%
35-	48%	47%
45-	41%	41%
55-	35%	34%

Table 3.12. Proportion of people with at least one condom-less short-term partner in the past 3 months by HIV status (mean over 30 runs) for South Africa

	Calendar year				
	1990	**1995**	**2000**	**2005**	**2010**
Whole population	24%	24%	18%	15%	13%
HIV+	59%	41%	28%	20%	16%
HIV+ diagnosed	-	40%	23%	17%	14%

Table 3.13. Origin of new infections for the median over the simulations which provide a good fit.

See section 3.13 for details on calibration of the model.

This shows the proportion of new infections that have been acquired from a person in primary HIV infection by year, and the proportion of new infections that have been acquired from a condom-less long-term partner by year. For infections from people with primary infection, there are little data from sub-Saharan Africa to my knowledge. Using data on sexual behaviour from Lilongwe in Malawi, Powers and colleagues estimated that 38.4% of HIV infections were from people who were themselves in PHI (587). For proportions of people infected by a condom-less long-term partner, the probabilities are comparable with (588).

	Source of infection						
	Partner in primary infection				**Condom-less long-term partner**		
	1990	**2000**	**2010**		**1990**	**2000**	**2010**
Overall	88%	43%	33%	Male	0%	21%	41%
				Female	45%	60%	68%

Table 3.14. Median HIV prevalence (%) by gender and age using the simulations which provide a good fit.

See section 3.13 for details on calibration of the model.

	Calendar year				
	1990	**1995**	**2000**	**2005**	**2010**
Males					
15-	0.2	4.8	7.3	7.1	5.8
25-	0.4	7.5	14.5	18.7	18.7
35-	0.3	5.5	11.8	15.9	18.3
45-	0.2	3.9	7.7	9.4	11.2
55-	0.0	2.4	4.7	5.1	5.7
Females					
15-	0.2	5.5	12.8	12.7	10.7
25-	0.2	7.0	17.8	25.2	27.8
35-	0.1	4.5	13.3	21.2	28.0
45-	0.05	2.5	6.8	10.7	14.7
55-	0.0	0.7	2.0	3.6	5.5

3.4. Natural history of HIV infection

The model of the natural history of HIV and the effect of ART has been derived previously and shown to provide generally a close fit to observed data relating to natural progression of HIV infection, comparing the output of the model with data coming mainly from observational studies conducted in Europe for the natural history (incubation period) (see (103;570;589), and associated supplementary material). Below I set out the structure of the model and explain what parameters represent. There is uncertainty associated with many of the values (see parameter distributions in Appendix XI).

3.4.1. Determination of changes in viral load and CD4 count

3.4.1.1. Initial viral load

The initial $\log_{10}$ VL (V_{set}) is sampled from a $Normal(4.0, 0.5^2)$ distribution, but truncated so that the maximum is 6.5.

This viral load (V_{set}) is assumed to be that reached after PHI. It is not used to determine the risk of transmission in PHI itself. Virus at the time of infection is assumed to be R5 tropic.

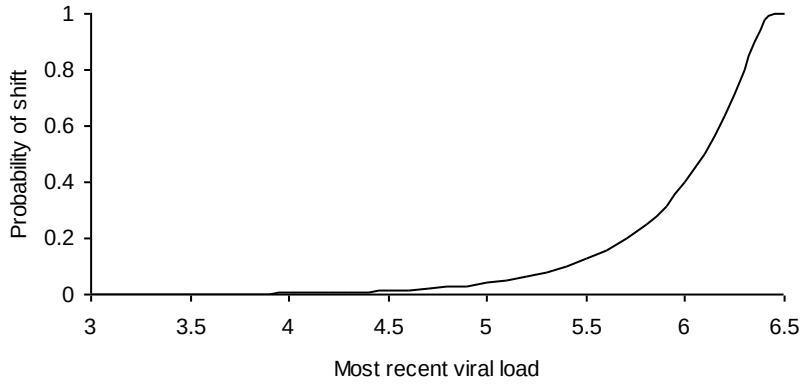
3.4.1.2. Change in viral load

VL change from period $(t-1)$ to period t (i.e. in 3 months), $vc(t-1)$, is given by sampling from a $Normal(gx * 0.02275, 0.05^2)$, where gx is sampled from a $LogNormal(ln(1), 0.20^2)$.

3.4.1.3. X4 virus

In each 3 month period, the virus can shift to be x4 virus with a probability given by $10^v * 0.0000004$, where v is the current $\log_{10}$ VL (see Figure 3.1).

Figure 3.1. Assumption on relationship between most recent viral load and probability of shift to x4 virus



Comment: This translates into a rate of 5% per year in a person with VL 30,000 copies/mL and 16% per year in a person with 100,000 copies/mL, which are broadly consistent with observed data (590).

3.4.1.4. Initial CD4 count

Initial CD4 count, modelled on the square root scale, $c(inf)$ is partially dependent on initial VL, v_{set} and given by:

$$c(inf) = mean\_sqrtcd4\_inf - (2 \times V_{set}) + Normal(0, 2^2)$$

where $mean\_sqrtcd4\_inf \sim Normal(30, 2^2)$ for South Africa, while the mean is 27 for Zimbabwe. The reason for this discrepancy is due to finding evidence that people of black race are likely to have lower CD4 count at infection after setting parameter values for South Africa and before doing so for Zimbabwe (575).

The initial CD4 count (not on square root scale) is truncated at the minimum and maximum value of respectively 324 (18^2) and 1500.

3.4.1.5. Change in CD4 count

As for VL, no attempt is made to model the dynamic CD4 count changes in PHI – the VL and the CD4 count are both assumed to have reached its settled state right from the first period.

The change in CD4 count from period $(t-1)$ to t, $ccsqr(t-1)$, are dependent on the current VL (i.e. VL at time t-1, *v(t-1)*) and are given by sampling from a Normal distribution with mean *fx* and variance $(sd\_cd4)^2$ multiplied by the values indicated in Table 3.15.

Table 3.15. Mean square root CD4 change according to viral load

Viral load at t-1, *v(t-1)*	Mean square root CD4 change (per 3 months), ccsqr(t-1)	
	South Africa	Zimbabwe
< 3.0	-0.03	0
3.0-	-0.08	-0.022
3.5-	-0.15	-0.085
4.0-	-0.20	-0.40
4.5-	-0.50	-0.40
5.0-	-1.00	-0.85
5.5-	-2.00	-1.30
6.0-	-2.50	-1.75

The change in CD4 count additionally is affected by adding the values indicated in Table 3.16, based on the current age.

Table 3.16. Additional change in square root CD4 count according to age

Age	Additional change in square root CD4 count
< 20	+0.15
20-	+0.09
25-	+0.06
30-	+0.00
35-	+0.00
40-	-0.06
45-	-0.09
50-	-0.15
60-	-0.20

People with X4 virus present experience an additional change in square root CD4 count of -0.25.

These estimates are derived based on synthesis of evidence from natural history studies (92;98;99;117;590-594) and were selected in conjunction with other relevant parameter values to provide a good fit to the incubation period distribution. Differences that have been found in initial VL by gender and age are not currently incorporated in the model.

Table 3.17. Incubation period by age.

Kaplan-Meier estimates with outcome WHO 4 event. These are calculated as median over the simulations with a good fit. Compare with (103;172).

	Years from infection					
	1	**3**	**5**	**10**	**15**	**20**
15-	0.3%	3%	10%	43%	75%	91%
25-	0.8%	5%	15%	55%	84%	95%
35-	0.9%	9%	22%	64%	91%	98%
45-	1.4%	11%	26%	74%	93%	99%
55-	1.8%	11%	30%	75%	96%	100%

3.5. HIV testing and diagnosis of HIV infection

HIV testing is assumed to have become available in ANCs in 1990 in South Africa and in 1994 in Zimbabwe, while for the rest of the population at *date_start_testing* (1996 for both countries).

For the South African model the basic probability of someone testing for HIV in any 3 month period, if he/she has not been tested for HIV in the last year, is assumed to increase linearly by *test_increase_rate* (see distribution in Appendix XI).

For the Zimbabwean model, gender and age specific rates of testing, separately for first test and repeat test apply. They are calculated as:

$$prob_{1st} = [(caldate(t) - 1996)^2] * incr\_1sttest$$

$$prob_{rep} = [(caldate(t) - 1996)^2] * incr\_reptest$$

until calendar year 2011.

The proportion ever tested and tested in the last year in 2006 and 2011, where DHS were conducted collected those data, is illustrated in section 8.2.2.

The probability of testing is independent of presence of WHO stage 3 or 4 conditions and it applies only if the person did not test for HIV in the last year; in other words HIV testing is assumed to occur with a frequency no more than annual.

A proportion of the population (*rate_noreached*) is assumed to be "resistant to HTC" and can never be tested for HIV unless symptoms occur (WHO stage 4 disease). This proportion is fixed and sampled from $LogNormal(ln(0.25), 0.12^2)$ for South Africa, while for the Zimbabwean epidemic, this proportion is assumed to be 20% in 1996, when HIV testing is introduced, and it declines linearly so that 5% are resistant by end of 2010 and it remains at that level afterwards. Justification for this assumption is given in section 8.2.3.

In addition those who did not have condom-less sex since last HIV test are assumed to have a 10-fold reduction in the probability of being tested for HIV for the South African model. While for the Zimbabwean model a 3-fold reduction in HIV testing is assumed for people who never had condom-less sex. Justification for this assumption is given in section 8.2.3.

In addition some individuals experience an additional probability of being tested for HIV based on their condition in the previous 3 months and on the calendar year (See Table 3.18).

Table 3.18. Probability of HIV testing for symptomatic people in 1989 and rate of increase over time

Situation	**Probability of HIV testing in 1996**	**Rate of increase per 3 months (Up to a probability of 0.95)**
Current AIDS defining condition	0.2	0.008
Current TB, but not an AIDS defining condition	0.1	0.005
Current WHO stage 3 disease, but not TB nor an AIDS defining condition	0.003	0.0012

AIDS: Acquired Immune Deficiency Syndrome; TB: tuberculosis; WHO: World Health Organization;

The result of the HIV test is assumed to be available immediately and to be 100% sensitive and specific, except during PHI (assumed to last 3 months) therefore people who are infected with HIV for at least 3 months and who get tested are diagnosed with HIV. From 2013 onwards the probability of being tested for HIV is assumed constant. These parameters have been chosen to reflect the situation respectively in South Africa (452) and Zimbabwe (519). In section 7.3.1 for South Africa and 8.2.2 for Zimbabwe the fit of HIV testing to data from national surveys is shown.

Among those who are not “resistant to HTC” (determined by *rate_noreached),* the proportion of HIV-positive people who are linked to care and therefore received a CD4 measurement and result to evaluate whether they are eligible to initiate ART is determined as the sum of *rate_noreached* and *prop_linkedtocare_diag* (See the value and distribution of these two parameters in Appendix XI).

3.5.1. HIV testing in antenatal clinics

The reason why pregnancies are included in this model is mainly to be able to simulate HIV testing in ANCs, and therefore a higher rate of testing in women overall, and to capture the impact of receiving ARVs to prevent MTCT on the development of resistance. Vertical transmissions are not modelled.

Given a woman had a CLLT partner in a 3 month period, and did not give birth in the last 9 months, in the model the probability that she becomes pregnant is age dependent. The probability for a woman aged 25 to 35 years is determined by the parameter *prob_pregnancy_base* (See distribution in Appendix XI). For the other age groups (15 to 25 years old up to 55 to 66 years), the following multiplicative factors, respectively *fold_preg1525*, *fold_preg2535*, 1, *fold_preg4555*, *fold_preg5565* (See distribution in Appendix XI) are multiplied by *prob_pregnancy_base,* to determine the probability of pregnancy in women who had condom-less sex in the previous 3 months. If they had condom-less sex with short-term partners the probability of pregnancy from each of the CLST partner is multiplied by the factor *fold_tr_newp*, to take into account of the lower number of sex acts per CLST partner than per CLLT partner.

These parameters have been chosen to reflect the cumulative average number of children ever born per woman, for the age group 15-24 up to 45 to 49 years old, estimated in a community survey in South Africa conducted in 2007 (595).

In pregnant women, who are not “resistant to HTC” the probability per pregnancy of attending an ANC and receiving an HIV test (for women not diagnosed yet with HIV) is assumed to increase over time. This probability from 1990 to 2013 for South Africa and to 2015 for Zimbabwe, is given by:

$$[(caldate(t) - 1990)^2] * rate\_testanc\_inc$$

See distribution of *rate_testanc_inc* in Appendix XI.

The maximum probability of attending an ANC is assumed to be 0.975.

Pregnant women who are diagnosed with HIV, since 2004 (*date_pmtct)*, the year when PMTCT with use of single dose NVP is assumed was introduced. The chances of receiving PMTCT are assumed to increase over time as given by:

$$(caldate(t) - date\_pmtct) * rate\_sd\_nvp$$

The maximum I assumed again to be 0.975.

With this parameter choice, 90% of pregnant women receive PMTCT by 2011, as has been estimated for South Africa (596).

3.6. Use of ART

3.6.1. Initiation of ART

ART is assumed was introduced in 2002 in South Africa and 2003 in Zimbabwe (*ART_intro_date* in Appendix XI). Eligibility criteria to be initiated on ART follow the national guidelines and in the time period where not available WHO guidelines (see sections 2.1.7 and 2.2.7).

3.6.2. Adherence to antiretroviral treatment

Each patient has a fixed "tendency to adhere", which is assumed constant for their entire lifespan. Nevertheless, their actual adherence varies from period to period, both at random and according to the presence of symptoms, depending on their underlying "tendency to adhere". Adherence is measured on a scale of 0 to 1 (sometimes reported as between 0 and 100%).

3.6.2.1. Adherence component which is fixed over time for a given patient

The "tendency to adhere" is indicated by the parameter *adhav*, while the period-to-period variability is indicated by the parameter *adhvar*. Adherence at any one period is determined as follows (although with modifications explained below):

$$adh(t) = adhav + Normal(0, adhvar)$$

$$\text{where } min[adh(t)] = 0 \text{ and } \max[adh(t)] = 1$$

Table 3.19. Adherence pattern used

Proportion of the population		Adhav	Adhvar
South Africa	Zimbabwe		
0.15	0.05	0.49	0.2
0.15	0.10	0.79	0.2
0.5	0.65	0.90	0.06
0.2	0.2	0.95	0.05

These estimates are based partially on observed adherence data (330;485;565) (see section 2.1.9 and 2.2.9 for more information), but also on adherence levels required to produce observed estimates of rates of resistance development and VF and also data on the proportion of patients at first VF who have no resistance mutations present (398;597-599). The choice of a slightly worse adherence pattern for South Africa compared to Zimbabwe was driven by the fact that I did not want to underestimate the potential development and transmission of resistance for South Africa. It is clear from data, mainly from South Africa, that the great majority of patients who started ART with 3 or more drugs are sufficiently adherent that VF rates (and so resistance accumulation is likely to have been slow also) are low (499;504;568). See section 2.1.10 for more detail on VF in patients on ART in South Africa and section 2.2.10 regarding Zimbabwe.

3.6.2.2. Effective adherence

We also considered the concept of effective adherence, $e\_adh(t)$, which reflects predicted adequacy of drug levels, whereby for those on regimens that do not include an NNRTI the effective adherence is as the adherence, but for those on NNRTI-containing regimens the effective adherence is considered to be 0.1 higher (on a scale from 0 to 1, this parameter is referred to as *add_eff_adh_nnrti* in Appendix XI), reflecting the long half-life of these drugs (600). Additionally, it is assumed that patients on ART are susceptible to occasional (rate 0.02

per year) severe temporary drops in drug level (i.e. effective adherence level), leaving them susceptible to viral rebound (but with low risk of resistance as the effective adherence drop is so profound). This phenomenon is assumed to be 3 times more frequent among those on PI regimens. This latter assumption is the only plausible means (at least within this model framework), together with the fact that the patient interrupt treatment without the clinician knowing it (see section 3.6.4) to explain why VF occurring on boosted PI regimens often occurs in the absence of resistance.

3.6.2.3. Effect of viral load measurement above 1000 copies/mL on adherence

Studies have indicated that VL frequently returns to undetectable levels after a measured VL>1000 copies/mL, largely attributable to targeting of adherence support (307;597). Adherence is assumed to be incremented by an average *adh_effect_of_vm_pop* (by an amount that varies by individual) when the VL has been measured to be above 1000 copies/mL in the past 6 month period (it can apply only once for each individual). In addition in 50% of the patients with a measured VL>1000 copies/mL there is a 0.2 probability of a one-off increase in adherence. For those with an increase in adherence the increase is sampled from a Uniform distribution with extremes 0 and 0.8, up to a maximum of 1 for the adherence.

Having a measured VL above 1,000 copies/mL in the last six months is assumed to have an effect on the probability of restarting ART in people who have interrupted. In particular this is multiplied respectively by 1.5, 2, 3 and 5 if the individual increase in adherence due to this effect is respectively 0.05, between 0.05 and 0.10, 0.10 and 0.25 and above 0.25.

The impact of a VL measurement on adherence is not modelled in Zimbabwe because it is assumed VL monitoring is not available.

3.6.3. Interruption of ART

The basic rate of interruption due to patient choice (*rate_int_choice)* is assumed to be 0.02 per 3 months. This rate depends on the person's underlying tendency to adhere and whether they have current toxicity. Table 3.20 shows by how much *rate_int_choice* is multiplied by for different levels of adherence and presence of toxicity.

Table 3.20. Multiplicative factor for rate of ART interruption based on underlying tendency to adhere and presence of toxicity on the rate of interruption

	Current presence of toxicity	
Underlying tendency to adhere	**No**	**Yes**
≥0.8	1	2
0.5-0.79	1.5	3
<0.5	2	4

These rates are reduced by half for people who have been continuously on ART for two years.

If ART is interrupted because of patient choice the probability per 3 month period that the interruption coincides with the interrupting/stopping visits to the clinic (i.e. LTFU) is determined by the parameter *prob_lost_art* (0.3) for patients with adherence average of 0.8 or more.

Patients with "tendency to adhere" between 0.5 and 0.8 experience a 50% higher probability of being lost per 3 month during ART interruption, while those with "tendency to adhere" less than 0.5 a double probability of being lost compare to those with high "tendency to adhere" (>0.8).

The rate of interruption due to choice and therefore the retention of people on ART are likely to vary by setting. The above rates were derived to be consistent with data from South Africa and Zimbabwe (291;554;601).

The basic rate of interruption per 3 months due to interruption of the drug supply (*prob_supply_interrupted*) is assumed to be 0.01 (See distribution in Appendix XI).

3.6.4. Interruption of ART without clinic/clinician being aware

It is known that in some instances, people on ART have such poor adherence that they have in fact interrupted or stopped ART entirely but, in the same way that the clinician is not always aware of the true adherence level, they are also not always aware when the person has completely interrupted ART. This means that the clinician may think a patient is virologically failing, because VL is high, when in fact this is due to interruption rather than resistance having developed. This can be seen from studies on people with VF in which a proportion have no identified DRMs (398;597;598) . Thus, when a person interrupts ART (but remains under care)

a variable is introduced, that indicates whether the clinician is aware, *clinic_aware_int_frac* (See distribution in Appendix XI). If a patient has interrupted ART with the clinician unaware then not only is the patient (wrongly) classified (by the clinician) as virologically failing, but a switch to second-line can potentially occur.

3.6.5. Re-initiation of ART after interrupting in patients still under follow-up

For patients who have interrupted ART due to choice but are still under clinic follow-up, the probability of restarting ART per 3 months in the base model is *rate_restart* (See distribution in Appendix XI). This probability is increased 3-fold and 5-fold if respectively a new WHO 3 and a new WHO 4 condition have occurred at *t-1*.

In addition, as mentioned in section 3.6.2, if VL monitoring is available a measured VL above 1,000 copies/mL in the last 6 months triggers an adherence intervention which can increase the rate of restart.

For patients who have interrupted ART due to interruption of supply the probability of restarting ART per 3 months (*prob_supply_resumed*) is 0.8.

3.6.6. Switch to second-line after failure of first-line ART

Whatever the definition of first-line ART failure (i.e. the criterion for the need to switch to second-line ART), the probability of switching per 3 month period after the criterion is met (*pr_switch*_line) is assumed to be 0.25 for South Africa and 0.15 for Zimbabwe. This corresponds to a median time to switch of 5 months for South Africa, as found in the clinic described by Fox and colleagues (499). It is possible that the switching rates at national level are even lower and that, if anything, I have overestimated the current number of people on second-line of treatment. Less data are available on number of people switched to second-line in Zimbabwe but data on the number of people on second-line suggest even lower switching rates than in South Africa (602).

3.6.7. Loss to follow-up while off ART

The probability per 3 months of interrupting/stopping clinic visits (i.e. being LTFU) while off ART (*rate_lost*) applies to patients both ART-naïve and ART-experienced.

In South Africa, in the first year since diagnosis it is assumed to be 0.3 for people with "tendency to adhere" (See section 3.6.2) of 0.8 or above; this is due to the necessity to match to data which found very low retention in pre-ART care (2;551-553). After one year since diagnosis, in the model for South Africa the probability of being LTFU is assumed to be a quarter of what it is in the first year: 0.075. This reduction was assumed to reflect the fact that retention of patients who have started ART is much better (291;530;601).

For Zimbabwe the data on retention in pre-ART care are substantially not existent and few data are available for retention on ART (554). I decided, in collaboration with Andrew Phillips who led the choice for the parameters in Zimbabwe, to have a simpler parameterization for Zimbabwe and assume it is 0.05, regardless of the length of time since diagnosis.

These parameters are increased by 1.5 fold if "tendency to adhere" (described in section 3.6.2) is between 0.5 and 0.8 and by 2-fold if the "tendency to adhere" is below 0.5.

See sections 7.3.3 and 7.3.5 for more details on retention in pre-ART care and once initiated on ART for South Africa and section 2.2.6 and 2.2.9 for Zimbabwe.

For people LTFU who are asymptomatic, the probability of returning to clinic per 3 months (*rate_return*) is 0.05 for South Africa, 0.04 for Zimbabwe, if the "tendency to adhere" is 0.8 or above. This is decreased by 2-fold if the "tendency to adhere" is between 0.5 and 0.8 and by 3-fold if the "tendency to adhere" is below 0.5. If a person develops a new WHO 3 or 4 event then they are assumed to return to the clinic with probability 0.8. These will vary by setting (1;483;484;603-605).

3.7. Effect of ART on viral load, CD4 count, resistance development and drug toxicity

3.7.1. Determination of viral load, CD4 count and acquisition of new resistance mutations while on ART

Potent ART regimens are known to reduce VL, which in turn leads to recovery of CD4 cell counts (606-608). Changes in the VL and CD4 counts whilst an individual is on ART are modelled differently to when an individual is ART-naïve.

Determination of VL, CD4 count and acquisition of new DRMs (variable *newmut(t)*) between $(t-1)$ to t depends on:

- effective adherence between $(t-1)$ to t,
- number of active drugs (*nactive(t-1)*),
- time on the current regimen,
- current VL

The way the values are generated is detailed in Table 3.21-Table 3.26 (page 172-page 177). For those on NNRTI regimens the new mutations risk is assumed to be that for the effective adherence category of 0.5 – 0.8 (i.e. maximal) even if *e_adh(t)< 0.5*, reflecting the fact that NNRTI resistance develops easily, even when drug exposure is very low.

In the following sections, 'starting current regimen' means starting ART for the first time or following a treatment interruption.

The changes in VL and CD4 count are based on observed data and observational studies (and to some extent RCTs, although responses tend to be better in trial participants), and provide long term estimates of VF rates and CD4 count increases in ART which are broadly consistent with observed data. Values of the "new mutation risk" parameter, *newmut(t)*, have been chosen in conjunction with the translation of presence of DRMs into reduce drug activity to provide estimates of resistance accumulation consistent with those observed in clinical practice (264;607-614).

Table 3.21. Viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk in first 3 months since ART initiation

The initial 3-month change in VL is described as the mean change from the patient's maximum VL to that point (*vmax*) on the log scale. This is the mean of a normal distribution with variance 0.2^2, from which the patient's value/change is sampled.

The change in CD4 count is described as the mean change between periods $(t-1)$ and t. This change is then multiplied by a factor which represents each individual's underlying propensity for CD4 count rise whilst on ART (given by the parameter *pt_cd4_rise_art*).

For the new mutation risk, this is a number that is multiplied by the VL (mean of values at $(t-1)$ to t). The resulting number, *newmut(t)*, is used when assessing whether a new DRM(s) have arisen.

	'Effective adherence' between *t-1* & *t*	**Number of active drugs**											
		3	**2.75**	**2.5**	**2.25**	**2**	**1.75**	**1.5**	**1.25**	**1**	**0.75**	**0.5**	**0.25**
Viral load (log change from *vmax*)	≥ 0.8	-3	-2.6	-2.2	-1.8	-1.5	-1.25	-0.9	-0.8	-0.7	-0.55	-0.4	-0.3
	≥ 0.5, < 0.8	-2	-1.6	-1.2	-1.1	-0.9	-0.8	-0.6	-0.5	-0.4	-0.25	-0.1	-0.05
	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	0	0.05	0.1	0.1	0.1	0.1
CD4 count change (*t-1* to *t*)	≥ 0.8	50	45	40	35	30	25	20	17	13	10	5	-2
	≥ 0.5, < 0.8	30	30	23	20	15	13	10	8	5	3	0	-7
	< 0.5	5	4	3	2	1	-1	-3	-6	-10	-11	-12	-13
New mutation risk (x log viral load)	≥ 0.8	0.002	0.01	0.03	0.05	0.1	0.15	0.2	0.3	0.4	0.45	0.5	0.5
	≥ 0.5, < 0.8	0.15	0.15	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table 3.22. Summary of viral load values between 3-6 months since starting current regimen and after 6 months if viral load at t-1 > 4 log copies/mL

This table applies to patients for whom it has been between 3 and 6 months since starting their current regimen, as well as patients who have been on their current regimen for more than 6 months but who have a VL > 4 log copies/mL (e.g. due to previous poor adherence). The change in VL is described as the mean change from the patient's maximum VL to that point (*vmax*) on the log scale. Otherwise, if the number in the table is underlined, it is the mean absolute value. This is the mean of a normal distribution with variance 0.2^2, from which the patient's value/change is sampled.

'Effective adherence' between *t-2* & *t-1*	**'Effective adherence' between *t-1* & *t***	**Number of active drugs**											
		3	**2.75**	**2.5**	**2.25**	**2**	**1.75**	**1.5**	**1.25**	**1**	**0.75**	**0.5**	**0.25**
≥ 0.8	≥ 0.8	0.5	0.8	1.2	1.4	2.0	2.7	-1.7	-1.15	-0.9	-0.75	-0.6	-0.4
≥ 0.5, < 0.8		1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.05	-0.9	-0.7	-0.5	-0.35
< 0.5		1.2	1.2	1.2	1.4	-2.0	-1.6	-1.2	-1.0	-0.9	-0.7	-0.5	-0.2
≥ 0.8	≥ 0.5, < 0.8	1.2	1.6	1.8	2.2	2.4	-2.4	-1.5	-0.9	-0.7	-0.55	-0.4	-0.3
≥ 0.5, < 0.8		2.5	2.5	2.5	2.5	-1.2	-1.1	-0.8	-0.65	-0.5	-0.35	-0.2	-0.05
< 0.5		-2.0	-1.8	-1.5	-1.35	-1.2	-1.1	-0.8	-0.65	-0.5	-0.2	-0.2	-0.05
≥ 0.8	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0	+0	+0	+0
≥ 0.5, < 0.8		-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0	+0	+0	+0
< 0.5		-0.5	-0.4	-0.3	-0.25	-0.2	-0.15	-0.10	-0.05	+0	+0	+0	+0

Table 3.23. Summary of CD4 count change (mean change between t-1 and t) between 3-6 months since starting current regimen and after 6 months if viral load at t-1 > 4 log copies/mL

This table applies to patients for whom it has been between 3 and 6 months since starting their current regimen, as well as patients who have been on their current regimen for more than 6 months but who have a VL > 4 log copies/mL (e.g. due to previous poor adherence).

The change in CD4 count is described as the mean change between periods $(t-1)$ and t. This change is then multiplied by a factor which represents each individual's underlying propensity for CD4 count rise whilst on ART (given by *pt_cd4_rise_art*). Once the mean of the underlying CD4 count is obtained, to obtain the (underlying) CD4 count, variability (SD = 1.2) is added on the square root scale.

'Effective adherence' between *t-2* & *t-1*	**'Effective adherence' between *t-1* & *t***	**Number of active drugs**											
		3	**2.75**	**2.5**	**2.25**	**2**	**1.75**	**1.5**	**1.25**	**1**	**0.75**	**0.5**	**0.25**
≥ 0.8	≥ 0.8	+30	+28	+25	+23	+21	+19	+3	-5	-9	-10.5	-12	-14
≥ 0.5, < 0.8		+30	+28	+25	+23	+7.5	+1.5	-4.5	-7	-9	-11	-13	-14.5
< 0.5		+30	+28	+25	+23	+7.5	+1.5	-4.5	-7.5	-9	-11	-13	-16
≥ 0.8	≥ 0.5, < 0.8	+15	+13	+10	+8	+7	+4	+0	-9	-11	-12.5	-14	-15
≥ 0.5, < 0.8		+15	+13	+10	+8	-4.5	-6	-10	-11.5	-13	-14.5	-16	-17.5
< 0.5		+7.5	+4.5	+0	-2	-4.5	-6	-10	-11.5	-13	-16	-16	-17.5
≥ 0.8	< 0.5	-13	-14	-15	-15.5	-16	-16.5	-17	-17.5	-18	-18	-18	-18
≥ 0.5, < 0.8		-13	-14	-15	-15.5	-16	-16.5	-17	-17.5	-18	-18	-18	-18
< 0.5		-13	-14	-15	-15.5	-16	-16.5	-17	-17.5	-18	-18	-18	-18

Table 3.24. Summary of new mutation risk between 3-6 months, and after 6 months if viral load at t-1 > 4 log copies/mL

This table applies to patients for whom it has been between 3 and 6 months since starting their current period of continuous therapy, as well as for patients whom it has been more than 6 months since their current period of continuous therapy but who have a high VL (e.g. due to previous poor adherence). The numbers given in the table below correspond to the 'new mutation factor', which is a number that is multiplied by the VL (mean of values at $(t-1)$ to t). The resulting probability, *newmut(t)*, is used when assessing whether a new mutation or mutations have arisen.

'Effective adherence' between *t-2* & *t-1*	**'Effective adherence' between *t-1* & *t***	**Number of active drugs**											
		3	**2.75**	**2.5**	**2.25**	**2**	**1.75**	**1.5**	**1.25**	**1**	**0.75**	**0.5**	**0.25**
≥ 0.8	≥ 0.8	0.002	0.01	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.5
≥ 0.5, < 0.8		0.002	0.01	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.5
< 0.5		0.05	0.05	0.03	0.05	0.05	0.1	0.2	0.3	0.4	0.45	0.5	0.25
≥ 0.8	≥ 0.5, < 0.8	0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
≥ 0.5, < 0.8		0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
< 0.5		0.10	0.15	0.2	0.2	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.25
≥ 0.8	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
≥ 0.5, < 0.8		0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
< 0.5		0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

Table 3.25. Summary of viral load (mean change from viral load max), CD4 count change (mean change between t-1 and t), and new mutation risk after 6 months, where viral load at t-1 < 4 log copies/mL.

Summary of VL (mean change from VL max), CD4 count change (mean change between t-1 and t), and new mutation risk after 6 months, where VL at *t-1* < 4 logs. For VL this is the mean of a Normal distribution with standard deviation 0.2, from which the patient's value/change is sampled. For the CD4 count patients vary in their underlying propensity for CD4 rise on ART (given by given by *pt_cd4_rise_art*) and the CD4 count change given here is multiplied by this factor. For the new mutation number, this is a number that is multiplied by the VL (mean of values at $(t-1)$ to t). The resulting probability, *newmut(t)*, is used when assessing whether a new mutation or mutations have arisen.

	'Effective adherence' between *t-1* & *t*	**Number of active drugs**											
		3	**2.75**	**2.5**	**2.25**	**2**	**1.75**	**1.5**	**1.25**	**1**	**0.75**	**0.5**	**0.25**
Viral load (log change from *vmax*)	**≥ 0.8**	0.5	0.9	1.2	1.6	-2.5	-2.0	-1.4	-1.15	-0.9	-0.75	-0.6	-0.3
	≥ 0.5, < 0.8	1.2	1.2	1.2	1.2	-1.2	-1.0	-0.6	-0.5	-0.4	-0.3	-0.1	-0.1
	< 0.5	-0.5	-0.4	-0.3	-0.25	-0.2	-0.2	-0.1	-0.1	-0.1	-0.1	-0.1	0
CD4 count change (*t-1* to *t*)	**≥ 0.8**	+30	+28	+25	+23	+21	+19	+3	-5	-9	-10.5	-12	-12
	≥ 0.5, < 0.8	+15	+13	+10	+8	-4.5	-7.5	-10	-12	-13	-14	-15	-15
	< 0.5	-13	-14	-15	-15.5	-16	-16.5	-17	-17	-18	-17	-17	-17
New mutation risk (x log viral load)	**≥ 0.8**	0.002	0.01	0.03	0.08	0.1	0.15	0.2	0.3	0.4	0.45	0.5	0.5
	≥ 0.5, < 0.8	0.15	0.18	0.2	0.25	0.3	0.3	0.3	0.35	0.4	0.45	0.5	0.5
	< 0.5	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05

3.7.2. Changes in viral load, CD4 count and new mutation risk if the number of active drugs in current regimen = 0

For 0 active drugs, these are the changes regardless of time from start of regimen.

Table 3.26. Changes in viral load, CD4 count and new mutation risk if the number of active drugs in current regimen is zero

	'Effective adherence' between *t-1* & *t*	**Number of active drugs 0**
Viral load (log change from *vmax*)	≥ 0.8	-0.3
	≥ 0.5, < 0.8	-0.1
	< 0.5	0
CD4 count change (*t-1* to *t*)	≥ 0.8	-15
	≥ 0.5, < 0.8	-17
	< 0.5	-18
New mutation risk (x log viral load)	≥ 0.8	0.5
	≥ 0.5, < 0.8	0.5
	< 0.5	0.05

3.7.3. Factors which affect the CD4 count rise

There are a number of effects and factors which are taken into account before the final CD4 count rise per 3 months is determined, as detailed below. There is a maximum CD4 count achievable when on ART, which is fixed for each patient, *cmax*. This estimate is based on observed CD4 counts in HIV-seronegative people (95;136).

3.7.3.1. Variable patient-specific tendency for CD4 count rise on ART

Patients are assumed to vary in their underlying propensity for CD4 count rise whilst on ART. Each person is given a value for their propensity, '*pt_CD4_rise_art*'. This value is fixed and remains constant for the individual over time and is the factor by which the CD4 count change is multiplied by in Table 3.21 (page 172), Table 3.23 (page 174), Table 3.25 and Table 3.26.

To reflect the fact that the rate of CD4 count increase on ART tends to diminish with time (609;615), for those with *pt_CD4_rise_art* > 1, this factor is modified by a factor 0.67 after 1 year of continuous treatment and by a factor of 0.5 after 3 years of continuous ART.

3.7.3.2. Accelerated rate of CD4 count loss if PI not present in regimen

The rate of change in CD4 count in people on failing regimens is largely based on data from the PLATO collaboration, for which patients were mainly on regimens containing a PI (129). If the regimen does not contain a PI, the change in CD4 count per 3 months is modified (additive effect) by *poorer_cd4_rise_on_failing_nnrti*, *(*See values in Appendix XI). This applies regardless of VL level, so PIs are assumed to lead to a more beneficial CD4 count change than NVP or EFV (the only two NNRTIs currently included in the Synthesis model for sub-Saharan Africa).

3.7.3.3. Variability in individual (underlying) CD4 counts for people on ART

Once the mean of the underlying CD4 count is obtained as described above for people on ART, to obtain the CD4 count, variability (*sd_cd4*) is added on the square root scale: 1.2 is the standard deviation. The estimate was based on unpublished analyses.

3.7.3.4. Viral load and CD4 count changes during ART interruption

During ART interruption, VL returns to previous maximum VL (*vmax*) in 3 months and adopts natural history changes thereafter.

The rate of CD4 count decline returns to natural history changes (i.e. those in ART-naïve patients) after 9 months, unless the count remains > 200 cells/μL above the CD4 count nadir, *cmin(t)*.

Before returning to the natural history, for the first 9 months, the rate of CD4 count decline depends on current VL (See Table 3.27).

Table 3.27. Summary of changes in CD4 count during ART interruption according to time off ART and current viral load

Time off ART	Current viral load (log copies/mL)	Distribution of change in CD4 count (cells/µL)
3 months, or >3 months and CD4 count in previous period is >300 above the minimum CD4 count to date	VL $\geq$ 5	Normal (-200,10)
	4.5 ≤ VL < 5	Normal (-160,10)
	VL < 4.5	Normal (-120,10)
6 months	VL $\geq$ 5	Normal (-100,10)
	4.5 ≤ VL < 5	Normal (-90,10)
	VL < 4.5	Normal (-80,10)
9 months	VL $\geq$ 5	Normal (-80,10)
	4.5 ≤ VL < 5	Normal (-70,10)
	VL < 4.5	Normal (-60,10)

If these changes lead to $c(t) < cmin(t)$ then $c(t) = cmin(t)$, i.e. current CD4 count is set as the CD4 count nadir.

These values are broadly based on evidence from a number of analyses of the effects of ART interruption (276;319;616-625).

3.8. Emergence of specific resistance mutations and their effect on drug activity

3.8.1. Modelling resistance

Resistance is modelled in terms of the presence or absence of mutations specific to the drugs in use. The choice of mutations to include reflects a balance between the desire to capture important specific effects and the need to limit the complexity of the model and the number of variables simulated. The IAS-USA resistance guidelines provided the basis for choice of mutations (626).

We do not specify the mutated amino acid for each position; it is assumed that for a given codon position, the mutations considered are those that confer resistance (e.g. for M184 this is I or V).

Unlike all other resistance mutations, M184 is assumed not to persist in majority virus after HIV infection; although like all other mutations, it does persist as minority virus.

3.8.2. Accumulation of resistance mutations

Newmut(t) (see Table 3.21 at page 172, Table 3.24 at page 175, Table 3.25 at page 176 and section 3.7.2) is a probability used to indicate the level of risk of new mutations arising in a given 3 month period. As mentioned this parameter and therefore the probability of acquiring resistance depend on: the number of active drugs, the time spent on ART (since initiated for the first time or since restarting it) and the effective adherence between t-1 & t and t-2 & t-1. If this chance comes up in a given 3 month period (determined by sampling from the binomial distribution) then the following criteria operate (presented per drug class):

Table 3.28. Probability of specific mutation arising

Resistance mutation	Probability of arising	Conditions
M184	0.8	if (on 3TC)
# TAMS increases by 1	0.2	if (on AZT or D4T) and (not on 3TC nor FTC)
	0.12	if (on AZT or D4T) and (on 3TC or FTC)
# TAMS increases by 2	0.01	if (on AZT or D4T) and (not on 3TC nor FTC)
	0.01	if (on AZT or D4T) and (on 3TC or FTC)
K65	0.01 (0.02*)	if (on TDF or DDI) and (on AZT or D4T)
	0.04 (0.10*)	If (on TDF or DDI) and (not on AZT or D4T)
L74	0.01	if on DDI
Q151	0.02	if (on DDI or D4T or AZT)
NNRTI mutations*	0.80	If on NVP or EFV
K103**	0.2	If on NVP
	0.7	If on EFV
Y181**	0.4	If on NVP
	0.1	If on EFV
G190**	0.2	If on NVP
	0.1	If on EFV
V32	0.04	if on LPV/r
I47	0.04	If on LPV/r
V82	0.04	If on LPV/r

*NNRTI mutations are considered all together in the model for South Africa; **the model for Zimbabwe was developed further to distinguish among the primary NNRTI DRMs.
3TC: lamivudine; AZT: zidovudine; d4T: stavudine; ddI: didanosine; EFV: efavirenz; FTC: emtricitabine; LPV: lopinavir boosted with ritonavir; NNRTI: non-nucleoside reverse transcriptase inhibitor; NVP: nevirapine; TAMS: Thymidine analogue mutations; TDF: tenofovir;

These values are chosen, in conjunction with values of *newmut(t)*, to provide estimates of accumulation of specific classes of mutation consistent with those observed in clinical practice (611;613;614;627-629). They reflect a greater propensity for some mutations to arise than others. This probably relates to the ability of the virus to replicate without the mutations (e.g. probably very low in the presence of 3TC for virus without M184V) as well as the replicative capacity of virus with the mutations. Over time as more data accumulate it may be possible improve these estimates of rates of accumulation of specific mutations.

3.8.3. Accumulation and persistence of resistance mutations in pregnant women receiving prevention of mother-to-child transmission

As described in section 3.5.1, the model simulates pregnancies in women who engage in condom-less sex, whether they are tested in ANC and whether they receive ARVs for PMTCT. The scale up of PMTCT services and the regimen recommended are described in Appendix IV for South Africa and Appendix VIII for Zimbabwe.

Single dose NVP and the most recent regimen have been associated with different risk of NNRTI resistance emergence (630): the first (*prob_nnresmaj_sd_nvp*) is assumed to be 0.35 per pregnancy and the second (*prob_nnresmaj_dual_nvp*) 0.045 (630).

There is evidence that even if NNRTI mutations are acquired in women receiving PMTCT, they tend to be lost and this does not seem to affect their virological response when in the future they start ART for their own health (631). It is assumed women who have acquired NNRTI resistance due to PMTCT, experience a rate of losing these mutations from majority virus per 3 months (*rate_loss_nnres_pmtct_maj*) and once they are present only in minority virus a rate of losing them completely (*rate_loss_nnres_pmtct_min*) of 0.25. Once they are lost completely then even if they start an NNRTI regimen, the mutations are not going to re-emerge.

3.8.4. New resistance to NNRTI arising as a result of ART interruption

It is assumed that, due to the long half-life of NNRTIs, stopping a regimen containing either EFV or NVP is associated with a probability of an NNRTI resistance mutation arising (*risk_res_stopping_nn*). This is assumed to be of 0.05 per 3 months for South Africa. In the model for Zimbabwe, NRRTI DRMs where modelled separately (K103, Y181 and G190) and the chance of each of them arising are respectively: 0.018, 0.006, 0.006.

In Chapter 6, I estimated the risk of NNRTI resistance emerging after interruption of NNRTI-based regimen.

3.8.5. Loss of acquired mutations from majority virus

It is assumed that DRMs acquired while on ART tend to be lost from majority virus with a certain probability from 3 months after stopping to take a drug that selects for that DRM, although these mutations will remain in minority virus.

The probability of losing mutations per 3 months (from 3 months after stopping) is summarised in the Table 3.29. These values were chosen based on the analysis conducted in Chapter 6 and evidence from studies in people interrupting ART (352;369;386;632-636).

Note that these probabilities all relate to people who have started ART and are not about persistence of TDR mutations (which is currently assumed to be indefinite, except for M184V).

Table 3.29. Mutation-specific probability of loss of resistant mutation from majority virus

Resistance mutation	Probability of loss (per 3 months)
M184V	0.8
L74V	0.6
K65R	0.6
Q151M	0.6
TAMS (lose all)	0.4
NNRTI mutations	0.2
Protease mutations	0.2

NNRTI: non-nucleoside reverse transcriptase inhibitors; TAMS: Thymidine analogue mutations;

3.8.6. "Regaining" mutations in majority virus after restarting ART

Mutations previously present in majority virus, remain in minority virus, are regained in majority virus when one of the drugs selecting for that mutation is restarted (see Table 3.30).

3.8.7. Determination of level of resistance to each drug and calculation of activity level of each drug

The level of resistance conferred by each DRM to ARVs is displayed in Table 3.30, where a value of 1 means full resistance, while a value of 0 means that the drug is fully active.

Table 3.30. Summary of level of resistance conferred by specific mutations

Mutation	Drug	Level of resistance	Condition
M184V	3TC	0.75	
1-2 TAMS	AZT or D4t	0.5	(no 3TC or FTC in regimen)
		0.5	(3TC or FTC in regimen- no M184V ever)
		0.25	(3TC in regimen- M184V ever)
3-4 TAMS	AZT or D4t	0.75	(no 3TC or FTC in regimen)
		0.75	(3TC or FTC in regimen- no M184V ever)
		0.5	(3TC in regimen- M184V ever)
5-6 TAMS	AZT or D4t	1.00	(no 3TC or FTC in regimen)
		0.75	(3TC or FTC in regimen- no M184V ever)
		0.75	(3TC in regimen- M184V ever)
2-3 TAMS	TDF	0.5	(no K65R ever, no 3TC in regimen)
		0.5	(no K65R ever, 3TC in regimen, no M184V ever)
		0.5	(no K65R ever, 3TC in regimen, M184V ever)
>=4 TAMS	TDF	0.75	(no K65R ever, no 3TC in regimen)
		0.75	(no K65R ever, 3TC in regimen, no M184V ever)
		0.5	(no K65R ever, 3TC in regimen, M184V ever)
> 3 TAMS	DDI	0.5	
Q151M	AZT or D4T	0.75	
	DDI	0.75	
K65R	D4T or TDF	0.5	
	DDI	0.75	
L74V	DDI	0.75	
NNRTI mutation	NVP or EFV	1.00	
1 from Pr 32, 47, 76, 82	LPV/r	0.25	
2 from Pr 32, 47, 76, 82		0.5	
3 from Pr 32, 47, 76, 82		0.75	
2-3 from Pr 46, 76, 82, 84, 90		max(r_lpr, 0.25)	
4 from Pr 46, 76, 82, 84, 90		max(r_lpr, 0.5)	

*NNRTI mutations are considered all together in the model for South Africa; **the model for Zimbabwe was developed further to distinguish among the primary NNRTI DRMs.
3TC: lamivudine; AZT: zidovudine; d4T: stavudine; ddI: didanosine; EFV: efavirenz; FTC: emtricitabine; LPV/r: lopinavir boosted with ritonavir; NNRTI: non-nucleoside reverse transcriptase inhibitor; NVP: nevirapine; TAMS: Thymidine analogue mutations; TDF: tenofovir;

These rules approximately follow the interpretation systems for conversion of mutations present on genotypic resistance test into a predicted level of drug activity (or, equivalently, of resistance; e.g. (637-640)). Currently interpretation systems differ in their prediction of activity for some drugs.

3.8.8. Calculation of activity level of drug

Every ARV is treated as being equally potent because virological efficacy depends only on number of active drugs, not which specific drugs they are on that are active. In reality, ARVs differ in potency but to my knowledge no reliable estimates are available to use. The exception is for boosted-PI drugs which are assumed to have double potency of all other drugs, based on their efficacy as monotherapy (641;642).

The number of active drugs in the regimen at time t, *nactive(t),* is given by 1 – level of resistance, as described in section 3.8.7. Activity levels of each drug in the regimen are summed to give the total number of active drugs.

3.9. Toxicities

Toxicities including gastrointestinal symptoms, rash, hepatoxicity, CNS toxicity, lipodystrophy, hypersensitvity reaction, peripheral neuropathy and nephrolithiasis can occur with certain probability on certain specific drugs. In section 1.8.5 and Appendix II, it is indicated which toxicities are included in the Synthesis heterosexual model and the evidence available from RCTs and cohort studies is summarized in Appendix II. For some of the conditions there are no common definitions and it is therefore more complicated to understand the actual incidence of these conditions across different studies. All toxicity variables are binary, i.e. if the individual develops a certain toxicity in a given 3-month period, it takes the value 1, otherwise 0.

3.9.1. Incidence of new current toxicity

All individuals do not have any toxicity before initiating ART. Table 3.31 presents the probability of respectively developing and continuing having a toxicity in any given 3-month period.

Table 3.31. Risk of development of toxicities to ART in the model (643-648)

Toxicity	Drug	Risk of development per 3 months	Probability of continuation if pre-existing
Nausea	LPV, ddI, AZT	0.03 (5-fold higher in 1st year)	0.5
Diarrhoea	LPV	0.03/0.02*	0.2/0.5*
	ddI	0.05	0.2/0.5*
Rash	EFV	0.03 (one-off risk in 1st 3 months)	
	NVP	0.1 (one-off risk in 1st 3 months)	
CNS	EFV	0.1 (in 1st year, 0 after)	0.8 (in 1st year) 0.9 (after 1st year)
Lipodystrophy	d4T	0.05	1.0
	AZT	0.015	1.0
Peripheral Neuropathy	d4T	0.02 (1.5 fold higher in 1st year)	1.0 if remain on d4T, 0 otherwise
	DdI	0.01 (1.5 fold higher in 1st year)	1.0 if remain on ddI,0 otherwise
Acute hepatitis	NVP	0.02 (one off risk in first and 2nd 3 month periods)	
Anaemia	AZT	0.03 (1.5 fold higher in 1st year)	0.2
Headache	AZT	0.1 (1.5 fold higher in 1st year)	0.4
Pancreatitis	ddI, d4T	0.001/0.0002*	
Lactic acidosis	AZT, ddI, d4T	0.0002	

AZT: zidovudine; d4T: stavudine; ddI: didanosine; EFV: efavirenz; LPV: lopinavir; NVP: nevirapine; TDF: tenofovir; *: Zimbabwe;

3.9.2. Switching of drugs due to toxicity

If toxicity is present then individual drugs may be switched due to toxicity. In most cases, the switch is to another in the same class, if such a drug (that has not been previously failed nor stopped due to toxicity) is available. This will vary by setting and availability of alternative drugs.

3.10. First-line ART failure definition

The definition for first-line failure depends on the availability of CD4 count and VL measures for monitoring.

I assumed that monitoring of people on ART follows the recommendation on national guidelines in South Africa: VL monitoring (See section 2.1.7).

In Zimbabwe it is assumed CD4 is measured 6 monthly from 2003 and treatment failure is defined as CD4<200 cells/μL (confirmed by a subsequent CD4 at the same visit <200 cells/μL), after at least one year on ART. This is a simplification of what is indicated in the guidelines (see section 2.2.7).

3.11. Outcomes from the model of patients on ART

Table 3.32-Table 3.36 (page 189-page 191) present outcomes of patients initiated on ART. In particular, Table 3.32 gives an overview of the status of patients over time since ART initiation. It shows that at one year since ART initiation 88% are still attending the clinic (most of them are still on ART, 86%), while the remaining are either dead (5%) or lost from care (7%). This closely reflects what reported in the literature (see Appendix XX, page 471). However because the Synthesis model is at national level, it does not model the transfer of people from one clinic to another and thus people who transfer from one clinic to another would be considered retained in care in the Synthesis model. As time moves on from ART initiation, the proportion of people retained on ART diminishes, with 63% still retained on ART at 10 years since ART initiation. Of those not retained, 68% of them are going to be dead (26% of those who initiated ART 10 years before), 24% to be lost from care (9% of % of those who initiated ART 10 years before) and the remaining are going to be in care but off ART, because they chose to interrupt ART but they are still engaged in care.

Table 3.33 summarizes the immunologic, virological and resistance outcome up to 20 years since ART initiation. It shows that by one year 13% (when considering definition a) will experience virologic failure and this will increase up to 40% by 20 years. This is going to be accompanied by development of resistance in most cases. However, by one year almost half of those who initiated ART will experience an increase of CD4 of at least 100 cells/μL (12% of 200 cells/μL) and by 5 years over 90% (80% if considering an increase of 200 cells/μL). These assumptions are comparable to data from the literature (499;649).

To fully describe the immunological reconstitution in people receiving ART, Table 3.34 (page 190) presents the increase in CD4 count in people exposed to ART and restricting to those currently on ART. It shows that by one year since ART initiation the median increase in CD4 cell count is 71 cells/μL, when considering all those initiated on ART and 81 cells/μL in those still on ART after one year. By five and ten years the median increase in CD4 cell count reaches levels respectively over 200 and 300 cells/μL.

Table 3.35 (page 190) illustrates the risk of interruption of ART, of being LTFU and of death by length of time since ART initiation. By one year since ART initiation 14% are assumed to have interrupted ART, however only 5% are assumed not to be engaged anymore and 4% to be dead. ART interruptions are assumed to be a quite common phenomenon and by ten years more than half of the patients are assumed will have had some ART interruption, however only a subset are going to be lost (18% by five years and 46% by twenty years).

Finally, Table 3.36 (page 191) presents, for those who have been LTFU, the risk of death and of returning back into care. Although people who have been lost can return into care, there is evidence that ART interruptions are very detrimental on the chance of surviving. This table shows that by 1 year since the first time a person is lost after ART initiation 9% will be dead, while 16% will be back in care. This increases over time, with 30% and 69% people dying by respectively three and ten years since the first time they were lost from care. Most of those who disengage from care return into care by five years, however afterwards the rate of returning into care slows down and only 63% return by ten years.

Table 3.32. Cross sectional analysis at 1, 5, 10 and 20 years since ART initiation of status of patients initiated on ART

These were estimated using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cells/μL*.

	Years from start of ART			
	1	**3**	**5**	**10**
On ART	86%	78%	74%	63%
Off ART, attending the clinic	2%	2%	2%	3%
Off ART, lost from care	7%	8%	9%	9%
Dead	5%	12%	15%	26%

ART: antiretroviral therapy; *In both South African and Zimbabwe the CD4 at ART initiation is much lower, such a higher CD4 was determined to minimize the time to produce these tables.

Table 3.33. Kaplan-Meier estimates of virological failure, resistance and immunological recovery

Kaplan-Meier estimates of percent with virological failure (> 500 copies/mL after at least 6 months on ART (a) or two consecutive VL, the 1st >400 copies/mL, followed by a value above 1000 copies/mL (b)), resistance (predicted susceptibility < 50%) to at least one drug, CD4 count rise of > 200/μL, using parameter values which provided the best fit, assuming no ART interruption and restricting to people with no transmitted drug resistance and assuming no super-infection with resistant virus, in the context of CD4 at ART initiation of 270 cells/μL. Compare, for example, with (499;649).

	Years from start of ART				
	1	**3**	**5**	**10**	**20**
Virological failure (a)	13%	21%	27%	32%	40%
Virological failure (b)	9%	19%	25%	31%	39%
Resistance	12%	19%	24%	29%	45%
CD4 count rise of >200/μL	12%	61%	80%	93%	96%
CD4 count rise of >100/μL	46%	82%	91%	97%	98%

ART: antiretroviral therapy;

Table 3.34. Median and interquartile range in change in CD4 cell count from ART initiation in people exposed to ART (i.e. ever started on ART) and in those on ART.

These were estimated using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cells/μL.

	Years from start of ART			
Change in CD4 count	**1**	**3**	**5**	**10**
In ART exposed people	71 (1,143)	121 (-27,238)	220 (-42,367)	304 (97,478)
In people on ART	81 (17,143)	151 (88,308)	261 (89,375)	356 (182,498)

ART: antiretroviral therapy;

Table 3.35. Kaplan-Meier estimates of percent interrupting ART, lost to follow-up after starting ART, and dead.

This is using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cell/μL. Both restricting to those in care and including those lost to care.

	Years from start of ART				
	1	**3**	**5**	**10**	**20**
Interruption of ART*	14%	33%	45%	67%	88%
Loss to care	5%	12%	18%	30%	46%
Death (in those under care)	3%	7%	10%	18%	40%
Death (including those lost)	4%	8%	14%	28%	56%

ART: antiretroviral therapy; *The interruption of ART does not mean that the patient is not attending the clinic, but simply that it is not taking ART. As mentioned above, the people not in care can go back to HIV care and restart ART.

Table 3.36. Cumulative risk of death and returning to care after first being lost to follow-up after starting ART.

These were estimated using parameter values which provided the best fit, in the context of CD4 at ART initiation of 310 cells/μL.

	Years from first lost (after starting ART)			
	1	**3**	**5**	**10**
Death while lost	9%	30%	50%	69%
Return after loss to care	16%	43%	55%	63%

ART: antiretroviral therapy;

3.12. Risk of clinical disease and death in HIV-infected people

The choices of parameter estimates in this section are broadly based on references (123;126;129;148;650). Factors were chosen to provide results consistent with observed data, including the incubation period for death and the time from AIDS to death in untreated people (103;117;651-653).

3.12.1. Occurrence of WHO stage 4 event

Occurrence of WHO stage 4 diseases (see (126;129;148)) is assumed to depend on CD4 cell count (see Table 3.37), VL (see Table 3.38 at page 193), age (See Table 3.39 at page 193), PCP prophylaxis and ART regimen.

3.12.1.1. Independent effect of CD4 cell count

Table 3.37. Rate of WHO 4 disease according to CD4 count in the model

CD4 cell count	Rate of WHO 4 diseases per 3 months (per 100 person-years)
≥650	0.2
[500-650)	1.0
[450-500)	1.3
[400-450)	1.6
[375-400)	2.0
[350-375)	2.2
[325-350)	2.5
[300-325)	3
[275-300)	3.7
[250-275)	4.5
[225-250)	5.5
[200-225)	6.5
[175-200)	8
[150-175)	10
[125-150)	13
[100-125)	17
[90-100)	20
[80-90)	23
[70-80)	28
[60-70)	32
[50-60)	40
[40-50)	50
[30-40)	80
[20-30)	110
[10-20)	180
[0-10)	250

3.12.1.2. Independent effect of viral load

The impact of VL on the rate of experiencing WHO stage 4 diseases is obtained by multiplying the CD4-specific rate by the factors indicated in Table 3.38.

Table 3.38. Multiplicative factor based on viral load on the rate of experiencing WHO stage 4 disease

Viral load level	Multiplicative factor
< 3.0 log copies/mL	0.2
3.0 - 4.0 log copies/mL	0.3
4.0 - 4.5 log copies/mL	0.6
4.5 - 5.0 log copies/mL	0.9
5.0 - 5.5 log copies/mL	1.2
> 5.5 log copies/mL	1.6

3.12.1.3. Independent effect of age

To take into account the fact that the risk of experiencing WHO stage 4 increases as age increases the rate is determined as:

$$rate_{WHO4} = rate_{WHO4} * \left(\frac{age}{38}\right)^{1.2}$$

See examples in Table 3.39.

Table 3.39. Example of multiplicative factor based on age on the rate of experiencing WHO stage 4 disease

Age	Multiply rate by
20	0.46
30	0.75
40	1.06
50	1.39

3.12.1.4. Independent effect of PCP prophylaxis

If the patient is on PCP prophylaxis, the rate of WHO stage 4 occurring is multiplied by 0.8.

From 1996, patients with a measured CD4 count below 350 cells/µL are assumed to have an 80% chance of starting PCP prophylaxis and those with a current WHO stage 3 or 4 condition 90% chance of starting it. They interrupt the use of PCP once they have a measured CD4 cell count above 350 cells/µL, if CD4 cell count is measured, or if the patients has been continuously on ART and did not experience WHO stage 4 or 3 in the last 6 months.

3.12.2. Occurrence of WHO stage 3 event

To obtain the rate of WHO stage 3 diseases occurring, the rate of WHO stage 4 occurring is multiplied by 5 (*fold_incr_who3*).

3.12.3. Occurrence of HIV-related death

To obtain the base rate of occurrence of an HIV related death, the rate of WHO stage 4 occurring is multiplied by 0.25 (*fold_decr_hivdeath*).

The base rate of HIV related death is then affected by presence of current TB and whether the patient has an AIDS defining condition. In the first case the rate is multiplied by 5 in South Africa and 10 in Zimbabwe (*incr_death_rate_tb*), in the second case by 2 and 10 (*incr_death_rate_adc*).

This different assumption regarding the impact of TB and AIDS on mortality in Zimbabwe compared to South Africa was necessary to be able to reproduce an epidemic such as that observed in Zimbabwe (in terms of the observed decline in HIV prevalence and death rates).

It is assumed 15% of HIV-related deaths (i.e. not including deaths that arise due to background mortality rates) are classified as non-HIV-related.

3.13. Calibration of the model

To calibrate the model to the South African epidemic, I used Approximate Bayesian Computation methods (654). In essence, this involves running multiple simulations which sample unknown parameter values from suitable distributions, which are meant to reflect the uncertainty around them, and then selecting those parameter sets where simulated model outputs are most consistent with observed data, by assessing the fit using a summary statistic. In the Synthesis model, there are multiple parameter values describing various elements of the underlying progression of HIV and the effect of ART. The model has been shown to give a good fit to data on these processes and, for the purposes of fitting the model to the HIV epidemic in a given country, I hold these parameter values fixed (58 for the South African model and 69 for the Zimbabwean model). They, thus, become part of the model structure rather than parameters to be sampled from. Nevertheless, some of the parameters are fixed and different in the model calibrated to South Africa and Zimbabwe, either because I decided

in collaboration with the other people working on the model to further develop the model, this is for example the case for including separately NNRTI mutations in the Zimbabwean model or because it was necessary to be able to calibrate the model to observed data (see section 3.12.3). Other differences are due not generally to new data becoming available but, especially for areas with more uncertainty such as resistance, give conservative results and so for example not underestimating the potential impact of resistance.

The parameters for which values are sampled from distributions of plausible values are mainly those which determine levels of condom-less sex and the rate of HIV transmission (28 for the South African model and only one for the Zimbabwean model). When sampling parameters which determine the HIV incidence and prevalence it is important to ensure that the parameter space sampled is chosen to be large enough to allow for extremities and that the parameterization is sufficiently flexible but also restricted enough to limit computation time. So for each run of the simulation model, I sampled at random a set of parameter values for those listed in Appendix XI with the distribution, and generate the HIV epidemic until the end of 2012. In order to improve the efficiency of the sampling I assumed correlation between the three following parameters: (a) Fold difference in transmission rate for a given VL (*fold_tr*), (b) rate of transmission in PHI (*tr_rate_primary*) and (c) factor to change overall average level of condom-less sex with short-term partners (*newp_factor*).

This is repeated 10,000 times in order to search for the best fitting parameter sets. For each run, the fit of the model to the observed data was assessed using a fit score; the sum of the deviances from the observed data (summed over the number of years data was available for, and for each type of data available), is quantified by $\frac{|D-M|}{D}$, where *D* is the observed data and *M* is the estimate produced by the Synthesis Model.

The data used to fit the model to the South African HIV epidemic are (41 points):

- HIV prevalence among adults aged 15 to 49 years (available for 2002, 2005, 2008, 2011) (452)
- HIV prevalence among young people, aged 15 to 25 years (available for 2002, 2005, 2008) (452)
- the proportion, gender-specific, of people who ever had an HIV test (available for 2002, 2005, 2008) (452)
- the number, gender-specific, who started ART (available from 2001 to 2011) (655)
- the proportion of new diagnoses with resistance (available from 2005 to 2010) (305).

Half weight was assigned to the deviance to the proportion of new diagnoses with resistance, because this estimate refers to southern Africa, rather than specifically South Africa and it may be not representative of all South Africa. The 30 simulations with the best fit (out of 10,000), in terms of average deviance, were selected (average deviance of less than 0.94).

The data used to fit the model to the Zimbabwean HIV epidemic (128 points) are:

- HIV prevalence among adults aged 15 to 49 years, separately from men and women (available for 2006, and 2011) (518;519)
- HIV prevalence for women aged 15 to 49 years in 1995 cited by Gregson (514)
- HIV prevalence in all 5-years age group between the age of 15 and 49 for women and 54 for men (available for 2006 and 2011) (518;519)
- the proportion, gender-specific, of people who ever had an HIV test (available for 2006 and 2011) (518;519)
- the proportion, gender-specific, of people who ever had an HIV test in all 5-years age group between the age of 15 and 49 for women and 54 for men (available for 2006 and 2011) (518;519)
- the proportion, gender-specific, of people who had an HIV test in the last 12 months (available for 2006 and 2011) (518;519)
- the proportion, gender-specific, of people who had an HIV test in the last 12 months separately for all 5-years age group between the age of 15 and 49 for women and 54 for men (available for 2006 and 2011) (518;519)
- the proportion of pregnant women who receive an HIV test in the ANC (available for 2006 and 2011)
- the proportion of pregnant women who receive an HIV test in the ANC separately for all 5-years age group between the age of 15 and 49 for women (available for 2006 and 2011)

A weight of 1 was assigned to all the deviance between the gender-specific estimate for the entire population 15 to 49 years old, while to the deviance for each 5-years age group was assigned a weight so that, all the age group together would sum up to a wait of 1.

Only the simulation with the best fit was selected and in Chapter 8 this simulation is illustrated together with the observed data used to calibrate the model. The fact that only one simulation is selected means that I could not present the 90% uncertainty range and so how the

parameters uncertainty propagated (only one parameter was sampled, while the other parameters were hand tuned). This choice was driven by feasibility; I do plan to use approximate Bayesian computational methods to calibrate the Zimbabwe HIV epidemic and to present 90% uncertainty range.

The purpose of fitting is to select those combinations of parameters which more closely reflect the HIV epidemic observed and, by selecting appropriate distribution from which to sample the parameters and appropriate threshold to select simulations that fit, produce some indication of the parameter uncertainty. In order to reflect in the output, the uncertainty in the input parameters, for South Africa I selected a subset of simulations who provided a good fit, rather than only one single simulation, and I presented the 90% uncertainty range (the 5^{th} and 95^{th} estimate across the simulations for that particular outcome). This measure of uncertainty clearly depends on the cut-off used to determine whether a simulation is consider to fit to the data or not and it is in some way an arbitrary choice. However the choice of the distributions from which parameters are sampled from are arbitrary as well, because it is difficult to quantify the uncertainty.

In order to fit the Synthesis model to observed data and to produce output measures up to 2013, expressed in absolute terms, which are relevant respectively for South Africa and Zimbabwe, I multiply the modelled population size by the ratio between the estimated adult population size (for South Africa in mid-2011 (481), for Zimbabwe in mid-2013 (434)) and the size of the modelled population (673 for South Africa, 222 for Zimbabwe).

3.14. My view on the Synthesis model

As mentioned, when I started working on the Synthesis model, the core of the model was already developed. Thus, I could not have the privilege of choosing how to model some processes within it. However, if there were processes or assumptions I was uncomfortable with, these were discussed with the other colleagues working on it and an agreement was found.

I think this model can provide (and has already provided) important contributions to inform policy decisions making processes, given its peculiarities. Differently from most of the other HIV mathematical models, which are deterministic compartmental models, it is an individual based stochastic model. This allows including a higher level of details, such as for example all the single steps in the continuum of care, while at the same time taking into account the emergence and transmission of resistance. In addition, it is very suitable to run cost-effectiveness analysis which are more and more often used, or at least considered, when making decisions.

On the other hand, its complexity and richness of details sometimes make it difficult to understand which parameters are driving the results observed and, although it improved over time, it still takes long time to run and therefore not always it is possible to run extensive sensitivity analyses.

4. Cost-effectiveness of expanding the population in care and/or the population eligible for antiretroviral therapy

4.1. Outline of the chapter

In the previous chapters the South African epidemic has been introduced and the Synthesis model has been thoroughly described. In this chapter the Synthesis model is used to evaluate the impact of expanding diagnosis, improving retention and modifying the eligibility criteria for ART initiation in South Africa.

There is in fact lots of debate regarding when to initiate ART on the basis of the clinical and the preventive benefit. The evidence on the clinical benefit is presented and a formal literature review on the preventive benefit of ART has been performed. Several mathematical models have addressed this question comparing slightly different strategies and different outcomes. To enable a straightforward comparison, the HIV Modelling Consortium, which is funded by Bill and Melinda Gates Foundation with the aim to enhance the scientific support in the decision making processes related to HIV public health and led by Imperial College (656), asked modellers using different mathematical models to evaluate exactly the same intervention in the South African setting. They collected in a systematic way the standardized outcomes from different models. The findings of the cost-effectiveness analysis using the Synthesis model are presented in this chapter and the results are compared to the findings from other mathematical models, which took part in this collaborative project led by the HIV Modelling Consortium.

4.2. Literature review of the preventive benefit of antiretroviral treatment

4.2.1. Background

The idea that ART could be used not only to reduce morbidity and mortality amongst HIV-positive people, but also to prevent onwards sexual HIV transmissions, by reducing the infectiousness of HIV-positive people, is not new. The ability of ART to suppress VL is well

documented (609;657;658) (see section 1.8.7) and many observational studies have found a strong association between plasma VL and the risk of onwards transmission (31;38;42;659).

In January 2008 some researchers formulated what has been called the 'Swiss Statement' (660), stating that:

> *"the risk of sexual transmission of HIV is negligibly low if three conditions are met: (i) the HIV-positive person is receiving antiretroviral therapy with excellent adherence; (ii) blood VL has consistently been undetectable (<40 copies per mL) for more than 6 months; and (iii) no [sexually transmitted diseases] STDs are present in either of the partners."*

This ignited a vigorous debate on whether there was strong enough evidence to support this statement.

The principle that ART can reduce HIV infectiousness to varying degrees at an individual level is largely agreed. However, at a population level, several factors could potentially limit the reduction in secondary transmission. These include the longer potential duration of infectiousness due to the longer survival of people receiving ART, the potential difficulty in maintaining viral suppression over long periods of time (mainly driven in sub-Saharan Africa by drug supply issues, adherence and being able to attend the clinic regularly), the fact that transmission often occurs when people are still in PHI or undiagnosed, and potential increases in sexual behaviour as a result of feeling better due to ART or being aware that ART reduces infectiousness. In addition, some have doubts as to whether ART initiation for all HIV-positive people should be implemented due to ethical difficulties, in particular the fact that there is no agreement regarding the individual clinical benefit of starting ART earlier, and whether it is the most cost-effective strategy.

The aim of this section is to present the results of a formal literature review on the population-effect of earlier initiation of ART to prevent new infections. This work was performed as part of the preparation of a technical report commissioned by the European Centre for Disease Prevention and Control (661) aimed at evaluating HIV treatment as prevention (including ART as prevention in HIV-positive people, PMTCT and post-exposure prophylaxis) and at discussing the implications for Europe. The review has been updated on the 19th November 2013 and it has now been published (662).

4.2.2. Conduct of the formal literature review

A formal literature search was conducted to identify all relevant original papers published in the most recent years, regarding the impact of using ART as prevention, rather than as treatment to prevent morbidity and mortality in HIV-positive individuals, focusing on the population-level effect. The search was conducted on all databases available on Web of Knowledge: Web of Science, MEDLINE, BIOSIS Citation Index, BIOSIS Previews and Journal Citation Report. I searched for all papers (excluding case report, biography, editorial, book, correction, report, review, patent, meeting, news, bibliography, letter) written in English, in several relevant subject areas (infectious diseases, virology, social issues, behavioural sciences, social sciences other topic, mathematics, life sciences biomedicine other topics, biomedical social sciences, mathematical computational biology) in the last 8 years (2006-2013) with topic 'HIV*' and 'antiretroviral*' and ('prevent*' or 'transmi*')) NOT Topic=('child*' or 'mother*' or 'vertical' or 'prophylaxis' or 'pregnan*' or 'herpes' or 'breast*' or 'tuberculosis'). The search was restricted to studies published after 1 January 2006 because this is the period in which most studies concerned with the impact of ART for prevention have been published. Relevant papers published before this period (e.g. Quinn NEJM 2000 (31)) were selected by hand searching papers already known to the authors and by checking the references of all selected papers and were also included in the review. In addition, for all papers selected it was checked whether there were any corrections. A possible limitation is the fact that the search was restricted to papers written in English. Nevertheless, journals with the highest impact factor are generally published in English and therefore I believe the likelihood that important studies on this topic were omitted from our review is minimal.

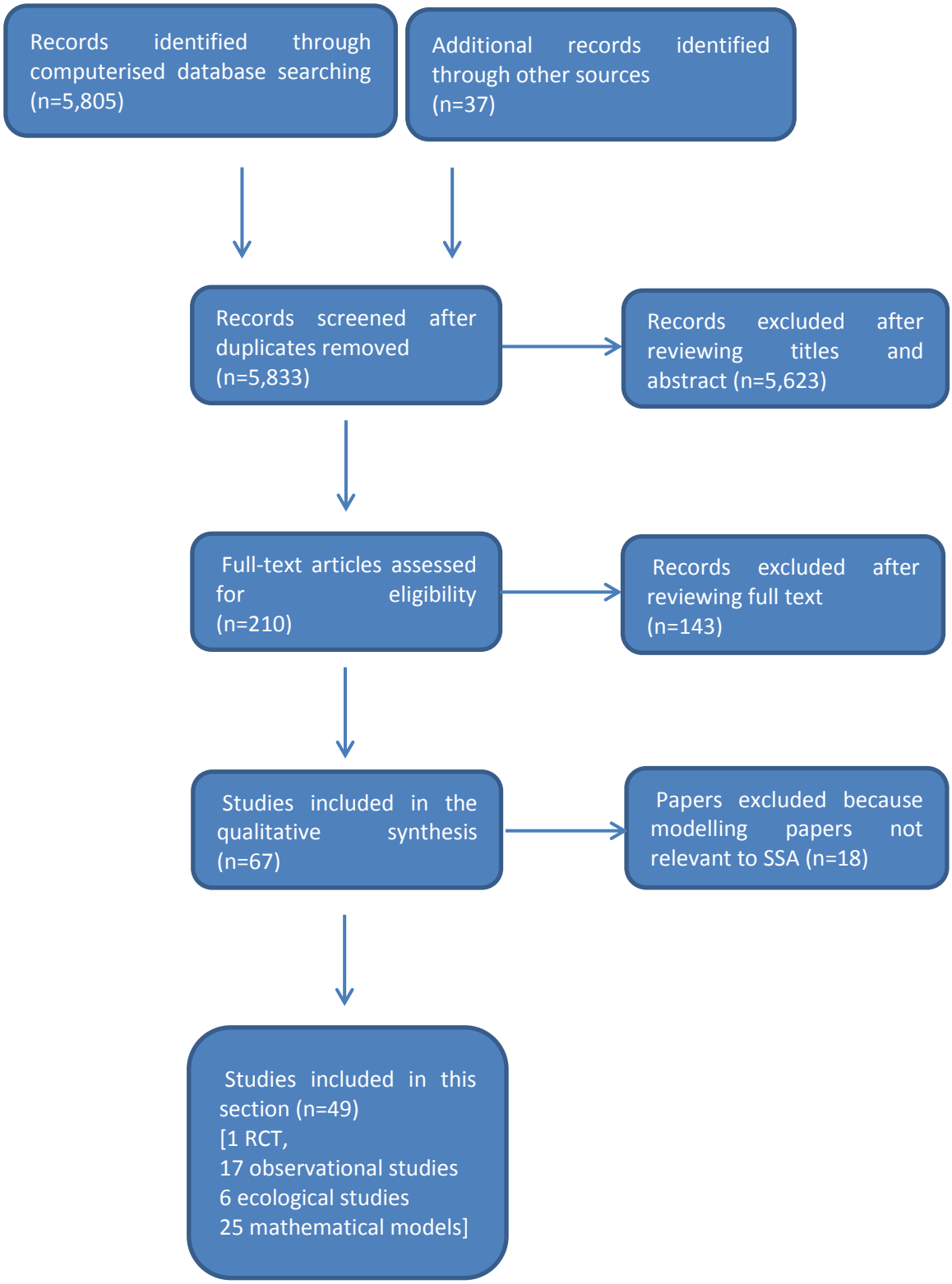
The search on Web of Knowledge for the European Centre for Disease Prevention and Control review was performed on the 5th September 2011 and updated on 19th November 2013. Papers found through the computerised database searching on Web of Knowledge were combined with those identified by hand-searching. Jemma O'Connor and I independently screened the records identified in September 2011 and I screened those identified thereafter, by reviewing the title and abstract to identify those eligible for full-text appraisal. If disagreement was found in the papers selected, these were discussed and an agreement was found. For the papers identified in September 2011 we both assessed the papers included based on the full text and information on the type of study, setting, follow-up period, sample size, population and outcome measures collected. All studies that evaluated the impact of ART on preventing new HIV infections compared to absence or delayed treatment in HIV-positive populations were included in the review, regardless of study design. There were no specific

requirements regarding the outcome measure used; any measure of HIV incidence or prevalence was considered acceptable. I interpreted the results and together with the other authors the manuscript was prepared.

5,805 (n=2,105 on 5th September 2011) papers were identified with the computerised database search and 34 through hand searching. After removing duplicates and excluding references considered not relevant by two independent persons (only the records published before 5th September 2011 were screened by two persons), 205 (n=166 on 5th September 2011) publications were fully reviewed and 62 (n=32 on 5th September 2011) were included in the formal literature review.

For the purpose of this chapter I excluded the papers where mathematical models were used to evaluate the impact of earlier ART initiation in specific settings different from sub-Saharan Africa, because these were beyond the scope of this PhD thesis. The results of the search are shown in Figure 4.1 and the papers identified by these literature searches are summarised in Appendix XII.

Figure 4.1. Flow chart of literature search



4.2.3. Observational studies

The association between VL and heterosexual transmission of HIV-1 has been reported by many observational studies of HIV serodifferent heterosexual couples (31;35;36;38;663).

The first evidence of an association between use of ART and HIV prevalence came from cross-sectional studies. Castilla and colleagues (430) observed in 393 steady heterosexual couples in Madrid, Spain, that the prevalence of HIV was 8.6% among partners of index cases who had not received ART, whereas no partner was infected in couples in which the index case had been on ART (p = 0.0123). Similar findings were reported by a small study (n=93 of serodifferent couples), where none of the new HIV infections was from couples where the partner was on ART (664).

Concordant results were found in longitudinal studies. In 2010, a very large observational study of people recruited to the 'Partners in HSV/HIV transmission' study (3381 couples) (431) confirmed the evidence of a reduction in HIV transmission for people on ART (the HIV-positive person was co-infected with HSV-2 and had a CD4≥250 cells/µL). They observed 103 genetically linked HIV-1 transmissions where only one occurred from an infected participant who had started ART, corresponding to a transmission rate of 0.37 (95% CI: 0.09, 2.04) /100 PYs, compared with 2.24 (95% CI: 1.84, 2.72) /100 PYs in those who had not initiated ART. In a study conducted in Spain (659) no HIV SCs occurred in 144 couples where the HIV-positive partner was taking ART in over 7,000 condom-less sex acts (corresponding to a risk of transmission of 0 and a 95% CI of 0 to 0.0005 per condom-less sex act), while 5 HIV SCs occurred in 341 serodifferent couples and over 10,000 condom-less acts of intercourse in which the HIV-positive partner was not taking ART (a risk of 0.0004 per condom-less intercourse; 95% CI: 0.0001, 0.0010). Similarly, the Rakai study (665), although on a small number of couples, reported that no HIV-1 transmissions occurred during 53.6 PYs on ART. A study following 2,993 couples from Rwanda and Zambia (5,609 PYs of follow-up) reported an HIV incidence of 0.7/100 PYs in couples where the HIV-infected partner was on ART, and 3.4/100 PYs in couples where the HIV-infected partner was not on ART (666). They were interested in investigating whether the impact of ART in reducing transmissions was different in the two genders and reported that if the woman was infected with HIV and on ART the incidence was 1.4/100 PYs (95% CI: 0.4, 3.7), 3.2/100 PYs (95% CI: 2.5, 3.9) if she was off ART, 0/100 PYs (95% CI: 0.0, 1.4) if the man was infected with HIV and on ART and 3.6/100 PYs (95% CI: 2.9, 4.5) if he was off ART. A very large study from China (n=38,862 serodifferent couples, 101,295 PYs of follow-up) was published in 2013 (667). They estimated a rate of HIV-infection of 2.6/100 PYs (95% CI: 2.4, 2.8) among the couples where the HIV-positive partner was ART-

naïve and 1.3/100 PYs (95% CI: 1.2, 1.3) among the couples where the HIV-positive partner was on ART. Interestingly, in this study they found that among people who inject drugs, the association between the risk of HIV transmission and the HIV-positive partner being on ART could not be confirmed (667). A word of caution came from a couple of studies from China and Uganda (668;669), that did not observe a statistical differences in SC rate between couples where the HIV-positive partner was receiving ART or not. The former (669) is a retrospective study conducted in the province of Henan, China, where 1,927 serodifferent couples were followed. One possible explanation to why they did not find any impact of ART in reducing the risk of HIV transmission could be low rates of viral suppression in those on ART (669). The second study (668) followed 586 couples in rural Uganda, of which in 60% the HIV-positive partner was on ART. In this setting, VL monitoring is not available and therefore it is not clear if those on ART had a suppressed VL.

Evidence that ART is reducing HIV incidence outside of controlled and well monitored settings, as is the case for RCTs, came from a very large cohort of HIV-uninfected individuals living in KwaZulu-Natal, South Africa (670). They observed that people living in areas with high coverage of ART had a lower risk of becoming infected with HIV than people living in areas with low coverage (e.g. the risk of HIV acquisition for a person living in a community with an ART coverage of 30–40% of all HIV-infected individuals was 38% less than for someone living in a community where ART coverage was less than 10% of all HIV-infected individuals).

Several meta-analyses have been conducted to estimate the risk of HIV transmission, according to ART status (429;671-673). One meta-analysis (429) on observational cohort studies of heterosexual HIV-serodifferent couples observed no transmissions among couples where the HIV-positive partner was treated with ART and had VL levels below 400 copies/mL (rate of 0/100 PYs; 95% CI: 0, 1.27). Loutfy et al. (674) considered the level of detectability specific to each study (which varied from 50 to 500 copies/mL) and estimated the risk of HIV transmission in people fully suppressed on ART to be 0 (95% CI: 0, 0.05) /100 PYs when VL was confirmed at the time of transmission and 0.14 (95% CI: 0.04, 0.31) /100 PYs when the VL was not confirmed. In a meta-analysis (672) of observational studies of serodifferent couples, when they restricted to data with adequate follow-up and in which triple ART was used, they estimated that ART reduces the risk of HIV transmission by 64% (RR = 0.36; 95% CI: 0.17, 0.75). Baggaley et al. (673) systematically reviewed the data on observational cohort study of serodifferent couples. Using the studies where it was possible to quantify the impact of ART on

the risk of HIV transmission, they estimated that ART reduces per-partner HIV-1 incidence rate by 91% (95% CI: 79, 96%).

In contrast to the many observational studies which have evaluated the relationship between VL and the risk of transmission among heterosexual couples, the direct empirical evidence regarding the relationship between ART use and the risk of HIV transmission in MSM is limited and only from high income countries (63). This topic is not discussed further given the main source of transmission in South Africa and Zimbabwe is through heterosexual sex and this version of the Synthesis model does not include transmission through people of the same sex.

4.2.4. Ecological Studies

Several ecological studies have provided evidence of a population-level association between the implementation of wide-scale ART and a decline in the number of new diagnoses (675-677), although a number of other studies, particularly amongst MSM have not concurred (678;679). An ecological study conducted in British Columbia, Canada (677) reported a strong and significant association between increased ART coverage and a decline in the number of new HIV diagnoses per year. Between 1996 and 2009 ART coverage in British Columbia increased by 547% and the number of new diagnoses decreased by 52%. Similar findings were reported from another study based on a cohort of all HIV-positive individuals in San Francisco (675). Community VL (i.e. the average VL among all individuals diagnosed with HIV) was calculated and analysed as a population-level marker of HIV transmission risk. A significant association was found between decreases in annual community VL and temporal decreases in the number of new HIV diagnoses. The authors observed that HIV incidence fell by over one-third in the years 2006 to 2008. Interestingly, during the same period there was an increase in the number of reported cases of rectal gonorrhoea. Although data on sexual risk behaviour were not collected, data on rates of rectal gonorrhoea were used as a surrogate marker for sexual risk behaviour. The authors argued that the reduction in the number of new infections in a period where risky sexual behaviour probably increased substantiates the hypothesis that achieving high level ART coverage is an effective and important approach towards the prevention of HIV transmission.

In Taiwan, a study was conducted using nationwide surveillance data (676) to assess the impact of a policy to provide free ART to all HIV-positive individuals on the rate of transmission. The introduction of the policy was associated with a 53% decrease in the rate of

transmission and was accredited with the effective control of the HIV epidemic in Taiwan. The incidence of syphilis was analysed in order to distinguish between the effect of ART and that of behavioural modifications. During the study period there was no statistically significant change in the incidence of syphilis in both the general population and the HIV-positive population. With thousands of new cases of syphilis reported each year, it is evident that risky sexual behaviour is prevalent and therefore, the authors argued that it is unlikely that the reduction in the HIV transmission rate was due to decreases in sexual risk behaviour. However, three studies (678-680) whose primary aim was to observe trends in recent HIV infections in MSM found that HIV incidence is increasing. These studies were conducted in Amsterdam, the UK and more generally in Europe and North America. This suggests that on-going HIV transmission is occurring despite access to effective ART.

The findings from ecological studies should be examined with extreme caution. Firstly, there is the possibility of ecological fallacy, whereby inferences about specific individuals are based solely upon aggregate statistics collected for the group to which those individuals belong, in which case the generalizability of the results is limited. Secondly, as with all observational studies it is difficult to rule out confounding which means that establishing causality can be problematic. Thirdly, the studies were restricted to measuring numbers of new diagnoses rather than the main aspect of interest: incidence of new HIV infections.

4.2.5. Randomized Controlled Trials

The strongest evidence to date on the ability of ART to reduce heterosexual HIV transmission comes from the HPTN 052 RCT (432). This study was designed to compare the effect of early versus delayed ART on transmission of HIV. 1,763 heterosexual serodifferent couples in which the HIV-positive person was ART-naive and had a CD4 count between 350-550 cells/µL were recruited from nine countries and couples were randomized to either immediate ART, or delayed initiation (ART was initiated after two consecutive CD4 counts ≤250 cells/µL). The primary endpoint was genetically linked HIV infection in HIV-negative partners. Three months after baseline, 89% of participants in the early therapy group had achieved viral suppression (<400 copies/mL) compared with 9% of the delayed therapy group. A total of 28 virologically linked transmissions were observed; only one occurred in the early therapy arm. This represents a 96% relative reduction in linked HIV transmissions as a result of initiating ART compared with deferral (hazard ratio [HR] = 0.04; 95% CI: 0.01, 0.27; p<0.001). These findings

are believed to be a result of sustained suppression of VL in genital secretions (432) and provide support for the use of ART in the prevention of HIV among heterosexuals. Analysis of the genetic sequences of HIV of two people who got infected with HIV in the HPTN 052 study, one in the early arm and one in the delayed arm, who were diagnosed after the index partner had initiated ART revealed that these infections occurred either before their HIV-positive partner initiated ART or at least before the viral replication was suppressed (681). This strengthens the evidence that people with suppressed VL induced by ART use have very low chances of transmitting HIV.

Although this study provides the most definitive evidence currently available to support use of ART to prevent sexual transmission of HIV, it is not without its limitations. Trial participants were in stable HIV- serodifferent relationships and may not be a representative sample of all heterosexual serodifferent couples in the general population. These couples were also receiving free condoms, couples counselling on risk-reduction, and treatment for sexually transmitted infections (STIs) which may have impacted upon the low incidence of HIV transmissions in the early therapy group; although it is not obvious that this could result in a bias between the arms. Reported condom use in the HPTN 052 study was extremely high: 96% of those in the early-therapy group and 95% of those in the deferred-therapy group reported 100% condom use during the study. This very high reported condom use rates are unlikely to reflect real life conditions and may be due to a social desirability bias.

Also, the findings are mainly applicable to vaginal heterosexual sex and uncertainty remains over the ability of ART to reduce infectivity through anal sex and through exchange of blood products (e.g. through needle sharing in people who inject drugs). The strong evidence in the context of heterosexual (mainly vaginal) transmission suggests that there are likely to be similar reductions in infectivity through other routes. However, given important biologic differences in transmission mechanisms for these transmission routes, it is not possible to confidently extrapolate existing evidence based mostly on vaginal transmission. In particular due to the higher per-contact probability of HIV transmission through anal intercourse compared to vaginal intercourse, it may be that the transmission threshold through anal intercourse may be lower and therefore that the risk of HIV transmission in people virologically suppressed may not be negligible (682;683). It is important that research in these areas is prioritized to support policy decisions regarding the use of ART as prevention.

For ethical reasons, HPTN 052 compared the effect of condoms alone among those not receiving ART and the effect of condoms and ART for the HIV-positive person on the probability of HIV transmission. Therefore the absolute risk of transmission on the early ART arm (1 in 893) does not represent the risk through condom-less sex when the HIV-positive person is on ART; rather the risk in the context of 96% consistent self-reported condom use plus ART. The risk of transmission through condom-less vaginal and anal sex for a person who has suppressed plasma VL remains uncertain and represents another knowledge gap. The PARTNER study, which is taking place in Europe amongst serodifferent couples, is addressing this question (684). So far we reported 0 genetically linked HIV transmission over 894 couple-years of follow-up in serodifferent couples (a third being MSM couples) where the index partner was on suppressive ART (VL<200 copies/mL) and we reported having condom-less sex, corresponding to a rate per 100 couple-years of follow-up of 0 (95% CI: 0, 0.4) (63). When restricting to follow-up where the HIV-negative partner reported anal sex within the couple, the rate was estimated to be 0 but with more uncertainty (95% CI: 0, 0.96). My role within the PARTNER study is to clean the data collected and to conduct the statistical analyses.

4.2.6. Mathematical Models

The effect of increasing the number of people receiving ART on HIV transmission and its cost-effectiveness has been analysed using several mathematical models (685-692).

Baggaley et al. (688), who were amongst the earliest to investigate the impact of increased ART coverage in a sub-Saharan epidemic, concluded that expanded ART coverage would not be an effective transmission prevention measure. They implied that this approach would not work regardless of the degree of ART coverage, as the total number of infections prevented would be marginal.

More recently, several modelling studies have suggested that expanded ART and increased testing would be effective in reducing HIV incidence (686;687;689) and could therefore offer public health benefits. Abbas et al. assessed the potential impact of ART on the heterosexual spread of HIV in a generalized epidemic in sub-Saharan Africa (687). The results of this study indicate that increasing ART coverage in 2006 at a national HIV prevalence of 5% would be more effective than later implementation when the prevalence of HIV was at 40%; the predicted reduction in the number of new HIV infections was 33% at 5% prevalence and 27% at 40% prevalence.

Wilson et al. (693) investigated the implications of the Swiss statement (660) at a population level, by means of a simple mathematical model. On the basis of Rakai study (31), they derived a mathematical relation between VL and the risk of HIV transmission per condom-less penetrative sexual contact. By assuming that each couple had 100 sex acts per year they calculated the cumulative probability of transmission to the serodifferent partner each year. The authors concluded that the risk of HIV transmission in heterosexual partnerships in the presence of effective ART is low but non-zero, and that the transmission risk in male homosexual partnerships is high over repeated exposures. Therefore they underlined the potential danger that the claim of non-infectiousness in effectively treated patients could cause if widely accepted, and condom use subsequently reduced.

The estimated effect of universal voluntary testing (annual testing of 90% of the entire population) and initiation of ART upon diagnosis, often referred to as “Test and Treat”, varies between models with implications as optimistic as HIV elimination (686) ranging to net harm under specific circumstances (694).

In 2009 Granich et al. (686) predicted, using a model calibrated to the epidemic in South Africa, that the test and treat strategy would reduce HIV incidence to less than 1 case per 1,000 people per year by 2016 and the prevalence to less than 1% within 50 years of its full implementation and that elimination could be feasible by 2020. Following the paper in 2009, they (691) evaluated the cost-effectiveness of different CD4 count threshold for ART initiation (CD4 count<200 cells/μL, CD4<350 cells/μL, CD4<500 cells/μL; any CD4 count) in the context of South Africa over the time frame 2011-2050, assuming high level of HIV testing (90% of the population tested annually). They concluded that all scenarios were cost-saving compared with the scenario where people were eligible to initiate ART when CD4 falls below 200 cells/μL, with a higher number of HIV infections and deaths saved as the CD4 count threshold increases: respectively 1.4, 2.9 and 4.3 million new HIV infections saved with CD4 count threshold of CD4 below 350 cells/μL, below 500 cells/μL and regardless of CD4 count respectively, while the number of deaths averted was respectively 1.5, 3.0 and 3.9 million. In sensitivity analysis they found that poor retention in care and predominant acute phase transmission played an important role and could reduce savings by 7%.

Kretzschmar et al. (695) generalized the model used by Granich et al. (686) to generate a number of hypothetical HIV epidemics and explore in which circumstances of ART uptake and drop out, HIV elimination would be achievable and whether it was cost-effective. They concluded that this goal was feasible only in populations with very low R_0 (basic reproduction

number; approximately 2 or lower) and high annual treatment uptake (approximately 85% coverage).

Hontelez et al. (696) assessed the impact of nine different model structures, capturing different levels of realism, on the long term outcome of universal voluntary test and treat (as defined by (686)). The most complex structure considered was the STDSIM model, while the simplest was very similar to Granich et al. model (686). They concluded that HIV elimination would be achieved by 2050 by universal test and treat and that this would be cost-effective. Nevertheless they predicted that the time to achieve this target is much longer than the 7 years estimated by Granich if more realism is included in the model.

Palombi et al. (697) used data from the Drug Resource Enhancement Against AIDS and Malnutrition Program (in Malawi and Mozambique), collected between January 2002 and July 2009 to evaluate the impact of initiating ART at different CD4 count thresholds. They compared a scenario of universal treatment (annual universal voluntary testing of adults, immediate ART of HIV-infected individuals with CD4 count <350 cells/μL and/or WHO stage 3 or 4 and treatment of patients with CD4 count >350 cells/μL when reaching this CD4 count threshold over time, and treatment of all HIV-infected pregnant women, regardless of CD4 or VL) to a scenario where 45% of individuals eligible for ART in Malawi receive it in each year. They estimated that annual incidence of HIV infection would decline from 7% to 2% in 2 years, the prevalence would halve, from 12% to 6%, in 11 years and mortality in HIV-infected individuals would decline by 50% in 5 years.

Some mathematical models focused their attention on specific aspects either of the cascade of care (689;690;698), or of characteristics related to treatment, such as toxicities, adherence (694) or survival of people on treatment (699).

A model by Bendavid (689) assessed the health benefits of four different strategies which involved combinations of test and treat, improved linkage to care and reduced LTFU. Model parameters were based on the epidemic in South Africa, where HIV transmission is predominantly heterosexual. Findings from the study showed that a comprehensive strategy which involves 90% of the population being tested and all HIV-positive individuals receiving ART within 6 months of diagnosis, perfect linkage to care and no LTFU, would result in a 73% reduction in the number of potential new infections in the South African population, over a 10 year period.

Andrews et al. (690) focused on understanding the impact of two important structural assumptions of mathematical models: linkage to care and population migration. In particular, they modified a previously published model, by including the process of linkage to care and population mobility, using data from a township near Cape Town in South Africa. They conclude that universal HIV testing and ART initiation upon diagnosis would not result in HIV elimination (defined as an incidence of <0.1%) within 30 years, even with optimistic assumptions about the linkage to care.

Anglaret et al. (694) explored, using a mathematical model mimicking the population living in sub-Saharan Africa with a CD4 count >500 cells/µL, under which circumstances initiating ART upon entry to care rather than when CD4 falls below 350 would result in more harm than benefit, focusing on mortality. They reported that initiating ART upon entry into care would result in lower mortality in 15 years in time (51.8% vs 56.7%). The circumstances where this was not the case are: if the rate of fatal ART toxicity was >1.0/100 PYs, if the rate of withdrawal from care was >1.2-fold higher or if the rate of ART failure due to poor adherence was >4.3-fold higher or if moderate rates of fatal ART toxicity (0.25/100 PYs) were combined with increased rates of withdrawal from care (>1.1-fold higher) and increased rates of treatment failure (>2.1-fold higher).

Klein et al. (698) evaluated the assumptions on retention on ART, when evaluating the cost-effectiveness of expanding treatment by either modifying the eligibility criteria from CD4<350 cells/µL to all people diagnosed with HIV or by improving HIV testing and linkage to care so that 80% of the population are in care when becoming eligible. They found that improving retention on ART should be prioritized because it is the strategy associated with the lowest incremental cost-effectiveness ratio (ICER) (see section 4.3.2.2), and only afterwards the focus should be on initiating more people on ART, and this should be pursued by improving HIV testing and linkage rather than more modifying the eligibility criteria.

Wagner et al. (699) investigated the importance on the assumption regarding survival time once initiated on ART. In particular, they considered that the assumption used by Granich et al. (686) of six additional years in people on ART whom CD4 count has fallen to 350 cells/µL compared to untreated people who reached that CD4 was too low. They assumed that people who initiated ART after their CD4 count reached 350 had 60% chance of surviving an additional 20 years or more. They found that modifying this assumption reduces the probability of eliminating HIV (defined as HIV incidence < 0.1/100 PYs), in particular using the long survival time, after 40 years the HIV incidence is around 0.3/100 PYs. Regarding the cost, they

estimated that over a 40 years period the annual cost would be doubled, by using the longer survival, and the cumulative cost 22% higher than reported by Granich et al. (691).

Eaton et al. (685) summarized and compared the findings from twelve independent mathematical models calibrated to South Africa. To eliminate the discrepancies assumed by different models in ART roll out they asked contributing modellers to assume ART was not available before 2012. From 2012, 84 scenarios where considered as a combination of different CD4 count thresholds for ART eligibility, level of ART access and level of retention. Three different CD4 count thresholds for ART eligibility were considered (CD4 count <200 cells/µL, CD4 count <350 cells/µL, and all HIV-infected individuals), seven different level of ART access, defined as the proportion of eligible individuals who eventually initiate ART, assumed to happen within one year since being eligible (50%, 60%, 70%, 80%, 90%, 95%, and 100%) and three different levels of retention, defined as the percentage of individuals remaining on ART after 3 years since initiating ART, excluding from both the numerator and the denominator those who had died while on ART (75%, 85%, 95% and 100% (no dropout)). In the short term (8 year time span) the models generally agreed and for example in a scenario with 80% access, 85% retention and ART initiation at CD4<350 cells/µL they found an HIV incidence between 35% and 54% lower than in a counterfactual scenario where ART was not introduced at all. More variability was found in the long-term (38 year time-frame). A subset of the models (n=7) investigated as well the impact ART had in South Africa, given the actual roll-out of ART. They estimated that current HIV incidence in South Africa was 17% to 32% lower than it would have been if ART were not available.

Johnson et al. (700) used two models calibrated to South Africa, the STI-HIV model and the ASSA 2003 model to understand the role condom use and ART roll-out had on reducing HIV incidence. They estimated, by reproducing the epidemic from 2000 to 2008, using household surveys and antenatal HIV prevalence data and mortality data, that the HIV incidence was 2.11/100 PYs (95% CI: 1.97, 2.26) in 2000–2005 and 1.86 (95% CI: 1.73, 2.00) in 2005–2008, using the STI-HIV model and be 1.90 (95%CI: 1.77, 2.03) in 2000–2005 and 1.62 (95% CI: 1.45, 1.79) in 2005–2008 using the ASSA 2003 model. They estimated that without use of condom the incidence would have been between 37% (95% CI: 34, 41%) (STI-HIV model) and 23% (95% CI: 14, 34%) (ASSA2003) higher, while without the use of ART between 8.1% (95% CI: 6.0, 9.4%) (STI-HIV model) and 1.4% (95% CI: 0.7, 2.6%) higher. This exercise underlined the importance condom use had in the decline in HIV incidence observed in South Africa.

Several authors of mathematical modelling studies have argued that the benefits of wide scale ART could be offset by increases in unsafe sexual practices (688;701).

Yusuf et al. (701) investigated which is the optimal combination of change in sexual habits and ART coverage that minimize the cost and the HIV incidence in the context of South Africa. They compared a scenario where only people with AIDS symptoms are eligible to receive ART to a scenario where individuals are eligible as soon as they have pre-AIDS stage and concluded that the optimum is reached by initiating people when they progress to pre-AIDS stage and by individuals remain faithful to their sexual partners, reduce the number of sexual partners to the minimum possible and avoid extra-marital affairs for the rest of their lives. With this scenario, in 10 years it could be possible to be close to eradication.

More recently, several mathematical models have investigated the impact of combination of prevention strategies (702-706), including HTC (and its impact on risk behaviour), VMC, Pre-Exposure Prophylaxis (PrEP) and high coverage of ART and/or ART at higher CD4 count.

Alsallaq et al. (702) evaluated the effect on HIV incidence of a combined intervention including high coverage of HTC, risk reduction following HIV diagnosis, VMC for HIV-uninfected men, and ART for HIV-infected people with CD4 count≤350 cells/μL, using a model calibrated to data from KwaZulu-Natal, the province in South Africa with the highest prevalence. They found that a dramatic effect could be achieved: 47% reduction in HIV incidence within 4 years and almost 60% within 25 years. Nevertheless they predicted an even higher reduction if ART was initiated upon diagnosis: 63% within 4 and 76% within 15 years.

Baernighausen et al. (704) investigated whether by increasing coverage of VMC and ART (maintaining the current CD4 count threshold to be eligible for treatment in South Africa) it was possible to achieve the same effect on HIV incidence, as universal testing and ART (frequent testing of the entire population and initiation of ART upon entry to care). They reported that the impact over the time span 2009-2020 would be approximately the same, but that $5 billion would be saved.

Hallett et al. focused on the impact of different PrEP implementation strategies in serodifferent couples in South Africa: (i) always, once the couple is identified as serodifferent, (ii) only until one year after the HIV-positive partner has been initiated on ART (promptly when CD4<200 cells/μL), (iii) only until ART initiation of the HIV-positive partner, (iv) only when trying to conceive a pregnancy or during pregnancy. In addition they evaluated the impact of PrEP strategy iii in combination with ART initiation at CD4<200 cells/μL or CD4<350 cells/μL, to

early ART initiation, CD4<500 cells/µL. They found that in low risk serodifferent couples (HIV incidence 1.8/100 PYs at risk) the most cost-effective strategy appeared to be ART initiation at CD4<500 cells/µL for the HIV-positive partner, while in high risk couples (HIV incidence around 8/100 PYs at risk) it was the combination of PrEP with ART initiation at CD4<350 cells/µL.

Cremin et al. (703) focused on the potential role of PrEP in combination with earlier ART initiation (on average at one year since HIV infection) and VMC and assessed the potential cost-effectiveness. They concluded that in a setting with a hyper endemic level of HIV, expanding early ART use (80% initiated one year since diagnosis), rather than providing PrEP to HIV-negative individuals, leads to a higher number of infections being averted and more quality-adjusted life-years (QALYs), but that on its own ART is not going to reduce HIV incidence to very low levels.

Finally, Alistar et al. (706) evaluated the impact of combination of ART use considering people eligible at CD4<350 cells/µL or for all those diagnosed with HIV and PrEP either in the general population or in high risk group. They considered 4 different coverage levels for this intervention: 25%, 50%, 75% and 100%. They concluded that ART initiation at diagnosis is the most cost-effective strategy at all coverage levels investigated (ICER ranging from $160 to $220 per QALY gained) and that the use of PrEP provides only a limited additional benefit.

Other mathematical models have evaluated the impact of early ART initiation in target populations, on the basis of VL (707), HIV stage (587) or of partner status, for example serodifferent couples (708;709).

Given VL is the main predictor of risk transmission, Murnane et al. (707) evaluated the impact of using VL measurements to determine whether to initiate people on ART. They used cross-sectional data on sexual behaviour collected during a RCT of HIV serodifferent couples from HIV-infected people with CD4 count >350 cells/µL to calculate the number of infections, using estimates of per sex-act infectivity. They compared the following scenarios: (i) ART initiation in all those with a CD4 count <500 cells/µL, (ii) ART initiation in all those with a VL ≥50,000 copies/mL, (iii) ART initiation in all those with a VL ≥10,000 copies/mL and (iv) ART initiation in all those infected with HIV. They reported that these interventions would avert respectively 1,569 (47.6%) (scenario i), 1,336 (40.5%) (ii), 2,401 (72.8%) (iii) and 3,165 (96.0%) (iv) of new HIV infections.

They underlined that in order to avert 40.5% of HIV infections (obtainable by initiating ART in all those with a VL ≥50,000 copies/mL) it would be necessary to treat 19.8% of infected

persons with CD4 counts above 350, while initiating ART when their CD4 count falls below 500 cells/µL would require treating 41.8% and would only avert around an additional 8% of HIV infections.

Powers and colleagues (587) investigated the impact of theoretical prevention interventions which would reduce the per contact transmission probability to 0.000033 targeted at PHI only, chronic infection only or both stages. The model was informed by comprehensive data on sexual behaviour and virological data collected in an STIs clinic in Lilongwe, Malawi. They estimated that 38.4% (95% credible interval: 18.6-52.3) of HIV infections were attributable to the PHI. Nevertheless, they found that an intervention that targeted this stage (assumed to start 3 weeks after infection and to last until the end of this phase, duration of 4.8 months) would not allow eliminating HIV even with 100% coverage. They considered a scenario comparable to test and treat, where people received an intervention on average 6 months since infection which reduces their infectiousness, as indicated above, and increases their life expectancy by 10-15 years. They found that only if the coverage was >99% would this lead to elimination in 30 years (annual HIV incidence <1/1,000).

El-Sadr (709) formulated a mathematical model in order to forecast the epidemic impact of treating HIV serodifferent couples with ART, to prevent transmission. The model was parameterised using data from Ghana, Lesotho, Malawi and Rwanda. It was concluded from this study that although treatment of serodifferent couples would not be sufficient to single-handedly control the HIV epidemic, achieving high ART coverage levels for serodifferent couples could significantly reduce incidence and prevent a substantial number of new infections in certain countries.

Walensky et al. (708) used data from serodifferent couples recruited in the RCT HPTN 052 to evaluate the cost-effectiveness of initiating ART when the CD4 count is between 350 and 550 cells/µL compared with when the CD4 count falls below 250 cells/µL, as in the HPTN 052 RCT, in the setting of South African and India. They found that in South Africa it was cost-saving in the short term (5 year horizon) and very cost-effective over a life time (ICER of $590 per life-year gained compared with a per capita gross domestic product [GDP] of $8,100), while in India it was cost-effective in the short term ($1,800 per life-year gained compared with a per capita GDP of $1,500) and very cost-effective over a life time ($530 per life-year gained). Therefore they concluded that early ART in this subgroup at such as high risk of HIV acquisition should be rolled out in resource limited settings (RLS).

As with all research methods, mathematical modelling studies are subject to limitations. The validity of conclusions drawn from models depends upon the reliability and completeness of the assumptions, on which the model parameters are based on. Therefore, the findings from mathematical modelling studies should be interpreted with this caveat in mind. It is difficult to identify the drivers of the difference between mathematical models. This is due to the fact that often they have different structures, make different assumptions, due to the uncertainty regarding some of the processes included in these models, evaluate slightly different scenarios and present results with different metrics. These last points are true as well when conducting analyses using data collected from observational studies, the only field where the analyses tend to be reported using a standardized approach are RCTs. An attempt towards understanding whether models are reaching different conclusions and why has been undertaking by the Modelling Consortium (685;692).

4.2.7. Recommendations on when to start antiretroviral treatment and rationale

The decision on when to start ART in an ART-naive person remains controversial. After a phase in the late 1990s, when in some settings ART was started in almost all people diagnosed with HIV in the hope of being able to eradicate HIV (and improve clinical outcomes), the decision on when to start ART has been driven by the clinical prognosis of the HIV-positive individual. The striking results of HPTN 052 (see section 4.2.5), showing that initiating ART reduces the risk of sexual transmission by 96%, had a big impact on guidelines recommendations. There is generally agreement on the fact that ART should be started once the CD4 count falls below 350 cells/μL, while there is no definitive agreement among the scientific community on whether, and to what extent, the CD4 count threshold should be higher. This is due to the fact that experts differ in the amount of evidence that they consider necessary and on the level of current evidence (710). It has not been established yet in a RCT whether initiating ART when the CD4 count is above 350 cells/μL is associated with a clinical benefit for the HIV-positive person compared to deferral to when the CD4 count reaches this level.

The HPTN 052 RCT compared clinical outcomes as a co-primary outcome. They found a significantly reduced risk of clinical disease in the intervention group (ART initiated at CD4>350 cells/μL; control group: ART initiated at CD4<250 cells/μL), mainly driven by a reduction in extrapulmonary TB, although the study power was low for serious clinically manifest disease endpoints.

In particular they found that the hazard of new onset of AIDS event was 36% lower (HR: 0.64; 95% CI: 0.43, 0.96) in those assigned to the early ART arm (CD4 between 350 and 500 cells/μL) compared to delayed ART. Similarly it decreased the incidence of the primary outcome (including AIDS clinical event and serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus and non-AIDS malignant disease) with an HR of 0.73 (95% CI: 0.52, 1.03) and halved the hazard of developing TB (HR = 0.49, 95% CI: 0.28-0.89) (711). Further evidence comes from the Strategies for Management of Antiretroviral Therapy (SMART) trial. In this RCT, participants were randomized either to continuous ART or to the "drug conservation arm", which meant ART was deferred until the CD4 count was below 250 cells/μL and continued until the CD4 count increased above 350 cells/μL, with subsequent stops and restarts using these CD4 counts as cutoffs. In a subset of the participants with CD4 count >350 cells/μL who were ART-naive at baseline, there was a reduced risk of clinical disease in those initiating ART upon entry into the study compared with those who deferred it (CD4 count <250 cells/μL), but the size of this subsample was small (n=477) (712). Both these trials were based on a comparison involving deferral until the CD4 count fell below 250 cells/μL, which is now no longer the standard of care. Therefore the potential long-term risks, such as adverse events and acquisition of drug resistance, of initiating ART at CD4 levels above 350 cells/μL remain uncertain. The START trial aims to answer this research question, in particular to determine whether very early ART (initiation when CD4 count >500 cells/μL) is superior to deferred ART (CD4 count <350 cells/μL, or when diagnosed with AIDS or other symptoms of HIV infection) in delaying the occurrence of a composite outcome consisting of AIDS, serious non-AIDS conditions, or death from any cause. This trial will help to establish whether any risks of very early ART initiation will be outweighed by the benefits to the individual, in terms of reduction in risk of serious clinical disease (284). The TEMPRANO trial is evaluating the impact on mortality and severe HIV related disease of four different options regarding the eligibility criteria to initiate ART and the treatment for TB: initiating treatment at diagnosis (upon recruitment in the study; with a CD4 count between 350 cells/μL and 800 cells/μL) with and without 6-month isoniazid prophylaxis for TB (285) compared to initiating ART according to 2010 WHO guidelines, CD4 below 350 cells/μL, again with or without 6-month isoniazid prophylaxis for TB. If the benefits of initiating ART at a higher CD4 count outweigh the disadvantages, then it makes sense clinically as well as from a public health perspective to recommend early ART initiation in all people diagnosed with HIV infection. If, on the other hand, there is found to be net harm as a result of this strategy, then a policy of earlier ART initiation in order to reduce transmission risk may be inappropriate in most circumstances. But if the risks and benefits appear to balance, the decision to initiate ART

would take into consideration an individual's preference, and in particular whether the individual wishes to use ART in order to reduce transmission risk. Thus, to a large extent, policy in this area will be driven by the results of the START and the TEMPRANO trial (and any similar trials that might take place), together with clinical considerations and individual choice (713). Unfortunately the TEMPRANO trial is not scheduled to be completed before the end of 2014 (285) and the START trial not before 2015 (284;713).

Although it might be considered difficult to imagine that starting ART earlier would result in a higher risk of mortality or morbidity, based on current knowledge, there is no evidence to guarantee that this is not the case. In addition to this main consideration when deciding whether to start treatment earlier, an HIV-positive person should take into consideration other factors. Firstly, the person should know that once treatment is started it should be continued for life, because interrupting ART increases AIDS-related and non-AIDS-related morbidity and risk of death (714). Secondly, high levels of adherence to ART should be maintained over time. This factor is crucial to achieve and maintain virological suppression, particularly on NNRTI based therapies, and therefore to delay disease progression, minimise the risk of resistance development and of onward HIV transmission. Thirdly, the person should bear in mind that although ARVs available now are much better tolerated, they can still have side effects. Tolerability may be an issue if a person is aware that these drugs could potentially not yet have any benefit for their own health, and that the long-term effects of some drugs are still unknown. It is important that this is made clear to people in whom ART is being initiated with a view to reducing infectiousness. Some wonder whether it is ethically acceptable to offer the possibility of starting ART earlier in absence of this evidence. Most would probably agree that it is ethical if the patient has received all the information necessary to make an informed decision.

Guidelines differ in the recommendation regarding when to initiate ART (see section 1.8.6). In the light of the evidence from the HPTN 052, WHO released "Guidelines on couples HIV testing and counselling and treatment and prevention for serodifferent couples" (715). They recommend that voluntary HTC with support for mutual disclosure should be offered to couples in antenatal care settings and to individuals with known HIV status and their negative partners and that the HIV-positive partner in serodifferent couples, even with CD4 count above 350 cells/µL should initiate ART to reduce the risk of HIV transmission.

The current debate, especially in countries with generalized epidemics, is whether ART should be initiated for all persons diagnosed (irrespective of CD4 count) as a preventive public health policy. Most of the discussion revolves around the implementation of such a program, the affordability and sustainability of this strategy in the long term and on whether high ART coverage in people in need of ART for clinical reason (CD4<350 cell/µL) should first be achieved. This is an area in which there are no trials, although community RCTs where some communities are allocated to higher testing and immediate ART initiation and others to standard of care, with HIV incidence as outcome, are currently ongoing in sub-Saharan Africa (PopART Study (716), Treatment As Prevention (Tasp) trial in KwaZulu-Natal (717), the Mochudi Prevention Project in Botswana (718)).

4.3. Cost-effectiveness of different adult ART eligibility criteria and coverage scenarios in South Africa

4.3.1. Rationale and description of the project

The finding that ART reduced the probability of transmitting HIV by 96% in stable serodifferent couples (432) suggested the potential, by increasing the number of people on ART, of curbing the HIV epidemic in countries with generalised epidemics. Nevertheless it is clear that implementing interventions such as - in the extreme - test and treat requires a large amount of resources and currently not all those with CD4≤350 cells/µL, which was the threshold recommended by WHO in 2010, are receiving ART. In South Africa in 2011 69% were estimated to be receiving ART of those eligible at that time and 80% in 2012 and overall in LMIC only 63% of those with CD4<350 cells/µL were receiving ART in 2012 (719). Even in countries who have achieved high coverage, many people still initiate ART late, due to lack of early HIV diagnosis or low linkage and retention in care (551;553). A large cohort study which included two sites in South Africa, Khayelitscha and Gugulethu, both in Cape Town, reported a median CD4 count at diagnosis respectively of 100 and 101 cells/µL for these two sites for the period 2004-2007 (720). A more recent study, conducted in Durban, reported that of people diagnosed between August 2010 and November 2011, 34% were diagnosed with a CD4 count <100 cells/µL (721).

Stakeholders, including donors and governments must make a decision on how to invest their limited resources in order to maximize the health gain, in this particular context whether to modify the eligibility criteria to initiate people on ART and increasing linkage and retention care or whether to implement other health programmes (704;722). Mathematical models can

give insights on the long term consequences in terms of epidemiological impact and costs of these different strategies (723). Many of them have evaluated the impact of modifying the ART eligibility criteria (i.e. different CD4 count thresholds) on the HIV epidemic in different countries (686;688;691;724-728). Nevertheless it is often difficult to compare the results because of the different metrics used in reporting the results and the different implementation of these results.

As part of the revision process of the guidelines for the use of ARVs, released in July 2013 (280), the WHO asked the HIV modelling Consortium to assess the cost-effectiveness of different ART eligibility criteria in different countries, by comparing the results from different mathematical models. Four countries were selected, South Africa, Zambia, India and Vietnam and twelve independent mathematical models took part in this comparison. I contributed by using the Synthesis model to evaluate the cost-effectiveness for South Africa, as did six other models. I programmed the strategies agreed and the outcome in the Synthesis model using the metrics indicated, I run the simulations and provided the outcomes to Jeff Eaton (both the health outcomes and the components of the programs: number of people receiving treatment, number of HIV tests used, etc.). Jeff Eaton summarized the results provided by the different mathematical modellers and together with economists (Nick Menzies and John Stover) they decided on the appropriate costs and applied them to the units provided. The results are presented and compared only for this country. The aim was to evaluate the impact and cost-effectiveness of changes to adult ART eligibility guidelines and improvements in HIV testing and linkage to care.

4.3.2. Methods

4.3.2.1. Scenarios considered and outcomes metrics

Three different thresholds for initiating adults in care on ART were considered: (1) CD4≤350 cells/µL, (2) CD4≤500 cells/µL and (3) all HIV-positive adults and two different scenarios: (a) maintenance of current levels of HIV testing, linkage to and retention in pre ART care, and ART uptake, referred to as the 'status quo' healthcare access scenario and (b) extensive increase in HIV testing and linkage to care so that 80% of those living with HIV are in care when they become eligible for ART. For all the simulations when evaluating this last scenario 80% of them were in care, however the fact that the CD4 threshold for example was modified to CD4≤500 cells/µL does not mean that all people with a CD4 below that threshold were initiated on ART.

They are assumed to be initiated the first time they have a visit and a measured CD4 is 500 cells/μL or less.

These 6 combinations were simulated over a twenty year period from 2014 to the end of 2033. Modifications in ART eligibility criteria were assumed to happen at the beginning of 2014 while changes in access, by increasing HIV testing and linkage to care, were assumed to be implemented over two years starting from the beginning of 2014. To evaluate the health benefit of the different strategies, modellers taking part in the project were asked to provide the HIV incidence and disability-adjusted life-years (DALYs) averted and information on the number of people on ART, the number of people initiating ART and the number of ART-naïve people in care and not in care, by CD4 count.

4.3.2.2. Cost and cost-effectiveness analysis

The cost-effectiveness analysis was conducted from a health system perspective, using the same costing across all models. The costs included are the service delivery cost of identifying people as HIV-positive and linking them to care, the service delivery cost of providing pre-ART care and ART-care, including the cost of programmatic support and supply chain (Table 4.1). All the costs indicated in Table 4.1 are in addition to the expenditure required to running the program and the cost of setting up the infrastructure which is spread over their useful life, rather than upfront. The sources of the costs indicated in Table 4.1, are indicated in the Supplementary Information of the manuscript (692). This work on cost sources has been conducted by Jeff Eaton, John Stover and Nicholas Menzies, and for this reason is not reported in detail here.

For the summary measure for the cost-effectiveness analysis, ICERs were calculated as the incremental cost per DALY averted over 20 years of an intervention compared to a less effective, less costly alternative. It indicates whether an intervention is likely to represent good value from available health sector resources. The number of DALYs averted takes into account increments in survival and quality of life, due to the clinical benefit for the HIV-positive person of receiving ART and due to the ability of ART to reduce infectiousness and therefore the number of new infections. Cost and health benefits were discounted by 3% per annum (729).

To determine cost-effectiveness an ICER needs to be compared to a cost-effectiveness threshold (CET). The CET represents opportunity costs of health sector resources - in terms of the health gains foregone as a result of resources being unavailable to deliver other scenarios (730). According to WHO recommended benchmarks (729), an intervention is considered ‘very

cost-effective' if its ICER is less than the country's per capita GDP (South Africa in 2012 $8,040) (731) and 'cost-effective' if it is less than three times per capita GDP. Nevertheless it is likely that the real CET is much lower: for example, in the UK, where in 2013 the per capita GDP was $37,300, the current CET used by NICE (National Institute for health and care excellence) is $22,000 (£ 13,000), much lower than the current GDP (732). This difference in determing the CET is due to the fact that in the UK, since years, cost-effectiveness analyses have been used to determine which health interventions will be provided by the national health system and which are not. Therefore, based on the budget available for health, the National Institute for health and care excellence determines the cost-effectiveness threshold for UK. The same cannot be said for most of the countries and, least of all, for sub-Saharan African countries, where healthcare, especially for people with HIV, is funded mainly by international donors rather than by the national government. For this reason, WHO indicated some benchmarks. In this analysis the CET recommendation by WHO are used.

The disability weights used come from the Global Burden of Disease Study 2012, which evaluated the value of life-years lived with defined health conditions, compared to full health, by sample surveys conducted in different parts of the world (733).

Table 4.1. Unit costs and disability weights (all costs in 2012 US dollars) (692)

	Costs in South Africa	**Health state**	**Disability weight[a]**
On ART, ARV cost (per PY)	$143	HIV+, CD4 >350 (untreated)[b]	0.053
On ART, non-ARV cost (per PY)	$422	HIV+, CD4 200–350 (untreated)	0.221
ART initiation, from pre-ART care (per initiation)	$95	HIV+, CD4 ≤200 (untreated)	0.547
ART initiation, not in pre-ART care (per initiation)	$126	HIV+, on ART	0.053
Pre-ART care, CD4 > 350 (per PY)	$205	TB disease	0.331
Pre-ART care, CD4 200–350 (per PY)	$238		
Pre-ART care, CD4 ≤200 (per PY)	$359		
HIV testing & linkage: general pop. (per client)	$20		
Healthcare utilization, CD4 >350, not in care (per PY)	$13		
Healthcare utilization, CD4 200–350, not in care (per PY)	$46		
Healthcare utilization, CD4 ≤200, not in care (per PY)	$167		
End of life cost (per death)	$160		
TB treatment (per case treated)	$364		
Supply chain management (percentage mark-up)[c]	20%		
Programmatic support (percentage mark-up)[d]	50%		

[a] Disability weights based on Salomon *et al.* (733). For individuals with co-morbidity (e.g. concurrent HIV and TB disease), disability weights were compounded multiplicatively. [b] It was assumed that HIV-infection with CD4 ≥350

incurs the same disability, 0.053, as individuals receiving ART. [c] Mark-up assessed on ARVs cost. [d] Mark-up assessed on all costs except for ARVs. ART: antiretroviral therapy; ARV: antiretroviral drug; PY: person-year; TB: tuberculosis;

4.3.3. Results

Using the Synthesis model (bar in yellow in Figure 4.2), I found, as did the other six models which simulated the different strategies in the context of South Africa, that changing the eligibility criteria to initiate ART to CD4 ≤500 cells/μL or all HIV-positive people was estimated to be very cost-effective over 20 years. In particular, the cost per DALYs averted over 20 years of changing ART eligibility criteria from CD4 ≤350 cells/μL to CD4 ≤500 cells/μL was $1,691 using the Synthesis model, and varied from $273 (Goals Model) to $1,560 (EMOD model) in the other 5 models (Menzies did not simulate this comparison), while the cost for changing the eligibility criteria from CD4 ≤350 cells/μL to all HIV-positive adults was $2,133 in the Synthesis model and it ranged from $438 (Goals Model) to $3,790 (STDSIM model) in the other 6 models.

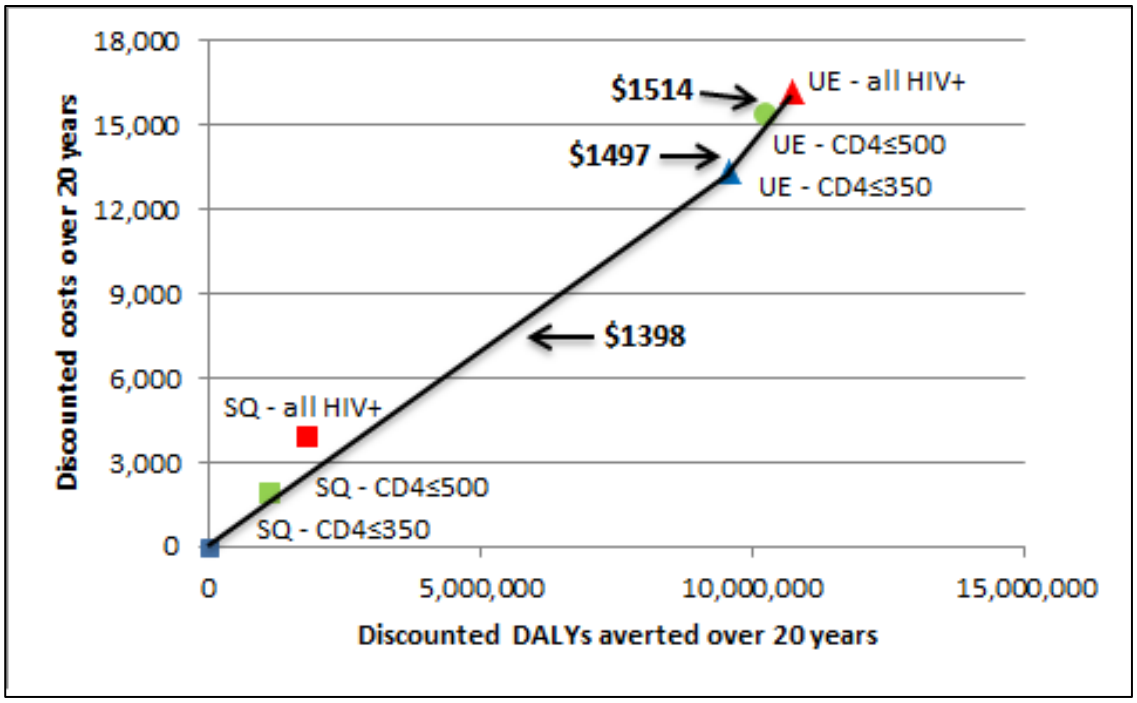
Figure 4.2. The incremental cost per DALY averted for expanding ART eligibility criteria by model in South Africa (692)

DALY: disability-adjusted life-year;
Note to Figure 4.2 (692): Results calculated over 20 years, with all costs and health benefits discounted at 3% per year. All costs are in 2012 US dollars. Values below the upper dashed line (three times per capita GDP) are defined as cost-effective; those below the lower dashed line (per capita GDP) are defined as very cost-effective. The Menzies model simulated only expanding eligibility to all HIV-positive adults. *Indicates that eligibility for patients with CD4 counts of 500 cells per μL or less is dominated by the other strategy (i.e. produces fewer health benefits at higher cost).

The cost per DALYs averted over 20 years of expanding HIV testing and linkage to care so that 80% of those who become eligible for ART are in care, while maintaining the CD4 threshold of 350 cells/μL to be eligible for treatment is $1,398 using the Synthesis model and it ranges from $686 (Menzies model) to $2701 (STDSIM model). Therefore using the Synthesis model the most cost-effective strategy among those considered is to expand HIV testing and linkage with a CD4 threshold for ART eligibility of CD4 ≤350 cells/μL (see Figure 4.3). This result suggests that the most cost-effective health intervention among those considered in the context of South Africa in the long term (20 years) is to first of all invest in expanding HIV testing and linkage to care to improve ART coverage among those in greatest need (CD4 ≤350 cells/μL); only once this intervention is fully implemented, to simultaneously adopt a threshold for ART eligibility of CD4 count of CD4 ≤500 cells/μL ($1,497) and afterwards to all HIV-positive people ($1515, see Figure 4.3). However if resources were very limited, in particular if the cost-effectiveness threshold for South Africa was less than $1,398, which is the lowest ICER across the interventions considered, using the Synthesis model (i.e. universal expansion with CD4 threshold to initiate ART of 350 cells/μL), my model suggests that South Africa should not try to implement any of the interventions considered, but if there are other interventions not considered here characterized by ICER lower than South Africa cost-effectiveness threshold these other interventions should be implemented.

Over a shorter time period ICERs were much higher. Over a 5 year period the most cost-effective strategy according to the Synthesis model is to modify the eligibility criteria to those with CD4<500 cells/μL, with an ICER of $4,892 per DALY averted, which is still very cost-effective, compared to an ICER of $1,691 per DALY averted over 20 years period. Across the models, the ICER over 5 years of modifying the eligibility criteria to those with CD4<500 cells/μL varied from $2,140 (Goals model) to $11,646 (EMOD) per DALY averted. This higher cost per DALYs averted over short period is due to the fact that the benefit of preventing new transmissions increases over time.

Figure 4.3. Cost-effectiveness analysis over 20 years using the Synthesis model



DALY: disability-adjusted life-year; SQ: status-quo (i.e. current patterns of healthcare access, see 4.3.2); UE: uniformly expanded healthcare access (i.e. 80% of those living with HIV are in care when they become eligible for ART);

The impact on HIV incidence of these different strategies of modifying the eligibility criteria to those with CD4<500 cells/μL is relatively modest, 5% over 20 years using the Synthesis model, and it varied from 4% (Goals model) to 12% (EMOD model). Expanding ART coverage by improving HIV testing and linkage to care with a CD4 threshold of 350 cells/μL would reduce HIV incidence by 6% in the Synthesis model, but by a higher amount in the other models: from 15% (BHH model) to 28% (Goals model). If all HIV-positive adults are eligible for ART and access to care is not expanded 9% of infections would be averted and 19% if it is expanded. The other models found similar magnitude of increase: between 12% (Goals) and 32% (Menzies) without access to care expansion and between 36% (BBH) and 60% (Goals) if HIV testing and linkage to care is improved.

The cost of strategies involving expansion of access to care is much higher than the costs of strategies which only involve only a change in the eligibility criteria (see Figure 4.4 at page 228). Figure 4.4 (page 228) shows the incremental undiscounted costs (in 2012 US dollars) for different ART eligibility and access strategies compared to continuation of the current situation. The portion of the bar underneath the horizontal line represents the cost saving and the total incremental cost is indicated by the solid dots. Each bar, within each strategy represents a model, in the same order as in Figure 4.2 (page 224), so the Synthesis model is

the sixth bar in each group and it is indicated by an orange arrow. The incremental cost of starting on ART earlier people who are already in care (i.e. attending the clinic regularly) is relatively low, due to the fact that the cost of additional years on ART is partially compensated by saving in the cost of pre-ART care and other healthcare cost. On the contrary, by expanding treatment access through increase HIV testing and linkage to care, there is an incremental cost due to additional HIV testing, pre-ART care monitoring and ART care for the additional people diagnosed.

Figure 4.4. The incremental cost over 20 years for different ART eligibility and access strategies compared to reference scenario (continuation of 2010 eligibility guidelines and status quo access to care)(692)

Instead of a bar there is an 'x' for the Menzies model for the strategy with CD4<500 cells/µL strategy, because Menzies did not simulate this strategy.
ART: antiretroviral therapy;

Findings from the Synthesis model, together with two other models (Menzies and EMOD), suggest that if the aim is to maximise the health gain per dollar spent, expanding access would have the lower cost per DALY averted (i.e. lowest ICER) and should be therefore the most appropriate choice. Nevertheless the four other models found that the strategy with the lowest cost per DALY averted is either changing the eligibility criteria to CD4<500 cells/μL (Goals, STDSIM and POPART) or to all HIV-positive people (BBH), without expanding access. Ultimately, both ways of expanding the number of people on ART: by changing the eligibility criteria or by improving HIV testing and linkage would be considered very cost-effective, according to WHO benchmarks, the differences among the models are mainly about which way to proceed first.

The results were quite sensitive for most of the models to the assumptions on the cost of testing and linkage to care and of pre-ART care (see Figure 4.5). Figure 4.5 shows the strategy with the lowest ICER for a given change in the cost of HIV testing and linkage to pre-ART care and pre-ART care. All the strategies are compared to the reference strategy assuming continuation of the current level of access to care and eligibility criteria to be initiation on ART of CD4 ≤350 cells/μL. The 'x' indicates the base scenario (i.e. 0% change in cost of HIV testing and linkage to pre-ART care and 0% change in the cost of pre-ART care). As the cost of testing people and linking them to care and the cost of pre-ART care decrease (bottom left corner) it becomes cost-effective to expand access to care (areas identified in green), while at the other extreme (top right corner) it becomes cost-effective only to change the eligibility criteria (area in purple). The Synthesis and the EMOD model show a similar pattern, with the combination of improvement in HIV testing and linkage to care and all the positive people being eligible for treatment being the most cost-effective strategy in a situation where the cost in diagnostic and linkage is reduced while the cost of pre-ART care increases (top left corner).

Figure 4.5. Threshold analysis showing the strategy with the lowest cost per DALY averted for different combination of percentage change in the cost of pre-ART care (vertical axis) and in the cost of HIV testing and linkage to care (horizontal axis) (692)

ART: antiretroviral therapy;

4.3.4. Discussion

In the context of South Africa, all the strategies considered were very cost-effective over a 20 year period, with a maximum ICER of $3,790 per DALY averted found for the strategy involving changing the eligibility criteria to all positive people in the STDSIM model. This cost per DALY averted is still less than half the 2012 South Africa per capita GDP ($8,040). These results can be partly explained by the relatively low cost of providing additional years of ART to people in care and by the clinical benefit and reduction in infectiousness in people receiving ART which results in a reduction in the number of new transmissions.

The models differ in identifying the most cost-effective strategy and therefore it is difficult to say the one that should be prioritized because it produces the greatest health benefit per dollar spent. Four models found that the most cost-effective strategy is to change the eligibility criteria, three to those with CD4 count <500 cells/µL and one to all those positive, while three models found that expansion of access to care should be prioritized. Despite differences in the most cost-effective strategy, all the models found almost a double reduction in HIV incidence could be achieved if access for those most in need (CD4<350 cells/µL) is improved so that 80% are in care when becoming eligible for treatment compared to only changing the eligibility criteria.

In this project, situations where resources were severely constrained, with waiting lists for patients eligible for treatment were not considered. In South Africa there are no longer waiting lists for ART initiation. In April 2013 the new South African guidelines recommended initiation to ART in patients with CD4 less than 350 cells/µL (226) and in the WHO guidelines released in July 2013 (280) it is recommended that if it is not possible to treat all those in need, treatment should be prioritised for patients most in need (CD4 ≤350cells/µL).

Increasing the number of people receiving ART, whether by changing the eligibility criteria or expanding access to care, requires high upfront costs but it generates health benefits and it is very cost-effective in the long term. Therefore it should be considered as a long term population health investment. Earlier mathematical models (691;734) which evaluated the cost-effectiveness of changing the eligibility criteria in the context of South Africa found that it could be even cost-saving over a 20 year period. This was not confirmed by any of the models included in this analysis.

In this exercise, only an increase up to 80% of people eligible being in care was considered. However, it is worth mentioning that an increase of further 10% up to 90% of the population eligible being in care is likely to cost more than the increase from 70 to 80%, for example. This is due to the fact that people easy to reach at this point would have been reached already and it becomes increasingly difficult to reach new people. This would require putting in place more efforts, at a higher cost.

As mentioned, all the seven independent models which evaluated the impact of expanding treatment in the context of South Africa agreed that all the strategies considered were very cost-effective over a twenty year period. Nevertheless there were differences in the order in which these strategies should be implemented and so which one should be prioritized. In particular, both the Synthesis model and the EMOD model, which are both individual-based stochastic models and include in more detail the steps HIV-positive people need to go through in order to be on successful ART, concluded that rather than modifying the eligibility criteria, the priority should be to increase the number of people in care. This suggests that the level of detail included is possibly having an impact on the results. In addition, the differences across models are believed to partially reflect the different structure of the models and the uncertainty in some of the parameters representing the epidemiology of HIV transmission and

different assumptions regarding the future treatment uptake in the reference scenario and long term effectiveness of treatment.

A parameter of particular importance for this analysis is the presence and magnitude of clinical benefit of starting treatment at a higher CD4 count for the person receiving treatment. As mentioned in section 4.2.7, two RCTs are currently on-going to address this question (284;285). Another source of uncertainty is whether it is feasible to scale up the prevention benefits observed in RCTs (735) and whether starting people at a higher CD4 count would affect their risk behaviour. As mentioned in section 4.2.3, there is evidence from KwaZulu-Natal in South Africa that people living in areas with higher coverage of ART experience a lower risk of HIV infection (670) and so far studies have not observed an increase in sexual behaviour among people initiating ART at higher CD4 count (736). As more data become available regarding these parameters and more generally on other assumptions underlying these models, this analysis should be updated.

The data on the cost of scaling up and running HIV care programmes and HIV testing services at a higher level than currently and the magnitude of the flow of patients are scarce and this contributes to the uncertainty on the estimates. As programmes providing HIV testing and care develop and become more established there is evidence that the unit costs tends to decrease (737;738). Nevertheless, it is not clear whether this would be true if expansion of access to care so that 80% of those who become eligible are in care at a national level, because it is likely that to achieve this it would not be enough to expand the existing sites but new infrastructure would also be required. Therefore the countries who first will adopt these strategies will provide important information on the epidemiological and economic impact of rolling out these strategies.

The fact that all these strategies are very cost-effective does not exclude the existence of other health interventions, which could provide a greater health benefit for the same amount of dollars spent. Barnighausen et al., as mentioned before, found for example that an intervention providing VMC to a larger number of people could have a lower cost per DALY averted than increasing ART coverage (739) and Njeuhmeli found that it could even be cost saving in the long term (740).

In response to the release of new guidelines from WHO, which it is likely took into account the impact on the population of expanding the eligibility criteria (i.e. this project), countries need to take decisions on whether to take those recommendations on board and to which extent. The Synthesis model suggests that increasing HIV testing and linkage to care should be the priority, but that modifying the eligibility criteria to all those with CD4<500 cells/μL, as recommended by WHO is very cost-effective and should be considered against other very cost-effective health interventions.

5. Predicted levels of HIV drug resistance in South Africa: potential impact of expanding diagnosis, retention and eligibility criteria for antiretroviral therapy initiation

5.1. Rationale

In the previous chapter the evaluation of the impact of expanding ART by increasing the number of people in care or/and modifying the threshold to consider people eligible for treatment in the context of South Africa and its comparison to the other mathematical models was presented.

The Synthesis model is the only one, among those included in the comparison for South Africa, to include the emergence and transmission of resistance. For this reason, I decided to focus my attention on the impact on the level of HIV drug resistance of modifying the eligibility criteria to initiate ART or alternatively expanding the number of people in care, by increasing HIV testing, linkage to care and retention in pre-ART and on-ART care. In fact the models included in the HIV Modelling consortium comparison (692) (see section 4.3) differ substantially in the level of detail incorporated and very few have thus far captured all the various processes that we have a reasonable understanding of due to extensive data sets (e.g. sexual risk behaviour, testing, PHI, VL, CD4 count, use of ART, adherence, resistance, drug failure, drug interruption, LTFU, occurrence of AIDS, non-AIDS death, etc.). This is not surprising as this requires a complex and highly parameterized model which has the disadvantage over simpler models that it is difficult to analyse and interpret. However, such models may have a useful role in providing more quantitative predictions of the effect on HIV incidence, of greater testing and earlier ART initiation in a given setting and have the advantage of carrying a level of detail which makes them suitable to be used as a basis for detailed economic analyses. The Synthesis model is one of them.

There is concern that the expansion of ART roll-out may impact future drug resistance levels and hence compromise the benefits of ART at an individual and population level. In one study in South Africa it has been estimated that 2.5% experience VF (two consecutive VL>5,000

copies/mL, despite an adherence promotion following the first raised VL) by one year since ART initiation, 12% at 5 years (292), and that 87.6% are virogically suppressed (VL<400 copies/mL) by one year. However, virological suppression estimates as low as 66% have been reported (304). Among people with VF in South Africa between 66% and 86% (597;597;598;627;741;742) had resistance detected in majority virus. Similar estimates have been observed in a study conducted in six African countries where at one year since ART initiation, among people with VL>1000 copies/mL, 70% had at least one DRM detected and 49% at least two, of which the most common were M184V (53.5%), K103N (28.9%), Y181C (15.5%) and G190A (14.1%) (398). A systematic review of RCTs estimated that around 5% of the participants experienced VF at 48 weeks. Of the samples successfully genotyped M184V mutation was present in 35% of those who started NNRTI-based regimen compared to 21% of those who started a boosted PI-based regimen, while the incidence of K65R was much lower: 5.3% in those who initiated an NNRTI-based regimen compared to 0% in people started on a boosted PI-based regimen (743). A more recent meta-analysis of RCTs comparing boosted PI-based regimens to NNRTI-based regimens found that at 48 weeks 3.3% of those receiving NNRTI-based regimen had resistance detected compared to 1.6% in those receiving boosted-PI regimens, with lower incidence of K65R (1.3% vs 0.7%) and M184V/I (3.2% vs 1.4%) (744). A meta-analysis aimed at assessing the impact of different frequencies of monitoring in patients on ART with CD4 count <200 cells/µL, reported that 88% of those monitored infrequently (not monitored or every 3 to 6 months) had resistance at VF, compared to 61% in those monitored frequently (3 months or more often) (745).

Selection of DRM is a concern not just for individual patients, who may have reduced treatment options, but also for society because of potential transmission of drug-resistant HIV, which could compromise the effectiveness of available first-line regimens for a substantial portion of the population and increase the need for costly second-line regimens. In the 2012 WHO HIV drug resistance report (305), among 44 population-based surveys conducted in recently infected populations in Africa between 2004 and 2010, the percentage of surveys reporting moderate (5-15%) levels of TDR increased from 18% in 2004-2006 to 41% in 2007-2010. A meta-analysis estimating trends in prevalence of HIV-1 drug resistance in recently and chronically infected ART-naïve individuals found a relative increase of 14% per year in the prevalence of NNRTI resistance in southern Africa (746). This is consistent with the finding that the proportion of people with NNRTI resistance at ART initiation increased from 3.4% in 2007 to 5.4% in 2010 in Africa (305).

One of the first surveys on TDR conducted in South Africa took place between 2002 and 2004 in the province of Gauteng, where the National ART programme began providing treatment in April 2002 and reported a low level of TDR (747). Surveys were conducted between 2005 and 2009 on women pregnant for the first time aged less than 25 years in the provinces of Gauteng and KwaZulu-Natal in South Africa. They showed that the prevalence of TDR was less than 5% for all drug classes in all the surveys conducted in the Gauteng province; while in the KwaZulu-Natal province NNRTI TDR seemed to be increasing over time reaching a level of between 5 and 15% in 2009 (748). In Cape Town the prevalence of TDR has been estimated at 2.5% (95% CI: 0-5.3%) in a study conducted in the public sector between 2002 and 2007 (742). Contrasting results came from a literature review and data mining (n=1618 sequences) conducted to estimate the trend over time in TDR in South Africa (749). They reported that the highest TDR rate was in 2002 (6.67%; 95%CI: 3.09-13.79%) and that it has been below 5% since then. Nevertheless, a recent study conducted among women of reproductive age who presented to screen for an HIV prevention trial in Durban reported that 7.4% of those with a VL>200 copies/mL (96% of those HIV-positive) had DRMs present in majority virus (750) and in people who experienced VF 21% of them were found to harbour NNRTI-resistance mutations at ART initiation (306). The PASER-M study, collecting data from patients living in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe estimated a prevalence of drug resistance at ART initiation of 5.6%, with prevalence of TDR in the three sites in South Africa Pretoria, White River and Johannesburg of respectively 1.1%, 4.8% and 4.5% (376). These data stress the importance of having regular estimates of the incidence and prevalence of HIV drug resistance at country level, and projections of potential future levels.

Wider ART coverage is highly likely to lead to an increase in the proportion of new infections with TDR; however it is difficult to predict whether the benefits of reduced incidence will out-weigh this risk of higher levels of resistance. As countries consider embarking on ART-based approaches to HIV prevention, an increased understanding of the potential effects of this policy shift on resistance is needed. I used the HIV Synthesis model calibrated to South Africa's epidemic to estimate and project current and future incidence and prevalence of drug resistance (acquired on ART and transmitted) under the current conditions. These outcomes are compared to the projected level of resistance in the context of expanded eligibility criteria to initiate ART (CD4 <500 cells/μL and in all people diagnosed with HIV compared with CD4 <350 cells/μL) and enhancements in diagnosis and retention in care.

5.2. Scenarios investigated

As mentioned before, there are two main approaches to increase the number of people receiving ART, either changing the CD4 threshold for ART initiation, or (not mutually exclusive) concentrating on maximising rates of diagnosis and linkage and retention in both pre-ART and ART care. This second approach would require substantial augmentation of health system infrastructure and reduction in social stigma associated with HIV and as such it represents a more ambitious undertaking than modifying the ART initiation threshold.

We consider two potential scenarios regarding diagnosis and retention. In one ("enhanced diagnosis and retention") significant improvements in HIV testing, linkage to care and retention in pre-ART care are made so that 80% of people who become eligible for ART are in care, and in addition retention on ART is improved so that 92% of patients are retained on ART one year after ART initiation (representing a 50% reduction in LTFU while on ART). These interventions are scaled up over 2014 and 2015. This is compared with a scenario assuming no change after 2012 in these factors, so the likelihood of moving along the continuum of care is assumed to remain as described in 2012 and so are the adherence levels, the availability of drugs and the likelihood of being initiated on ART if eligible. Within each of these two scenarios, three different ART initiation policies are considered: at CD4 count below 500 cells/μL (currently recommended by WHO (280)), at time of diagnosis regardless of CD4 count, or continuation of the existing policy in South Africa of initiation at CD4 counts below 350 cells/μL (226).

The simulations from 2013 to the end of 2032 started from the epidemics which provided a good fit to the observed data (n=30, see section 3.13). Multiple runs for each scenario and ART initiation policy have been generated and the median or the mean is presented, as indicated. The median is presented with the uncertainty range: the 5th and 95th percentile across all simulations, so it captures part of the uncertainty in the parameters. It is important to note that for the reduction in HIV incidence from 2012 to 2032, both the 95% CI and the 90% uncertainty range (UR) are presented. The first reflects the stochastic variability, while the second the uncertainty on the parameters.

5.3. South African HIV epidemic at the end of 2012 predicted by the Synthesis model

The characteristics of the epidemic, as predicted by the model, at the end of 2012, are summarised in Table 5.1 (page 239). The median and 90% uncertainty range (90% range across the 30 simulations with the best fit to the South African epidemic) are reported (on average they differ by less than 18% to the data used to calibrate the model, see section 3.13). The 90% uncertainty range reflects my choice of the a priori distribution for the parameters sampled and the choice of the threshold to consider a simulation as fitting to the observed data.

We estimated that of the 33.6 million people aged 15 to 65 years living in South Africa 5.3 million are infected with HIV, which corresponds to an HIV prevalence of 15.9%. Of these 73% are predicted to be diagnosed with HIV. The median CD4 count at diagnosis, across all those who have been diagnosed up to the end of 2012, is assumed to be relatively high at 367 cells/μL. However, the median CD4 count at ART initiation, across all those who have initiated ART up to 2012, is much lower at 116 cells/μL. Based on fitting to data on the proportion with TDR amongst those just diagnosed with HIV from the WHO surveillance data from sub-Saharan Africa up to 2010, the modelled percentage of newly diagnosed people with DRMs present in majority virus in 2012 is 5.9% and the proportion initiating ART with NNRTI-resistant virus in majority virus (NRMV) is 3.7%. On the other hand, the median percentage of people infected with HIV in 2012 who have TDR is much higher at 13.8%, with a slightly lower proportion infected with key NNRTI-associated mutations (10.4%).

Table 5.1. Descriptive characteristics at baseline (end of 2012) simulated by the Synthesis model (adult population, 15-65 years old) compared to data from the literature

		Median (90% range)[a]	Value reported in the literature	Notes and source
Number alive in population (in millions)		33.6 (32.7 - 34.1)	31.9	2013 (435)
			34.8	2013 (433)
Number of people living with HIV (in millions)		5.3 (4.6 - 6.2)	5.7 (5.5-6.0)	2012, age 15+ (450)
HIV prevalence (%)		15.9 (13.6 - 18.4)	18.8 (17.5-20.3)	2012, age 15-49 (440)
HIV Incidence (per 100 PYs)		1.1 (0.6-1.6)	1.72 (1.4, 2.1)	2012, age 15-49 Lag-Avidity EIA
			1.9 (0.8, 3.1)	2008-12, Mathematical Model
Death rate (per 100 PYs)[d]	among HIV- people	0.7 (0.6 - 0.8)	1.4 M, 0.8 F	Whole pop 15-65, 1997 (437)
	among people on ART with CD4>350 cells/µL	0.8 (0.2 - 1.7)	Month 1: 14.7 (10.5–20.7); Month 2: 10.6 (7.1–16.0); Months 3-4: 5.1 (3.3–7.7); Months 5-6: 5.1 (3.3–7.9); Months 7-12: 27 (19–40);	Low income settings (751)
	among people on ART with CD4≤350 cells/µL	5.1 (2.8 – 9.1)		
	among HIV+ ART-naïve (diagnosed or not)	3.7 (2.7-4.9)	-	-
	among HIV+ people, exposed to ART, off ART	14.4 (8.2 - 21.5)	-	-
Testing				
% of men ever tested for HIV		57.3 (52.9 - 62.1)	59.0 (57.2 - 60.8)	2012, age 15+ (440)
% of women ever tested for HIV		66.2 (61.6 - 69.9)	71.5 (70.1 - 72.9)	2012, age 15+ (440)
% of people who tested for HIV in the last year		36.1 (30.8 – 39.4)	43.4	2012, age 15+(440)
% of HIV-positive people diagnosed		73.5 (70.7 - 77.3)	37.8 M, 55.0 F	"Aware HIV positive" 2012, age
Median CD4 count at diagnosis[b]		367 (340 - 388)	100 (45-161)	2004-08, Khayelitsha (720)
			357 (238–500)	2010-11, Johannesburg (752)
Antiretroviral treatment				
Number of men on ART (in 1000s)		639 (482 - 795)	551	2011 (451)
Number of women on ART (in 1000s)		1,111 (909 - 1,281)	1,090	
% of HIV-positive people on ART		32.0 (29.7 - 36.2)	-	-
% of HIV diagnosed people on ART		43.3 (41.1 - 47.2)	-	-

% on ART of those not ART-naive or with current CD4<200	64.0 (62.3 – 66.6)	79 (70-85)	2011 (451)
Median CD4 at ART initiation[b]	116 (105 - 128)	123 (55-184)	2005-09 (753)
		103 (45-164)	2002-08 (601)
% with VL suppressed among those on ART	89.5 (88.4-91.2)	12 months: 87.6; 36 months: 88.1; 60 months: 83.8;	2001-07 (292)
% of people on ART on second-line	9.9 (8.7 - 11.4)	-	-
Resistance			
% of new infections with TDR (any class)[d]	13.8 (5.1 - 26.7)	-	-
% of new infections with NNRTI resistance[d]	10.4 (4.1 - 20.3)	-	-
% of new diagnoses with TDR (any class)[d]	5.9 (2.0 - 9.6)	<5	2005-2009 on women pregnant for the 1st time aged<25 years in Gauteng (748)
		between 5 and 15	2009 on women pregnant for the 1st time aged<25 years in Kwazulu-
		2.5 (95% CI: 0-5.3)	Public sector between 2002 and 2007 in Cape Town (742)
		6.67 (95%CI: 3.1-13.9)	2002, literature review and data mining (749)
		<5	Since 2002, literature review and data mining (749)
% of people on ART[c] with VL>500 copies/mL[d] with resistance	84.9 (81.0 - 88.1)	66 and 86	Programmes in South Africa (597;597;598;627;741;742)
% with less than 3 active drugs at ART initiation[d,e]	9.3 (4.8 - 13.8)	-	-
% with NRMV at ART initiation[d]	3.3 (1.4 - 7.0)	3.4	2007 Africa (305)
		5.4	2010 Africa (305)
		5.6	Any resistance, three sites in South
		1.1	Any resistance, Pretoria
		4.8	Any resistance, White River
		4.5	Any resistance, Johannesburg

% of HIV+ with resistant mutation in majority virus[d]	9.6 (8.1 - 11.7)	-	-
% of HIV+ with NNRTI resistant mutation in majority virus[d]	7.4 (5.9 - 9.7)	-	-

a – 90% range over the 30 simulations who provided the best fit, b – across all adults who have been respectively staged or initiated on ART by end of 2012, c – at least 6 months on ART are required, d - average over 1 year (2012), e – In the model having less than 3 active drugs correspond to have drug-resistant mutations present in majority or minority virus; ART: antiretroviral therapy; F: female; Lag-Avidity EIA: enzyme-linked immuno assay Limiting Antigen Avidity; M: male; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRMV: non-nucleoside reverse transcriptase inhibitor resistant virus in majority virus; TDR: transmitted drug resistance; VL: viral load;

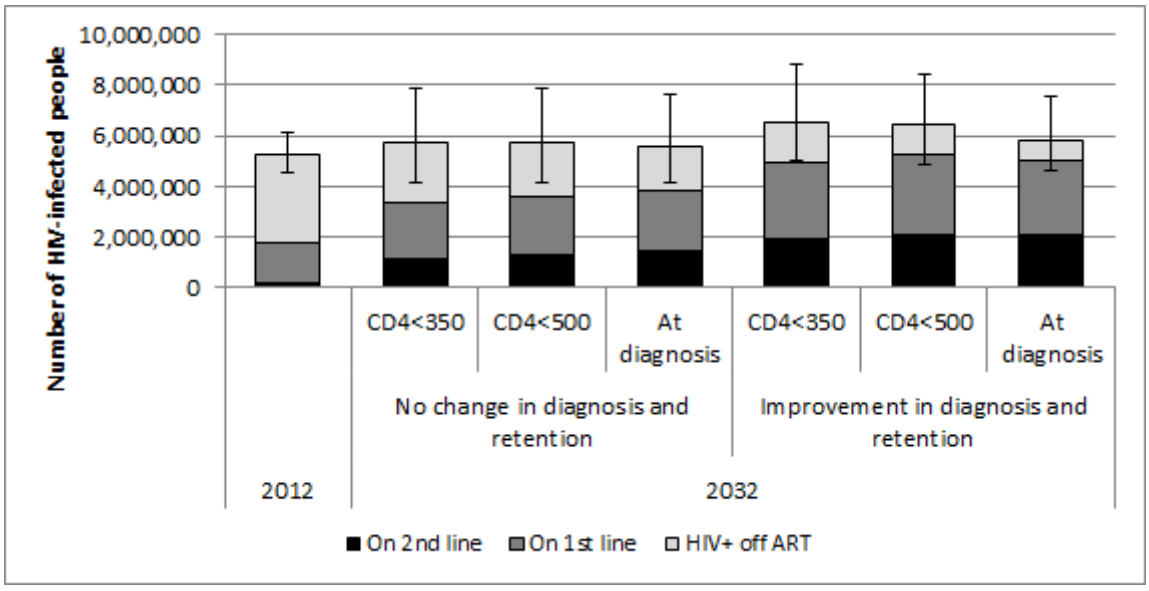
5.4. Impact of different diagnosis and retention scenarios

5.4.1. Impact on the number of people on treatment

Figure 5.1 presents the number of people HIV-positive and receiving first and second-line treatment under the two different diagnosis and retention scenarios and the three ART initiation policies. In 2012, 5.3 million are estimated to be HIV-positive and 1.8 million adults to be receiving ART, of which 9.9% are second-line regimens.

By 2032, assuming current levels of diagnosis, retention and ART initiation eligibility criteria are maintained, 3.3 million are projected to be receiving ART, with 35% (1.1 million) on second-line regimens. Changing the threshold at which a person is eligible for treatment is predicted to have minimal impact on the number of people on ART and on the number requiring second-line regimens. However, under a scenario of enhanced diagnosis and retention between 4.9 and 5.2 million will be on ART, of which 40%-42% (2.0-2.1 millions) on a second-line regimen.

Figure 5.1. Estimated number of people HIV+, stratified by first-line or second-line of treatment regimen (median value and 90% uncertainty range [UR])



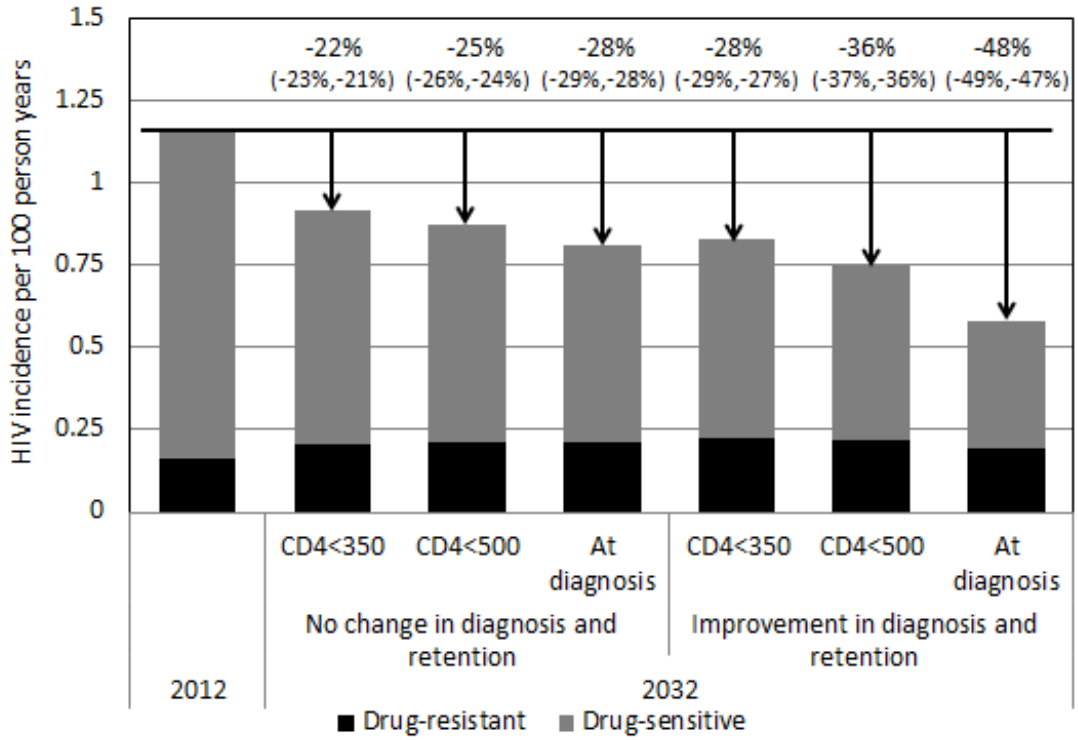
Median % (90% UR) proportion on second-line	9.9 (9-11)	34.6 (30-39)	35.7 (31-41)	37.6 (32-42)	39.6 (35-44)	40.5 (36-44)	42.0 (38-45)

ART: antiretroviral therapy; UR: uncertainty range;

5.4.2. Impact on HIV incidence

In Figure 5.2 the average HIV incidence, stratified by whether the virus is drug-sensitive or drug-resistant in 2012 and in 20 years time is displayed. Overall HIV incidence is predicted to be 22% lower (95% CI: -23%, -21%) in 20 years time under the current scenario. With no enhancement in diagnosis and retention, changing ART eligibility criteria, from 350 cells/µL to 500 cells/µL or at diagnosis, has only a moderate effect: an additional 3% and 6% reduction in incidence respectively (up to 28%). The same reduction in HIV incidence (28%) can be achieved if, instead, there is an enhancement in diagnosis and retention and the ART initiation threshold is maintained at CD4<350 cells/µL. A change in initiation threshold to CD4<500 cells/µL, in addition to the enhancement in diagnosis and retention, confers 36% reduction in HIV incidence in 20 years time and ART initiation at diagnosis leads to a 48% reduction (95%CI:-49%,-47%). Average HIV incidence with TDR is estimated to be 0.16 occurrences per 100 PYs in 2012. Modifying the CD4 count at which a person is eligible to initiate ART (from 350 cells/µL to 500 cells/µL or at diagnosis regardless of CD4) has a negligible impact on future incidence of new infections with TDR, whatever the scenario on diagnosis and retention. Because the number of new infections is increasing, the proportion of new infections with TDR does increase as the eligibility criteria expand and if improvement in diagnosis and retention occurs. The reason why the number of new infections with TDR remains stable despite HIV incidence decreasing, as more people receive ART (more from the left to the right in Figure 5.2), is due to the fact that more people are on suppressive treatment but more people are exposed to ART and develop resistance and these represent a greater percentage of those who are transmitting HIV.

Figure 5.2. HIV incidence with drug sensitive and drug-resistant virus in 2012 and in 2032 (average and 95% confidence interval for HIV incidence change), according to access to care and retention on ART and ART initiation policy



Med (90% UR) % of new infections with TDR	13.8 (5-27)	22.5 (9-41)	24.1 (10-43)	26.2 (11-45)	27.7 (12-48)	30.0 (12-51)	33.6 (14-56)
Med (90% UR) % of new diagnosis with TDR	5.9 (2.0-9.6)	14.0 (5.5-25.6)	12.2 (4.3-22.2)	9.6 (3.4-18.2)	15.2 (6.1-27.4)	9.1 (2.9-17.8)	1.5 (0.0-5.1)
Med HIV incidence (90% UR)	1.1 (0.7-1.7)	0.9 (0.4-1.6)	0.8 (0.4-1.4)	0.8 (0.4-1.3)	0.8 (0.4-1.4)	0.7 (0.3-1.3)	0.6 (0.3-1.0)
Med % reduction in HIV incidence (90% UR)	-	-24 (-46,+8)	-26 (-50, +3)	-30 (-51,-0)	-29 (-52,-0)	-37 (-64,-7)	-49 (-72,-19)

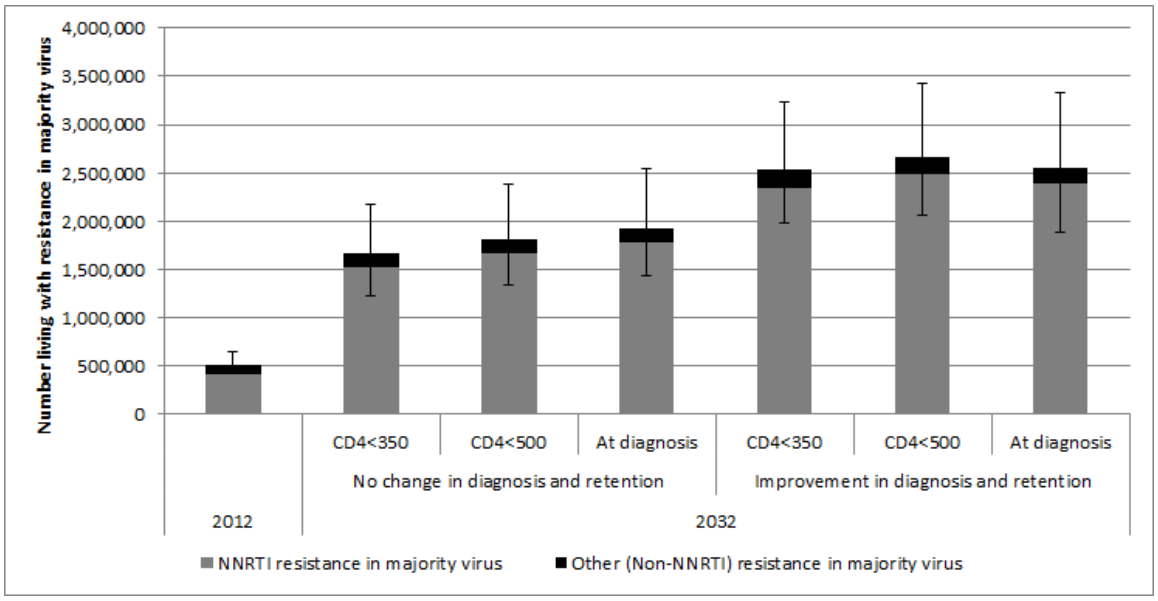
Med: median; TDR: transmitted drug resistance; UR: uncertainty range; UR: unceratinty range;

5.4.3. Impact on the number of people living with resistant virus

Figure 5.3 shows the estimated number of people living with any resistance in majority virus (i.e. detectable and assumed transmissible) in 2012 and projected numbers in 20 years' time in South Africa. In 2012, 9.6% of those living with HIV are estimated to be living with resistant

virus in majority virus (represented by the entire bar), corresponding to 508,800 people, of which 77% (the section of the bar in grey) NNRTI resistant virus, which is of more interest, given NNRTI are used on first-line.

Figure 5.3. Estimated number of people living with resistance in majority virus in South Africa in 2012 and 2032 (median and 90% UR)



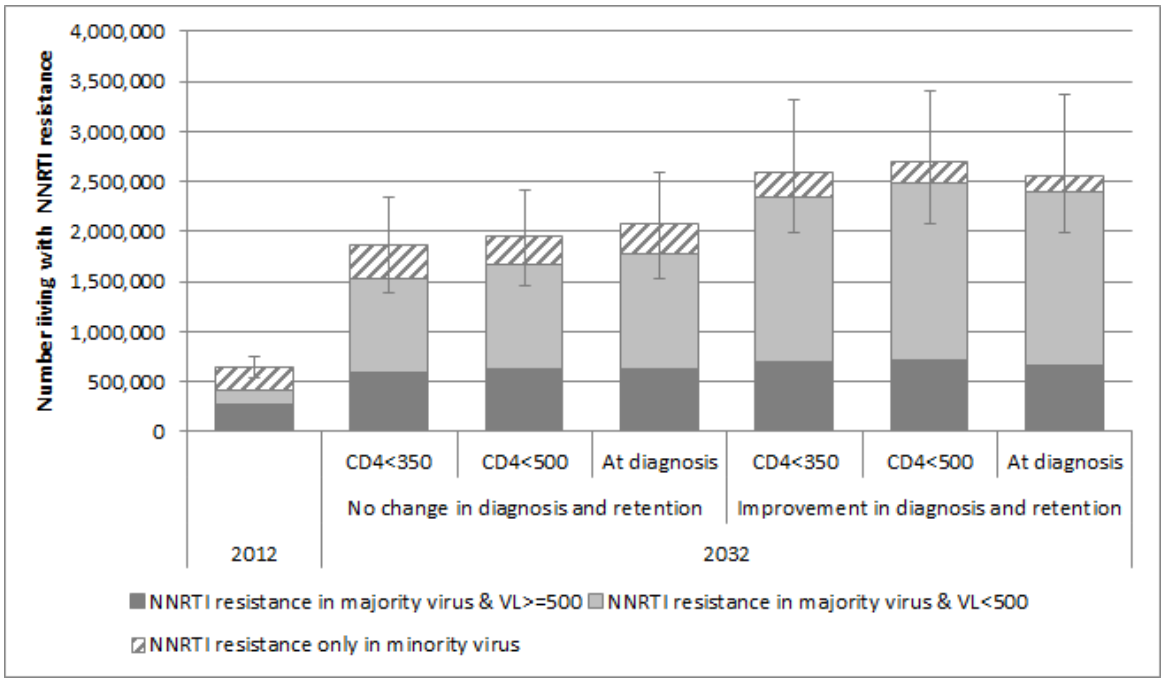
% with resistance in majority virus of those living with HIV (15-65)	9.6 (8.1-11.7)	28.4 (22.7-35.1)	31.2 (25.1-37.8)	34.3 (27.9-40.4)	38.2 (32.4-43.9)	41.4 (35.5-46.9)	44.2 (38.6-49.2)
% with resistance In majority virus in adults 15-65	1.5 (1.3-1.9)	4.5 (3.4-5.8)	4.9 (3.7-6.4)	5.2 (3.9-6.7)	6.6 (5.2-8.4)	7.0 (5.4-8.9)	6.7 (5.0-8.6)

NNRTI: non-nucleoside reverse transcriptase inhibitor;

Figure 5.4 focuses on the number of people living with NNRTI-resistant virus (majority or minority) in 2012 and in 20 years' time and illustrates whether it is present in majority virus and with a VL above or below 500 copies/mL or whether it is present only in minority virus and therefore assumed not transmissible. In 2012, 652,000 people are estimated to have NNRTI resistance, of which 42% (approximately 275,000) are people with NRMV with VL above 500 copies/mL (see footnote of Figure 5.4), and therefore have an increased risk of transmitting NNRTI drug-resistant virus (43). If existing policies continue, the number of people living with NNRTI resistance is predicted to be 2.8-fold higher in 2032 (from 652,000 in 2012 to 1,862,000). Of these, 68% are predicted to be on ART with suppressed VL or to have resistance in minority virus. Therefore the subset of the population with an increased risk of transmitting NNRTI-resistant virus (VL>500 copies/mL and NRMV) is approximately 594,000. Modifying the CD4 threshold at which a person is eligible to start ART from 350 cells/µL to 500 cells/µL or to all people diagnosed with HIV, regardless of CD4 count, without the enhancement in diagnosis and retention, results in a 3.0- and a 3.2-fold increase, respectively, in the number of people living with NNRTI resistance, compared to the level in 2012.

Alternatively, with enhanced diagnosis and retention and people with CD4 between 350 and 500 cells/µL additionally becoming eligible to initiate ART, the number of people carrying NNRTI resistance in 2032 is expected to be 4.1 fold higher than in 2012. However, 73% are predicted to be on ART with suppressed VL or have the resistant virus in minority virus, yielding approximately 719,000 individuals with a VL above 500 copies/mL and NRMV.

Figure 5.4. Estimated number of people living with NNRTI drug resistance in South Africa in 2012 and in 2032 (median value and 90% UR)



Med (90% UR) number (in thousands) of people with NRMV and VL>500 copies/mL	275 (204-350)	594 (423-850)	620 (447-841)	625 (428-837)	706 (498-1010)	719 (508-942)	655 (482-881)
% (90% UR) with NRMV of those living with HIV (15-65)	7.4 (6-10)	26.4 (25-27)	29.1 (27-30)	32.1 (30-32)	36.0 (34-36)	38.7 (37-39)	41.3 (39-41)
% (90% UR) with NRMV amongst all adults 15-65	1.2 (1.0-1.4)	4.1 (3.1-5.2)	4.5 (3.4-5.8)	4.8 (3.6-6.1)	6.1 (4.9-7.7)	6.5 (5.1-8.2)	6.3 (4.7-8.0)
Status of people living with NRMV:							
NRMV with VL≥500 copies/mL	42%	32%	32%	30%	27%	27%	26%
NRMV with VL<500 copies/mL	21%	50%	53%	56%	63%	65%	67%
In minority virus	37%	18%	15%	14%	10%	8%	7%

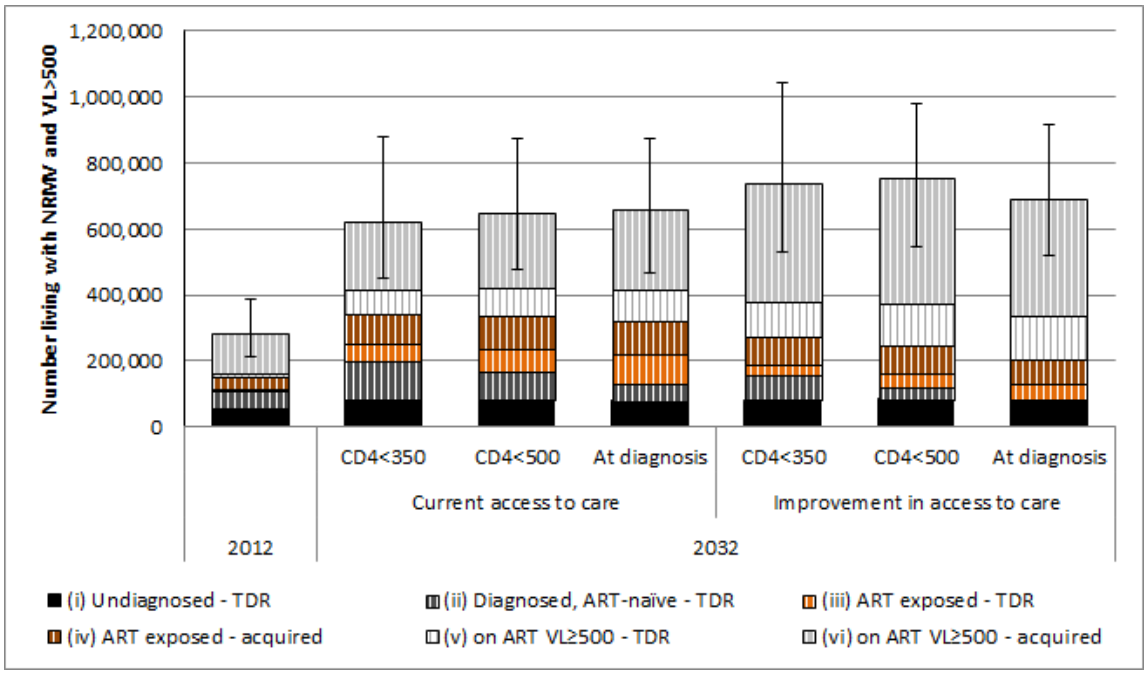
Med: median; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRMV: non-nucleoside reverse transcriptase inhibitor resistant virus in majority virus; UR: uncertainty range; VL: viral load;

Figure 5.5 goes into even more detail and shows the characteristics of people living with NNRTI-resistant virus in majority virus and VL≥500 copies/mL (indicated in Figure 5.4 in dark grey). Starting from the bottom of the bar, this population has been divided in (i) "Undiagnosed – TDR", people infected with NNRTI-resistant virus living with undiagnosed HIV, (ii) "Diagnosed ART-naïve – TDR", people infected with NNRTI-resistant virus, diagnosed with HIV but not initiated on ART, (iii) "ART exposed - TDR": people infected with NNRTI-resistant virus, who have been exposed to ART, but currently off treatment, (iv) "ART exposed – acquired", people infected with NNRTI-sensitive virus, who have been exposed to ART, but currently off treatment, (v) "on ART VL≥500 – TDR", people infected with NNRTI-resistant virus, who are currently on ART with VL≥500 copies/mL, (vi) "on ART VL ≥500 – acquired", people infected with NNRTI-sensitive virus, who are currently on ART with VL ≥500 copies/mL.

In 2012, 20% of people living with NRMV and VL≥500 copies/mL are undiagnosed, around 20% are diagnosed but ART naïve, 15% have been exposed to ART but are currently not on treatment and 45% of them are on ART. In 20 years' time this last group is expected to represent between 45 and 50% if the current access to care is maintained and between 65 and 75% if an improvement in access to care and retention on ART occurs.

Regarding the source of these resistant cases, whether acquired or transmitted, I found that the percentage of people with resistant virus which can be originally ascribed to TDR is predicted to increase from 33% in 2012 to 38% in 2032 without enhancement of diagnosis and retention, but to remain stable at approximately 33% should an enhancement in diagnosis and retention and a change in the CD4 threshold at which people are eligible to initiate ART to CD4<500 cells/µL, occur.

Figure 5.5. Estimated number of people living with NRMV and VL above 500 copies/mL in South Africa in 2012 and 2032 (median and 90% UR)

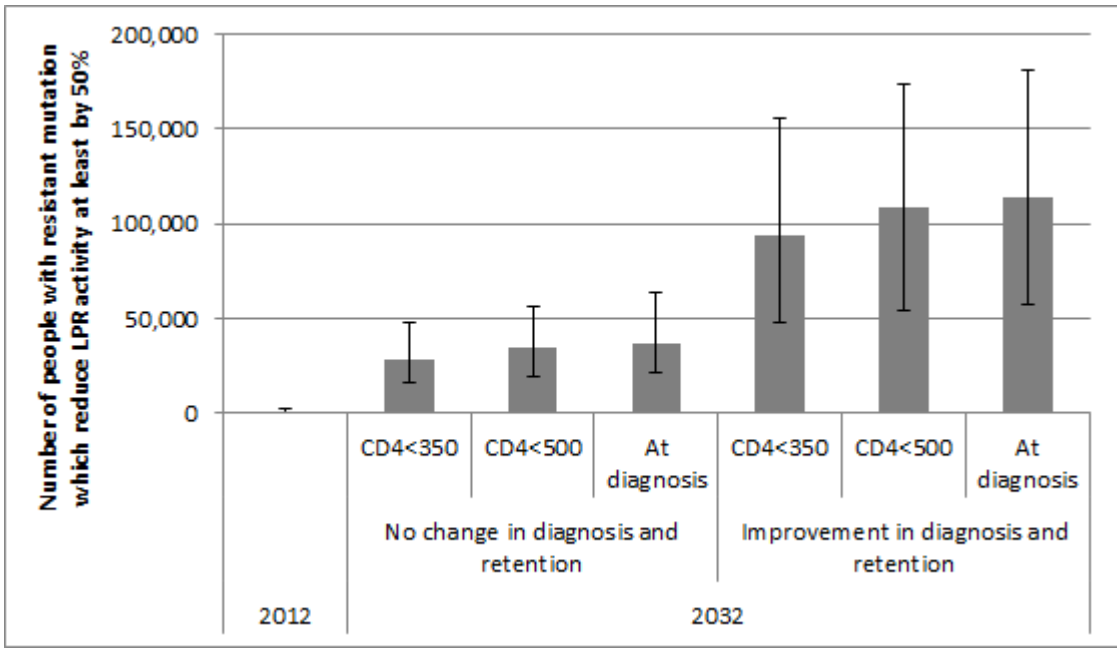


Status of people living with NRMV and VL>500 copies/mL							
Undiagnosed	20%	12%	13%	14%	11%	12%	13%
Diagnosed ART-naïve	19%	21%	13%	8%	11%	3%	0%
ART exposed	15%	20%	26%	27%	13%	15%	13%
On ART VL≥500 copies/mL	45%	46%	49%	51%	65%	69%	75%

ART: antiretroviral therapy; NRMV: non-nucleoside reverse transcriptase inhibitor resistant virus in majority virus; TDR: transmitted drug resistance; VL: viral load;

Figure 5.6 shows the estimated number of people with resistant mutations in majority virus which reduce susceptibility to LPV, a PI used as second-line, at least by half. I estimated that at the end of 2012 there are no people for whom susceptibility to LPV is reduced at least by half. In 20 years' time, as second-line use become more prevalent, around 30,000 are expected to have resistance mutations which reduce LPV activity at least by half and around 100,000 if improvement in retention and diagnosis occur. The impact is going to be very similar if ATV is used in second-line. Nevertheless this is only a minority compared to the total number of people living with resistant mutations in majority virus, given the low probability of acquiring PI mutations in the first place.

Figure 5.6. Estimated number of people with resistant mutations in majority virus which reduces lopinavir activity at least by half



LPR: lopinavir;

5.5. Discussion

There is great interest in expanding ART by increasing the number of HIV-positive people in care and by changing the initiation threshold. My results suggest that prevalence of drug resistance and need for more expensive second-line regimens are likely to increase substantially in future years as ART roll-out continues, even if policies are not changed. This is an inevitable consequence of having an increasing number of people on ART. Nevertheless, if current levels of diagnosis, retention, eligibility criteria to initiate ART (CD4<350 cells/μL) and VL monitoring are maintained, in 20 years' time over 60% of people with drug resistance to first-line agents are projected to be on a suppressive, second-line regimen. Likely due largely to the increase in the number of people on ART with viral replication suppressed, overall HIV incidence is predicted to drop by 22% in 20 years, if current levels of diagnosis and retention are maintained. It is noteworthy that by substantially improving diagnosis and retention, while maintaining as ART initiation policy CD4<350 cells/μL, it is possible to achieve the same reduction in HIV incidence as a change in the ART initiation threshold to all people diagnosed, with the important difference that the first will avoid ART initiation in persons for whom the individual health benefits remain unproven and will allow more deaths to be averted.

However, the feasibility of implementing the scenario of enhanced diagnosis and retention is difficult to assess.

The decrease is predicted to be 36%, if diagnosis and retention are increased substantially and a policy of ART initiation at CD4 below 500 cells/µL is adopted. Incidence of HIV infections with TDR is predicted to remain stable. However, due to an overall decrease in HIV incidence the proportion of new infections with TDR is projected to increase substantially (from 14% in 2012 to 30% in 20 years' time).

It must be recognised that the high levels of increase in diagnosis and retention assumed in these simulations would require major investment, not only to provide treatment to higher numbers of people, but to significantly strengthen health systems to dramatically improve pre-ART and on ART retention and care. Public health interventions to promote social acceptance and reduce stigma will be necessary to achieve these high levels of diagnosis, linkage to care and retention. Interventions such as home-based HTC (754), self-testing (755) and mobile voluntary counselling and testing (VCT) supported by community mobilisation (756) have been demonstrated to be feasible and effective in increasing the number of people tested for HIV. Provision of POC CD4 measurement at the same time and place of HIV testing (757) and formal pre-ART care services providing counselling, regular review, clinical staging, social and psychological support and prevention and management of OIs, such as TB, have been shown to increase, both, the proportion evaluated for ART eligibility and, the number of people, initiated on ART (758). Once on ART, models of care which require less frequent contact with the health service and adherence monitoring by community groups have been found to be effective in minimising the number of people LTFU (753).

Data on new infections with TDR come mainly from WHO surveillance studies. In these, a resistance test is conducted among samples from newly diagnosed individuals less than 25 years of age and/or with a CD4>500 cells/µL (if available) and no previous pregnancy, if female (759). These criteria increase the likelihood that people surveyed are likely to have been recently infected with HIV and ART-naive. In this work, the modelled proportion of new diagnoses with resistance in 2012 is 5.9%, similar to that obtained when restricted to people with the criteria used in WHO surveys (data not shown). This figure is much lower than the percentage of new infections with TDR estimated to be 14% by the Synthesis model. The difference between the proportion with TDR at infection and at diagnosis may be explained by the time-lag between infection and diagnosis, in that those currently diagnosed with HIV may

have been infected earlier, when resistance levels were lower. In addition, some DRMs may not persist in majority virus after infection (386).

Other mathematical models find that in RLS the prevalence of acquired and transmitted resistance will increase with greater ART availability (688;760). Blower et al. predicted that providing ART to 10%-50% of an HIV-infected population, was likely to result in 5.9% of new infections having resistance in 10 years after treatment roll-out (760). Given the initial plan to roll out ART in Africa to 3 million individuals ((761) reference by (726)) corresponding to 5–10% of the HIV-infected population, Blower et al. (726) estimated that after 10 years, the proportion of new infections with TDR to be below 5%. Recently, Wagner et al. (699) investigated the impact of universal access to treatment compared to a universal "test and treat" strategy in South Africa on HIV incidence and TDR. They predicted that the incidence of TDR would remain below 0.1% and that widespread access to treatment could, in some cases, even reduce transmission due to the increased selection of drug-resistant strains in people on ART, which were assumed to be 50% less transmissible than wild-type strains.

Nichols and colleagues (762) evaluated the impact of three different ART eligibility thresholds (CD4<200 cells/µL, CD4<350 cells/µL and CD4<500 cells/µL) on the number of infections averted and TDR prevalence, in two different settings: Kampala (Uganda) and Mombasa (Kenya). Similarly to my analysis, they observed a reduction in HIV incidence in both settings by raising the CD4 threshold at which people living with HIV are eligible for ART from 350 cells/µL to 500 cells/µL, driven by a reduction in HIV incidence. They found an increase in prevalence of TDR from levels of 8.3% in Kampala and 12.3% in Mombasa, up to around 19% in 10 years' time in both locations if ART is initiated at CD4<500 cells/µL, while if the ART eligibility threshold is CD4 below 350 cells/µL the increase is much more contained. Although I reported a slightly different outcome (i.e. the proportion of new infections and of new diagnosis with TDR), I also found an increase in TDR when raising the CD4 threshold to be eligible for ART.

These general trends in drug resistance I have predicted for South Africa may well be relevant for other countries in sub-Saharan Africa, but there are differences worth noting. One main factor is that VL monitoring is routinely available in South Africa, therefore people failing first-line regimens may be expected to switch to second-line more quickly after VF than in other settings and we have previously shown, using the Synthesis model, that TDR levels are diminished with introduction of VL monitoring (571). Furthermore, levels of adherence, virological suppression and rates of ART interruption (TI) between settings are likely to result in

differences in resistance (763), but I suggest that any relatively small difference between countries in these factors would have a modest impact on my main overall predicted trends.

In 20 years' time, which is the time frame used in this analysis, it is possible that in South Africa current NNRTIs will not be part of the first-line regimen anymore. Integrase inhibitors, such as dolutegravir, could potentially be available soon in FDC with a similarly low cost and lower level of toxicity. The new South African guidelines recommend a third-line regimen (226) but currently the public health service offers two lines of treatment. Given the uncertainty regarding when these drugs will actually become available, it was considered appropriate to assume as ART regimen those currently in use in South Africa, and therefore those who fail the second-line regimen will remain on a boosted PI-regimen.

It is plausible as well that, in the future, POC VL will become available with possibility for more frequent VL measurements which could slightly reduce TDR. Therefore, my estimates are potentially conservative for predicted NNRTI resistance. In addition, if high levels of TDR emerge, it is possible that WHO would recommend, for example, changing the first-line to a boosted PI-regimen. This possible policy change has not been included in these simulations and would sharply curb the transmission of resistant-virus. These model projections could be updated in the future if it becomes clearer that important changes in ART programmes have occurred.

In conclusion, my results suggest that while increases in prevalence of drug resistance are likely as ART coverage is increased, incidence of resistance is unlikely to significantly rise and concern over resistance development should not, in itself, inhibit increases in ART coverage. Health system strengthening to improve treatment diagnosis and retention in care, to increase community acceptance and to reduce stigma may limit incident infection and mitigate transmitted and acquired drug resistance.

6. Determinants of presence of NNRTI-resistance mutations after interrupting or stopping ART which contained an NNRTI

6.1. Introduction

In Chapters 4 and 5 I used the Synthesis model to evaluate the impact, and cost-effectiveness, of increasing the number of people on ART in South Africa and in particular the impact on resistance dynamics. In order to address those questions I had to make assumptions regarding the presence of NNRTI-resistance mutations in people who had been exposed to NNRTIs. NNRTIs constitute the foundation of ART regimens in LMIC, including Zimbabwe (228) and South Africa (226), with more than 9.7 million people on ART in LMIC at the end of 2012 (764). It is therefore crucial to understand the potential scope for resistance to develop to such regimens and if present in majority virus, potentially be transmitted (584). This has important implications for the number of people who are going to be in need of second-line therapy once they restarted ART and on the number of new infections with TDR. One critical under-researched aspect of this is the extent to which NNRTI mutations are present in majority virus amongst people who have interrupted or stopped ART. There are two main circumstances under which this can happen. People can have drug resistance mutations (DRMs) present in majority virus while being off treatment because they interrupted ART after having experienced VF while on ART and developed resistance and these DRMs persisted in majority virus (369). The second circumstance under which this can occur is in people who interrupted an NNRTI-regimen without having experienced VF, who then acquire DRMs, due to the long half-life of NNRTIs compared to the nucleoside backbone rendering people effectively on NNRTI monotherapy for several weeks after stopping all ART (763;765;766).

Although treatment programmes have generally been successful, it is relatively common for people to interrupt ART and potentially to be LTFU. The most frequent reported reasons for interrupting treatment are toxicities, adverse events and side effects, but other reasons include patients' decision, pill burden, treatment fatigue, perceived lack of benefit, costs, pharmacy stock out and poor access to drugs (767). In some cases people who are not

attending the clinic any more are not LTFU but they have simply transferred to another clinic without informing the clinic.

In the first years since roll-out of ART in Sub Saharan Africa, the loss to follow-up at 12 months since ART initiation was estimated to be 15%, with variability ranging from 0% to 44% across thirteen different African cohorts (751). A systematic review including more recent studies in the same area (1) reported an attrition rate at 12 months of 22.6% (range 7-45), of which 59% were LTFU and the remainder had died. Nevertheless the high attrition rate tends to decline over time with an attrition of 25% and 29% respectively at 24 and 36 months. A large cohort study from South Africa reported a rate of ART interruption of 12.8/100 PYs (95% CI: 11.4, 14.4) with up to three TIs per patient and a rate of resuming therapy of 21.4/100 PYs (484). Another large (n=11,397) retrospective cohort study in South Africa including patients starting ART between 2004 and end of 2008, reported that in the first year on ART, 60% of patients remained in care and 12% missed laboratory visits and came back to care by 12 months (483).

Even in developed countries it is common for people to be LTFU or to interrupt treatment. In the UK, for example, the rate of potential LTFU (no CD4 measured for ≥1 year) is 12/100 PYs (768), while the rate of interruption has been estimated to be 2/100 PYs in the UK (769) and up to 6/100 PYs in Eurosida, a large cohort study including mainly countries in Europe (770).

This chapter has two main aims. The first aim is to evaluate in patients who have documented NNRTI-resistance while on ART who then stopped all ARVs composing the regimen, the persistence of NNRTI mutations over time, I will refer to this as the “analysis on persistence of NNRTI mutations”. The second is to quantify the extent to which NNRTI mutations can be detected in the rebound viraemia following TI of suppressive NNRTI-based ART, I will refer to this as the “analysis on emergence of NNRTI mutations”.

6.2. Literature review

6.2.1. Treatment interruptions

As mentioned previously, patients on ART may ask the clinician if they can have a break off treatment, because of either side-effects of the drugs they are taking or because they experience treatment fatigue, regardless of tolerability or for other personal reasons. One option that was considered by clinicians until a few years ago was to undertake what was

referred to as a "structured treatment interruption", as a strategy to postpone their next regimen until the majority virus has reverted back to wild-type. Because, in the absence of ART, wild-type virus is the fittest virus and therefore becomes the predominant virus, it was hypothesized that interrupting ART could expand treatment options for patients in need of salvage therapy (i.e. the last treatment option available).

Two main types of structured TIs were considered: CD4-guided, where ART was stopped at a high CD4 count and re-initiated at a certain low CD4 both defined a priori (714;771;772) and timed-cycle strategy, where ART is stopped for a fixed period of time (319;773;774). Pant Pai conducted two systematic reviews evaluating the impact of structured TIs, one in in chronically suppressed (775) and one in unsuppressed (776) people. They concluded that there was a lack of benefit in terms of morbidity and mortality for people with unsuppressed VL and potential harm in people suppressed. The largest RCT which evaluated the impact of CD4 guided structured TI, the SMART study ("Strategies for Management on Antiretroviral Therapy"), showed that these structured TIs increase the hazard of progression to AIDS or death by 2.6 (95% CI: 1.9, 3.7) and of serious non-AIDS events by 6.6 (95% CI: 1.5, 29.1) compared to patients who remained continuously on treatment throughout the period (714). For these reasons TIs are not recommended and if patients wish to discontinue the regimen they are receiving they are encouraged to switch to another regimen (777).

6.2.2. Persistence of NNRTI-resistance mutation in people who virologically fail with resistance detected who then stopped treatment

As mentioned before, despite the increasing effectiveness of ART, the proportion of people experiencing VF in South Africa is not negligible (292;304) and most of them harbour resistance in majority virus (597;598;627;742) (See section 5.1).

Even in developed countries, including the United Kingdom, where the data used in this chapter come from, it is not rare to experience VF. A paper published in 2005 using the UK CHIC data, the cohort used in this chapter, reported that by 6 years since ART initiation the cumulative risk of VF was 36% and of developing resistance to at least one major IAS-USA mutation, 27% (614). These estimates were recognised by the authors as lower limit estimates, because sequencing results were not available for many VFs. On the other hand there is evidence that in settings with more recently approved ARVs, characterized by higher effectiveness, the proportion of people failing treatment with multi-drug resistance is decreasing (778).

The first studies to quantify the persistence over time of DRMs after interrupting (779;780) or switching treatment regimen (781;782) focused on mutations which confer resistance to AZT. Subsequently, several small studies, looking at a wider range of mutations, showed that TIs could lead to a more drug sensitive circulating virus (318;369;634;783-786).

Devereux et al. (369) looked at the prevalence of DRMs (primary DRMs considered were 30N, 461I/L, 82A, 90M, 70R, 184I/V and 215Y/F, none of them is an NNRTI mutation) in people who had been exposed to several regimens (mean=5, range 3 to 9) and had developed resistance while on treatment with a subsequent resistance test available after stopping treatment respectively within 2 weeks, between 2 weeks and 2 months since stopping treatment and between 2 and 6 months. They estimated that in all people with a resistance test within 2 weeks DRMs were detected, and respectively in 68% and in 15% if the resistance test was conducted within 2 months or afterwards. This study, although small (n=25) clearly indicated that the majority of DRMs would not be detectable anymore after a relative short time since stopping ART. This finding was confirmed by few small studies which evaluated the persistence of mutations conferring resistance to NRTI and PI (318;783;787;788). Verhofstede et al. reported that in 86% of patients, whether they switch to a regimen containing only PI (n=5) or whether they interrupted treatment (n=9) DRMs were not present anymore within 14 days to 2 months since stopping a reverse transcriptase inhibitor based regimen (only one patient was exposed to NNRTI and NNRTI-resistance mutations were therefore not investigated) (783). Deeks et al. (318) observed that in patients (n=16) with multi drug resistance on PIs, the virus appeared susceptible on sequencing to PIs after 12 weeks of TI. In order to determine the length of persistence of DRMs, Bi et al. designed a small study where plasma and peripheral blood mononuclear cells were sampled and analysed monthly in 16 people (n=7 exposed to NNRTI but without NNRTI-resistance) with resistant virus who had interrupted treatment (788). They estimated that the median time to complete reversion to wild-type was 6.3 months (interquartile range [IQR]: 3.2-20.7 months) if looking at plasma samples and 9.2 (IQR: 5.7-13.8 months) using peripheral blood mononuclear cells samples and using plasma samples by 3.2 months 50% of the DRMs had switched to wild-type. A larger study (n=132) was published in 2009 (787) looking at persistence of NRTI DRMs. They found that NRTI-resistance mutations vary in persistence over time and become undetectable independently of each other in the majority of patients.

The studies which included the persistence of NNRTI mutations reported a less rapid shift to wild-type virus (634;784-786;789-792). In a study of 38 patients with multiple failing regimens who had interrupted ART for 3 months, 32% of which with at least one NNRTI mutations (11 with K103N, 6 with Y181C and with G190A/S), in around 60% of patients wild-type virus was found after 3 months of TI but among those with NNRTI mutations only 17% (n=2) reverted back to wild-type (784). Among those who interrupted treatment while having a detectable VL (n=48), Miller et al. reported that in 62% the virus shifted completely to wild-type and in particular the prevalence of NNRTI-resistance at ART interruption in those who interrupted an NNRTI was 58% for EFV, 73% for NVP and 87% for DLV and by the end of the TI (at least 2 months) these were reduced respectively to 12%, 37% and 37% (785). In Birk et al. only four primary (three K103N and one G190A) and two secondary (one L100I and one K101E) NNRTI mutations were detected and half of them disappeared during a median observation time of respectively 25 and 14 days (634). Similarly Delaugerre et al. observed that in 55% of patients who interrupted treatment for a median of 8 weeks (range: 4 – 24 weeks), DRMs for at least one of the classes of drugs they were resistant to were no longer detected in majority virus; in particular in nine out of eleven patients with NNRTI-resistance mutations, these were no longer detected in majority virus (786). Halfon et al. (792) assessed in 11 patients who failed multiple drug regimens, the persistence of DRM during a 3 month structured TI, using two different assays: DNA sequencing and line probe assay. Only 18% (n=2) of patients completely reverted to wild-type virus, according to both genotyping assays and two additional people reverted to wild-type but only according to one of the two assays. In particular they observed that the LiPA assay detected the resistance mutant population for up to 52 days longer than sequencing in over 60% of the codons. Ruiz et al. (789) looked at the prevalence of DRMs after 12 weeks of structured TI in people who had been exposed to at least two different triple combinations of ART for at least 6 months each, had failed all previous regimen and who had two consecutive VL above 1,000 copies/mL at TI (n=22). At the time of the TI, 95% of participants had NRTI-resistance mutations, 80% NNRTI-resistance mutations and 90% PI-resistance mutations. After 12 weeks of TI 35% of them reversed completely to wild-type virus and the median number of DRMs detected decreased from 6 to 1.5 in the RT gene (4 to 1 for mutations conferring resistance to NRTIs and 1 to 0 for mutations conferring resistance to NNRTI) and from 5 to 1 in the PR gene. Similarly to Ruiz et al., Benson et al. (790) used the data from patients randomized to the structured interruption arm in the AIDS Clinical Trial Group Protocol A5086, to evaluate the persistence of DRM after 16 weeks of TI in 41 patients with DRMs conferring resistance to multiple classes of drugs. After 16 weeks of TI 28% had complete reversion of primary DRMs and 39% partial reversion (reversion of at least one but

not all primary DRMs conferring resistance). Outside of the context of RCTs, Balduin et al. (791) observed that in people who interrupted treatment, for various reasons including toxicities, patient choice and resistance, 21% (3 out of 14) lost all the DRMs present before interrupting treatment (at the resistance test in median 67 day after TI, IQR: 21-159), 50% (n=7) had a reduction in the number of DRMs and in the remaining 29% (n=4) no change in the number of DRM was observed. Most of them were exposed to the first three classes of drugs, and at interruption 10 had resistance to NNRTI and around 40% of them lost from majority virus NNRTI-resistance mutations during the TI.

The largest study (n=90) to my knowledge to investigate the pattern of loss of DRMs from majority virus, including NNRTI-resistance mutations, used data collected in the CPCRA 064 study at baseline (at TI) and at 2 and 4 months since structured TI beginning (765). The CPCRA 064 was a RCT which assessed the effect of 4 months of structured TI followed by salvage treatment in patients virologically failing with multi-drug resistance. They observed that after 4 months of structured TI only 33% of the participants had completely reverted to wild-type and confirmed that the mutations reversion rate was higher in patients with higher baseline CD4 (318). Among the DRMs conferring resistance to NNRTI considered (those present in more than 10% of the sample: V108I, Y181C, K103N, L100I, G190A), the most prevalent at baseline (at the beginning of TI) was K103N (53.6%) followed by Y181C (39.3%), V108I and G190A (21.4%) and L100I (14.3%). Between 39% (Y181C) and 62% (K103N) of these DRMs revert by the end of the 4 months and generally the rate of reversion increased over the 4 months of structured TI.

6.2.3. Emergence of NNRTI mutations, in people who stop NNRTI-based regimen without having experienced virological failure

Among people who have not experienced VF and who interrupt an NNRTI-based regimen, there is a risk that they then develop NNRTI-resistance. This is due to the prolonged half-life of NNRTIs (plasma half-lives between 35 and 45 hours, with persistence in some cases for two weeks or more (793-795)) compared to ARVs from other classes (for example most NRTIs have half-lives between 2 and 6 hours (796)) and to their very low genetic barrier, with only one mutation sufficient to confer a high level of resistance to these drugs. If the drugs forming a regimen have dissimilar half-lives, as is the case for patients receiving an NNRTI in combination with two NRTIs, and all drugs are interrupted simultaneously, this may result in a

functional NNRTI monotherapy in the days and weeks after discontinuation of the regime, unable to maintain virological suppression and leading to a risk of emergence of resistance (777). In patients receiving NNRTI monotherapy, NNRTI-resistance mutations emerge relatively quickly (797). Therefore to avoid the potential for NNRTI monotherapy, if the patient wants to stop treatment it is recommended to stop the NNRTI five to seven days before the other ARVs or switch the NNRTI to a PI and then stop the whole regimen in a few weeks (793;798;799).

There is variability across people of different ethnicity in plasma half-lives of NNRTIs; in particular, there is evidence that people carrying a G→T substitution at position 516 of the cytochrome P450 2B6 gene, which is more common in people of black-African descent, have slower clearance of EFV. In patients with GG genotype at position 516 plasma EFV concentrations are estimated to exceed the 95% inhibitory concentrations for wild-type virus (i.e. 46.7 ng/ml) for a median of 5.8 days (IQR: 4-8 days) compared to 7 days (IQR: 5-8 days) for people with 516 GT and 14 days (IQR: 11-21 days) for people with genotype TT at position 516 (800). Other studies highlighted that non-caucasian people have a slower clearance of EFV, as well as women (801). Within the DART trial, set in Uganda and Zimbabwe, they conducted a small sub-study (n=21) aimed to evaluate NVP elimination in people undertaking a structured TI with NVP stopped 7 days before AZT and D4T ("staggered interruption"). They measured NVP concentrations at 0, 1, 2, 3 and 4 weeks after TI: 83% had NVP detected at 1 week, 26% at 2 weeks, while in the samples collected afterwards NVP was not detected, suggesting that probably the interruption of NVP in African people should be staggered by additional 7-10 days (802).

Several studies have investigated the emergence of NNRTI-resistance in people interrupting an NNRTI-containing regimen, mainly in the context of studies investigating the efficacy of structured TIs (763;766;799;803-805). Among people with suppressed VL structured TIs do not provide any benefit (775) and there is evidence that NNRTI-resistance can emerge in up to 23% of those who interrupt it (805).

The first studies to investigate the emergence of resistance after TIs either focused on NRTI and PI-resistance mutations (806;807) or were very small in sample size (805;808), but they highlighted the fact that DRMs could emerge after people had stopped treatment. In particular in the study by Arnedo et al. (805) genotypic resistance test was conducted at ART initiation, immediately before interrupting the treatment and two weeks after the structured TI. They reported that at two weeks after TI, DRMs were detected in 26% of patients, in 54% of them

these mutations were not found either at baseline or at the time of interruption. Regarding NNRTI-resistance mutations, they found that 23% of those receiving NNRTI-based regimen (3 out of 13) had NNRTI-resistance mutations detected two weeks after interrupting it and they were all de-novo. Hare et al. conducted an analysis similar to that subsequently undertaken by Geretti et al. (766); they used standard population sequencing and allele-specific polymerase chain reaction to assess the presence of NNRTI-resistance mutations at the first virological rebound (VL>5000 copies/mL) after TI. They reported that 41% experience virological rebound within 4 weeks since TI, 85% within 8 weeks and 100% within 60 weeks and that 20% of patients had NNRTI-resistance mutations detected, with higher prevalence (45%) in people with VL between 51 and 400 copies/mL at TI compared with people with VL below 50 copies/mL (14%) (803). Izopet et al. used a subsample (n=86) of patients recruited in the ANRS Window trial and randomized to the intermittent arm (8 weeks off ART and 8 weeks on). They observed an increase in NNRTI-resistance mutations by the end of the study in people receiving NNRTI-based regimen (96 weeks) with 9% having NNRTI-resistance detected at time 0, 3% at 8 weeks (after 8 weeks of ART interruption) and 12% at 96 weeks, with a peak of 27% at 88 weeks (804). Similarly, the Trivacan trial (773) evaluated the efficacy of fixed structured TIs with a different length of time (2 months off treatment followed by 4 months on ART ("2/4 ART arm")) compared with continuous treatment in terms of the proportion of people with CD4<350 cells/µL at 24 months (primary outcomes), mortality, morbidity, cost of care, genotypic resistance, adherence and toxicity. Although they found that the "2/4 ART arm" was non inferior, one of the reasons why they concluded that the "2/4 ART" strategy should not be recommended was the considerably higher risk of developing resistance. At 24 months since the introduction of the strategy they found that 9% of the participants in the continuous arm had at least one DRM compared with 24% in the "2/4 ART arm". When focusing on the NNRTI-resistance mutations, 3% had at least one NNRTI-resistance mutation in the continuous arm at 24 months compared with 21% in the 2/4 ART arm and concluded that the additional risk of NNRTI-resistance mutations acquiring was around 5% per NNRTI interruption. Dybul et al. (809) investigated the impact of cycles of 4 weeks of structured TIs followed by 8 weeks on ART compared to continuous ART. This RCT was prematurely interrupted (after 52 patients had been enrolled), due to the frequent emergence of resistance in people assigned to the intermittent arm, receiving an EFV-based regimen (3 out of 8). The same happened to the fixed-cycle structured TI arm (one week on ART and one week off ART) in the Staccato study, where 53% (n=19) of those assigned to this arm developed VF and 20% of those on a NNRTI regimen had resistance mutations detectable in majority virus (774).

The TIBET RCT (771), where people with CD4 count>500 cells/µL and VL below 50 copies/mL were randomized either to continuous therapy or CD4 guided structured TIs, confirmed the finding from the SMART trial of the risks of ART interruptions (714). In addition they observed that 32% of those assigned to the CD4-guided TI arm on an NNRTI-based regime with resistance test available (n=19) acquired NNRTI-resistance mutations de-novo during the TI.

The largest analysis to the best of my knowledge is the one conducted by Geretti et al. published in 2013 (766) on a subsample (n=131) of patients enrolled in the SMART trial (See section 4.2.7). Using data from this RCT in 2008 Fox et al. (763) showed that in people assigned to the conservation arm with virological suppression (VL<400 copies/mL) at the time of TI, emergence of NNRTI-resistance (at least one NNRTI mutation) within 2 months since TI occurred in respectively 16.4% of those who interrupted simultaneously, 12.4% of those who had a staggered interruption (i.e. they interrupted NNRTI on average 7 days before the other ARVs in the regimen) and 4.2% with switched interruption (i.e. the NNRTI was switched with a boosted-PI for a short period before interrupting the regimen all together). Following this project, Geretti et al. (766) aimed to estimate the risk of resistance emerging in people interrupting suppressive NNRTI-regimen using a more sensitive testing (Sanger sequencing, allele-specific polymerase chain reaction, and ultra-deep sequencing) and to evaluate the association between resistance detection and NNRTI concentration after TI and virological response after treatment re-initiation. They reported that at four weeks since NNRTI interruption 61% (out of 31) and 87% (out of 39) patients had measurable concentrations of NVP (>0.25 ng/ml) or EFV (>5 ng/ml) respectively. After NNRTI interruption, 17% had at least 1 NNRTI-resistance mutation on resistance test, conducted a median of 8 weeks after TI. In 36% (n=8) of the patients with NNRTI-resistance detected, it was detected only by sensitive testing. They found that the odds of finding NNRTI-resistance was almost 8-fold higher if NVP or EFV concentrations were above the median measured in the study population. In contrast to what was found by Fox et al., they found on the same population, but using more sensitive assays, that people who had staggered TI did not have a lower risk of NNRTI mutations arising and had a risk four times higher of NRTI mutations being detected compared to simultaneous TIs.

Contrary to the findings of most RCTs on structured TI, Palmisano et al. reported that people assigned to five structured TIs of respectively 1, 1, 2, 2 and 3 months off-ART each followed by 3 months on ART were more likely to develop resistance to PIs (47% of 30) than to NNRTIs (20% of 99) (810). No difference was found in the cumulative risk of having VF (24% in the continuous ART arm, 95% CI: 15.3, 32 and 26% in the structured TI arm, 95% CI: 15.4, 36.2). In

those randomized to have structured TI 28% had resistance detected on at least one occasion, with 50% of them having one single mutation and 29% having two. The most frequent resistant mutations were M184V/I (33%), K103N (11.4%) and M41L (7%).

Unstructured TIs have an even worse impact in terms of morbidity and mortality (767) and should therefore be avoided. Very few studies investigated the development of resistance mutations following an unstructured TI (811-814) and unfortunately there are no large cohort studies from developing countries reporting on this issue (767). A study conducted in France (811) evaluated the predictors of NNRTI-resistance acquisition in 71 patients with early virological response. They observed over a median of 29 months that 28% (n=20) experience VF and 60% of those with a resistance test had major NNRTI-resistance mutations in majority virus. Interestingly they found that VF occurrence was associated with repeated drug holidays (defined as ≥48 h of unplanned drug cessation), and this was the only predictor of NNRTI-resistance emergence. Sanchez et al. (812) focused their attention on 20 patients who had interrupted treatment while virologically suppressed, because of adverse events, comorbidities or patients' choice. At one month since TI 90% of them were virologically unsuppressed. Of 15 patients who were receiving EFV or NVP, 27% (n=4) patients developed major NNRTI-resistance in majority virus (three K103N and one V106A/V). Among patients initiating fixed-dose NNRTI-based regimen (3TC, D4T and NVP) in Uganda, 65% interrupted treatment for more than 48 hours, according to electronic medication monitors. In this group 13% had developed resistance by the end of the study, while among those who never interrupted treatment none of them developed resistance (813). Another study in Uganda looked at the level of virological suppression among participant on ART, mainly (91%) on NNRTI-based regimen. Among those on NNRTI regimen 22% (n=27) experience VF over a median follow-up of 38 weeks, and in 72% of those with a resistance test NNRTI mutations were detected in majority virus, with the most common mutation being K103N (814).

6.3. Methods

6.3.1. Study population

I conducted analyses to address, firstly the persistence of NNRTI-resistance mutations in patients who have documented NNRTI-resistance while on ART who then stopped all ARVs,

and secondly to assess the extent to which NNRTI mutations are detected in the rebound viraemia in patients interrupting suppressive NNRTI-based ART.

Both the analyses used data from patients in the UK resistance database (see section 6.3.1.1) linked to the UK CHIC cohort study (see section 6.3.1.2), who have interrupted/stopped an NNRTI-base regimen (not necessarily simultaneously, but with NNRTI stopped maximum 14 days before the other drugs).

For the first analysis ("analysis on persistence of NNRTI mutations"), participant were eligible to be included if they had a resistance test while on ART which detected NNRTI-resistance mutations, who then stopped all the ARVs composing their ART regimen, while, for the second analysis ("on emergence of NNRTI mutations"), eligibility criteria were having stopped an NNRTI regimen (not necessarily simultaneously) despite being virologically suppressed (VL below 200 copies/mL after at least 6 months on ART) at TI, without having experienced VF nor having evidence of NNRTI-mutations on previous resistance tests.

6.3.1.1. The UK HIV drug resistance database

The UK HIV drug resistance database includes over 90% of the HIV resistance tests performed as part of routine clinical practice throughout the UK. It was established in 2001 by the UK Collaborative Group on HIV Drug Resistance formed by laboratories performing HIV resistance test in the UK, clinical sites using resistance tests for clinical practice, experts on HIV drug resistance, the MRC Clinical Trials Unit, UCL Centre for Virology, the UK CHIC study, Public Health England (at the time called Health Protection Agency) and the UK Department of Health. The reasons for setting up the UK HIV drug resistance database were to assess the prevalence of drug resistance in recent and untreated infections over time, to characterize the pattern of drug resistance in patients failing therapy, to evaluate the effect of specific mutations on virological response and to help identify the determinants of HIV antiretroviral drug resistance (815). This collaboration was initially funded by the UK Department of Health as surveillance data on the level of HIV drug resistance in treated and untreated patients. It contains data on resistance tests conducted in the UK between 1996 and the end of 2007 (tests performed in 2008 for which information are available are also included) and it includes 50,224 resistance tests (version provided in January 2009). By the end of 2012 over 101,000 tests were available, nevertheless I decided not to update this analysis using this more updated dataset, because it is unlikely to result in a much higher number of people eligible in this analysis (patients who interrupted NNRTI), given it is recommended not to interrupt ART.

Nineteen centres currently contribute data to the UK HIV drug resistance database: ten in London (the Chelsea and Westminster Hospital, the Guy's and St. Thomas' NHS Foundation Trust, PHE London, Imperial College Health NHS Trust, King's College Hospital, Royal Free Hospital, St George's Hospital, St Bartholomew's and The London NHS Trust, St Mary's Hospital, University College London Hospitals) and nine in the rest of the UK: the Addenbrooke's Hospital (Cambridge), PHE Birmingham Public Health Laboratory (Birmingham), Leeds Teaching Hospitals NHS Trust (Leeds), Liverpool Specialist Virology Centre - Royal Liverpool University Hospital (Liverpool), Manchester Specialist Virology Centre - Central Manchester Foundation Trust (Manchester), Royal Infirmary of Edinburgh (Edinburgh), Royal Victoria Infirmary (Newcastle), South Tees Hospitals NHS Trust (Middlesbrough), West of Scotland Specialist Virology Centre - Gartnavel General Hospital (Glasgow).

Each centre provides all the full nucleotide sequences analysed in the previous calendar year. These are then aligned to an amino acid reference sequence and the mutations found are then fed into Stanford's HIVDB algorithm (411) (see section 1.9.10.1). In addition, information on patient demographics, clinical details, ART history and laboratory markers at the time of the resistance test are collected. All these data are collected by the MRC Clinical Trials Unit which coordinates the study.

These data are then linked to the UK CHIC study, because there is substantial overlap in the centres taking part in these two studies.

6.3.1.2. The UK CHIC study

The UK Collaborative HIV Cohort Study (UK CHIC study) is a prospective cohort study pooling data collected for routine clinical care of people with HIV who attended one of the 19 clinics in the UK taking part in this study since 1st January 1996. This study was initiated in 2001 and is funded by the MRC. The aim is to assess the uptake of and response to ART, to identify the predictors of virological and immunological failure in patients receiving ART and to characterize changes over time in AIDS-defining illnesses and mortality.

People living with HIV may have attended more than one clinic and therefore there could be duplicate records between centres contributing to the study. All patients attending one of these centres were matched on the basis of their soundex code, date of birth and other clinical information if considered potential duplicates were flagged and electronically and manually checked. If they were identified as duplicates, a composite record for this patient was included. The data collected include demographics, laboratory data such as absolute and

percent CD4 count, VL levels, Hb, platelets, etc. and ART history (start and stop dates as well as reasons for stopping) and AIDS diagnosis and deaths.

To date, 19 centres take part in the UK CHIC database: 10 in London (Chelsea & Westminster Healthcare NHS Trust, Kings College Hospital NHS Foundation Trust, Mortimer Market Centre - Royal Free and University College Medical School, Royal Free NHS Trust and Royal Free University College Medical School, St. Mary's Hospital - Imperial College Healthcare NHS Trust, Barts and The London NHS Trust, North Middlesex University Hospital NHS Trust, Homerton University Hospital NHS Trust, South London Healthcare NHS Trust, St. George's Healthcare NHS Trust) and nine in the rest of the UK, Brighton and Sussex University Hospitals NHS Trust (Brighton), The Lothian University Hospitals NHS Trust (Edinburgh), North Bristol NHS Trust (Bristol), University Hospitals of Leicester NHS Trust (Leicester), South Tees Hospitals NHS Foundation Trust (Middlesbrough), York Teaching Hospitals NHS Foundation Trust (York), Coventry & Warwickshire NHS Trust (Coventry), The Royal Wolverhampton NHS Trust (Wolverhampton) and Ashford & St.Peter's Hospitals NHS Foundation Trust (Chertsey and Ashford in Surrey). These centres contributed to over 47,200 patients.

6.3.2. Statistical analysis

To assess the persistence of NNRTI mutations in people who experienced VF with presence of NNRTI-resistance mutations, the proportion with NNRTI-resistance in majority virus at the first resistance test after TI was calculated as well as the median time between the TI and the resistance test, if performed. Baseline covariates were examined and compared between patients who had and did not have a resistance test after discontinuing ART to investigate whether people who received a resistance test were different compared to those who did not receive it. Baseline covariates assessed were gender, age, ethnicity, mode of infection, calendar year of TI, presence of a resistance test pre-ART and, if applicable, presence of NNRTI-resistance mutations pre-ART, VL level and CD4 count at TI, CD4 count nadir, time between the resistance test conducted while on ART and the TI, type of TI (staggered or simultaneous), specific NRTI and NNRTI exposure, specific NNRTI-resistance mutations detected before TI, HIV subtype and reason for TI. The categorical variables were compared between people with and without a resistance test following TI using Chi-squared test and Fisher’s exact test (when the expected frequency of one cell was <5), while the continuous variables using the Kruskal-Wallis non parametric test. A modified Poisson regression approach (see Appendix XIII) was used to assess adjusted RRs (aRRs) of having a resistance test performed.

Those who had a resistance test following TI were included in the main analysis aimed at estimating the persistence time of NNRTI-resistance mutations and identifying the predictors of presence of NNRTI-resistance mutations. The mutations associated with resistance to EFV or NVP considered were those indicated in the IAS-USA December 2011 list (816), except for K103S, which was include in the IAS-USA list in 2011 but not in 2008. To identify the risk factors for having NNRTI-resistance mutations present in majority virus after TI and quantify the strength of the association the same approach mentioned in the previous paragraph was used (modified Poisson regression approach). The key covariate of interest for this analysis was clearly the length of time between TI and the resistance test performed off-ART. Other covariates investigated, established a priori, include calendar year of TI, VL at TI, specific NNRTI mutations detected at the resistance test performed while on treatment, subtype, VL and CD4 count at resistance test off-ART, exposure to specific NNRTI and NRTI's and type of TI (staggered or simultaneous).

Similarly, for the analysis on emergence of NNRTI-resistance mutations in patients who interrupted a suppressive NNRTI regimen (VL consistently below 200 copies/mL after at least 6 months on ART), who had no evidence of NNRTI-mutations on previous resistance tests, I, firstly, evaluated whether there were significant differences between those who had a resistance test performed during the TI and those who did not and then investigated the predictors of NNRTI-resistance emerging. The same statistical approach used for the previous analysis was used and similar baseline covariates were considered: demographic variables, ARVs experienced, length of virological suppression, time from TI to resistance test, CD4 count nadir, CD4 count at TI and at resistance test, VL at TI, maximum VL ever measured and subtype.

Several sensitivity analyses were considered for this second analysis. The first restricting to patients who interrupted an NNRTI-based regimen, without having experiencing VF, with a VL of 50 copies/mL or less at TI. The rationale for this analysis is that people with such a low VL are unlikely to store mutations in majority virus and therefore if mutations are observed at the following resistance test while off treatment it is very likely that they have been selected de-novo. The second sensitivity analysis focused on people who had a resistance test performed within 2 and 6 months since stopping the ART regimen. In fact, mutations that arise during an ART interruption could rapidly be lost if the patient remains off ART, but this is unlikely to occur in a shorter period of time. In addition I investigate whether there was a difference in

the detection of NNRTI-resistance mutations in people who interrupted ART simultaneously or who had a staggered TI.

All statistical analyses were performed using SAS 9.3.

6.4. Results on persistence of NNRTI mutations over time

6.4.1. Patient characteristics

Out of the 4,892 patients in the UK CHIC study who had at least one resistance test performed after starting ART, 32% (n=1,567) had NNRTI-resistance mutations detected in majority virus and among these, 353 interrupted an NNRTI-regimen following the resistance test. The patients eligible for this analysis (n=353) were primarily men (78%), mostly having acquired HIV through sex with men (62%) with a median age of 40 years old (IQR: 35-44) and subtype B (75%). The ART discontinuations occurred between 1998 and 2008, median June 2004 (IQR: August 2002 – February 2006). Only a minority of those who interrupted treatment after having experienced VF with NNRTI-resistance mutations detected were virologically suppressed (<50 copies/mL) and they had a median CD4 count at TI of 309 cells/μL (IQR: 163-475). The NNRTI-based regimen was interrupted simultaneously only in 35% of cases with a median of 10 months (IQR: 2 months – 2.4 years) after the resistance test detected NNRTI-resistance in majority virus. Unfortunately the reason for TI was poorly reported in the database (80% unknown) and for this reason its association with the risk of NNRTI-resistance persisting over time was not evaluated. For 86% of the sample there was no resistance test available before initiating treatment and so it is not possible to exclude they were infected with a resistant virus. The NRTI most people had been exposed to was 3TC (92%) followed by AZT (83%), and ddI and d4T with around 70% exposed to each of them. Among the NNRTI, people were exposed either to NVP (64%) or EFV (45%), and the most common NNRTI mutations harboured were K103N (51%), Y181C (18%) and G190A (11%) (See Table 6.1 and Table 6.2 at page 271).

Out of 353 patients included 68 (19.3%; 95% CI: 15.5, 23.8) had a resistance test after interrupting treatment, a median 4 months after TI (IQR: 1 month - 1.3 years). These people were not significantly different, based on the factors considered, to those who did not have a resistance test performed after TI, except for age, calendar year of TI and having being exposed to TDF. In particular those with a resistance test were a median 2 years younger (medians: 38 vs 40), were more likely to have interrupted treatment in an earlier calendar year (medians: June 2003 vs August 2004) and were less likely to be exposed to TDF (25% vs 40%).

Table 6.1. Baseline characteristics, according to the presence of a resistance test off-ART

		All sample (n=353)		Patients with a resistance test during this off-ART period:				
				Yes (n=68)		No (n=285)		p-value
Gender, n male (%)		274	(78%)	56	(82%)	218	(76%)	0.30
Age, med (IQR)		40	(35-44)	38	(42-23)	40	(35-44)	0.02
Ethnicity, n (%)*	**White**	245	(71%)	48	(72%)	197	(71%)	0.95
	Black	87	(25%)	16	(24%)	71	(25%)	
	Other	14	(4%)	3	(4%)	11	(4%)	
Mode of infection, n (%)**	**MSM**	214	(62%)	47	(72%)	167	(60%)	0.06
	Heterosexual	103	(30%)	17	(26%)	86	(31%)	
	Other	27	(8%)	1	(2%)	26	(9%)	
Calendar year of TI, med (IQR)		Jun2004	Aug2002-Feb2006	Jun2003	Nov2001-May2005	Aug2004	Nov2002-Apr2006	0.0023
VL suppression at TI, n (%)		86	(24%)	12	(18%)	74	(26%)	0.15
VL suppression at resistance test off-ART, n (%)		-	-	5	(7%)	-	-	
Simultaneous TI, n (%)		124	(35%)	26	(38%)	98	(33%)	0.55
NNRTI-resistance, pre-ART, n (%)	**No resistance test**	303	(86%)	59	(87%)	244	(87%)	0.58
	No NNRTI mutations	47	(13%)	8	(12%)	39	(12%)	
	NNRTI mutations	3	(1%)	1	(1%)	2	(1%)	
Years between resistance test on ART and TI, med (IQR)		0.8	(0.2-2.4)	0.8	(0.3-1.9)	0.8	(0.2-2.4)	0.75
Years between TI and resistance test off ART, med (IQR)		-	-	0.31	(0.1-1.3)	-	-	-
CD4+ cells count (cells/µL) at TI, med (IQR)		309	(163-475)	356	(178-516)	300	(160-473)	0.48
CD4+ nadir count (cells/µL), med (IQR)		102	(33-190)	94	(19-171)	102	(38-200)	0.37
CD4+ cells count (cells/µL) at resistance test off-ART, med (IQR)		-	-	218	(86-370)	-	-	

*n=346;**n=344; ART: antiretroviral therapy; IQR: interquartile range; med: median; MSM: men who have sex with men; NNRTI: non-nucleoside reverse transcriptase inhibitor; TI: treatment discontinuation;
VL: viral load;

Table 6.2. Additional baseline characteristics, according to the presence of a resistance test off-ART

		All sample (n=353)		Patients with a resistance test during this off-ART period:				
				Yes (n=68)		No (n=285)		p
NNRTI exposure, n (%)	**NVP**	226	(64%)	42	(62%)	184	(65%)	0.67
	EFV	160	(45%)	26	(38%)	134	(47%)	0.19
NRTI exposure, n (%)	**AZT**	293	(83%)	57	(84%)	236	(83%)	0.84
	DdC	56	(16%)	13	(19%)	43	(15%)	0.41
	DdI	247	(70%)	50	(74%)	197	(69%)	0.48
	D4t	238	(67%)	47	(69%)	191	(67%)	0.74
	3TC	323	(92%)	64	(94%)	259	(91%)	0.48
	ABC	145	(41%)	33	(49%)	112	(39%)	0.16
	TDF	131	(37%)	17	(25%)	114	(40%)	0.02
	FTC	18	(5%)	3	(4%)	15	(5%)	1.00
Follow-up NNRTI-resistance mutations before TI, n (%)	**L100I**	1	(0%)	0	(0%)	1	(0%)	1.00
	K101E	8	(2%)	1	(1%)	7	(2%)	1.00
	K101H	0	(0%)	0	(0%)	0	(0%)	nc
	K101P	1	(0%)	0	(0%)	1	(0%)	1.00
	K103N	179	(51%)	40	(32%)	139	(49%)	0.14
	V106A	9	(3%)	2	(1%)	7	(2%)	0.69
	V106M	9	(3%)	2	(1%)	7	(2%)	0.69
	V108I	9	(3%)	1	(3%)	8	(3%)	1.00
	Y181I	1	(0%)	0	(0%)	1	(0%)	1.00
	Y181C	62	(18%)	12	(4%)	50	(18%)	0.98
	Y181V	0	(0%)	0	(0%)	0	(0%)	nc
	Y188C	3	(1%)	2	(1%)	1	(0%)	0.10
	Y188L	22	(6%)	3	(1%)	19	(7%)	0.78
	Y188H	1	(0%)	1	(0%)	0	(0%)	0.19
	G190S	8	(2%)	1	(0%)	7	(2%)	1.00
	G190A	38	(11%)	3	(4%)	35	(12%)	0.08
	P225H	2	(1%)	0	(0%)	2	(1%)	1.00
Subtype at resistance test after TI, n (%)^	**A**	18	(5%)	2	(3%)	16	(6%)	0.48
	B	265	(75%)	51	(75%)	214	(75%)	
	C	37	(10%)	8	(12%)	29	(10%)	
	CRF11_CPX	1	(0%)	1	(1%)	0	(0%)	
	D	8	(2%)	0	(0%)	8	(3%)	
	F (F1)	1	(0%)	0	(0%)	1	(0%)	
	G	6	(2%)	2	(3%)	4	(1%)	
	H	1	(0%)	0	(0%)	1	(0%)	
	U	16	(5%)	4	(6%)	12	(4%)	

^Subtype A1 and A2 have been merged, as only one person had A2;

3TC: lamivudine; ABC: abacavir; AZT: zidovudine; d4T: stavudine; ddC: zalcitabine; ddI: didanosine; EFV: efavirenz; FTC: emtricitabine; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NVP: nevirapine; TDF: tenofovir; TI: treatment interruption;

6.4.2. Estimation of the persistence of NNRTI-resistance mutations in people interrupting NNRTI-based regimen

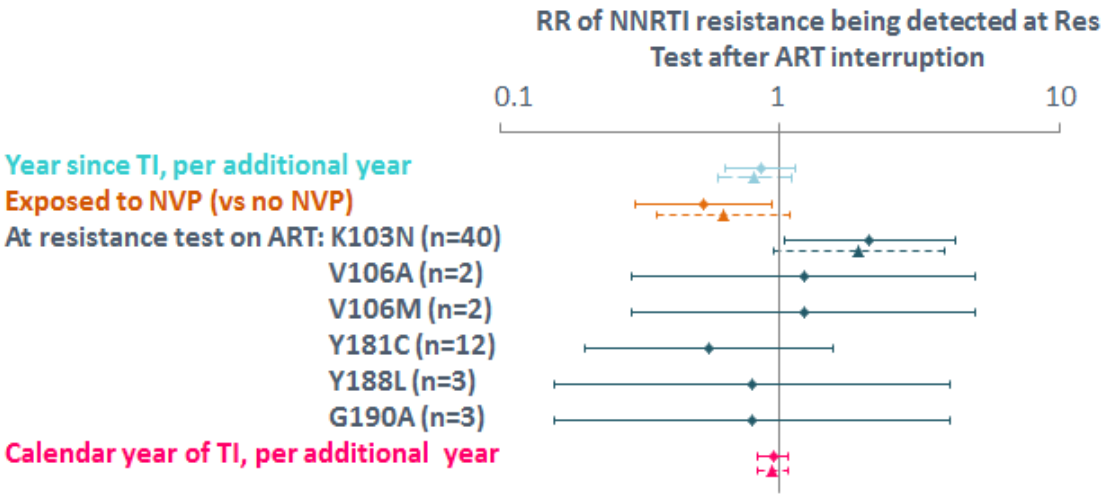
Out of the 68 people with a resistance test available after stopping ART, a considerable proportion, 41% (95% CI: 31, 55; n=28), had NNRTI-resistance mutations detected in majority virus. The resistance test was conducted a median 4 months after stopping ART, more rapidly in those in which resistance was detected (median time 1 month, IQR: 11 days-10 months) than in those were NNRTI-resistance was not detected any more (median time 6 months IQR: 1 month-1.3 years; p-value=0.0435).

The factors which a priori were established could impact on the presence of NNRTI-resistance mutations at the test performed after TI are those included in Table 6.1 (page 270) and Table 6.2 (page271). The variables significantly associated with the outcome were calendar year of TI, time between TI and the day the resistance test was performed, being exposed to NVP, presence of K103N at the resistance test conducted before TI, being exposed to FCT, and previous use of FTC. These, except for previous use of FTC, because only 3 persons were in this category, were all included as covariates in univariate (continuous line in Figure 6.1) modified Poisson regression models. In addition I considered all the NNRTI mutations with a frequency of at least two.

In the multivariable model (dashed line) only the variables associated with NNRTI-resistance in univariate analysis were included. Figure 6.1 shows that although the two factors which were found to predict presence of NNRTI mutations in univariate analysis (being exposed to NVP and presence of K103N) are not independent predictors in the multivariate analysis, the interpretation of the result does not really change.

The risk of detecting resistance mutations seems to decline as time since stopping treatment (lines in light blue) and calendar year (lines in purple) increase, although neither were statistically significant in univariate or multivariate analysis (aRR per additional year since stopping ART=0.82; 95% CI: 0.61, 1.10; aRR per additional calendar year=0.94; 95% CI: 0.83, 1.07). People exposed to NVP, rather than EFV, seem to be less likely to have resistance detected (aRR=0.63; 95% CI: 0.37, 1.08) and people harbouring K103N, the most common NNRTI-resistance mutation (n=40), seem to have a higher chance of having resistance detected after stopping ART (aRR=1.90; 95% CI: 0.95, 3.82). As indicated by the very wide CI, due to the very small sample size, unfortunately it was not possible to properly assess the role of the other NNRTI mutations.

Figure 6.1 Relative risk of NNRTI-resistance being detected at resistance test (univariate and multivariate results)

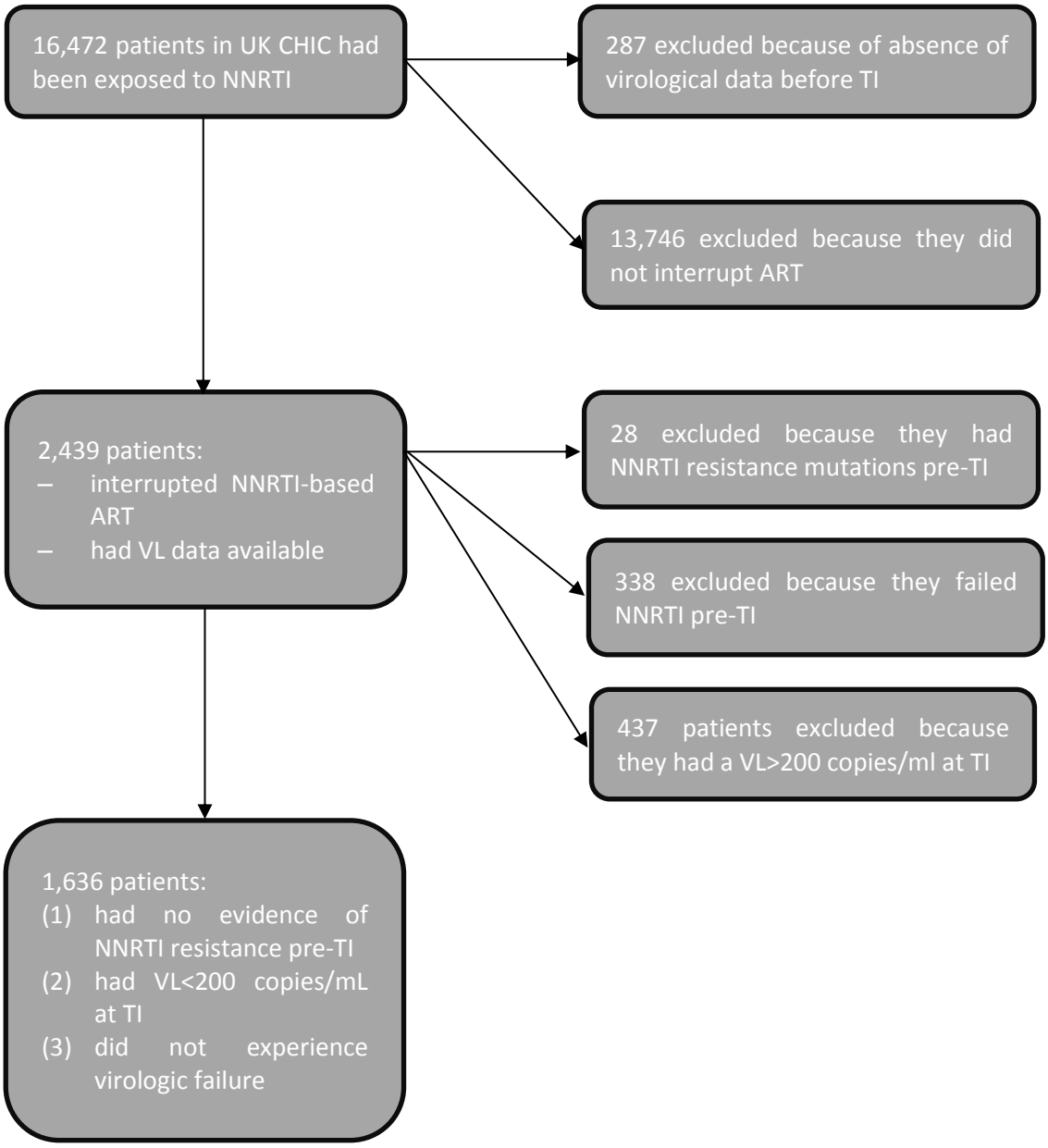


6.5. Results on presence of NNRTI mutations in patients who stopped an NNRTI regimen without having experienced virological failure

6.5.1. Patients' characteristics

Among 16,472 people living with HIV enrolled in the UK CHIC database who had been exposed to NNRTIs, 2,439 patients interrupted NNRTI-based ART, according to medical records and had VL data available, so it was possible to ascertain whether they were suppressed (See Figure 6.2). Among these, 1,636 patients, who had interrupted NNRTI-based treatment, had no evidence of NNRTI mutations on a resistance test (although people without a resistance test before TI were included), had VL suppressed (<200 copies/mL) at TI and had not experienced VF, defined has a VL>200 copies/mL after at least 6 months on a certain regimen, were included in this analysis.

Figure 6.2. Overview of patients eligible for the study



The patients, included in this analysis, come from the same cohort of patients used for the analysis previously described in this chapter and therefore present very similar characteristics (see Table 6.3): mainly composed by men (69%), of white ethnicity (54%), slightly younger median age (38 years old vs 40 years old in the previous analysis), less dominated by MSM (45% compared with 62% in the previous analysis). The median calendar year of TI, among these patients who did not experience VF, was April 2004 (IQR: February 2002-December 2006), after a median of 20 months (IQR: 8 months-3 years and 8 months). At TI 87% had a VL <50 copies/mL and CD4 count of 415 cells/µL (median; IQR: 271-586) and they had been suppressed (VL<200 copies/mL) for 12 months (median, IQR: 4-30 months). The reason for TI is not reported in the table because 80% is unknown and it could not be considered as a potential covariate. Of those included, most (77%) did not have a resistance test pre-ART nevertheless given their consistently suppressed VL it is assumed unlikely that they harboured resistance mutations to the regimen they were receiving. As was the case for the previous analysis, the NRTI most people had been exposed to was 3TC (83%) followed by AZT (66%), while the other NRTI drugs had been used in 25% of the patients or less. Regarding the NNRTIs, 60% had been exposed to EFV and 51% to NVP while the other drugs were used by less than 1% (data not shown). At TI 53% were on EFV, 48% on NVP, 72% were on 3TC, followed by 48% on AZT and 23% on TDF.

Table 6.3. Baseline characteristics according to the presence of a resistance test after TI

		All sample (n=1636)		Patients with a resistance test after TI (while off-ART)				
				Yes (n=208)		No (n=1428)		p-value
Sex, n male (%)		1137	(69%)	136	(65%)	1001	(70%)	0.1678
Ethnicity*, n (%)	White	885	(54%)	113	(56%)	772	(55%)	0.4005
	Black	595	(36%)	71	(35%)	524	(38%)	
	Other	115	(7%)	19	(9%)	96	(7%)	
Mode of infection**, n (%)	MSM	732	(45%)	115	(57%)	617	(47%)	0.0089
	HT	683	(42%)	80	(40%)	603	(46%)	
	Other	97	(6%)	6	(3%)	91	(7%)	
Age, median (IQR)		38	(33-45)	35	(30-40)	38	(33-45)	<.0001
Calendar year of TI, med (IQR)		Apr 2004	(Feb200; Dec2006)	Jan 2003	(Sep2001; Sep2004)	Sep 2004	(Mar2002; Apr2007)	<.0001
VL at TI <50 copies/mL, n(%)		1421	(87%)	172	(83%)	1249	(87%)	0.0600
Maximum VL achieved on ART***, med (IQR)		251	(50-2,780)	400	(60-18,500)	230	(50-2010)	0.0040
Length of time with VL<200 (months), med (IQR)		12	(4-31)	8	(2-23)	12	(4-32)	<.0001
Resistance test pre-ART, n (%) (if done, no NNRTI mutations detected)		384	(23%)	51	(25%)	333	(23%)	0.7029
Years ART initiation - TI,		1.70	(0.63-3.62)	1.05	(0.40-2.71)	1.77	(0.68-3.69)	<.0001
Most recent CD4 count (cells/µL) at TI, med (IQR)		415	(271-586)	456	(305-640)	408	(270-576)	0.0102
CD4+ nadir count (cells/µL), med (IQR)		295	(140-466)	379	(230-513)	280	(135-453)	<.0001
NNRTI at TI, n (%)	NVP	779	(48%)	127	(61%)	652	(46%)	<.0001
	EFV	864	(53%)	81	(39%)	783	(55%)	<.0001
	DEL	2	(0%)	1	(0%)	1	(0%)	0.2382
	TMC-125	3	(0%)	0	(0%)	3	(0%)	1.0000
NRTI at TI, n (%)	AZT	778	(48%)	132	(48%)	646	(45%)	<.0001
	DdC	2	(0%)	1	(0%)	1	(0%)	0.2382
	DdI	176	(11%)	20	(7%)	156	(11%)	0.5692
	D4t	229	(14%)	33	(12%)	196	(14%)	0.4060
	3TC	1179	(72%)	177	(64%)	1002	(70%)	<.0001
	ABC	253	(15%)	34	(12%)	219	(15%)	0.7066
	TDF	369	(23%)	21	(8%)	348	(24%)	<.0001
	FTC	240	(15%)	8	(3%)	232	(16%)	<.0001
# of drugs exposed to, n (%)	<3	2	(0%)	0	(0%)	2	(0%)	0.5254
	3	886	(54%)	108	(52%)	778	(55%)	
	4 or 5	544	(33%)	68	(33%)	476	(33%)	
	6-12	204	(12%)	32	(15%)	171	(12%)	

*n=2,440; **n=2351; ***n=2,181;

3TC: lamivudine; ABC: abacavir; ART: antiretroviral therapy; AZT: zidovudine; d4T: stavudine; ddC: zalcitabine; ddI: didanosine; DEL: delavirdine; EFV: efavirenz; FTC: emtricitabine; HT: heterosexual; IQR: interquartile range; med: median; MSM: men who have sex with men; nc: not possible to calculate; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NVP: nevirapine; TDF: tenofovir; TI: ART interruption; VL: viral load;

6.5.2. Estimation of the risk of having NNRTI-resistance detected after interrupting a suppressive NNRTI-based regimen

Of 1,636 eligible patients, 13% (n=208; 95% CI: 11%, 14%) had a resistance test performed after stopping suppressive NNRTI-based ART and were therefore eligible to estimate the risk of having NNRTI-resistance detected in the rebound viraemia.

The covariates significantly associated with the presence of a resistance test after TI in univariate analysis (see Table 6.3) were included in the multivariate model, except for the drugs people were exposed to, because it was preferred to include the drugs they were actually on when they interrupted treatment . Independent predictors of having a resistance test were older calendar year of ART interruption (range 1997-2008, aRR per 1 more recent calendar year=0.89; 95% CI: 0.85, 0.93; p<0.0001), higher maximum VL achieved on ART pre-TI (aRR per 1 log increase=1.14; 95% CI: 1.04, 1.26; p-value=0.0042), younger age (aRR per 1 year older=0.96; 95% CI: 0.94, 0.97; p<0.0001), higher CD4 count nadir (aRR per 100 cells/µL increase=1.08; 95% CI: 1.04, 1.12; p<0.0001) and being on 3TC at TI (aRR=1.99; 95% CI: 1.39, 2.87; p<0.0001).

Among the 208 individuals with a resistance test performed after stopping suppressive NNRTI-based ART, 12% (n=25, 95% CI: 8, 17) had ≥1 NNRTI-resistance mutation detected at the first resistance test following TI. In those with at least one NNRTI resistance mutation detected the median time between TI and the resistance test was 12 months (IQR: 3-20 months). The most frequently detected NNRTI mutation is by far K103N (55% out of 29 mutations, present in 64% of patients, n=16), followed by G190A (10%, n=3), three mutations (K101E, V108I, Y181C) with 7% (n=2) (see Figure 6.3) and four mutations L100I, V106A, Y188L, P225H with only 1 occurrence (3.4%). There was no occurrence of K101H/P, V106M, Y181/V, Y188C/H or G190S.

Figure 6.3. Distribution of NNRTI-resistance when detected after ART interruption

When including in a multivariate model the factors found significant in univariate analysis with detection of NNRTI-resistance mutations (data not shown; CD4 count at TI, CD4 nadir and NVP at TI, NVP exposure), except for NVP exposure because collinear with NVP at TI, the only independent predictor was CD4 nadir, with a higher chance of NNRTI-resistance being detected the lower the CD4 nadir (aRR for 100 cells/µL increase in CD4 nadir=0.67; 95% CI: 0.53, 0.85; p=0.001).

In sensitivity analysis, it was evaluated whether restricting to patients who stopped their ART regimen while having a VL of 50 copies/mL or below would affect the results. As shown in Table 6.3 (page 276), 1421 patients (87%) had a VL of 50 copies/mL or less and were included. A similar proportion, compared with 13% (95% CI: 11%, 14%) in the main analysis, had a resistance test performed after ART interruption: 12% (n=172, 95% CI: 10, 13). Of those with a resistance test, 12% (20/172; 95% CI: 7, 17%) had NNRTI-resistance detected, the same as in the main analysis (12%; 95% CI: 8, 17).

The second sensitivity analysis focused on people who had a resistance test performed within 2 months since stopping ART (n=55/208, 26%). Their chance of NNRTI-resistance being detected at the resistance test performed after interrupting treatment was 7% (4/55; 95% CI: 2, 17%). When considering a window of 6 months rather than 2, the results were still similar: 9% (95% CI: 4, 17%).

In addition, similar levels of NNRTI-resistance were observed in people with simultaneous (n=188) and staggered interruptions (n=20): 12% (23/188; 95% CI: 7, 17%) and 10% (2/20; 95% CI: 1, 32%), although only less than 10% had simultaneous interruption and therefore it is difficult to draw conclusions given the very small sample size.

6.6. Discussion and conclusions

6.6.1. Summary and interpretation of main results

To the best of my knowledge this is the largest study to evaluate the detection of NNRTI-resistance in the rebound viraemia that follows interruption of a suppressive NNRTI-based regimen and amongst the largest, with the exception of the study conducted by Paquet et al. (765), to estimate the persistence of NNRTI-resistance mutations in people interrupting treatment after having experienced VF. These data allow me to address these two questions in the context of clinical routine, outside of the context of well controlled RCTs, as is the case for most studies evaluating the emergence of NNRTI-resistance mutations.

The studies which have evaluated the length of time NNRTI-resistance mutations persist in majority virus, with the risk of being transmitted, often did not focus specifically on NNRTIs and are characterized by substantial variability with estimates of prevalence of NNRTI-resistance mutations in patients with resistance test after interrupting between 20 and 83%. This variability can partly be explained by the very small sample size of these studies that when selecting patients who were on NNRTI-based regimen range from 4 (634) to a maximum of 90 patients (765), this can produce very biased estimates. Another reason for this discrepancy is due to the fact that the prevalence of NNRTI-resistance mutations has been estimated at different times after interrupting treatment: from 25 days to 4 months and this can off course contribute to the variability in estimates, due to the decay of resistance mutations in absence of drug pressure.

In this study I found that in patients who have documented NNRTI-resistance while on ART who then stopped all ART, 41% had NNRTI-resistance persisting at the first resistance test after interrupting treatment (in median performed 4 months after stopping ART). As expected the patients who had NNRTI-resistance mutations detected had the resistance test conducted more rapidly compared to those in which NNRTI mutations were not detected (median = 1

month, IQR: 11 days-10 months, vs a median time of 6 months, IQR: 1 month-1.3 years; p-value=0.0435), suggesting that the loss of DRMs may occur as a consequence of emerging wild-type virus and the reversion to a more fit state (318;765;817). The estimate of a prevalence of 41% in people who had a resistance test in median 4 months after the TI is lower than previously reported by most studies (765;784;790), but in line with others (785). Nevertheless it is difficult to compare my estimates to previous published studies because in the UK resistance database study, given its observational nature, it was not predefined when the resistance test was performed, while in some of these studies the resistance test was performed at a precise time after TI.

The main factor of interest for this analysis was the time between the TI and the resistance test performed off-ART. The data seem to suggest that the risk of detecting resistance mutations declines over time by 18%, although this was not statistically significant potentially due to the relatively small sample size. This risk seem to decline slightly (6%) as well as calendar year increases and this is likely to be to the fact that people who had the first ART interruption more recently in time are more likely to have been exposed to a lower number of regimens. This data seem to suggest that K103N, the NNRTI-resistance mutations most commonly found in this study, is more likely to persist. This has been previously reported by some studies (797), but not in others (765).

Regarding the emergence of NNRTI-resistance mutations in patients interrupting suppressive NNRTI-base regimen, this study confirms that the detection of NNRTI-resistance is a relatively common phenomenon, occurring in 12% of patients who have a resistance test (in median conducted 12 months after the TI; IQR: 3-20 months). Previous studies (763;766;799;803-805) estimated emergence of NNRTI-resistance mutations between 11% (766) and 37% (809), but this was measured either between 2 weeks (805) and 2 months (763) since TI or at the end of few cycle of structured TI (773). Studies have shown that when interrupting suppressive NNRTI regimen, NNRTI-resistance mutations can emerge and then in absence of drug pressure they can disappear again (804), therefore given the long time between the TI and when the resistance test was performed it is possible that in this study more than 12% selected NNRTI-resistance de novo, but they were not detectable anymore by standard assays by the time the resistance test was conducted.

To explore this hypothesis I restricted to people who had a resistance test performed within 2 months since stopping ART (26% of the sample), but I found that the chance of NNRTI-

resistance being detected at the resistance test was even lower, 7%, but with an upper limit of the 95% CI of 17%.

By far the most common NNRTI mutation detected off-ART was K103N, which emerged in 55% of patients with a resistance test available. This is not surprising and it has been previously reported (803;805). The only factor that was found to independently predict the selection of NNRTI-resistance mutations was the CD4 nadir with a higher chance of NNRTI-resistance being detected the lower the CD4 nadir, as previously found by other studies (766).

When restricting to patients who stopped their ART regimen while having a VL of 50 copies/mL or less, the results did not change, contrarily to what has been found in other studies, where people interrupting treatment with a VL below 50 copies/mL were less likely than those with a VL between 50 and 400 copies/mL (766) to acquire NNRTI-resistance mutations. In this study only 13% had a VL between 50 and 200 copies/mL, therefore there was not enough power to detect that difference.

Finally I investigated whether the results changed if staggered interruptions are used, rather than simultaneously, as has been previously shown (763). This study was not able to establish the extent to which these results change, because only 20 people had a staggered TI (95% CI for detection of NNRTI-resistance mutations: 1, 32%) and the remaining 188 simultaneously interrupt treatment.

6.6.2. Limitations of the analysis

There are several limitations that characterize this study. For both analyses, although a subject could have more than one TI after being exposed to NNRTI, I looked only at the first NNRTI interruption. For the analysis on emergence of resistance the interest was on the de novo selection of NNRTI-resistance mutations so I considered only the first treatment NNRTI interruption to minimize the chances that NNRTI-resistance mutations were present before stopping ART. In fact, there is evidence that repeat interruptions of the same regimen increase the risk of acquiring DRMs (804;818). Some individuals did not acquire DRMs at the first interruption, but they did after more interruptions of the same regimen (818). On the contrary, Arnedo Valero et al. found that the number of mutations did not increase as the number of interruptions did (805).

In the analysis on the emergence of NNRTI-resistance mutations in people interrupting suppressive NNRTI regimen, it is not possible to exclude these NNRTI-resistance mutations being present, in minority or majority virus, before the TI. The great majority did not have a

resistance test pre-ART or before the TI while on ART, therefore it was not possible to distinguish between the re-appearance of previous existing mutations that emerged as a result of previous regimens or was transmitted and selection of de novo mutations. Since all of the patients eligible for this analysis had a VL suppressed at TI (<200 copies/mL in the main analysis and <50 copies/mL in sensitivity analysis) it was not possible to conduct (nor would it have been clinically indicated) a genotypic resistance testing and so there is no information on which mutations were present at interruption. Highly sensitive assays have demonstrated that drug resistant viruses can be selected and replicate despite ART induced VL suppression (819).

In addition, I investigated whether there were any differences at baseline among those who received a resistance test or not after interrupting a suppressive NNRTI-based regimen and I identified the independent predictors of having a resistance test performed in multivariate analysis. I considered all the variables agreed a priori, among those available within the UK CHIC and UK resistance database, which were hypothesized could have an impact on the decision on whether the patient would receive a resistance test. However, it is not possible to exclude the presence of other unmeasured factors, or not available to me, which could have had an influence on whether a patient would receive a resistance test or not.

For both analyses, the presence of NNRTI-resistance mutations was determined by population sequencing rather than more sensitive assays. Studies using both standard genotyping assays and ultra-sensitive genotyping (e.g. Sanger sequencing, allele-specific polymerase chain reaction or ultra-deep sequencing) have shown that more NNRTI mutations (i.e. low frequency drug resistant variants) are detected when ultra-sensitive assays are used (766;803;808). Therefore patients may be believed to have wild-type virus at the time of the resistance test if mutations are present in low frequency (808). Thus this estimate is likely to be an under-estimate of the selection of de novo resistant mutations when treatment is interrupted. The same is true for the persistence of NNRTI mutations, it is possible that they still persist but in such small frequencies that standard genotyping test is not able to detect them.

In addition these data contain information routinely collected in clinics and whether the patient received a resistance test after interrupting treatment was not part of a protocol study but depended on the clinician choice. Therefore, although I did not find major differences between those who received and those who did not receive a resistance test, it is not possible to exclude confounding and likely that those with a resistance test performed had a higher chance of NNRTI-resistance mutations being present.

6.6.3. Conclusions

To conclude, this study confirmed that emergence of NNRTI-resistance mutations is common in people interrupting treatment and this is relevant because it has consequences on the efficacy of treatment once it is restarted. In those who interrupt after having experienced VF due to resistance emergence around 40% had NNRTI-resistance mutations detected after a median of 4 months since interrupting and this has serious implications for the transmission and spread of resistant virus. These estimates are useful for informing models that incorporate HIV drug resistance emergence and transmission and provide additional evidence for the potential risk on resistance of ART interruptions.

7. How should the South African ART programme be enhanced to cost-effectively deliver health gains?

7.1. Introduction

In chapters 4 and 5 I presented the findings from the assessment of the impact on HIV incidence and on the levels of drug-resistance of expanding access to care and eligibility criteria for ART initiation in South Africa. I found that expanding access to care to 80% of the HIV-infected population, while maintaining the eligibility criteria to initiate ART at CD4<350 cells/µl is the most cost-effective strategy according to the Synthesis Model, while some other models found that the most cost-effective strategy is to modify the eligibility criteria to CD4<500 cells/µl or to all people diagnosed with HIV, without expanding the number of people in care (692). The reason why different models reach different conclusions is not completely clear, but could be due to different assumptions in the models, different structures, including due to different levels of detail being included. As well as explicitly modelling the development and transmission of drug resistance, the Synthesis model allows for people to be lost from care after being initiated on ART and to come back to care, which is not the case for all models included in the comparison.

The WHO 2013 ART guidelines set ambitious goals, including initiating all patients on ART at CD4<500 cells/µL (280). However, several programmes in South Africa have highlighted that losses from the cascade of care represent a major barrier to maximizing population health benefits from ART. It is increasingly recognized that engagement in HIV medical care plays a crucial role in maximizing health outcomes at a population level: maintenance of viral suppression in people HIV-positive, reduction in their risk of progressing to AIDS, and reduction in the risk of HIV transmission. The possibility that reinforcing the "cascade of care" (defined in section 7.1.1) could be one of the best options to produce further health benefits, at least in the short term, has been previously suggested (820). Programme managers face a difficult decision over levels of resources and effort to commit to initiating patients earlier on ART compared to improving implementation of ART delivery. For these reasons I decided to try to understand which step in the cascade of HIV care, from being diagnosed with HIV to being virologically suppressed on ART, is most influential on HIV incidence and death, and which step is the most cost-effective to improve. This question requires the use of mathematical models, because it is not straightforward to understand whether more deaths can be averted for

example by avoiding late ART initiation (achievable by improving linkage to care and retention in pre-ART care) or by improving retention once on ART; in particular, as it is unclear for example whether people who are not engaged into care would look for healthcare when developing symptoms. Similar reasoning is true for averting HIV infections.

7.1.1. Definition of cascade of HIV care

As discussed before, an incredible expansion in ART availability has been observed in LMIC, nevertheless lots of people do not receive ART for very long, because of the early mortality and loss to follow-up. Patients who initiate ART with a low CD4 count experience a very high mortality: 3-fold higher for those with CD4 count at ART initiation below 25 cells/µL compared to above 50 cells/µL (493), largely due to ADCs and OIs such as TB and cryptococcus meningitis (821;822). There is also strong evidence that interrupting ART is detrimental for the patient (714;770).

In an effort to understand what are the obstacles and challenges to successful treatment, a number of stages the patient has to go through to be successfully treated have been identified and they are referred to as the "cascade of care" (823-825). Fox et al. provided first of all a series of definition for concepts related to pre-ART care (See Table 7.1) and proposed a nomenclature for the stages of pre-ART care (See Figure 7.1):

i. from being diagnosed with HIV (i.e. first positive HIV test) to ART eligibility assessment (i.e. receipt of the CD4 result or clinical assessment and refer to either pre-ART or ART care), also referred to as "linkage to care".
ii. from completion of the first ART eligibility assessment (which should correspond to the referral to pre-ART care) until ART eligibility (this applies only to people who are not eligible for ART at the ART eligibility assessment), also referred to as "retention in pre-ART care".
iii. from determination of ART eligibility to ART initiation (this period includes "treatment readiness" visits, adherence training and treatment education).

Once they are initiated on ART a fourth step is required to achieve and maintain VL suppression (823;825):

iv. adherence to ART medication, which includes being retained in care.

Table 7.1. Definitions of key concepts in pre-ART care (824)

Figure not available due to copyright restrictions

Figure 7.1. Stages of pre-ART care (551)

Figure not available due to copyright restrictions

More recently Hallett and Eaton (820) proposed to modify the cascade of care to allow for alternative path through the steps, already identified and proposed by others (823;824), in particular to allow people who dropped out from the cascade of care at early stages to come back into care. They noticed that the number reported to be initiated on ART with very low CD4 counts was not compatible with the numbers reported regarding the different steps in the cascade of care. They hypothesize that the reason for this discrepancy is that many people who initiate ART had not been retained in pre-ART care since their first HIV test, so they drop out during the pre-ART care and then come back later, when their CD4 is already very low or reinitiate ART after being lost, rather than initiating it for the 1st time.

Unfortunately, many patients are lost at each step of the cascade (551). Lots of patients initiate ART late, a long time after eligibility criteria had been met, even in settings with high ART coverage (826;827) and many fail to achieve VL suppression once initiated on ART (304). Strengthening the cascade would allow increased survival, as more people would initiate ART at a CD4 count closer to the eligibility threshold and higher levels of viral suppression.

It is therefore important to have accurate measures of loss to follow-up. Measuring engagement and retention in HIV care is difficult, because this process includes multiple clinic visits over time and because the fact that a person may not be attending a specific clinic does not necessarily mean that the patient is not receiving HIV care.

7.1.2. Definition of loss to follow-up when enrolled in an ART programme

Being able to follow people who are on ART over time is critical to ensure adherence to treatment, to assess treatment response, to evaluate the potential emergence of drug resistance and toxicities and to access other healthcare services (828).

There is not a consensus definition for being LTFU (829;830), although some have been proposed (829;831;832), making it very difficult to compare performance across different programmes and countries. Different reference time points have been used: since the last scheduled appointment (833-837) and since the last clinic visit (493;751;838;839) and with different time lengths.

The definition of LTFU proposed by WHO is more than 90 days from the missed clinical visit or drug pick-up (832). Chi et al. used data from a cohort in Lusaka to determine after which length of time it is most appropriate to consider a person LTFU. In particular they looked at how many people were coming back to care in the following year of those considered LTFU and found that considering a person LTFU 56 days after a missed visit was the definition characterized by higher accuracy (Sensitivity of 84%; 95% CI: 83, 85; specificity of 97%; 95% CI: 97, 98), and lowest misclassification: 5% (95% CI: 5, 5). For this reason 60 days which performed similarly well, was proposed (831). In 2011 Chi and colleagues repeated this analysis but using observational data from 111 health facilities representing over 180 thousands patients from 19 different countries (829). They found that the definition of LTFU which minimised misclassification was an interval of 180 days since last patient visit (7.7% of misclassification, 95% CI: 7.6%, 7.8%) and therefore they recommended this definition.

A couple of studies evaluated characteristics associated with LTFU (830) and the estimated rates of LTFU, AIDS-defining events, and death (840) according to the LTFU definition used. Shepherd and colleagues found that in Mozambique at two years since initiating ART, depending on the LTFU definition used, the estimates of LTFU varied from 22% to 84%, estimated mortality from 11% to 16%, and occurrence of AIDS-defining events from 6% to 8% (840). Li and colleagues found that the proportion considered LTFU in a study in Lusaka, Zambia, varied from 26% if the definition of LTFU was >=365 days late since last appointment to 36% if the definition was >=90 days since last encounter and respectively the LTFU rate per 100 PYs ranged from 8.7 to 13.6. Li and colleagues reported that in their population the patient characteristics associated with LTFU were consistent across definitions: younger age, male gender, lower body mass index (BMI), higher CD4 count, and lower Hb (830), therefore although it is important to have a standardised definition for comparability this should not affect the ability to identify those in whom interventions should be tailored to.

In 2010 Fox and colleagues published a systematic review, including 39 cohorts in sub-Saharan Africa, estimating programme attrition (sum of deaths and LTFU) to be 22.6% at 12 months, 25.0% at 24 months, and 29.5% at 36 months (1). The studies conducted in South Africa assessing retention on ART are summarised in section 7.3.5.

Regardless of the length of time to consider a person LTFU, the rates of loss reported in the literature have been very high and concern has grown in the scientific and public health community. On the other hand, most of the studies assessing loss to follow-up in resource limited settings (RLS) have been conducted from the clinic point of view and considered people LTFU if the person did not come back to that specific clinic, while it is possible that they transferred to another clinic and were therefore still being seen elsewhere in the country's healthcare system. For this reason, tracking studies, in which people considered LTFU and either eligible to initiate ART (841) or initiated on ART (837;838) are traced to ascertain their vital status, have become quite popular. In these studies clinical trackers, either trained healthcare workers or volunteers search in the community for patients who are considered lost from the clinic through telephone calls, home visits and social networks.

A meta-analysis of these tracing studies (842), reported that 63% of patients could be contacted and their status ascertained (range across studies: 45%-86%), 40% of these had died (95% CI: 33%, 48%), with significant heterogeneity across studies. Within the African programs, the mortality among patients considered LTFU ranged from 12% to 87% and this was inversely

associated with the rate of LTFU up in the programme. Tracing studies conducted in South Africa are described in more detail in section 7.3.5.

Understanding the real magnitude of the problem and the reasons for disengaging from care are fundamental to improve retention in HIV care and on ART and, thus, long-term benefit of ART. It is not surprising that many people who are considered LTFU have in fact transferred to another clinic, given the population movements, rapid ART scale-up and decentralization of care. In most countries in sub-Saharan Africa with generalized epidemics, ART delivery was initially provided in urban hospital centres and later expanded to lower-level health clinics and rural sites (843;844). Another common reason for disengaging from care, transferring to a different clinic or not adhering to treatment is the fear of stigma and discrimination, which has been reported in a few studies (845-847).

7.2. Brief literature review on barriers to HIV care and effective interventions to reduce the loss from the cascade of care

It is important to be able to identify which patients are at highest risk of being lost from the cascade of care and what are the reasons behind it, so that interventions can be targeted to this group. Nevertheless, it is not clear what is the most effective intervention to improve long-term retention among people living HIV and it is likely that the effectiveness of interventions differs across programmes and within programmes between different groups of patients. I am briefly going to list for each step of the cascade of care the main barriers to access and engagement with HIV care in sub-Saharan Africa, and then which interventions have proven to be effective in overcoming these issues in these settings. More detail (which was excluded from the main text due to the word limit) is provided in Appendix XIV. Interventions for specific subgroups of the population, such as MSM, female sex workers, people who inject drugs and adolescents are not discussed because they are outside the scope of this thesis.

7.2.1. Awareness of HIV status: barriers and effective interventions

Barriers to HIV testing are numerous, including fear of learning HIV status, of stigma and discrimination, lack of perceived HIV risk, perceived lack of confidentiality of the HIV test result, the inconvenience and opportunity costs of testing, the lack of capacity of the health

system due to staff shortages and high workload and poor infrastructure, to encourage and test for HIV more widely (471;848;849).

The low uptake of HIV testing until around ten years ago led to the development of alternative approaches to the standard client-initiated voluntary counselling and testing (VCT). These include:

- PITC, which consists of the health workers routinely offering HIV testing to all people attending the clinic with the option for them to "opt-out". This strategy is recommended by WHO since 2007 for all adults and adolescents in countries with generalised epidemics (471). This strategy has been shown to be highly acceptable and feasible (849;850), contributing to increasing the uptake of HIV, especially in ANCs (851). Efforts to increase HIV testing, through PITC, in specific groups of patients such as TB patients and inpatients, have been extremely successful (850;852).
- Couple VCT, was conceptualized as a means to increase HIV testing among men, given the success observed of PITC in ANCs. A few RCTs investigated the efficacy of encouraging couple counselling and testing of sexual partners within ANCs with mixed findings (853-855).
- Home-Based Voluntary HIV Testing (HBT), where mobile teams go door-to-door and offer an HIV test to generally all adults, or adults living with HIV-positive household members and children aged 0-14 years with an HIV-infected mother living in the household, has given very successful results. This strategy has allowed the reaching of groups of the population previously underserved, such as poorer people (856) and people living in rural areas, reducing late diagnoses (857) and more generally increasing the probability of being tested for HIV (754;858-862) and of receiving the result of the test (863). More recently, some studies have assessed interventions addressing simultaneously multiple steps of the cascade of care including HBT, with successful results [see (864) in section 7.2.8].
- Workplace HIV counselling and testing, where people are offered the possibility to be tested for HIV at the workplace, has been demonstrated to be very efficacious in a RCT (865). Nevertheless there is huge variability in uptake using this strategy across studies (862). A factor that seems to be important to guarantee the success of this strategy is that the services are led by people openly living with HIV (866).
- Mobile HIV testing, which consists of offering HIV testing and counselling (HTC) in public locations, generally accompanied by mass-media campaigns, has been widely

assessed with very successful results. A meta-analysis estimated the uptake of HTC through mobile testing to be 87% (95% CI: 85%, 88%) with a wide range from 27% in a study conducted in Zimbabwe (867) up to 100% in Kenya (868).

- School-based HIV educational programs (excluding very young children, <5 years old), have been evaluated only in one study in sub-Saharan Africa. This took place in KwaZulu-Natal in South Africa and targeted high school girls (aged 12-25) (869), as they are at higher risk of becoming HIV-positive than boys of that age. Here they found that the uptake was similar to other community based approaches: 85% (95% CI: 83%, 86%).
- HIV self-testing (ST) consists of an individual collecting their own sample (typically saliva or a finger prick blood sample), and performing the test in private on their own (870). This approach has been found to lead to very high uptake both in the general population, in Blantyre, Malawi (755;871;872) and among healthcare workers in Kenya (873) and in Cape Town (874).

7.2.2. Linkage to care: barriers and effective interventions

While HIV testing has increased dramatically in the last few years due to the massive effort to scale up HIV testing, a problem that is now emerging is the fact that people who test positive fail to be subsequently linked to care (i.e. to receive ART eligibility assessment, including the result of the CD4 count test if conducted), leading to late presentation for ART. It has been estimated that in sub-Saharan Africa only 57% (95% CI: 48, 66%) of those who are aware of their HIV-positive status completed assessment of ART eligibility (553). The estimates on linkage to care in South Africa are presented in section 7.3.2.

Several studies have been conducted to identify the reasons for people not linking to care (16 reported in a systematic review from South Africa). The most common major barriers were transport costs and distance, stigma and fear of disclosure to their partner and/or family, human resource shortages at the clinics, long waiting times, fear of drug side effects, the need to take time off work and, for women, fear of violence or relationship break-up (875-877). A consistent finding across studies was that males and people of younger age were less likely to link to care.

Despite the dramatic losses at this point, most of the research has focused on interventions to boost HIV testing and retention in care, once initiated on ART, while much less research is available regarding this step and the retention in pre-ART care.

Implementation studies demonstrated that it is possible to substantially reduce the loss at linkage to care. Successful interventions are:

- referral programs (878), which facilitate referral from HIV testing to health centres where people can receive ART eligibility assessment (often the HIV testing and ART eligibility assessment are not conducted in the same site);
- patient/peer navigators (876), which are people living with HIV trained as counsellors that visit the people newly diagnosed with HIV to support them to be enrolled into HIV care;
- use of POC CD4 count testing at time of receipt of positive HIV test result (757;879); these are portable devices which generally allow for the result of the CD4 count to be available on the same day that it is measured.
- home-based ART initiation for those who self-test positive (880), which consists in offering the possibility of being initiating on ART at home rather than having to attend the local clinic facility for confirmatory test and ART eligibility assessment.

7.2.3. Retention in pre-ART care: barriers and effective interventions

Loss to follow-up in people who have been diagnosed with HIV and found not eligible at ART assessment can be very high. At least three systematic reviews have assessed the attrition between diagnosis and ART initiation (551-553). Rosen et al. estimated that in sub-Saharan Africa more than 50% of the people could be lost during this stage (551), although it is likely that some would return back into care if symptoms present. Estimates specific for South Africa are summarised in section 7.3.3. The barriers reported for this stage of the cascade of care are similar to those reported for linkage to care and for retention once initiated on ART: distance to the clinic, transport costs, other competing necessities and for some the fact that, if their CD4 count is very high, they are aware they are not going to be eligible for a while (875).

Interventions shown to be effective, although not always in RCTs, include:

- structural services, such as cash transfers for transportation (881) and food assistance programs (882) (although this study was conducted outside of sub-Saharan Africa in Haiti);

- free CTX prophylaxis (883);
- intensified post-test counselling, provided by trained counsellors, and enhanced peer-support, involving monthly home visits by community support agents (884);

7.2.4. Prompt initiation on ART: barriers and effective interventions

Barriers to timely initiation on ART once identified as eligible also include issues related to the health system such as not offering ART and drug stock outs, but also resistance from the patients, who fear drug toxicities and drug interactions (885). In a study in Soweto of newly diagnosed people, they found that of those found eligible 20% refused to be referred to initiate ART and most of them (92%) did not change their mind even after 2 months of counselling. The major reason reported was 'feeling healthy' (37%), despite their CD4 being below 200 cells/µL (886).

Interventions found to enhance prompt initiation on ART include:

- POC CD4 measurements (757;887);
- postponement of adherence counselling from the period between being identified as eligible and ART initiation to the period after ART initiation (888);

7.2.5. Retention on ART and adherence: barriers

In order to be adherent to ART, it is necessary to be able not only to follow dosing regimens but also to refill prescriptions. Thus barriers to retention and adherence overlap. For this reason they are presented in the same section.

There are disparate reasons for being lost from care, after ART initiation. They have been divided into “unintentional” and “intentional (889).

Among the “unintentional” the following have been reported:

- competing needs, such as education or food for their children (890;891);
- financial constraints, in particular transport costs (275;892-894) and the necessity to pay for ART (847);
- time needed for clinic attendance (i.e. the necessity to take time off work to visit the clinic)(275);
- alcohol abuse (567);
- mental disorders, such as symptoms of depression (491;567;895) and anxiety (895);
- fear of disclosing HIV status (485;846;890;896) and more generally fear of stigma and discrimination (275;847;890;892;897);

Among the “intentional” reasons:

- dissatisfaction with care due to low-quality services (e.g. lack of confidentiality and privacy, drug stock shortages, problems with missing paperwork such as transfer papers or clinic cards, constrained number of health personnel and therefore not sufficient time spent with the provider) (275;847;890);
- dissatisfaction with care due to poor access (e.g. long waiting time and unavailability of extended and weekend clinic hours) (275);
- healthcare providers' attitudes and poor communication skills (890;891);
- medication side effects (847;893);
- complexity of drug regimens (846;889);
- religious beliefs or the use of traditional medicine (847;890;892;897;898;898;899) and in particular not believing in the higher efficacy of ART compared to traditional medicine;

The evidence regarding factors which can boost adherence is scarcer. Having a social role (e.g. having a family) and the social responsibilities connected to it (e.g. having to provide for children) often represents a strong incentive to adhere (847), together with desires for the future, such as getting married or having children and believing in the value of treatment (891;898-901). This positive attitude depends clearly on the ability to cope with an HIV diagnosis (847) and of being able to get social support through family, treatment support groups, or faith-based organizations (890;891;899).

Finally, some studies focused on identifying risk factors associated with a higher risk of being LTFU. Factors commonly reported are:

- having initiated ART while pregnant (753;902;903);
- having initiated ART as inpatients (753);
- a high nadir CD4 count (above 200 cells/µL) or CD4 count at baseline (484;753), although the opposite has been reported as well: people initiated on ART with a CD4 between 200-350 cells/µL being less likely to be LTFU than those with a CD4 at baseline <200 cells/µL (904);
- male gender (484;892);
- younger age (753;903);

A factor which, on the contrary, has been found to be associated with a higher probability of being maintained in care is having received 6 months of pre-ART care (753;905;906).

Predictors of sub-optimal adherence include issues related to the delivery and characteristics of ART regimens, such as:

- not speaking the same language as site staff (898);
- having a complex dosing regimen (489) and therefore difficulty with the schedule of doses (487);
- running out of pills (487);
- medication adverse events (907;908) and perceived side effects (898);
- long waiting times (898);

Similar factors to those which characterize people more likely to be LTFU, characterize people more likely to have suboptimal adherence:

- younger age (489);
- male gender (488);
- lower education (488);
- being single (never married) (909);
- being away from home (487;898;910);
- feeling better on treatment (898);
- fear of being stigmatised (487);
- being malnourished or at least not able to have at least three meals per day (911);
- low monthly income (909) or being unemployed (487);
- contact with psychiatric care service (908) and alcohol use (898);
- being too busy or forgetting it (910);
- use of traditional medicine (898);

7.2.6. Retention on ART: effective interventions

Several interventions have been found effective in improving retention on ART. These include:

- tracing systems, which means that community health workers either call or visit the patients after missed appointments to ascertain their status (whether they had stopped treatment, whether they had transferred to another clinic or whether they had died) and invite those who had interrupted treatment to come back to care (494;842;912);
- community-based ART programs (CBART), which include a quite wide range of different interventions, but all aimed at reducing the number of visits to the clinic and

at providing support to the patients through peers or community health workers (913-920);

- nurse rapid assessment model, which consists of nurses briefly contacting weekly or bi-weekly individuals initiating ART with CD4 counts of 100 cells/µL or less (921);
- structural services, consisting of payment of school fees or rent, provision of shelter, employment at the program, interest-free loans, adult literacy instruction, income-generating activities, transport, skills-building activities, food assistance for patient in need monetary supplements (912;922);

7.2.7. Adherence: effective interventions

Interventions which have been demonstrated to be effective in improving adherence in RLS include:

- mobile phone short messages, in particular weekly messages, in some cases where the patients were asked to reply within 48 hours (923;924);
- individual adherence counselling at the time of ART initiation (925);
- use of community based treatment partners (including DOT) (926);
- patient adherence treatment supporter (usually a family member, a friend, a community health worker or a peer health worker), which either provides psychosocial support, educates them on ART use, measures the patient's adherence, reminds them to pick up the medications or assesses their adverse events and triages to other healthcare providers if necessary. The evidence for this intervention is mixed (927-929);
- DOT (930) in combination with:
    - patient adherence treatment supporter (926;931;932), although some negative results have been found (933);
    - educational counselling (932);
- modified DOT, which consists of 24 weeks of twice weekly health centre visits for nurse-observed pill ingestion, adherence support, and medication collection (926);
- structural services, such as monetary supplements and food rations, in patients with food insecurity or underweight at ART initiation (934-936), although the impact in some cases was found on BMI but not reflected on VL or adherence outcomes (937). This intervention has been found to be quite costly compared to the others (938).

7.2.8. Approaches which improve the cascade of care at multiple steps

To date no single intervention has been found to be effective in improving substantially the whole continuum of care. Nevertheless different interventions have tackled losses at more than one step in the cascade, especially because the barriers across the continuum are often similar.

Interventions which have been demonstrated effective at improving more than one step in the cascade of care include:

- Decentralization of HIV care provision and task-shifting, in other words delegating tasks usually performed by physicians (at least in high income countries) to staff with lower-level qualifications, such as nurses or other non-physician figures. This practice has been found to be efficacious at improving several outcomes:
    - level of HIV testing (939);
    - access to ART (number of people initiated) (939);
    - clinic efficiency (940);
    - retention in care (843;941-944) (without compromising the level of healthcare in patients on ART (945));
    - Adherence to ART (946);

This strategy is recommended by WHO (947) for countries with severe health worker shortages.

- Integration of HIV/AIDS services into other healthcare services, such as:
    - TB services (948) (949). This has increased dramatically the level of HIV testing in people with TB (948) (949) and enrolment into HIV care (949);
    - ANCs (950-953). This integration has been found to improve dramatically enrolment of pregnant women on ART (953;954) and it is now widely implemented;
- Health information system (i.e. electronic medical records) have been effective in reducing:
    - the number of missed appointments, and therefore the clinic efficiency (955);
    - the waiting time to see the provider (955);
    - the proportion of people LTFU (955);

In addition, combinations of approaches, aimed at improvements across the entire continuum of care, are now being considered. Those found effective are the following:

- HBT in combination with POC CD4 count testing and lay counsellor follow-up visit at months one, three and six (864) demonstrated efficacious at improving:
    - uptake of HIV testing;
    - linkage to care;
    - retention in pre-ART care;
    - viral suppression in people on ART;
- pre-ART care package characterized by three main features: task shifting to nurses and lay HIV counsellors, focus on a patient care pathway and active patient tracing for patients not presenting at the clinic for an appointment (758). This package improved:
    - linkage to care;
    - prompt initiation of ART for eligible patients;

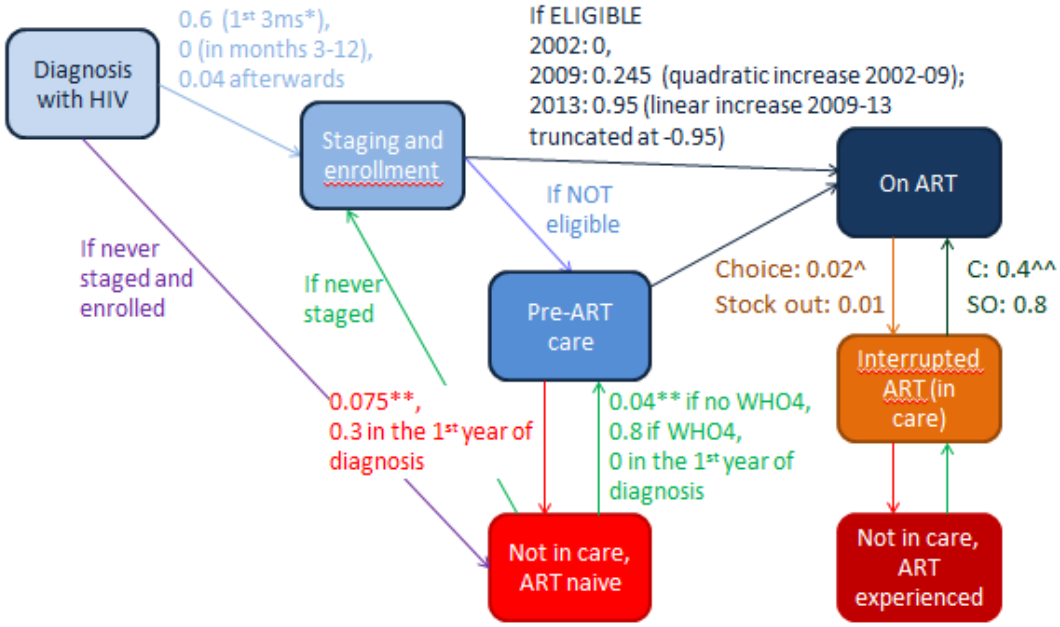
7.3. Cascade of HIV care in South Africa

Figure 7.2 summarizes how people diagnosed with HIV transition between the different steps in the cascade of care within the Synthesis model. Most of the parameters are not directly informed by studies, but outcomes of the cascade of care are (the proportion linked to care, retained in pre-ART care, etc.; see Figure 7.3-Figure 7.7 at page 301-305)). By one year since diagnosis the Synthesis model assumes at least 60% are linked to care, where they are staged to evaluate whether they are eligible for ART. If eligible, it is assumed there is a probability of initiating ART that increasing over calendar years up to 0.95 in 2013. It was necessary to assume such a high probability of ART initiation in order to fit to the number of people on ART reported in the literature (see section 2.1.8). If staged and not eligible they are monitored in pre-ART care, where they have a probability of 0.075 of being lost per 3 month and a probability 0.04 per 3 month of returning into care, but much higher (0.8 per 3 months) if they have a WHO stage 4 condition. If on ART, it is assumed they have a probability of 0.02 per 3 months of interrupting ART in the first two years and 0.01 per 3 months afterwards. Those who have interrupted ART experience a rate of 0.4 per 3 months of restarting ART and if they have interrupted ART they can be lost from care at the same rate they are lost from pre-ART care.

Figure 7.3-Figure 7.7 (page 301-page 305) show the values for various steps in the cascade of care assumed in the Synthesis model (median across simulations in black dotted line [brown

for women in Figure 7.3] and UR black line [brown for women in Figure 7.3]) and observed (data) on the ground (dots in different colours).

Figure 7.2. Transitions within the cascade of care in the Synthesis transmission model

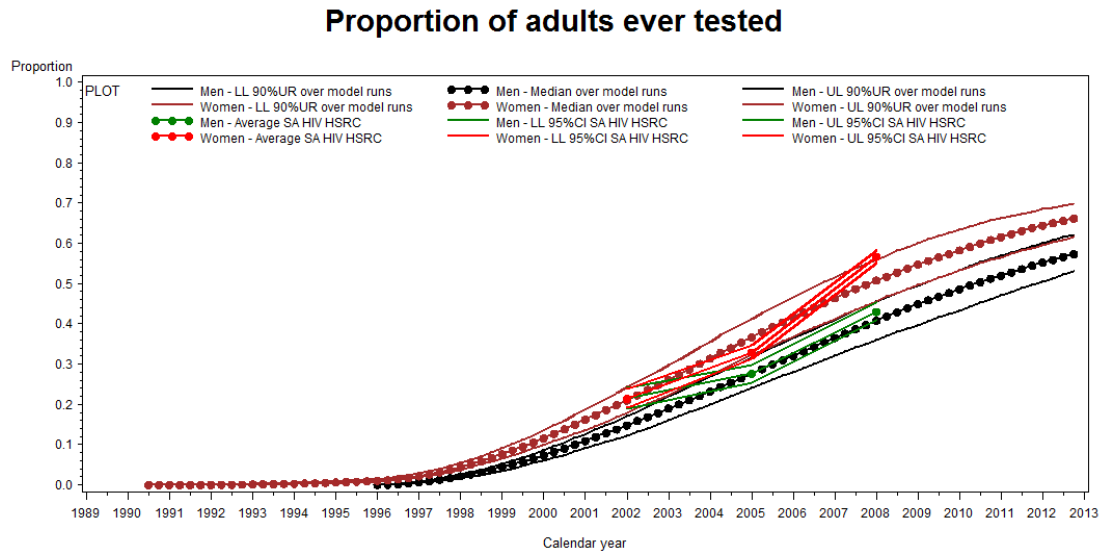


Notes to Figure 7.2: The rates are per 3 months; *This applies only to people without WHO4, WHO3 events or TB in the last 6 months, those have a rate of 1; ** for a person with high person-specific tendency to adhere (PSTA); rate of loss 2-fold for people with low PSTA; rate of return half and a 1/3 if the person has respectively medium or low PSTA; ^for a person with high PSTA and no current toxicities; up to 4 times higher for person with low PSTA and current toxicities; After 2 years is halved^^ 3 and 5 times higher for respectively people with WHO3 and 4;

7.3.1. HIV testing in South Africa

The first step in the cascade of care is being tested for HIV. The uptake of HIV testing in South Africa has been described in section 2.1.5 (Appendix IV contains information on PITC uptake in ANCs). In the Synthesis model the rates of HIV testing have been chosen by fitting to observed data on the gender-specific proportion of adults ever tested, collected in the HSRC surveys in 2002, 2005 and 2008 (see Figure 7.3).

Figure 7.3. Proportion of adults (15-65 years old) ever tested for HIV



UR: uncertainty range; LL: lower limit; UL: upper limit; SA HIV HSRC: South Africa National HIV HSRC surveys conducted in 2002, 2005 and 2008

An indirect indication of the level of HIV testing is the median CD4 at diagnosis and the proportion of people who present with a low CD4 at diagnosis. The median CD4 count at diagnosis in South Africa has been found to vary from 100 cells/µL (720) to 489 cells/µL (956) and the proportion diagnosed late (with CD4 count < 200 cells/µL) from 9.6% (956) to 54.3% (957). The studies conducted in South Africa which reported this information are summarized in Appendix XV (This is not meant to be a systematic review but it includes the largest studies reporting these information).

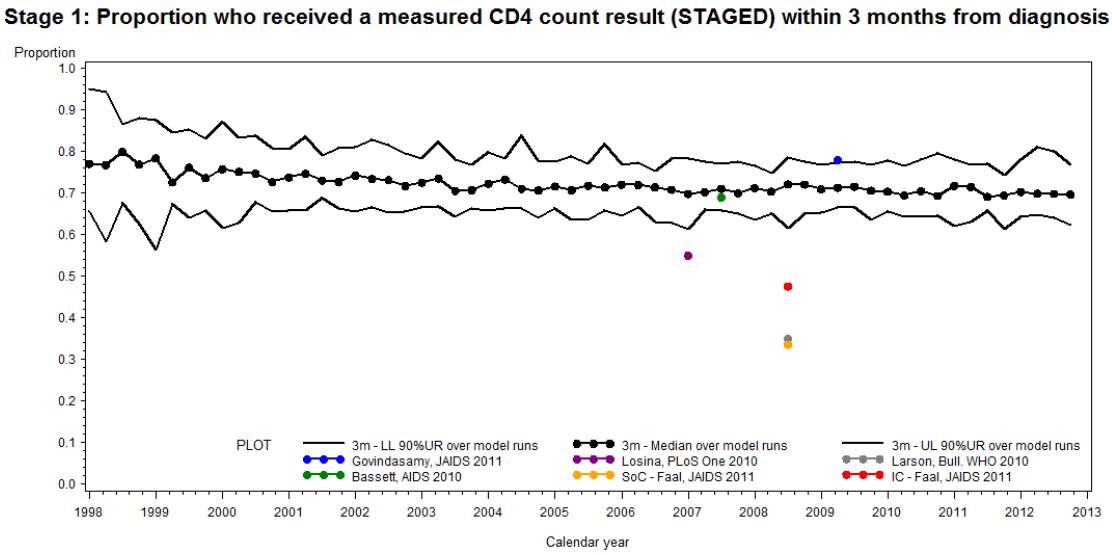
7.3.2. Linkage to care in South Africa

Once diagnosed with HIV, people can be lost at different stages before or after starting ART. In South Africa, the proportion of people who received an ART eligibility assessment (i.e. received the CD4 count result or were clinically evaluated to determine whether eligible to be initiated on ART) after being diagnosed at national level is unknown. HIV care programmes have found levels from 29% in a study conducted in 2001 (958) up to level of 78% (956), defined as a person returning for CD4 count result (although only 42% of these were reported to enrol into care) in a study conducted in 2008-09.

Figure 7.4 shows the proportion of people who received ART eligibility assessment within 3 months of diagnosis, as proposed by Fox et al. (824), from 1998, when a significant number of

people were tested for HIV and ART was available. The coloured dots represent estimates from different studies and they are positioned in terms of calendar year, approximately half way through when the study was conducted. The studies indicated in Figure 7.4 are summarised in Appendix XVI.

Figure 7.4. Stage 1: Proportion linked to care (who received ART assessment, "staged") within 3 months since diagnosis



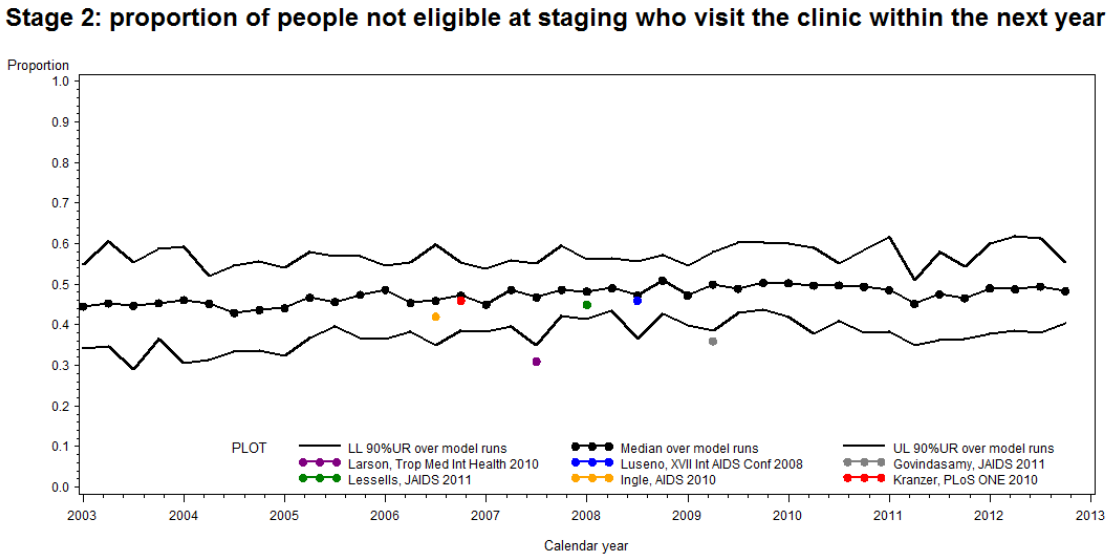
UR: uncertainty range; LL: lower limit; UL: upper limit;

7.3.3. Retention in pre-ART care in South Africa

Figure 7.5 shows the proportion of those who were not eligible at staging, who visit the clinic within the next year, in accordance with one of the definitions proposed by Fox et al. (824), except for the fact that I did not distinguish according to whether they were ART eligible at last assessment or not.

In South Africa, this has been found to vary from 31% (604) to 57% (959) (see Appendix XVII). This is well captured by the model; in fact most of the estimates are included within the 90% UR. The estimates which are not in this range are lower than the levels reconstructed by the model. Nevertheless the observed data could potentially underestimate retention due to the fact that people go to different clinics. There is evidence from studies which investigated what happens to people who are considered LTFU, that many of them have actually attended a different clinic in the last three months (960-962).

Figure 7.5. Stage 2: proportion of people not eligible at staging who visit the clinic within the next year



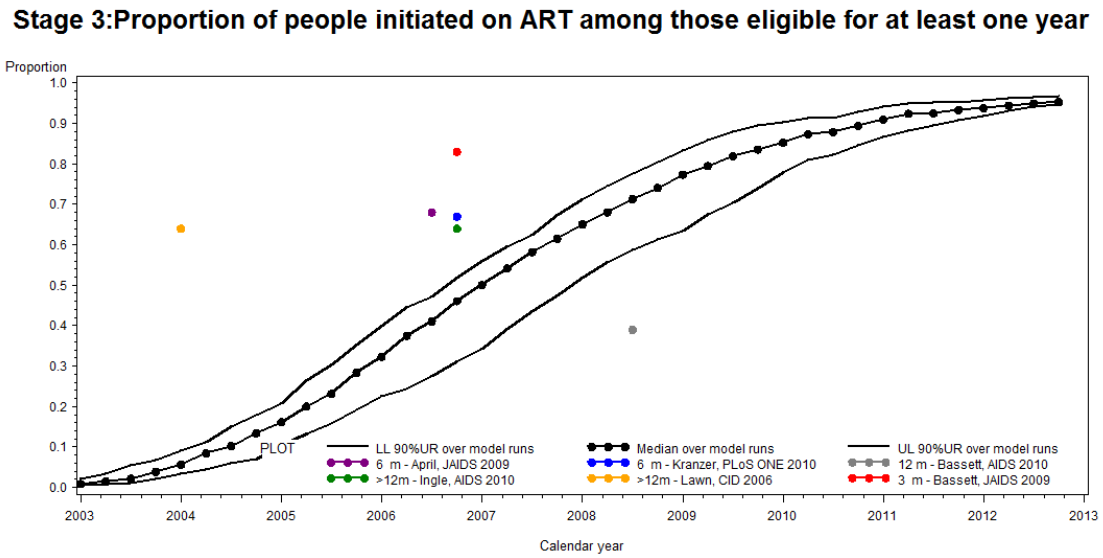
UR: uncertainty range; LL: lower limit; UL: upper limit;

7.3.4. Initiation of ART, once eligible, in South Africa

Figure 7.6 shows the proportion initiated on ART of those who have been eligible to start ART for 12 months, starting from 2003 when ART became available. This has been estimated in studies, conducted mainly between 2003 and 2009 to be between 39% (963) and 68% (958) (see Appendix XVIII). The proportion of patients eligible for one year who initiated ART as reconstructed by the model is lower than the estimates from the single studies, but this reflect the fact that those estimates come from areas/clinics where ART was available, while the model reflects the situation in South Africa overall. In order for the model to reflect the number of people who have initiated ART (451), it was necessary to assume that by 2013 95% of those eligible for ART (measured CD4 count <350 cells/µl and in care) were initiated on ART.

In addition, Appendix XIX summarizes the median CD4 count at ART initiation reported in South Africa. This ranges from 43 cells/µl in one of the first sites who provided ART (477) up to 279 cells/µl, reported by Kranzer et al. for the calendar year 2006 (484) (In most of the setting at that calendar year ART eligibility criteria was CD4<200 cells/µl, therefore this represent an exception).

Figure 7.6. Stage 3: Proportion initiated on ART among those identified as eligible for at least one year



UR: uncertainty range; LL: lower limit; UL: upper limit;

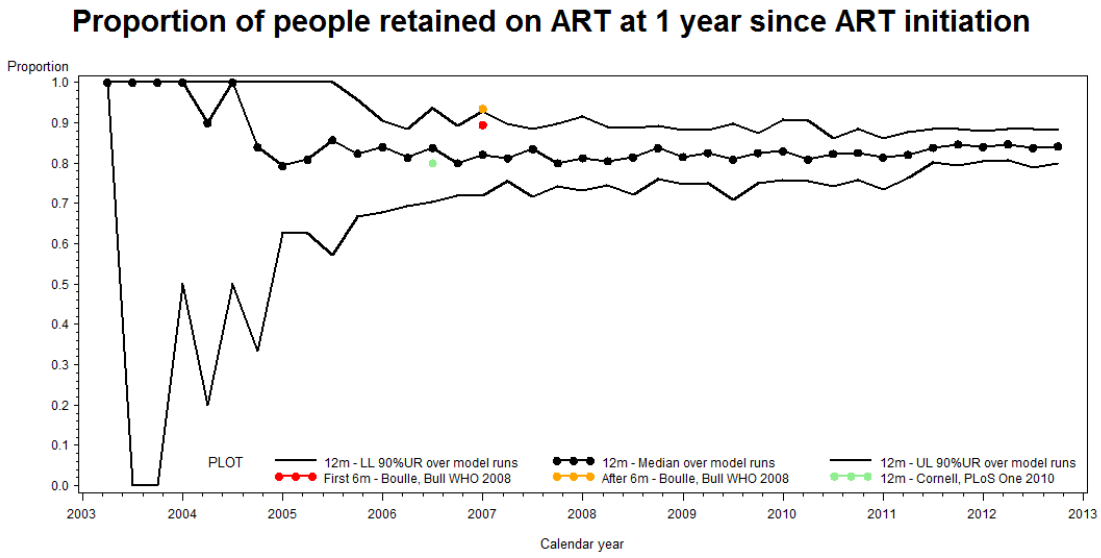
ART is assumed to have been introduced in 2003 and the eligibility criteria for ART initiation reflects national ART guidelines for South Africa: <200 cells/µL or WHO stage 4 before mid-2010 (225), CD4 counts ≤350 cells/µL irrespective of the WHO clinical stage after mid-2010 (230) (See section 2.1.7). In 2005, approximately 100,000 HIV-infected adults were receiving ART in South Africa and this number increased to 1.6 million by mid-2011 (451).

7.3.5. Retention on ART in South Africa

One of the first studies to evaluate the retention on ART in sub-Saharan Africa was conducted by Braitstein et al. (751). They found, across 13 African cohorts that on average 15% were LTFU at 12 months following ART initiation, with variability ranging from 0% to 44% across programs. Subsequently Rosen and colleagues conducted a systematic review of studies which evaluated retention and reported a weighted mean attrition rate, over 33 African cohorts, of 1.8%–3.3% per month (2). This was updated in 2010 (1).

Patients can be lost from care at any point in time, before and after having initiated ART. It is estimated that the proportion retained on ART at 1 year since initiation varies between 55% (964) and 93% (965) (See Appendix XX for a summary of the studies).

Figure 7.7. Proportion of people retained on ART at 1 year since ART initiation



7.3.6. Switch to second-line in South Africa

The number of people who are switched to second-line in South Africa is relatively low. Among those who experienced VF (see section 2.1.10 and Appendix VI) only between 16.9% at 12 months since VF (500) and 62% (74% switch to second-line of those who experience VF with at least 6 months of follow-up after failure) over a median follow-up of 15.6 months (499) were switched to second-line regimen. The time to switch people to second-line from identification of VF among those who did switch has been estimated to be between 5 (4.6 months; IQR: 2.1-8.7) (499); 5.3 months (IQR: 2.2-11.2) (292)) and 12 months (501). However, the fact that for example Johnston and colleagues found that at 12 months only 17% were switched to second-line clearly indicates that not all patients in need of switch are switched to second-line and the fact that the time taken to switch people can be much longer than 5 months.

Among all people initiating on ART it is estimated that 1% are switched to second-line at 1 year (499;966), around 4% at 3 years (495) and 10% at 5 years (499).

7.4. Methods

The 'HIV Synthesis' model calibrated to South Africa and described in detail in Chapter 3 was used to evaluate the value of potential improvements in each step of the cascade of care and of changing in the eligibility criteria to initiate ART, over 20 years in South Africa.

7.4.1. Analysis details

The impact of seven single different improvements characterized by an increase in the number of people receiving (appropriate) ART, implemented over 2014 and 2015, was considered (the letter code to be used as a label for the scenario is given in parentheses):

1. modifying the eligibility criteria to be initiated on ART to CD4<500 cells/µl (F),
2. modifying the eligibility criteria to be initiated on ART to all HIV-positive people (D),
3. increasing HIV testing so that 85% ever tested for HIV (T),
4. reducing the proportion of people lost at diagnosis so that 85% are linked to care by 1 year since diagnosis (L),
5. improving pre-ART retention, so that 72% are retained in pre-ART care at 1 year since staging, of those not eligible (P),
6. improving retention on ART, so that 92% are on ART at 1 year since initiating (A),
7. reducing the time to switching to second-line to 5 months after VF (S).

These improvements were compared to a reference scenario, referred to as option R, characterized by the maintenance of the current level of testing, linkage to care retention in pre-ART care and on ART and rate to switch to second-line, in people experiencing VF. In addition I considered twelve combinations of the scenarios indicated above, including a combination of all the scenarios considered.

Although I did not indicate specific ways of achieving these improvements, their magnitude is in line with the efficacy of scenarios found to be effective (see section 7.2). The only exceptions are the change in the CD4 threshold to initiate people on ART and the reduction in the delay to switch people to second-line, for which there is no evidence yet on how easy and feasible it is to implement them. I assumed the scenarios were fully implemented and people eligible for treatment and in care are assumed to have a probability of 0.95 of initiating ART within 3 months.

One key assumption relating to people who are LTFU is that if a WHO stage 4 condition is experienced then it is assumed there is an 80% chance of coming back into care. While the literature on loss to follow-up and its predictors is very rich, although variable, very few studies have investigated how many people resume therapy after interrupting ART and not attending the clinic (and therefore be considered LTFU) (967). They estimated that 42% of those who interrupted treatment for more than 30 days returned to care within 3 years and identified as predictors of resuming therapy being a woman, being older than 30 years old and being within the first year since stopping therapy. They did not mention whether patients resuming ART were more or less likely to have had a WHO stage 4 in the meantime, but reported that their CD4 at resumption (median=150) was similar to their CD4 at ART initiation (median=138), suggesting that being sick could potentially play a role. Other mathematical models considered even more dramatic assumptions such as assuming that people who are lost before ART initiation come back to care only when sick (690).

VF, in line with South African Guidelines (225;226;230), was defined until mid-2010 as a VL above 400 copies/mL followed by a consecutive VL above 5,000 copies/mL (VL measured 6 monthly), afterwards as a VL above 400 copies/mL followed by a consecutive VL above 1,000 copies/mL, measured within 3 months (VL measure at 6 and 12 months and then annually).

7.4.2. Economic analysis

The 20 scenarios (7 single improvements and 13 combinations of single improvements) are compared on the basis of their costs and health outcomes, which are both discounted to present value at 3% per annum (729), over 20 years. Health outcomes are summarised in the form of QALYs: a continuous measure capturing both mortality and morbidity effects including those related to onward HIV transmission. One year of healthy life corresponds to one QALY, while if a person is dead a value of zero QALYs is given. For this analysis some conditions are assumed to reduce the QALYs to less than 1: toxicities (0.95), WHO stage 3 (0.78), TB (0.60) and WHO stage 4 (0.46) (968).

Costs are estimated based upon resource use (e.g. number of tests, number of clinic visits) and associated unit costs are listed together with the sources in Table 7.2.

Table 7.2. Unit cost and disability adjusted weights and their sources

Item	Cost (US $)	Source where available
ART cost (1st line: TDF+3TC+NVP)	$97 per year	(969)
WHO stage 4*	$200	-
WHO stage 3*	$20	-
TB*	$50	-
CTX	$5 per year	-
Clinic Visit	$40	-
CD4 measurement	$15	(970)
VL measurement	$45	(970)
HTC (all costs fully loaded)	$10	(692)

*This cost is incurred every 3 months where the person has this condition.
3TC: lamivudine; ART: antiretroviral therapy; CTX: co-trimoxazole; HTC: HIV testing and counselling; NVP: nevirapine; TB: tuberculosis; TDF: tenofovir; VL: viral load; WHO: World Health Organization;

The benefits of improving implementation are investigated, firstly without any additional costs for implementation initiatives and then with the following indicative fixed implementation delivery costs:

- $0.50 per person without diagnosed HIV (so either HIV-negative or positive and not diagnosed; i.e. the target population for testing) if the scenario includes increased testing ,
- $50 per person linked to care, per PY retained in pre-ART care, per PY retained on ART and per person switch to second-line was applied if, respectively, the scenario included increased linkage to care, retention in pre-ART care, on ART and reducing the time to switch to second-line.

Results are presented across a range of CET (see section 4.3.2.2): from $1,000 up to $12,000, similar to current South African per capita GDP (In 2013 $11,500 (971)). Despite WHO recommended benchmarks being one per capita GDP for an intervention to be considered “very cost-effective” (729), I decided to present results based on much lower CETs, because these are more likely be used on the ground.

Costs and health outcomes are rescaled to provide figures relevant to the entire adult population (15-65 years old) of South Africa.

7.4.3. South Africa - current situation modelled

Table 7.3 illustrates the situation regarding the cascade of care at the end of 2013 as reconstructed by the model.

By 2013 I estimated 62% would have been ever previously tested for HIV, comparable to the estimate from the HSRC national survey conducted in 2012 reporting 65.5% ever tested for HIV (440). Regarding the linkage to care, there is lots of variability in the literature in the way this estimate is expressed, making the comparison more difficult. I assumed 71% were linked to care by one year (i.e. received the result of the CD4 measurement to evaluate whether eligible for treatment and clinical staging) and 42% were retained in pre-ART care at 1 year since diagnosis among people found not eligible for ART. In order to match with the total number of people newly initiated on ART I had to assume the probability of initiating treatment when accessing care and eligible for treatment increased over time and reached levels of 95% by 2013 (not shown in Table 7.3, see Figure 7.6 at page 304). 84% were assumed to be retained on ART at 1 year since having initiated ART and the time to switch to second-line once having virologically failed is 12 months (501).

Table 7.3. Characteristics of the epidemic at the end of 2013

	Model, median (UR) - End of 2013	**Observed data**
CD4 eligibility criteria to be initiated on ART (in cells/µl)	CD4<350	CD4 <350 (226)
% ever tested for HIV	62% (29% in the last year)	51% in 2008 (24.7% in the last year) (452), 65.5% ever tested in 2012 (440)
% linked to care by 1 year since diagnosis	71% (63%-76%)	35% by 3 months since diagnosis (957) to 78% (956)
% retained in pre-ART care at 1 year since diagnosis in those not eligible for ART at staging	42% (38%-47%)	31% (604) to 57% (959)
% retained on ART care at 1 year since ART initiation	84% (80%-88%)	55% (964) to 93% (965)
Median time to switch to second-line since VF	12 months (12 months-12 months)	5 months (499) to 12 months (501)

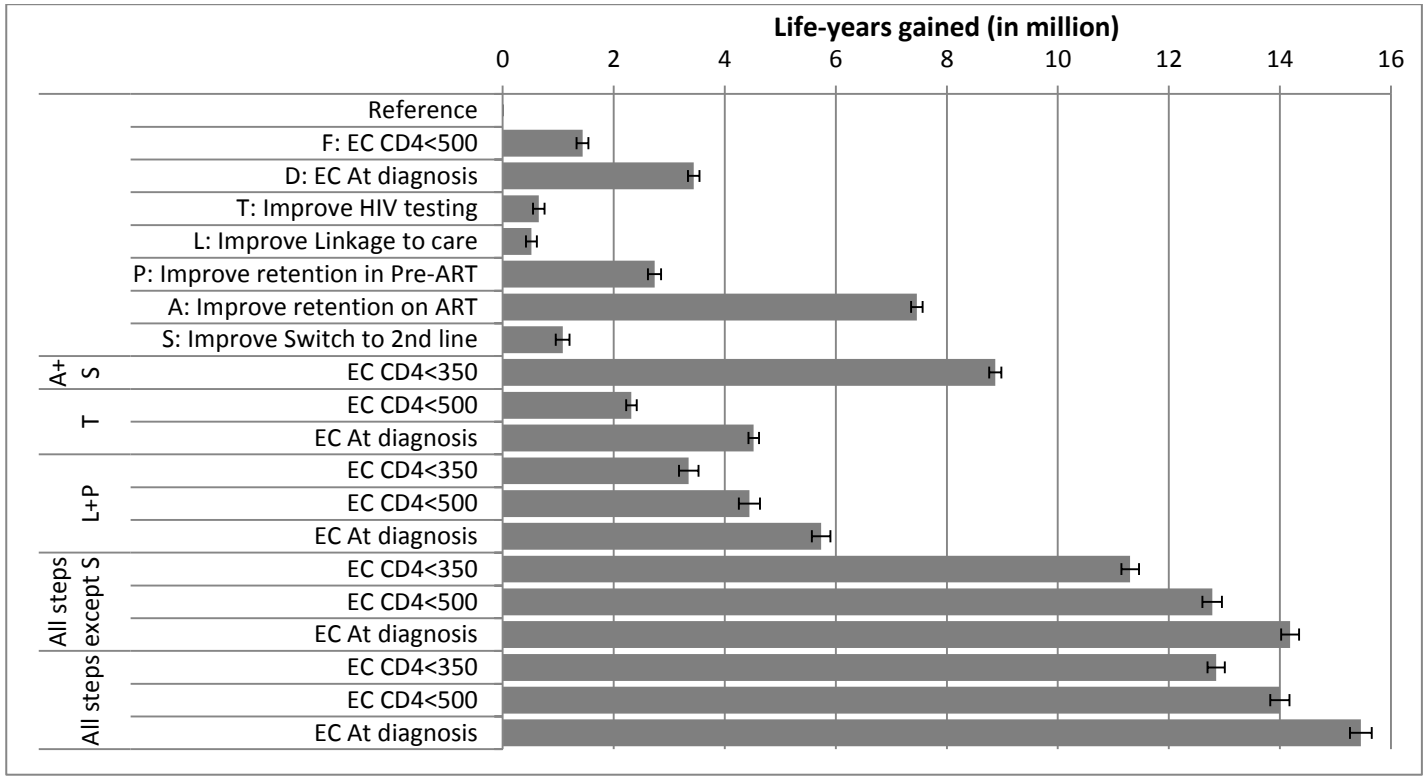
90% UR: 90% uncertainty range;

7.5. Results

In the reference scenario over the next 20 years the model estimates 797 million of life-years are accumulated in the entire adult population of South Africa (aged 15-65). Figure 7.8 shows the life-years gained over 20 years in South Africa by implementing each of the scenarios described in the section 7.4.1 compared to the reference scenario. Figure 7.9 (page 312) and Figure 7.10 (page 313) show respectively the number of deaths averted among HIV+ people and the number of HIV infections prevented.

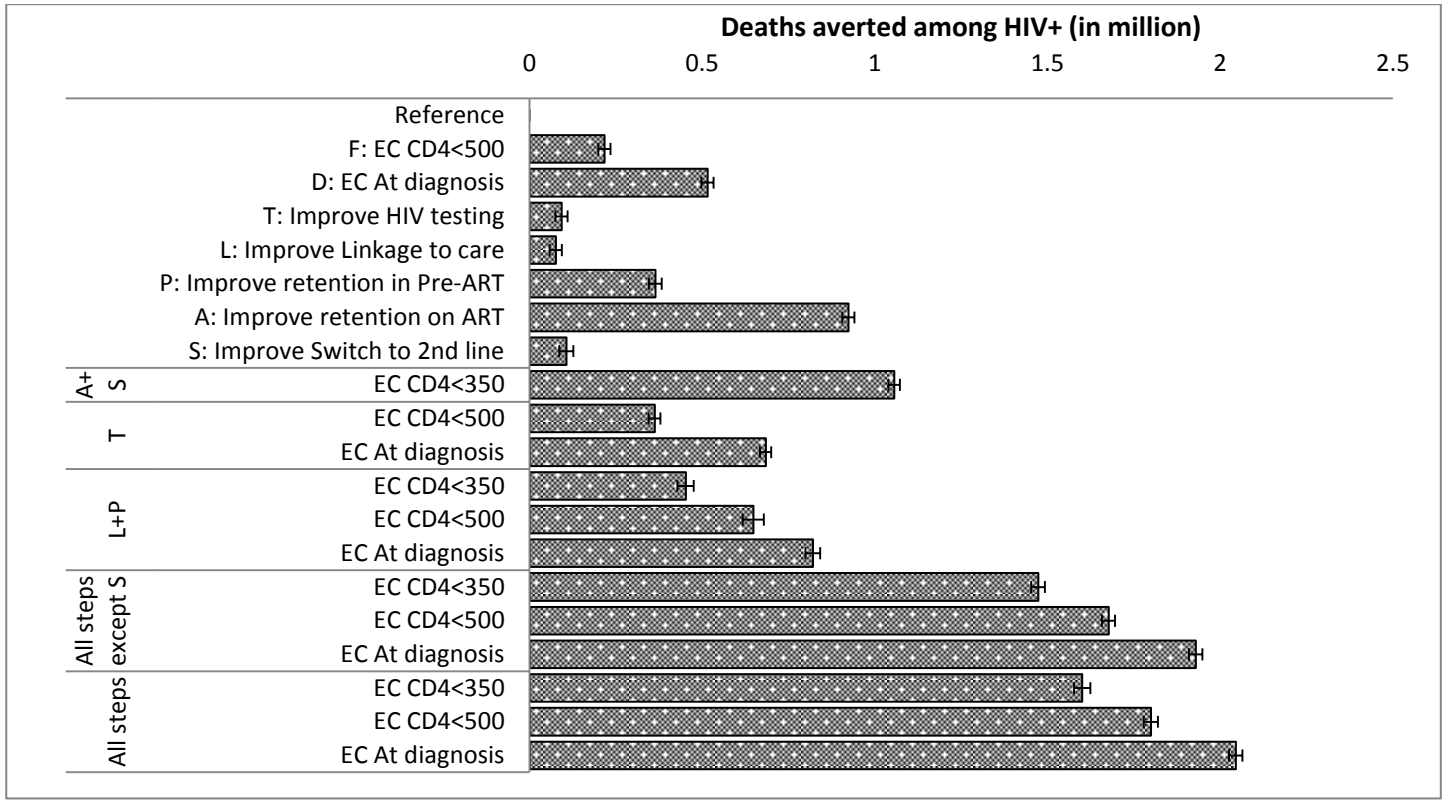
The single improvement which leads to the highest increment in total life-years over 20 years is the improvement in retention on ART (7.5 million life-years gained in the country over 20 years) (see Figure 7.8), which leads to the greatest reduction in deaths among HIV+ people (923,000 adult deaths averted in South Africa over 20 years) (see Figure 7.9 at page 312), despite only an assumed relatively modest increase in retention (8%). Modifying the eligibility criteria so that all people diagnosed with HIV are eligible to initiate ART saves the highest number of new HIV infections (760,000) (see Figure 7.10 at page 313), but results in an increment in life-years of 3.4 million, compared to 7.5 million obtained by improving retention on ART. By improving all steps of the cascade of care and modifying the eligibility criteria so that all people diagnosed with HIV are eligible for ART, 15 million life-years over 20 years can be gained (see Figure 7.8).

Figure 7.8. Impact of single and combination of improvements in the cascade of care, in terms of life-years gained over 20 years



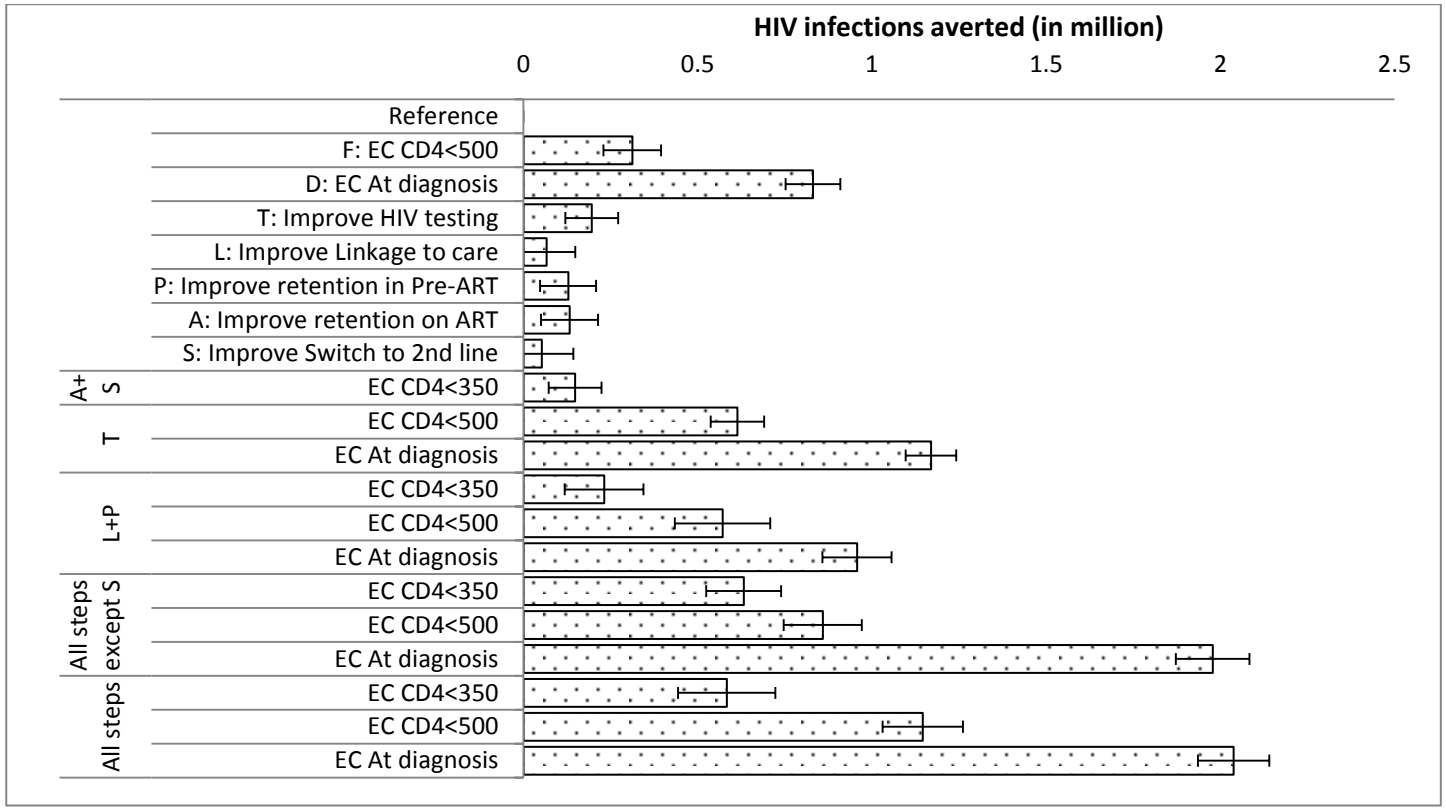
EC: eligibility criteria;

Figure 7.9. Impact of single and combination of improvements in the cascade of care, in terms of deaths averted among HIV+ over 20 years



EC: eligibility criteria;

Figure 7.10. Impact of single and combination of improvements in the cascade of care, in terms of HIV infections averted over 20 years



EC: eligibility criteria;

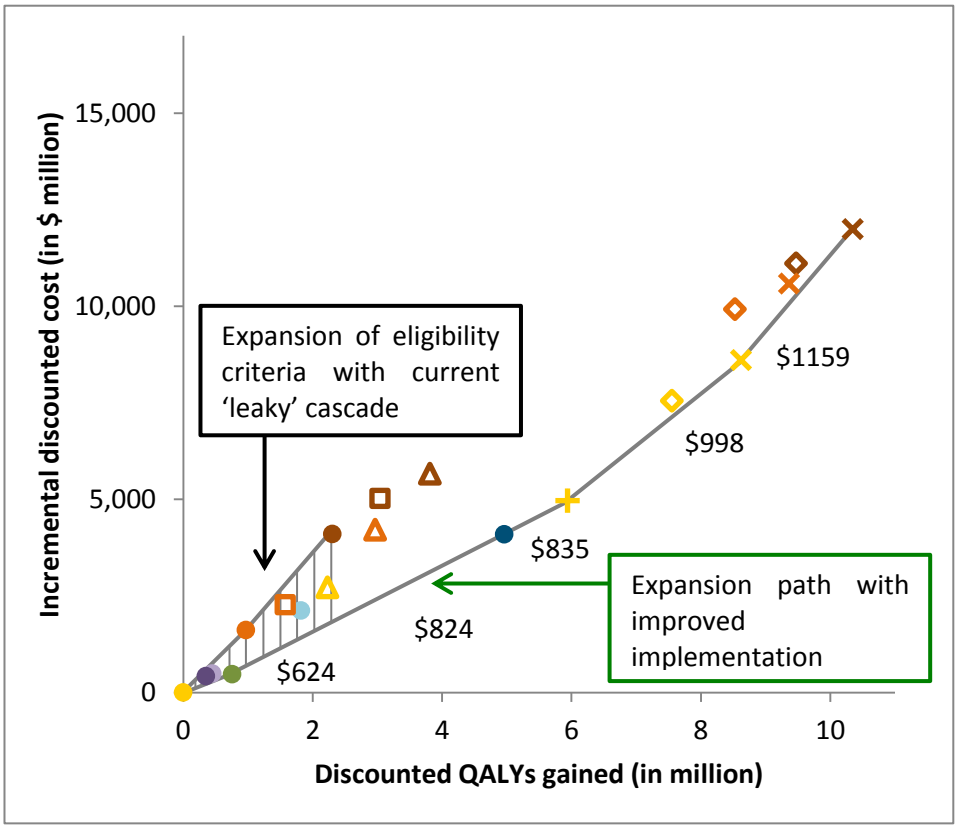
Figure 7.11a and Figure 7.11b illustrate the value of strengthened implementation in South Africa, without including the cost of the implementation initiatives (Figure 7.11a), representing therefore the maximum value achievable, and the value including some illustrative costs (Figure 7.11b). By not including the cost of implementation, I mean that the cost of attracting people to test for HIV, in care or to restart ART is not included, but the cost of higher number of tests being conducted or more people receiving ART, because of the intervention, would be included (All the costs included are listed in Table 7.2). In each of them two cost-effectiveness frontiers are presented: one across the scenarios aimed at improving how care is delivered (scenarios T, L, P, A, S and their combinations) and one across the scenario where the eligibility criteria to be initiated on ART are modified to either CD4<500 cells/µL, as recommended by WHO (280) or to all people diagnosed with HIV. The area between the two frontiers represents the area of potential gain from improving implementation.

Figure 7.11a shows that improving retention on ART (indicated by the letter A, dot in blue) while maintaining the eligibility criteria to CD4<350 cells/µL would deliver 2.7 million more discounted QALYs compared to modifying the eligibility criteria to all people diagnosed with HIV with the current leaky cascade. When including a cost of $50 per PY on ART, improving retention on ART is still preferred compared to increasing the eligibility criteria to CD4<500 cells/µL or at diagnosis.

The results illustrated in Figure 7.11 indicate that strengthening the cascade should be prioritized before increasing the eligibility criteria. In particular it suggests that the initiative that should be prioritized is reducing the delay in switching to second-line from 12 to 5 months, given that this initiative is characterized by the lowest ICER (US$ 734 when including a cost of $50 per person switched). This is followed by improving retention on ART at 1 year to 92% and reducing the delay in switch (ICER = US $1,314 per QALY gained), assuming a cost of $50 per person-year on ART is considered, as well as a cost of $50 for each person switched to second-line. The next steps, if the country can afford it, would be to improve all steps considered while still maintain the current eligibility criteria in South Africa and only once this is fully implemented to also move to change the eligibility criteria to initiate ART to all people diagnosed with HIV (ICER: US $1,563 per QALY gained).

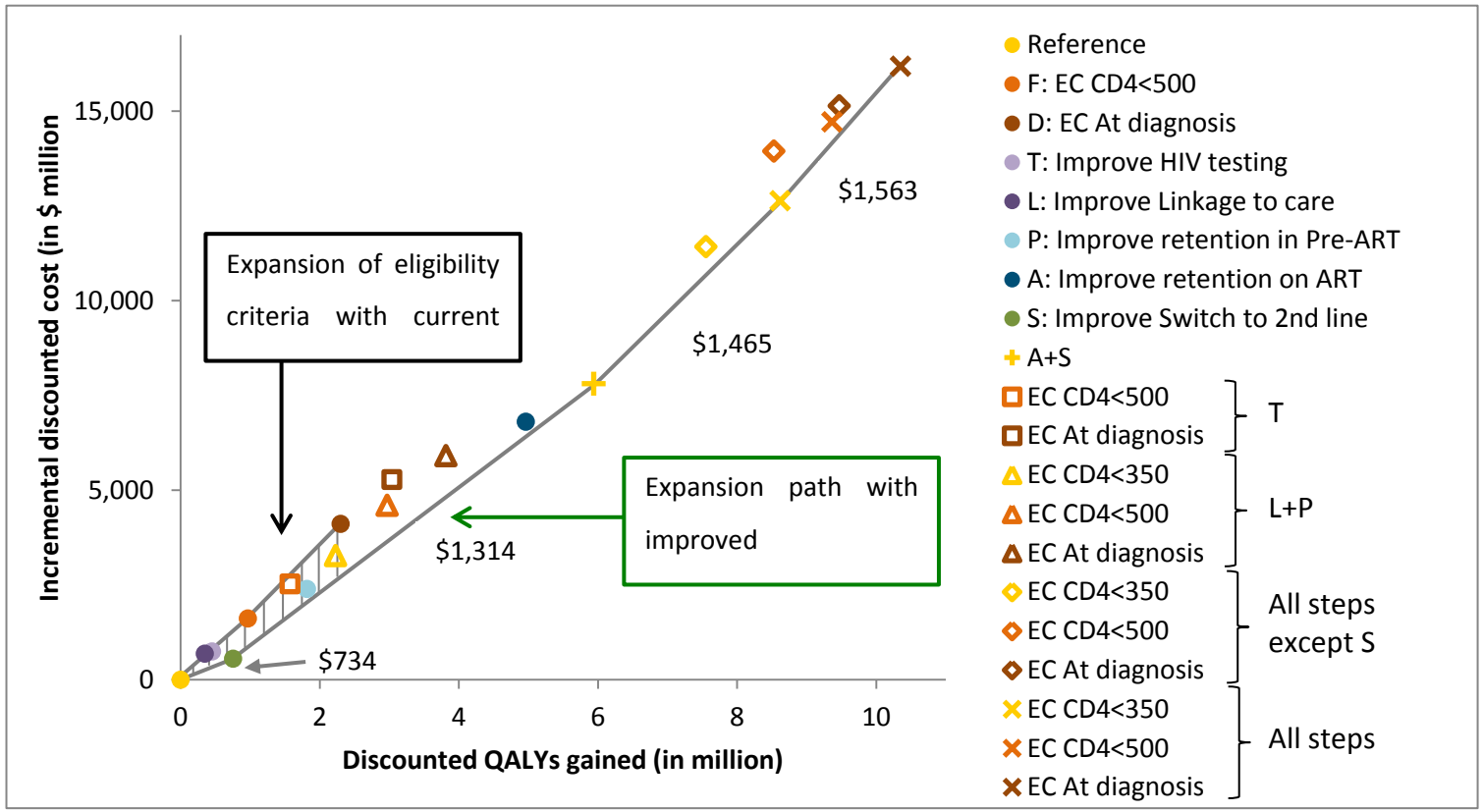
Figure 7.11. Value of strengthened implementation in South Africa

a. Maximum value (no costs of implementation initiatives included)



See legend in Figure 7.11b. QALY: quality-adjusted life-years;

b. Indicative value (illustrative costs of implementation initiatives included)



QALY: quality-adjusted life-years; EC: eligibility criteria;

The aim of this analysis is to provide a framework to design ART programme improvements (as conveyed by the scenarios I compared) that could strengthen the cascade of HIV care, without focusing on the specific improvements which would be characterized by a certain efficacy and cost. Therefore, I calculated the maximum cost these initiatives can have in order to still be cost-effective, at different CETs (see Table 7.4).

These results show that at a CET of US $1,000 improving HIV testing, linkage to care or retention in pre-ART care should not be implemented. This is likely to be due to possible inefficiency of pre-ART care at higher CD4 levels (i.e. patients attending the clinic visits at cost, but without any benefit, because not yet eligible for treatment), given that in the reference scenario it is assumed people who are lost from care experience an 80% chance of coming back into care when symptomatic.

Conversely, at a CET of US $1,000, an intervention that improves retention on ART from 84% to 92% could cost up to $16 per PY on ART, and an intervention to reduce the delay from 12 to 5 months could cost up to $171 per person-switched. This is simply another way of expressing the same results. As the CET increases, all five scenarios become worth considering and it becomes increasingly possible to spend more for each of them because they all provide additional health benefit.

Table 7.4. Maximum cost of the scenario to be cost-effective at the CET indicated (South Africa GDP in 2012 $11,600) (considering only the single scenarios)

Potential scenario	**$ cost is per....**	**Cost –effectiveness threshold (CET)**			
		$1,000	**$2,000**	**$5,000**	**$12,000**
T: Improve HIV testing	person not diagnosed with HIV	-	$0.80	$3	$10
L: Improve Linkage to care	person linked to care	-	$54	$261	$743
P: Improve retention in Pre-ART	PY in pre-ART care	-	$278	$1,279	$3,616
A: Improve retention on ART	PY on ART	$16	$108	$382	$1,023
S: Improve Switch to second-line	person switched to second-line	$171	$624	$1,985	$5,159

ART: antiretroviral therapy; PY: person-year;

7.6. Discussion

Policymakers need to determine how best to spend available resources on ART to generate health gains in the population. I found that, in the context of South Africa at least, the single improvement which leads to the highest increment in total life-years over 20 years is to

improve retention on ART, mainly due to the fact that it allows aversion of the greatest number of deaths over 20 years. When assessing whether to try to better implement the current recommended policies or to modify the eligibility criteria to initiate people earlier, I found that, even though modifying the eligibility criteria to initiate ART at diagnosis averts the highest number of new HIV infections, it results in a lower health gain (in terms of QALYs) and at a higher cost.

The initiative characterized by the lowest ICER, and which should be prioritized, is the reduction in the delay in switch in those failing treatment virologically from 12 to 5 months. An improvement of this magnitude is feasible and a median delay of 5 months has been reported in a programme in South Africa (499). For this initiative an additional cost of $50 was applied for each switch that occurred (on top of the cost of VL monitoring of $45 for the VL measurement conducted at 6 and 12 months and then annually, the cost of the visit, $40 every 3 months, and of the other costs listed in Table 7.2), it is possible that to achieve this improvement the cost is higher (although note that this $50 does not include the costs of the VL tests needed to diagnose VF or the cost of the second-line drugs, only cost of instigating the switch). The maximum cost per person switched that this scenario can be varies from $171 if the CET is $1,000 up to $5,159 if the CET is $12,000. Given the illustrative cost assumed, if the actual CET of South Africa is $1,314 or more, the initiatives of improving retention on ART combined with reducing the delay to switch to second-line should be implemented. This allows accrual of almost 5 million extra discounted QALYs compared to the reference scenario, and 4.5 million more compared to the scenario where only the delay in switch is reduced, but it is associated with a higher cost per QALY gained ($1,314). Improving retention on ART so that at 1 year up to 92% are retained on ART (although this would have an impact on longer term retention as well) seems feasible: at 6 months retention of 93% has been reported (965) and levels of 90% have been reported at 12 months in the earlier year of ART scale up (if I ignore whether they received ART in the same clinic or transferred to another clinic) (478;601).

Only once this initiative is implemented, it is appropriate to move to more expensive initiatives and if the CET is $1,563 or more and the improvements can be delivered at the cost indicated it is cost-effective to pay to improve HIV testing, linkage to care, retention in pre-ART care, retention on ART, switch to second-line and offering ART to all people diagnosed with HIV.

When looking at the maximum these initiatives can cost to be cost-effective, I found that at the CET of $1,000 it is not appropriate to invest in HIV testing or in increasing linkage to care or retention in pre-ART care. This is likely to be due to the fact that the model assumes, as

mentioned in 7.4.1, that people experiencing a WHO stage 4 condition have an 80% chance of coming back into care in care .

7.6.1. Findings from other mathematical models

A few mathematical models have evaluated the impact of improvement at different single steps of the cascade of care, such as HIV testing in several countries in sub-Saharan Africa (860;972-976), prevention of loss to follow-up in Cote d'Ivoire (977) and return into care of patients initiated on ART through tracing in Malawi (978) or more generally the impact of improving the return to HIV care of people lost from care, after having initiated ART in South Africa (698).

Here I focus only on models which evaluated the impact of improvement in at least one step in the cascade of care in South Africa. In 2011, Walensky et al. (979) assessed the cost-effectiveness of an HIV screening conducted once, every 5 years or every year. They reported that a one-off HIV screening was dominated by the other strategies and that five-year screening was the most cost-effective with an ICER per QALY gained of $1,570. This analysis is not directly comparable to my results but in line with the Synthesis model, which in the reference scenario assumes around 30% of the population are tested every year, finds that a more frequent HIV testing, such as every year, is not cost-effective.

Andrews et al. (690) aimed to evaluate the impact of including in a simple mathematical model (previously used to assess the impact of test and treat, i.e. annual HIV testing and ART initiation at diagnosis (686)) two additional elements: the fact that only a modest proportion accept to be tested for HIV and, if positive, to be initiated on ART and the fact that those who either refuse to test or are lost before ART initiation are less likely to come back into care.

Related to improvements in the cascade of care, they evaluated the impact of modifying two assumptions. They compared the impact of modifying the probability of initiating ART in patients eligible at HIV diagnosis from 92% (assumed by Granich et al. (686)) to 53% as found in a study evaluating the linkage to care from mobile testing unit (956). In addition they assessed the impact of modifying the conditions that allow people who decline HIV testing or who are LTFU before starting ART to come back into care: either people who are lost before ART initiation or who refuse testing have the same probability of coming back to care (so that with a linkage to care of 92%, 99.9% would be in care within 3 years), as assumed by Granich et al. (686), or only at the final stage of HIV infection with symptomatic disease. They found

that HIV incidence would drop from 2.5% to 0.07% by 2030 and 0.03% by 2040 with 92% linkage and to respectively 0.11% and 0.05% if the linkage to care is more realistically 53%. Once assuming that people who are lost from care come back to care only when symptomatic (a more strict assumption than mine) the HIV incidence was reduced to 0.26% by 2030 and 0.15 by 2040 if the linkage is 92% and respectively 0.49% and 0.33% if the linkage is 53%.

That model is a much simpler model and does not distinguish between the linkage to care step (i.e. receiving the CD4 result to assess for ART eligibility) and, for those found eligible, the probability of initiating ART. I did not investigate the combination of improving linkage to care (from 71% to 85%) and modifying the eligibility criteria to all people diagnosed with HIV, but I compared simultaneously modifying improvement in linkage to care (from 71% to 85%) and retention in pre-ART care (from 42% to 72%), referred to as "L+P" and initiating people on ART at diagnosis (although with my assumption regarding these improvements not being as optimistic as Granich et al. (686)). I found that 957,000 HIV infections can be averted over 20 years, compared to if linkage and retention in pre-ART care are increased, and 831,000 infections averted if people are initiated at diagnosis without improving the linkage and the retention in pre-ART care.

Another model evaluated the impact on mortality of reducing the time to initiate ART in patients found eligible for ART (980). This was certainly an issue in the past and studies conducted in South Africa reported this issue in the early years of ART roll-out: up to 2005 (293;981), nevertheless this is likely to be much less of an issue nowadays given the eligibility criteria to be initiated on ART has been raised from below 200 cells/µL to 350 cells/µL, by the fact that to my knowledge there are no longer waiting list to be treated and the median CD4 at diagnosis and ART initiation increased over time. For this reason, and in order to fit with the number of people newly initiated on ART, I had to assume the probability of initiating ART within 3 months in patients in care increased over time up to levels of 0.95 by 2013.

A mathematical model recently published (698) (see section 4.2.6), evaluated the impact of increasing the proportion who would come back to care in patients lost from care after ART initiation and compared this to modifying instead the eligibility criteria so that all people diagnosed with HIV are eligible for ART. Similarly to me, they found that improving retention on ART should be prioritized compared to modifying the eligibility criteria.

A possible limitation of my analysis is the fact that instead of evaluating the long-term effect of precise scenarios such as, for example, tracing of patients LTFU or offer of transport voucher or food rations to retain people on ART, I assessed the cost-effectiveness of different

improvements at single steps of the cascade of care, assuming each of them roughly halves the proportion of people lost at each step. The reason for this choice is that I wanted to provide some indication regarding which steps attention should be focused on in the cascade of care, in terms of recommending areas where interventions could be useful.

7.7. Conclusions

In conclusion, this modelling exercise helps us to understand which scenarios will have the most impact on maximising life-years, and shows that improving retention on ART would have the greatest impact. This analysis indicates that policymakers should seek to strengthen the cascade of HIV testing and treatment (in particular by improving retention on ART and switch to second-line treatment as appropriate) before raising the CD4 count eligibility criteria. Further research on what initiatives could improve implementation of ART, and how much these are likely to cost, would be very valuable. In the longer term, greatest health gains can be achieved by both improving implementation and increasing eligibility for ART, but this requires substantial commitment of resources.

8. Assessment of the potential impact and cost-effectiveness of HIV self-testing in resource limited settings

8.1. Introduction

8.1.1. Background

In RLS, many people living with HIV in need of ART still do not have access to treatment, or HIV care more broadly, due to being unaware of their HIV status. HIV testing in RLS has been increasing dramatically in the last five years, from a level of 20% of people living with HIV knowing their HIV status (10% overall) in 2005 and 2007 in countries with high HIV burden (982) to 50% in 2012 (983), and South Africa and Zimbabwe are not exceptions (see sections 2.1.5 and 2.2.5). Nevertheless, at least 50% of people living with HIV are unaware of their status (984) and cannot therefore access HIV care and treatment and thus take measures to reduce their risk of infecting other people. In Zimbabwe, according to the last Demographic and Health survey (DHS) conducted in 2011, only 20% of men and 34% women had tested for HIV in the last year (519). The reasons for not actively seeking an HIV test through current HIV testing strategies provided by healthcare workers (standard voluntary counselling and testing [VCT], PITC, etc.) are numerous, including fear of stigma and discrimination, perceived lack of confidentiality, and the inconvenience and opportunity costs of testing.

Given the need for expanding HIV testing uptake and frequency, it is important to consider new delivery strategies. One such option is HIV self-testing (ST), which has been described in section 7.2.1. Many of the barriers people encounter when having an HIV test may be addressed through the use of ST. For these reasons, stakeholders, including donors and government are considering whether investments should be made in developing and promoting the marketing and delivery of ST in RLS, in order to increase uptake of HIV testing.

In both RLS and high-income countries regulated ST kits are generally not available, with the US and Kenya being among the few exceptions. In July 2012, the FDA approved the first kit which can be used for ST, the OraQuick In-Home HIV Test (985), which is now sold over the

counter in the US for US $40. The Kenyan government has promoted their use by, for example, making available 10,000 Calypte Aware HIV 1/2 Oral Mucosal Transudate rapid tests to the public in 2007, through the National AIDS and STD Control Programme. In addition, in sub-Saharan Africa preliminary research on the use of ST has been conducted in Kenya (873), Malawi (755;871;872), Zambia (986) and South Africa (874;987) and studies are currently ongoing.

8.1.2. Potential advantages and disadvantages of HIV self-testing

The main advantages of ST over the standard HTC, provided by a healthcare worker, are its convenience, confidentiality and empowerment for users. These characteristics could potentially allow people who have never tested before to test but also increasing the frequency of repeat testing in those who have previously tested. Empirical research on acceptability and uptake of ST in the general population (872) and among health workers (873;874) is very high, although the evidence is quite limited, while no data are available for other subgroups at high risk of HIV infection in sub-Saharan Africa (See section 8.2.2.1). In addition, ST could reduce the overall cost of testing due to limited or no involvement of healthcare workers at the time of screening and the lack of requirement for infrastructure (988) (see section 8.2.2.7) and reduce transmissions, by making more people aware of their HIV status. In fact, awareness of HIV status can have important consequences for risk behaviour. There is evidence from a systematic review on developing countries that people who receive VCT and test HIV-positive report lower condom-less sexual behaviour than people who did not receive VCT (48) and among those testing HIV-negative using VCT there is no evidence of higher condom-less sexual behaviour compared to those who did not receive VCT (48). The evidence is more mixed regarding the impact on sexual behaviour of PITC (47) and to my knowledge there are no data available from RLS on the potential change in risk behaviour following ST (see section 8.2.2.6).

There are some concerns related to ST: firstly, the risk that people who self-test positive do not look for a confirmatory HTC and subsequently may not be linked to care (i.e. not receive ART eligibility assessment); secondly, the psychological impact of receiving an HIV-positive result without the immediate support of a person trained in post-test counselling, with potentially serious consequences. A cluster RCT conducted in Malawi (755) evaluated the impact of a proactive intervention to enable confirmatory HTC and linkage to care, home ART initiation,

highlighting the need for a proactive intervention following ST to ensure people engage into care upon a positive ST (See sections 8.2.2.3 and 8.2.2.4). In the same study, they collected information on coercive ST (872) (See section 8.2.2.5).

Finally, accuracy of ST is a concern (989). The FDA approved OraQuick in-Home HIV test kit has shown very high sensitivity and specificity (over 99%) when conducted and interpreted by trained providers (985;990), and when conducted by lay people but read by a provider (991). However, when conducted by and interpreted by lay people, the specificity is still very high (over 99%) (871;874;985;992), while data on sensitivity are more variable (871;874;985;992) (See section 8.2.2.2).

Formative research is currently ongoing regarding the accuracy of oral ST in the field, the acceptability across different subgroups of the population, how to deliver ST and how to ensure that people receive confirmatory test, if self-tested positive, and, once diagnosed with HIV, be linked to care and the potential harms of ST (993).

8.1.3. Rationale and aim

Mathematical models can provide insight into the potential impact of introducing ST at a population level over a longer term, and can help determine whether introducing free or subsidized ST kits would be cost-effective.

Several mathematical models have evaluated the impact and/or cost-effectiveness of expanding HIV testing in high income countries (994-1000) and in RLS (972-974;979). To my knowledge, the impact of introducing ST in RLS has not yet been evaluated.

8.2. Methods

To address this aim, the HIV Synthesis model, described in detail in Chapter 3 is used. This section presents the main assumptions related to the introduction of ST, together with the evidence to support them and the details on how the analysis has been conducted.

8.2.1. Setting

For this study, I calibrated the HIV Synthesis Transmission Model to reflect the HIV epidemic in Zimbabwe. This decision was driven by the need to model realistic gender and age specific levels of HIV testing and prevalence to accurately predict the impact of introducing ST.

The choice of Zimbabwe as the setting was guided by several factors: first, the Zimbabwe government is interested in exploring ST; second, because I am involved in other projects in Zimbabwe and I have links with the Zimbabwe Ministry of Health and health economists working there and third, because I wanted to choose a country with a relatively high HIV prevalence to maximise the efficiency of the simulation for another project I am working on aimed at evaluating the potential impact and cost-effectiveness of using resistance testing in RLS to monitor people on ART.

The HIV epidemic in Zimbabwe has been extensively described in section 2.2. Table 8.1 summarizes the main demographic information for Zimbabwe and its response to the HIV epidemic. The population the HIV Synthesis model focuses on is the adult population aged 15 to 65 years, which was estimated to be 7.5 million in mid-2013 (513). The HIV prevalence in people aged 15 to 49 years was at levels of 15% in 2011 (519), but as shown in Figure 8.1, it peaked in the mid-90s and has declined since then.

As is the case in much of sub-Saharan Africa, HIV testing has been increasing dramatically in Zimbabwe in the last few years (see section 2.2.5). In the DHS conducted in 2006 and 2011, the estimated percentage who reported ever testing for HIV was in 2006, 26% for women and 19% for men and in 2011, 60% for women and 39% for men (519). The estimated percentage tested in the last 12 months, which better informs the current levels of testing compared to the percentage ever tested, increased from 7% in 2006 to around one quarter of the population in 2011, with higher levels in women (34%) than in men (20%) and significantly lower levels in the youngest age group (15-19 years old: 18% in women, 7% in men) and in the oldest group considered (40-49 years old: 26% in women, 23% in men (519). In ANCs, in 2011, 59% of pregnant women were tested, received the result of the test and received HIV counselling (45% in women aged between 15 and 19 years) (519).

ART is now widely available in Zimbabwe with over 500,000 people receiving ART by the 1st quarter of 2013, representing 80% of those in need [based on the Zimbabwe recommendations at the beginning of 2013 (CD4<350 cells/µl) (228)]. Retention on ART is relatively high: 86% at 12 months from start of ART.

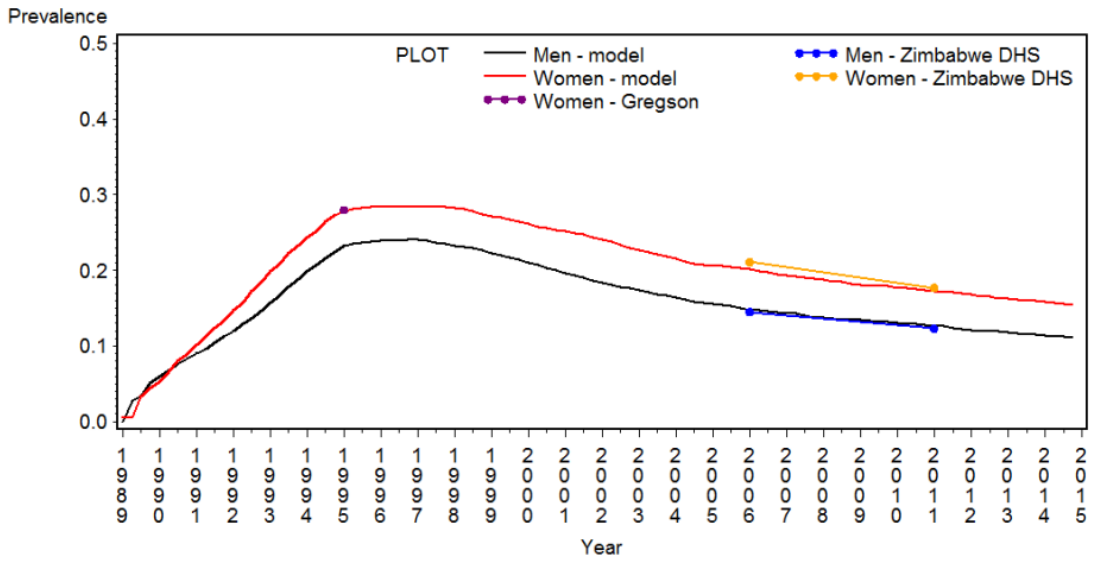
Table 8.1. Information on the HIV epidemic in Zimbabwe

	Value	Year	Source
Population 0+ years old (in million)	13.2	2013.5	CIA (513)
Population 15-65 years old, n (in million)	7.5	2013.5	CIA (513)
HIV prevalence, 15-49	15.2%	2011	DHS (519)
% ever tested	39% M, 60% F	2011	DHS (519)
% of pregnant women attending ANCs tested for HIV	59%*	2011	DHS (519)
% tested in the last year	20% M, 34% F	2011	DHS (519)
Number of adults on ART	544,158	1st quarter 2013	Global fund report(545)
ART coverage	80%	2011	Zimbabwe Global AIDS response progress report (530)2012
Of those who started ART 12 months ago, % known to be still on	86%	2011	

*It refers to the last two years; ANC: Antenatal clinic; ART: antiretroviral therapy CIA: Central Intelligence Agency; DHS: Demographic and Health Survey; M: males; F: females;

Figure 8.1 shows the HIV prevalence, gender-specific, in red for women and in black for men, reconstructed by the Synthesis model together with prevalence data estimated from nationally representative surveys (519) and other sources (514).

Figure 8.1. Gender-specific HIV prevalence – reconstruction by the HIV Synthesis model



DHS: Demographic and Health Survey;

8.2.2. Main assumptions relevant for the implementation of the introduction of self-testing

8.2.2.1. Assumptions on scale up of HIV testing

In the Synthesis model, HIV testing was assumed introduced in 1996 (see section 1.14.5). At that time I assumed 20% of the population were "resistant to HTC" (in the Synthesis model this means they have no possibility to getting tested for HIV unless symptomatic) and that this decreased linearly to 5% by the end of 2010. Limited data are available to inform this parameter (proxy variables are the proportion who reported never being tested for HIV and, more precisely, the proportion who refuse HTC); nevertheless I considered it important to take this into account, given the evidence that not everyone accepts HIV testing for various reasons (1001). The level of acceptability of PITC in RLS is extremely variable from levels of 99%, observed in inpatients in Uganda (852) to 31% among outpatients in South Africa (1001). Among pregnant women the level of acceptability of PITC seems to be higher, varying from 76 to 99.9% (851), while the estimated acceptability of HBT has been estimated in a meta-analysis to be 83% (754). This huge variability seems to be related mainly to the quality of the intervention delivered and to calendar time. Acceptability seems to have increased over time due to the reduction in stigma and higher availability of ART.

For the remainder of the population ("non-resistant to HTC"), increasing gender and age-specific rates of HIV testing (for the 1st time and of repeat testing) since 1996 were assumed, to reflect the level of testing observed in the DHS (519). Pregnant women experience an additional probability of being tested in the ANC, which increased over time (519).

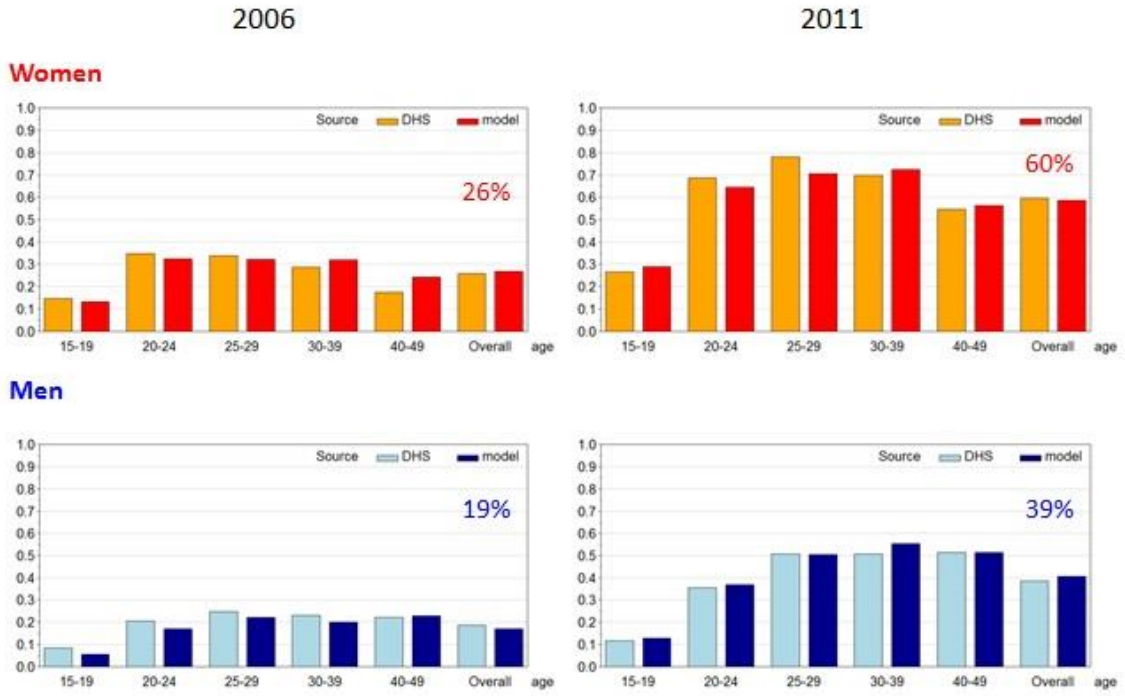
For people who never had condom-less sex (recall that the model does not distinguish between not having sexual intercourse and having a sexual intercourse using condom) a 3-fold reduction in the rate of testing was assumed. This has been observed in the Zimbabwe DHS where people who reported never having had sex are less likely to test for HIV: the proportion ever tested for HIV in this subgroup was 15% in men and 17% in women and the proportion tested in the last year 8% and 9% compared to 20% and 34% in the population 15-49 years old overall (519).

People with acute symptoms (WHO stage 4, 3 or active TB) are assumed to have a higher chance of testing for HIV in that 3 month period and a higher chance of being linked to care once diagnosed. In 2015 the probability of testing as a result of the symptoms was 0.8, 0.48 and 0.12 for people with WHO stage 4 event, TB and WHO stage 3 event respectively.

Figure 8.2 and Figure 8.3 show, respectively, the proportion ever tested for HIV and the proportion tested for HIV in the last year in 2006 and 2011, as assumed by the model and as observed in the DHS surveys in the different age groups (15-19,20-24, 25-29,30-39,40-49 and overall) among men and women (519).

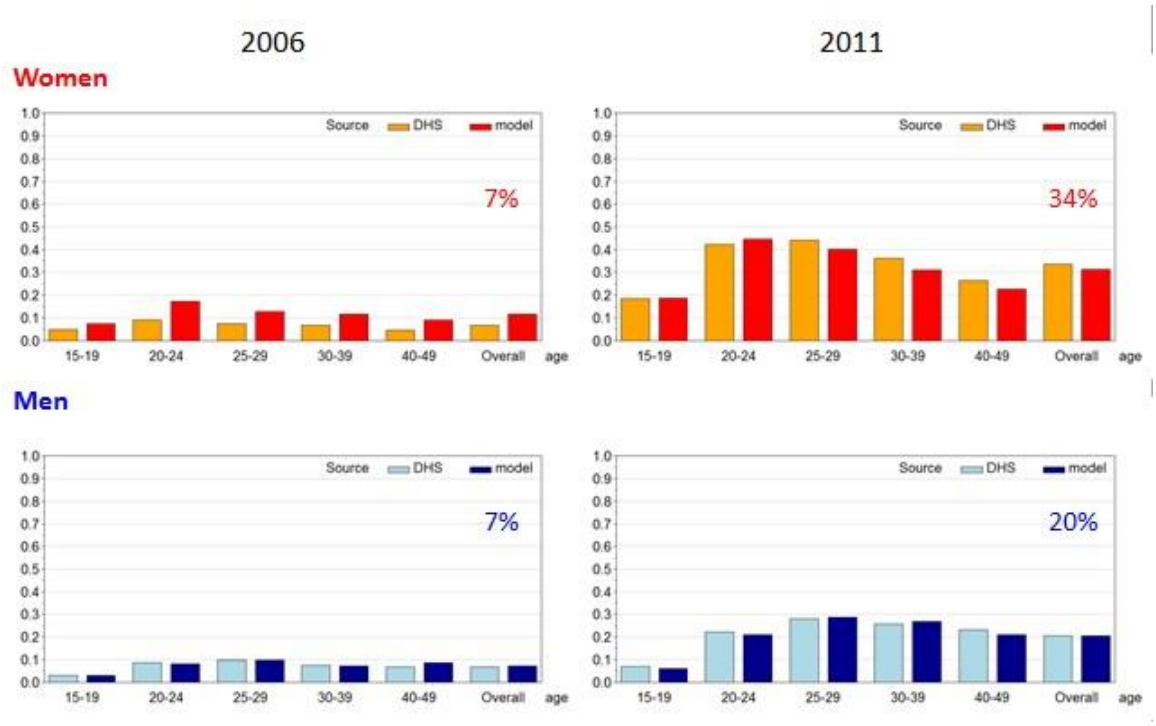
The model does not distinguish how the standard HTC is delivered, whether it is PITC, VCT or home-based HTC, but only on whether it is conducted by a healthcare worker (referred to as HTC) or by the individual him or herself (i.e. ST).

Figure 8.2. Gender and age-specific proportion ever tested for HIV reconstructed by the model and observed in DHS surveys



The percentages indicated in the graphs are the overall estimates from the DHS. DHS: Demographic and Health Survey;

Figure 8.3. Gender and age-specific proportion tested in the last year, reconstructed by the model and observed in the DHS surveys



The percentages indicated in the graphs are the overall estimates from the DHS. DHS: Demographic and Health Survey;

8.2.2.2. Assumptions on HIV self-testing and HIV testing and counselling accuracy

Aspects to consider for any HIV test, whether conducted by a healthcare worker or as a ST, are the accuracy (sensitivity and specificity) and the time between HIV infection and when the test can reliably detect infection (the "window period"). As mentioned, poor accuracy of ST has long been a concern (989), but more recent studies have consistently found moderate accuracy, with variability across different ST kits. The FDA approved OraQuick kit, when used and interpreted by lay people, has shown specificity over 99% (871;874;985;992), while sensitivity has been found to vary from 66.7 (95% CI: 30.9-91.0), reported in a small pilot study of unsupervised ST conducted among healthcare workers in South Africa (874), up to over 99% (871;992). In addition, minor procedural errors and request for extra help have been reported in a small proportion (10%) of populations evaluated (871). Accuracy has been evaluated for a few other HIV kits used for ST, including Calypte AWARE HIV-1/2 Oral Mucosal Transudate (1002;1003), Abbott Determine HIV1/2 (1004;1005), Capyllus HIV-1/2 (1005) and Determine HIV Combo (1006). The latter test, in contrast to the other kits, can detect both antibodies and antigens, decreasing the HIV 'window period'. There are several studies on-going evaluating the accuracy of kits for ST by lay people.

For the purpose of this analysis, I assumed the sensitivity of the ST to be 92% and the specificity 99%, as found in the studies conducted pre-FDA approval (985). The standard HTC, using rapid test, conducted by a healthcare worker, is assumed to be more accurate than ST; with a sensitivity of 98%, as it has been estimated (990) and a specificity of 100%. The specificity of the HTC is believed to be relatively high, I assumed it to be 100% because confirmatory tests are conducted when a person has an initial HIV-positive test and therefore it is unlikely that a person will be diagnosed with HIV if not infected. The other reason for assuming the specificity to be 100% is that it was an issue to simulate in the model elements, such as VL, in people who are diagnosed HIV-positive when not infected with HIV. In addition, both HIV tests, whether conducted by a trained person or as ST, are assumed to be an antibody tests and therefore not able to detect HIV infection during the first 3 months since HIV infection. This is the window period usually reported and it is the minimum it can be assumed in the Synthesis model given variables are updated 3-monthly.

8.2.2.3. Assumptions on probability of having a confirmatory HIV testing and counselling following a positive HIV self-test

A crucial modelling parameter is how many of those who test HIV-positive using ST have a subsequent confirmatory test conducted by a healthcare worker, which can allow them to be truly diagnosed from the perspective of the healthcare system and provides the first stage in linkage to care. This parameter will be difficult to measure given the confidentiality inherent in ST. Some indication comes from a study conducted in Malawi (872), where 89% of used ST kits were anonymously returned. Analysis of results of these used ST kits suggests that 75% of positive results were disclosed to a counsellor. If this disclosure means they had a confirmatory HTC this would suggest around 75% of positive people were formally ‘diagnosed’ (i.e. received a confirmatory HIV test performed by a trained person).

In the Synthesis model, I assumed that once a person has a positive result using ST, an HTC, performed by a trained person, is necessary in order for the person to be considered “diagnosed with HIV” and therefore potentially being linked to care and eventually being initiated on ART. I assumed people who had a positive ST result had an 80% chance by 1 year of having a confirmatory HTC as a direct consequence of the ST. After more than 1 year since the positive ST result, if an HTC has not been done, the probability of having a HTC as a direct consequence of the positive self-test is 0 (see Figure 8.4).

Figure 8.4. Proportion of people who received a confirmatory HIV testing and counselling performed by a healthcare worker as a direct consequence of a positive self-test by different time points

HTC: HIV testing and counselling;

8.2.2.4. Assumptions on linkage to care and eligibility criteria to initiate ART

A further concern is the possibility for low linkage to care, as well as differential retention in care, once a confirmatory HTC has been done (i.e. the person is truly diagnosed, from the health system perspective). This is an issue providers already struggle with under the current HIV testing strategies. If the population choosing to self-test is fundamentally different from those who choose to have standard HTC (for example, more marginalized), it is possible that retention in care after diagnosis may be more challenging. In the study conducted in Malawi, one year after ST and with home-assessment being available 78% of those who disclosed their reactive ST result to counsellors linked to care (872). There are no other data on this topic, to the best of my knowledge though research is currently underway.

I assumed linkage to care following diagnosis, (where diagnosis is defined as a positive result to an HTC) to be 60% at one year since diagnosis. When this analysis was conducted the data by Choko et al. (872) were not yet available , therefore if anything I may have underestimated the impact of ST. A systematic review on linkage to care in sub-Saharan Africa found that the proportion of people who received CD4 count results or clinical staging by one year since diagnosis was 59% (median; range: 35%-88%) (551). I assumed that those who were diagnosed, as a consequence of having a positive ST, once diagnosed with HIV had the same

chance of being linked to care as those who were diagnosed with HIV without having a previous positive ST.

Once in care the eligibility criteria to initiate ART was assumed to be CD4 <500 cells/μL, in line with the Zimbabwe (229) and WHO ART guidelines (280). On the other hand, I did not model potential future implementation of prevention of mother-to-child transmission (PMTCT) option B+ (provision of life-long ART for pregnant and breast-feeding women).

8.2.2.5. Assumptions on psychological impact of HIV self-testing

An additional concern is regarding the psychological impact of receiving an HIV-positive result without the immediate support of a trained counselor. In terms of modeling, this could have implications for cost-effectiveness, since a lower quality of life among a proportion of those who test positive using a ST would be factored into measures of effectiveness (QALYs or DALYs). A study conducted in Malawi in the general population reported that 2.9% of the participants who self-tested were coerced into HIV testing and men were more likely to be coerced than women (872). However, 94% of those who were coerced into ST would still recommend ST and so it remains unclear whether this finding should be a serious concern.

No other data are available to my knowledge from RLS in this regard and no serious harms have been reported in other settings (988). In addition, there are no data available regarding the psychological impact via other testing methods (988). Research studies assessing the impact of introducing ST are currently collecting information on potential social harms or abuse associated with ST. For this reason I did not assume any reduction in the quality of life after conducting an ST or a standard HTC.

8.2.2.6. Assumptions on change in risk behaviour following an HIV test

Learning one's HIV status may lead to behaviour modification to reduce the risk of becoming infected, or of infecting others. A meta-analysis reported that people who test HIV-positive through VCT in LMIC have significantly lower odds of reporting an increased number of partners, compared to those who did not have an HIV test (OR = 0.61; 95% CI: 0.37, 0.997; p = 0.048) and higher odds of reporting condom use (OR = 3.24; 95% CI: 2.29, 4.58; p < 0.001) (48). Among those who tested HIV-negative, there was no evidence of behaviour change, (although only a couple of studies evaluated this (1007;1008)). With PITC (47), most studies, but not all, reported an increase in condom use among different subgroups of the population and in different countries, in both people who tested HIV-negative and positive. Regarding ST, to my

knowledge, the only data available come from a study among MSM in New York, which reported that the 10 people identified as HIV-positive through ST did not have sexual intercourse after learning their result (1009).

The model assumes that there is no change in condom-less sex in people who test HIV-negative, while those who test HIV-positive reduce condom-less sex with casual partners by 17% in the first 8 months (9% afterwards) and by 13% with CLLT partners. The same behaviour is assumed following ST.

8.2.2.7. Assumptions on HIV self-testing and HIV testing and counselling cost

A few studies have highlighted that the cost could potentially be a significant barrier to accessing ST, even in high income countries (991;1010;1011), given that where currently available ST kits must be purchased while HTC is generally free. In a study in Singapore only 28% of respondents reported they would pay at least US $15 for a self-test kit (991). In a study among MSM in Seattle similar findings were reported: 13% would only use ST if it was free, and 42% would pay US $20 or more for a ST kit (1011). Cost is likely to be an even greater barrier to ST in RLS.

Research studies on ST so far have distributed ST kits for free in order to evaluate the acceptability and accuracy of ST and if provided, pre-test counselling and demonstration on how to use ST kits has been provided by community counsellors (755), likely at a lower cost than if delivered by a healthcare worker. Studies in which people were repeating ST in RLS have not been conducted, but it is possible that the pre-test counselling could be reduced and maybe even omitted when repeating ST.

The cost of the rapid HIV test kit used in the clinic is relatively low. In RLS it ranges between US $0.50 and US $2 (1012). Although the cost WHO and other agencies pay for the oral fluid–based test, OraQuick (the version to be used by trained people), in RLS is among the highest among the leading rapid tests, costing around US $4 (1013). The price is variable depending on the country and volume purchased. Moreover, the method of distribution is likely to have a major impact on the cost of ST. The overall cost of delivering the HTC, including distribution of the kit, infrastructure, personnel cost is substantially higher than the cost of delivering ST. On average, it has been estimated to be US $10 in a study in Zambia (692), with a much higher cost for conducting an HIV-positive test, mainly driven by the post-test counselling, compared to an HIV-negative test. I assumed the fully loaded costs of a HTC being US $9 for a negative

test and US $25 for a positive test or a confirmatory test following a positive ST, so that the average is around US $10.

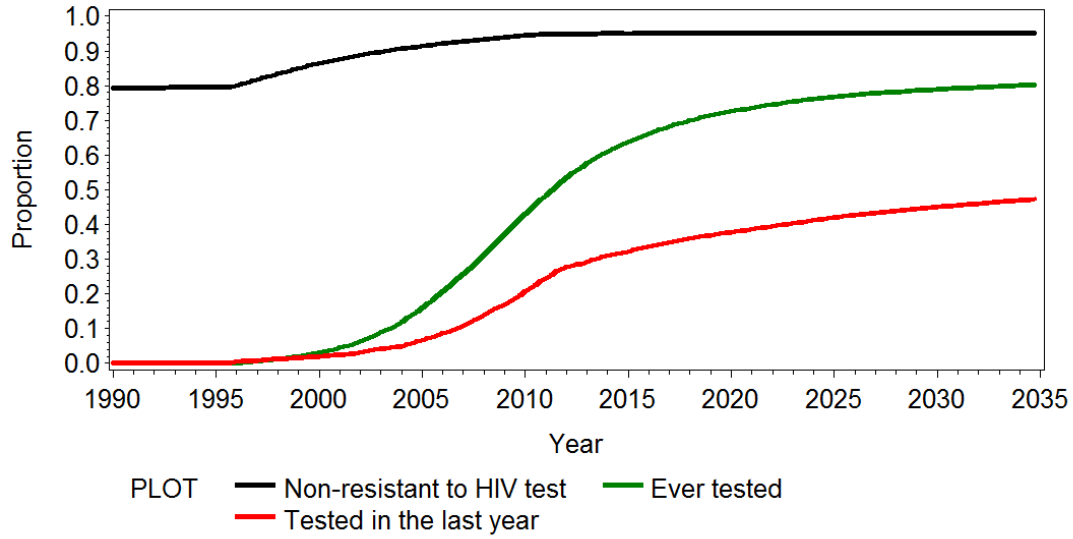
The cost of ST is assumed to be US $3 per unit. There are no data on the fully loaded costs of delivering ST in RLS mainly because it has not been scaled yet at national levels and the cost is likely to depend on how the self-tests are distributed.

8.2.3. Analysis details

I used a single simulation of the Zimbabwean HIV epidemic until 2015 based on a single set of parameter values, with levels of HIV prevalence, proportion ever tested and tested in the last 12 months comparable to those observed in the DHS (519) (see Figure 8.1 at page 326, Figure 8.2 at page 328, Figure 8.3 at page 329).

From 2015, I compared two possible base case scenarios: a reference scenario (RS), where ST is not introduced and there is continued reliance on HTC alone and the ST scenario, where ST is made available to the general population aged 15-65 years from 2015. In the reference scenario, the rates of first time and repeat testing increase linearly by 0.005 per year (the proportion tested for HIV in the last year is 37% in 2015 increasing up to 50% in 2035) and the rate of being linked to care, retained in pre-ART care and initiated on ART, if eligible, continues as before 2015. Multiple runs were simulated from 2015 for 20 years to reduce stochastic variation. Figure 8.5 shows the modelled proportion non-resistant to HTC test (willing to receive an HIV test), the proportion ever tested for HIV and the proportion tested for HIV in the last year from the epidemic start to 2035.

Figure 8.5. Summary of the assumption on HIV testing in the reference scenario



The introduction of ST is assumed to have three main effects:

- halving of the population unwilling to receive a HTC (from 5% to 2.5%)
- substitution of 10% first time and 30% repeat HTC with ST
- increase in the rate of first time and repeat testing by 20%, due to the availability of ST

Availability of ST is not assumed to affect HTC conducted in ANC. These assumptions are based on limited current evidence available (described in sections 8.2.3.1-8.2.3.3) but overall are believed to be conservative in estimating the potential benefits of ST.

8.2.3.1. Data on uptake of HIV self-testing among those resistant to HIV testing and counselling

In sub-Saharan Africa, a few studies have evaluated hypothetical acceptability of ST (871;987), and some the actual uptake of ST when made available, and in particular among people who are resistant to testing by existing available means (871-874). A study conducted in Malawi, where ST was made available through community counsellors, found that 76% of over 16,000 residents had used ST at 12 months since its introduction, with 43% being first time testers (872). A study conducted among healthcare workers in 7 hospitals in Kenya found that the uptake was 89%. Among healthcare workers who self-tested, most (92%) had tested before, and from these data I cannot estimate how many of those who accepted the self-test were resistant to HTC (873). Similarly a pilot study conducted among healthcare workers in Cape Town, reported a 93% uptake of unsupervised ST (874), with 13% being first time testers.

Other studies have evaluated the uptake of ST, without distinguishing whether these people were resistant to HTC or not, or on whether they were first-time or repeat tests, but not in sub-Saharan Africa (1009). A recent meta-analysis, including all the studies published at the time of its preparation (3 studies), estimated uptake of ST to be 87% (862). While studies are few and may not be generalizable, they represent the available data regarding the uptake of ST and more specifically the potential uptake among those who may currently be resistant to HTC. Formative research is currently being conducted in Kenya and Zimbabwe to evaluate acceptability and/or uptake in subgroups of the population at high risk for HIV infection, such as MSM, sex workers and serodifferent couples.

8.2.3.2. Data on impact of HIV self-testing availability on the rate of HIV testing among those not resistant to HIV testing and counselling

I am also interested in the extent to which availability of ST would, by providing a convenient and confidential option, increase the probability of testing in people who are not resistant to HTC but who have never been tested before; similarly, I am interested in the frequency of repeat ST. To my knowledge the only relevant information comes from a study among MSM in Australia (1014), unlikely to be applicable in the context of sub-Saharan Africa. No data on the long term impact of ST availability on the frequency of HIV testing are available. Reasonably, the research thus far has focused on evaluating accuracy, acceptability and uptake of ST.

8.2.3.3. Data on the substitution of HIV testing and counselling, conducted by a healthcare worker, with HIV self-testing

A further important consideration when modelling the potential effectiveness and cost-effectiveness of ST is what proportion of future tests (that would have occurred under provider-delivered strategies), would be conducted via ST if available. Again, this might be different for first time versus repeat testing and will depend on the cost of different strategies. It may be cost-saving to introduce ST if its provision is less expensive than HTC, despite its lower sensitivity and the necessity for a confirmatory HTC for those self-testing positive.

It is therefore important to quantify the extent of uptake of this substitution and the characteristics of those who would substitute HTC with ST, particularly regarding sexual behaviour. The only research which provides some indication of this parameter is reported preferences for ST versus HTC methods, and these data are largely from high income countries

(871;1004;1015-1018). I may not be able to accurately estimate this parameter until ST is more widely available. For example, 38.9% of MSM in Madrid reported that ST would be the most favorable way of receiving an HIV test (1015), 61% of known HIV-positive people recruited in a clinic in Seattle reported that they would have preferred to self-test if they did not know their status (1016), and among people attending an HIV testing facility in the US 89% would have preferred to self-test (1004). Of those who took part in an evaluation of ST in tablet computer-based-kiosks within the emergency department, 96.9% reported they would "probably" or "definitely" test themselves at home if ST kits were available to buy, but 26% preferred ST compared to 34% who preferred HTC (1018). From RLS, among potential HIV testers in India, 86% preferred ST over clinic-based testing (1017), and in a study conducted in Malawi 92% of a general population of community members opted for supervised ST (ST followed by confirmatory HTC) over standard VCT (871).

8.2.3.4. Sensitivity analysis

The parameters characterized by more uncertainty were varied in sensitivity analysis to understand how they affect the results (see section 8.3.2) and therefore what the impact might be if the main assumptions are not correct. Nine parameters were varied in univariate sensitivity analyses: cost of ST, sensitivity of ST, probability of confirmatory HTC as a direct consequence of a positive ST, probability of being linked to care by one year after a positive HTC (whether prompted by a ST or not), reduction in condom-less sex for those diagnosed with a positive ST, eligibility criteria to initiate ART, magnitude of increase in the rate of first and of repeat testing due to the introduction of ST, and the level of substitution of ST for HTC. The three most determinant parameters of cost-effectiveness were also varied in bivariate analyses to explore whether there were particular combinations of these parameters where ST was cost-effective.

8.2.4. Assumptions on health benefits and costs

The two scenarios (RS and ST scenario) were compared on the basis of their costs and health outcomes (729). Health outcomes are expressed in terms of DALYs averted, which take into account both improvements in survival, quality of life associated with averted HIV infections and reduced HIV symptom burden in people receiving ART (733). Both the DALYs and the costs (See Table 8.2), from a healthcare prospective, are summed over a 20 year time horizon starting in 2015, rescaled to provide figures relevant to the entire adult population of

Zimbabwe and discounted by 3% per annum in accordance with WHO-CHOICE recommendations (729).

In order to calculate the DALYs the disability weights used are (733):

- 0.55: for WHO 4 event
- 0.40: for TB
- 0.22: for WHO 3 event

Table 8.2. Unit costs and their sources

Item	Cost (US $)	Sources where available
ART cost (1st line: TDF+3TC+NVP)	$97 PY	(969)
ART cost (second-line AZT+3TC+ATZ/r)	$279 PY	(969)
Supply chain of ARVs	20% of the cost of ARVs	-
WHO stage 4*	$200	-
WHO stage 3*	$20	-
TB*	$50	-
CTX	$5 PY	-
Clinic Visit	$20	-
CD4 measurement	$10	-
HTC (all costs fully loaded)	$9 for negative, $25 for positive, on average $10	(692)
ST	$3	Assumption

*This cost is incurred every 3 months where the person has this condition; 3TC: lamivudine; ART: antiretroviral therapy; ARVs: antiretroviral drugs; ATZ/r: atazanavir boosted with ritonavir; AZT: zidovudine; CTX: co-trimoxazole; HTC: HIV testing and counselling; NVP: nevirapine; PY: per-year; ST: HIV self-testing; TB: tuberculosis; TDF: tenofovir;

Results from cost-effectiveness analyses inform us on the cost to gain a life-year or to avert a DALY compared to the cheapest option. This information is important for the decision maker and it is usually compared to the CET (See section 4.3.2.2) (i.e. the "willingness to pay" to gain a life-year or to avert a DALYs), which, as mentioned in section 4.3.2.2, is usually below three-times the country's per capita GDP (Zimbabwe US $ 500 in 2012 (1019)) (729).

Results are presented across a range of CET: from $0 (an extreme case, implying a health system would only be concerned with reducing costs) to $10,000 (a relatively high threshold only likely to be relevant in well financed health systems with full coverage of interventions offering health gains at less than this amount).

Due the stochastic variation inherent in the model a high number of simulations are required so figures are presented on a discrete rather than a continuous scale.

8.3. Results

8.3.1. Main results

Introduction of ST, as assumed in the base case scenario, led to a 6% higher proportion tested for HIV in the past year compared to the reference scenario in 2035 (56% vs 50%, see Table 8.3) and to 83% of the population ever being tested for HIV, compared to 79% if ST is not introduced. Although it is assumed ST would result in a slightly higher proportion of the population ever tested and tested in each year, it results in a very similar proportion of people diagnosed with HIV (<1% higher for ST scenario), because not all those who receive a positive ST would access a confirmatory test performed by a health care worker and would therefore be considered diagnosed. Thus, as only people diagnosed can be linked to care and eventually be initiated on ART, the proportion on ART is very similar as well.

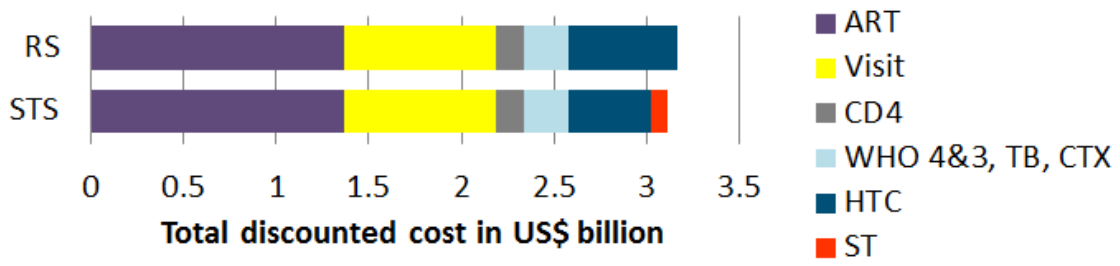
The total discounted costs over 20 years for HIV testing and resulting HIV care and ART under the reference scenario base case assumptions is estimated to be almost US $3.2 billion (see Figure 8.6). Of this, 43% is attributable to the cost of ARVs, around a quarter to the cost of clinic visits and almost 20% to HTC. The ST scenario, would lead to savings over 20 years of US $53 million (95% CI: 49, 58 million), a reduction of 1.7% in costs, due primarily to a partial replacement of more expensive HTC conducted on HIV-negative people with cheaper ST, although the cost of diagnosing a positive person would be slightly higher, because this person would receive a ST ($3), before being identified as positive with an HTC ($25). The introduction of ST would result in a relatively small health gains, with approximately 102,000 DALYs averted (95% CI: 62,000-142,000) (see Table 8.4 at page 342), because it allows to identify slightly more people as positive and slightly higher number of people receiving ART. As the introduction of ST (as specified) produces health benefits and allows saving money, it can be considered cost-saving.

Table 8.3. Predictions over time in the two main scenarios (median over simulations)

	Data	**Model**				
	DHS (519)	**Baseline**	**Reference**		**Self-testing**	
	2011	**2015**	**2025**	**2035**	**2025**	**2035**
HIV prevalence (%)	15	14	11	7	11	7
% ever tested for HIV	50	65	77	79	80	83
% tested for HIV in the last year	28	37	46	50	53	56
% diagnosed	-	83	94	96	95	96
% on ART (of those HIV+)	-	53	71	76	71	76

ART: antiretroviral therapy; DHS: Demographic and Health Survey;

Figure 8.6. Total discounted cost over 20 years in US $ billions



ART: antiretroviral therapy; CTX: co-trimoxazole; HTC: HIV testing and counselling; RS: reference scenario; ST: HIV self-testing; STS: HIV self-testing scenario; TB: tuberculosis;

8.3.2. Sensitivity analyses

I conducted several sensitivity analyses to evaluate whether the results were robust to changes in the main parameters. Table 8.4 (page 342) summarizes the cost-effectiveness of the base case and alternative assumptions in sensitivity analyses at different CETs, as well as the increments in total discounted costs and total discounted DALYs averted (with 95% CI) with ST scenario compared to the reference scenario.

In general, for any scenario in which DALYs are averted, the probability that ST is cost-effective will increase with increasing CET, because at some point the cost of the DALYs averted become affordable. In contrast, for scenarios which lead to a loss in DALYs, ST is less likely to be cost-effective with increasing CET because at some point the money saved from ST scenario is not worth the loss in DALYs.

The results are particularly driven by costs. If the cost of ST is the same as a negative HTC test (US$ 9) it is only cost-effective at a CET of US $5,000 per DALY averted or more because it results in higher costs (US $118 million greater than under reference scenario), but relatively small health gains. If, however, ST was to cost US $5 or less, then the ST scenario would be cost-effective even at a CET of US $500, keeping other base case assumptions fixed (Table 8.4 at page 342, Figure 8.8 at page 343 and Figure 8.9 at page 344).

The level of substitution of HTC with ST affects the results, at first sight, in a slightly counter-intuitive way (See Figure 8.7 at page 343). The reason why at a low CET, once a certain level of substitution occurs (horizontal axis), the introduction of ST is cost-effective, regardless of the

probability of HTC as direct consequence of a positive self-test (and therefore the chance of being diagnosed), is that at low CET whether an intervention is cost-effective is determined mainly by the costs. The substitution of more expensive HTC with ST in negative people allows saving money and even if it does not result in a health gain, it results as cost-effective. However, at higher CETs more concern is given to health gains meaning that ST is only cost-effective at higher levels of substitution if it is likely to lead to a confirmatory HTC resulting in future health gains for patients, because patients once self-tested positive have a high chance of being diagnosed and therefore access HIV care and treatment. The programmatic implication is that high levels of support to ensure linkage to care are likely to offer even greater value in better resourced health systems, but ST support programmes are likely to be important in all settings for ST to be effective in improving health.

Both Figure 8.8 (page 343) and Figure 8.9 (page 344) illustrate that ST is clearly more likely to be cost-effective the lower the cost of ST, and in particular even if the CET is of $1,000 (assuming the other parameters do reflect reality) ST cannot cost more than $8, but for this to be so high, only a very modest increase in ST must occur (Figure 8.8). Figure 8.8 shows that if the substitution of standard HTC with ST is modest (for example 20% for the substitution of repeat test and 7% for first time test), the cost of ST has to be low: $3 or less if the CET is $1 and up to $4 at higher CET. However if the level of substitution of HTC with ST is higher, more money can be spent for each ST and it would still result as a cost-effective intervention.

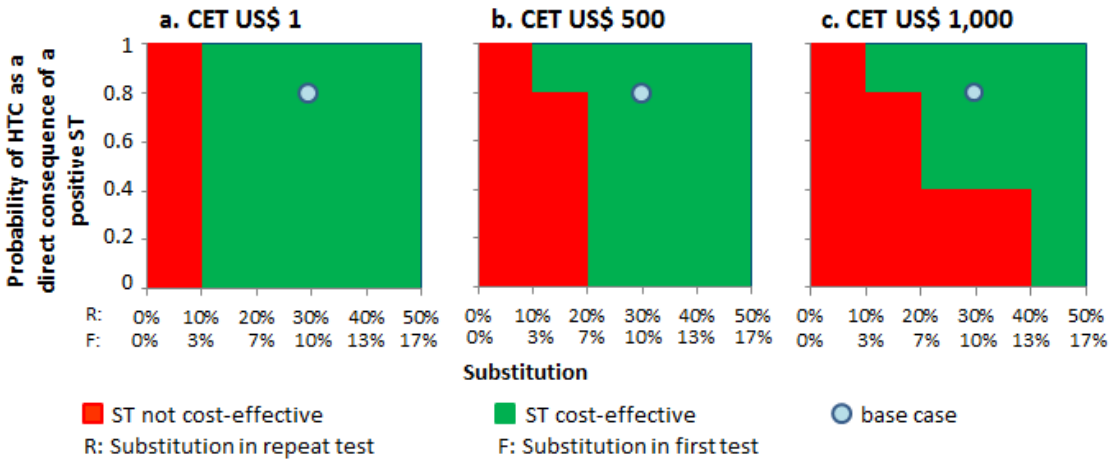
Regarding the levels of increase in the rate of first test and of repeat testing due to the availability of ST (Figure 8.9 at page 344), I found that the greater the levels of increase, the greater the health gains associated with ST but also the greater the cost. Therefore, as the CETs increase the health gains from ST become relatively more important and more expansive use of ST would be preferred. This also has important programmatic implications for delivery of ST and shows that appropriate targeting of ST is likely to be particularly important in less well-resourced health systems.

Table 8.4. Cost-effective scenarios (HIV self-testing- or reference scenario) under base case and alternative assumptions, according to cost-effectiveness threshold

		Cost-effectiveness threshold in US $					Total incremental discounted costs* in US $ millions, compared to RS (95% CI)	Discounted incremental DALYs averted* in thousands, compared to RS (95% CI)
		0	500	1,000	5,000	10,000		
Base case (See section 8.2.3)		STS	STS	STS	STS	STS	-53 (-58;-49)	102 (62;142)
Cost of ST = US $9 (B: US $3)		RS	RS	RS	STS	STS	123 (119;127)	102 (62;142)
Sensitivity of ST = 0.55 (B: 0.92)		STS	RS	RS	RS	RS	-77 (-81;-74)	-157 (-193;120)
Probability of HTC as a direct consequence of a pos ST = 0.37 (B: 0.8)		STS	RS	RS	RS	RS	-79 (-83;-75)	-166 (-203;-130)
Probability of linkage to care following diagnosis for those who had a ST by 1 year = 0.4 (B: 0.6)		STS	STS	RS	RS	RS	-93 (-98;-88)	-166 (-211;-122)
ART initiation at CD4 < 350 cells/µL (B: CD4 < 500 cells/µL)		STS	STS	RS	RS	RS	-159 (-163;-155)	-252 (-293;-211)
No reduction in condom-less sex following a pos ST (B: as HTC)		STS	STS	RS	RS	RS	-75 (-79;-70)	-129 (-173;-86)
Increase in rate of 1st test due to ST (B: 20%)	2.5%	STS	STS	RS	RS	RS	-86 (-92;-79)	-141 (-206;-76)
	7.5%	STS	STS	RS	RS	RS	-85 (-91;-77)	-138 (-202;-75)
Increase in rate of repeat test due to ST (B: 20%)	2.5%	STS	STS	RS	RS	RS	-100 (-106;-94)	-117 (-176;-57)
	7.5%	STS	STS	RS	RS	RS	-93 (-98;-88)	-96 (-144;-47)
Substitution (B: 30% repeat, 10% 1st test)	5% of repeat, 2% 1st test	RS	STS	STS	STS	STS	47 (42;53)	209 (163;255)
	15% of repeat, 5% 1st test	STS	STS	STS	STS	STS	-2 (-11;8)	139 (55;223)
	25% of repeat, 8% 1st test	STS	STS	STS	STS	STS	-35 (-43;-26)	118 (36;198)

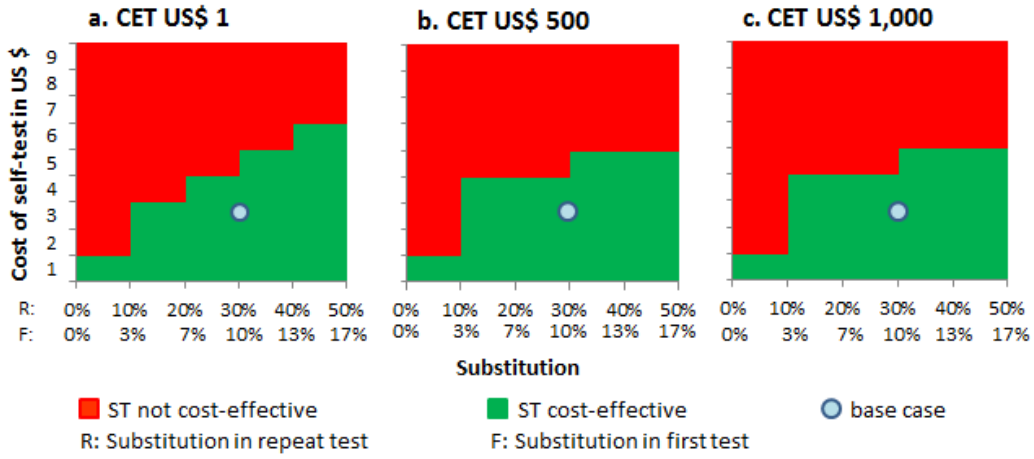
B: base case assumptions; CI: confidence interval; DALY: disability-adjusted life-year; HTC: HIV testing and counselling; pos: positive; RS: Reference scenario; ST: HIV self-testing; STS: HIV self-testing scenario; the discounted total cost of the RS over 20 years from 2015 is US $3,168 million.

Figure 8.7. Cost-effective scenario under different assumptions of substitution and probability of HIV testing and counselling as a direct consequence of a positive self-test



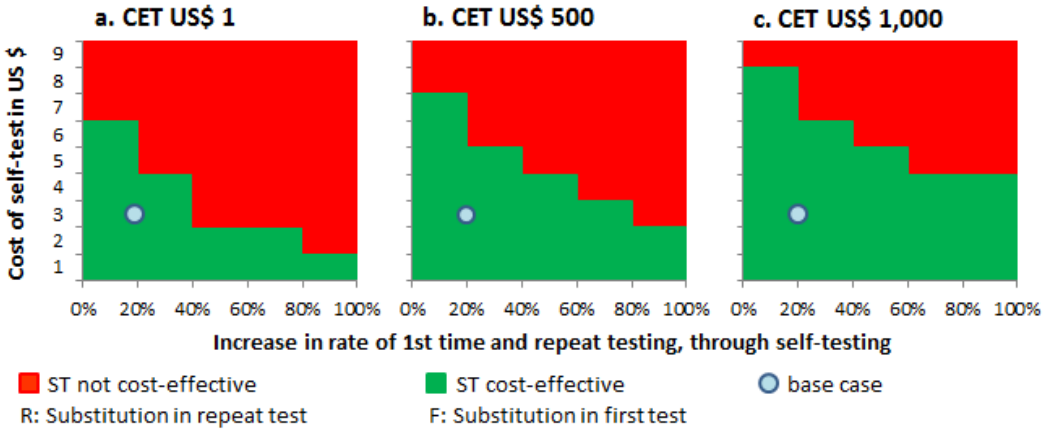
CET: cost-effectiveness threshold; HTC: HIV testing and counselling; ST: HIV self-testing

Figure 8.8. Cost-effective scenario under different assumptions of substitution and cost of self-test



CET: cost-effectiveness threshold; ST: HIV self-testing;

Figure 8.9. Cost-effective scenario under different assumptions of increase in the rate of 1st test and of repeat test and cost of self-test



CET: cost-effectiveness threshold; ST: HIV self-testing

8.4. Discussion

ST holds the promise of expanding the reach of HIV testing. It may enable some people to test who would otherwise not choose provider-based HTC due to issues of stigma, confidentiality, cost, or other barriers to access. It may also support more frequent testing for all in the population due to greater convenience. As the basis for affirming HIV status, leading to linkage to care, receipt of ART for those eligible, as well as prompting individuals who learn they are HIV-positive to reduce the risks of onward HIV transmission to others, the potential health gains from ST are clear. What is more, my results show that ST may also reduce costs, enabling savings in HIV testing programmes that can be reinvested in further expansion of testing or in delivery of other HIV and healthcare interventions.

Overall, given the characteristics of ST specified in the base case assumptions, I estimate that the introduction of ST will allow savings of around US $50 million over 20 years in Zimbabwe, with a modest (102,000, in the context of an adult population of 7.5 million in mid-2013) number of DALYs averted. If these assumptions hold in other settings, ST should always be introduced regardless of how poorly or well-resourced a health system is – it leads to a win-win situation of better health outcomes at reduced cost. If I assume a CET of $500 (similar to Zimbabwe per capita GDP in 2012), the US $50 million saving could be used to avert at least 100,000 DALYs by introduction of interventions with ICERs ≤ $500 per DALY averted. The monetary value of introducing ST to Zimbabwe (calculated as net monetary benefit: health

gains times CET plus cost savings (730)) would be US $104 million over 20 years; indicating huge benefits associated with supporting the availability of ST in the country.

However, the population costs and health effects of ST depend upon a range of complex and interacting factors, and not all plausible scenarios will unambiguously result in health gains and/or lower costs. The sensitivity analyses provide insight into what determines the magnitude of population health gains and suggest what programmatic recommendations may support optimal implementation of ST.

Firstly, the cost of ST relative to HTC appears to be the most important factor determining cost-effectiveness, particularly at lower CETs. The OraQuick HIV test kit designed for clinical use was sold for US $4 in low income countries in 2005 (1013). Lower cost alternatives to ST would lead to additional gains. The cost of distributing ST cannot be ignored, but it is expected to be significantly lower than the cost of providing HTC. To the best of my knowledge, data on the cost of rolling out ST are not currently available, and the only study conducted in sub-Saharan Africa evaluating the uptake of ST distributed the kit through community counsellors (755).

Secondly, I evaluated the impact of introducing ST in addition to HTC in a setting such as Zimbabwe, with a high level of HIV diagnosis and ART coverage; in 2015, before the introduction of ST, an estimated 82% of people with HIV are diagnosed. It is likely that the impact of introducing ST would be even greater the higher the proportion of people with HIV who are undiagnosed.

Thirdly, in some circumstances, ST may lead to improved health outcomes but also higher costs as compared to the reference scenario, if the overall level of testing (i.e. the increase in the rate of first time and repeat testing) increases dramatically due to the availability of ST. The few studies conducted so far on uptake of ST have found it to be extremely acceptable (872-874). Studies in Malawi, for example, have shown that 76% of adult avail themselves of ST by 12 months following its introduction (872). In settings with higher CETs the potential for health improvement will usually outweigh higher costs, but when the CET is lower the cost burden from an increased number of tests will be felt more acutely. Appropriate targeting of ST is likely to be necessary in such situations.

There is also a risk in some circumstances that ST may lead to worse health outcomes if ST is substituted for HTC but the likelihood an individual will receive confirmatory HTC is low. This suggests that, to be translated into health gains, there is perhaps a limit to the degree to which

ST should be substituted for HTC, and importantly, that ST needs to be accompanied by proactive interventions to support confirmatory HTC. A study in Malawi (755) investigated one scheme that could provide complementary benefits - offering ART initiation at home among people who self-test - and found this significantly increased the probability of initiating ART within 6 months.

Finally, there is always potential for unintended adverse consequences associated with any public health intervention, so countries should closely monitor their experiences with introducing ST. Linkage to care, promoting counselling services, reporting of testing outcomes needs to be strengthened in support of such public health interventions.

There are a few limitations which affect these analyses. First I assumed that people who are "resistant to HTC" are a random sample of the population. The people who are classified as "resistant to HTC" are in fact not likely to be a random sample, but possibly more marginalized, or people with many sexual partners who fear stigma in attending the clinic. The Synthesis model could incorporate the effect of age, gender and condom-less sex, for example, as data accrue to inform the magnitude of any effects. The issue is finding good evidence to inform this parameter.

Another limitation, linked to the previous one, regards the characteristics of people who opt for ST. Again I evaluated the introduction of ST in the entire population aged 15-65 years, assuming the uptake of ST is random among those non-resistant to HTC. Since the earliest debates on ST, one of the advantages cited has been the potential for increased confidentiality, which could appeal to marginalised groups more affected by stigma, such as sex workers and MSM. To my knowledge there are no data available yet on the characteristics of those who opt for ST rather than HTC, except for some data regarding uptake of ST by age (872), and on the uptake of ST in marginalized groups.

Mathematical models are a simplification of reality, so they would not include all variables which characterize these groups. The Synthesis model for example could incorporate dependence on age, gender and sexual behaviour while other models may include specific subgroups, characterised by different routes of HIV transmission. This parameter is particularly important because if ST availability encourages testing in those resistant to HTC, and who are at increased risk of HIV, this could impact their risk behaviour and/or their infectiousness (if they receive ART), and therefore the number of new infections they contribute to.

8.5. Conclusions

In conclusion, these results suggest that the introduction of ST may well be not only cost-effective, but cost-saving under the assumptions described in the base case scenario. Under these assumptions, ST should be made available even in the most resource constrained settings. It has great potential to increase knowledge of HIV status in RLS, where over half of HIV-infected individuals are currently unaware of their status.

Notably, in some circumstances it may be necessary to target ST to those with certain risk factors and it is likely ST will need to be accompanied by other measures to encourage confirmatory HTC.

This analysis and mathematical modelling more generally can help to answer this question, though field data is required in order to accurately estimate important model parameters. While some data exist on the acceptability, uptake and accuracy of ST, there are several parameters for which evidence is limited. To increase the accuracy of this model and better inform policy making it is necessary to collect more data from well-powered studies on the cost of ST, the magnitude of replacement, the probability of having a HTC test following a positive self-test and the magnitude of increase in the rate of first and repeat testing if ST is introduced.

9. Summary and Conclusions

9.1. Summary of main findings

The discovery of highly effective ARVs and the increased availability of these treatments in sub-Saharan Africa, by far the area of the world most affected by this epidemic, means that many people now have a life expectancy than seemed impossible only a few years ago. However, despite extraordinary advances in the scale up of HTC and ART availability, many people still cannot benefit from them. By the end of December 2012, 9.7 million in LMIC were estimated to be receiving ART, of which 1.7 million initiated on treatment over 2011 (764). Further efforts are needed to reach the target of 15 million people receiving ART by 2015.

Donors and stakeholders are faced with important decisions on how to maximise the health benefit, given the limited resources available, taking into account potentially negative consequences of these interventions, and which interventions provide the greatest value.

In Chapter 1, after a brief introduction on the biology of the virus, I reviewed how the HIV virus is transmitted, how the disease progresses in people infected with HIV, which treatments are available and recommended for HIV-positive people, how ART resistance can develop and be transmitted and the HIV prevention methods available included in the Synthesis model; while, in Chapter 2, I provided a short background on the HIV epidemic in South Africa and in Zimbabwe. This extensive introduction was necessary, given that all these components are related or included in the Synthesis model of HIV transmission, progression and the effect of treatment, which is used to address four of my research questions. Increasing focus has been placed on resistance to ART, because this is a growing concern in countries where ART is scaled up and not many mathematical models capture this factor, particularly not in a way that is specific to ARVs. In developed countries, patients usually receive a resistance test before initiating ART to determine whether they have any detectable DRMs (due to TDR or previous use of ART) so that they can be initiated on fully active regimens. In LMIC this is not the case. In addition, while VL monitoring is usually routinely conducted in developed countries to identify treatment failure in a timely way, this is not the case in most countries in sub-Saharan Africa. South Africa is an exception, VL monitoring has been available there and recommended to monitor people on ART; nevertheless many people are not switched to second-line even after prolonged VF. Factors which facilitate the development of resistance are suboptimal

adherence and TIs. The latter has been found to be relatively common in sub-Saharan Africa for various reasons including drug stock outs, difficulties for patients in attending the clinic due to competing priorities or because of the distance from the clinic. All these factors contribute to the onward transmission of HIV drug resistant virus.

Chapter 3 describes the HIV Synthesis transmission model, which is used to address the research questions addressed in Chapter 4, 5, 7 and 8. The original core of the model was developed by Andrew Phillips but together with a colleague working on the progression model, Fumiyo Nakagawa, and I, we have jointly modified the model in several ways over time. One of my major contributions has been to focus on calibrating the model to specific settings such as South Africa and Zimbabwe and in developing parts of the model necessary to answer the questions I was interested in. Regarding HIV testing, I introduced the process of HIV testing in the general population and in women attending ANC in the South African model and a more detailed age and gender-specific HIV testing process with the availability of ST in the Zimbabwe model. Regarding the linkage to care, retention in pre-ART care and on ART, I modified the model to better reflect the cascade observed on the ground and to be able to provide results in the format agreed with the HIV Modelling Consortium. I developed as well the part of the model on circumcision, given VMC has been found to be an effective prevention intervention and both the countries considered in this thesis are scaling up VMC programmes. In addition I developed the possibility of using PrEP within the Synthesis model and its impact in reducing the risk of acquiring HIV, but as well the possibility that people who are infected with HIV while on PrEP could develop resistance. This has not been included in the PhD.

Chapter 4 has two main parts: the first presents a formal literature review on the preventive benefit of ART, while the second part aims to evaluate the impact and cost-effectiveness of changes in adult ART eligibility guidelines and improvements in HIV testing and linkage to care in the South African setting. The literature review has been conducted in collaboration with the European Centre for Disease Prevention and Control, but includes evidence on the efficacy of ART in reducing the risk of transmitting HIV from high, middle and low income countries. The strongest evidence available on the preventive benefit of ART is the HPTN052 RCT (432). Using the Synthesis model I evaluated the cost-effectiveness of alternative strategies for expanding access to ART. I found that modifying the eligibility criteria to initiate ART from CD4≤350 cells/µL to CD4 ≤500 cells/µL or to all HIV-positive people was very cost-effective over 20 years. Nevertheless I estimated that the cost per DALY averted of changing ART

eligibility criteria to CD4 ≤500 cells/μL or to all HIV-positive people was quite substantial, respectively $1,691 and $2,133, among the highest costs across the mathematical models which addressed this question within the HIV modelling Consortium. I found that the most cost-effective option amongst those considered was instead expanding HIV testing and linkage to care so that 80% of those who become eligible for treatment are in care, while maintaining the CD4 threshold of 350 cells/μL; this option would cost $1,398 per DALY averted.

Since the Synthesis model was the only model within the HIV Modelling Consortium addressing the question in Chapter 4 for South Africa which included resistance, in Chapter 5 I attempted to estimate the impact of different ways of expanding access to ART in South Africa on the levels of HIV drug resistance. I found that, even if new policies are not put in place and the roll-out of ART continues at the current pace, the number of people carrying HIV drug resistant virus and the consequent need for second-line regimens is going to increase by at least 2 fold. This is a consequence of having an increasing number of people on ART and it is due to the fact that people interrupt treatment and fail to perfectly adhere to treatment for various reasons and the fact that this resistant virus can then be transmitted. However, the Synthesis model suggests that 60% of those who in 20 years' time will have developed resistance to drugs in the first-line regimen could be virologically suppressed on a second-line regimen. In addition I found that by substantially improving diagnosis and retention while maintaining the eligibility criteria at CD4<350 cells/μL, it is possible to reduce the number of new HIV infections to the same extent that could be achieved by expanding the eligibility criteria to all people diagnosed with HIV, while saving more deaths and avoiding initiating ART in people for whom the clinical benefit is still under discussion.

When modelling the development and transmission of DRMs, two pieces of information for which the evidence is limited, even from developed countries, are the extent to which resistance mutations persists in people who stopped treatment after experiencing VF due to development of resistance and the extent to which NNRTI mutations can be acquired following interruption of treatment due to the long half-life of NNRTI compared to the other components of the regimen. To address this question, in Chapter 6, I used data from an observational study performed in the UK and used these estimates to inform the Synthesis model. I found that among patients in the UK HIV drug resistance database who have documented NNRTI resistance while on ART who then interrupted it, 41% had NNRTI resistance which persisted at the first resistance test after interrupting treatment (in median

performed 4 months after stopping ART). While, in those who interrupted suppressive NNRTI-based regimen, 12% of patients who had a subsequent resistance test had NNRTI resistance detected (in median conducted 12 months after the interruption; IQR: 3-20 months).

As HTC and ART is scaled up in South Africa and other settings in sub-Saharan Africa, it is becoming apparent that one of the most crucial issues once people are diagnosed with HIV is to make sure they are maintained along the continuum of care, so that they can initiate ART in a timely way once eligible and then achieve the maximum benefit while on ART. In Chapter 7, I explored at which steps within the cascade of care from diagnosis to maintenance of virological suppression while on ART, it is worth intervening to reduce the losses, in particular in terms of HIV infections, deaths averted and cost-effectiveness. I found that among improvements which would reduce the losses by 50% at the following steps: linkage to care, retention in pre-ART, retention on ART, switch to second-line, the improvement which provides the greatest health benefit is the one aimed at increasing retention on ART. This is due to the fact that it allows a substantial reduction in the number of deaths. In addition, when comparing these strategies where the cascade of care is strengthened with modification in the eligibility criteria by raising the CD4 count threshold, I found that policy-makers should first strengthen the cascade of care and only as a second step expand the eligibility criteria. To inform this decision, I estimated what is the maximum cost the intervention could cost in order to be cost-effective. The interventions for which more money can be spent are those who provide more value in terms of health benefit, those leading to improved retention on ART and timely switch to second-line.

In Chapter 8, a different public health intervention was explored: the introduction of ST. I used the Synthesis model to evaluate the cost-effectiveness of introducing ST in the general population in Zimbabwe taking into account the potential advantages and disadvantages of ST.

The advantages include the fact that ST represents a good opportunity to save money given the lower cost of providing this type of test and the fact that it could reach people who are not willing to have an HTC, provided by a counsellor. The disadvantages include the lower accuracy of ST compared to HTC, conducted by trained counsellors and the need to have a confirmatory test to be diagnosed with HIV and potentially linked to care and initiated on ART if necessary. I found that ST may well be cost-saving, given its lower cost and the fact that, by reaching more people, provides a moderate health benefit.

9.2. Relevance and limitations of main findings

In this thesis, I have focused on the impact of different public health actions (different ways of expanding access to care and whether to introduce HIV ST) mainly on HIV incidence, resistance dynamics and cost-effectiveness in two settings in sub-Saharan Africa, South Africa and Zimbabwe.

The evidence of the preventive benefit of ART has triggered lots of discussion and some of the most widely used guidelines now recommend either ART initiation in all HIV-positive people (265;281) or below CD4 count ≤500 cells/μL (280). As part of the revision process of the guidelines that WHO then published in July 2013, WHO asked the HIV Modelling Consortium to evaluate the value of expanding the eligibility criteria by increasing the CD4 count threshold, compared to the expansion of access to care in people eligible for ART according to the 2010 WHO guidelines (277). I took part in this collaboration, using the Synthesis model and these results are presented in Chapter 4 and compared to the findings from the other mathematical models which were involved. This process is very useful to facilitate comparisons across mathematical models and collaborations between modellers. When the results are consistent across each other, it is very reassuring, while on the other hand, when discrepancies arise, it is often quite difficult to be able to disentangle exactly what drove those differences, due to different structures of the models. In this comparison for example all models agreed that modifying the eligibility criteria was very cost-effective, nevertheless three out of seven models, including the Synthesis model, found that the priority should be the expand access to care rather than modifying the eligibility criteria.

Subsequently I used the same model to evaluate the impact on resistance of expanding access to care including an improvement in retention on ART. These findings are presented in Chapter 5; on one hand, they can reassure decision makers regarding the fact that expanding the eligibility criteria should not increase the number of people carrying the NNRTI resistance mutations (and they should lead to a reduction in the total number of new HIV infections), on the other hand they should make them aware of the fact that a considerable proportion of people will be in need of more expensive second-line treatment. The price of the first-line regimen has been reduced dramatically over time in LMIC, and FDC for the first-line regimen have been available in South Africa since April 2013. Efforts should now be put in place to

reduce further the cost of second-line treatment, given many people will be in need of it in the future.

When addressing the question in Chapter 5, I realized that there are relatively few data available on resistance from RLS; VL monitoring is only performed in a few countries and resistance test data are very rarely available. It is well established that people who initiate ART should avoid interrupting treatment, given the detrimental effect on health (714); nevertheless ART interruptions do occur for various reasons. Data on people who interrupt ART are difficult to collect, given clinicians do not recommend this practice and it is unlikely that a resistance test is performed if a person interrupts treatment while on a suppressive regimen. The analyses presented in Chapter 6 on presence of resistance in people after TI, although performed on a relatively small sample size, are among the largest studies conducted to answer these questions. They have important implications for the transmission of drug resistant virus and confirm the fact that both the persistence of DRMs in people who have stopped treatment and the emergence of NNRTI resistance in people who interrupted suppressive ART are common phenomenon.

This analysis was conducted on the UK HIV drug resistance database, which contains resistance tests routinely performed in the clinics, linked with the UK CHIC study which contains clinical information on HIV patients from most of the large HIV clinics in the UK. Given TIs are not recommended any more, most of the data that contributed to these analyses are relatively dated and come from patients who potentially have been exposed to a large number of regimens and to less effective ones than those currently available. In addition, these data were collected in patients living in the UK, who are mainly infected with viral subtype B, therefore it is not possible to exclude that these estimates would be different in a setting such as sub-Saharan Africa, where the main subtype is C. It would be interesting to be able to collect information on ART interruptions and resistance mutations in patients on ART in South Africa to be able to refine my estimates on predictions of resistance in this country.

Different interventions have been evaluated in different settings to strengthen the cascade of care and some of them, such as POC CD4 counts, CBART programmes, and structural interventions including monetary supplements and food rations, have been found to be effective. In Chapter 7, I highlighted the fact that the step in the cascade at which an improvement (that reduces the loss by 50%) is more effective is retention on ART, this corresponds to an increase of 8% retained on ART at one year from initiation. The most cost-

effective intervention is to reduce the delay to switch people to second-line; this is the step at which more money can be spent given it provides the greatest health benefit. I provided the maximum cost the single intervention could cost in order to be cost-effective; this piece of information provides a useful framework to design interventions that could improve the cascade of HIV care. The time required to switch to second-line, once having experienced virological failure, are not available at a national level in South Africa. Nevertheless the delay in switching to second-line has been flagged up as an issue (500;501) and there is evidence from South Africa that in some clinics it is possible to reduce the time before switching to 5 months (499). However it is not clear how much it would cost to implement such an intervention and a similar situation is true for improving retention on ART. It would be interesting, now that I suggested that these steps in the cascade of care are those research should focus on, to assess how to achieve those improvements.

In addition, models which incorporate the process of being lost from care and of coming back into care, need to make assumptions regarding whether symptomatic people are more likely to come back to care. The evidence available is mainly anecdotal because it is very difficult to collect information on people who are disengaged from care.

I believe the findings in Chapter 8 are of key importance. ST has been approved by the FDA in 2012 (985), and several countries, stakeholders and donors, including the Bill and Melinda Gates Foundation who prompted this work, are now evaluating whether ST should be introduced and therefore whether investment should be made in marketing and distribution of this technology. To my knowledge, this is the first study which evaluated the cost-effectiveness of introducing ST in RLS. The finding that ST is not only cost-effective in a setting such as Zimbabwe but that it could even be cost-saving could contribute in convincing stake holders and decision makers in investing in the marketing and distribution of this diagnostic technology. The assumptions for this analysis are based mainly on the strong evidence coming from a study conducted in Blantyre, Malawi, for what concerns accuracy (871;872), probability of having a confirmatory test (872) and acceptability and uptake of HIV testing (872). It is clear that, if assumptions do not hold in other settings, the impact of ST could be very different, but there is no reason to believe this should be the case in a setting such as Zimbabwe or in other countries in sub-Saharan Africa.

In addition I highlighted the factors which mostly contribute to determine whether the introduction of ST is cost-effective; this should help informing what future research should focus on in this regard.

Generally, mathematical models can provide useful insights in the decision making process, nevertheless they depend on which evidence is available and on whether this is captured appropriately by the model. The fact that the Synthesis model was usually in line with the other models involved in the HIV Modelling Consortium is reassuring, although all models could be wrong because of each relying on the same incorrect assumptions or the same unrepresentative data.

When evaluating the impact and the cost-effectiveness of a policy it is standard to look at the impact over a relatively long time frame such as 20 years or even longer (e.g. life-time) to make sure the policy introduced has time to produce the full benefit. It is important to bear in mind that the longer the time-frame the more the estimates are characterized by uncertainty. I made quite conservative assumptions regarding the scale up of ART and of interventions such as VMC and I assumed, for example, that the ART regimens available would not change in the next 20 years, although this is unlikely to be true. It is standard practice to assume the current situation will remain for the length of the time frame, given it is unknown what and when the changes will be implemented in the future.

9.3. Concluding remarks

Decisions regarding how to expand access to ART in South Africa and whether Zimbabwe and other countries in sub-Saharan Africa should introduce ST are very complex. In this thesis I evaluated the cost-effectiveness of different strategies and highlighted the benefits and the disadvantages of the different options and in particular addressed the concerns regarding the spread of drug resistant virus. I hope this thesis will inform the decision making process regarding how to maximise health benefits in these countries and indicate where further research is needed to help refine my findings and make better informed decisions.

Appendix I. Licensed antiretroviral drugs

Class of drug	Generic name	Acronym	FDA approval (211)	Medicines Control Council South Africa approval (1020;1021)	Medicines Control Authority of Zimbabwe approval (1022)
NRTIs	abacavir	ABC	1998	2001	2002
	didanosine	ddI	1991	1992	Before 2004 (1023)
	didanosine	ddI EC	2000	2003	-
	emtricitabine	FTC	2003	2007	2013
	lamivudine	3TC	1995	1996	1997
	stavudine	D4T	1994	1998	2004
	tenofovir	TDF	2001	2007	2008
	zalcitabine	ddC	1992 (no longer marketed)	1993	Before 2004 (1023)
	zidovudine	AZT	1987	1992	1989
PIs	amprenavir	APV	1999 (no longer marketed)	2001	Before 2004 (1023)
	atazanavir	ATV	2003	2007	2010
	darunavir	DRV	2006	2010(1024)	2012
	fosamprenavir	FOS-APV	2003	2012	-
	indinavir	IDV	1996	1996	Before 2004 (1023)
	lopinavir and ritonavir	LPV/r	2000	2002	2003
	nelfinavir	NFV	1997	1999	Pending in 2003 (1023)
	ritonavir	RTV	1996	1997	2000
	saquinavir (hard gel)		1997 (no longer marketed)	1999	Not approved in 2003 (1023)
	saquinavir (soft gel)	SQV	1995	1997	Pending in 2003 (1023)
	tipranavir	TPV	2005	NL by Oct 2013 (1025)[1]	Not approved
NNRTIs	delavirdine	DLV	1997	NL by Oct 2013 (1025)[1]	Not approved in 2003 or by 2014
	efavirenz	EFV	1998	1999	2006
	etravirine	ETV	2008	2011 (1026)	Not approved
	nevirapine	NVP	1996	1998	2000
	rilpivirine	RPV	2011	NL by Oct 2013 (1025)[1]	Not approved
Entry inhibitor	maraviroc	MVC	2007	2013 (1027)	Not approved
Fusion inhibitor	enfuvirtide	T-20	2003	Not L by Oct 2013 (1025)[1]	Not approved

Class of drug	Generic name	Acronym	FDA approval (211)	Medicines Control Council South Africa approval (1020;1021)	Medicines Control Authority of Zimbabwe approval (1022)
Integrase inhibitors	raltegravir	RAL	2007	2011 (1028)	Not approved
	dolutegravir	DTG	2013	Not approved	Not approved
	Elvitegravir	-	2012[2]	Not approved	Not approved
Combined NRTI	abacavir + lamivudine	ABC+3TC	2004	2012(1029)	2013
	abacavir + zidovudine + lamivudine	ABC+AZT+3TC	2000	2003	2002
	emtricitabine + tenofovir	FTC+TDF	2004	2007	2009
	lamivudine + zidovudine	3TC+AZT	1997	2000	1999
	lamivudine + tenofovir	3TC+TDF	-	2012(1030)	2010
	lamivudine + stavudine	3TC+D4T	-	2010(1031)	2004
Multiclass combination	efavirenz + emtricitabine + tenofovir	EFV+FTC+TDF	2006	2010 (1031)	2010
	efavirenz + lamivudine + tenofovir	EFV+3TC+TDF	-	2012(1032)	2012
	efavirenz + lamivudine + zidovudine	EFV+3TC+AZT	-	2010 (1024)	2007
	nevirapine + lamivudine + stavudine	NVP+3TC+D4T	-	2010 (1033)	2004
	nevirapine + lamivudine + zidovudine	NVP+3TC+AZT	-	2011 (1034)	2006
	nevirapine + lamivudine + tenofovir	NVP+3TC+TDF	-	-	2013
	emtricitabine + rilpivirine + tenofovir	FTC+RPV+TDF	2011	2013 (1035)	-
	elvitegravir + cobicistat + emtricitabine + tenofovir	ELV+COB+FTC+TDF	2012	-	-

1 - The Medicine Control Council [South Africa] lacks a publicly accessible database of antiretrovirals registered since 2004, these drugs where not listed in the drugs registered; 2 - Elvitegravir and cobicistat have been approved only in fixed-dose combination together with tenofovir and emtricitabine;

EC: enteric-coated (this formulation has a delayed release); FDA: U. S. Food and Drug Administration; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor;

Appendix II. Toxicities to antiretrovirals most used in South Africa and Zimbabwe

Toxicities to stavudine

D4t is very well tolerated over the first 6 months but can lead to several serious side effects and it has been estimated in a study from South Africa that almost a third of patients discontinue d4T, due to toxicity within 3 years (645). The most frequently (>5%) reported adverse events of d4T are headache, nausea, lipodystrophy and peripheral neuropathy (644). The most serious adverse events are lipodystrophy, pancreatitis, lactic acidosis and steatohepatitis (rare) (644).

Peripheral neuropathy consists of nerve damage in the feet, legs, and hands, and may cause numbness, tingling, or severe pain in the extremities. This occurs in between 15 and 30% of people receiving d4T (643;646), particularly in those on higher doses, with more advanced HIV disease, or who were also taking ddI (1036). A study in Cambodia found that 7% of people developed peripheral neuropathy within the first year, 17% by the third year and 19% by the sixth year (1037). If d4T is stopped, the neuropathy usually gets better after about two weeks and if symptoms disappear, d4T can be restarted at half the recommended dose.

Another major concern with the use of d4t is the development of lipodystrophy, changes in body fat distribution and more specifically usually fat loss from the limbs, buttocks, and face. It can occur in between 30% (1038) up to 72% of those treated with d4T by 6 years (1037). A RCT comparing NRTI-containing and NRTI-sparing regimens in ART-naïve patients found higher frequency of lipoatrophy, defined as at least 20% loss in extremity fat, in people receiving d4t: 42% by 96 weeks of treatment (1039). Its prevalence in RLS has been estimated 34% in Rwanda (1038) and 46% in western India (1040). This side effect can have important psychological effects, such as depression (1041) and has also been found to be associated with increased risk of metabolic disorders and cardiovascular disease (CVD) (1042-1044), although the D:A:D study, a very large study including more than 30,000 HIV-infected patients in high income countries, failed to find an association between D4T and CVD (1045). This fat loss seems to stop after the dose of d4T is reduced to 30mg twice daily, stopped altogether (1046) or people are switched from d4T to ABC or TDF for example (1047-1049). Generally people who switch away from d4t tend to gradually gain limb fat over time, compared to those who continue on d4t, who generally lose limb fat (1048;1050;1051). Nevertheless, it has been observed to persist after 5 years in some studies, even if the implicated drugs are discontinued (1052).

Severe steatohepatitis, a type of liver disease, characterized by inflammation of the liver with concurrent fat accumulation in liver, and/or pancreatitis, a very serious condition characterised by sudden onset of abdominal pain, fever, vomiting or general worsening of health due to inflammation of the pancreas, can lead to a metabolic abnormality called lactic acidosis (1053). This is a life-threatening condition characterised by the following symptoms: nausea, fatigue, weight loss, abdominal pain, dyspnoea and eventual circulatory collapse (644). Its incidence in people receiving NRTIs has been estimated between 0.85 and 2.7/1,000 PYs (1054-1056), although higher rate up to 1% have been observed in southern Africa (1057;1058) and among women. A study of people initiating ART in South Africa and Soweto found a rate of lactic acidosis of 16.1/1,000 PYs among women and a much lower rate in men (1.2/1,000 PYs) (1059). Of all NRTIs, D4T has been associated with a two to three fold higher risk of having hyperlactatemia compared to people receiving AZT-based regimens (1060;1061). It usually develops within the first few months of treatment with d4T, and if NRTIs are not stopped it can lead to death.

Pancreatitis occurs in around 2-3% of people taking d4T monotherapy and <1% receiving d4T based-ART regimens although the risk of this occurring is greater in patients who have had pancreatitis in the past.

Less serious side-effects of d4T, which are most likely to occur during the early weeks of treatment, are nausea, vomiting, listlessness, chills, fever, diarrhoea, constipation, headaches, abdominal pain and dehydration.

Given the severe toxicities d4T can cause, especially peripheral neuropathy and lipodystrophy, a meta-analysis was conducted to re-assess whether a lower dose of d4T compared to that which was originally recommended (40mg twice daily), could reduce the side-effects without affecting the efficacy. They found a trend towards a lower frequency of side-effects at a lower dose but no difference in efficacy between doses of 40 mg, 30 mg or 20 mg. On the basis of this meta-analysis the WHO in 2007 recommended countries to switch to a 30mg dose (1062).

Despite these side effects, D4T played a critical role in the scaling up of ART, due to its low cost, availability in dual and triple FDC, easy intake (no administration with food or large amounts of liquids required) and no requirement of laboratory monitoring. In 2009, WHO recommended to phase out completely d4T (278), but at the end of 2009, 57% of HIV regimen in LMIC still contained d4t (1063). The generic combination of TDF, FTC and EFV, currently recommended as 1st line costs US $158 (with 3TC and EFV US $139), around 3-times more than d4t in combination with 3TC and NVP (US$ 55) (969). This has led to delay in phasing out d4T.

An RCT is currently ongoing in South Africa, Uganda and India led by Francois Venter evaluating whether low dose (20 mg) D4T is non inferior to TDF-based regimens (1064).

Toxicities to zidovudine

The severe toxicities which can occur when using AZT are lactic acidosis, lipoatrophy, anaemia (1-4%) and neutropaenia (1-2%), and the most common (>5%) are headache, asthaenia, nausea and nail pigmentation (644). In a study from South Africa it has been estimated that 8% discontinue AZT, due to toxicity within 3 years (645).

Hyperlactatemia can occur when receiving AZT, although the frequency is two to three folds lower than in people receiving d4T-based regimens, typically less than 1% (1060;1061). There is some evidence that AZT triggers lipodystrophy, but in smaller proportions than D4T. For example, a study comparing the proportion of people with leg fat measures <10% threshold value among people receiving respectively AZT or D4T found a prevalence respectively of 48% and 67% (1065) and a RCT comparing different NRTI-containing and NRTI-sparing regimens in ART-naïve patients found a frequency of lipoatrophy, defined as at least 20% loss in extremity fat, of 42% in people receiving d4t and of 27% in people receiving AZT by 96 weeks of treatment (1039). Switching away from AZT has been found to lead to gain in limb fat over time, compared to those who continue on AZT (1048;1050;1051;1066).

Anaemia consists of a decrease in number of red blood cells or in a reduction in Hb in the blood, and is usually accompanied by quite vague symptoms, but it has been found to be negatively associated with quality of life (1067), disease progression and survival (1068;1069). Presence of anaemia (Hb<10 g/dL) in HIV patients before starting ART is quite common and in Southern Africa is around 15 and 20% (647;1070;1071). Studies in patients receiving AZT generally found a substantial increase in Hb maintained at 48 weeks, both in high income (1072-1074) and low income countries (648), nevertheless the incidence of anaemia differs in the two settings.

In RLS the incidence of anaemia (Hb<10g/dl) in patients receiving AZT is very variable: 18.2/100 PYs in the Western Africa, 6.6 in Eastern Africa, 9.7 in Southern Africa, 22.9 in Central Africa, 11.8 in Asian, 19.5 in Caribbean and Central and South America regions (647). A study in Cambodia found that 13% developed anaemia within the first 6 months receiving AZT, 2.5% severe anaemia (1075). These data come from observational studies and it is possible that patients with documented Hb measurements are more likely to be at risk of anaemia than patients without assessment. Nevertheless in an analysis conducted in the DART trial (carried

out in Zimbabwe and Uganda) where patients with anaemia at baseline were excluded, 11.8% developed grade 2-4 anaemia, 6.6% grade 4 (Hb<6.5 g/dL) by week 48 (648) and in a RCT in Botswana 3.7% developed anaemia (Hb<10 g/dL) within 2 years (1076). AZT has been found to double the risk of anaemia, but other factors have a similar impact including higher VL, lower Hb levels before starting therapy, female sex, older age, previous clinical AIDS disease, low CD4 and BMI and African American ethnicity (645;647;648;1068;1070;1075-1077).

Neutropaenia is a condition characterized by an abnormally low number of neutrophils, a type of white blood cell whom main function is to defend against infections by destroying bacteria in the blood. Thus, patients with these condition are more susceptible to bacterial infections (1078) and, without medical intervention, the condition may become life-threatening (neutropenic sepsis). These episodes tend to last around two weeks (1079). The prevalence of neutropenia (absolute neutrophil count $\leq 1.3\times10^{9}$/l) at initiation of ART has been estimated to be 14% but there is significant variation across regions (1071). This study used data from the US, Haiti, Brazil, Peru, Malawi, South Africa, Zimbabwe, India and Thailand and found for example that the prevalence of neutropaenia in the US and South Africa were around 15%, but levels above 25% were found in Malawi (1071). In the phase II RCT for AZT absolute neutrophil counts fell after 12 weeks of treatment to < 1000/ul and < 500/ul respectively in 24% and 7% of patients with AIDS (216). A meta-analysis evaluating the impact of AZT-containing regimen compared with D4T-containing regimens reported a prevalence of neutropenia (at least on dose below 1500 mg) varying from 26% to 43% in patients receiving AZT compared to 15% to 31% in patients on d4T (1080). In a study on patients with neutropenia they evaluated the incidence of bacterial infections, if AZT was temporarily discontinued only when the polymorphonuclear leukocytes (PMN) cell count fell to <500/µl (1081). They found that the incidence of bacterial infection during periods of severe neutropenia (PMN <500/µl) in patients receiving AZT was 230% higher than when the PMN count was between 500-1000/µl, and 600% higher than when the count was > 1000/µl, but no significant difference in incidence of bacterial infections in patients with the PMN count between 500 and 1000/µl and non-neutropenic periods, suggesting that AZT can be continued in patients with PMN of 500/µl. This was confirmed in subsequent studies. A RCT conducted in Botswana comparing different ART regimen options in ART-naïve people found that at 2 years since initiating AZT 2.3% developed neutropaenia which resulted in treatment modification, not significantly different from the level observed in people receiving d4t (1076).

Less serious side effects such as headache, asthaenia (a condition characterized by lack of muscle strength, malaise, dizziness, or fatigue), nausea and nail pigmentation are quite

common (>5%) (644). Medicines to control nausea and headache are usually prescribed before starting AZT.

Toxicities to didanosine

ddI presents similar severe adverse events to D4T and AZT: lactic acidosis, steatohepatitis, pancreatitis (1-7%) and peripheral neuropathy. The most common adverse events (>5%) are nausea and diarrhoea (644).

As mentioned before, both severe steatohepatitis and pancreatitis, which occur respectively between 1-2% and between 8% and 23% (1082-1084) when using ddI monotherapy, can cause lactic acidosis (1053). Pancreatitis usually develops after 10-18 weeks of treatment and represents one of the most important clinical toxicities of this agent (1083): 14% of the reported cases with ddI-induced pancreatitis were fatal cases (1085). Lactic acidosis is rare. ddI has been found to double the risk of hyperlactatemia (> 5 mmol/l, including those with acidosis), estimated to be 7.3/1,000 PYs, while the rate of lactic acidosis is 3.2/1,000 PYs (1086).

Peripheral neuropathy also represents an important ddI-induced toxicity. It has been observed after 18 to 30 weeks of treatment in around 15% of patients exposed to it (1083). Nausea and diarrhoea are quite common and tend to occur in the first few weeks.

Toxicities to lamivudine and emtricitabine

3TC and FTC, in contrast with other NRTI, are largely safe drugs. Their commonest side-effects are headache, fatigue, and nausea, which tend to occur during the first weeks of treatment and to subside over time. Other less common side-effects include decreased appetite, diarrhoea, skin rash, and abdominal pain. In those infected with HBV, rebound of HBV viraemia which can lead to culminant hepatitis can occur in patients discontinuing these drugs (644). In addition if they are used as the sole anti-HBV agent in HIV-positive people co-infected with HBV, resistance develops in 90% by 4 years with similar rebound phenomena seen.

Toxicities to tenofovir disoproxil fumarate

TDF does not have any common adverse events (>5%), but can have some serious events such as nephrotoxicity (a decline in kidney function acute or chronic secondary to a toxin, including

drugs), osteopaenia and exacerbation of HBV infection (in those co-infected) after withdrawal (644).

Renal function is usually expressed in terms of creatinine clearance, which is a surrogate measure of glomerular filtration rate. It is generally considered normal if the estimated glomerular filtration rate (eGFR) ≥90 ml/min, mild renal dysfunction if the eGFR is between 60 and 89 ml/min, moderate renal dysfunction if the eGFR is between 30 and 59 ml/min and severe renal dysfunction if eGFR<30 ml/min (1087). People infected with HIV, particularly those with pre-existing renal dysfunction are at higher risk of nephrotoxicity (1088-1094); a meta-analysis conducted in the US estimated a 3.87 higher risk of renal disease in people infected with HIV compared with uninfected people and a 3.32 higher risk for people with AIDS compared to others (1095). There is evidence that people in Africa have a 3 to 4 fold higher risk of chronic kidney disease (CKD) compared to people in high income countries (1096) and that generally people of African descent are at increased risk of renal failure (1097). Other risk factors of renal failure include CD4 cell count, late stage of HIV and age (1095). Glomerular proitenuria (large amounts of protein in the urine) has been found to be associated with older age, current use of TDF, HCV co-infection, AIDS and a CD4 count less than 200 cells/μL (1098). The DART trial reported that at baseline 45% of HIV-positive participants had mild renal insufficiency (eGFR between 60 and 89 ml/min/1.73m (2)), but in only 7% was moderate (eGFR between 30 and 59 ml/min/1.73m (2)), and 0.2% grade 3 or 4 (1099). In South Africa the prevalence of mild renal dysfunction was 30%: 5.2% had moderate renal dysfunction (1090) and 6% CKD (1100); in Zambia 25% had mild renal dysfunction, 7.8% moderate and 1.0% severe (1101).

TDF is associated with a glomerular toxicity, a direct tubular disease and a 10% reduction in eGFR during the first year which then seems to reach a plateau (610;1102;1103). An analysis including ART-naïve patients involved in two RCTs in Europe, the US and South America comparing TDF found small differences in eGFR but failed to find clinically relevant renal disease or adverse events (1104). The incidence of renal serious adverse event of any type in patients receiving TDF was estimated to be 0.5/100 PYs and of graded increase in serum creatinine 2.2% (644). In prospective observational studies 2-3% of patients receiving TDF for an average of 1 year developed moderate or severe renal dysfunction (eGFR<60 ml/min) (1091). In Eurosida, for example, they found that HIV-positive people exposed to TDF for more than 3 years had an incidence of CKD approximately of 2.5/100 PYs compared with an incidence around 0.8 for people who were not exposed to TDF (1105). A large observational study conducted in the US came to a similar conclusion with a 34% increased risk of

proitenuria, 11% greater risk of rapid decline in kidney function (defined as ≥3 ml/min per 1.73 m^2 annual decline) and 33% higher risk of CKD per year of exposure to TDF (1106). A meta-analysis of prospective studies including RCT and observational studies found a significantly higher loss of kidney function among people receiving TDF compared with control subjects (mean difference in calculated creatinine clearance approximately 4 mL/min), but a quite modest clinical manifestation: 0.7% higher risk (risk difference) of acute renal failure, no evidence of increased risk of severe proteinuria (1107). A more recent meta-analysis found that people on ART had a 46% reduction in risk compared to treatment-naïve people, while people who had been exposed to TDF had a 56% increased risk of renal failure compared to people treated with non-TDF therapy (1095). In the DART trial, by 4 years 2.8% experienced an eGFR<30 ml/min/1.73m^2 and 5.0% CKD and the adjusted eGFR increased by respectively 1, 9 and 6 ml/min/1.73m^2 with respectively TDF, ABC and NVP (1099). In a cohort study in South Africa 2.4% experienced nephrotoxicity and the rate to develop it for those with respectively normal, mild and moderate dysfunction at baseline were 0.4, 2.5 and 10.7/100 PYs (1090). Of those who developed nephrotoxicity, it has been observed that 28.6% subsequently died with a median of 2.3 months since nephrotoxicity diagnosis (1090). Few studies evaluated the risk of mortality in HIV-positive patients according to their baseline renal functionality. A study conducted in Zambia found respectively a 70%, 130% and 330% increased risk of mortality at or before 90 days in those with mild, moderate and severe reduced creatinine clearance. After 90 days they were still at higher risk of mortality compared to those with normal renal function: 1.4 folds for those with mild dysfunction, 1.9 for those with moderate and 3.6 for those with severe insufficiency (1101).

Osteopaenia, osteoporosis and osteonecrosis have been observed in ART-naïve and ART-treated patients. It is unclear the role ARVs play in reducing bone mineral density (BMD). Osteonecrosis is a condition caused by reduced blood flow to bones in the joints and can cause pain, arthritis and limited use of the joints interested. The prevalence of symptomatic osteonecrosis in HIV-infected patients has been estimated between 0.1 and 1.3% and asymptomatic osteonecrosis at 4% (1108). The odds of having a reduction in BMD in HIV-positive adults has been estimated 6.4 fold and the odds of osteoporosis (a BMD of 2.5 standard deviations or more below the mean peak bone mass which is the average of young, healthy adults) 3.7 fold compared with uninfected controls (1109). A RCT comparing d4T and TDF found a higher decrease in BMD from baseline in people receiving TDF compared to d4T (610). TDF has been found associated with a slightly increased risk of osteopaenia over 3 years (lumbar spine) but not with increased risk of fracture (610).

In addition if TDF is interrupted in people with HBV, against which TDF is active, this can lead to rebound of HBV DNA levels ("flares") (1110-1112) which can cause fulminant hepatitis.

Finally, rare cases of lactic acidosis in people receiving TDF have been reported (1113).

Toxicities to efavirenz

Use of EFV is usually accompanied by few common (>5%) adverse events related to the CNS, such as headache, dizziness, insomnia, vivid dreams (>50%) and increased alanine transaminase levels and some severe adverse events such as rash, hepatotoxicity (HT), Stevens-Johnson syndrome and fetal CNS malformations (644).

CNS side effects tend to occur in over half of the patients receiving EFV during the first one to four weeks of therapy (259;1114) and tend to be resolved by week 4 (259;1115). Nevertheless, symptoms like mild anxiety and bad dreams may last in up to 50% of patients for more than six months (1116;1117), even after two years since initiating (1118). They are generally only mild to moderate symptoms and only a small minority discontinue EVF because of CNS side-effects (in a RCT 6% (1115)). This toxicity seem to occur more frequently in African American than in European-Americans (1119;1120) and this is at least partially explained by different prevalence of polymorphism in the cytochrome which metabolizes EFV, associated with slower EFV clearance, increasing the exposure to EFV and the risk of developing CNS toxicity (1121;1122). Recent studies have reported that switching from the combination EFV, TDF and FTC to the combination containing RPV, FTC and TDF improves CNS side effects (1123).

In people taking EFV, a mild-to moderate rash can develop within two weeks from initiating EFV-based ART in approximately 10 to 35% of the patients in RCTs (259); usually it can be controlled using antihistamines and it resolves within around two to four weeks since initiating EFV-based therapy and it does not tend to lead to discontinuation of EVF (2% or less in RCTs) (259;1124). The incidence of severe rash, such as erythema multiforme and in particular Stevens-Johnson syndrome, in patients receiving EFV has been estimated to be around 0.1% (644). Stevens–Johnson syndrome is a form of a life-threatening skin condition, in which cells die, because the epidermis separates from the dermis.

HT has been found to be associated with most ARVs, including EFV (1125). In high income countries, the monitoring of patients on ART are primarily based on serum alanine transaminase and aspartate transaminase (AST) levels, liver enzymes that serve as a 'proxy' for liver inflammation and damage. HT is classified into five categories (grades 0–4) (1126):

- grade 0: <1.25 fold the upper limit of normal (ULN);

- grade 1: 1.25–2.5 fold the ULN;
- grade 2: 2.6–5.0 fold the ULN,
- grade 3: 5.1–10 fold the ULN;
- grade 4: >10 fold the ULN

The mechanism through which severe HT (grade 3 or 4) develops is direct antiretroviral toxicity, hypersensitivity, immune reconstitution in people with chronic viral hepatitis and steatohepatitis, which has been discussed earlier. HT has been reported in around 2% of patients taking EFV, of which around 60% grade 3 and 20% grade 4 (1127). 50% of those with grade 3 HT had clinical signs or symptoms identified and most of those with grade 4 HT; nevertheless, in the first 6 months, HT has not been found to be associated with an increased risk of mortality (1127). HT tends to be more common in patients co-infected with HBV or HCV (1128), for example in an observational study in patients receiving EFV they found that the incidence of severe HT was 0/100 PYs in patients not co-infected with HCV and 10% in patient co-infected with HCV (1128). The prevalence of HCV in patients infected with HIV is not negligible: 34% in the Eurosida study (1129), 7.2% in Thailand (1130) and generally less in Africa with an estimated prevalence of 1.9% in the CAESAR study conducted in South Africa (1131) and 8.2% in a small study conducted in Nigeria (1132).

There is limited evidence that, in pregnant women, EFV may harm the fetus during the first trimester, while in the second and third trimester EFV use is safe (644). In the early 2000s retrospective case reports were published of babies born with severe abnormalities attributed to neural tube defects (myelomeningocele), who had been exposed to EFV during the early phase of gestation (1133;1134). This led the manufacturer and the FDA to recommend avoiding the drug to pregnant women in March 2005 (1135). Nevertheless it is difficult to ascertain whether the incidence of abnormalities in babies is higher in women taking EFV compared to women not taking it and the causal relationship between EFV and birth defects. A systematic review and meta-analysis of prospective studies observed that treatment with EFV during the first three months of pregnancy did not increase the risk of birth abnormalities (1136). The overall incidence of birth abnormalities, in children born from women who received EFV in the first trimester of pregnancy, was 2.9%, and the prevalence of neural tube defects was 0.08%, comparable to ranges reported in the general population in many developed and developing countries. Nevertheless, many of the studies included in the meta-analysis are characterized by small sample size and in some they did not control for confounding factors. Up against the ambiguity regarding the possible causal relationship

between EFV and birth defects, women receiving EFV are advised to use barrier contraception for vaginal sex and an additional form of contraception, such as oral contraceptives.

Toxicities to nevirapine

NVP is characterized by few severe adverse events similar to EFV, such as rash, HT and Stevens-Johnson syndrome and NVP hypersensitivity reaction; with the only common (>5%) adverse event being an increase in transaminase levels (644). In a study from South Africa it has been estimated that 8% of the patients discontinue NVP due to toxicity within 3 years (645).

In the first RCTs, approximately 10% to 35% of people initiating NVP based ART regimen developed skin rash within one to four weeks of treatment (253;254;1137;1138). Subsequently, it was found that starting treatment with half the dose recommended and increasing it to reach the full dose within four weeks could reduce NVP-associated rash to approximately 5% and discontinuation due to NVP-associated rash down to 2% or less (1139;1140). Usually the rash resolves after two to four weeks (1140) and thereafter, most of the patients experience very few or no side-effects. In 2008 the FDA issued safety labelling revisions for NVP, recommending discontinuation of NVP in patients who experienced severe rash or any rash with constitutional symptoms and to wait increasing the dose in patients experiencing mild to moderate rash without constitutional symptoms during the 14-day lead-in period of 200 mg/day until the rash has resolved, with a maximum total duration of the once daily lead-in dosing period of 28 days (1141). Stevens-Johnson syndrome is quite rare in patients receiving NVP with an incidence between 0.2% and 0.6% (644;1139;1140).

HT represents one of the primary concerns regarding NVP use (264;294;1128;1142-1145).

Both skin and hepatic reactions are hypersensitivity reactions which can occur in patients receiving NVP. The risk of HT has been estimated in a meta-analysis of RCTs conducted by the manufacturer to be 10.7% (1145), with extremes as high as 17% in an RCT conducted in South Africa (294). A recent trial in high income countries found a risk of 7% (1139). Similar estimates come from observational studies with a rate of severe HT varying from 18.6/100 PYs in patients receiving NVP in Thailand (1130) to as low as 1.1/100 PYs in a small study conducted in New York City with lower prevalence of HBV (9%) and HCV (12%) (1146). The presence of HCV (1142) or HBV (1128;1130) has been found to increase the risk of severe hepatoxicity by 2 to 4 fold.

Around half of these hepatic reactions are accompanied with fever, rash or arthralgia and less by severe rash, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial edema, and only rarely, Stevens-Johnson syndrome or toxic epidermal necrolysis. These symptoms are signs of a hypersensitivity reaction which is likely to be linked to at least some of these hepatic failures. In the 2NN study, where NVP and EFV were compared, significantly more hepatobiliary abnormalities in people receiving NVP than EFV were observed and more frequently in those receiving once rather than twice daily NVP (264). Most of these transaminase elevations associated with NVP use occur within the first four, six weeks (1139;1145); thereafter the incidence is not greater than with other ARVs (1145). An RCT comparing the new NVP extended release (NVP XR) formulation dosed once daily to the NVP immediate release (NVP IR) found that 4.8% in the NVP XR had grade 3 or 4 alanine aminotransferase (ALT) abnormalities compared to 7.1% in the NVP IR group (1139). Hepatic events occurred in 9.1% of patients in the NVP IR group compared to 5.5% in the patients receiving NVP XR, but a much smaller proportion had symptoms of hepatitis: respectively 2.4% and 1.6% (1139).

Analysis of reported events seems to suggest that women with high CD4 cell counts are at higher risk for symptomatic, even life-threatening, hepatic events (294;1147). Women have been found to have approximately a double risk of experiencing hepatic event, symptomatic hepatic event or grade 3 or 4 transaminase increase compared to men (1139). Contrasting results have been reported regarding the occurrence of HT in patients at different levels of CD4 cell count. Analysis of RCTs found a higher risk of HT in women than in men and in patients with higher CD4 cell counts (1147). Two women (0.5%) who received NVP in the non-comparative trial FTC-302, died from fulminant hepatic failure and both had CD4 counts >400 cells/µL (1147). Women who initiated NVP with a CD4 counts above 250 cells/µl had an incidence of symptomatic hepatic events 10-fold greater than in women with CD4 counts of 250 cells/µl or less at NVP initiation and among men, those with CD4 counts greater than 400 cells/µl at NVP initiation had a 6 fold risk compared with men with CD4 counts of 400 cells/µl or lower at NVP initiation (6.3% vs. 1.2%) and for some patients, hepatic injuries continued to progress even after interrupting NVP (1147). Other studies have not found an association between CD4 cell counts at NVP initiation and severe NVP HT (1148;1149). A meta-analysis published in 2008 found no statistically significant difference in the occurrence of HT between those with high and low CD4 count (1150).

On the basis of the safety and efficacy data, mainly from RCTs, in 2005 the FDA and the European Medicine Agency added warnings in the NVP product information recommending against the use of NVP in adults men with a CD4 count >400 cell/µl and in women with a CD4 count >250 cell/µl, with the exception of situations where the benefits outweigh the risk beyond doubts (1151). The ART guidelines recommend not using NVP-based combinations as first regimen in women with CD4 count >250 cells/µl at ART initiation or in men with CD4 count >400 cells/µl (281), while patients on ART with CD4 count above these thresholds as a consequence of NVP-containing therapy can safely continue the regimen they are on without an increased risk of adverse hepatic event (1152).

Some studies have reported that pregnant women have an increased risk of severe HT (1153). Nevertheless, a meta-analysis evaluating the safety of NVP in pregnant women, estimated a 39% lower risk of NVP-toxicity in women with CD4 <250 cells/µl compared to pregnant women with higher CD4 cell count, with consistent results when restricting to prospective studies or to severe HT (1154).

Toxicities to lopinavir boosted with ritonavir

The adverse event which can sometimes occur with LPV/r are hepatoxicity and nephrotoxicity, while common (>5%) adverse events include hypertriglyceridaemia, hypercholesterolemia, asthaenia, nausea and diarrhoea (644).

In ART-naïve patients, LPV/r can cause moderate to severe elevation (grade 3 or 4, >5 ULN) in serum aminotransferase: in 1-12% elevation of ALT and between less than 1% up to 10% of AST (1155;1156). The incidence does not seem to differ if the dose is once or twice daily (1157;1158) and it does not seem to differ from other boosted PIs (251;1159-1162).

These elevations are usually asymptomatic and can usually resolve even without modifying the ART regimen. In patients ART-experienced similar frequencies (<10%) of aminotransferase elevations have been observed, similarly to other boosted PIs (1155;1163-1166).

LPV/r seems to lead to chronic renal impairment (1105), when administered in combination with TDF (1167-1169), even when selecting people without previous impairment (eGFR of≥90 mL/min) independently of being co-administered with TDF (1170). In particular the rate of progression to a confirmed eGFR<70 mL/min seem to be increased by 11% per year of exposure to LPV/r while the rate of developing CKD seem to be increased even more (adjusted incidence rate ratio: 1.22 per year of exposure) (1170).

PIs, including LPV/r, have been associated with a higher increase in lipid levels, in particular in total cholesterol and low-density lipoprotein cholesterol levels, than NNRTIs, which are known to increase levels of high density lipoprotein cholesterol (1171), body fat changes and metabolic disorders. Body fat changes have been estimated to occur in 35% of patients after four years on LPV/r *(1172).* Among 10 and 25% of people receiving LPV/r experience elevated lipids, in particular those with high cholesterol or triglycerides before initiating treatment (1172-1175). These increases in lipids are mild in most of them and treatment discontinuation related to lipid elevation is rare (1176;1177). The increase in blood cholesterol and triglyceride levels is due to the low-dose RTV rather than the LPV component (1178).

A few studies found an association between CVDs and use of PIs (1179-1181). The D:A:D study, a very large observational study, estimated the incidence of myocardial infarction (MI) in people not exposed to PI to be 1.53/1,000 PYs, while in people exposed to PI for more than 6 years to be 6.01/1,000 PYs (1181). The RR of MI per year of exposure to PIs, adjusting for exposure to other drug classes and CVD risk factor (except for lipids), is 1.16 (95% CI: 1.10, 1.23), compared to 1.05 per year of exposure to NNRTIs. This increased risk was only partially explained by increased in lipid levels, and in particular by total cholesterol and high density lipoprotein while the other half was unexplained (1181). A more recent analysis conducted on the D:A:D study (1182), evaluated the risk of MI for specific ARVs and found an increased risk of MI in people exposed to LPV/r (relative rate per year of exposure of 1.13; 1.09 [95% CI: 1.01, 1.17] after adjusting for lipids but not reduced further after adjusting for other metabolic parameters). A case-control study nested within a cohort study conducted in France (1183) also found a significant increase in risk of MI for LPV/r (1.33; 95% CI: 1.09, 1.61 per year) and the other PIs, with the only exception of SQV. A meta-analysis published in 2013 (1184) estimated a RR of MI in people recently exposed (usually defined as within last 6 months) to PI of 2.13 (95% CI: 1.06, 4.28) and a RR of MI of 1.22 (95% CI: 1.01, 1.47) per additional year of exposure to LPV. These results are in contrast with a previous meta-analysis based on secondary analyses of RCTs, which found no increased risk from CVD in people exposed to PIs for an average of 1 year, compared with people exposed to NRTI-only (1185).

The most common side-effects when using LPV/r, as mentioned, are asthaenia, nausea and diarrhoea. Moderate or severe diarrhoea occurred in around 15% to 20% (1156;1157) in people receiving once-daily compared to between 5% and 15% in people receiving twice-daily LPV/r (1156;1157) in RCTs. The initial onset of this side effect tends to occur in the first week and after 4 months in less than half of those who experienced this side effects it still persists (1157). Nausea is quite common as well occurring in around 10% of study participants (644).

Toxicities to atazanavir boosted with ritonavir

ATV is characterized by several of serious adverse events: first degree atrioventricular (AV) block and nephrotoxicity, including nephrolithiasis and by a common (>5%) adverse event, indirect hyperbilirubinaemia, an increase in bilirubin levels in the blood (644).

The hyperbilirubinaemia induced by ATV is the commonest side effects, occurring in up to 45% of patients taking ATV. This side effect tends to appear during the first week of starting ATV. It does not seem to be clinically relevant, no correlation has been found between increase in bilirubinaemia and hepatic transaminase levels (1186), but can cause jaundice, a yellowing of the skin and the whites of the eyes. A large study of ART-naïve patients reported that 33% experienced severe hyperbilirubinaemia, but only 5% developed jaundice and less than 1% discontinued treatment because of hyperbilirubinaemia (1187). Studies in PI experienced patients, found higher incidence of grade 3-4 bilirubin elevations (≥2.6 ULN), up to 49% in those receiving ATV/r and 20% in those receiving ATV/SQV, of which respectively 9% and 2% very severe (grade 4), but none of the patients discontinued because of this side effect (1163). There seems to be a dose relationship between ATV, occurrence of jaundice and discontinuation because of this side effect: with 6% of patients experiencing jaundice with a dose of 200 mg and 400 mg and 12% if the dose is 500 mg and with discontinuation of respectively 5%, 6% and 9% with doses of 200 mg, 400 mg and 500 mg (1186).

There is evidence that ATV prolongs the PR interval of the electrocardiogram in some patients, reflecting abnormalities in AV conduction (1188). These abnormalities, in healthy volunteers and in patients, have been found to be asymptomatic and generally limited to first-degree AV block. The prevalence of asymptomatic first-degree AV block in RCTs where electrocardiograms were conducted, was 5.9% in patients treated with ATV, 5.2% in patients treated with LPV/r and 10.4% in patients treated with nelfinavir and 3.0% in patients treated with EFV (1188).

Subsequent studies reported a prolongation of the PR interval of the electrocardiogram at 1 month since switching from other PIs to ATV (1189). Another studies of 75 patients receiving ATV found that at 1 year since start taking it, 56 individuals had a median increase in QRS interval of 5 milliseconds, new asymptomatic bundle blocks were observed in 4 patients and one further patient receiving the β-blocker atenolol developed first-degree AV block (1190). They also observed increases in PR interval after 1 year but these were not statistically significant.

The association between ATV and the risk of developing CKD seem to be even stronger than the association between LPV/r and renal outcomes in combination with TDF (1167;1168;1191) or not (1105), and even in patients without previous renal impairment (1170). In particular the D:A:D study found that ATV increase the rate of progression to a confirmed eGFR <70mL/min by 19% per year of exposure (1.19; 95% CI: 1.09, 1.32) in patients with an eGFR ≥90 mL/min before starting ATV/r (1170). ATV/r has been found associated as well with other renal impairments, such as acute interstitial nephritis (1088;1192), abnormal proximal renal tubular function (1193) or nephrolithiasis, calculi in the kidneys (1194-1196) which can result in renal failure (1197). These impairments are quite rare compared to for example the nephrotoxicity due to TDF.

Appendix III. List of standard abbreviations for amino-acids

Amino acid	3-letter	1-Letter	Nucleotide triplets
Alanine	Ala	A	GCU,GCC,GCA,GCG
Arginine	Arg	R	GCU,CGC,CGA,CGG,AGA,AGG
Asparagine	Asn	N	AAU,AAC
aspartic acid	Asp	D	GAU,GAC
Cysteine	Cys	C	UGU,UGC
glutamic acid	Glu	E	GAA,GAG
Glutamine	Gln	Q	CAA,CAG
Glycine	Gly	G	GGU,GGC,GGA,GGG
Histidine	His	H	CAU,CAC
Isoleucine	Ile	I	AUU,AUC,AUA
Leucine	Leu	L	UUA,UUG,CUU,CUC,CUA,CUG
Lysine	Lys	K	AAA,AAG
Methionine	Met	M	AUG
Phenylalanine	Phe	F	UUU,UUC
Proline	Pro	P	CCU,CCC,CCA,CCG
Serine	Ser	S	UCU,UCC,UCA,UCG,AGU,AGC
Threonine	Thr	T	ACU,ACC,ACA,ACG
Tryptophan	Trp	W	UGG
Tyrosine	Tyr	Y	UAU,UAC
Valine	Val	V	GUU,GUC,GUA,GUG

A: adenine; G: guanine; C: cytosine; U: uracil; T: thymine;

Appendix IV. Fertility and prevention of mother-to-child transmission in South Africa

Fertility

Fertility estimates in South Africa are calculated through household surveys and census data, because it was only in the 1990s that South Africa started having regular collection of national data of vital events, and unfortunately births are still not universally reported.

South Africa is characterized by the lowest fertility rates in sub-Saharan Africa and this has been so since 1960 (595). Table A.1 shows the total fertility rate and the average number of children ever born per woman.

Table A.1. Fertility in South Africa

Source	Year	Women age group	Total fertility rate (births per woman)	Average number of children ever born per woman
World Bank (1198)	1996	-	3.04	-
	2001	-	2.84	-
	2006	-	2.63	-
	2007	-	2.58	-
	2011	-	2.44	-
Population census (595)	2006	-	2.84	-
Community survey (595)	2006	-	2.80	-
	2007	15-24	-	0.361
		25-34	-	1.496
		35-44	-	2.726
		45-49	-	3.202

Prevention of mother-to-child transmission

A PMTCT national programme was introduced in South Africa only in 2002 after the court ordered the South African government to develop one within a year (1199). Nevertheless in 2005 just under 50% of pregnant women were tested for HIV.

In 2008 the Department of Health released guidelines for the implementation of the PMTCT programme (1200) recommending:

- AZT and NVP from 28 weeks' gestation

- NVP treatment for pregnant women during labour and for the babies within 72 hours since birth
- ART for pregnant women with a CD4 count below 200 cells/μL

In the same year, given the MTCT coverage was still around 12%, a national PMTCT accelerated plan ("The A-plan") was rolled out, to ensure the NSP target of reducing MTCT to 5% by 2011 was achieved (1199).

By 2010, 98% of health facilities were offering PMTCT, 87% of HIV-positive pregnant women were receiving ART to reduce PMTCT and MTCT at six week was estimated to be 3.5% (450).

In 2010, new guidelines for PMTCT were released in South Africa (1201), recommending:

- AZT from 14 weeks,
- ART for pregnant women with CD4 cell count of 350 cells/μL or less
- NVP prophylaxis to the baby for six week (if the mother is on ART or not breastfeeding) or until one week after the cessation of breastfeeding

In 2011 MTCT dropped even further from 3.5% in 2010 to 2.7% in 2011 (473).

In 2013 PMTCT guidelines have been revised to offer:

- ART for all HIV-positive pregnant women for the breastfeeding period with a CD4 count above 350 cells/μL or forever if already eligible for ART according to national guidelines (CD4 of 350 cells/μL or less or with TB).
- ART for all babies born from HIV-positive mother (regardless of the mother's CD4 count or stage)

Appendix V. Virological suppression in South Africa

Source	Population	Year	Follow-up months, median (IQR)	Definition of virological suppression	% with virological suppression (95% CI)
Orrell (489)	289 ART-naïve patients in a university clinic in Cape-Town	1996-2001	-	VL<400 copies/mL of those on triple ART	11 months: 70.9%
Nachega (487)	66 patients in Chris Hani Baragwanath Hospital's Adult HIV Clinic in Soweto	-	18	VL<400 copies/mL of those on ART	73% (if adherence >95%); 88% (if adherence ≤95%)
Coetzee (477)	287 patients starting ART in a public community based programme in Khayelitsha	2001-03	13.9	VL<400 copies/mL of those on triple ART	3 months: 88.1% 6 months: 89.2% 12 months: 84.2% 18 months: 75.0% 24 months: 69.7%
Barth (306)	313 patients in Limpopo (rural) receiving 1 NNRTI and 2 NRTIs as 1st line regimen	2003	-	Achieved VL<50 of those on ART	12 months: 73%
Wouters (1202)	268 in the Free State public sector ART program (eligible if CD4 count <200 cells/ml and/or WHO stage 4)	2004	-	VL<400 copies/mL of those on ART	6 months: 83.5% 12 months: 84.7%
Orrell (307)	929 ART-naïve patients in Nyanga district, near Cape Town	2002-05	6 (3-14). Total 760 PYs	VL<400 copies/mL of those on ART	12 months: 96% 24 months: 96%
				VL<50 copies/mL of those on ART	12 months: 85% 24 months: 85%
Badri (1203)	360 patients enrolled in the Cape Town AIDS Cohort through participation in multicentre phase III RCT	1996-2006	24.7 (4.7–51.6) Total 591 PYs	Achieved VL<400 copies/mL	91.7

Source	Population	Year	Follow-up months, median (IQR)	Definition of virological suppression	% with virological suppression (95% CI)
Boulle 2008 (1204)	3970 patients starting NVP or EFV based ART (some with concomitant rifampicin-based antitubercular therapy) in a community–based ART program	2001-06	-	VL<400 copies/mL of those on ART	At 6 months: NVP no TB: 91.7 (90.0-93.3) NVP TB: 83.7 (76.5-89.4) EFV no TB: 94.3 (91.6-95.3) EFV TB: 93.6 (91.6-95.3) At 12 months: NVP no TB: 87.8 (85.3-90.0) NVP TB: 80.0 (71.5-86.9) EFV no TB: 91.9 (89.0-94.3) EFV TB: 92.0 (89.0-94.4) At 18 months: NVP no TB: 86.0 (82.7-88.8) NVP TB: 80.0 (69.6-88.1) EFV no TB: 89.6 (84.9-93.2) EFV TB: 88.5 (83.5-92.4)
Barth (496)	609 ART-naïve adults in a PHC with GP administering ART in Elansdoorn (rural)	2003-06	-	VL<400 copies/mL of those on ART	12 months: 83%
				VL<400 copies/mL of those initiated on ART	12 months: 55%
				Achieved VL<400 of those on ART	12 months: 94%
				VL<50 copies/mL of those on ART	12 months: 70%
				VL<50 copies/mL of those initiated on ART	12 months: 46% 24 months:18%
				Achieved VL<50 of those initiated on ART	12 months: 83%
Gandhi 2009 (1205)	119 TB/HIV co-infected patients enrolled in ART programme in a government hospital in Msinga in KwaZulu-Natal	2003-06	-	VL<400 copies/mL of those on ART	6 months: 83% 12 months: 88%

Source	Population	Year	Follow-up months, median (IQR)	Definition of virological suppression	% with virological suppression (95% CI)
Bedelu (843)	NGO programme in Lusikisiki (Eastern Cape)	2004-06	-	VL<400 copies/mL of those on ART with VL measurement (n=296)	12 months: 89.5 (85.5–92.8)
Boulle (292)	7,323 in 3 public PHCs in Khayelitscha in Western Cape	2001-07	-	VL<400 copies/mL of those on ART	12 months: 87.6% 36 months: 88.1% 60 months: 83.8%
Innes (495)	1416 patients initiating ART (eligible if CD4 <250 cells/µL, a WHO stage 4 condition or a WHO stage 3 condition and CD4 count <350 cells/µL)in a multisite workplace programme	2002-07	-	VL<400 copies/mL of those on ART	24 months: 60%; 36 months: 61%
Fatti (1206)	29 203 from 47 PHCs, 9 district hospitals and 3 regional hospitals in 4 different provinces	2004-07	-	VL<400 copies/mL of those with VL measure	12 months: 86.6% (85.8%-87.4%) 24 months: 86.3% (84.8%-87.6%) 36 months: 85.7% (81.5%-89.2%)
Barth (304)	Systematic review (Presented only summary of data from South Africa)	Papers published before 06/2009	-	VL<400 copies/mL of those on ART	6 months: 75%-92% 12 months: 66%-90% 24 months: 60%-72% 36 months: 61%
				VL<400 copies/mL of those initiated on ART	6 months: 83% 12 months: 55%-77% 24 months: 75%
				VL<50 copies/mL of those on ART	6 months: 63%-83% 12 months: 63%-70% 24 months: 65%
				VL<50 copies/mL of those initiated on ART	12 months: 46%

Source	Population	Year	Follow-up months, median (IQR)	Definition of virological suppression	% with virological suppression (95% CI)
Sanne (1207)	7,583 patients in a public clinic in Johannesburg	2004-08	20.3 (Total 13,417 PYs)	VL<400 copies/mL of those on ART with VL measurement	1-6 months: 90.8%
Mutevedzi (497)	5,719 patients in PHCs in rural KwaZulu-Natal	2004-08		VL<25 copies/mL of those initiated on ART	12 months:77%
Barth (498)	735 patients initiated ART in Limpopo	-	36	VL<50 copies/mL of those initiated on ART	63% 80% if only those with > 3-month follow-up included
				Achieved VL<50 copies/mL of those initiated on ART	76%
Hamers (966)	2588 ART naïve patients from 13 clinics: 2 in Kenya, 1 in Nigeria, 3 in South Africa, 3 in Uganda, 3 in Zambia and 1 in Zimbabwe;	2007-09	-	VL<400 copies/mL of those on ART	12 months: 90% (95% CI: 89%, 91%)
				VL<400 copies/mL of those initiated on ART	12 months: 70% (95% CI: 68%, 71%)
Fatti (1208)	66,953 patients: 19,668 (29.4%) received community based adherence support and 47,285 (70.6%) patients who did not receive it	2004-10	14.8 months (7.7–25.5; 100,295 PYs)	VL<50 copies/mL of those initiated on ART	At 6 months: community based adherence support: 76.6% (75.8% to 77.5%) No community based adherence support: 72% (71.3% to 72.5%)

ART: antiretroviral treatment; CI: confidence interval; EFV: efavirenz; GP: general practitioner; IQR: interquartile range; NGO: non-governmental organization; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase; NVP: nevirapine; PHC: primary healthcare clinic; PY: person-year; RCT: randomized controlled trial; TB: tuberculosis; VL: viral load; WHO: World Health Organization;

Appendix VI. Virological failure and development of drug resistance in South Africa

Source	Population	Year	Months of follow-up, median (IQR)	Definition of virological rebound or failure	% who experience
Bisson 2008 (1209)	Patients in private healthcare programmes from 9 countries in southern Africa	2000-03	21 (17-24)	VL>1000 copies/mL among those who reached VL<400 copies/mL (n=1,101)	14%
				VL>1000 copies/mL	6 months (n=958): 25% 12 months(n=872): 26%
Barth (306)	313 patients in Limpopo (rural) receiving 1 NNRTI and 2 NRTI as 1st line regimen	2003	-	VL>1000 copies/mL after reaching VL<50 copies/mL in the first year on ART	13%
Orrell (307)	929 ART-naïve patients in Nyanga district, near Cape Town	2002-05	6 (3-14). Total 760 PYs	Single VL>1000 copies/mL (VL measured every 4 months)	12 months: 8% 24 months: 17%
				2 consecutive VL>1000 copies/mL	12 months: 3% 24 months: 5%
				% who re-suppress after VL>1000 copies/mL	53%
Badri (1203)	330 patients enrolled in the Cape Town AIDS Cohort through participation in multicentre phase III RCT	1996-2006	24.7 (4.7–51.6) Total591 PYs	VL>≥ 1,000 copies/mL following VL<400 copies/mL	54.2% Rate of viral failure of 24.7 patient-months (IQR: 4.7–51.6)
Barth (496)	609 adults; PHC with GP administering ART in Elansdoorn (rural)	2003-06	-	VL >1000 copies/mL among those who reached VL<400	10%
Boulle (292)	7,323 in 3 public PHCs in Khayelitscha in Western Cape	2001-07	-	2 consecutive VL>5,000 copies/mL, despite enhanced adherence promotion after the first VL>5,000 copies/mL	60 months: 14% (95% CI: 12%, 16%)

Source	Population	Year	Months of follow-up, median (IQR)	Definition of virological rebound or failure	% who experience
Fox (499)	23,456 ART naïve patients I 5 programs within the IEDEA-SA collaboration, including around 10% of patients on ART in SA	2000-08	15.6 (Range across sites: 13-17), on ART 22; Total 29,935	2 consecutive VL>400 copies/mL after 6 months on 1st line ART with the 2nd value >5000 copies/mL despite stepped-up adherence	12 months: 3.5% 24 months: 8.5% 36 months: 16.9%
				2 consecutive VL>1,000 copies/mL after 6 months on 1st line ART with the 2nd value >5000 copies/mL despite stepped-up adherence	12 months: 3.2% 24 months: 8.0% 36 months: 15.0%
				VL>5,000 copies/mL or 2 VL>400 copies/mL after having achieved VL<400 copies/mL	16.5% (95% CI: 15.9, 18.2)
Barth (498)	735 patients initiated ART in Limpopo	-	36	VL>1000 copies/mL during follow-up	16% 20% if only those with >3-month follow-up included
Hamers (398)	2588 ART naïve patients from 13 clinics: 2 in Kenya, 1 in Nigeria, 3 in South Africa, 3 in Uganda, 3 in Zambia and 1 in Zimbabwe;	2007-09	-	VL>1000 copies/mL of those on ART (VL measure at 0 and 12 months)	12 months:8.2%
Johnston 2012 (500)	13,537 patients starting 1st-line ART with at least 1 VL measurement after 6 months of ART in the Aurum Institute ART programme, including 56 clinics serving employees of large, predominantly mining companies and 81 urban and peri-urban private GP. ART free of charge	2003-09	31.2 (20-42)	2 consecutive VL >1000 copies/mL ≤9 months apart, both ≥6 months after ART initiation	17.9%: 31.1% from workplace clinics 10.7% from 51 community clinics

ART: antiretroviral treatment; CI: confidence interval; GP: general practitioner; IQR: interquartile range; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase; PHC: primary healthcare clinic; PY: person-year; RCT: randomized controlled trial; SA: South Africa; VL: viral load;

Appendix VII. Virological outcomes on second-line regimen in South Africa

Source	Population	Year	Follow-up, median (IQR)	Definition of outcome	Value of the outcome
Barth (498)	735 patients initiated ART in Limpopo		36	% achieving virological suppression after switching to second-line	81%
Boulle (292)	7,323 in 3 public PHCs in Khayelitscha in Western Cape	2001-07	-	VL<400 copies/mL of those on second-line ART	12 months since ART initiation: 80% 24 months: 66% 36 months: 79.4% 48 months: 70.7% 60 months: 75.9%
Johnston 2012 (500)	1668 patients with VF enrolled in the Aurum Institute ART programme, including 56 clinics serving employees of large, predominantly mining companies and 81 urban and peri-urban private general practitioners. ART free of charge	2003-09	Total PYs 1921.8	% who achieve virological suppression after VF	12 months: 13.2%
				% dead at 12 months after VF	12 months: 4.6%
Johnston 2012 (1210)	417 patients who switched regimen: 205 from a workplace programme and 212 from community programmes	2003-10	-	VL<400 copies/mL between 2 weeks to 15 months of switching regimens	15 months from switch: 48.3% (workplace) and 72.0% (community)
				VL rebound (>400 copies/mL after initial suppression after switch)	35.6% (workplace) and. 13.2% (community)
Johnston 2014 (1211)	122 patients who switched to second-line regimen with virological data	2003-08		% who suppress (VL <400 copies/mL 2 weeks to 15 months following switch)	68%

Source	Population	Year	Follow-up, median (IQR)	Definition of outcome	Value of the outcome
Schoffelen (503)	210 patients switched to second-line at the Ndlovu Medical Centre in Elandsdoorn (rural)	2004-10	20 [IQR: 11–35].	VL<400 copies/m of those on ART	12 months: 71.9% 24 months: 75.0%
				VL<400 copies/m of those initiated on ART	67.5%
				VL<50 copies/mL of those on ART	12 months: 60.9% 24 months: 64.3%
				VL<50 copies/mL of those initiated on ART	58.1%
				VL>1,000 copies/mL after initial virological response	14.7%
Murphy (505)	136 patients who switched to second-line regimen in the Sinikithemba Outpatient HIV/AIDS Clinic at McCord Hospital in Durban (PEPFAR and DoH funded)	-	34 (20-44)	VL>1,000 copies/mL among those on ART	12 months: 25% 18 months:21% 24 months: 25%
Fox 2010 (1212)	328 on second-line therapy at an urban public sector clinic in Johannesburg	2004-08	-	Two consecutive VL >1000 copies/mL on ART	12 months (n=262): 22.6 (17.8, 27.9)
Van Zyl (502)	93 on second-line regimen in 2 public health clinic in Khayelitsha, Cape Town	-	11.5** (9–21.5)	VL >500 copies/mL	12 months: 39.89 (30.3, 49.9)
El -Khatib (504)	115 from 2 outpatient clinics at the largest hospital in Africa located outside Johannesburg	2008	-	VL>400 copies/mL of those on second-line ART	24 months: 32.33 (24.1, 41.1)
Levison (1213)	202 starting second-line in the Gugulethu Clinic in Nyanga, a peri-urban township of Cape Town	2002-10	6**	% with viral failure (VL >400 copies/mL)	6 months (n=167): 25.30 (19.0, 32.1)

*: if not indicated it refers to switch to second-line, because of virological failure; **: mean time rather than median;
ART: antiretroviral treatment; DoH: Department of Health [South Africa]; IQR: interquartile range; PEPFAR: President's Emergency Plan for AIDS Relief; PHC: primary healthcare clinic; PY: person-year; PEPFAR: VF: virological failure; VL: viral load;

Appendix VIII. Fertility and prevention of mother-to-child transmission in Zimbabwe

Fertility

Fertility estimates for Zimbabwe have been estimated from the censuses. The civil registration of births and deaths was introduced in 1890 and was compulsory for white settlers until 1980. Since 1986 notification and registration of the birth, still-birth or death of any person in Zimbabwe is compulsory (1214), nevertheless in the period 2000-2009 it was estimated only between 24 and 37% of deaths were reported (1215).

The fertility in Zimbabwe has been declining in the last 30 years from 5.5 births per woman in the period 1984-88 (520) to a minimum of 3.8 documented in the DHS in 2005-06, while in 2011 it was slightly higher: 4.1 children per woman (519). In the future it is projected to decrease even further down to 2.74 in the period 2025-30. Table A.3 (page 387) summarizes the estimates on the total fertility rate in Zimbabwe.

Prevention of mother-to-child transmission

PMTCT has been an integrated part of the HIV response since 1999 (539). Nevertheless at the end of 2001 only 4% of those in need of PMTCT were receiving it (1216). In 2002, a national PMTCT programme was launched integrating PMTCT in the reproductive health services (528), providing single dose NVP (1217).

The national guidelines for use of ART published in 2010 (228) contained recommendations on how to assess pregnant women and which regimens to prescribe. They recommend that all women should be tested for HIV at the first visit and then:

- If HIV-negative they are recommended to retest after 3 months for HIV and to repeat the HIV test in the last trimester
- If HIV-positive they should be assessed for ART eligibility and:
    - If eligible for ART (see section 2.2.7) they should be initiated on ART, but without using D4T or EFV, preferably TDF+FTC+NVP

- If not eligible they should initiate PMTCT prophylaxis and be reassessed for ART eligibility at every visit. The recommended PMTCT prophylaxis consists of twice daily AZT for the mother from 14 weeks of gestation, AZT+3TC+single dose NVP at labour and a 7 days course of AZT+3TC after the delivery and for the baby different dosages of NVP during the breastfeeding period.

The coverage of HIV testing in ANC was still very low in 2005-06 at level of 23% (518); by 2011 it more than doubled (59%) (519), but it was still dramatically low compared to other countries such as South Africa for example where it is universal. Similarly, the PMTCT coverage among HIV-positive women was very low in 2007 with only 22% of women receiving PMTCT but by 2011 98% of women were receiving PMTCT (530).

The new national antiretroviral guidelines, released in 2013 (229), recommend what has been referred to as option B+: initiation of life-long ART for all pregnant women.

Table A.2. Prevention of mother-to-child transmission in Zimbabwe

Source		Calendar Year	Population	% pregnant women tested in ANC	% of HIV+ pregnant women who received PMTCT	Number of HIV+ pregnant women who received sNVP and/or other PMTCT regimen
Zimbabwe DHS	(518)	2006	15-49 15-19 20-24 25-29 30-39 40-49	22.6% 20.2% 25.7% 20.8% 22.5% 11.9%	- - - - - -	- - - - - -
	(519)	2011	15-49 15-19 20-24 25-29 30-39 40-49	59.1% 44.9% 59.6% 66.5% 58.8% 49.1%	- - - - - -	- - - - - -
Zimbabwe multiple indicators monitoring (548)		2007-09	15-49	58.1% (53.4% received the result)	-	
Global AIDS Response (530)		2007 2009 2010 2011		- - - -	22% 59% 84% 98%	- - - -
Global fund reports (545)		2010 2011 2012 Jan-Mar2013	-	- - - -	94.0% 95.5% 97.5% -	44,444 44,770 59,224 13,444

ANC: antenatal clinic; DHS: Demographic and Health Survey; PMTCT: prevention of mother-to-child transmission; sNVP: single dose nevirapine;

Table A.3. Fertility in Zimbabwe

Source		Year	Women age group	Total fertility rate (births per woman)
World Bank (1198)		2004	-	4.0
		2005		4.0
		2006		3.9
		2007		3.9
		2008		3.9
		2009		3.8
		2010		3.7
		2011		3.6
Zimbabwe YAS 2001-02 (522)		1999-2001	15-29	2.4
Zimbabwe Population Census	2002 (511)	2002	-	3.6
	2012 (510)	2012	-	3.8
Zimbabwe DHSs	1988 (520)	1984-1988	-	5.5
	1994 (516)	1991-94	-	4.3
	1999 (517)	1996-99	-	4.0
	2005-06 (518)	2003-05	-	3.8
	2011 (519)	2010-11	-	4.1
UNICEF (548)		2009	-	3.7
CIA (513)		2014	-	3.56
UN Secretariat (436)		1995-2000	-	4.20
		2000-05		4.01
		2005-10		3.90
		2010-15		3.51
		2015-20		3.20
		2025-30		2.74

CIA: Central Intelligence Agency; DHS: Demographic and Health Survey; UN: United Nations; UNICEF: United Nations Children's Fund; YAS: Zimbabwe Young Adult survey;

Appendix IX. Retention on ART in Zimbabwe

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Months since ART initiation	Total attrition		Retained in care	
							Died	Lost to follow-up	Transferred to care	Retained at original site
Mutasa-Apollo (554)	Nationally representative multi-stage retrospective cohort study of Zimbabwe National ART Programme	2007-10	3,919	>90 days late for a scheduled visit with the healthcare provider or pharmacy	16	6	4.1	4.9	Excluded	90.7 (86.1-93.8)
						12	4.8	16.1		78.1 (69.7-84.7)
						24	6.7	23.5		68.8 (58.5-77.5)
						36	8.5	25.2		64.4 (55.7-72.3)
Bygrave (558)	25 PHCs (MSF) in rural district of Buhera in Manicaland province among patients aged 10 to 30 years	2005-08	898	Not attended the clinic for >90 days since end of the last prescription	15 (8-21)	6	Rate: 6.2 (95% CI: 4.9, 7.7) /100 PYs. Min in 10-15 years old: 3.6 (95% CI: 2.0, 6.3) /100 PYs, max in 24-30 years old 7.7 (95% CI: 5.8, 10.4) /100 PYs	Rates: min in 10-15 years old: 4.2 (95% CI: 2.5, 7.0)/100 PYs, max in 19-24 years old: 16.8 (95% CI: 11.6, 24.3) /100 PYs	-	87.5 in 19-24 years old to 98% in 10-15 years old;
						12				83% in 19-24 years old to 93% in 10-15 years old;
						24				75% in 19-24 years old to 92% in 10-15 years old;

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Months since ART initiation	Total attrition Died	Retained in care Lost to follow-up	Transferred to care	Retained at original site
Rasschaert (560)	2 ART programmes (MSF), 1 in Thyolo district (Malawi) and 1 in Buhera, Manicaland, where patients could be in care always in hospital (HO), initiated in hospital and transferred to the health centre (HOT) or always in the health centre (HC) [People who interrupted ART are censored as well]	2003-08	9,721 in Buhera	≥90 days late for a scheduled visit	-	6	Of those on ART: 1% in HOT, 9% in HO	Of those on ART: 1% in HOT, 13.5% in HO	Censored	88% (78% in HOT to 98% in HO)
						12	2.5% in HOT, 11% in HO	2% in HOT, 18% in HO		84% (75% in HOT to 97% in HO)
						24	4.0% in HOT, 12% in HO	3% in HOT, 23% in HO		80% (71% in HOT to 94% in HO)
						30	4.5% in HOT, 14% in HO	4% in HOT, 24% in HO		79% (66% in HOT to 92% in HO)
Wandeler (559)	6 ART programmes (SolidarMed, NGO): 2 in Zimbabwe (Bikita and Zaka, both in Masvingo Province), 2 in Lesotho and 2 in Mozambique, part of IEDEA collaboration	2005-2010	1777 in Bikita, 1254 in Zaka	Not returning to the clinic for 6 months or longer.	-	12[b]	6.4 (5.5-7.4)	10.6 (9.4-11.8)	Censored	83.1 (81.7-84.5)
						24[b]	7.4 (6.4-8.5)	13.4 (12.0-14.9)		79.2 (77.5-80.8)
						36[b]	9.0 (7.6-10.5)	15.7 (13.9-17.6)		75.1 (72.8-77.3)

A: Kaplan-Meier estimates; b: Competing risk estimates;

ART: antiretroviral treatment; CI: confidence interval; HOT: initiated in hospital and transferred to the health centre; HO: in care always in hospital; HC: in care always in the health centre; MSF: Medicins Sans Frontieres; NGO: non-governmental organization; PHC: primary healthcare clinic; PY: person-year;

Appendix X. Alternative sexual behavioural models

As mentioned, an alternative sexual behaviour structure has also been developed, the table below shows how it differs compared to the main one (referred to as RBM =17).

The main one is called the "asymmetric" model because it is asymmetric by gender, with the proportion of women having > 10 partners higher than for men, representing sex workers.

The probability of sampling a symmetric model when simulating the South Africa epidemic was 0.4: 0.05 for respectively RBM 2 and 5, 0.1 for respectively RBM 7, 10 and 12. In the remaining 60% of cases an asymmetric RBM is sampled: 0.2 for RBM 17, 0.1 for respectively RBM 9, 11, 13 and 4.

Table A.4. Distribution of condom-less sex short-term partners at time 0, at the beginning of the epidemic

		Males (g=1)		**Females (g=2)**	
		Symmetric RBM	**Asymmetric RBM (alternative)**	**Symmetric RBM**	**Asymmetric RBM (alternative)**
CLST partners in period t	**0**	0.55	0.90	0.55	0.93
	1	0.30	0.07	0.30	0.05
	Medium (2-9)*	0.05	0.03	0.05	0.0185
	High (≥10)**	0	0	0	0.0015

*Poisson(1.5); **Poisson(2*swn); CLST: condom-less short-term; RBM: risk behavioural model;

There is a 5% chance that the symmetric RBM is sampled, 95% that the asymmetric is sampled

Table A.5. Values of f_{gij} (values determining probability of transitioning between CLST partner risk behaviour groups) for different risk behavioural model

Table A.5a. Values of f_{gij} for RBM 4, 9, 11, 13, 17 (Probability of these RBM being sampled 0.6)

		CLST partners in period t			
		0	**1**	**Medium (2-9)**	**High (≥10)**
Males					
CLST partners in period t-1	**0**	0.89	0.08	0.03	0.00
	1	0.80	0.15	0.05	0.00
	Medium (2-9)	0.35	0.27	0.38	0.00
	High (≥10)	0.00	0.00	0.00	0.00
Females					
CLST partners in period t-1	**0**	0.93	0.05	0.02	0.00025
	1	0.86	0.11	0.03	0.0005
	Medium (2-9)	0.53	0.08	0.38	0.001
	High (≥10)	0.005	0.00	0.00	0.995

CLST: condom-less short-term; RBM: risk behavioural model;

Table A.5b. Values of f_{gij} for risk behavioural model 10, 12 (Probability of these risk behavioural model being sampled 0.2)

		CLST partners in period t			
		0	**1**	**Medium (2-9)**	**High (≥10)**
Males					
CLST partners in period t-1	**0**	0.80	0.17	0.03	0.00001
	1	0.90	0.08	0.02	0.00001
	Medium (2-9)	0.15	0.35	0.50	0.00001
	High (≥10)	0.25	0.05	0.20	0.50
Females					
CLST partners in period t-1	**0**	0.80	0.17	0.03	0.00025
	1	0.90	0.08	0.02	0.00025
	Medium (2-9)	0.15	0.35	0.50	0.001
	High (≥10)	0.04	0.03	0.03	0.90

CLST: condom-less short-term;

Table A.5c. Values of f_{gij} for risk behavioural model 2, 7 (Probability of these risk behavioural model being sampled 0.15)

		CLST partners in period t			
		0	**1**	**Medium (2-9)**	**High (≥10)**
Males and Females					
CLST partners in period t-1	**0**	0.77	0.13	0.10	0.00
	1	0.55	0.32	0.13	0.00
	Medium (2-9)	0.15	0.70	0.15	0.00
	High (≥10)	0.01	0.00	0.00	0.99

CLST: condom-less short-term;

Table A.5d. Values of f_{gij} for risk behavioural model 5 (Probability of these risk behavioural model being sampled 0.05)

		CLST partners in period t			
		0	**1**	**Medium (2-9)**	**High (≥10)**
Males					
CLST partners in period t-1	**0**	0.80	0.17	0.03	0.00
	1	0.90	0.08	0.02	0.00
	Medium (2-9)	0.15	0.35	0.50	0.00
	High (≥10)	0.00	0.00	0.00	0.00
Females					
CLST partners in period t-1	**0**	0.80	0.17	0.03	0.00025
	1	0.90	0.08	0.02	0.00025
	Medium (2-9)	0.15	0.35	0.50	0.001
	High (≥10)	0.005	0.005	0.00	0.99

CLST: condom-less short-term;

Table A.6. Proportion of the population who experience only very low sexual risk behaviour (*p_rred_p*) and reduction in sexual behaviour in these subsamples

		Proportion affected by the reduction		Reduction in sexual behaviour
		Males (g=1)	Females (g=2)	
Risk behavioural model	**2**	0.2	0.2	0.01
	4	0.35	0.5	0.1
	5,7	0.2	0.35	0.01
	9-13, 17	0.35	0.5	0.01

Table A.7. Values of r_{ga} (factor determining relative level of sexual risk activity)

		Risk behaviour model							
		2,7	**4,9**	**17**	**5,10,12**	**2,7**	**4,9**	**17**	**5,10,12**
		Males (g=1)				Females (g=2)			
Age group	**15-**	0.75	0.65	0.35	0.85	1.15	1.5	3.2	1.5
	20-	0.75	0.65	0.45	1.0	1.15	1.5	3.5	1.5
	25-	1.0	1.0	1.3	1.4	1.0	1.0	3.0	1.3
	30-	1.0	0.8	0.5	1.2	0.85	0.8	1.5	1.0
	35-	0.65	0.65	0.35	1.0	0.55	0.5	0.7	0.8
	40-	0.45	0.5	0.3	0.8	0.35	0.35	0.7	0.6
	45-	0.35	0.4	0.3	0.6	0.2	0.1	0.7	0.5
	50-	0.23	0.35	0.15	0.5	0.15	0.05	0.6	0.4
	55-	0.18	0.25	0.25	0.4	0.08	0.04	0.4	0.3
	60-	0.10	0.15	0.15	0.3	0.04	0.02	0.3	0.2

Table A.8. Proportion with a condom-less sex long-term partner at the beginning of the epidemic and probability of starting a CLLT partnership

		Proportion with a CLLT partner at the beginning of the epidemic		Probability of starting a CLLT		
Risk behavioural model		**2,4,5,7,9-13**	**17**	**2,5,7,10,12**	**4,9,11,13**	**17**
Age group partners	15-	0.4	0.42	0.15	0.10	0.07
	25-	0.5	0.65	0.10	0.07	0.09
	35-	0.5	0.65	0.05	0.05	0.035
	45-	0.5	0.58	0.01	0.01	0.035
	55-	0.5	0.45	0.005	0.005	0.02

CLLT: condom-less long-term partner;

Appendix XI. Parameter values and distributions

Parameters relating to sexual behaviour

As mentioned in section 3.3, sexual risk behaviour is modelled as the number of short-term (e.g. casual) partners and presence of a long-term partner in each 3 month period and, as for all variables modelled, is updated in 3 month periods. The status of the long-term partner, in terms of HIV infection, diagnosis and ART use, is tracked over time. The values of the parameter that determine the sexual behaviour are listed below. If they were sampled from a distribution the distribution is reported.

For the parameters which are normally distributed the mean and the variance are indicated, while for the parameters lognormally distribution the mean and the variance of the variable's natural logarithm are indicated.

Table A.9. Parameters and distribution relating to sexual behaviour

Parameter (variable name in the program)	**Value (or distribution)**	
	South Africa	**Zimbabwe**
Sexual behaviour		
Sexual behaviour model structure	60% base structure (RBM=4), 40% alternative structure (with no sex workers; see section 3.3, other RBMs)	100% base structure

Factor to change overall average level of condom-less sex with short-term partners (*newp_factor*)	lognormal(ln10,0.3^2), if *fold_tr**<=1 and *tr_rate_primary**<=0.2;
	lognormal(ln4,0.3^2), if *fold_tr*> 1 and *tr_rate_primary*> 0.2;
	lognormal(ln6,0.3^2), otherwise;
		9

Poisson mean for highest short-term partner group (>10 CLST partner) (see section 3.3.1) (*swn*)	Gamma(20,2) (mode=19/2=9.5) if *fold_tr**<=1 and *tr_rate_primary**<=0.2; Gamma(8,2) (mode=7/2=3.5) if *fold_tr*> 1 and *tr_rate_primary*> 0.2; Gamma(14,2) (mode=13/2=6.5) otherwise;	7
Mean of the Poisson distribution from which is sampled the number of CLST partners (*highsa*)	NA	4.5
Probability of having a new CLLT partner for people in the age group 15-35 (*eprate*)	NA	0.1

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	**Zimbabwe**
Change in propensity to have a long-term condom-less sex partner ("risk") after HIV diagnosis (i.e. mainly reflects the chance of starting to adopt 100% condom use or cease sexual intercourse) (*ch_risk_diag*)	Beta (8,10) (mode=7/16=0.44)	0.69
Change in propensity to have short-term ("new") condom-less sex partners after HIV diagnosis (*ch_risk_diag_newp*)	Beta(6,2) (mode=5/6=0.83)	0.83
Date at which population level reduction in condom-less sex with short-term and long-term partners started (*date_ch_risk_beh*)	Uniform (1991,1998.75)	NA
Date at which the slope in the population level reduction in condom-less sex behaviour with short-term partners changes (*date_ch_risk_beh_2*)	Uniform (1999,2005.75)	NA
Date at which the population level reduction in condom-less sex behaviour with short-term partners stops (*date_ch_risk_beh_3*)	Uniform (2006,2009.75)	NA
Annual reduction in propensity to have condom-less sex ("risk behaviour") with short-term partners in the period between *date_ch_risk_beh* and *date_ch_risk_beh_2* (*rate_ch_risk_beh*)	Lognormal(ln0.065,0.75)	NA
Annual reduction in propensity to have condom-less sex ("risk behaviour") with short-term partners in the period between date_ch_risk_beh_2 and date_ch_risk_beh_3 (*rate_ch_risk_beh_2*)	lognormal(ln0.025,0.5^2)	NA
This parameter is the fold increase in the proportion who do not have condom-less sex, of those who had condom-less sex at the time before, relative to before *date_ch_risk_beh* (*ch_risk_beh_ep*) [This parameter applied after *date_ch_risk_beh*]	(Beta(10,2)) [Mean=1.2]	0.5
HIV prevalence threshold who triggers the reduction in sexual behaviour (*prev_threshold_rb_change*)	NA	Uniform(0.1,0.4))

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	Zimbabwe
Pregnancy		
Base probability of pregnancy per 3 months of condom-less sex. It applies to women 35-45. (*prob_pregnancy_base*)	Uniform(0.035,0.075)	0.037
Multiplicative factor to the base probability of pregnancy for women 15 to 25 years old (*fold_preg1525*)	Uniform(1.015,1.065)	1.04
Multiplicative factor to the base probability of pregnancy for women 25 to 35 years old (*fold_preg2535*)	Uniform(1.005,1.055)	1.03
Multiplicative factor to the base probability of pregnancy for women 45 to 55 years old (*fold_preg4555*)	Uniform(0.95,1.0)	0.975
Multiplicative factor to the base probability of pregnancy for women 55 to 65 years old (*fold_preg5565*)	Uniform(0.9,0.95)	0.925

**fold_tr* is a multiplicative factor which change rate of transmission, *tr_rate_primary* is the rate of transmission in PHI. CLST: condom-less short-term; NA: not applicable; RBM: risk behavioural model;

swn and *newp_factor* are sampled to be inversely correlated with a multiplicative factor which changes the rate of transmission (*fold_tr*) and rate of transmission in PHI (*tr_rate_primary*) to ensure that a high proportion of epidemics generate have a prevalence which fits to the South Africa epidemic (without this factor many more epidemics would be generated where prevalence is very low, if *fold_tr*, *tr_rate_primary*, *swn* and *newp_factor* are all low, or very high, if all four values are high – the aim is to achieve good sampling efficiency without imposing too much constraint on epidemics generated).

Parameters relating to HIV transmission

Table A.10. Parameters and distribution of parameters related to HIV transmission, transmission of resistant virus and persistence of ARV-drugs resistance mutations transmitted

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	Zimbabwe
Fold difference in transmission rate for a given VL (see section 3.3.5) (*fold_tr*)	Lognormal(ln1,0.5^2)	1
Rate of transmission in PHI (lasting 3 months) (*tr_rate_primary*)	beta(2,7) (mode=1/7=0.15)	0.25
Transmission rate when plasma VL is < 500 cps/mL (*tr_rate_undetec_vl*)	lognormal(ln0.0001,1^2)	0.001
Fold higher rate of acquisition for women compared to men (higher rate of transmission from men to women, compared with women to men) (*fold_change_w*)	lognormal(ln1.5,0.5^2)	1.5
Fold higher rate of acquisition in young women compared with older women (*fold_change_yw*)	lognormal(ln3,0.4^2)	2
Fold higher rate of acquisition in people with STIs (*fold_change_sti*)	lognormal(ln3,0.3^2)	3
Fold rate of acquisition in men circumcised (*fold_circ*)	0.5	
Fold lower transmission rate per 3 months for short-term partners compared with long-term partners (reflecting average lower number of sex acts) (*fold_tr_newp*)	beta(5,10) (mode=4/13=0.31)	0.36
Adjustment to factor determining extent to which some transmitted resistance is effectively immediately lost (even from minority virus) (*res_trans_factor*)	lognormal(1,0.3^2)	lognormal(1.0, 0.3^2)
Probability per 3 months of loss of persistence of transmitted mutations from majority virus to minority virus (same for each mutation) (*rate_loss_persistence*)	lognormal(ln0.04,0.3^2)	0.04

PHI: primary HIV infection; VL: viral load;

Parameters relating to natural progression

For HIV-infected people the variables modelled include: PHI (a period of raised infectivity of 3 months duration), VL, CD4 count, presence of specific resistance mutations, adherence to ART, risk of AIDS and death.

Table A.11. Parameters relating to natural history of HIV

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	Zimbabwe
Initial CD4 count at infection (square root scale) (*mean_sqrtcd4_inf*)	30	27
Factor adjusting basic rate of natural cd4 decline (see section 3.4) (*fx*)	0.9	1.4
Factor adjusting basic rate of natural VL change (see section 3.4) (*gx*)	1	1
Fold increase in risk of WHO 3 condition, compared with risk of WHO 4 condition, for given level of CD4 count, VL and age (*fold_incr_who3*)	5	5
Fold decrease in risk of HIV-related death, compared with risk of WHO 4 condition, for given level of CD4 count, VL and age (*fold_decr_hivdeath*)	0.25	0.25
Increase in death rate in 3 months period in which a WHO 4 condition is present (*incr_death_rate_adc*)	5	10
Increase in death rate in 3 months period in which TB is present (*incr_death_rate_tb*)	2	10

TB: tuberculosis; VL: viral load; WHO: World health Organization;

Parameters relating to circumcision, HIV testing, linkage to care and retention in pre-ART care and on ART

Table A.12. Parameters and distributions on HIV care delivery (including circumcision)

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	Zimbabwe
Circumcision		
Baseline prevalence of circumcision (before VMC was rolled out for HIV prevention) (*prev_circ*)	42%	10%
Start date of VMC roll out (*mc_int*)	2008	2008
Annual increase in probability of VMC (*incr_anprob_circ*)	Between date of starting rolling out and mid-2009: 0.001 Between 2009.5-2010.5: 0.015	Between date of starting rolling out and beginning of 2015: 0.003
HIV testing		
Date of start testing for HIV in ANCs	1990	1994
Date of start of testing for HIV (*date_start_testing*)	1996	1996
Annual rate of increase in testing probability over time (*test_increase_rate*)	Uniform(0.02,0.035)	NA
Annual quadratic increase in the probability of being tested in ANCs for pregnant women (*rate_testanc_inc*)	0.00195 (*rate_testanc_inc* – only up to first trimester of 2013)	0.0025 (*rate_testanc_inc* – only up to first trimester of 2015)
Probability per 3 months of being tested for HIV for those with WHO stage 4 condition (*test_rate_who4*) in 1996	0.2	0.2
Absolute rate of increase per 3 months of test_rate_who4; up to 2015) (*inc_test_rate_who4*)	0.008	0.008
Probability per 3 months of being tested for HIV for those with TB (*test_rate_tb*) in 1996	0.1	0.1
Absolute rate of increase per 3 months on *test_rate_tb*; up to 2015. (*inc_test_rate_tb*)	0.005	0.005
Probability per 3 months of being tested for HIV for those with WHO stage 3 condition (*test_rate_who3*) in 1996	0.03	0.03
Absolute rate of increase per 3 months on test_rate_who4; up to 2015. (*inc_test_rate_who4*)	0.0012	0.0012
Proportion of the population resistant to HIV testing (no probability of testing unless with WHO 4 condition, in which case they will be tested) (*rate_noreached*)	lognormal(ln0.25,0.12)	20% in 1996 it declines linearly to 5% by 2010 and 5% thereafter

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	**Zimbabwe**
Linkage to care		
Probability of being linked to care at 3 months since diagnosis (for people without WHO4, WHO3 events in the last 3 months or TB in the last 6 months) (*prop_linkedtocare_diag*)	0.4	0.4
Probability of being linked to care at 3 months since diagnosis for people with WHO4 events in the last 3 months or TB in the last 6 months	1	0.95
Probability of being linked to care at 3 months since diagnosis for people with WHO3 events in the last 3 months	1	0.85
Retention in pre-ART care and on ART		
Rate of loss to follow-up per 3 months among those not on ART (*rate_lost*).	0.3. This applies in the first year since diagnosis, (actual probability also depends on average willingness to adhere – see section 3.6); after 1 year since diagnosis the parameter is a quarter of *rate_lost*: 0.075	0.05
Probability (per 3 months) of return to care for person LTFU within 1st year from diagnosis, if no WHO 4 condition present.	0	0.05
Probability (per 3 months) of return to care for person LTFU after at least 1 year since diagnosis, if no WHO 4 condition present (*rate_return*) (actual probability also depends on average tendency to adhere – see section 3.6.7)	0.04	0.05
Probability (per 3 months) of return to care for person LTFU if WHO 4 condition occur	0.8	0.8
Probability (per 3 months) of simultaneously being LTFU amongst those stopping ART (*prob_lost_art*) (actual probability also depends on tendency to adhere – see section 3.6.3)	0.3	0.27
Base probability (per 3 months) of restart of ART in those remaining under care who have stopped/interrupted ART (this is also influenced by presence of WHO 3 or 4 conditions) (*rate_restart*)	0.4	0.2

ANC: antenatal clinic; NA: not applicable; TB: tuberculosis; VMC: voluntary medical circumcision; WHO: World Health Organization;

Parameters relating to antiretroviral treatment

The model of progression of HIV and the effect of ART has been shown to provide a generally close fit to observed data relating to the effect of ART, comparing the output of the model with data coming mainly from Europe and South Africa (1218-1221).

Table A.13. Parameters determining ART roll-out and effect of ART on progression

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	Zimbabwe
Delivery of ART care		
ART introduction date (*ART_intro_date*)	2002	2003
PMTCT introduction date with sNVP (*date_pmtct*)	2004	2004
Annual rate of increase in use of PMTCT in pregnant women attending ANC (*rate_sd_nvp* - up to a maximum of 97.5)	0.25	0.15
Probability (per 3 months) of switching to second-line treatment, given first-line failure (by whatever definition is being used) (*pr_switch_line*)	0.25	0.15
Adherence to antiretroviral therapy		
Pattern of tendency to adhere across individuals, expressed as proportion of doses taken (*adhav*)	15% *adhav*=0.49 15% *adhav*=0.79 50% *adhav*=0.90 20% *adhav*=0.95	5% *adhav*=0.49 10% *adhav*=0.79 65% *adhav*=0.90 20% *adhav*=0.95
Reduction in adherence resulting from presence of TB or a WHO 4 condition (*red_adh_tb_adc*)	0	0.1
Average reduction in adherence resulting from current toxicity (the actual reduction varies by individual person) (*red_adh_tox*)	0	0.05
Additional "effective" adherence for people on NNRTI regimens due to longer half-life (*add_eff_adh_nnrti*)	0.1	0.1
Average (amount differs by individual) increase in adherence in patients who have a measured VL in the last 6 months above 1,000 copies/mL (*adh_effect_of_vm_pop*)	0.2	NA
Extent to which the average CD4 change is more favourable on a virologically failing PI/r-regimen compared with an NNRTI-regimen (*poorer_cd4_rise_on_failing_nnrti*)	-10	-6

Parameter (variable name in the program)	Value (or distribution)	
	South Africa	**Zimbabwe**
CD4		
Standard deviation for intra-subject variation in CD4 count and (*sd_cd4*)	1.2	1.2
Standard deviation for the measurement error in CD4 count (*sd_measured_cd4*)	2.0	1.7
Standard deviation representing inter-patient variation in rate of CD4 rise - when CD4 is rising (*patient_cd4_rise_art*) (after 2 years on ART is divided by 4)	Lognormal(0,0.5)	0.2
ART interruption		
Underlying probability (per 3 months) of interrupting ART (actual probability also depends on presence of current toxicity and average adherence – see section 3.6.3) (*rate_int_choice*)	0.02	0.02
Probability (per 3 months) of drug stock out, and hence ART interrupted (*prob_supply_interrupted*)	0.01	0.01
Probability (per 3 months) that drug supply resumed after stock-out (*prob_supply_resumed*) [i.e 80% chance that stock-out lasts 3 months only]	0.8	0.8
Acquisition of ART resistance mutations		
Fraction of people who stop ART (and are still visiting the clinic) for whom the clinic is aware of the interruption. If they are not aware they treat the patient as if they were on ART (and hence may switch to the next line having wrongly classified them as virologically failing) (*clinic_aware_int_frac*)	0.5	0.7
Probability of an NNRTI resistance mutation arising in the 3 months after having stopped NNRTI (due to effective monotherapy due the long half-life) (*risk_res_stopping_nn*)	0.05	0.018 for K103, 0.006 for Y181 and 0.006 for G190
Probability per pregnancy of NNRTI resistance emergence in pregnant women receiving sNVP for MTCT (*prob_nnresmaj_sd_nvp*)	0.35	0.35
Probability per pregnancy of NNRTI resistance emergence in pregnant women receiving AZT during pregnancy, sNVP + AZT during labour and TDF + FTC single dose after delivery (*prob_nnresmaj_dual_nvp*)	0.045	0.045
Probability per 3 months of loss of NNRTI mutations, acquired due to PMTCT, from majority virus to become only in minority virus (*rate_loss_nnres_pmtct_maj*)	0.25	0.25
Probability per 3 months of loss of virus with NNRTI mutations acquired due to PMTCT, from minority virus to effectively be extinct altogether (*rate_loss_nnres_pmtct_min*)	0.25	0.25

ANC: antenatal clinic; ART: antiretroviral therapy; AZT: zidovudine; FTC: emtricitabine; MTCT: mother-to-child transmission; NNRTI: non-nucleoside reverse transcriptase inhibitor; PMTCT: prevention of mother-to-child transmission; sNVP: single dose NVP; TB: tuberculosis; TDF: tenofovir; WHO: World Health Organization;

Appendix XII. Summary of selected papers on antiretroviral therapy for prevention of HIV transmission

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Randomized controlled trials				
Cohen, 2011, New England Journal of Medicine (432)	To compare the effect of early vs delayed ART on HIV transmission (early = ART at diagnosis; delayed = ART after two consecutive CD4 counts ≤250 cells/μL)	RCT (HPTN 052)	1,763 HIV serodifferent couples from nine countries: Botswana, Kenya, Malawi, South Africa, Zimbabwe, Brazil, India, Thailand and United States 2005–2010	A total of 39 HIV transmission events were observed, of which 28 were virologically linked (incidence rate: 1.2 per 100 PYs; 95% CI: 0.9, 1.7). Of 28 linked transmissions, 1 was in the early-therapy group. A HR in the early-therapy group of 0.11 (95% CI: 0.04, 0.32; p<0.001). HIV- positive people starting ART at study entry had a clinical benefit compared with people starting ART when CD4 count falls below 250 cells/μL. Results support the use of ART as a part of a public health strategy to reduce the spread of HIV infection.
Ecological studies				
Das, 2010, PLoS One (675)	To assess relationships between mean and total community VL and annual numbers of newly diagnosed HIV cases	Ecological/cohort study	All reported HIV-positive individuals in San Francisco, United States (n=12,512) 2004–2008	Decreases in annual measures of mean and total community VL were observed and were significantly associated with temporal decreases in the number of new HIV diagnoses.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Dukers, 2002, AIDS (679)	To investigate whether dramatic increases in sexually transmitted diseases and sexual risk behaviour among homosexual men in Amsterdam, the Netherlands, indicate a resurgence of the HIV epidemic	Ecological study/cohort study	3,090 male participants from Amsterdam, who participated in 1991–2001 HIV prevalence surveys, who self-identified as homosexual (approximately 15% of all participants) and who consented to blood HIV testing (96.3% of all homosexual participants) were included	The incidence of HIV increased during the study period, as did rates of syphilis and gonorrhoea. The authors also reported an increase in risk behaviour among homosexual men, highlighting the need for preventive action, especially for those who have recently been infected.
Fang, 2004, Journal of Infectious Diseases (676)	To estimate the HIV transmission probability ratio in the Taiwanese population, before and after the implementation of the free-ART policy	Ecological/cohort study	4,390 HIV-positive individuals included in Taiwan's HIV surveillance data 1984–2002	The authors noted that there was a 53% decrease in the HIV transmission rate during the period of free access to ART compared with the previous time period, and this contributed to the control of the HIV epidemic in Taiwan. Therefore, they concluded that the widespread use of ART can be an effective measure to control HIV epidemics in countries with a low prevalence. To differentiate the effect of ART from that of behavioural changes, the incidence of syphilis in the general population and among HIV-positive patients was also analyzed, for comparison. There was no statistically significant change in the incidence of syphilis, in the general population or among HIV-positive patients, during the same period.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Grulich, 2008, Sexual Health (680)	To describe trends in HIV notifications and in other measures of HIV incidence in homosexual men in developed countries	Literature review of ecological studies (search conducted in 2007)	Surveillance data from Europe, Canada, United States, Australia and New Zealand Data from 1996	The study concluded that there was a near-universal increase in notification of HIV diagnoses in homosexual men in the developed world. They reported that determining the degree and extent of the increases in incidence in homosexual men is very important for being able to develop appropriate public health responses in the evolving HIV epidemic.
Montaner, 2010, Lancet (677)	To estimate the association of new HIV-positive tests with VL, year and number of individuals on ART	Ecological/cohort study	British Columbia, Canada 1996–2009	The number of individuals actively receiving ART in British Columbia increased from 837 to 5,413 (547%; p=0.002), and the number new HIV diagnoses fell from 702 to 338 cases per 100,000 people per year (−52%; p=0.001). The overall correlation between number of individuals on ART and number of new HIV diagnoses per year was −0.89 (p<0.0001).

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Mathematical models				
Abbas, 2006, Journal of Acquired Immune Deficiency Syndromes (687)	To estimate the potential impact of ART on the heterosexual spread of HIV infection and AIDS mortality in RLS	Mathematical model	The model parameter set was chosen to mimic an epidemic in a sub-Saharan African nation reaching an endemic prevalence of 40% in the sexually active population 15–49 years of age	The authors suggested that implementing ART at 5% HIV prevalence to 100% of AIDS cases would decrease the number of new HIV infections and cumulative deaths from AIDS after 10 years by 11.2% (IQR: 1.8–21.4) and 33.4% (IQR: 26–42.8), respectively. A later implementation of ART at endemic equilibrium (40% prevalence) was predicted to be less effective, decreasing new HIV infections and cumulative deaths from AIDS by 10.5% (IQR: 2.6–19.3) and 27.6% (IQR: 20.8–36.8), respectively. The authors concluded that ART is predicted to have individual and public health benefits that increase with time and with the proportion of infected persons treated.
Alistar, 2014, BMC Medicine (706)	To evaluate the cost-effectiveness of different coverage for the combination of ART at CD4<350 cells/µL and at diagnosis and PrEP in the general population and in high-risk individuals	Compartmental mathematical model	The model reproduce the HIV epidemic in South Africa	The authors found that modifying the eligibility criteria so that all people diagnosed with HIV are eligible is the most cost-effective strategy at all coverages considered (ICER ranging from 160-220 per QALY gained). While PrEP provided only a limited additional benefit.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Alsallaq, 2013 PLoS One, (702)	To assess the impact on HIV incidence of an intervention combining high coverage of HTC, risk reduction following HIV diagnosis, VMC for HIV-uninfected men, and ART for HIV-infected persons To identify the factors that influence this impact, and whether there is a synergy between the components	Mathematical model	The model was calibrated to data from KwaZulu-Natal, South Africa	The authors found that, compared with current levels of HTC, VMC, and ART, the intervention with ART initiation at CD4 count <350 cells/μL could reduce HIV incidence by 47% (from 2.3 new infections per 100 PYs to 1.2 per 100 PYs) and by almost 60% (to 1 per 100 PYs) within 4 and 25 years respectively. Drivers of the short-term impact were uptake of HTC and reductions in risk behaviour following testing, while drivers of the long-term effects were the periodic HTC and retention in ART programmes. If the intervention included ART initiation upon diagnosis, HIV incidence could be reduced by 63% and 76% respectively within 4 and 15 years. The authors found a synergy between the intervention components and highlighted that it takes 10–15 years to see the full impact.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Andrews, 2012 Journal of Infectious Diseases, (690)	To evaluate the importance of structural assumptions regarding linkage to care and population mobility	Mathematical model	The model was parameterized using demographic, clinical, migration, emigration and linkage data from a township in Cape Town, South Africa	The authors used a previously published model and refined modelling linkage to care and population mobility. They found that elimination of HIV transmission (defined as an incidence of <0.1%) would not occur within 30 years, even with optimistic assumptions about the linkage rate. In addition they reported that models were more sensitive to structural assumptions about linkage to care than to parameter values, and that including population mobility further attenuated the reduction in HIV incidence due to ART as prevention.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Anglaret, 2013 Antiviral Therapy, (694)	To understand the circumstances under which starting ART upon entry to care, rather than at CD4 count <350 cells/µL could lead to more risks than benefits for patients with high CD4 counts	Mathematical model	Model parameters were chosen to mimic the HIV epidemic among sub-Saharan African adults with CD4 counts >500 cells/µL	15-year mortality was 56.7% if the eligibility criteria to initiate ART is CD4<350 cells/µL and 51.8% if people initiate ART upon entry to care. 15-year mortality was consistently lower with immediate ART unless the rate of fatal ART toxicity was >1.0/100 PYs or the rate of withdrawal from care was >1.2-fold higher or the rate of ART failure due to poor adherence was >4.3-fold higher if the eligibility criterion to initiate ART was CD4 count <350 cells/µL compared with upon entry to care. In multivariate sensitivity analysis, the authors reported higher mortality when ART was initiated upon entry to care compared with CD4 count <350 cells/µL when moderate rates of fatal ART toxicity (0.25/100 PYs) were combined with increased rates of withdrawal from care (>1.1-fold higher) and increased rates of treatment failure (>2.1-fold higher).

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Baernighausen, 2012, Proceedings of the National Academy of Sciences of the United States of America (704)	To evaluate whether it is possible to achieve the same impact, obtainable by initiating ART upon entry into care, and possibly at a lower cost, by increasing coverage of VMC and ART at CD4 count <350/µL	Mathematical model	The model was calibrated to data from South Africa	The impact of high ART coverage together with high VMC coverage on HIV incidence is approximately the same as obtained by initiating ART upon entry to care, for USD 5 billion less over 2009–2020. The cost per infection averted is respectively $ 1,096 for VMC, $6,790 for ART and $8,375 for treatment as prevention (defined here as frequent testing of the entire population and initiation of ART upon entry to care). The cost per death averted is $5,198 for VMC, $5,604 for ART and USD 7,739 for treatment as prevention. The authors concluded that the most cost-effective HIV prevention strategy is to expand VMC coverage and then scale up ART, but the most cost-effective HIV-mortality reduction strategy is to scale up VMC and ART together.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Baggaley, 2006, PLoS Medicine (688)	To explore through the use of modelling, the epidemiological impacts of alternative strategies of initiating ART	Mathematical model	The model parameter set was chosen to mimic an epidemic in a resource-poor setting.	The authors reported that ART cannot be seen as a direct prevention measure for HIV transmission, regardless of the degree of coverage and therefore that counselling of patients to promote safe sexual practices is crucial and must aim to be durable over time. Scaling up treatment of pre-AIDS patients resulted in higher number of infections being averted per PY of treatment, but the absolute number of infections averted remained small.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Bendavid, 2010, Archives of Internal Medicine (689)	To assess the epidemiological health effect of four different treatment strategies including test and treat, linkage to care and reducing loss to follow-up	Mathematical model	The model parameter set was chosen to mimic the South African HIV population where HIV transmission is predominantly heterosexual	The authors estimated that the number of new infections in the adult South African population that would occur over the next 10 years is 4.5 (95% CI: 3.8, 5.1) million in the status quo strategy, and 1.2 (95% CI: 0.9, 1.6) million in a comprehensive strategy; a 73.2% reduction. They found that even relatively modest improvements in linkage to care and prevention of loss to follow-up could lead to substantial reductions in mortality and number of new HIV infections. A 10% higher linkage and 6% reduction in loss to follow-up was associated with a 36% reduction in HIV infections compared with UTT alone.
Cremin, 2013, AIDS (703)	To evaluate the potential impact and cost-effectiveness of ART-based HIV prevention strategies (PrEP for HIV-negative persons and ART initiation at higher CD4 count for HIV-positive persons)	Mathematical model	The model reflects a hyperendemic setting with relatively low levels of condom use	Provision of ART to more HIV-positive individuals at a higher CD4 count, rather than providing PrEP to HIV-negative individuals, leads to a higher number of infections being averted and more quality-adjusted life-years. Nevertheless ART alone is unable to reduce HIV incidence to very low levels.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Eaton, 2012, PloS Medicine (685)	To compare the results from several mathematical models simulating the same ART intervention programmes to understand the extent to which models agree about the epidemiological impact of expanded ART	12 independent mathematical models	Models were calibrated to South Africa	For a scenario in which 80% of HIV-infected people start ART on average 1 year after the CD4 count falls below 350 cells/ml and 85% remain on treatment after 3 years, the models found that HIV incidence would be 35–54% lower 8 years after the introduction of ART, compared with a counterfactual scenario where ART is not available. The models found heterogeneity in long-term projections (38 years) of HIV incidence, as well as on the impact of more optimistic interventions, such as immediate ART initiation. The number of PYs of ART per infection averted over 8 years varied from 5.8 to 18.7. Considering the actual roll-out of ART in South Africa, seven models estimated that current HIV incidence was 17% to 32% lower than it would have been if ART were not available.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
El-Sadr, 2011, AIDS (709)	To predict the epidemic impact of treating HIV serodifferent couples to prevent transmission	Mathematical model	The model was parameterized using data from Ghana, Lesotho, Malawi and Rwanda	The model suggested that reduction in HIV incidence due to treatment of serodifferent couples will be greatest in populations with higher HIV prevalence and/or a greater percentage of couples in serodifferent partnerships. The authors conclude that, although treatment of serodifferent couples is unlikely to be the sole answer for controlling HIV epidemics, it could significantly reduce HIV incidence and prevent a substantial number of infections in certain countries if high coverage levels are reached.
Granich, 2009, Lancet (686)	To explore the effect of various HIV testing and treatment strategies on the long-term dynamics of the epidemic	Deterministic mathematical model	The model parameter set was chosen to mimic the epidemic in South Africa as the test case for a generalized HIV epidemic, assuming an almost exclusively heterosexual epidemic	The model suggests that UTT in the context of other prevention interventions could reduce transmission to the point at which elimination might be feasible by 2020 in a generalized epidemic, such as that in South Africa.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Granich, 2012, PLoS One (691)	To investigate the cost-effectiveness of expanded ART access in South Africa	Mathematical model and economic analysis	The model parameter set was chosen to mimic the adult South African HIV epidemic from 2011 to 2050, assuming 90% annual HIV testing coverage. Four ART eligibility scenarios were considered, offering ART at: (i) CD4 count<200 cells/µL (current practice); (ii) CD4<350 cells/µL; (iii) CD4<500 cells/µL; (iv) any CD4 count	Over 40 years, 7.6 million new HIV infections and 10.4 million deaths were predicted under current standards (scenario (i)). For the other scenarios these figures were (ii) 6.2 and 8.9 (iii) 4.7 and 7.4 (iv) 3.3 and 6.5, respectively. All scenarios were cost-saving compared with scenario (i), with breakeven by (ii) 2013 and (iv) 2023. Sensitivity analyses suggested that poor retention in care and predominant acute phase transmission could reduce savings by 7%. Expanding access to care could potentially reduce the number of new infections and result in cost savings.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Hallett, 2011, Plos Medicine, (705)	To evaluate the cost-effectiveness of earlier ART and/or PrEP in serodifferent couples in South Africa	Microsimulation model	The model simulates two types of stable serodifferent heterosexual couples in South Africa: low risk (HIV incidence 1.8/100 PYs at risk), similar to those recruited in the study Partners in Prevention HSV/HIV Transmission study cohort and what they considered more typical with an HIV incidence around 8 /100 PYs at risk	They compared 4 different PrEP implementations strategies: (i) always once the couple is identified as serodifferent, (ii) only until one year after the HIV-positive partner has been initiated on ART, (iii) only until ART initiation of the HIV-positive partner, (iv) only when trying to conceive a pregnancy or during pregnancy. This was evaluated in the context of the HIV-positive partner being initiated on ART at CD4<200 cells/µL or CD4<350 cells/µL. In addition they compared strategy (iii) with ART initiation in the HIV-positive partner at CD4<500 cells/µL. They found that strategy (iii) was the most cost-effective strategy because the initial higher cost of PrEP was counterbalance by saving in ART, because of the reduction in HIV incidence. When comparing to earlier ART initiation this was the most cost-effective strategy for the low risk couples, while for the higher risk couples the combination of PrEP (iii) and ART initiation at CD4<350 cells/µL was associated with the best cost-effectiveness.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Hontelez, 2013, Plos Medicine, (696)	To explore the impact of different model structure and assumption on the long-term impact (38 years) of UTT (90% coverage of annual HIV testing and ART initiation at diagnosis)	9 different mathematical models, from a deterministic model similar to Granich (686) to the most complex considered being STDSIM	The model reproduces the South African HIV epidemic.	They found that all model predicted that UTT would lead to HIV elimination (HIV incidence of <1/1,000) by 2050. However they found that models capturing a higher level of realism and complexity predict that it would take longer to achieve HIV elimination, but would still conclude that it is a cost-effective intervention.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Johnson, 2012, Journal of the Royal Society Interface (700)	To assess the extent to which prevention and treatment programmes have reduced HIV incidence	Two dynamic mathematical models (STI-HIV Interaction Model and ASSA2003 AIDS and Demographic Model)	The models mimic the adult South African HIV epidemic from 2000 to 2008, using household survey and antenatal HIV prevalence data and death data to estimate HIV incidence	STI-HIV: Real-life incidence of HIV estimated to be 2.11 (95% CI: 1.97, 2.26) in 2000–2005 and 1.86 (95% CI: 1.73, 2.00) in 2005–2008. Incidence was reduced by 37% (95% CI: 34, 41%) compared with if no condoms had been used, and by 8.1% (95% CI: 6.0, 9.4%) in the absence of ART, ASSA2003: Real-life incidence of HIV was estimated to be 1.90 (95% CI: 1.77, 2.03) in 2000–2005 and 1.62 (95% CI: 1.45, 1.79) in 2005–2008. Incidence was reduced by 23% (95% CI: 14, 34%) compared with if no condoms had been used, and by 1.4% (95% CI: 0.7, 2.6%) in the absence of ART. Increased condom use therefore appears to be the most significant factor explaining the recent decline in HIV incidence in South Africa.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Klein, 2014, AIDS, (698)	To understand the impact of ART drop out and re-enrollment in HIV care once lost from care on the cost-effectiveness of expanding access to care and modifying the eligibility criteria from CD4<350 cells/µL to all people diagnosed with HIV, see Eaton et al. (692)	Individual based stochastic model, called EMOD-HIV, calibrated to South Africa	The model was calibrated to the HIV epidemic in South Africa	They considered three level of re-enrolment after being drop out: 0%, 50% and 100% and an additional strategy of 0% drop-out, under the circumstance of ART initiation at CD4<350 cells/µL and ART initiation at diagnosis. They found that the initial most cost-effective approach is to improve retention on ART and only once this target has been achieved it is cost-effective to initiate more people on ART. The most cost-effective way to increase the number of people on ART they found was by increasing HIV testing and linkage to care, while maintaining the eligibility criteria at CD4<350 cells/µL rather than changing the eligibility criteria so that all people diagnosed are eligible for ART.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Kretzschmar, 2013, Proceedings of the National Academy of Sciences of the United States of America (695)	To determine whether a treatment as prevention strategy can lead to HIV elimination, and whether achieving this goal is likely to be cost-effective	Deterministic mathematical model	A number of hypothetical HIV epidemics were considered, defined according to their basic reproduction number (R_0)	When infectivity is set at its baseline values, annual treatment uptake of more 70% is needed for elimination, which corresponds, to approximately 85% coverage. The authors found that elimination is only feasible in populations with very low R_0 (approximately 2 or lower) and high annual treatment uptake.
Murnane, 2012, PLoS One (707)	To investigate the utility of VL-guided ART initiation to prevent HIV transmission	Mathematical model	The model uses data from an RCT of 3,381 HIV serodifferent couples without ART from 7 countries in southern and east Africa	Treating all with persons with a CD4 count <500 cells/µL would avert 1,569 (47.6%) new infections. Treating all with persons with a VL ≥500,000 copies/mL would avert 1,336 (40.5%) new infections. Treating all persons with a VL ≥100,000 copies/mL would avert 2,401 (72.8%) new infections. Universal treatment would avert 3,165 (96.0%) new infections. Inclusion of VL in ART initiation guidelines could permit targeting ART resources to HIV-1-infected persons who have a higher risk of transmission.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Palombi, 2012, Clinical Infectious Diseases (697)	To model the effect of initiating ART at CD4 count >350 cells/µL on HIV transmission, with the intent of extending ART to the entire HIV-positive population within a short period of time	Mathematical model	The model mimics the HIV epidemic in sub-Saharan Africa using cohort data from the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Program (in Malawi and Mozambique). January 2002–July 2009	A 5-fold reduction in infectivity (from 1.6% to 0.3%) occurred within 3 years when triple ART was used. The annual incidence of HIV infection decreased from 7% to 2% in 2 years, and the prevalence was halved, from 12% to 6%, in 11 years. The authors concluded that treatment of all infected individuals could result in substantial reductions in incident HIV infections and argue that a targeted implementation strategy with wide population coverage would be feasible in sub-Saharan Africa.
Powers, 2011, Lancet, (587)	To model the impact of an intervention reducing the per contact probability to 0.000033, targeted to early infection (first 6 months), chronic infection or both	Deterministic mathematical model	The model included sexual behavioural data and virological data from a STIs clinic in Lilongwe, Malawi and calibrated to HIV prevalence data from sentinel ANC in Lilongwe.	The authors found that the early stage is responsible for 38.4% (95% credible interval: 18.6-52.3) of infections, but that targeting this stage (they assumed the intervention would reasonably be able to be introduced only 3 weeks from infection) would not lead to elimination in 30 years. An intervention targeted at chronic infection would lead to <1/1,000 new infections per year, if the coverage is >95% and this does not lead to an increase in life-expectancy (as it is the case for ART) or if the coverage is >99% with an increase in life-expectancy of 10-15 years.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Wagner, 2013, Mathematical Biosciences and Engineering, (699)	To model the potential impact of a universal test-and-treat strategy, based on annual HIV testing for all South African adults and providing immediate ART for all HIV-positive adults regardless of CD4 count	Mathematical model	The model mimics the adult HIV epidemic in South Africa	The authors found that modelling an increased length of survival time on ART in order to reflect a more realistic situation than previous studies had a significant impact on the probability of HIV elimination using a test-and-treat strategy. The authors concluded that an increased length of survival time on ART reduces the probability of eliminating HIV and decreases the cost-effectiveness of using universal test-and-treat strategies.
Walensky, 2013, New England Journal of Medicine (708)	To compare cost-effectiveness of early initiation of ART (CD4 count between 350 and 550 cells/µL) compared with delayed ART (<250 cells/µL), for five-year and lifetime outcomes of cumulative HIV transmissions	Mathematical model	Model of HIV-positive partners in heterosexual serodifferent couples in South Africa and India (using data from HPTN 052 study)	Early ART remained very cost-effective over a lifetime under most modelled assumptions in the two countries. The authors concluded that early ART for serodifferent couples in RLS could have individual, public health, and economic benefits.
Wilson, 2008, Lancet (693)	To estimate the cumulative risk of HIV transmission from HIV serodifferent couples, where the index partner is effectively treated over a prolonged period	Mathematical model	Mathematical model of heterosexual and homosexual serodifferent couples applying HIV transmission risk calculated using data from the Rakai study to estimate HIV transmission risk and Australian data for sexual risk behaviour	The risk of HIV transmission in heterosexual couples in the presence of effective treatment is low but not zero and the transmission risk in male homosexual partnerships is high over repeated exposures. There is potential for substantial increase in HIV incidence.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Yusuf, 2012, Journal of Biological Dynamics (701)	To model the effect of change in sexual habits and increased ART coverage to find the optimal combination of the two measures that will minimize cost while reducing HIV incidence	Mathematical model	Model parameters were chosen to mimic the HIV epidemic in South Africa 2006	The authors concluded that implementation of a proposed strategy whereby individuals remain faithful to their sexual partners, reduce the number of sexual partners to the minimum possible and avoid extra-marital affairs for the rest of their lives and initiation of ART in people in the pre-AIDS stage would reduce the number of new cases leading towards eradication by 10 years.
Observational Studies				
Anglemyer, 2013, Journal of the American Medical Association, (672)	To evaluate the association of ART with risk of HIV transmission in serodifferent couples	Meta-analysis	9 observational studies (49,083 couples) and 1 RCT (1,763 couples) of HIV transmission risk in serodifferent couples according to whether the HIV-positive partner was on ART. Observational studies: Italy, Brazil, Spain, China, Zambia, Rwanda, Uganda, Botswana, Kenya, South Africa, and Tanzania. RCT: Botswana, Brazil, India, Malawi, Kenya, South Africa, Thailand, United States and Zimbabwe Published 1994–2012	ART was associated with a lower risk of transmission partners in 8 observational studies (rate ratio ranged from 0.08 to 0.91), while in one study no association was found. The estimated summary rate ratio of 0.58 (95% CI: 0.35, 0.96) was obtained for the 9 observational studies. In sensitivity analyses, excluding the studies without adequate person-time data or in which only one antiretroviral drug was used, the summary rate ratio was 0.36 (95% CI: 0.17, 0.75).

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Apondi, 2011, AIDS (1222)	To investigate HIV heterosexual transmission risk among HIV-positive adults on ART	Prospective cohort study	928 HIV serodifferent couples in Uganda with the HIV-positive partner receiving ART; 81% had more than 3 years' follow-up	Estimated HIV transmission risk decreased by 91% from 47.3 per 1,000 PYs at study entry to 4.2 per 1,000 PYs after 36 months. Despite increased sexual activity among HIV-positive individuals over 3 years on ART, risky sex and estimated risk of HIV transmission remained lower than baseline levels.
Attia, 2009, AIDS (429)	To synthesize the evidence on the risk of HIV transmission through condom-less sexual intercourse according to VL levels in plasma and treatment with ART	Systematic review and meta-analysis of observational cohort studies of HIV serodifferent couples	11 cohorts reporting on 5,021 serodifferent couples and 461 HIV-transmission events	The rate of transmission overall from ART-treated patients was 0.46 (95% CI: 0.19, 1.09) per 100 PYs, based on 5 events. The transmission rate from a seropositive partner with VL <400 copies/mL on ART, based on 2 studies, was 0 (95% CI: 0.0, 1.27) and 0.16 (95% CI: 0.02, 1.13) per 100 PYs if not on ART, based on 5 studies and 1 event.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Baggaley, 2010, International Journal of Epidemiology (1223)	To assess the per-act and per-partner HIV transmission risk from anal intercourse exposure for heterosexuals and MSM and its implications for HIV prevention	Systematic review and meta-analysis	4 publications reporting per-act and 12 publications reporting per-partner studies	The predicted HIV transmission probabilities per-act for condom-less vaginal intercourse or CLIAI and CLRAI with successful ART are 0.013 and 0.061%, respectively, i.e. 96% lower than without therapy. Using another function of infectivity by plasma VL, the predicted per-act condom-less vaginal intercourse/CLIAI and CLRAI estimates with successful ART are 0.0002 and 0.0011%, respectively, i.e. 99.9% lower than without therapy.
Baggaley, 2013, Epidemiology (673)	To systematically review the effect of ART on HIV transmission and to conduct a meta-analysis of HIV-1 infectiousness per heterosexual partnership	Systematic review and meta-analysis of observational prospective studies	9 studies where it was possible to compare between ART and non-ART users within studies (ART-stratified studies) and 41 studies that did not stratify by ART use	The authors estimate that incidence rates were 0.2 per 100 PYs (95% CI: 0.07, 0.7) and 3.6 per 100 PYs (95% CI: 2.0, 6.5) for couples where the HIV-positive partner was on ART and not on ART, respectively ($p<0.001$). This represents a 91% (95% CI: 79, 96%) reduction in per-partner HIV-1 incidence rate with ART use. [The results are reported only for the 9 studies where the comparison was between ART and non-ART users.]

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Birungi, 2012 Journal of the International AIDS Society (668)	To evaluate the association between the HIV-positive partner being on ART and the risk of the HIV-negative partner of becoming infected with HIV	Observational cohort study	586 serodifferent heterosexual couples aged ≥18 years, where the HIV-positive partner was a client of The AIDS Support Organization in Jinja, rural Uganda. The HIV-positive partner was on ART if eligible (CD4 count ≤250 cells/µL or WHO Stage III or IV disease) or not on ART, if not yet eligible	There were 9 new HIV infections in serodifferent couple where the HIV-positive partner was on ART and 8 new infections in couples where the HIV-positive partner was off ART, for an overall incidence rate ratio of 1.16 (p=0.564). Therefore the authors did not find an association between the HIV-positive partner being on ART and the risk of the partner becoming infected with HIV.
Castilla, 2005, J Acquir Immune Defic Syndr (430)	To estimate the impact of ART use on HIV prevalence among steady HIV serodifferent couples	Cross-sectional analysis	393 steady HIV serodifferent couples seen in care between 1991 and 2003 in Madrid, Spain	HIV prevalence among partners of index cases who had not received ART was 8.6%, whereas no partner was infected in couples in which the index case had been treated with ART (p=0.0123). HIV prevalence among non-index partners decreased from 10.3% during the pre-ART period (1991–1995) to 1.9% during the late ART period (1999–2003; p=0.0061).
Del Romero, 2010, British Medical Journal (659)	To estimate the risk and probability of heterosexual transmission of HIV from people living with HIV on ART	Cross-sectional and longitudinal analysis of a cohort study	476 stable (reporting this sexual relationship as the only risk exposure) HIV serodifferent heterosexual couples followed in 1989 and in 2008 in Madrid, Spain	9.2% HIV prevalence in non-index partners at enrolment, where the index partner was not on ART (n=44), 0% in couples where the index partner was on ART (n=149). The authors concluded that transmission of HIV from successfully treated people cannot be excluded.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Donnell, 2010, Lancet (431)	To assess the effect of ART use by HIV-positive people on risk of transmission to their uninfected partner	Observational analysis of RCT data (Partners in HSV/HIV transmission study)	Study of 3,381 HIV serodifferent couples from 14 sites in 7 countries in East and Southern Africa followed between November 2004 and October 2008; the index HIV-positive person was both HIV and HSV-2 positive with a CD4 count ≥250 cells/μL	1/103 genetically linked HIV transmissions were from an infected participant who had started ART, corresponding to transmission rates of 0.37 (95% CI: 0.09, 2.04) per 100 PYs in those who had initiated ART and 2.24 (95% CI: 1.84, 2.72) per 100 PYs in those who had not – a 92% reduction (adjusted IRR: 0.08; 95% CI: 0.00, 0.57; p=0·004).
Jia, 2013, Lancet (667)	To investigate the rate of HIV transmission between heterosexual HIV serodifferent couples, according to ART status of the HIV-positive partner	Retrospective observational cohort study	38,862 HIV serodifferent heterosexual couples (101,295 PYs of follow-up) participating in national HIV epidemiology and treatment databases between 1 January 2003 and 31 December 2011 in China	Rate per 100 PYs of HIV infection were 2.6 (95% CI: 2.4, 2.8) among couples where the HIV-positive partner was ART-naive, and 1.3 (95% CI: 1.2, 1.3) among couples where the HIV-positive partner was receiving ART. Adjusted HR was 0.74 (95% CI: 0.65, 0.84) for ART-naive vs treated. This reduction was seen across almost all demographic subgroups except for people who people who inject drugs. Therefore treatment as a prevention strategy is a feasible public health strategy.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Jin, 2010, AIDS (1224)	To estimate per-contact probability of HIV transmission in homosexual men due to various forms of UAI in the era of ART	Health In Men (HIM) study, observational longitudinal cohort study	1,427 community-based HIV-negative homosexual men in Sydney, Australia followed from June 2001 to June 2007	Estimated per-contact probability of HIV transmission: 1.43% (95% CI: 0.48, 2.85) for receptive UAI if ejaculation occurred inside the rectum; 0.65% (95% CI: 0.15, 1.53) for receptive UAI if withdrawal prior to ejaculation; 0.11% (95% CI: 0.02, 0.24) for insertive UAI in circumcised men; 0.62% (95% CI: 0.07, 1.68) for insertive in uncircumcised men.
Loutfy, 2013, PLoS One (674)	To estimate the risk of heterosexual HIV transmission between serodifferent couples when the HIV-positive partner has a fully suppressed VL on ART	Systematic review and meta-analysis	Systematic review of 1 RCT and 5 cohort studies estimating HIV transmission rate when an HIV-positive partner has a fully suppressed VL on ART, published up to November 2012	The estimated HIV incidence was 0 (95% CI: 0, 0.05) per 100 PYs when the suppressed VL was confirmed at the time of transmission and 0.14 (0.04–0.31) per 100 PYs regardless of whether the VL was confirmed as suppressed or not. This corresponds to a pooled OR for on ART vs not on ART of 0.05 (95% CI: 0.01, 0.17). The authors suggest there is minimal risk of sexual HIV transmission for heterosexual serodifferent couples when the HIV-positive partner had full viral suppression on ART, with caveats regarding sexual intercourse type, STIs and condom use.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Melo, 2008, Sexually Transmitted Diseases (664)	To estimate sexual HIV transmission rates and assess the behavioural and clinical factors for HIV transmission	Observational cohort study	93 HIV-serodifferent couples from Porto Alegre, southern Brazil, followed between 2000 and 2006 with no prior ART use	Among couples where the index person started ART (n=41) no SCs occurred, while in the remaining couples (n=52), SCs were observed (incidence: 11.5%; 95% CI: 4.81, 22.45).
Reynolds, 2011, AIDS (665)	To evaluate the impact of ART on HIV transmission rates among HIV serodifferent couples	Observational cohort study (Rakai)	250 HIV serodifferent heterosexual couples in Rakai, Uganda, followed between 2004 and 2009	42 HIV transmissions were seen in 459.4 PYs before ART initiation (incidence: 9.2 per 100 PYs; 95% CI: 6.59, 12.36). In 32 couples in which the HIV index partners started ART, no HIV transmissions occurred during 53.6 PYs.
Sullivan, 2009, IAS abstract (666)	To estimate the incidence density of HIV transmission by ART status of the HIV-infected partner in the serodifferent couples	Observational cohort study	2,993 HIV-serodifferent couples in Rwanda and Zambia followed for 5,609 PYs in 2002–2008	There were 4 new HIV infections in the couples where the HIV-positive partner was on ART and 171 in the couples where the partner was not on ART. The estimated HIV incidence density was 0.7% in couples where the HIV-positive partner was on ART, and 3.4% when off ART (rate ratio: 0.21; 95% CI: 0.08, 0.59).
Tanser, 2013, Science (670)	To assess whether substantial reductions in HIV incidence can be obtained in practice, outside of RCTs and in the context of sub-Saharan Africa	Observational prospective cohort study	Cohort of individuals who were HIV-negative at baseline (total follow-up 16,667 PYs) in rural KwaZulu-Natal, South Africa followed between 2004 and 2011	The authors found that the risk of HIV acquisition for a certain individual decreased significantly with increasing ART coverage in the surrounding local community.

First author, year of publication, journal, reference	Study aim	Study design	Study population and study period	Results/conclusions
Wang, 2010, J of Acquir Immune Defic Syndr (669)	To estimate the HIV transmission risk and assess the behavioural, clinical, and quality-of-life risk factors for HIV transmission	Observational cohort study	1,927 HIV serodifferent heterosexual couples followed between January 2006 and December 2008 in Henan, China. HIV-positive individual was former plasma donor	84 HIV transmissions occurred over 4918 PYs, an incidence of 1.71/100 PYs. Most respondents (80.4%) had spouses who were on ART. There was no statistical difference in the SC rates between those couples who had a spouse on ART (4.8%) and those couples whose HIV-positive spouse was not on ART (3.2%) (p=0.12).

AIDS: acquired immunodeficiency syndrome; ART: antiretroviral therapy; CI: confidence interval; CLIAI: condom-less insertive anal intercourse; CLRAI: condom-less receptive anal intercourse; HIV: human immunodeficiency virus; HTC: HIV testing and counselling; ICER: incremental cost-effectiveness ratio; IQR: interquartile range; IRR: incidence rate ratio; MSM: men who have sex with men; OR: odds ratio; PrEP: pre-exposure prophylaxis; PY: person-year; QALY: quality-adjusted life-years; RCT: randomized controlled trial; RLS: resource limited settings; SC: seroconversion; STIs: sexually transmitted infections; UAI: condom-less anal intercourse; UTT: universal test and treat; VL: viral load; VMC: voluntary medical circumcision;

Appendix XIII. Modified Poisson Regression analysis

This appendix presents the rationale and the theory behind the use of the modified Poisson regression analysis. It introduces briefly the logistic regression, generally used for bivariate data, and the Poisson regression, which has the advantage over the logistic regression of providing a more intuitive outcome and finally it describes the modified Poisson regression, which allows to correctly quantify the association between a certain outcome and a covariate, using the more intuitive RR and correctly estimating the error for the RR.

Rationale

Often, we wish to investigate whether or not the person experiences an event of interest, in this case whether they had a resistance test following ART interruption (Aim 1a) and in those who had a resistance test how many still had NNRTI resistance (Aim1b). In this case the outcome is binary (dichotomous), because there are only two possible outcomes, either they did have the resistance test or not. Most common binary outcomes in epidemiological research are success/failure, alive/dead. The outcome is often referred to as an event and we are interested in the probability of an event occurring. This can be expressed in terms of risk or odds.

The risk on an event occurring by a certain time point (t) can be calculated as:

$$Risk\ of\ event = p = \frac{Number\ of\ people\ with\ the\ event\ during\ the\ study\ period}{Number\ of\ people\ without\ the\ event\ at\ the\ START\ of\ the\ study\ period}$$

while the odds of an event is defined as:

$$Odds\ of\ event = \frac{Number\ of\ people\ with\ the\ event\ over\ the\ study\ period}{Number\ of\ people\ without\ the\ event\ over\ the\ study\ period} = \frac{p}{1-p}$$

Thus, p is used to calculate the odds of the event occurring.

To measure the association between a certain event *y* and a certain factor *x*, for example exposed to a certain predictor (x=1) and unexposed (x=2), two common measures of association are the RR, also called risk ratio, defined as:

$$Relative\ risk = \frac{Risk_1}{Risk_2} = \frac{p_1}{p_2}$$

and the odds ratio (OR):

$$Odds\ Ratio\ (OR) = \frac{odds_1}{odds_2} = \frac{p_1/(1-p_1)}{p_2/(1-p_2)}$$

Both measures can vary from 0, when the risk/odds in the group exposed is 0, to ∞, when the risk/odds in the group unexposed is 0. A value of 1 means that the risk/odds of an event occurring in the two groups is the same, a value greater than 1 that the group exposed (x=1) has greater risk/odds of an event than the second, the opposite if the value is less than 1.

When the outcome is rare, conventionally less than 10% (the probability of occurring is very small, p~0), the odds of an event is similar to the probability of an event and so the difference between a RR and an OR is negligible.

When the outcome is dichotomous, the most commonly used techniques are logistic regression and Poisson regression; although Poisson regression can be used more generally for count data.

Logistic regression

A probability (p) of an event is a number between 0 and 1. In order to perform a logistic regression analysis this has to be transformed so that it takes values between minus infinity (-∞) and infinity (+∞). The transformation to use logistic regression is called logit, which is the logarithm of the odds of the event. The logistic regression is used to model the log of the odds, where the name logistic comes from the fact that we use the log transformation to do the analysis.

Equation 8.1 Logistic regression model

$$log\left(\frac{p}{1-p}\right) = \alpha + \beta_1 x_1 + \beta_2 x_2 + \cdots + \beta_n x_n$$

The α is the intercept, the value of logit (log-odds) when all the covariates (x_1,…x_n) have a value of 0, β_1… β_n are regression coefficients and x_1...x_n are explanatory variables, covariates.

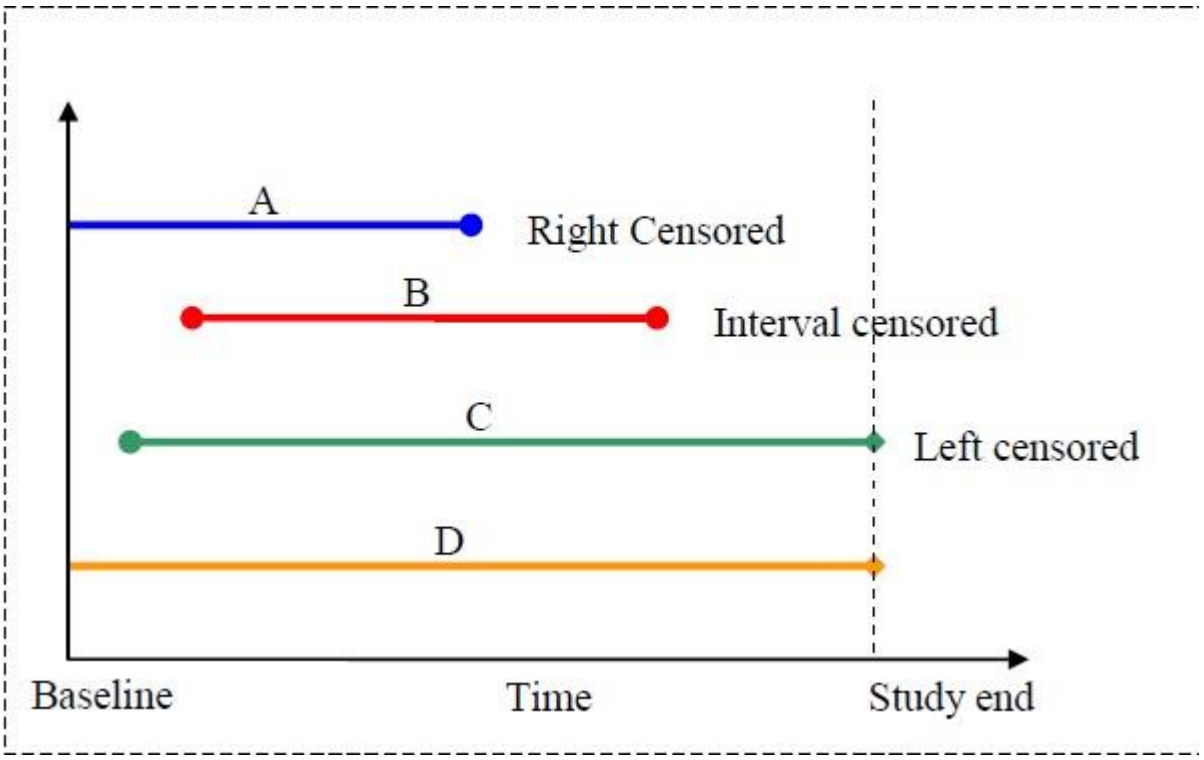
In equation 8.1, the coefficient (β_i) from the model reflects the independent effect of the variable (x_i) that is not explained by the other factors. The equation can be used to predict the probability that an event occurs for each individual by using the estimated for the intercept and the coefficient and the value of x_1,…,x_n for that particular individual. As you can see from equation 8.1, this type of model assumes a linear relationship between the explanatory variables and the log odds of an event. It can be used to estimate the OR that compares the outcomes from two groups of patients (exposed, x=1, and unexposed, x=2) by anti–logging the coefficients (β_i).

If not all people are followed for the same amount of time, the risk of an event, or the odds, are not the most appropriate measure, because they do not take into account for how long the patients have been followed for. When participants are followed for a variable length of time, the Poisson regression is regarded as an appropriate technique for analysing rare events.

Poisson regression analysis

Poisson regression analysis, as well as survival analysis, allows dealing with follow-up time and censored data. An observation is censored if the value is only partially known. In case of time to event data, they can be right censored, left censored or interval censored. The figure below shows the three different kinds of censoring.

Figure. Examples of different types of censoring



The most common type of censoring, is right censoring, which occurs when the period of observation (follow-up) is stopped before the event of interest has occurred, therefore what is known is that by the end of the study the patient has not experienced the event of interest, but it is not known whether the event ever occurred after the date of censoring and when. Left censoring occurs when the patient has already experienced a period of time (without the event) before they are formally followed in the study, so usually the patient is not included into the study. Interval censoring happens when both occur.

If censoring was ignored and only complete data considered, information would be disregarded and could bias the conclusion on the distribution of event times.

The Poisson regression analysis is similar to logistic regression, but the outcome variable is a rate, rather than the odds an event, although it can be applied to binomial data and in that case the outcome variable is the risk of an event.

$$Rate\ of\ event = \frac{Number\ of\ people\ with\ the\ event\ during\ the\ study\ period}{Total\ number\ of\ person - years\ of\ follow - up}$$

One year of follow-up can be accumulated if a single person is followed for 1 year, or 12 persons are followed for a month. If the rate is X per 100 PY of follow-up, this means that if we followed 100 people for 1 year we would expect X number of events to occur. A rate is a number between 0 and infinity. If more than 20 events are observed then 95% confidence intervals (CIs) are calculated using the normal approximation to the Poisson distribution. Where the number of events is ≤ 20 then the exact Poisson distribution is used to calculate the 95% CI.

Poisson regression analysis is used to model the rate ratios and again allows for adjustment of numerous different variables. As the assumptions of linear regression again are not met, the log of the rate or the risk is modelled and then it is transformed. The model is interpreted in a similar way to logistic regression, but instead of ORs the estimates are rates ratios or risk ratio, also called "relative rates". Assuming that a certain subject *i* has an underlying risk indicated as $\pi(x_i)$, which is a function of the factor x_i, because $\pi(x_i)$ must be positive, as it is the case in the logistic regression, the logarithmic function is an obvious choice

$$log[\pi(x_i)] = \alpha + \beta_1 x_1 + \cdots + \beta_n x_n$$

The RR is then giving by anti-logging the coefficient ($exp(\beta_i)$).

To calculate the 95% CI for the RR, the Delta method is used. The logarithm of the RR has a sampling distribution that is approximately Normal with a variance that can be estimated by a formula (Delta methods) based on the number of subject in each group and the event rate. Using this method, a CI which is symmetric around log(RR) can be defined as:

$$CI = log(RR) \pm SE \times z_{\propto}$$

Where z_α is the standard score for the level of significance α (usually 0.05) and SE is the standard error. By anti-logging the lower and upper limit, an asymmetric CI around the RR can be obtained.

Modified Poisson regression analysis

Despite the fact that only if the event is very rare the difference between an OR and a RR is negligible, the OR is often interpreted as a RR, leading to potential exaggeration of the effect communicated.

For this analysis I wanted to express the results in terms of RR, so I wanted to use a Poisson regression model. The issue is that when Poisson regression model is applied to binomial data , the error for the estimated RR will be overestimated (1225).

If the outcome is binomial the data can be summarized as:

Table A.14. Notation for 2-by-2 table

	y=1 (event)	**y=0 (no event)**	**Total**
x=1 (exposed)	A	B	n_1=a+b
x=0 (unexposed)	c	D	n_0=c+d
			n=n_1+n_2

By using the standard likelihood theory, it is obtained that the antilog of the intercept is the risk of event in the unexposed/reference group.

$$exp(\hat{\alpha}) = \frac{c}{n_0}$$

And the antilog of the coefficient β_i , in case of binary outcome is:

$$\widehat{RR} = exp(\hat{\beta}_i) = \frac{an_0}{cn_1}$$

With the estimated variance of the RR given by

$$\widehat{var}(\widehat{RR}) = \frac{1}{a} + \frac{1}{c}$$

When the distribution of the data is binomial, as mentioned the error is mispecified. This problem can be resolved by using a robust error variance procedure known as sandwich estimation. The corrected variance is calculated as:

$$var(\widehat{RR}) = \frac{1}{a^2}\sum_{i=1}^{n_1}[y_i - exp(\alpha + \beta_1 + \cdots + \beta_n)]^2 + \frac{1}{c^2}\sum_{i=1}^{n_0}[y_i - exp(\alpha + \beta_1 + \cdots + \beta_n)]^2$$

which is consistently estimated by

$$\widehat{var}\left(\widehat{RR}\right) = \frac{1}{a} - \frac{1}{n_1} + \frac{1}{c} - \frac{1}{n_0}$$

This estimator is identical to the Delta Method.

If this technique is used I will refer to the Poisson regression as “modified Poisson regression”.

Appendix XIV. Literature review on barriers to HIV care and effective interventions to reduce the leakage in the cascade of care

Additional details on effective interventions to improve awareness of HIV status

Provider-initiated testing and counselling

A cross-sectional study conducted in Botswana 11 months after the introduction of PITC in health centres reported a very favourable response from people who thought it could help to decrease barriers to test, HIV-related stigma and increase access to ART, but it raised concern due to the fact that over half of the people felt they could not refuse it (849). A systematic review focusing on the operational implementation of PITC programmes in sub-Saharan Africa (up to November 2010) reported that although the introduction of PITC had been effective in testing large number of people there was lots of variability across different programmes on the proportion of people who were offered PITC, varying from 24% in a study of outpatients in Ethiopia (1226) up to 94% in a study conducted in South Africa among TB patients (1227). Large variability was found as well on acceptability of PITC and linkage to care for those identified as positive, from 31% in a study among outpatients in South Africa (1001) up to 99% in a study of inpatients in Uganda (852).

A case series study in two primary healthcare clinics in South Africa, where uptake of HIV testing was compared before and after PITC implementation, showed an increase in HIV testing from 31% to 55%. In addition after three months only 3.8% of those found HIV-positive had registered for onsite HIV treatment, highlighting the need for proactive interventions to link people to care once identified as HIV-positive (1228).

A systematic review evaluating the impact of PITC in achieving universal testing of pregnant women estimated that before the implementation of PITC HIV testing uptake ranged from 5.5% to 78.7% and afterwards it increased by a range of 9.9% to 65.6%, with testing uptake ≥85% in eight out of ten studies identified (851).

Nevertheless concerns about difficulty in refusing PITC have been reported (849) and in the literature there is high variability in the proportion of people who were offered PITC (1226;1227) and who accepted it (852;1001). The main barriers to optimal implementation of

PITC included issues related to the logistic, data systems, constraints in human resources in overstretched health systems (1229), but also l difficulty in ensuring linkage to care (1228).

Among specific groups of patients such as TB patients and inpatients, successful results have been reported. In a pilot study conducted in an integrated TB and HIV services in Kenya, where PICT was offered to TB patients and suspects, after a community sensitization campaign and staff training, 89% agreed to test for HIV, showing very high acceptability in this group of patients (850). A RCT investigated the efficacy of offering inpatient PITC in an urban hospital in Uganda compared to offering referral cards and travelling reimbursement to test one week later, after discharge found that in the intervention group 99% tested for HIV compared to 69% in the control group (852).

Couple voluntary counselling and testing

A study conducted in Dar El Salam, Tanzania (853) randomized women attending ANC to individual- or couple-VCT with their sexual partner to arrange at a subsequent visit: 71% of those assigned to individual-VCT tested for HIV compared to 39% of those randomized to couple-VCT. A study conducted in Khayelitsha, Cape Town, South Africa (855) randomized women attending ANC, to either invite (provided with a written invitation) their male sexual partner to VCT or to a pregnancy information session (control). The outcomes were women's acceptance to invite their partners and uptake of VCT in their male sexual partner. In both arms all women accepted to invite their partners, 35% of women for whom their partner was invited for VCT brought their partner for an ANC visit compared to 26% of those who invited their partner for a pregnancy information session. Of more interest, those invited for VCT were almost twice as likely to test for HIV (32% vs 11%), highlighting that providing a written invitation is an efficacious strategy in increasing HIV testing in partner of pregnant women. A study conducted in Congo focused in understanding in which venue male partners were more likely to test for HIV between a neighbourhood health centre, bar or church (854). They found that the uptake of HIV testing in male partners was low: 26% in bars, 21% in church and 18% at the health centres.

Home-based HIV voluntary counselling and testing

Offering the possibility of VCT at a location of the patient choice, rather than at the clinic, was demonstrated in an early RCT conducted in Zambia to increase the probability of being tested

for HIV almost by 5 times (858). 84% of them chose home as favourite location. One of the first studies investigating the possibility of delivering HIV test results at home was conducted in rural Uganda: following a sero-survey conducted in 2001, delivery of HIV counselling and HIV results at home was offered in four study villages. This increased uptake of results from 10 to 37%, and qualitative data within the same studies highlighted the main barriers to testing were inconvenience, fear of stigmatization, and emotional vulnerability of receiving results from public facilities (863). A meta-analysis of 21 studies conducted in five different countries in sub-Saharan Africa (Uganda, Malawi, Kenya, South Africa, and Zambia) reported that Home-Based Voluntary HIV Testing (HBT) uptake ranged from 58% to 99.8%, with a pooled proportion of 83% (95% CI: 80%, 86%) (754), including studies were only household members of people living with HIV or on ART were offered HBT (859-861). Another recent meta-analysis estimating the uptake of different community based-approaches estimated 80% of those offered HBT accepted it and 88% if HBT was offered to household members of an HIV-positive person and people who may have been exposed to HIV (862).

Workplace HIV counselling and testing

The offer of testing for HIV at the workplace occupational clinic, rather than off-site was demonstrated in a RCT conducted in Zimbabwe to lead to an HIV testing uptake of 51% compared to 19% if people were given a voucher to test for HIV off-site at one chain of free-standing VCT centres (865).

A subsequent study conducted in Nigeria, evaluated whether the uptake of HTC at the workplace was different if the peer education was coordinated by people openly living with HIV or by members of staff of unknown HIV status (866). They found that after six months of the intervention implementation the uptake of HTC was four times in the companies where people openly living with HIV were coordinating the intervention.

Although this HIV testing strategy allows one to reach only people who are employed, and plausibly only in large businesses, this study clearly showed that convenience and accessibility to HIV testing are crucial factors. A meta-analysis (862), including in addition to this RCT few other observational studies mainly from sub-Saharan Africa, estimated an overall uptake of 67%, with a wide range from 20% (1230) up to 92% (1231).

Mobile HIV testing for the general population

In the Project Accept, one of the largest RCTs ever conducted, they implemented an intervention including community mobilization through HIV working groups and outreach coordinators, mobile VCT in community centres and other public places, and post-test support services (1232). The overall efficacy of this intervention (mean difference in the proportion of patients receiving HTC in the intervention community compared to control community) was 40.2% (95% CI: 15.5, 64.7) (756). The proportion of people tested for HIV was in Tanzania 37% in the intervention communities compared to 9% in the control communities, in Thailand 69% vs 23% and in Zimbabwe 51% vs 5%.

School-based HIV educational programs

Only a handful of studies worldwide have evaluated the impact of school-based HTC and using observational studies. Across the community-based approaches, this is the one with the lowest uptake (62%; 95% CI: 40%, 85%). Nevertheless this estimate contains a small study conducted in US with an uptake of 20% and a study conducted in Zimbabwe in children aged 5 years or less, which are out of the focus of this thesis (862). The only study conducted in sub-Saharan Africa is presented in section 7.2.1 (869).

Self-testing

In sub-Saharan Africa most of the research on ST has been conducted in Blantyre, Malawi. Initially they conducted a feasibility study (871) where people sampled from the community were offered the possibility of ST plus confirmatory HTC (parallel testing with two rapid finger-prick blood tests), standard HTC alone, or no testing. 92% opted for ST after a brief demonstration and illustrated instructions showing that ST was highly acceptable. In a subsequent study they offered ST through community counsellors to all communities involved in the study, and randomly assigned them to receive facility-based HIV care alone (control arm) or optional home-based assessment and initiation of HIV care (intervention arm) (755). After 12 months 76% of over 16,000 residents had used ST at 12 months since its introduction and 78% of those who disclosed their reactive ST result to counsellors linked to care (872).

In addition, a couple of studies have been conducted among healthcare workers in sub-Saharan Africa. The first reported that among healthcare workers from 7 hospitals in Kenya the uptake was 89% (873) and in a pilot study among healthcare workers in Cape Town 93% (874).

Additional details on effective interventions to improve linkage to care

Referral programs and patient navigator

Only very few studies have evaluated the impact of this intervention. In a study in a rural district in northern Tanzania a referral system to link people diagnosed at a VCT clinic with a government-run HIV treatment clinic in a nearby city was conducted. This system consisted of the use of two detachable-part referral forms, with unique matching numbers on each side to make it easier to access HIV clinics and to allow clinics to check whether people enrolled into HIV care, and to trace those who had given consent, were introduced (878). In addition they provided transportation allowances and a "community escort" from a local home-based care organization in patients attending the HIV clinic, who could offer counselling services. They observed that in the first 18 months the proportion of patients who enrolled at the HIV clinic within a week increased from 18% to 64%, although the proportion who did not register went never below 17%. This intervention was followed by a national HIV testing campaign, which produced a 70% increase in the number of clients referred to HIV compared to the previous 6 months and unfortunately also an increase (7%) in the proportion who remained unregistered.

In a cross-sectional study conducted in Nyanza Province, Kenya during August–September 2009, they assessed the linkage to care following a community-based HTC campaign, of an intervention for people found HIV-positive including: provision of a referral to care, offer of a rapid CD4 count (most received the result within 3h, 30% of them were asked to come back the following day to collect the result) and offer of being visited by a “patient navigator”, who could guide them to enrol into HIV care (876). They found that 87% of patient newly identified as positive received a CD4 count measurement, 63% reported they were enrolled into HIV care within 3 months and 81% reported being enrolled by 10 months (although only 80% could be located and therefore reported whether they were linked to care or not).

Point-of- care CD4

Compared to the traditional laboratory methods, POC CD4 assays do not require transport of blood samples to a centralized laboratory, high technical expertise to conduct flow cytometry and often complex software or systems to ensure results are returned to the patients when they come back to the clinic (879). This technology increased substantially the likelihood of having a CD4 count measured (OR = 4.2; 95% CI: 3.5, 4.9) and of receiving the CD4 count result in those who had a CD4 count measurement (OR = 2.8; 95% CI: 1.5, 5.6).

An important example comes from a cohort study in Mozambique where the introduction of POC CD4 in the primary healthcare clinics allowed a decrease in loss to follow-up before completion of ART assessment (defined as having ART assessment within 90 days from enrolment) from 57% to 21% (757).

Home-based ART initiation following positive self-test

A cluster RCT evaluated this intervention in Blantyre, Malawi (755). In this study, given the confidentiality of ST, they could not measure how many of those who self-tested positive had ART eligibility assessment during a certain time period, for this reason they compared the percentage of adult initiating ART in the two arms and found that it was almost 3-fold in the communities where there was the possibility of home-ART initiation (RR = 2.9; 95% CI: 2.1, 4.2). In addition they found that there was no difference in the % of adults initiating ART if ST was available without home-based ART initiation or if ST was not available, underlining the fact that in order for ST to be effective a proactive intervention to link people to care must be in place.

Additional details on effective interventions to improve retention in pre-ART care

Structural services (free services, cash transfer for transportation, food rations)

To overcome the fact that distance to the clinic is often reported as a barrier to retention in care, some studies have evaluated whether cash transfers for transportation could partly solve this problem. A RCT conducted in Mbarara, Uganda evaluated the impact of a cash transfer of 10,000 to 15,000 Uganda Shillings ($5–$8) to be used for transportation. Only 18% (n=14) of those receiving the cash transfer were LTFU compared to 34% (n=23) in the control group (881) [This paper is not currently available on line because of issues in the CROI website, but this study represents the only RCT evaluating the impact of cash transfer and it has been mentioned in many reviews, for example (828)].

A cohort study in central Haiti evaluated the impact of targeted food assistance programs to people with HIV and either: TB, a BMI<18.5kg/m^2, CD4 count <350/µL (in the prior 3 months) or severe socio-economic conditions within a comprehensive HIV program. At both 6 and 12 months, timely attendance at monthly clinic visits was better in the food assistance group than in the non-food group. The mean number of scheduled visits attended at 6 months (out of 6 visits) was 5.5 for the food assistance group compared to 2.8 ($p < 0.0001$) among those who did not received the support, and at 12 months (out of 12 visits) it was respectively 9.7 and 8.3

(p = 0.007). This study included both patients not yet eligible for ART (30%) and receiving ART, so it does not distinguish between retention in pre-ART care and on ART (882).

It has been demonstrated that food incentives are effective in improving retention in pre-ART care, for example in a study conducted among children in India (1233), nevertheless this has not been assessed yet in sub-Saharan Africa (1234).

Free co-trimoxazole prophylaxis

The provision of free CTX prophylaxis to people not yet eligible for ART has been observed to be effective in improving retention in care in a cohort study in Kenya. They observed that retention in care at 12 months was 84% when free CTX prophylaxis was provided compared to 63% before this happened. After adjusting for confounders, patients enrolled before the introduction of free CTX were more than twice (adjusted HR = 2.6, 95% CI: 1.9, 3.6) as likely to be LTFU compared to those who received free CTX (883).

Intensified post-test counselling and enhanced peer-support

Based on the hypothesis that a reason for the low retention in pre-ART care is the lack of understanding of the importance of engaging in pre-ART care, a RCT was conducted in Uganda evaluating the efficacy of intensified post-test counselling, provided by trained counsellors, together with monthly home visits by community support agents. They found that the proportion who enrolled in pre-ART care (by attending the nearest health centre for a clinical check-up in the subsequent five months) increased by 80% (RR = 1.8, 95% CI: 1.4, 2.1) (884).

Additional details on interventions to improve prompt initiation on ART

Point-of-care CD4

POC CD4, which has been shown to increase linkage to care, is also effective in increasing initiation of ART in those eligible. In a three arm RCT conducted in South Africa patients were randomized to either receive a CD4 count result at time of HIV diagnosis (using POC CD4), to receive written information and standard of care (CD4 collection after 1 week) or standard of care alone. They observed 49% attrition in the standard of care arms and those who received

CD4 result at diagnosis were significantly more likely to present for ART initiation by 3 months (RR = 2.1; 95% CI: 1.4, 3.2) (887).

Similarly in Mozambique they found that the introduction of POC CD4 in the primary healthcare clinics, which allowed completing ART eligibility assessment within three days (median) rather than thirty-two, increased the proportion of patients initiating ART within 60 days from 12% to 22% (757).

Postponement of adherence counselling during the early treatment period

As mentioned, before initiating treatment patients need to undergo adherence counselling visits, nevertheless this is not always the case and it is not clear whether there is a benefit in receiving this adherence counselling session before initiating ART rather than at ART initiation.

A study in Uganda reported that the first resulted in a 49 day delay in ART initiation (since the person was identified as eligible) compared to a 14 day delay if the adherence counselling is provided at ART initiation, without providing any benefit in the first three months in terms of the proportion with average adherence >90% (adjusted OR = 0.8; 95% CI: 0.4, 1.5), absence of treatment gaps longer than 72 hours (adjusted OR = 0.7; 95% CI: 0.2, 1.9), or proportion with VL>400 copies/mL at the visit after 3 months (adjusted OR = 1.1; 95% CI: 0.4, 3.1) (888).

Additional details on barriers to retention on ART and adherence

The first studies to investigate the obstacles in retaining people in care in South Africa were conducted in the Themba Lethu clinic in Johannesburg (892;893). They highlighted the fact that financial constraints was among the major barriers (34% in (892) and 14% in (893)) in particular the transport cost and the necessity to pay for ART. A study conducted in Uganda reported that patients could spend between 30% and 50% of their monthly income to cover transport cost to the access clinic care and ART (894). While side effects of ART were initially reported by 19% of patients LTFU as a reason for it (893), this proportion soon decreased to very low levels in more recent studies(<5%) (892;892;960).

A few psychological barriers have emerged as well as predictors of low retention, such as the fear of disclosing their HIV status (892;897), and religious beliefs or the use of traditional medicine (892;897).

In more recent years factors which have been identified as predictors of adherence to ART include mental disorders, such as symptoms of depression (491;567;895), although there are

some mixed results (567), anxiety (895) and alcohol disorders, although there are very limited data (567).

Several qualitative studies, designed to better understand the reasons why people are lost from care, have been conducted in South Africa (275;847;890;898;900;901). Major reasons reported for not adhering to ART were related to the health system: having to pay for ART (847), experiencing low-quality services (e.g. lack of confidentiality and privacy, drug stock shortages, problems with missing paperwork such as transfer papers or clinic cards, constrained number of health personnel and therefore not sufficient time spent with the provider), issues related to access to care (e.g. long waiting time, difficulty in taking time off work and in booking appointments, risk of forced disclosure due to attending certain clinics or support groups) and feeling better on treatment (275;847;890;898).

Healthcare providers' attitudes and poor communication skills during counselling were also found to be associated with poor adherence to ART (890;891). In addition, it is not uncommon for people to deny the existence their own HIV status, to have more trust in traditional medicine providers than western medicine (847;890;898;899) and in particular not to believe that ART is superior to alternative treatments and in few cases were even poisonous. Finally HIV infection is often perceived as a consequence of a 'bewitchment', which requires therefore consultation with traditional medicine practitioners or faith healers in conjunction or instead of science-based medicine (890;898;899).

Among the unintentional barriers to adherence, costs, as mentioned before, whether direct (treatment cost) (847) or indirect (e.g. transport cost) (275;847) represent one of the key issues, especially because people need to balance amongst compelling competing needs, such as, for example, education or food for their children (890;891). Even more so in situations characterized by the absence of social security and health insurance, social networks play a key role in providing emotional and economic support (847;891;900). It is very difficult to achieve optimal adherence without disclosing HIV to anyone, because it is difficult to reorganize daily activities to include treatment without help from a supporter (847;891) or to get the resources to attend the clinic without help (847;891;900). On the other hand many people are worried about disclosing their HIV status because of fear of stigma and of being rejected by their partners (485;846;890;896). Nevertheless a more recent study found stigma was much less influential than, for example, structural barriers (275). If people managed to disclose their HIV status, they usually receive adherence support and help from group support and family. This

seems to make them feel responsible for treatment success as a form of reward to these people and at the same time it seems like they feel the need to succeed to guarantee help for the future (1235).

Some studies investigated risk factors associated with a higher risk of being LTFU. These include being pregnant at ART initiation (753;902;903), plausibly due to the burden of attending both ANCs and HIV clinics, although there are some contrasting results (1236), and having initiated ART as inpatients (753). An additional factor is having a high nadir CD4 count (above 200 cells/µL) or CD4 count at baseline (484;753), although some conflicting evidence comes from a study conducted in Lesotho, where they found that people initiated on ART with a CD4 between 200-350 cells/µL were 39% less likely to be LTFU than those with a CD4 at baseline <200 cells/µL (904). These conflicting results can partially be explained by the fact that patients with high CD4 counts are more likely to move for work-related reasons while those with low CD4 levels are at higher risk for unascertained deaths (i.e. died but considered lost by the clinic).

A factor, which emerged as protective against being LTFU is having received 6 months of pre-ART care (753) and noticeably in the private sector where it has been found to lead to lower direct cost and decreased mortality (905;906).

Demographic factors associated with a higher risk of being LTFU include male gender (484;892), younger age (753;903) which was found below the age of 30 years to double the risk of being lost from care (903).

Additional details on effective interventions to improve retention on ART

Tracing systems

Following the alarming level of LTFU, several studies have attempted to ascertain the real status of people who were not attending the clinic anymore and to reliably determine whether they were dead, transferred to another clinic or had stopped treatment. In order to do so they implemented tracing systems where people who were considered lost by the clinic (i.e. they had not attended the clinic usually for 3 months) were contacted either by phone or visited at home. This requires a good recording system regarding visit attendance and patient contact information in order to be able to identify the patients who defaulted and to be able to contact them.

A meta-analysis of treatment outcomes of patient considered LTFU (842) reported that the treatment status of 63% of the patients could be ascertained (range across studies: 45% - 86%) and among these 40% were dead (95% CI: 33%, 48%; range across studies: 12%-87%). Not surprisingly they found an inverse association between the rate of LTFU and mortality, which declined from around 60% to 20% as the proportion patients lost to the programme increased from 5% to 50%.

A systematic review of the effect of physical tracing on the estimates of retention on ART, updated to 2011 (494) found that ART programmes which included physical tracing activities classified less people as LTFU (7.6% vs. 15.1%; p<.001), more as dead (10.5% vs. 6.6%; p = .006) and retained more people on ART (80.0 vs. 75.8%; p = .04), of which more retained at the original clinic (80.0% vs. 72.9%; p = .02). Therefore these interventions seem not only to improve the knowledge of patients' vital status, but also the actual re-engagement into care.

Confirmation of the efficacy of tracing systems in improving retention on ART comes also from a very large ecological study including clinics from ten countries in sub-Saharan Africa (912). They reported that attrition was significantly lower in the clinics offering some form of tracing, either by phone, letters, or home visits for patients missing scheduled visits, (53% of the clinics) at 6 months (aRR = 0.86; 95% CI: 0.73, 0.99) and at 12 months since ART initiation (aRR = 0.84, 95% CI: 0.74, 0.96).

Community-based ART programs (including task-shifting and decentralization)

Community-based ART programs (CBART) have been developed as a response to congested health services, to deliver ART to patients underserved because of long distances to HIV care services and to sustain ART adherence.

These programmes can be divided at least into three main groups (913):

(i) home-based ART care, where community health workers, peer community health workers or volunteers visit patients at home to deliver ART medications, monitor patients clinical status by using a checklist (including signs and symptoms of toxicities or disease progression), referring sick patients to the clinic and provide adherence support.

(ii) patient-led community, where patients clinically stable on ART can join community ART groups and they take in turns to visit the clinic to collect ART medications for

all the members of the group and report on clinical status of the other members (913).

(iii) "adherence club" care, where patients stable on ART meet 2 monthly to receive pre-package medications, health assessment and to discuss HIV related topics.

The first type of CBART have been evaluated and implemented in Uganda and Kenya, the second in Mozambique and the third in South Africa.

A cluster RCT conducted in Uganda demonstrated that home-based HIV care through trained lay workers (4-6 weeks training, responsible for 35-40 patients) visiting patients at home every month was equivalent to standard clinic-based care in terms of VF (at 12 months: 84% of those receiving CBART had VL<500 copies/mL compared to 83% in the facility based cohort), mortality (11% in both arms), LTFU (1% in the CBART and 2% in the facility-based cohort) and proportion of patients reporting 100% adherence (94% in CBART versus 91% in facility-based care group) (914). After 36 months, the two arms were still equivalent with 14% of patients having died in the CBART program and 13% in the facility-based care group (916). Several other prospective observational studies in Uganda where CBART was implemented found similar outcomes at 12 and 24 months. Again in Uganda, another type of CBART program was implemented. The difference compared to the previous model is that this was run by community volunteers, who received two days of training and visited weekly a maximum of five people living with HIV to deliver the ART medications, offer them adherence support and refer them to the clinic if they were sick. This prospective cohort study showed that treatment outcomes were similar between patients receiving CBART and facility-based care, with 30% attrition (i.e. LTFU or death) at 24 months (917;918).

In Kenya, community health workers were selected among people living with HIV and receiving ART, they were referred to as community care coordinators and given 7-day didactic training followed by two months of practical training (919). Each of them is responsible for up to 20 clinically stable patients and their duty is to visit the patients monthly to deliver ART medication, monitor and support adherence, and refer them to the clinic if there is clinical need. Otherwise the patients visit the clinic only every three months compared to monthly for the patients not in the CBART programme. They found no significant difference in terms of clinical outcomes (including VL, CD4 count and risk of OIs) between the two groups after 1 year since the implementation of the intervention in terms of LTFU (5% in both arms), mortality (1% in the CBART arm vs 0% in the facility-based arm) and VL suppression in those retained on ART (89% in the CBART arm vs 86% in the facility-based arm).

Observational cohort studies of similar forms of CBART have confirmed these findings. An example comes from Rwanda where they compared CBART programs (including offer of home visits from a community health worker, DOT, food rations, transportation stipends, and other support as needed) to the Rwanda national model programs (920). They found that being in a CBART was associated with a reduced chance of being dead or LTFU in the first year of ART (HR = 0.17; 95% CI: 0.09, 0.35; $p < .0001$).

In Mozambique, the second type of CBART was implemented. Given the highly resource constrained circumstances the Mozambique Minister of Health in collaboration with MSF designed an ART programme, where patients who had been on ART for at least six months, who had a CD4 count above 200 cells/μL and clinically stable on ART could join a community ART group of maximum six people. This allowed a reduction in the number of times each person has to visit the clinic (producing a saving in cost and time for the patients) and allowed patients to receive support and health monitoring from people in the same situation. This programme has so far produced excellent results with 97.5% of patients retained on ART (median follow-up 13 months) (1237) and 95.7% still in care at a median follow-up of 21 months (913).

The third type of group-based model of care was assessed in Khayelitsha, South Africa (915). In this case adult patients who had been on ART for at least 18 months, with current CD4 count >200 cells/μL and virologically suppressed were invited to take part in "adherence clubs", occurring outside of the clinical consultation area. These were composed of 15–30 patients and occurred every two months facilitated by trained counsellors. During these “adherence clubs”, the counsellor distributes pre-packaged medicines to all participants, weighs the patients, administers a symptom-based general health assessment and leads group discussion on HIV related topics requested by the participants. Patients who report symptoms of HIV progression, adverse drug events or who have lost weight are referred to the clinic to be assessed by a nurse. Once a year, a nurse takes part in the adherence clubs to measure CD4 and VL in all participants. Outcomes were compared to patients attending clinic-based nurse-led care. The rate of LTFU (i.e. absence of contact with the service in the 6 months following the analysis closure) or death was 30/1,000 PYs in those taking part in the adherence club compared to 117/1,000 PYs for those receiving routine facility-based nurse-led care, while the rate of virological rebound was respectively 32 and 90/1,000 PYs. After adjusting for

confounders, “adherence club” participation reduced LTFU by 57% (HR = 0.43, 95% CI: 0.21, 0.91) and virological rebound by 67% (HR = 0.33, 95% CI: 0.16, 0.67).

Nurse-based rapid assessment

In LMIC the mortality in people receiving ART peaks in the first 3 months of ART, driven by people initiating ART at very low CD4 count. In an attempt to contain this phenomenon, an intervention called “High Risk Express Care”, providing weekly or bi-weekly rapid contacts with nurses for individuals initiating ART with CD4 count of 100 cells/µL or less was implemented in Kenya. This was found to be effective in reducing mortality (adjusted HR = 0.6; 95% CI: 0.4, 0.8), and LTFU (adjusted HR = 0.6; 95% CI: 0.5, 0.7) in people receiving this intervention compared with standard care (943).

Structural services (monetary supplements, food supplements)

Given the cost of transport and the conflicting needs have often been reported as a barrier to retention of people on ART, studies have assessed the impact of providing socioeconomic support on retention and mortality.

A study in an outreach community program in Uganda offering socio-economic support, such as school fees, rent payment or provision of shelter, employment at the program, interest-free loans, adult literacy instruction, income-generating activities, transport, skills-building activities, and food assistance for patient in need reported that after 10 years 41% were retained in the clinic and those not retained in care were either LTFU (74%, of which 50% transferred to another clinic) or dead (26%) (922). They found that patients who did not receive socio-economic support were significantly more likely to be LTFU compared to people who received one (HR = 1.5; 95% CI: 1.4, 1.6) or two or more (HR = 6.7; 95% CI: 5.6, 7.7) socio-economic supports. Similarly for mortality, people who did not receive support were more likely to die compared to those who received one (HR = 1.5; 95% CI: 1.2, 1.9) and two or more (HR = 4.3; 95% CI: 2.9, 6.2).

A large ecological study conducted in ten countries in sub-Saharan Africa found a marginal effect of the availability of food rations to support adherence (available in 17% of the clinics) on retention on ART at 6 months (aRR = 0.82, 95% CI: 0.64, 1.05) but not at 12 months (aRR = 0.98, 95% CI: 0.78, 1.21) (912).

Additional details on effective interventions to improve adherence

Mobile phone short messages

A systematic review on adherence interventions in sub-Saharan Africa published in 2011 (927) and a meta-analysis on the same subject (1238) both identified only two studies, both RCTs which investigated the impact of mobile short messages (923;924). They were both conducted in Kenya and they both found this intervention to be efficacious. Lester et al. conducted a multisite RCT ("WelTel Kenya1") (924) where patients initiating ART were randomized to either receive weekly short message service (SMS) from a clinic nurse and asked to reply within 48 hours or to standard care. They found that people receiving the intervention were more likely not only to report to be adherent (self-reporting having taken >95% of prescribed doses in the past 30 days), 61% compared to 50%, but also more likely to be virally suppressed (57% vs 48%), although these were still very low. Pop-Eleches et al. (923) evaluated four different SMS reminder interventions: daily short message, daily long message, weekly short message and weekly long message. They found that 53% of those receiving weekly messages had an adherence of at least 90% (measured using the medication event monitoring system over 48 weeks) compared to 40% in the control arm and they were slightly less likely to have ART interruptions of 48 hours or more (81 vs. 90%, P = 0.03). Conversely, daily messages and long weekly text messages were not found to be efficacious in improving adherence.

Education and counselling

A factorial RCT conducted in Kenya comparing four different options, counselling alone (three counselling sessions around the time of ART initiation), alarm (pocket electronic pill reminder carried for 6 months), counselling and alarm, and none of both, demonstrated that individual adherence counselling at the time of ART initiation could reduce the risk of VF (VL ≥5,000 copies/mL) by 18 months by 59% (HR = 0.41; 95% CI: 0.21, 0.81; p = 0.01) and the chance of having adherence below 80% at the monthly visit by 29% (HR = 0.71; 95% CI: 0.49, 1.01; p = 0.055) (925). On the contrary the alarm was not found to be effective in improving any of the outcomes.

Patient adherence treatment supporter

Several studies have evaluated specifically the role of community based treatment-supporters on retention on ART and specifically on adherence (928). In these studies the treatment supporter is generally a member of the family, a friend, a community health worker or a peer health worker (another person infected with HIV), but their role varies across studies from providing psychosocial support to the patient to educating them on ART use, to measuring the patient's adherence, to reminding them to pick up the medications (including DOT) to assess their adverse events and triage to other healthcare providers (927). The results on the effectiveness of this intervention are mixed, whether from RCTs or observational studies (927).

To my knowledge only two RCTs (928;929), evaluated the effect of "treatment supporters" on their own and another three in combination with other adherence interventions (931;933;1239).

A cluster RCT was conducted in Rakai Uganda, where the treatment supporter was a peer living with HIV who provided clinic and home-based counselling on clinical aspects and adherence to ART, and social support. They found no difference in lack of adherence (pill count <95%), cumulative risk of VF or at 24 week VF, but at VF rates at 96 weeks were significantly lower in those receiving treatment support (RR = 0.5; 95% CI: 0.3, 0.8) and the same at 192 weeks (RR = 0.59, 95% CI: 0.22, 1.60) (929). Similarly, a small RCT conducted in a district hospital Uganda (928), in which a treatment supporter intervention was offered in addition to the standard adherence package (use of adherence diaries to self-monitor adherence; regular individual and group education by peer-workers and late attendee tracing) provided to all people receiving ART failed to find a significant difference in mean adherence (monthly clinic-based pill counts; at 28 week 99.1% vs 96.3%).

Two of the three RCTs which evaluated combinations of adherence interventions including treatment supporter found them to be effective: one including DOT and education (931) and one only DOT (1239).

The first of the three RCTs which evaluated combinations of adherence interventions including DOT was conducted in Beira in Mozambique (931). In this study, education about treatment and adherence was provided by peers, who were responsible for identifying and helping to overcome adherence barriers, observing medication intake 6 days a week and of generally supporting the patient . Significantly higher adherence (self-reported adherence over the last 7

days) was observed at 6 months (92.7% vs. 84.9%; difference 7.8; 95% CI: 0.02, 13.0) and at 12 months (94.4% vs. 87.7%, difference 6.8; 95% CI: 0.9, 12.9) in the intervention group.

The second study was conducted in Nigeria (1239) and found that patients in the intervention arm were 2 times more likely to have optimal adherence (drug pickup adherence ≥ 95%) at week 24 (OR = 3.1, 95% CI: 1.9, 4.9) and almost 100% more likely at week 48 (OR = 1.9; 95% CI: 1.3, 2.9). Nevertheless the intervention did not provide a long-term (at 48 weeks) clinical benefit in term of immunological response (CD4 count increase) or mortality, while in terms of virological response it increased by 60% the probability of achieving undetectable VL at week 24 (61.7% vs 50.2%; OR = 1.6, 95% CI: 1.1, 2.3), but this effect was no longer significant by week 48 (65.3% vs 59.4%; OR = 1.3, 95% CI: 0.9, 1.8).

Finally in Tanzania, a RCT with three different adherence interventions was conducted (933): (i) regular adherence counselling (control), (ii) regular counselling plus a calendar and (iii) regular counselling with a treatment supporter failed to find differences in self-reported adherence over a mean of 14.5 months and only 0.7% reported adherence of 95% or below, potentially due to desirability bias.

Structural services (monetary supplements, food supplements)

Since one of the main barriers to collect medication is the cost of transport and the necessity to take time off work to attend the clinic, quite recently a few studies have started investigating the impact of structural services, such as monetary supplements and food rations on adherence to antiretroviral medications.

Cantrell et al. conducted a pilot RCT in patients with food insecurity in Zambia, which demonstrated that food supplementation was associated with improved adherence to ART, measured as medication possession ratio (70% having >95% adherence in the intervention group vs 48% in the control arm), but the study failed to find a direct benefit on immunological response or weight gain, potentially because of lack of power to detect a difference (934).

A RCT conducted in Malawi in patients initiating ART underweight (BMI<18.5) reported that receiving ready-to-use fortified spread for 14 weeks was more efficacious than corn-soy blend in increasing BMI (2.2 vs 1.7) and fat free body mass (2.9 vs 2.2 kg), while no significant difference in terms of CD4 count, VL, quality of life, or adherence was found between the two groups (937). Nevertheless this benefit in BMI was not maintained 9 months after having stopped the supplementary food (1240). A cohort study in Zambia confirmed the findings from RCTs: higher adherence after 6 months (measured using pharmacy dispensation records) in

people receiving food assistance compared to non-recipients (98% vs 89%), but again no significant effects in terms of weight gain or immunological response (CD4 count change) (935). More promising results came from a small observational study conducted in Nigeria (n=180) where they compared the treatment outcomes of two groups initiating ART, one receiving standard of care and the other receiving material support if they had CD4<200 cells/µL and/or WHO stage 3 or 4 or with BMI<18.5 kg/m^2. They found that people who received support were less likely to die (death rate ratio = 0.19; p<0.05), had a greater increase in CD4 count (+ 114 vs. + 68 CD-4 cells/µL; p<0.05) and were more likely to be adherent (98.4% vs 77.5%; p<0.005) (936).

Compared to the other interventions to improve adherence, this intervention has significant costs, a retrospective study in Mozambique estimated the cost of providing food assistance to patients living with HIV in 2009 to be $288 over 3 months per patient, of which 1% is capital and 99% is recurrent cost and it is mainly due to the cost of food (49%), followed by the cost of transport (24%) (938).

Additional details on approaches which improve the cascade of care at multiple steps

Decentralization of HIV care provision and task-shifting

In the last few years the provision of HIV care has expanded from few hospitals located in the main cities to a greater number of smaller clinics, often requiring shifting of activities to nurses and lay counsellors. Task shifting (see section 7.2.8) is considered an inevitably required means to expand rollout of ART in RLS, given the shortage of human resources. This different approach of delivering care has been introduced in several countries in sub-Saharan Africa (Kenya, Uganda, Rwanda, Zambia, South Africa, Lesotho, Mozambique, Malawi, Democratic Republic of Congo, and Nigeria). The efficiency has been demonstrated to increase in programmes taking on board this approach, because it gives senior clinical staff more time to spend with complicated patients and non-HIV related tasks, and it reduces waiting time and, plausibly as a consequence, LTFU (940).

The fact that structural barriers, such as the distance from the clinic and transportation represent major obstacles to retention in care was clearly demonstrated by the fact that decentralized programmes offering ART through primary healthcare clinics and community support, such as the Medicine Sans Frontiers programme in Lusikisiki, a rural district in South Africa (843) were able to minimize LTFU (2% compared to 19% at the central hospital site). A study from Lesotho, one of the first countries to decentralize HIV care services, reported that

women initiating ART in hospitals rather than in nurse-led decentralized health centres were not more likely to be retained in care at three years (defined as alive and receiving ART; 69.7% compared to 68.7%) while men were more likely to be retained in the decentralized health centres (68.8%) compared with the hospital (54.7%), and even after adjusting for confounders, such as CD4 count and WHO stages, this effect persisted (in men OR of being retained in decentralized services: 1.53, 95% CI: 1.20, 1.96) (1241).

A few other studies have shown that decentralizing of health centres can reduce LTFU substantially (941-944). An additional benefit is that it can reduce dramatically clinic costs, given doctor salaries can be the largest cost in an antiretroviral clinic budget.

Although it has been found that decentralizing care reduces waiting time, loss to follow-up and costs, it is crucial to ensure that task-shifting does not result in a lower level of healthcare. To my knowledge there is only one RCT which evaluated the effectiveness of task-shifting for ART delivery in sub-Saharan Africa. They found that nurse-managed ART care was non-inferior to doctor-managed care in urban clinics in Johannesburg and Cape Town, South Africa, with HRs for composite failure (including mortality, viral failure, treatment-limiting toxic effects, and adherence to visit schedule) of 1.09 (95% CI: 0.89, 1.33) over a median follow-up of 120 weeks (945).

An example of decentralization comes from the Thyolo District in Malawi (939), where since mid-2003, the Ministry of Health in collaboration with Medecins Sans Frontiers implemented a model of care decentralizing HIV care to health centres and task-shifting some activities to lay counsellors. One of the activities which were delegated to lay counsellors was HTC and this led to an increase in uptake of HIV testing from 1300 tests per month to 6500 test per months in 2009.

As mentioned in section 7.2.1 regarding improving access to HIV testing, decentralization of HIV services to peripheral health centres, combined with task shifting has been effective also in improving ART initiations. These studies have not evaluated whether people were initiated promptly when found to be eligible but more broadly whether it increased access to ART. In a study in Malawi for example, delegating ART initiations to non-physician clinicians almost doubled ART enrolment, with good programme outcomes (939). Another successful example of decentralization comes from Cameroon (946). In a cross-sectional survey of HIV-positive

patients (response rate 90%) from different level of the healthcare delivery (central, provincial and district), they found that although not surprisingly district treatment centres had more limited technical and human resources, after adjustment for other explanatory factors, immunological outcomes were similar in patients to those followed up at the central district level, and adherence to ART was actually better than at the central level.

Similarly, a study from a rural district in Malawi evaluated the outcome of people who were monitored, once initiated on ART in decentralized health centres or not. They found that people who were decentralized were less likely to die (adjusted OR = 0.19; 95% CI: 0.15, 0.25) and to be LTFU (adjusted OR = 0.48; 95% CI: 0.40, 0.58). Nevertheless this could be due to the fact that stable patients are more likely to be decentralized (844).

Integration of HIV/AIDS services into other healthcare services

Another barrier that became clear was the fact that people had to attend different clinics for different health issues. To overcome this issue integration of HIV care services into other healthcare services such as TB services and antenatal services was implemented in some programmes in South Africa, and integration of ANC is widely adopted in RLS. The idea was as well that this approach could strengthen the whole health system.

A systematic review published in 2013 (953) found only four studies (all cohort studies), which compared services where ART provision was integrated into ANC vs services which did not integrate ART, in terms of ART coverage (proportion on ART of those eligible based on national guidelines), enrolment on ART, retention on ART, mortality or HIV transmission (950-952). They did not find any studies which assessed this comparison in maternal and child health clinics. They estimated that enrolment of pregnant women on ART was double in clinics where ART was provided within (RR = 2.09; 95% CI: 1.78, 2.46) and that ART coverage was also slightly higher (RR = 1.37; 95% CI: 1.05, 1.79). Retention on ART was reported only in one of these studies (950), which found no difference in the retention on ART after 90 days (87.8% in the ANC clinics where ART was integrated and 91.3% in the referral HIV clinics for pregnant women on ART). A more recent retrospective cohort study conducted in Cape Town (South Africa) compared three different settings where to initiate ART for pregnant women: ART integrated into ANC clinic, ART services located close to the ANC clinic and at some distance from the ANC clinic (954). Among almost 15,000 women seeking antenatal care of which 17% HIV-positive and eligible for ART (based on CD4 count <200 cells/µL), 55% initiated ART if ART provision was

integrated into ART compared to 38% and 45% if ART was provided respectively next or at a certain distance from the ANC clinic.

To my knowledge the only RCT which evaluated the effects of integrating HIV treatment into ANC was conducted in rural Kenya (1242). They compared six clinics which provided fully integrated services (HIV treatment services provided in the ANC clinic) to six clinics which did not provide integrated services (ANC clients referred to a separate HIV clinic for ART). The final results have not been presented yet but they reported facing major challenges including frequent staff turnover, stock-outs of essential supplies, transportation challenges, and changes in national guidelines.

Given the wide overlap between the HIV epidemic and TB (almost a quarter of HIV related deaths attributable to TB) WHO recommends integrating HIV and TB services. A systematic review (1243) estimated that on average 87% of patients with TB tested for HIV (standard deviation = 12%) and that on average 38.4% received ART during TB treatment (95% CI: 17.5, 59.3; range across studies: 14%-100%). The low uptake of ART could partly be due to differences in ART eligibility, nevertheless for example a study in Zambia found that 88% of patients co-infected with TB and HIV were eligible for ART but only 59% enrolled (1244). One of the first examples of integration of HIV and TB services came from Khayelitscha in South Africa, an area where around three quarters of people with TB are co-infected with HIV. Here since 2002 the integration of these services was evaluated and subsequently implemented (948). They reported that the proportion of TB patients who were tested for HIV increased from 30% to 56% in a clinic which integrated TB and HIV services; in particular 87% of patients who were offered HIV testing accepted it.

A study from Lusaka in Zambia evaluated the feasibility of integrating HIV care into primary healthcare clinics (together with the introduction of PITC). They reported high acceptability of this approach, between 50 and 60% of patients accepted HIV testing and between 42% and 58% enrolled in care (949).

Health information systems (i.e. electronic medical records)

It seems obvious that electronic medical records (EMR) can be very helpful in delivering better medical care and in being able to identify people who drop out of care and attempt to re-engage them in care. In addition, patients who miss a clinical appointment and then attend the clinic for unscheduled visits affect the ability to plan the work load in the clinic. A

demonstration of the contribution EMR can make came from a study conducted in a community-based HIV clinic in Kampala, Uganda, (955) serving patients on ART (62%) or not yet eligible for treatment. They introduced EMR and same day patient tracing and observed that the mean number of missed appointments per day reduced from 21 (out of an average of 78 scheduled visits per day) to 8 (out of 70 scheduled visits per day), 6 months after the implementation of the EMR and tracing, that LTFU reduced from 11% to 5% and the median waiting time to see the provider from almost 5 hours to an hour and a half.

Short message service communication

The increasing availability of mobile phones among people living with HIV in LMIC represent a good opportunity to easily contact patients and potentially to improve retention in care.

A RCT, WelTel Kenya1, is currently being conducted in Nairobi (Kenya) evaluating whether weekly text messages over 1 year following diagnosis, requiring a reply within 48 hours are effective in improving linkage to care (i.e. completion of ART eligibility assessment), retention in pre-ART care leading to timely ART initiation (in those not eligible for ART) and adherence and VL suppression among those initiating ART (1245).

Combinations of approaches

A pilot study has been conducted in rural KwaZulu-Natal in South Africa combining HBT with POC CD4 count testing and follow-up visits to smooth the linkage of HIV-infected people to local HIV clinics. The uptake of HIV testing was 91%, confirming the high acceptability of HBT strategy and 90% of those not receiving ART at baseline (whether new diagnoses or people aware of their HIV-positive status who were not engaged in care) had visited an HIV clinic by 3 months, and of those eligible for treatment (CD4 ≤200 cells/μL in South Africa guidelines when the study was conducted) 80% had initiated ART. Among HIV-infected participants who were eligible for ART at baseline, mean VL decreased by 3.23 log copies/mL ($p<0.001$) and the proportion with VL suppression increased from 20% to 80% between baseline and the sixth month (864).

Another package of interventions which has been successfully implemented in Swaziland, is a pre-ART care package characterized by three main features: task shifting to nurses and lay HIV counsellors, focus on a patient care pathway and active patient tracing for patients not presenting at the clinic for an appointment. This intervention led to improvement at different steps of the cascade of care: linkage to care (proportion who received eligibility assessment)

460

increased from 59% before the intervention to 76% at the end of follow-up, prompt initiation of ART for eligible patients which increased from 53% to 81% and the median time from being identified as eligible for treatment to initiation decreased from 61 to 14 days (758).

Appendix XV. Median CD4 count at diagnosis in South Africa

Author	Setting	Year of the study	N (newly diagnosed with HIV)	Definition of late stage disease	Late stage HIV disease at diagnosis	Median (IQR) CD4 cells/µL at diagnosis
April (958)	Hospital, PHC in Cape Town	2001-06	1,340	CD4<200 cells/µL	Overall: 36%*	Overall: 276*
Bassett (841)	Semi private hospital in Durban (patients are charged)	2006	501**	-	-	159 (65–299)
Ingle (1246)	36 public sector clinics in Free state Province	2004-07	44,844	-	-	170 (76-318)
May (720)	Gugulethu and Khayelitsha, both in Western Cape Province***	2004-08	Gugulethu: 1,611; Khayelitsha: 4,397;	-	-	101 (48-159); 100 (45-161);
Larson (957)	Public academic hospital in Johannesburg	2008-09	352	CD4<200 cells/µL	54.3%	185 (67-353)
Govindasamy (956)	Mobile testing unit in Cape Metropolitan Region, Western Cape	2008-09	192	CD4<200 cells/µL	9.6%	489 (457-520)****
Drain (721)	4 outpatient clinics VCT in Durban	2010-11	830	CD4<100 cells/µL	33.6%	186 (70-345)
Clouse (752)	PHC in Johannesburg (pregnant women)	2010-11	300	-	-	357 (238–500).

*Not significant trend over time; ** The study was restricted to people eligible for ART (CD4≤200 cells/µL or WHO stage 3 or 4); ***Results for cohort outside South Africa are not presented; ****Mean (95% CI); IQR: interquartile range; PHC: primary healthcare clinic; VCT: voluntary counselling and testing;

Appendix XVI. Proportion linked to care (completed ART assessment) in South Africa [modified from (551;553)]

Author	Setting	Year of the study	N (newly diagnosed with HIV)	CD4 measurement (95% CI) [time]	Returned for CD4 results (95% CI) [time]	Enrolled in HIV care [time]
April (958)	Hospital, PHC in Cape Town	2001-06	1,123	-	2001: 29% [6 months] 2006: 67% [6months]	-
Ingle (1246)	36 public sector clinics in Free state Province	2004-07	44,844	74% [by study censor date]	-	-
Losina (1247)	Semi-private hospital in Durban	2006-07	454	55% (50%-59%) [8 weeks]	85% (81%-89%) [of those who measured CD4 within 8 weeks] Overall 47% (42%-51%) [by study censor date]	
Bassett (963)	Semi private hospital in Durban	2006-08	1,474	69% (66%-71%) [3 months]	-	-
Luseno (1248)	Community based trial in Gauteng Province	Not reported	199	-	-	46% [by study censor date]
Naidoo (1249)	Clinic in Johannesburg	Not reported	224	-	47% (41%-54%) [1 week]	-
Faal (887)	Urban healthcare clinic in Johannesburg (RCT)	2008	344		49% [1 week]	
Kranzer (967)	Hospital, PHC in Cape Town	2004-09	988	63% (60%-66%) [6 months]	-	-
Larson (957)	Public academic hospital in Johannesburg	2008-09	416	85% [12 weeks]	35% (30%-40%) [12 weeks]	-

Author	Setting	Year of the study	N (newly diagnosed with HIV)	CD4 measurement (95% CI) [time]	Returned for CD4 results (95% CI) [time]	Enrolled in HIV care [time]
Govindasamy (956)	Mobile HIV testing service in Cape Town	2008-09	192	Self-reported access to HIV care	78% (72%-84%) [by study censor date]	42% [by study censor date] of those who received CD4 count
Clouse (959)	PHC in Johannesburg (pregnant women excluded)	2010	842	-	70% (67-73%) [3 months since diagnosis]	-

ART: antiretroviral treatment; PHC: primary healthcare clinic; RCT: randomized controlled trial;

Appendix XVII. Proportion retained in pre-ART care in South Africa [modified from (551;553)]

Author	Setting	Year of the study	N (HIV+ not eligible for ART)	Definition of retention in pre-ART care	Retention in pre-ART care (95% CI) [time]
Lessells (1250)	Public sector clinics in rural KwaZulu-Natal	2007	4,233	Repeat CD4 count	45% (43-46%) [13 months since 1st CD4 count] CD4 201-350: 51.6% (49.1-54.0) CD4 351-500: 43.2% (40.5-45.9) CD4 >500: 34.9% (32.4-37.4)
Ingle (1246)	36 public sector clinics in Free state Province	2004-07	11,039	Visit	42% (41-43%) [6 months since enrolment]
Larson (604)	Public academic hospital in Johannesburg	2007-08	356	1st pre-ART medical appointment	31% (27-36%) [1 year]; CD4 200-350: 6% (2-11%) [4 months], 35% (27-44) [1 year]; CD4 >350: 14% (10-19%) [9 months], 11% (8-16%) [1 year]
Kranzer (967)	Hospital, PHC in Cape Town	2004-09	419	Repeat CD4 count	46% (41-50%) [study censor date, up to 5 y of follow-up]
Luseno (1248)	Community based trial in Gauteng Province	-	199	Visited referral site after HIV test	46% (39-53%) [study censor date]
Govindasamy (956)	Mobile testing unit in Cape Metropolitan Region, Western Cape	2008-09	192	Self-reported access to HIV care	36% (28%-44%) [between 6 and 18 months from HIV diagnosis; mean time of 3 months to access care for those who did]
Clouse (959)	PHC in Johannesburg (no pregnant women)	2010-11	221	Returned for CD4 test	57% (49%-65%) [1 year]
Clouse (752)	PHC in Johannesburg (pregnant women)	2010-11	112	Returned for any visits after delivery	49% (40–58%) [study censor date]
			50 (visit after delivery)	received a repeat CD4 count after delivery	52% (38.2–66%) [study censor date]

ART: antiretroviral therapy; PHC: primary healthcare clinic;

Appendix XVIII. Proportion initiated on ART of those eligible in South Africa [modified from (551;553)]

Author	Setting	Year of the study	N (patient eligible for ART)	Percent (95% CI) initiating ART [time]	Median (IQR) time to initiate ART (expressed in days) from initial eligibility (i.e. CD4 count measure that indicated eligibility)
Lawn (1251)	Community Health Centre in Gugulethu, Western Cape Province	2002-05	1,235	75% [study censor date]	34 (28–50).
April (958)	Hospital, PHC in Cape Town	2001-06	2001: ~29[a] 2006: ~86%[a]	2001: 0% [6 months] 2006: 68% (57%-78%) [6 months]	-
Bassett (841)	Semi private hospital in Durban	2006	501	81% [<=3 months last required pre-ART visit]	110 (70-119) [To 1st ART training][b]
Kaplan (902)	PHC for women in Gugulethu, Western Cape Province	2002-07	2,131	82% (81%-84%) [study censor date]	-
Ingle (1246)	36 public sector clinics in Free state Province	2004-07	22,083	68% (67-68%) [by 2 year since being eligible]	-
Murphy (1252)	General hospital in Durban (Patients with TB or OI discharged and referred to semi-private hospital)	2006-07	49	45% [6 months]	83 (34-119)
Ahonkhai (483)	71 Catholic Bishops Conference/Catholic Relief Services HIV treatment clinics in 8 different South African provinces	2004-08	11,397 (CD4<200 cells/µL)	-	28 (14-53) [from enrolment]
Bassett (963)	Semi private hospital in Durban	2006-08	538	39% (35%-43%) [study censor date, median follow-up 12 months]	-

Author	Setting	Year of the study	N (patient eligible for ART)	Percent (95% CI) initiating ART [time]	Median (IQR) time to initiate ART (expressed in days) from initial eligibility (i.e. CD4 count measure that indicated eligibility)
Kranzer (967)	Hospital, PHC in Cape Town	2004-09	219	67% (60%-73%) [6 months since HIV test if ART eligibility confirmed within 6 months from HIV test]	
Pepper (1253)	Integrated TB-HIV clinic in Cape Town (TB patients, type of clinic not indicated)	Not available	100	66% (57-75%) [during TB treatment]	-
Clouse (959)	PHC in Johannesburg (pregnant women excluded)	2010	589	73% (69%-78%) [3 months]	23 days (12-36)
Clouse (752)	PHC in Johannesburg (pregnant women)	2010-11	115	81% (73–87%) [ART initiation prior to delivery of those with CD4 staging, median 9.5 weeks between ART initiation and delivery]	27 days (17–41) [from HIV testing]
			139	67% (59–74%) [ART initiation prior to delivery of all those ART-eligible]	

a: the exact number of people eligible for ART was not reported but the % eligible was indicated in a graph and the number of sero-positive in each year reported; b: 3 ART-training visit are scheduled one week apart before ART initiation; ART: antiretroviral therapy; CI: confidence interval; IQR: interquartile range; OI: opportunistic infection; PHC: primary healthcare clinic; TB: tuberculosis;

Appendix XIX. Median CD4 count at ART initiation in South Africa

Author	Setting	Year of the study	N (patients initiating ART)	Eligibility criteria to initiate ART	Median (IQR) CD4 cells/µL at ART initiation
Coetzee (477)	Public community based programme in Khayelitsha	2001-03	287	WHO stage 3 or 4 and CD4<200 cells/µL (eligibility criteria for inclusion in the study)	43
Nachega (1254)	Private programme (majority of patients from SA, with payment from patients)	1998-2004	2,817	CD4<350 cells/µL on 2 occasions or WHO stage 4	171 initiating NVP, 136 initiating EFV
Nachega (1255)	Private sector programme with multiple workplace locations (subsidized by employers)	1999-2004	7,080	WHO stage 3 or 4 and CD4<200 cells/µL ; Additional criteria to ensure the patient was ready to initiate ART were required (having a 'treatment assistant', home-visit, evidence of disclosure, attendance on time for at least 3 visits over a minimum of 4 months)	149 (65-227)
Oijkutu (482)	Semi private hospital in Durban	1999-2004	309	WHO stage 4 or CD4<200 cells/µL	65
Charalambous (1256)	Multiple locations at workplace	2002-05	2,262	WHO stage 4, irrespective of CD4 count; CD4 of 250-350 and WHO stage 3; CD4<250 cells/µL, irrespective of WHO stage.	158
Bekker (478)	Public clinic in Gugulethu, Western Cape Province	2002-05	1,139	WHO stage 4 or CD4<200 cells/µL	2002/3: 84 (42-139) 2003/4: 89 (49-149) 2004/5: 110 (55-172)
Lawn (Lawn et al. 2006)	Community Health Centre in Gugulethu, Western Cape Province	2002-05	1,235	WHO stage 4 or CD4<200 cells/µL	100 (47-160)
Rosen (964)	Public, partial payment	2005-06	100	CD4<200 cells/µL (Eligibility into the study)^	97
	Private, no payment		100		84
	NGO, partial		100		60
	NGO, partial		100		104

Author	Setting	Year of the study	N (patients initiating ART)	Eligibility criteria to initiate ART	Median (IQR) CD4 cells/µL at ART initiation
Boulle (292)	3 public PHCs in Khayelitscha in Western Cape	2001-07	7,323	WHO stage 4 (excluding extra pulmonary disease) or CD4<200 cells/µL	2001/02: 43 (13-95) 2003: 72 (26-126) 2004: 85 (37-141) 2005: 100 (44-157) 2006: 109 (52-169) 2007: 131 (64-191)
Grimwood (1257)	NGO in collaboration with DoH in several locations in South Africa	2003-07	6,469	Not indicated	117
Barth (498)	NGO clinic co-founded by South Africa DoH in rural area of Limpopo province	-	735	WHO stage 4 and CD4<200 cells/µL	68 (20-140)
Wang (903)	Clinic in mine workers communities in Northwest Province	2004-07	925	WHO stage 4 or CD4<200 cells/µL	111 (41-214)
Mac Pherson (1258)	Public clinic in Bushbuckbridge district in Mpumalanga Province	2005-07	1,353	WHO stage 4 or CD4<200 cells/µL and psychosocial preparedness to undertake ART	93 (37-148)
Cornell (601)	8 cohorts from 4 provinces in South Africa (Western Cape, Free State, Gauteng and KwaZulu-Natal)	2002-08	44,177	Not indicated	Overall:103 (45-164); 2002/03: 68 2007: 113
Ahonkhai (483)	71 Catholic Bishops Conference/ Catholic Relief Services HIV treatment clinics in 8 different South Africa provinces	2004-08	11,397 (CD4<200 cells/µL)	WHO stage 3 or 4 or CD4<200 cells/µL	101 (43-160)
Sanne (1207)	Public clinic in Johannesburg	2004-08	7,583	Not indicated	87 (31-158)
Nglazi (1259)	Community Health Centre in Gugulethu, Western Cape Province	2002-09	3,162	WHO stage 4 or CD4<200 cells/µL	2002/04: 87 (45-145) 2007/08: 121 (60-178)
Kranzer (484)	Peri-urban township in Western Cape	2004-09	1,154	Partly with the criteria of WHO stage 4 or CD4<200 cells/µL and partly (NIH funded) WHO stage 3 or CD4<350 cells/µL	Overall: 122 (54-190); 2004: 137 2006: 279

Author	Setting	Year of the study	N (patients initiating ART)	Eligibility criteria to initiate ART	Median (IQR) CD4 cells/µL at ART initiation
Boyles (753)	7 public PHCs and one public hospital in Eastern Cape Province	2005-09	1,805	WHO stage 4 or CD4<200 cells/µL	123 (55-184)

^ They reported that according to clinic staff not many people with CD4>200 cells/µL are initiated on ART because of clinical conditions; DoH: Department of Health [South Africa]; EFV: efavirenz; IQR: interquartile range; NGO: non-governmental organization; NIH: national institutes of health; NVP: nevirapine; PHC: primary healthcare clinic; WHO: World Health Organization;

Appendix XX. Retention on ART in South Africa [modified from (1;2)]

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Coetzee (477)	Public community based programme in Khayelitsha	2001-03	287	>3 months late for a visit or medication pickup or no visit in past 3 months	13.9	13.2%	0.3%[a]	1.0%	82.5%
Nachega (1254)	Private programme (most patients from South Africa, with payment from patients)	1998-2004	2,817	Leaving medical insurance fund or AID for AIDS program	24	2.0%	11.2%	0.0%	86.8%
Oijkutu (482)	Semi private hospital in Durban	1999-2004	309	No clinic visit within 6 months of end of study	8.4[b]	15.9%	7.4%	0.0%	76.7%
Nachega (1255)	Private sector programme with multiple workplace locations in South Africa (subsidized by employers)	1999-2004	7,080	Having no VL results after ART initiation.	19.5[b]	5.4%	25.4%	-	69.2%
Brinkhof (493)	3 free ART Programmes (CTAC, Khayelitsha, OPERA)	2000-05	624[c]	No visit between 6 and 12 months since ART initiation	12	6%	2%	-	92%
Bekker (478)	Public clinic in Gugulethu, Western Cape Province	2002-05	1,139	Missing 2 consecutive clinic visits or no visit in past 3 months	12.3[b]	6.8%	2.9%	10.5%	79.7%
Lawn (1251)	Community Health Centre in Gugulethu, Western Cape Province	2002-05	927	>4 weeks late for a scheduled clinic or pharmacy visit and who were neither transfers out nor relocations		5%	5%	2%	88%

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Charalambous (1256)	Multiple locations at workplace	2002-05	2,262	-	18.7[b]	5.0%	25.1%	-	69.9%
Fairall (1260)	Public clinic in Free State Province	2004-05	3,619	-	6 (3-9, max 19)	1 year: ~10%[d]	-	-	-
Khan (1261)	Public	2004-05	684	Failure to collect ART	36	18.0%	5.3%	3.9%	72.8%
Reuter (1262)	Public in Lusikisiki	2005	430		12	13.5%	19.3%	4.0%	67.2%
			595			16.8%	2.2%	4.9%	81.0%
Boulle (291)	43 sites in Western Cape ART Programme (Public)	2001-06	12,587	>90 days since last contact	Maximum 48 months	6.5% [At 6 months]; 8.4% [At 1 year]; 22.5% [At 4 years]	4.1% [At 6 months]; 6.1% [At 1 year]; 1.2% [At 4 years]	2.7% [At 6 months]; 4.5% [At 1 year] 2.5% [At 4 years]	87% [At 1 year] 74% [At 4 years]
Rosen (964)	Public, partial payment	2005-06	100	>3 months late for last visit	12	2.1%	23.9%	0.0%	74.0%
	Private, no payment		100			18.9%	26.1%	0.0%	55.0%
	Rural NGO, partial		100			12.9%	15.1%	0.0%	72.0%
	Peri-urban NGO, partial		100			7.0%	6.0%	0.0%	87.0%
Boulle (292)	3 public PHCs in Khayelitscha in Western Cape	2001-07	7,323	>6 months without a clinic visit	Max 5 years	15.5% (13.1-18.3%) at 5 years	23.4% (20.5-26.6%) at 5 years	-	-
Cornell (1263)	Public clinic in Gugulethu, Western Cape Province	2002-07	2,196	Absent from the clinic from >3 months	Women: 1 (0.5—1) Men: 0.9 (0.4-1)	7.%	6.2%	3.2%	83.5%

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Kaplan (902)	PHC for women in Gugulethu, Western Cape Province	2002-07	1,677	No clinic visit ≥ 12 weeks (i.e. not having drugs for at least 4 weeks)	36[d]	Pregnant: 1 year: 5%[d] 3 years: 5%[d] Not Pregnant: 1 year: 8%[d] 3 years: 11%[d]	Pregnant: 1 year: 16%[d] 3 years: 32%[d] Not Pregnant: 1 year: 7%[d] 3 years: 13%[d]	-	-
Grimwood (1257)	Public	2003-07	6,469	-	24	9.0%	11.4%	0.0%	79.6%
Dahab (1264)	Public	-	267	>1 month late for 6 months visit	6	6.7%	8.6%	1.1%	83.5%
Wang (903)	Clinic in mine workers communities in Northwest Province	2004-07	925	Not returning for a scheduled visit or medication pick-up within first 6 months since ART initiation	-	23.1% [6 months]	5.6% [6 months]	2.4% [6 months]	68.8% [6 months]
Mac Pherson (1258)	Public clinic in Bushbuckbridge district in Mpumalanga Province	2005-07	1,353	>1 day late for appointment, could not be traced, and did not come back during study period	8.6[b]	9.2%[24 months]	2.6%[24 months]	4.7%[24 months]	83.6%[d] [24 months]

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Cornell (601)	8 cohorts from 4 provinces in South Africa (Western Cape, Free State, Gauteng and KwaZulu-Natal)	2002-08	44,177	>6 months since last contact at the date of closure of the cohort database		At 1 year: 2002/03: 8.9 (7.4-10.7) 2004: 7.2 (6.5-7.9) 2005: 7.4 (6.9-7.9) 2006: 6.2 (5.8-6.7) 2007:5.6 (5.1-6.0)	At 1 year: 2002/03: 1.1 (0.6-1.9) 2004: 8.6 (7.9-9.4) 2005: 10.3 (9.7-10.9) 2006: 13.1 (12.5-13.7) 2007: 23.5 (22.7-24.3)	-	At 1 year: 2002/03: 90.1 (88.2-91.7) 2004: 84.8 (83.8-85.8) 2005: 83.1 (82.3-83.8) 2006: 81.5 (80.8-82.1) 2007: 72.3 (71.4-73.1)
Sanne (1207)	Public clinic in Johannesburg	2004-08	7,583	>3 months late for a scheduled visit and that the tracing team could not get information on	20.3	5.1% [during follow-up]	16.4% [during follow-up]	-	At 1 year: 82.8% (81.9-83.6%) At 4 years: 74.4% (73.2-75.6)
Peltzer (1265)	Three public hospitals in Uthukela in KwaZulu-Natal	2007-08	735	Not traceable at 12 months	12 months	13.8% [at 12 months]	4.0% [at 12 months]	7.9% [at 12 months]	75.9% [at 12 months]
Nglazi (1259)	Community Health Centre in Gugulethu, Western Cape Province	2002-09	3,162	≥12 weeks since last visit	29 (14-46)	Overall 10.6%; 15.2% (13.1-17.6%) [at 6 years]	Overall 18.7%;	Overall 10.3%; 21.6% [at 6 years]	Overall 61.4%;

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Kranzer (484)	Peri-urban township in Western Cape	2004-09	1,154	>30 days late for ART refill at the pharmacy	17.4 (6-39)	16.9%	-	-	-
Ahonkhai (483)	71 Catholic Bishops Conference/ Catholic Relief Services HIV treatment clinics in 8 provinces in South Africa	2004-09	11,397	Not having visits involving lab measurement between 40 and 400 days since ART initiation		9% early death (within 7 months);	17% missed laboratory visits and did not returned to care by 1 year.	-	Retention on ART 63% [13 months]
Boyles (753)	7 public PHCs and one public hospital in Eastern Cape Province	2005-09	1,805	No contact for > 6 months before the end of the study period	13.3 (5.4-25.0)	11.1%	6.5%	10.9%	71.5%
O' Connor (965)	Four PHCs in Johannesburg (Patients stable on ART on average on ART for 18 months)	2007-09	3,361	>6 weeks late for ART visit with 3 failed attempt to contact them telephonically	6[b] (2-11)	0.2%[e]	3.9%	2.9%	92.6%
Fatti (1266)	38 low caseload (median 488 patients) clinic and 16 high caseload (median 2031 patients) clinics from an NGO in 4 Provinces (KwaZulu-Natal, Western Cape, Eastern Cape, Mapulanga)	2004-10	40,861	>3 months late for a scheduled appointment		5.1% (4.9-5.4%) [12 months] 6.8% (6.5-7.1%) [24 months]	Low caseload: 6.4% (5.9-7.0%) [12 months]; 11.2% (10.4-12.2%) [24 months]; High caseload: 8.6% (8.3-9.0%) [12 months]; 14.9% (14.3-15.4%) [24 months]	-	At 3 6 months: Low caseload: 78.8% (76.7-80.8%), High caseload: 73.9% (73.1-74.7%)

Author	Setting	Year of the study	N (HIV+ who initiated ART)	Lost to follow-up definition	Median follow-up (months)	Total attrition		Retained in care	
						Died	Lost to follow-up	Transferred to care	Retained at original site
Barth (498)	NGO	-	735	Not reported	37.0[b]	23.3%	12.0%	6.4%	58.4%
Clouse (959)	PHC in Johannesburg	2010-11	299	No clinic attendance > 3 months since last scheduled visit. Patients		2.4% (1.1-4.8%)	-	10.4 [12 months]	67%. Among those who did not transfer: 80.2% (75.3%-84.5%) [6 months]; 95.3% (91.7%-97.6%) [6-12 months]
Clouse (752)	PHC in Johannesburg (pregnant women)	2010-11	90[f]	Not returning for at least visit after delivery	-	-	-	-	82.8 % (72.1-90.6%)
Mutevedzi (1267)	17 public PHCs in KwaZulu-Natal Province	2004-12	4,674	> 180 days since last clinic visit	33	14.5%	11.9%	5.6%	68`% overall. 61% [5 years]

a: Transfer rate after 1 y (rate at median follow-up not reported); b: Mean follow-up reported instead of median; c: presenting only data from South Africa; d: Kaplan Meier estimates; e: it includes only people who died and were considered lost; f: initiated ART before delivery;-ART: antiretroviral therapy; NGO: non-governmental organization; PHC: primary healthcare clinic;

Appendix XXI. Proportion switched to second-line regimen in South Africa

Source	Population	Year	Follow-up, median (IQR)	Type of analysis (intention to treat or on treatment)	Proportion who switched to second-line (if indicated is from time since ART initiation)*
Coetzee (477)	287 patients starting ART in a public community based programme in Khayelitsha	2001-03	13.9	Of those initiated on ART	4.2%
Orrell (307)	929 patients in Nyanga district, near Cape Town	2002-05	6 (3-14). Total 760 PYs	Of those on ART	2.2% 17% (for drug toxicity)
Innes (495)	1416 patients initiating ART (eligible if CD4 <250 cells/µL, a WHO stage 4 condition or a WHO stage 3 condition and CD4 count <350 cells/µL) in a multisite workplace programme	2002-07	-	Of those initiated on ART	3 years: 4%
Barth (498)	735 patients initiated ART in Limpopo		36	Of those initiated on ART	4%
Hamers (966)	2588 ART naïve patients from 13 clinics: 2 in Kenya, 1 in Nigeria, 3 in South Africa, 3 in Uganda, 3 in Zambia and 1 in Zimbabwe;	2007-09		Of those initiated on ART	1 year: 1%
Fox (499)	23,456	2000-08	15.6 (Range across sites: 13-17), on ART 22; Total 29,935	Of those initiated on ART	1 year: 1% 5 years: 10.1% (9.0%-11.4%)
				Of those who experience VF (n=1348)	62%
				Of those who experience VF with ≥6 months of follow-up after failure (n=897)	74%

Source	Population	Year	Follow-up, median (IQR)	Type of analysis (intention to treat or on treatment)	Proportion who switched to second-line (if indicated is from time since ART initiation)*
Johnston 2012 (500)	1668 patients with VF in the Aurum Institute ART programme (56 clinics for employees of large, mostly mining companies and 81 urban and peri-urban private GPs). ART free of charge	2003-09	Total PYs 1921.8	Of those who experienced VF	12 months since VF: 16.9%

ART: antiretroviral treatment; GP: general practitioner; NGP: non-governmental organization; VF: virological failure;

Appendix XXII. Research published or presented at an international conference

Cambiano, V, Connor, O, Phillips, A, Rodger, A, Lodwick, R, Pharris, A, Lampe, F, Nakagawa, F, Smith, C & van de Laar, M. (2013) Antiretroviral therapy for prevention of HIV transmission: implications for Europe. Euro.Surveill, 18. **(Chapter 4 first part)**

Eaton JW, Menzies NA, Stover J, **Cambiano V**, Chindelevitch L, Cori A, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. Lancet Global Health 2014; 2(1):e23-e34. **(Chapter 4 second part)**

Cambiano V, Bertagnolio S, Jordan MR, Pillay D, Perriens JH, Venter F, Lundgren J & Phillips A (2014) Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation. AIDS, 28 Suppl 1, S15-S23. **(Chapter 5)**

Cambiano V, Castro H, Chadwick D, Smit E, Geretti AM, Dunn D, Phillips A, on behalf of UK HIV Drug Resistance Database & UKCHIC study (2014) Detection of NNRTI Resistance Mutations After Interrupting NNRTI-Based Regimens. Abstract 593, Conference on Retroviruses and Opportunistic Infections. **(Chapter 6)**

Cambiano V, Bertagnolio S, Jordan M, Lundgren J, Miners A, Pillay D, Revill P, Venter F, Phillips A (2014) Effectiveness of Potential Improvements in the Cascade of HIV Treatment and Care in South Africa. Abstract 1066, Conference on Retroviruses and Opportunistic Infections. **(Chapter 7)**

Cambiano V, Ford D, Mabugu T, Napierala Mavedzenge S, Miners A, Mugurungi O, Nakagawa F, Revill P, Phillips A (2014) Assessment of the Potential Cost-Effectiveness of HIV Self-Testing in Resource Limited Settings. Abstract 1045, Conference on Retroviruses and Opportunistic Infections. **(Chapter 8)**

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Table not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Paper not available due to copyright restrictions.

Detection of NNRTI resistance mutations after interrupting NNRTI-based regimens

Valentina Cambiano[1], Hannah Castro[2], David Chadwick[3], Erasmus Smit[4], Anna Maria Geretti[5], David Dunn[2], Andrew Phillips[1]

on behalf of UK HIV Drug Resistance Database & UK CHIC study.

1. UCL, London, UK; 2. MRC CTU at UCL, London, UK; 3. South Tees Hospital NHS Foundation Trust, Middlesbrough, UK; 4. Birmingham Heartlands and Solihull NHS Trust, Birmingham, UK; 5. University of Liverpool, Liverpool, UK;

BACKGROUND

There is evidence that NNRTI mutants emerge after interruption of suppressive NNRTI-based ART, due to the long half-life of NNRTIs. This has implications for both loss of treatment options for people undergoing ART interruption and potential transmission of drug resistance.

The aim of this study was to quantify the extent to which NNRTI mutations can be detected in the rebound viremia following interruption of suppressive NNRTI-based ART.

METHODS

The study population comprised patients from the UK HIV Drug Resistance Database and from the UK Collaborative HIV Cohort study (UK CHIC).

Figure 1 illustrates the eligibility criteria and the size of the population eligible for the analysis.

Virologic failure is defined as a VL>200 copies/ml, after at least 6 months on a certain regimen.

Resistance

Only resistance tests conducted after treatment interruption (TI) while off ART were considered.

NNRTI resistance was defined as at least one major NNRTI mutation according to the IAS-USA list (2008).

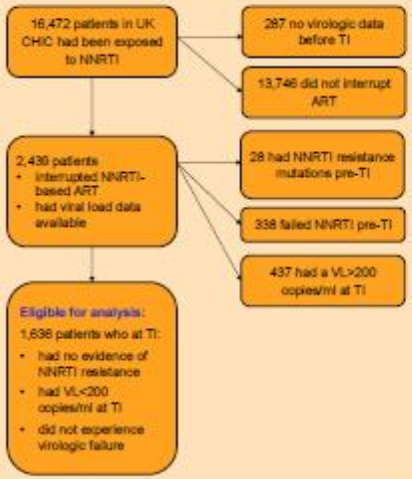
Statistical analysis

- Firstly, it was assessed whether there were significant differences, for the covariates listed below, between those who had a resistance test performed during the TI and those who did not. Chi-square test for categorical variable and Kruskal Wallis test for continuous variables were used. Crude and adjusted relative risks (RR) of having a resistance test performed after TI were calculated using a modified Poisson regression approach.
- Covariates considered include: demographic variables, calendar year of TI, whether the viral load (VL) was below 50 copies/ml at TI, length of virologic suppression, whether a resistance test was conducted pre-ART, time from ART initiation to TI, CD4 count at TI and CD4 count nadir, type of antiretroviral drug at TI and type and number of antiretroviral drugs experienced before TI (not shown).
- For the main analysis, the same approach was used to identify predictors of having NNRTI resistance detected in the rebound viremia after TI.
- Additional covariates considered include time from TI to resistance test, CD4 count at resistance test off-ART and subtype

Publication/grant info: UK CHIC and UK HDRD were funded by the Medical Research Council, UK (Grant numbers G0000135, G0800327 and G0800774). This work was supported by the UK Medical Research Council (grant G0800718 and the European Community's 7th Framework programme (FP7/2007-2013) under the Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN; grant 223131). The views expressed in this poster are those of the researchers and not necessarily those of the MRC.

RESULTS

Figure 1.Overview of patients eligible for the analysis



Predictors of resistance test availability

- Of 1,636 eligible patients, 13% (n=208) had a resistance test performed after stopping suppressive NNRTI-based ART. Table 1 illustrates the characteristics of the people who did and did not have a resistance test after treatment interruption.
- The covariates significantly associated with the presence of a resistance test after TI (mode of infection, age, calendar year of TI, maximum VL achieved, length of time with VL<200 copies/ml, years from ART initiation to TI, most recent CD4 count at TI, CD4 nadir, being on NVP, EFV, AZT, 3TC, TDF, FTC) were considered in a multivariate model.
- Independent predictors of having a resistance test were:
  - older calendar year of TI (range 1997-2008, aRR per 1 more recent calendar year = 0.89; 95% confidence interval [CI]: 0.85-0.93; p<0.0001)
  - higher maximum VL on ART pre-TI (aRR per 1 log increase=1.14; 95% CI: 1.04-1.26; p=0.0042)
  - younger age (aRR per 1 year older = 0.98; 95%CI: 0.94-0.97; p<0.0001)
  - higher CD4 count nadir (aRR per 100 cells/µl increase=1.08; 95%CI: 1.04-1.12; p<0.0001)
  - being on 3TC at ART interruption (aRR = 1.99; 95%CI: 1.39-2.87; p<0.0001).

Detection of NNRTI resistance mutations

- Among the 208 individuals with a resistance test performed after stopping suppressive NNRTI-based ART (see characteristics in table 1), **12% (n=25, 95% CI: 8%-17%) had ≥1 NNRTI resistance mutation detected at the first resistance test following ART treatment interruption.**
- **In those with at least 1 NNRTI resistance mutation detected the median time between TI and the resistance test was 12 months (IQR: 3-20 months).**
- The distribution of NNRTI resistance mutations, when detected after ART interruption is illustrated in Figure 2. K103N was the most prevalent mutation. There was no occurrence of K101H/P, V106M, Y181/V, Y188C/H or G190S.

Table 1. Baseline characteristics

		All eligible patients (n=1,636)		Patients with a resistance test after TI (while off-ART)				
				Yes (n=208)		No (n=1,428)		p
Male, n (%)		1,137	(69%)	138	(66%)	1,001	(70%)	0.1678
Ethnicity*, n (%)	White	885	(54%)	113	(56%)	772	(55%)	0.4005
	Black	595	(36%)	71	(35%)	524	(38%)	
	Other	115	(7%)	19	(9%)	96	(7%)	
Mode of infection**, n (%)	MSM	732	(45%)	115	(57%)	617	(47%)	0.0089
	HT	683	(42%)	80	(40%)	603	(46%)	
	Other	97	(6%)	6	(3%)	91	(7%)	
Age, med (IQR)		38	(33-45)	35	(30-40)	38	(33-45)	<.0001
Calendar year of TI, med (IQR)		Apr04	(Feb02; Dec06)	Jan03	(Sep01; Sep04)	Sep04	(Mar02; Apr07)	<.0001
VL at TI <50 copies/ml, n (%)		1,421	(87%)	172	(83%)	1,249	(87%)	0.0600
Maximum VL on ART, med (IQR)		251	(50-2,703)	406	(60-20,536)	230	(50-1,974)	0.0033
Months with VL<200 copies/ml, med (IQR)		12	(4-30)	6	(2-21)	12	(4-32)	<.0001
Resistance test pre-ART, n (%) (if done, no NNRTI mutations were detected)		384	(23%)	51	(25%)	333	(23%)	0.7029
Years ART initiation - TI, med (IQR)		1.70	(0.63-3.62)	1.05	(0.40-2.71)	1.77	(0.68-3.68)	<.0001
Most recent CD4 count (cells/µl) at TI, med (IQR)		415	(271-586)	468	(305-640)	408	(270-576)	0.0102
CD4+ nadir count (cells/µl), med (IQR)		295	(140-466)	379	(230-513)	280	(135-453)	<.0001
NNRTI at TI, n (%)	NVP	779	(48%)	127	(61%)	652	(46%)	<.0001
	EFV	864	(53%)	81	(39%)	783	(55%)	<.0001
	Other	5	(0%)	1	(0%)	4	(0%)	0.6243
NRTI at TI, n (%)	AZT	778	(48%)	132	(48%)	646	(45%)	<.0001
	DdC	2	(0%)	1	(0%)	1	(0%)	0.2382
	DdI	178	(11%)	20	(7%)	156	(11%)	0.5692
	D4I	229	(14%)	33	(12%)	196	(14%)	0.4060
	3TC	1,179	(72%)	177	(64%)	1,002	(70%)	<.0001
	ABC	253	(15%)	34	(12%)	219	(15%)	0.7066
	TDF	369	(23%)	21	(8%)	348	(24%)	<.0001
	FTC	240	(15%)	8	(3%)	232	(16%)	<.0001

MSM: men having sex with men; HT: heterosexual; med: median; IQR: interquartile range; *n=3440; **n=2351; ***n=2181

Detection of NNRTI resistance mutations

Figure 2. NNRTI resistance mutations detected after NNRTI interruption

- The only independent predictor of NNRTI resistance being detected (in a multivariate model including CD4 cell count at TI, CD4 nadir and NVP at TI) was CD4 nadir (aRR for 100 cells/µl increase in CD4 nadir = 0.67; 95% CI: 0.53-0.85; p=0.001).

Sensitivity analysis

1. Patients who stopped their ART regimen while having a VL ≤ 50 copies/ml (n=1,421, 87%) with a resistance test after TI (172/1421, 12%)
   - 12% (20; 95%CI: 7-17%) had NNRTI resistance
2. People who had a resistance test performed within 2 months since TI (n=55/208, 26%).
   - 7% (4; 95% CI: 3-19%) had NNRTI resistance
3. People who had a resistance test performed within 6 months since TI (n=94/208, 45%).
   - 9% (8; 95% CI: 4-17%) had NNRTI resistance
4. Simultaneous TI, with resistance test (n=188):
   - 12% (23; 95% CI: 7-17%) had NNRTI resistance
5. Staggered TI, with resistance test (n=20):
   - 10% (2; 95% CI: 1-32%) had NNRTI resistance

CONCLUSIONS

- To our knowledge this is the largest study to evaluate the detection of NNRTI resistance in the rebound viremia that follows interruption of a suppressive NNRTI-based regimen.
- It confirms that resistance is a relatively common phenomenon, occurring in 12% of patients tested.
- These estimates support the concept that interruption of EFV or NVP based ART carries a significant risk to the patient and informs models that incorporate HIV drug resistance emergence and transmission.

Effectiveness of potential improvements in the cascade of HIV treatment and care in South Africa

Valentina Cambiano[1], Silvia Bertagnolio[2], Michael R Jordan[2], Jens Lundgren[3], Alec Miners[4], Deenan Pillay[1], Paul Revill[5], Francois Venter[6], Andrew Phillips[1].
1. UCL, London, UK; 2. HIV Department, WHO, Geneva, Switzerland; 3. University of Copenhagen, Copenhagen, Denmark; 4. LSHTM, London, UK; 5. University of York, York, UK; 6. University of the Witwatersrand, Johannesburg, South Africa.

Correspondence:
e-mail: v.cambiano@ucl.ac.uk
Tel number: +44 (0)2077940500 (Ext: 34570)

Background

- The new WHO 2013 ART guidelines set ambitious goals of initiating all patients on ART at CD4<500 cells/mm³. However, several programmes in South Africa (SA) have highlighted that leakages in the cascade of care represent a major barrier to maximizing population health benefits from ART.
- Implementation studies demonstrated that it is possible to substantially reduce the leakages at different steps of the cascade of care.
- Programme managers face a difficult decisions over levels of resources and effort to commit to initiating patients earlier on ART compared to improving implementation of ART delivery.

The aim of this study is to evaluate the value of potential improvements in each step of the cascade of care and of changing in the eligibility criteria to initiate ART, over 20 years in South Africa.

Methods

HIV Synthesis Transmission Model

The 'HIV Synthesis transmission model', an individual-based stochastic model of heterosexual HIV transmission, progression and treatment of HIV infection (Phillips et al., AIDS 2011, 25(6): 43–850), calibrated to South Africa was used.

Table 1 illustrates the situation regarding the cascade of care at the end of 2013, and the intervention considered (assumed implemented over 2014 and 2015). The maintenance of this status is referred to as option R.

One key assumption relating to people who are lost is that if a WHO stage 4 condition is experienced then it is assumed there is an 80% chance of coming back into care.

Table 1. Assumptions regarding the cascade of care in South Africa and the potential

	Model		Observed data
	End of 2013	Change considered (label)	
CD4 eligibility criteria (EC) to be initiated on ART (in cells/μl)	CD4<350	CD4< 500 (F) At diagnosis (D)	CD4 <350 (2013 South African Guidelines)
Population ever tested for HIV	62% (29% in the last year)	85% (T)	51% in 2008 SA National HIV Prevalence, Incidence, Behaviour and Communication Survey
Linked to care by 1 year since diagnosis	71%	85% (L)	35% (Larson 2010 WHO Bull) to 78% (Govindasamy 2011 JAIDS)
Retention in pre-ART care at 1 year since ART eligibility asssessment in those not eligible for ART	42%	71% (P)	31% (Larson 2010 Trop Med Int Health) to 46% (Luseno 2008 XVII Conference)
Retention on ART care at 1 year since ART initiation	84%	92% (A)	80% (Cornell 2010 AIDS) to 93.% (Boulle 2008 Bull WHO)
Median time to switch to 2nd line since virological failure	12 months	5 months (S)	Assumption

In addition combination of the above are considered.

Acknowledgements
Thanks to UCL Computing Services for use of Legion high performance cluster computing (Legion@UCL). This work was funded by European Community's Seventh Framework Programme (FP7/2007-2013) under the project [2]Collaborative HIV and anti-HIV Drug Resistance Network (CHAIN)-grant agreement number 223131

Methods

Economic Analysis

The 19 scenarios are compared on the basis of their costs and health outcomes, which are both discounted to present value at 3% per annum, over 20 years. Costs are estimated based upon resource use (e.g. number of tests, number of clinic visits) and associated unit costs:

- ART cost (1st line: TDF+3TC+NVP): $97 per year [Source: MSF report 2013)
- WHO stage 4: US$200; WHO stage 3: $20; TB: $50; Cotrimoxazole (CTX) per year $5
- Clinic Visit: $40; CD4 measurement $15; VL cost $45; HIV test (all costs fully loaded) $10;

The benefits of improving implementation are investigated; firstly without any additional costs for implementation initiatives (figure 3a) and then with the following indicative fixed implementation delivery costs (figure 3b):

- $0.5 per person not diagnosed with HIV (either HIV negative or positive and not diagnosed) if an intervention to increase testing was included,
- $50 per person linked to care, per person-year retained in pre-ART care, per person-year retained on ART and per switch to 2nd line was applied if respectively an intervention to increase linkage to care, retention in pre-ART care, on ART and reducing the time to switch to 2nd line was introduced.

Health outcomes are summarised in the form of quality-adjusted life years (QALYs). Expected costs and health outcomes under both scenarios can be compared using incremental cost-effectiveness ratio (ICER) to establish whether each intervention is likely to represent good value from available health sector resources.

Costs and health outcomes are rescaled to provide figures relevant to the entire adult population (15-65 years old) of South Africa.

Results

Figure 1. Life years gained over 20 years (in million) in South Africa

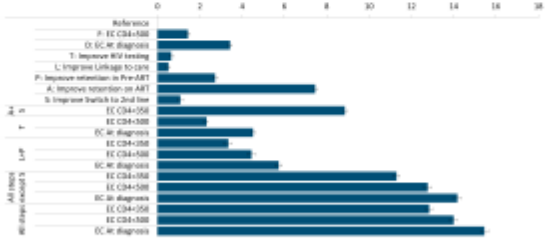
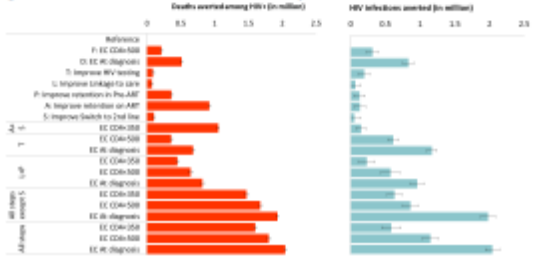


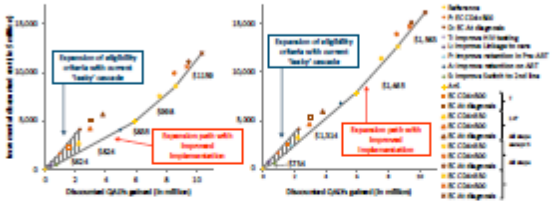
Figure 2. Deaths and HIV infections averted over 20 years



Results

Figure 3. Value of strengthened implementation in South Africa

a. Maximum value (no costs of implementation initiatives included)
b. Indicative value (illustrative costs of implementation initiatives included)



In Figure 3a and 3b two cost-effectiveness frontiers have been presented, one across the interventions aimed at improving how care is delivered (interventions T, L, P, A, S and their combinations) and one across the intervention where the eligibility criteria to be initiated on ART are modified to either CD4<500 cells/mm³, as recommended by WHO or to all people diagnosed with HIV. The area between the two frontiers represents the area of potential gain from improving implementation.

Table 2. Maximum cost of the intervention to be cost-effective at the CET indicated (considering only the single interventions applied to improve the current leaky cascade)

Potential intervention	$ cost is per....	Cost –effectiveness threshold (CET)			
		$1,000	$2,000	$5,000	$12,000
T: Improve HIV testing	person not diagnosed with HIV	-	$0.8	$3	$10
L: Improve Linkage to care	person linked to care	-	$54	$261	$745
P: Improve retention in Pre-ART	person-year in pre-ART care	-	$278	$1,279	$3,616
A: Improve retention on ART	person-year on ART	$16	$108	$382	$1,023
S: Improve Switch to 2nd line	person switched to 2nd line	$171	$624	$1,985	$5,159

Note: South Africa GDP in 2012 US$ 11,600

The estimates indicated in table 2 provide the framework to design interventions that could improve the cascade. For example interventions aimed at reducing the delay in switching to 2nd line (from 12 to 5 months) or at improving the retention on ART (from 84% to 92%) can be more expensive per unit considered because they lead to greater health benefit.

Conclusions

- Policymakers need to determine how best to spend available resources on ART to generate health gains in the population. The single improvement which leads to the highest increment in total life years over 20 years is improvement of retention on ART (7.5 million), which leads to the greatest reduction in deaths among HIV+ people (923,000), despite only an assumed relatively modest increase in retention (8%).
- Modifying the ART eligibility criteria to initiate ART at diagnosis averts the highest number of new HIV infections (831,000), but results in a lower increment in life years of 3.4 million. The specified improvements at all steps of the cascade allow a gain of over 15 million life years over 20 years.
- Our analysis indicates that policymakers should seek to strengthen the cascade of HIV testing and treatment (in particular by improving retention on ART and switch to 2nd line) before raising the eligibility criteria. Further research on what initiatives could improve implementation of ART, and how much these are likely to cost, would be very valuable.
- In the longer term, greatest health gains can be achieved by both improving implementation and increasing eligibility for ART, but this requires substantial commitment of resources.

Assessment of the Potential Cost-Effectiveness of HIV Self-Testing in Resource Limited Settings

Valentina Cambiano[1], Debbie Ford[2], Travor Mabugu[3], Sue Napierala Mavedzenge[4], Alec Miners[5], Owen Mugurungi[6], Fumiyo Nakagawa[1], Paul Revill[7], Andrew Phillips[1]

1.UCL, London, UK; 2. MRC CTU at UCL, London, UK; 3. University of Zimbabwe, Harare, Zimbabwe; 4. RTI International, San Francisco, US; 5. LSHTM, London, UK; 6. Ministry of Health, Harare, Zimbabwe; 7. University of York, York, UK

Correspondence:
e-mail: v.cambiano@ucl.ac.uk
Tel number: +44 (0)2077940500 (Ext: 34570)

Background

Despite the dramatic increase in HIV testing in low and middle income countries in the last few years, over 50% remain unaware of their HIV status.

Implementation studies demonstrated that HIV self-testing (ST) is highly acceptable, could overcome some of the obstacles to testing for HIV and allow savings in costs, given its potentially lower implementation cost compared to provider-delivered HIV testing and counselling (PHTC).

Donors and stakeholders are evaluating whether investments should be made to support product development, promotion and marketing of self-testing in resource limited settings.

The aim of this study is to evaluate the potential benefits of introducing self-testing, in addition to the standard provider-delivered PHTC, over 20 years, using Zimbabwe as an example setting.

Methods

HIV Synthesis Transmission Model

The analysis uses an updated version of the 'HIV Synthesis transmission model', an individual-based stochastic model of heterosexual HIV transmission, progression and treatment of HIV infection (Phillips et al., AIDS 2011, 25(6): 43–850).

Updates for the present analyses include age and gender specific rates of first time and repeat testing, including self-testing, and calibration to reflect HIV prevalence and age and gender specific levels of testing observed in Zimbabwe. A 3-fold reduction in rate of testing for people who never had condom-less sex is incorporated and increased rates of PHTC for women attending antenatal clinics and for subjects experiencing symptoms. A proportion (5%) are assumed to be not willing to be tested for HIV and will only be tested if symptoms occur.

Table 1. Assumptions on PHTC and ST

Parameter		Value	Source
Accuracy of ST		SE = 0.92; SP = 0.99	FDA Approval Oraquick In-Home HIV test
Accuracy of PHTC		SE = 0.98; SP = 1	Pant Pai, Lancet Inf Dis 2012
Probability of PHTC as a direct consequence of a +ve ST (+ve ST is not sufficient to be defined as diagnosed)		0.8 by 1 year since +ve ST	Assumption
Probability of linkage to care after HIV diagnosis (by 1 year since diagnosis)		0.6 (same value whether diagnosis was triggered by +ve ST or not)	Rosen, AIDS 2011
Change in condom-less sex following:	a +ve PHTC	with primary P: -13%, with casual P: -17% in the first 6 ms, -9% after	Kennedy, AIDS Behav 2012; Fonner, Cochrane 2012
	a -ve PHTC	No change	Cremin, Aids Behavior 2010
	a ST	As for PHTC	Assumption
Disability weights		WHO 4 event: 0.55; TB: 0.40; WHO 3 event: 0.22	Salomon, Lancet 2012
Cost PHTC (fully loaded)		Neg US $9; Pos US $25	US $10 overall in Eaton, Lancet Global Health 2014
Cost of ST		US $3	Assumption
CD4 threshold for ART		<500 cells/mm³	Zimbabwe MoH

SE = sensitivity; SP = specificity;

Methods

Scenarios modelled

The HIV epidemic in Zimbabwe is simulated up to 2015, based on existing data on HIV prevalence and HIV testing (DHS survey 2006 and 2011).

From 2015, we compare the following two scenarios:

- **Reference Scenario (RS):** ST is not introduced and the rates of 1st time and repeat testing increase linearly by 0.5% per year and the scale up of ART continues at the same rate as before 2015
- **Self-testing scenario (STS - base case):** ST is introduced for the general population aged 15-65 years old and has the following three main effects:
  a. halving of the population not willing to receive an HIV test (from 5 to 2.5%);
  b. substitution of 10% first time and 30% repeat PHTC tests with STs;
  c. an overall increase in the rate of first time and repeat testing by 20%, due to the availability of ST.

Availability of ST is not assumed to affect PHTC testing in antenatal care settings. These assumptions, and those in table 1, are based on limited current evidence available but overall are believed to be conservative in estimating the potential benefits of ST.

Economic Analysis

The two scenarios are compared on the basis of their costs and health outcomes, which are both discounted to present value at 3% per annum, over 20 years. Costs are estimated based upon resource use (e.g. number of tests, number of clinic visits) and associated unit costs:

- ART cost (1st line: TDF+3TC+NVP): US $97 per year (Source: MSF report 2013)
- WHO stage 4: US $200; WHO stage 3: US $ 20; TB: US $50; Cotrimoxazole (CTX) per year US $5
- Clinic Visit: US $20; CD4 measurement US $ 10;

Health outcomes are summarised in the form of disability-adjusted life years (DALYs). Expected costs and health outcomes under both scenarios can be compared using incremental cost-effectiveness analysis to establish whether ST is likely to represent good value from available health sector resources.

Results are presented across a range of cost-effectiveness thresholds; from US $0 (an extreme case, implying a health system would only be concerned with reducing costs) to US $10,000 (a relatively high threshold only likely to be relevant in well financed health systems with full coverage of interventions offering health gains at less than this amount). Costs and health outcomes are rescaled to provide figures relevant to the entire adult population (15-65 years old) of Zimbabwe. Due to the stochastic variation inherent in the model a high number of simulations are required so figures representing multivariate sensitivity analyses are presented on a discrete rather than a continuous scale.

Table 2. Predictions over time in the two main scenarios (median over simulations)

	Data - DHS	Model				
		Baseline	Reference		Self-testing	
	2011	2015	2025	2035	2025	2035
HIV prevalence (%)	15	14	11	7	11	7
% ever tested for HIV	50	65	77	79	80	83
% tested for HIV in the last year	28	37	46	50	53	56
% on ART (of those HIV+)	-	53	71	76	71	76

Acknowledgements
Thanks to UCL Computing Services for use of Legion high performance cluster computing. This work was funded by the Bill & Melinda Gates Foundation

Results

Figure 1. Total discounted cost over 20 years in US $ billions

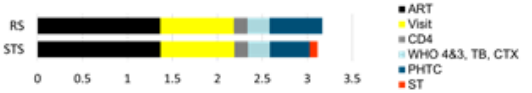


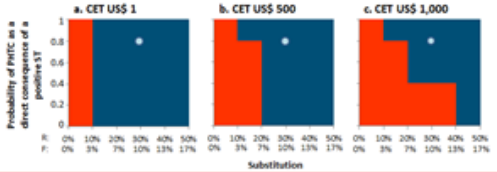
Figure 2a. Cost-effective scenario (STS or RS) under base case and alternative assumptions and according to cost effectiveness threshold (CET)

	CET in US $ thousands 0 0.5 1 5 10	Δ discounted costs* in US$ million (95%CI)	Discounted DALYs averted* in thousands (95%CI)
Base case (See section "Scenario modelled" in methods)		-53 (-58;-49)	102 (62;142)
Cost of ST = US $9 (B: US $3)		123 (119;127)	102 (62;142)
Sensitivity of ST = 0.55 (B: 0.92)		-77 (-81;-74)	-157 (-193;120)
Probability of PHTC as a direct consequence of a pos ST = 0.37 (B: 0.8)		-79 (-83;-75)	-166 (-203;-130)
Linkage to care following diagnosis for those who had a ST 0.4 by 1 year (B: 0.6)		-93 (-98;-88)	-166 (-211;-122)
ART initiation at CD4 < 350 cells/mm³ (B: CD4 < 500 cells/mm³)		-159 (-163;-155)	-252 (-293;-211)
No reduction in condom-less sex following a pos ST (B: as PHTC)		-73 (-79;-70)	-129 (-173;-86)
Increase in rate of 1st test due to ST (B: 20%)	2.5%	-86 (-92;-79)	-141 (-206;-76)
	7.5%	-83 (-91;-77)	-138 (-202;-75)
Increase in rate of repeat test due to ST (B: 20%)	2.5%	-100 (-106;-94)	-117 (-176;-57)
	7.5%	-93 (-98;-88)	-96 (-144;-47)
Substitution (B: 30% repeat, 10% 1st test)	5% of repeat, 2% 1st test	47 (42;53)	209 (163;255)
	15% of repeat, 5% 1st test	-2 (-11;8)	139 (55;223)
	25% of repeat, 8% 1st test	-35 (-43;-26)	118 (36;198)

*Compared to the RS (total discounted life-years 120.5 million); B: base case assumption

■ ST not cost-effective ■ ST cost-effective ○ base case

Figure 2b. Two-way sensitivity analysis under three different cost-effectiveness thresholds



Results

Under our base case assumptions, our results suggest that the introduction of ST is not only cost-effective but cost-saving, with an estimated saving of around US $ 53 million over 20 years in Zimbabwe and a small (100,000) number of DALYs averted.

However, the population costs and health effects of ST depend upon a range of complex and interacting factors, many of which are currently uncertain due to limited data. In particular, while most scenarios may lead to cost-savings, a number of plausible scenarios do not result in DALYs averted. It will therefore be important to update these predictions as more data become available.

(1) Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. Trop Med Int Health 2010 Jun;15 Suppl 1:1-15.

(2) Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med 2007 Oct 16;4(10):e298.

(3) Sharp PM, Bailes E, Robertson DL, Gao F, Hahn BH. Origins and evolution of AIDS viruses. Biol Bull 1999 Jun;196(3):338-42.

(4) Goto T, Nakai M, Ikuta K. The life-cycle of human immunodeficiency virus type 1. Micron 1998 Apr;29(2-3):123-38.

(5) Klimas N, Koneru AO, Fletcher MA. Overview of HIV. Psychosom Med 2008 Jun;70(5):523-30.

(6) Smith JA, Daniel R. Following the path of the virus: the exploitation of host DNA repair mechanisms by retroviruses. ACS Chem Biol 2006 May 23;1(4):217-26.

(7) Holmes EC. On the origin and evolution of the human immunodeficiency virus (HIV). Biol Rev Camb Philos Soc 2001 May;76(2):239-54.

(8) Kanki PJ, Travers KU, MBoup S, Hsieh CC, Marlink RG, Gueye-NDiaye A, et al. Slower heterosexual spread of HIV-2 than HIV-1. Lancet 1994 Apr 16;343(8903):943-6.

(9) Woodman Z, Williamson C. HIV molecular epidemiology: transmission and adaptation to human populations. Curr Opin HIV AIDS 2009 Jul;4(4):247-52.

(10) Cohen MS, Hellmann N, Levy JA, DeCock K, Lange J. The spread, treatment, and prevention of HIV-1: evolution of a global pandemic. J Clin Invest 2008 Apr;118(4):1244-54.

(11) Plantier JC, Leoz M, Dickerson JE, De OF, Cordonnier F, Lemee V, et al. A new human immunodeficiency virus derived from gorillas. Nat Med 2009 Aug;15(8):871-2.

(12) Vallari A, Holzmayer V, Harris B, Yamaguchi J, Ngansop C, Makamche F, et al. Confirmation of putative HIV-1 group P in Cameroon. J Virol 2011 Feb;85(3):1403-7.

(13) HIV sequence database. HIV and SIV Nomenclature. HIV sequence database 2012 February 2 [cited 2013 Jul 10];Available from: URL: http://www.hiv.lanl.gov/content/sequence/HelpDocs/subtypes-more.html

(14) WHO HIV/AIDS Programme. Immunization, Vaccines and Biologicals. WHO 2013 [cited 2013 Jul 10];Available from: URL: http://www.who.int/immunization/topics/hiv/en/index1.html

(15) Hemelaar J, Gouws E, Ghys PD, Osmanov S. Global trends in molecular epidemiology of HIV-1 during 2000-2007. AIDS 2011 Mar 13;25(5):679-89.

(16) Berger EA, Murphy PM, Farber JM. Chemokine receptors as HIV-1 coreceptors: roles in viral entry, tropism, and disease. Annu Rev Immunol 1999;17:657-700.

(17) Mccune JM. The dynamics of CD4+ T-cell depletion in HIV disease. Nature 2001 Apr 19;410(6831):974-9.

(18) Engelman A, Cherepanov P. The structural biology of HIV-1: mechanistic and therapeutic insights. Nat Rev Microbiol 2012 Apr;10(4):279-90.

(19) Fauci AS, Pantaleo G, Stanley S, Weissman D. Immunopathogenic mechanisms of HIV infection. Ann Intern Med 1996 Apr 1;124(7):654-63.

(20) Potter SJ, Lacabaratz C, Lambotte O, Perez-Patrigeon S, Vingert B, Sinet M, et al. Preserved central memory and activated effector memory CD4+ T-cell subsets in human immunodeficiency virus controllers: an ANRS EP36 study. J Virol 2007 Dec;81(24):13904-15.

(21) Stebbing J, Gazzard B, Douek DC. Where does HIV live? N Engl J Med 2004 Apr 29;350(18):1872-80.

(22) Blankson JN, Persaud D, Siliciano RF. The challenge of viral reservoirs in HIV-1 infection. Annu Rev Med 2002;53:557-93.

(23) NIH. HIV Replication Cycle. http://www niaid nih gov/topics/hivaids/understanding/biology/Pages/hivReplicationCycle aspx 2012 April 3 [cited 2013 Jul 7];Available from: URL: http://www.niaid.nih.gov/topics/hivaids/understanding/biology/Pages/hivReplicationCycle.aspx

(24) Buchanan AM, Cunningham CK. Advances and failures in preventing perinatal human immunodeficiency virus infection. Clin Microbiol Rev 2009 Jul;22(3):493-507.

(25) Lewthwaite P, Wilkins E. Natural history of HIV/AIDS. Medicine 2009 Jul;37(7):333-7.

(26) Varghese B, Maher JE, Peterman TA, Branson BM, Steketee RW. Reducing the risk of sexual HIV transmission: quantifying the per-act risk for HIV on the basis of choice of partner, sex act, and condom use. Sex Transm Dis 2002 Jan;29(1):38-43.

(27) Chitwood DD, McCoy CB, Inciardi JA, McBride DC, Comerford M, Trapido E, et al. HIV seropositivity of needles from shooting galleries in south Florida. Am J Public Health 1990 Feb;80(2):150-2.

(28) Donegan E, Stuart M, Niland JC, Sacks HS, Azen SP, Dietrich SL, et al. Infection with human immunodeficiency virus type 1 (HIV-1) among recipients of antibody-positive blood donations. Ann Intern Med 1990 Nov 15;113(10):733-9.

(29) Adler MW. ABC of Aids: Development of the epidemic. BMJ 2001 May 19;322(7296):1226-9.

(30) Atkins MC, Carlin EM, Emery VC, Griffiths PD, Boag F. Fluctuations of HIV load in semen of HIV positive patients with newly acquired sexually transmitted diseases. BMJ 1996 Aug 10;313(7053):341-2.

(31) Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire-Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. N Engl J Med 2000 Mar 30;342(13):921-9.

(32) Royce RA, Sena A, Cates W, Jr., Cohen MS. Sexual transmission of HIV. N Engl J Med 1997 Apr 10;336(15):1072-8.

(33) Powers KA, Poole C, Pettifor AE, Cohen MS. Rethinking the heterosexual infectivity of HIV-1: a systematic review and meta-analysis. Lancet Infectious Diseases 2008;8(9):553-63.

(34) Marmor M, Sheppard HW, Donnell D, Bozeman S, Celum C, Buchbinder S, et al. Homozygous and heterozygous CCR5-Delta32 genotypes are associated with resistance to HIV infection. J Acquir Immune Defic Syndr 2001 Aug 15;27(5):472-81.

(35) Fideli US, Allen SA, Musonda R, Trask S, Hahn BH, Weiss H, et al. Virologic and immunologic determinants of heterosexual transmission of human immunodeficiency virus type 1 in Africa. AIDS Res Hum Retroviruses 2001 Jul 1;17(10):901-10.

(36) Mehendale SM, Ghate MV, Kumar BK, Sahay S, Gamble TR, Godbole SV, et al. Low HIV-1 incidence among married serodiscordant couples in Pune, India. Jaids-Journal of Acquired Immune Deficiency Syndromes 2006;41(3):371-3.

(37) Fraser C, Hollingsworth TD. Interpretation of correlations in setpoint viral load in transmitting couples. AIDS 2010;24(16):2596-7.

(38) Lingappa JR, Hughes JP, Wang RS, Baeten JM, Celum C, Gray GE, et al. Estimating the Impact of Plasma HIV-1 RNA Reductions on Heterosexual HIV-1 Transmission Risk. PLoS One 2010 Sep 13;5(9).

(39) de V, I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med 1994 Aug 11;331(6):341-6.

(40) Anderson RM, May RM. Epidemiological parameters of HIV transmission. Nature 1988 Jun 9;333(6173):514-9.

(41) Leynaert B, Downs AM, de V, I. Heterosexual transmission of human immunodeficiency virus: variability of infectivity throughout the course of infection. European Study Group on Heterosexual Transmission of HIV. Am J Epidemiol 1998 Jul 1;148(1):88-96.

(42) Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. J Infect Dis 2005 May 1;191(9):1403-9.

(43) Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. J Infect Dis 2008 Sep 1;198(5):687-93.

(44) Lewis F, Hughes GJ, Rambaut A, Pozniak A, Leigh Brown AJ. Episodic sexual transmission of HIV revealed by molecular phylodynamics. PLoS Med 2008 Mar 18;5(3):e50.

(45) Wawer MJ, Makumbi F, Kigozi G, Serwadda D, Watya S, Nalugoda F, et al. Circumcision in HIV-infected men and its effect on HIV transmission to female partners in Rakai, Uganda: a randomised controlled trial. Lancet 2009 Jul 18;374(9685):229-37.

(46) Gnanakaran S, Bhattacharya T, Daniels M, Keele BF, Hraber PT, Lapedes AS, et al. Recurrent signature patterns in HIV-1 B clade envelope glycoproteins associated with either early or chronic infections. PLoS Pathog 2011 Sep;7(9):e1002209.

(47) Kennedy CE, Fonner VA, Sweat MD, Okero FA, Baggaley R, O'Reilly KR. Provider-Initiated HIV Testing and Counseling in Low- and Middle-Income Countries: A Systematic Review. AIDS Behav 2012 Jul 3.

(48) Fonner VA, Denison J, Kennedy CE, O'Reilly K, Sweat M. Voluntary counseling and testing (VCT) for changing HIV-related risk behavior in developing countries. Cochrane Database of Systematic Reviews 2012;(9).

(49) Baeten JM, Kahle E, Lingappa JR, Coombs RW, Delany-Moretlwe S, Nakku-Joloba E, et al. Genital HIV-1 RNA predicts risk of heterosexual HIV-1 transmission. Sci Transl Med 2011 Apr 6;3(77):77ra29.

(50) Fleming DT, Wasserheit JN. From epidemiological synergy to public health policy and practice: the contribution of other sexually transmitted diseases to sexual transmission of HIV infection. Sex Transm Infect 1999 Feb;75(1):3-17.

(51) Gray RH, Wawer MJ, Brookmeyer R, Sewankambo NK, Serwadda D, Wabwire-Mangen F, et al. Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1-discordant couples in Rakai, Uganda. Lancet 2001 Apr 14;357(9263):1149-53.

(52) Weiss H. Epidemiology of herpes simplex virus type 2 infection in the developing world. Herpes 2004 Apr;11 Suppl 1:24A-35A.

(53) Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M, et al. Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. J Infect Dis 2000 Oct;182(4):1090-6.

(54) Schacker T, Ryncarz AJ, Goddard J, Diem K, Shaughnessy M, Corey L. Frequent recovery of HIV-1 from genital herpes simplex virus lesions in HIV-1-infected men. JAMA 1998 Jul 1;280(1):61-6.

(55) Schacker T, Zeh J, Hu H, Shaughnessy M, Corey L. Changes in plasma human immunodeficiency virus type 1 RNA associated with herpes simplex virus reactivation and suppression. J Infect Dis 2002 Dec 15;186(12):1718-25.

(56) Boily MC, Baggaley RF, Wang L, Masse B, White RG, Hayes RJ, et al. Heterosexual risk of HIV-1 infection per sexual act: systematic review and meta-analysis of observational studies. Lancet Infectious Diseases 2009;9(2):118-29.

(57) Rottingen JA, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known? Sex Transm Dis 2001 Oct;28(10):579-97.

(58) Hayes RJ, Schulz KF, Plummer FA. The cofactor effect of genital ulcers on the per-exposure risk of HIV transmission in sub-Saharan Africa. J Trop Med Hyg 1995 Feb;98(1):1-8.

(59) Celum C, Wald A, Lingappa JR, Magaret AS, Wang RS, Mugo N, et al. Acyclovir and Transmission of HIV-1 from Persons Infected with HIV-1 and HSV-2. New England Journal of Medicine 2010 Feb 4;362(5):427-39.

(60) Allen S, Tice J, Van de PP, Serufilira A, Hudes E, Nsengumuremyi F, et al. Effect of serotesting with counselling on condom use and seroconversion among HIV discordant couples in Africa. BMJ 1992 Jun 20;304(6842):1605-9.

(61) Halperin DT, Shiboski SC, Palefsky JM, Padian NS. High level of HIV-1 infection from anal intercourse: a neglected risk factor in heterosexual AIDS prevention. 2002 Jul 7; Barcelona, Spain 2013.

(62) Baggaley RF, White RG, Boily MC. HIV transmission risk through anal intercourse: systematic review, meta-analysis and implications for HIV prevention. Int J Epidemiol 2010 Aug;39(4):1048-63.

(63) Rodger A, Bruun T, Cambiano V, Vernazza P, Estrada V, Van Lunzen J, et al. HIV Transmission Risk Through Condomless Sex If HIV+ Partner On Suppressive ART: PARTNER Study. 2014 Mar 4; Boston, MA 2014.

(64) van GF, de Lind van Wijngaarden JW, Baral S, Grulich A. The global epidemic of HIV infection among men who have sex with men. Curr Opin HIV AIDS 2009 Jul;4(4):300-7.

(65) Dunkle KL, Jewkes RK, Murdock DW, Sikweyiya Y, Morrell R. Prevalence of Consensual Male-Male Sex and Sexual Violence, and Associations with HIV in South Africa: A Population-Based Cross-Sectional Study. PLoS Med 2013 Jun;10(6):e1001472.

(66) Wu L, LaRosa G, Kassam N, Gordon CJ, Heath H, Ruffing N, et al. Interaction of chemokine receptor CCR5 with its ligands: multiple domains for HIV-1 gp120 binding and a single domain for chemokine binding. J Exp Med 1997 Oct 20;186(8):1373-81.

(67) Martinson JJ, Chapman NH, Rees DC, Liu YT, Clegg JB. Global distribution of the CCR5 gene 32-basepair deletion. Nat Genet 1997 May;16(1):100-3.

(68) Rezza G, Titti F, Tempesta E, di GM, Weisert A, Rossi GB, et al. Needle sharing and other behaviours related to HIV spread among intravenous drug users. AIDS 1989 Apr;3(4):247-8.

(69) Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. Am J Med 1997 May 19;102(5B):9-15.

(70) Busch MP, Operskalski EA, Mosley JW, Lee TH, Henrard D, Herman S, et al. Factors influencing human immunodeficiency virus type 1 transmission by blood transfusion. Transfusion Safety Study Group. J Infect Dis 1996 Jul;174(1):26-33.

(71) Cardo DM, Culver DH, Ciesielski CA, Srivastava PU, Marcus R, Abiteboul D, et al. A case-control study of HIV seroconversion in health care workers after

percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. N Engl J Med 1997 Nov 20;337(21):1485-90.

(72) Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. MMWR Recomm Rep 2005 Sep 30;54(RR-9):1-17.

(73) Des Jarlais DC, Semaan S. HIV prevention for injecting drug users: the first 25 years and counting. Psychosom Med 2008 Jun;70(5):606-11.

(74) Sloand EM, Pitt E, Klein HG. Safety of the blood supply. JAMA 1995 Nov 1;274(17):1368-73.

(75) Takei T, Amin NA, Schmid G, Dhingra-Kumar N, Rugg D. Progress in global blood safety for HIV. J Acquir Immune Defic Syndr 2009 Dec;52 Suppl 2:S127-S131.

(76) Mayaux MJ, Blanche S, Rouzioux C, Le CJ, Chambrin V, Firtion G, et al. Maternal factors associated with perinatal HIV-1 transmission: the French Cohort Study: 7 years of follow-up observation. The French Pediatric HIV Infection Study Group. J Acquir Immune Defic Syndr Hum Retrovirol 1995 Feb 1;8(2):188-94.

(77) Newell ML, Dunn DT, Peckham CS, Semprini AE, Pardi G. Vertical transmission of HIV-1: maternal immune status and obstetric factors. The European Collaborative Study. AIDS 1996 Dec;10(14):1675-81.

(78) Thorne C, Newell ML. Mother-to-child transmission of HIV infection and its prevention. Curr HIV Res 2003 Oct;1(4):447-62.

(79) Pitt J, Brambilla D, Reichelderfer P, Landay A, McIntosh K, Burns D, et al. Maternal immunologic and virologic risk factors for infant human immunodeficiency virus type 1 infection: findings from the Women and Infants Transmission Study. J Infect Dis 1997 Mar;175(3):567-75.

(80) UNAIDS. Global fact sheet: World AIDS Day 2012. UNAIDS 2012 December 1 [cited 2013 Jul 14];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/20121120_FactSheet_Global_en.pdf

(81) Mofenson LM. Mother-child HIV-1 transmission: Timing and determinants. Obstet Gynecol Clin North Am 1997 Dec;24(4):759-84.

(82) Cavarelli M, Scarlatti G. Human immunodeficiency virus type 1 mother-to-child transmission and prevention: successes and controversies. J Intern Med 2011 Dec;270(6):561-79.

(83) Connor EM, Sperling RS, Gelber R, Kiselev P, Scott G, O'Sullivan MJ, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. N Engl J Med 1994 Nov 3;331(18):1173-80.

(84) Marinda ET, Moulton LH, Humphrey JH, Hargrove JW, Ntozini R, Mutasa K, et al. In utero and intra-partum HIV-1 transmission and acute HIV-1 infection during

pregnancy: using the BED capture enzyme-immunoassay as a surrogate marker for acute infection. Int J Epidemiol 2011 Aug;40(4):945-54.

(85) AIDS Education & Training Centers National Resource Center. HIV Classification: CDC and WHO Staging Systems. AIDS Education 2012 June [cited 2013 Jul 13];Available from: URL: http://www.aids-ed.org/aidsetc?page=cg-205_hiv_classification

(86) WHO. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. WHO 2007 [cited 2013 Jul 8];Available from: URL: http://www.who.int/hiv/pub/guidelines/HIVstaging150307.pdf

(87) Centers for Disease Control and Prevention. 1993 revised classification system for HIV infection and expanded surveillance case definition for AIDS among adolescents and adults. MMWR Recomm Rep 1992 Dec;41(RR-17):1-19.

(88) Vergis EN, Mellors JW. Natural history of HIV-1 infection. Infect Dis Clin North Am 2000 Dec;14(4):809-vi.

(89) Mindel A, Tenant-Flowers M. ABC of AIDS: Natural history and management of early HIV infection. BMJ 2001 May 26;322(7297):1290-3.

(90) Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary human immunodeficiency virus type 1 infection. N Engl J Med 1991 Apr 4;324(14):961-4.

(91) Schacker TW, Hughes JP, Shea T, Coombs RW, Corey L. Biological and virologic characteristics of primary HIV infection. Ann Intern Med 1998 Apr 15;128(8):613-20.

(92) Touloumi G, Pantazis N, Babiker AG, Walker SA, Katsarou O, Karafoulidou A, et al. Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates. AIDS 2004 Aug 20;18(12):1697-705.

(93) Lodi S, Phillips A, Touloumi G, Geskus R, Meyer L, Thiebaut R, et al. Time From Human Immunodeficiency Virus Seroconversion to Reaching CD4+ Cell Count Thresholds < 200, < 350, and < 500 Cells/mm(3): Assessment of Need Following Changes in Treatment Guidelines. Clinical Infectious Diseases 2011 Oct 15;53(8):817-25.

(94) Differences in CD4 cell counts at seroconversion and decline among 5739 HIV-1-infected individuals with well-estimated dates of seroconversion. J Acquir Immune Defic Syndr 2003 Sep 1;34(1):76-83.

(95) Maini MK, Gilson RJ, Chavda N, Gill S, Fakoya A, Ross EJ, et al. Reference ranges and sources of variability of CD4 counts in HIV-seronegative women and men. Genitourin Med 1996 Feb;72(1):27-31.

(96) Haase AT. Population biology of HIV-1 infection: viral and CD4+ T cell demographics and dynamics in lymphatic tissues. Annu Rev Immunol 1999;17:625-56.

(97) Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. N Engl J Med 1993 Feb 4;328(5):327-35.

(98) O'Brien TR, Rosenberg PS, Yellin F, Goedert JJ. Longitudinal HIV-1 RNA levels in a cohort of homosexual men. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1998 Jun 1;18(2):155-61.

(99) Sabin CA, Devereux H, Phillips AN, Hill A, Janossy G, Lee CA, et al. Course of viral load throughout HIV-1 infection. J Acquir Immune Defic Syndr 2000 Feb 1;23(2):172-7.

(100) Mellors JW, Rinaldo CR, Jr., Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. Science 1996 May 24;272(5265):1167-70.

(101) Wandel S, Egger M, Rangsin R, Nelson KE, Costello C, Lewden C, et al. Duration from seroconversion to eligibility for antiretroviral therapy and from ART eligibility to death in adult HIV-infected patients from low and middle-income countries: collaborative analysis of prospective studies. Sex Transm Infect 2008 Aug;84 Suppl 1:i31-i36.

(102) Munoz A, Wang MC, Bass S, Taylor JM, Kingsley LA, Chmiel JS, et al. Acquired immunodeficiency syndrome (AIDS)-free time after human immunodeficiency virus type 1 (HIV-1) seroconversion in homosexual men. Multicenter AIDS Cohort Study Group. Am J Epidemiol 1989 Sep;130(3):530-9.

(103) Babiker A, Darby S, De Angelis D, Kwart D, Porter K, Beral V, et al. Time from HIV-1 seroconversion to AIDS and death before widespread use of highly-active antiretroviral therapy: a collaborative re-analysis. Lancet 2000 Apr 1;355(9210):1131-7.

(104) Munoz A, Kirby AJ, He YD, Margolick JB, Visscher BR, Rinaldo CR, et al. Long-term survivors with HIV-1 infection: incubation period and longitudinal patterns of CD4+ lymphocytes. J Acquir Immune Defic Syndr Hum Retrovirol 1995 Apr 15;8(5):496-505.

(105) Pantazis N, Morrison C, Amornkul PN, Lewden C, Salata RA, Minga A, et al. Differences in HIV natural history among African and non-African seroconverters in Europe and seroconverters in sub-Saharan Africa. PLoS One 2012;7(3):e32369.

(106) Post FA, Badri M, Wood R, Maartens G. Aids in Africa - Survival according to AIDS-defining illness. South African Medical Journal 2001 Jul;91(7):583-6.

(107) Mocroft AJ, Lundgren JD, d'Armino MA, Ledergerber B, Barton SE, Vella S, et al. Survival of AIDS patients according to type of AIDS-defining event. The AIDS in Europe Study Group. Int J Epidemiol 1997 Apr;26(2):400-7.

(108) Kitayaporn D, Tansuphaswadikul S, Lohsomboon P, Pannachet K, Kaewkungwal J, Limpakarnjanarat K, et al. Survival of AIDS patients in the emerging epidemic in Bangkok, Thailand. J Acquir Immune Defic Syndr Hum Retrovirol 1996 Jan 1;11(1):77-82.

(109) Morgan D, Mahe C, Mayanja B, Whitworth JAG. Progression to symptomatic disease in people infected with HIV-1 in rural Uganda: prospective cohort study. British Medical Journal 2002 Jan 26;324(7331):193-6.

(110) Gail MH, Tan WY, Pee D, Goedert JJ. Survival after AIDS diagnosis in a cohort of hemophilia patients. Multicenter Hemophilia Cohort Study. J Acquir Immune Defic Syndr Hum Retrovirol 1997 Aug 15;15(5):363-9.

(111) Todd J, Glynn JR, Marston M, Lutalo T, Biraro S, Mwita W, et al. Time from HIV seroconversion to death: a collaborative analysis of eight studies in six low and middle-income countries before highly active antiretroviral therapy. AIDS 2007 Nov;21:S55-S63.

(112) Lutalo T, Gray RH, Wawer M, Sewankambo N, Serwadda D, Laeyendecker O, et al. Survival of HIV-infected treatment-naive individuals with documented dates of seroconversion in Rakai, Uganda. AIDS 2007;21:S15-S19.

(113) Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R, Whitworth JAG. HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? AIDS 2002 Mar 8;16(4):597-603.

(114) Mekonnen Y, Geskus RB, Hendriks JC, Messele T, Borghans J, Miedema F, et al. Low CD4 T cell counts before HIV-1 seroconversion do not affect disease progression in Ethiopian factory workers. J Infect Dis 2005 Sep 1;192(5):739-48.

(115) Urassa W, Bakari M, Sandstrom E, Swai A, Pallangyo K, Mbena E, et al. Rate of decline of absolute number and percentage of CD4 T lymphocytes among HIV-1-infected adults in Dar es Salaam, Tanzania. AIDS 2004 Feb 20;18(3):433-8.

(116) Murray J, Sonnenberg P, Nelson G, Bester A, Shearer S, Glynn JR. Cause of death and presence of respiratory disease at autopsy in an HIV-1 seroconversion cohort of southern African gold miners. AIDS 2007 Nov;21 Suppl 6:S97-S104.

(117) Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med 1997 Jun 15;126(12):946-54.

(118) Phillips AN, Eron JJ, Bartlett JA, Rubin M, Johnson J, Price S, et al. HIV-1 RNA levels and the development of clinical disease. North American Lamivudine HIV Working Group. AIDS 1996 Jul;10(8):859-65.

(119) Mellors JW, Kingsley LA, Rinaldo CR, Jr., Todd JA, Hoo BS, Kokka RP, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. Ann Intern Med 1995 Apr 15;122(8):573-9.

(120) O'Brien TR, Blattner WA, Waters D, Eyster E, Hilgartner MW, Cohen AR, et al. Serum HIV-1 RNA levels and time to development of AIDS in the Multicenter Hemophilia Cohort Study. JAMA 1996 Jul 10;276(2):105-10.

(121) Lyles CM, Graham NM, Astemborski J, Vlahov D, Margolick JB, Saah AJ, et al. Cell-associated infectious HIV-1 viral load as a predictor of clinical progression and survival among HIV-1 infected injection drug users and homosexual men. Eur J Epidemiol 1999 Feb;15(2):99-108.

(122) Carre N, Boufassa F, Hubert JB, Chavance M, Rouzioux C, Goujard C, et al. Predictive value of viral load and other markers for progression to clinical AIDS after CD4+ cell count falls below 200/microL. SEROCO & HEMOCO Study Group. Int J Epidemiol 1998 Oct;27(5):897-903.

(123) Touloumi G, Hatzakis A, Rosenberg PS, O'Brien TR, Goedert JJ. Effects of age at seroconversion and baseline HIV RNA level on the loss of CD4+ cells among persons with hemophilia. Multicenter Hemophilia Cohort Study. AIDS 1998 Sep 10;12(13):1691-7.

(124) de WF, Spijkerman I, Schellekens PT, Langendam M, Kuiken C, Bakker M, et al. AIDS prognosis based on HIV-1 RNA, CD4+ T-cell count and function: markers with reciprocal predictive value over time after seroconversion. AIDS 1997 Dec;11(15):1799-806.

(125) DeGruttola V, Hughes M, Gilbert P, Phillips A. Trial design in the era of highly effective antiviral drug combinations for HIV infection. AIDS 1998;12 Suppl A:S149-S156.

(126) Phillips A, Pezzotti P. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004 Jan 2;18(1):51-8.

(127) Sabin CA, Devereux H, Phillips AN, Janossy G, Loveday C, Lee CA. Immune markers and viral load after HIV-1 seroconversion as predictors of disease progression in a cohort of haemophilic men. AIDS 1998 Jul 30;12(11):1347-52.

(128) Collier AC, Coombs RW, Schoenfeld DA, Bassett RL, Timpone J, Baruch A, et al. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine. AIDS Clinical Trials Group. N Engl J Med 1996 Apr 18;334(16):1011-7.

(129) Ledergerber B, Lundgren JD, Walker AS, Sabin C, Justice A, Reiss P, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. Lancet 2004 Jul 3;364(9428):51-62.

(130) Spijkerman IJ, Prins M, Goudsmit J, Veugelers PJ, Coutinho RA, Miedema F, et al. Early and late HIV-1 RNA level and its association with other markers and disease progression in long-term AIDS-free homosexual men. AIDS 1997 Sep;11(11):1383-8.

(131) Yerly S, Perneger TV, Hirschel B, Dubuis O, Matter L, Malinverni R, et al. A critical assessment of the prognostic value of HIV-1 RNA levels and CD4+ cell counts in HIV-infected patients. The Swiss HIV Cohort Study. Arch Intern Med 1998 Feb 9;158(3):247-52.

(132) Tollerud DJ, Clark JW, Brown LM, Neuland CY, Pankiw-Trost LK, Blattner WA, et al. The influence of age, race, and gender on peripheral blood mononuclear-cell subsets in healthy nonsmokers. J Clin Immunol 1989 May;9(3):214-22.

(133) Yu LM, Easterbrook PJ, Marshall T. Relationship between CD4 count and CD4% in HIV-infected people. Int J Epidemiol 1997 Dec;26(6):1367-72.

(134) Pirzada Y, Khuder S, Donabedian H. Predicting AIDS-related events using CD4 percentage or CD4 absolute counts. AIDS Res Ther 2006;3:20.

(135) Malone JL, Simms TE, Gray GC, Wagner KF, Burge JR, Burke DS. Sources of variability in repeated T-helper lymphocyte counts from human immunodeficiency virus type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. J Acquir Immune Defic Syndr 1990;3(2):144-51.

(136) Bofill M, Janossy G, Lee CA, MacDonald-Burns D, Phillips AN, Sabin C, et al. Laboratory control values for CD4 and CD8 T lymphocytes. Implications for HIV-1 diagnosis. Clin Exp Immunol 1992 May;88(2):243-52.

(137) Darbyshire J, Schoenfeld DA, Weller IV. Clinical trials in HIV infection: current problems and future directions. AIDS 1991;5 Suppl 2:S167-S173.

(138) Deuffic-Burban S, Losina E, Wang B, Gabillard D, Messou E, Divi N, et al. Estimates of opportunistic infection incidence or death within specific CD4 strata in HIV-infected patients in Abidjan, Cote d'Ivoire: impact of alternative methods of CD4 count modelling. Eur J Epidemiol 2007;22(10):737-44.

(139) Jaffar S, Grant AD, Whitworth J, Smith PG, Whittle H. The natural history of HIV-1 and HIV-2 infections in adults in Africa: a literature review. Bull World Health Organ 2004 Jun;82(6):462-9.

(140) Morgan D, Malamba SS, Maude GH, Okongo MJ, Wagner HU, Mulder DW, et al. An HIV-1 natural history cohort and survival times in rural Uganda. AIDS 1997 Apr;11(5):633-40.

(141) Meyer L, Chaix ML, Nagy Z, Venet A, Deveau C, Pacanovski J, et al. Low CD4 T cell counts in sub-Saharan African subjects enrolled at the time of HIV-1 primary infection in the French ANRS PRIMO cohort. 2007 Jul 22; Sydney 2007.

(142) Keller M, Lu Y, Lalonde RG, Klein MB. Impact of HIV-1 viral subtype on CD4+ T-cell decline and clinical outcomes in antiretroviral naive patients receiving universal healthcare. AIDS 2009 Mar 27;23(6):731-7.

(143) Lewden C, Thiebaut R, Boufassa F, Coulibaly A, Malateste K, Seng R, et al. Comparison of early CD4 T-cell count in HIV-1 seroconverters in Cote d'Ivoire and France: the ANRS PRIMO-CI and SEROCO cohorts. J Acquir Immune Defic Syndr 2010 Feb;53(2):260-5.

(144) Katubulushi M, Zulu I, Yavwa F, Kelly P. Slow decline in CD4 cell count in a cohort of HIV-infected adults living in Lusaka, Zambia. AIDS 2005 Jan 3;19(1):102-3.

(145) May M, Wood R, Myer L, Taffe P, Rauch A, Battegay M, et al. CD4(+) T cell count decreases by ethnicity among untreated patients with HIV infection in South Africa and Switzerland. J Infect Dis 2009 Dec 1;200(11):1729-35.

(146) Muller V, von W, V, Yerly S, Boni J, Klimkait T, Burgisser P, et al. African descent is associated with slower CD4 cell count decline in treatment-naive patients of the Swiss HIV Cohort Study. AIDS 2009 Jun 19;23(10):1269-76.

(147) Troude P, Chaix ML, Tran L, Deveau C, Seng R, Delfraissy JF, et al. No evidence of a change in HIV-1 virulence since 1996 in France. AIDS 2009 Jun 19;23(10):1261-7.

(148) Phillips AN, Lee CA, Elford J, Webster A, Janossy G, Timms A, et al. More Rapid Progression to Aids in Older Hiv-Infected People - the Role of Cd4+ T-Cell Counts. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology 1991;4(10):970-5.

(149) Lange N, Carlin BP, Gelfand AE. Hierarchical Bayes Models for the Progression of HIV Infection Using Longitudinal CD4 T-Cell Numbers. Journal of the American Statistical Association 1992 Sep 1;87(419):615-26.

(150) Taylor JMG, Cumberland WG, Sy JP. A Stochastic Model for Analysis of Longitudinal AIDS Data. Journal of the American Statistical Association 1994 Sep 1;89(427):727-36.

(151) Pehrson P, Lindback S, Lidman C, Gaines H, Giesecke J. Longer survival after HIV infection for injecting drug users than for homosexual men: implications for immunology. AIDS 1997 Jul;11(8):1007-12.

(152) Sterling TR, Lyles CM, Vlahov D, Astemborski J, Margolick JB, Quinn TC. Sex differences in longitudinal human immunodeficiency virus type 1 RNA levels among seroconverters. J Infect Dis 1999 Sep;180(3):666-72.

(153) Anastos K, Gange SJ, Lau B, Weiser B, Detels R, Giorgi JV, et al. Association of race and gender with HIV-1 RNA levels and immunologic progression. J Acquir Immune Defic Syndr 2000 Jul 1;24(3):218-26.

(154) Prins M, Robertson JR, Brettle RP, Aguado IH, Broers B, Boufassa F, et al. Do gender differences in CD4 cell counts matter? AIDS 1999 Dec 3;13(17):2361-4.

(155) Webber MP, Schoenbaum EE, Gourevitch MN, Buono D, Chang CJ, Klein RS. Temporal trends in the progression of human immunodeficiency virus disease in a cohort of drug users. Epidemiology 1998 Nov;9(6):613-7.

(156) Arien KK, Troyer RM, Gali Y, Colebunders RL, Arts EJ, Vanham G. Replicative fitness of historical and recent HIV-1 isolates suggests HIV-1 attenuation over time. AIDS 2005 Oct 14;19(15):1555-64.

(157) Keet IP, Veugelers PJ, Koot M, de Weerd MH, Roos MT, Miedema F, et al. Temporal trends of the natural history of HIV-1 infection following seroconversion between 1984 and 1993. AIDS 1996 Nov;10(13):1601-2.

(158) Taylor JM, Kuo JM, Detels R. Is the incubation period of AIDS lengthening? J Acquir Immune Defic Syndr 1991;4(1):69-75.

(159) Easterbrook PJ, Yu LM, Goetghebeur E, Boag F, McLean K, Gazzard B. Ten-year trends in CD4 cell counts at HIV and AIDS diagnosis in a London HIV clinic. AIDS 2000 Mar 31;14(5):561-71.

(160) Carre N, Prins M, Meyer L, Brettle RP, Robertson JR, McArdle H, et al. Has the rate of progression to AIDS changed in recent years? AIDS 1997 Nov;11(13):1611-8.

(161) Galai N, Lepri AC, Vlahov D, Pezzotti P, Sinicco A, Rezza G. Temporal trends of initial CD4 cell counts following human immunodeficiency virus seroconversion in Italy, 1985-1992. The Human Immunodeficiency Virus Italian Seroconversion Study. Am J Epidemiol 1996 Feb 1;143(3):278-82.

(162) Herbeck JT, Gottlieb GS, Li X, Hu Z, Detels R, Phair J, et al. Lack of evidence for changing virulence of HIV-1 in North America. PLoS One 2008;3(2):e1525.

(163) Muller V, Ledergerber B, Perrin L, Klimkait T, Furrer H, Telenti A, et al. Stable virulence levels in the HIV epidemic of Switzerland over two decades. AIDS 2006 Apr 4;20(6):889-94.

(164) Vanhems P, Lambert J, Guerra M, Hirschel B, Allard R. Association between the rate of CD4+ T cell decrease and the year of human immunodeficiency virus (HIV) type 1 seroconversion among persons enrolled in the Swiss HIV cohort study. J Infect Dis 1999 Dec;180(6):1803-8.

(165) Sinicco A, Fora R, Raiteri R, Sciandra M, Bechis G, Calvo MM, et al. Is the clinical course of HIV-1 changing? Cohort study. BMJ 1997 Apr 26;314(7089):1232-7.

(166) Crum-Cianflone N, Eberly L, Zhang Y, Ganesan A, Weintrob A, Marconi V, et al. Is HIV becoming more virulent? Initial CD4 cell counts among HIV seroconverters during the course of the HIV epidemic: 1985-2007. Clin Infect Dis 2009 May 1;48(9):1285-92.

(167) Crum-Cianflone NF, Ren Q, Eberly LE, Ganesan A, Weintrob A, Marconi V, et al. Are HIV-positive persons progressing faster after diagnosis over the epidemic? J Acquir Immune Defic Syndr 2010 Aug;54(4):e6-e7.

(168) Potard V, Weiss L, Lamontagne F, Rouveix E, Beck-Wirth G, Drogoul-Vey MP, et al. Trends in post-infection CD4 cell counts and plasma HIV-1 RNA levels in HIV-1-infected patients in France between 1997 and 2005. J Acquir Immune Defic Syndr 2009 Nov 1;52(3):422-6.

(169) Dorrucci M, Phillips AN, Longo B, Rezza G. Changes over time in post-seroconversion CD4 cell counts in the Italian HIV-Seroconversion Study: 1985-2002. AIDS 2005 Feb 18;19(3):331-5.

(170) Pantazis N, Porter K, Costagliola D, De Luca A, Ghosn J, Guiguet M, et al. Temporal Trends in Prognostic Markers of HIV-1 Virulence and Transmissibility. 2014 Mar 4; Boston, MA 2014.

(171) Moss AR, Bacchetti P, Osmond D, Krampf W, Chaisson RE, Stites D, et al. Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. Br Med J (Clin Res Ed) 1988 Mar 12;296(6624):745-50.

(172) Darby SC, Ewart DW, Giangrande PL, Spooner RJ, Rizza CR. Importance of age at infection with HIV-1 for survival and development of AIDS in UK haemophilia population. UK Haemophilia Centre Directors' Organisation. Lancet 1996 Jun 8;347(9015):1573-9.

(173) Nyirenda M, Hosegood V, Barnighausen T, Newell ML. Mortality levels and trends by HIV serostatus in rural South Africa. AIDS 2007 Nov;21 Suppl 6:S73-S79.

(174) Zaba B, Marston M, Crampin AC, Isingo R, Biraro S, Barnighausen T, et al. Age-specific mortality patterns in HIV-infected individuals: a comparative analysis of African community study data. AIDS 2007 Nov;21 Suppl 6:S87-S96.

(175) Pezzotti P, Phillips AN, Dorrucci M, Lepri AC, Galai N, Vlahov D, et al. Category of exposure to HIV and age in the progression to AIDS: longitudinal study of 1199 people with known dates of seroconversion. HIV Italian Seroconversion Study Group. BMJ 1996 Sep 7;313(7057):583-6.

(176) Brink AK, Mahe C, Watera C, Lugada E, Gilks C, Whitworth J, et al. Diarrhea, CD4 counts and enteric infections in a community-based cohort of HIV-infected adults in Uganda. J Infect 2002 Aug;45(2):99-106.

(177) Colebunders R, Francis H, Mann JM, Bila KM, Izaley L, Kimputu L, et al. Persistent diarrhea, strongly associated with HIV infection in Kinshasa, Zaire. Am J Gastroenterol 1987 Sep;82(9):859-64.

(178) Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. AIDS 2004 Feb 20;18(3):547-54.

(179) Patnaik P, Jere CS, Miller WC, Hoffman IF, Wirima J, Pendame R, et al. Effects of HIV-1 serostatus, HIV-1 RNA concentration, and CD4 cell count on the incidence of malaria infection in a cohort of adults in rural Malawi. J Infect Dis 2005 Sep 15;192(6):984-91.

(180) Whitworth J, Morgan D, Quigley M, Smith A, Mayanja B, Eotu H, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda: a cohort study. Lancet 2000 Sep 23;356(9235):1051-6.

(181) Eskild A, Magnus P, Petersen G, Sohlberg C, Jensen F, Kittelsen P, et al. Hepatitis B antibodies in HIV-infected homosexual men are associated with more rapid progression to AIDS. AIDS 1992 Jun;6(6):571-4.

(182) Gilson RJ, Hawkins AE, Beecham MR, Ross E, Waite J, Briggs M, et al. Interactions between HIV and hepatitis B virus in homosexual men: effects on the natural history of infection. AIDS 1997 Apr;11(5):597-606.

(183) Konopnicki D, Mocroft A, de WS, Antunes F, Ledergerber B, Katlama C, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. AIDS 2005 Mar 24;19(6):593-601.

(184) Llibre JM, Garcia E, Aloy A, Valls J. Hepatitis C virus infection and progression of infection due to human immunodeficiency virus. Clin Infect Dis 1993 Jan;16(1):182.

(185) Quan CM, Krajden M, Grigoriew GA, Salit IE. Hepatitis C virus infection in patients infected with the human immunodeficiency virus. Clin Infect Dis 1993 Jul;17(1):117-9.

(186) Dorrucci M, Pezzotti P, Phillips AN, Lepri AC, Rezza G. Coinfection of hepatitis C virus with human immunodeficiency virus and progression to AIDS. Italian Seroconversion Study. J Infect Dis 1995 Dec;172(6):1503-8.

(187) Wright TL, Hollander H, Pu X, Held MJ, Lipson P, Quan S, et al. Hepatitis C in HIV-infected patients with and without AIDS: prevalence and relationship to patient survival. Hepatology 1994 Nov;20(5):1152-5.

(188) Macias J, Pineda JA, Leal M, Abad MA, Garcia-Pesquera F, Delgado J, et al. Influence of hepatitis C virus infection on the mortality of antiretroviral-treated patients with HIV disease. Eur J Clin Microbiol Infect Dis 1998 Mar;17(3):167-70.

(189) Sabin CA, Telfer P, Phillips AN, Bhagani S, Lee CA. The association between hepatitis C virus genotype and human immunodeficiency virus disease progression in a cohort of hemophilic men. J Infect Dis 1997 Jan;175(1):164-8.

(190) Piroth L, Duong M, Quantin C, Abrahamowicz M, Michardiere R, Aho LS, et al. Does hepatitis C virus co-infection accelerate clinical and immunological evolution of HIV-infected patients? AIDS 1998 Mar 5;12(4):381-8.

(191) Lesens O, Deschenes M, Steben M, Belanger G, Tsoukas CM. Hepatitis C virus is related to progressive liver disease in human immunodeficiency virus-positive hemophiliacs and should be treated as an opportunistic infection. J Infect Dis 1999 May;179(5):1254-8.

(192) Chen TY, Ding EL, Seage Iii GR, Kim AY. Meta-analysis: increased mortality associated with hepatitis C in HIV-infected persons is unrelated to HIV disease progression. Clin Infect Dis 2009 Nov 15;49(10):1605-15.

(193) Zhang X, Xu J, Peng H, Ma Y, Han L, Ruan Y, et al. HCV coinfection associated with slower disease progression in HIV-infected former plasma donors naive to ART. PLoS One 2008;3(12):e3992.

(194) Ernst D, Greer M, Akmatova R, Pischke S, Wedemeyer H, Heiken H, et al. Impact of GB virus C viraemia on clinical outcome in HIV-1-infected patients: a 20-year follow-up study. HIV Med 2014 Apr;15(4):245-50.

(195) Modjarrad K, Vermund SH. Effect of treating co-infections on HIV-1 viral load: a systematic review. Lancet Infect Dis 2010 Jul;10(7):455-63.

(196) Hoffman IF, Jere CS, Taylor TE, Munthali P, Dyer JR, Wirima JJ, et al. The effect of Plasmodium falciparum malaria on HIV-1 RNA blood plasma concentration. AIDS 1999 Mar 11;13(4):487-94.

(197) Kublin JG, Patnaik P, Jere CS, Miller WC, Hoffman IF, Chimbiya N, et al. Effect of Plasmodium falciparum malaria on concentration of HIV-1-RNA in the blood of adults in rural Malawi: a prospective cohort study. Lancet 2005 Jan 15;365(9455):233-40.

(198) Mermin J, Lule JR, Ekwaru JP. Association between malaria and CD4 cell count decline among persons with HIV. J Acquir Immune Defic Syndr 2006 Jan 1;41(1):129-30.

(199) Mouala C, Houze S, Guiguet M, Abboud P, Pialoux G, Viget N, et al. Imported malaria in HIV-infected patients enrolled in the ANRS CO4 FHDH study. J Acquir Immune Defic Syndr 2008 Sep 1;49(1):55-60.

(200) Walson JL, Sangare LR, Singa BO, Naulikha JM, Piper BK, Yuhas K, et al. Evaluation of impact of long-lasting insecticide-treated bed nets and point-of-use water filters on HIV-1 disease progression in Kenya. AIDS 2013 Jan 16.

(201) WHO U. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults. WHO 2006 August 7 [cited 2013 Sep 1];Available from: URL: http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf

(202) Anglaret X, Chene G, Attia A, Toure S, Lafont S, Combe P, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. Cotrimo-CI Study Group. Lancet 1999 May 1;353(9163):1463-8.

(203) Wiktor SZ, Sassan-Morokro M, Grant AD, Abouya L, Karon JM, Maurice C, et al. Efficacy of trimethoprim-sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV-1-infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomised controlled trial. Lancet 1999 May 1;353(9163):1469-75.

(204) Sarngadharan MG, Popovic M, Bruch L, Schupbach J, Gallo RC. Antibodies reactive with human T-lymphotropic retroviruses (HTLV-III) in the serum of patients with AIDS. Science 1984 May 4;224(4648):506-8.

(205) WHO. HIV testing and counselling. WHO 2014 [cited 2014 Apr 12];Available from: URL: http://www.who.int/hiv/topics/vct/about/en/

(206) Perry KR, Ramskill S, Eglin RP, Barbara JA, Parry JV. Improvement in the performance of HIV screening kits. Transfus Med 2008 Aug;18(4):228-40.

(207) U.S.Food and Drug administration. FDA approves first rapid diagnostic test to detect both HIV-1 antigen and HIV-1/2 antibodies. FDA 2013 August 8 [cited 2014 Apr 12];Available from: URL: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm364480.htm

(208) Fiscus SA, Cheng B, Crowe SM, Demeter L, Jennings C, Miller V, et al. HIV-1 viral load assays for resource-limited settings. PLoS Med 2006 Oct;3(10):e417.

(209) Smit PW, Sollis KA, Fiscus S, Ford N, Vitoria M, Essajee S, et al. Systematic review of the use of dried blood spots for monitoring HIV viral load and for early infant diagnosis. PLoS One 2014;9(3):e86461.

(210) Ritchie AV, Ushiro-Lumb I, Edemaga D, Joshi HA, De RA, Szumilin E, et al. SAMBA HIV Semiquantitative Test, a New Point-of-Care Viral-Load-Monitoring Assay for Resource-Limited Settings. J Clin Microbiol 2014 Sep;52(9):3377-83.

(211) U.S.Food and Drug administration. Antiretroviral drugs used in the treatment of HIV infection. U S Food and Drug Administration 2013 August 20 [cited 2013 Sep 7];Available from: URL: http://www.fda.gov/ForConsumers/byAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm118915.htm

(212) Hirsch MS, Kaplan JC. Treatment of human immunodeficiency virus infections. Antimicrob Agents Chemother 1987 Jun;31(6):839-43.

(213) Wright K. AIDS therapy. First tentative signs of therapeutic promise. Nature 1986 Sep 25;323(6086):283.

(214) NIH. Classes of HIV/AIDS Antiretroviral Drugs. http://www niaid nih gov/topics/HIVAIDS/Understanding/Treatment/pages/arvdrugclasses aspx 2009 March 26 [cited 2013 Sep 7];Available from: URL: http://www.niaid.nih.gov/topics/HIVAIDS/Understanding/Treatment/pages/arvdrugclasses.aspx

(215) Fischl MA, Richman DD, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987 Jul 23;317(4):185-91.

(216) Richman DD, Fischl MA, Grieco MH, Gottlieb MS, Volberding PA, Laskin OL, et al. The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. N Engl J Med 1987 Jul 23;317(4):192-7.

(217) Dournon E, Matheron S, Rozenbaum W, Gharakhanian S, Michon C, Girard PM, et al. Effects of zidovudine in 365 consecutive patients with AIDS or AIDS-related complex. Lancet 1988 Dec 3;2(8623):1297-302.

(218) Lange JM, Cooper DA, Danner SA. Antiretroviral treatment: state of the art and future directions. AIDS 1991;5 Suppl 2:S181-S188.

(219) de Bethune MP. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), their discovery, development, and use in the treatment of HIV-1 infection: a review of the last 20 years (1989-2009). Antiviral Res 2010 Jan;85(1):75-90.

(220) Larder BA, Kemp SD. Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). Science 1989 Dec 1;246(4934):1155-8.

(221) Larder BA, Darby G, Richman DD. HIV with reduced sensitivity to zidovudine (AZT) isolated during prolonged therapy. Science 1989 Mar 31;243(4899):1731-4.

(222) Rooke R, Tremblay M, Soudeyns H, DeStephano L, Yao XJ, Fanning M, et al. Isolation of drug-resistant variants of HIV-1 from patients on long-term zidovudine therapy. Canadian Zidovudine Multi-Centre Study Group. AIDS 1989 Jul;3(7):411-5.

(223) Darbyshire J, Foulkes M, Peto R, Duncan W, Babiker A, Collins R, et al. Zidovudine (AZT) versus AZT plus didanosine (ddI) versus AZT plus zalcitabine (ddC) in HIV infected adults. Cochrane Database Syst Rev 2000;(2):CD002038.

(224) Jablonowski H. Studies of zidovudine in combination with didanosine and zalcitabine. J Acquir Immune Defic Syndr Hum Retrovirol 1995;10 Suppl 1:S52-S56.

(225) South Africa National Department of Health. National Antiretroviral Treatment Guidelines. South Africa National Department of Health 2004 [cited 2011 Aug 24];Available from: URL: http://southafrica.usembassy.gov/media/2004-doh-art-guidelines.pdf

(226) South Africa National Department of Health. The South African antiretroviral treatment guidelines 2013. South Africa National Department of Health 2013 March 24 [cited 2013 Aug 29];Available from: URL: http://www.kznhealth.gov.za/medicine/2013_art_guidelines.pdf

(227) Ministry of Health and Child Welfare Z. Guidelines for Antiretroviral Therapy in Zimbabwe. Ministry of Health and Child Welfare,Zimbabwe 2005Available from: URL: http://catalogue.safaids.net/publications/guidelines-antiretroviral-therapy-zimbabwe-2005

(228) National Drug and Therapeutic Policy Advisory Commitee, The AIDS and TB Unit MoHaCWZ. Guidelines for antiretroviral therapy in Zimbabwe. National Drug and Therapeutic Policy Advisory Commitee 2010 May [cited 2013 Nov 13];Available from: URL: http://apps.who.int/medicinedocs/documents/s19254en/s19254en.pdf

(229) National Medicine and Therapeutics Policy AdvisoryCommittee (NMTPAC) and The AIDS and TB Directorate MoHaCZ. Guidelines for Antiretroviral Therapy for the Prevention and Treatment of HIV in Zimbabwe. Ministry of Health 2013 NovemberAvailable from: URL: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&ved=0CEYQFjAD&url=http%3A%2F%2Fwww.mcaz.co.zw%2Findex.php%2Fdownloads%2Fcategory%2F9-guidelines%3Fdownload%3D99%3Azimbabwe-arv-guidelines&ei=Y-1cU-7OHcSIOO38gIgP&usg=AFQjCNH4lXwy01yiIDXob5zPkG7NBuSFHg&bvm=bv.65397613,d.d2k

(230) South Africa National Department of Health. The South African antiretroviral treatment guidelines 2010. South Africa National Department of Health 2010 [cited 2011 Jul 4];Available from: URL: http://apps.who.int/medicinedocs/documents/s19153en/s19153en.pdf

(231) Collier AC, Coombs RW, Schoenfeld DA, Bassett R, Baruch A, Corey L. Combination therapy with zidovudine, didanosine and saquinavir. Antiviral Res 1996 Jan;29(1):99.

(232) Revicki DA, Moyle G, Stellbrink HJ, Barker C. Quality of life outcomes of combination zalcitabine-zidovudine, saquinavir-zidovudine, and saquinavir-zalcitabine-zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter. PISCES (SV14604) Study Group. AIDS 1999 May 7;13(7):851-8.

(233) Carr A, Chuah J, Hudson J, French M, Hoy J, Law M, et al. A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo1 study. AIDS 2000 Jun 16;14(9):1171-80.

(234) Hammer SM, Squires KE, Hughes MD, Grimes JM, Demeter LM, Currier JS, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. N Engl J Med 1997 Sep 11;337(11):725-33.

(235) Wensing AM, van Maarseveen NM, Nijhuis M. Fifteen years of HIV Protease Inhibitors: raising the barrier to resistance. Antiviral Res 2010 Jan;85(1):59-74.

(236) Garcia F, Romeu J, Grau I, Sambeat MA, Dalmau D, Knobel H, et al. A randomized study comparing triple versus double antiretroviral therapy or no treatment in

HIV-1-infected patients in very early stage disease: the Spanish Earth-1 study. AIDS 1999 Dec 3;13(17):2377-88.

(237) Lederman MM, Connick E, Landay A, Kuritzkes DR, Spritzler J, St CM, et al. Immunologic responses associated with 12 weeks of combination antiretroviral therapy consisting of zidovudine, lamivudine, and ritonavir: results of AIDS Clinical Trials Group Protocol 315. J Infect Dis 1998 Jul;178(1):70-9.

(238) Mathez D, Bagnarelli P, Gorin I, Katlama C, Pialoux G, Saimot G, et al. Reductions in viral load and increases in T lymphocyte numbers in treatment-naive patients with advanced HIV-1 infection treated with ritonavir, zidovudine and zalcitabine triple therapy. Antivir Ther 1997 Jul;2(3):175-83.

(239) Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. Lancet 1998 Feb 21;351(9102):543-9.

(240) Notermans DW, Jurriaans S, de WF, Foudraine NA, de Jong JJ, Cavert W, et al. Decrease of HIV-1 RNA levels in lymphoid tissue and peripheral blood during treatment with ritonavir, lamivudine and zidovudine. Ritonavir/3TC/ZDV Study Group. AIDS 1998 Jan 22;12(2):167-73.

(241) Fernandez-Montero JV, Barreiro P, Soriano V. HIV protease inhibitors: recent clinical trials and recommendations on use. Expert Opin Pharmacother 2009 Jul;10(10):1615-29.

(242) Michelet C, Ruffault A, Sebille V, Arvieux C, Jaccard P, Raffi F, et al. Ritonavir-saquinavir dual protease inhibitor compared to ritonavir alone in human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2001 Dec;45(12):3393-402.

(243) Kirk O, Katzenstein TL, Gerstoft J, Mathiesen L, Nielsen H, Pedersen C, et al. Combination therapy containing ritonavir plus saquinavir has superior short-term antiretroviral efficacy: a randomized trial. AIDS 1999 Jan 14;13(1):F9-16.

(244) Walmsley S, Bernstein B, King M, Arribas J, Beall G, Ruane P, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med 2002 Jun 27;346(26):2039-46.

(245) Dragsted UB, Gerstoft J, Youle M, Fox Z, Losso M, Benetucci J, et al. A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial. Antivir Ther 2005;10(6):735-43.

(246) Murphy RL, da Silva BA, Hicks CB, Eron JJ, Gulick RM, Thompson MA, et al. Seven-year efficacy of a lopinavir/ritonavir-based regimen in antiretroviral-naive HIV-1-infected patients. HIV Clin Trials 2008 Jan;9(1):1-10.

(247) Rivas P, Morello J, Garrido C, Rodriguez-Novoa S, Soriano V. Role of atazanavir in the treatment of HIV infection. Ther Clin Risk Manag 2009 Feb;5(1):99-116.

(248) Surleraux DL, Tahri A, Verschueren WG, Pille GM, de Kock HA, Jonckers TH, et al. Discovery and selection of TMC114, a next generation HIV-1 protease inhibitor. J Med Chem 2005 Mar 24;48(6):1813-22.

(249) Larder BA, Hertogs K, Bloor S, Eynde C, DeCian W, Wang Y, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS 2000;14(13).

(250) Clotet B, Bellos N, Molina JM, Cooper D, Goffard JC, Lazzarin A, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. The Lancet 2007;369(9568):1169-78.

(251) Ortiz R, Dejesus E, Khanlou H, Voronin E, van LJ, Andrade-Villanueva J, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS 2008 Jul 31;22(12):1389-97.

(252) Floridia M, Bucciardini R, Ricciardulli D, Fragola V, Pirillo MF, Weimer LE, et al. A Randomized, Double-Blind Trial on the Use of a Triple Combination Including Nevirapine, a Nonnucleoside Reverse Transcriptase HIV Inhibitor, in Antiretroviral-Naive Patients With Advanced Disease. JAIDS Journal of Acquired Immune Deficiency Syndromes 1999;20(1).

(253) Montaner JS, Reiss P, Cooper D, Vella S, Harris M, Conway B, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. JAMA 1998 Mar 25;279(12):930-7.

(254) D'Aquila RT, Hughes MD, Johnson VA, Fischl MA, Sommadossi JP, Liou SH, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. A randomized, double-blind, placebo-controlled trial. National Institute of Allergy and Infectious Diseases AIDS Clinical Trials Group Protocol 241 Investigators. Ann Intern Med 1996 Jun 15;124(12):1019-30.

(255) Podzamczer D, Ferrer E, Consiglio E, Gatell JM, Perez P, Perez JL, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). Antivir Ther 2002 Jun;7(2):81-90.

(256) Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities after switching from HIV-1 protease inhibitors to nevirapine. AIDS 1999 May 7;13(7):805-10.

(257) Barreiro P, Soriano V, Blanco F, Casimiro C, de la Cruz JJ, Gonzalez-Lahoz J. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. AIDS 2000 May 5;14(7):807-12.

(258) Ruiz L, Negredo E, Domingo P, Paredes R, Francia E, Balague M, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with hiv-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. J Acquir Immune Defic Syndr 2001 Jul 1;27(3):229-36.

(259) Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiest D, Stanford J, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir

plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med 1999 Dec 16;341(25):1865-73.

(260) Friedl AC, Ledergerber B, Flepp M, Hirschel B, Telenti A, Furrer H, et al. Response to first protease inhibitor- and efavirenz-containing antiretroviral combination therapy. The Swiss HIV Cohort Study. AIDS 2001 Sep 28;15(14):1793-800.

(261) Bozzette SA, Joyce G, McCaffrey DF, Leibowitz AA, Morton SC, Berry SH, et al. Expenditures for the care of HIV-infected patients in the era of highly active antiretroviral therapy. N Engl J Med 2001 Mar 15;344(11):817-23.

(262) Phillips AN, Pradier C, Lazzarin A, Clotet B, Goebel FD, Hermans P, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. AIDS 2001 Dec 7;15(18):2385-95.

(263) Cozzi-Lepri A, Phillips AN, d'Arminio MA, Piersantelli N, Orani A, Petrosillo N, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study. J Infect Dis 2002 Apr 15;185(8):1062-9.

(264) van LF, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. Lancet 2004 Apr 17;363(9417):1253-63.

(265) Thompson MA, Aberg JA, Hoy JF, Telenti A, Benson C, Cahn P, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. JAMA 2012 Jul 25;308(4):387-402.

(266) European AIDS Clinical Society (EACS). Guidelines Version 6.1. http://www eacsociety org/Portals/0/Guidelines_Online_131014 pdf 2012 November [cited 2013 Sep 9];Available from: URL: http://www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf

(267) European AIDS Clinical Society (EACS). EACS Guidelines, Version 7.0. www.eacsociety.org/Portals/0/Guidelines_Online_131014.pdf . 2012. 26-11-2013.
Ref Type: Online Source

(268) Madruga JV, Cahn P, Grinsztejn B, Haubrich R, Lalezari J, Mills A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-1: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007 Jul 7;370(9581):29-38.

(269) Lazzarin A, Campbell T, Clotet B, Johnson M, Katlama C, Moll A, et al. Efficacy and safety of TMC125 (etravirine) in treatment-experienced HIV-1-infected patients in DUET-2: 24-week results from a randomised, double-blind, placebo-controlled trial. Lancet 2007 Jul 7;370(9581):39-48.

(270) Pommier Y, Johnson AA, Marchand C. Integrase inhibitors to treat HIV/AIDS. Nat Rev Drug Discov 2005 Mar;4(3):236-48.

(271) Lennox JL, Dejesus E, Lazzarin A, Pollard RB, Madruga JV, Berger DS, et al. Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in

treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. Lancet 2009 Sep 5;374(9692):796-806.

(272) Rockstroh JK, Lennox JL, Dejesus E, Saag MS, Lazzarin A, Wan H, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. Clin Infect Dis 2011 Oct;53(8):807-16.

(273) Jeantils VMH&CL. Pregnancy and a regimen containing raltegravir: a pilot study on the Materno Foetal Safety. Denver, Colorado 2013.

(274) Chao SH. The HIV landscape in a managed care environment: current challenges and potential solutions. J Manag Care Pharm 2006 Sep;12(7 Suppl B):S2-S5.

(275) Miller CM, Ketlhapile M, Rybasack-Smith H, Rosen S. Why are antiretroviral treatment patients lost to follow-up? A qualitative study from South Africa. Trop Med Int Health 2010 Jun;15 Suppl 1:48-54.

(276) Mocroft A, Youle M, Moore A, Sabin CA, Madge S, Lepri AC, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. AIDS 2001 Jan 26;15(2):185-94.

(277) WHO. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach.- 2010 rev. WHO 2010 July [cited 2011 Aug 24];Available from: URL: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf

(278) WHO. Rapid Advice: Antiretroviral Therapy for HIV Infection in Adults and Adolescents. WHO 2009 [cited 2013];Available from: URL: http://www.who.int/hiv/pub/arv/rapid_advice_art.pdf

(279) Hogg RS, Yip B, Chan KJ, Wood E, Craib KJ, O'Shaughnessy MV, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. JAMA 2001 Nov 28;286(20):2568-77.

(280) WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. WHO 2013 June 30 [cited 2013 Jul 15];Available from: URL: http://www.who.int/hiv/pub/guidelines/arv2013/en/index.html

(281) Panel on Antiretroviral Guidelines for Adults and Adolescents., Department of Health and Human Services. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services 2013 February 12 [cited 2013 Sep 15];Available from: URL: http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf

(282) Kitahata MM, Gange SJ, Abraham AG, Merriman B, Saag MS, Justice AC, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009 Apr 30;360(18):1815-26.

(283) Sterne JA, May M, Costagliola D, de WF, Phillips AN, Harris R, et al. Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies. Lancet 2009 Apr 18;373(9672):1352-63.

(284) Strategic Timing of Antiretroviral Treatment (START). http://clinicaltrials gov/ct2/show/NCT00867048 2011 [cited 2011 Nov 20];Available from: URL: http://clinicaltrials.gov/ct2/show/NCT00867048

(285) Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (ANRS 12136 TEMPRANO). http://clinicaltrials gov/show/NCT00495651 2013 March 8 [cited 2013 Nov 26];Available from: URL: http://clinicaltrials.gov/show/NCT00495651

(286) Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, et al. AIDS across Europe, 1994-98: the EuroSIDA study. Lancet 2000 Jul 22;356(9226):291-6.

(287) Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargalianos P, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998 Nov 28;352(9142):1725-30.

(288) Palella FJ, Jr., Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N Engl J Med 1998 Mar 26;338(13):853-60.

(289) Public Health England. HIV in the United Kingdom: 2013 Report. Public Health England 2013 November [cited 2014 Apr 13];Available from: URL: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317140300680

(290) Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. Lancet 2008 Jul 26;372(9635):293-9.

(291) Boulle A, Bock P, Osler M, Cohen K, Channing L, Hilderbrand K, et al. Antiretroviral therapy and early morality in South Africa. Bulletin of the World Health Organization 2008 Sep;86(9):678-87.

(292) Boulle A, Van CG, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. AIDS 2010 Feb 20;24(4):563-72.

(293) Lawn SD, Myer L, Orrell C, Bekker LG, Wood R. Early mortality among adults accessing a community-based antiretroviral service in South Africa: implications for programme design. AIDS 2005 Dec 2;19(18):2141-8.

(294) Sanne I, Mommeja-Marin H, Hinkle J, Bartlett JA, Lederman MM, Maartens G, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. J Infect Dis 2005 Mar 15;191(6):825-9.

(295) Barnighausen T, Herbst K, Tanser F, Newell ML, Bor J. Unequal Benefits From ART: A Growing Male Disadvantage in Life Expectancy in Rural South Africa. 2014 Mar 4; Boston, MA 2014.

(296) Yiannoutsos CT, Johnson LF, Boulle A, Musick BS, Gsponer T, Balestre E, et al. Estimated mortality of adult HIV-infected patients starting treatment with combination antiretroviral therapy. Sex Transm Infect 2012 Dec;88 Suppl 2:i33-i43.

(297) Miller V, Staszewski S, Nisius G, Lepri AC, Sabin C, Phillips AN. Risk of new AIDS diseases in people on triple therapy. Lancet 1999 Feb 6;353(9151):463.

(298) Miller V, Sabin CA, Phillips AN, Rottmann C, Rabenau H, Weidmann E, et al. The impact of protease inhibitor-containing highly active antiretroviral therapy on progression of HIV disease and its relationship to CD4 and viral load. AIDS 2000 Sep 29;14(14):2129-36.

(299) Ciancio BC, Trotta MP, Lorenzini P, Forbici F, Visco-Comandini U, Gori C, et al. The effect of number of mutations and of drug-class sparing on virological response to salvage genotype-guided antiretroviral therapy. Antivir Ther 2003 Dec;8(6):611-6.

(300) Zaccarelli M, Tozzi V, Lorenzini P, Trotta MP, Forbici F, Visco-Comandini U, et al. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. AIDS 2005 Jul 1;19(10):1081-9.

(301) Barreiro PM, Dona MC, Castilla J, Soriano V. Patterns of response (CD4 cell count and viral load) at 6 months in HIV-infected patients on highly active antiretroviral therapy. AIDS 1999 Mar 11;13(4):525-6.

(302) Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to highly active antiretroviral therapy. AIDS 2001 Nov 23;15(17):2251-7.

(303) Bannister WP, Kirk O, Gatell JM, Knysz B, Viard JP, Mens H, et al. Regional changes over time in initial virologic response rates to combination antiretroviral therapy across Europe. J Acquir Immune Defic Syndr 2006 Jun;42(2):229-37.

(304) Barth RE, van der Loeff MFS, Schuurman R, Hoepelmon AIM, Wensing AMJ. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. Lancet Infectious Diseases 2010 Mar;10(3):155-66.

(305) WHO HIV/AIDS Programme. The HIV drug resistance report - 2012. WHO 2012 [cited 2013 May 5];Available from: URL: http://apps.who.int/iris/bitstream/10665/75183/1/9789241503938_eng.pdf

(306) Barth RE, Wensing AM, Tempelman HA, Moraba R, Schuurman R, Hoepelman AI. Rapid accumulation of nonnucleoside reverse transcriptase inhibitor-associated resistance: evidence of transmitted resistance in rural South Africa. AIDS 2008 Oct 18;22(16):2210-2.

(307) Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. Antiviral Therapy 2007;12(1):83-8.

(308) Snedecor SJ. Dynamic treatment model to examine the association between phenotypic drug resistance and duration of HIV viral suppression. Bull Math Biol 2005 Nov;67(6):1315-32.

(309) Gardner EM, Burman WJ, Steiner JF, Anderson PL, Bangsberg DR. Antiretroviral medication adherence and the development of class-specific antiretroviral resistance. AIDS 2009 Jun 1;23(9):1035-46.

(310) Ratner L, Haseltine W, Patarca R, Livak KJ, Starcich B, Josephs SF, et al. Complete nucleotide sequence of the AIDS virus, HTLV-III. Nature 1985 Jan 24;313(6000):277-84.

(311) van der Kuyl AC, Berkhout B. The biased nucleotide composition of the HIV genome: a constant factor in a highly variable virus. Retrovirology 2012;9:92.

(312) Tang MW, Shafer RW. HIV-1 antiretroviral resistance: scientific principles and clinical applications. Drugs 2012 Jun 18;72(9):e1-25.

(313) Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science 1996 Mar 15;271(5255):1582-6.

(314) Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 1995 Jan 12;373(6510):123-6.

(315) Tang JW, Pillay D. Transmission of HIV-1 drug resistance. J Clin Virol 2004 May;30(1):1-10.

(316) Quinones-Mateu ME, Weber J, Rangel HR, Chakraborty B. HIV-1 Fitness and Antiretroviral Drug Resistance. AIDS Rev 2001;3:223-42.

(317) Vandamme AM, Camacho RJ, Ceccherini-Silberstein F, De LA, Palmisano L, Paraskevis D, et al. European recommendations for the clinical use of HIV drug resistance testing: 2011 update. AIDS Rev 2011 Apr;13(2):77-108.

(318) Deeks SG, Wrin T, Liegler T, Hoh R, Hayden M, Barbour JD, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. N Engl J Med 2001 Feb 15;344(7):472-80.

(319) Lawrence J, Mayers DL, Hullsiek KH, Collins G, Abrams DI, Reisler RB, et al. Structured treatment interruption in patients with multidrug-resistant human immunodeficiency virus. N Engl J Med 2003 Aug 28;349(9):837-46.

(320) Hammer SM, Katzenstein DA, Hughes MD, Gundacker H, Schooley RT, Haubrich RH, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. AIDS Clinical Trials Group Study 175 Study Team. N Engl J Med 1996 Oct 10;335(15):1081-90.

(321) Lima VD, Harrigan R, Murray M, Moore DM, Wood E, Hogg RS, et al. Differential impact of adherence on long-term treatment response among naive HIV-infected individuals. AIDS 2008 Nov 12;22(17):2371-80.

(322) Maggiolo F, Airoldi M, Kleinloog HD, Callegaro A, Ravasio V, Arici C, et al. Effect of adherence to HAART on viroloaic outcome and on the selection of resistance-conferring mutations in NNRTI- or PI-Treated patients. Hiv Clinical Trials 2007 Sep;8(5):282-92.

(323) Martin M, del CE, Codina C, Tuset M, De Lazzari E, Mallolas J, et al. Relationship between adherence level, type of the antiretroviral regimen, and plasma HIV type

1 RNA viral load: a prospective cohort study. AIDS Res Hum Retroviruses 2008 Oct;24(10):1263-8.

(324) Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clin Infect Dis 2003 Oct 15;37(8):1112-8.

(325) Tam LW, Chui CK, Brumme CJ, Bangsberg DR, Montaner JS, Hogg RS, et al. The relationship between resistance and adherence in drug-naive individuals initiating HAART is specific to individual drug classes. J Acquir Immune Defic Syndr 2008 Nov 1;49(3):266-71.

(326) Kagay CR, Porco TC, Liechty CA, Charlebois E, Clark R, Guzman D, et al. Modeling the impact of modified directly observed antiretroviral therapy on HIV suppression and resistance, disease progression, and death. Clin Infect Dis 2004 Jun 1;38 Suppl 5:S414-S420.

(327) Mitty JA, Stone VE, Sands M, Macalino G, Flanigan T. Directly observed therapy for the treatment of people with human immunodeficiency virus infection: a work in progress. Clin Infect Dis 2002 Apr 1;34(7):984-90.

(328) Liu H, Golin CE, Miller LG, Hays RD, Beck CK, Sanandaji S, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. Ann Intern Med 2001 May 15;134(10):968-77.

(329) Braithwaite RS, Shechter S, Roberts MS, Schaefer A, Bangsberg DR, Harrigan PR, et al. Explaining variability in the relationship between antiretroviral adherence and HIV mutation accumulation. Journal of Antimicrobial Chemotherapy 2006;58(5):1036-43.

(330) Bangsberg DR, Moss AR, Deeks SG. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. J Antimicrob Chemother 2004 May;53(5):696-9.

(331) Bangsberg DR, Acosta EP, Gupta R, Guzman D, Riley ED, Harrigan PR, et al. Adherence-resistance relationships for protease and non-nucleoside reverse transcriptase inhibitors explained by virological fitness. AIDS 2006 Jan 9;20(2):223-31.

(332) King MS, Brun SC, Kempf DJ. Relationship between adherence and the development of resistance in antiretroviral-naive, HIV-1-infected patients receiving lopinavir/ritonavir or nelfinavir. J Infect Dis 2005 Jun 15;191(12):2046-52.

(333) Larder BA, Kellam P, Kemp SD. Convergent combination therapy can select viable multidrug-resistant HIV-1 in vitro. Nature 1993 Sep 30;365(6445):451-3.

(334) Margot NA, Isaacson E, McGowan I, Cheng AK, Schooley RT, Miller MD. Genotypic and phenotypic analyses of HIV-1 in antiretroviral-experienced patients treated with tenofovir DF. AIDS 2002 Jun 14;16(9):1227-35.

(335) Bazmi HZ, Hammond JL, Cavalcanti SC, Chu CK, Schinazi RF, Mellors JW. In vitro selection of mutations in the human immunodeficiency virus type 1 reverse transcriptase that decrease susceptibility to (-)-beta-D-dioxolane-guanosine and suppress resistance to 3'-azido-3'-deoxythymidine. Antimicrob Agents Chemother 2000 Jul;44(7):1783-8.

(336) Tozzi V, Zaccarelli M, Narciso P, Trotta MP, Ceccherini-Silberstein F, De LP, et al. Mutations in HIV-1 reverse transcriptase potentially associated with hypersusceptibility to nonnucleoside reverse-transcriptase inhibitors: effect on response to efavirenz-based therapy in an urban observational cohort. J Infect Dis 2004 May 1;189(9):1688-95.

(337) Whitcomb JM, Parkin NT, Chappey C, Hellmann NS, Petropoulos CJ. Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. J Infect Dis 2003 Oct 1;188(7):992-1000.

(338) Naeger LK, Margot NA, Miller MD. Increased drug susceptibility of HIV-1 reverse transcriptase mutants containing M184V and zidovudine-associated mutations: analysis of enzyme processivity, chain-terminator removal and viral replication. Antivir Ther 2001 Jun;6(2):115-26.

(339) Cong ME, Heneine W, Garcia-Lerma JG. The fitness cost of mutations associated with human immunodeficiency virus type 1 drug resistance is modulated by mutational interactions. J Virol 2007 Mar;81(6):3037-41.

(340) Garcia-Lerma JG, MacInnes H, Bennett D, Weinstock H, Heneine W. Transmitted human immunodeficiency virus type 1 carrying the D67N or K219Q/E mutation evolves rapidly to zidovudine resistance in vitro and shows a high replicative fitness in the presence of zidovudine. J Virol 2004 Jul;78(14):7545-52.

(341) Boyer PL, Sarafianos SG, Clark PK, Arnold E, Hughes SH. Why do HIV-1 and HIV-2 use different pathways to develop AZT resistance? PLoS Pathog 2006 Feb;2(2):e10.

(342) Vandamme AM, Van LK, De CE. Managing resistance to anti-HIV drugs: an important consideration for effective disease management. Drugs 1999 Mar;57(3):337-61.

(343) Harrigan PR, Salim M, Stammers DK, Wynhoven B, Brumme ZL, McKenna P, et al. A mutation in the 3' region of the human immunodeficiency virus type 1 reverse transcriptase (Y318F) associated with nonnucleoside reverse transcriptase inhibitor resistance. J Virol 2002 Jul;76(13):6836-40.

(344) Julias JG, McWilliams MJ, Sarafianos SG, Alvord WG, Arnold E, Hughes SH. Mutation of amino acids in the connection domain of human immunodeficiency virus type 1 reverse transcriptase that contact the template-primer affects RNase H activity. J Virol 2003 Aug;77(15):8548-54.

(345) von W, V, Ehteshami M, Demeter LM, Burgisser P, Nijhuis M, Symons J, et al. HIV-1 reverse transcriptase connection domain mutations: dynamics of emergence and implications for success of combination antiretroviral therapy. Clin Infect Dis 2010 Sep 1;51(5):620-8.

(346) Turner D, Brenner B, Routy JP, Moisi D, Rosberger Z, Roger M, et al. Diminished representation of HIV-1 variants containing select drug resistance-conferring mutations in primary HIV-1 infection. J Acquir Immune Defic Syndr 2004 Dec 15;37(5):1627-31.

(347) Hachiya A, Kodama EN, Sarafianos SG, Schuckmann MM, Sakagami Y, Matsuoka M, et al. Amino acid mutation N348I in the connection subdomain of human

immunodeficiency virus type 1 reverse transcriptase confers multiclass resistance to nucleoside and nonnucleoside reverse transcriptase inhibitors. J Virol 2008 Apr;82(7):3261-70.

(348) Gupta S, Fransen S, Paxinos EE, Stawiski E, Huang W, Petropoulos CJ. Combinations of mutations in the connection domain of human immunodeficiency virus type 1 reverse transcriptase: assessing the impact on nucleoside and nonnucleoside reverse transcriptase inhibitor resistance. Antimicrob Agents Chemother 2010 May;54(5):1973-80.

(349) Hachiya A, Shimane K, Sarafianos SG, Kodama EN, Sakagami Y, Negishi F, et al. Clinical relevance of substitutions in the connection subdomain and RNase H domain of HIV-1 reverse transcriptase from a cohort of antiretroviral treatment-naive patients. Antiviral Res 2009 Jun;82(3):115-21.

(350) Wang K, Samudrala R, Mittler JE. HIV-1 genotypic drug-resistance interpretation algorithms need to include hypersusceptibility-associated mutations. J Infect Dis 2004 Dec 1;190(11):2055-6.

(351) Oude Essink BB, Back NK, Berkhout B. Increased polymerase fidelity of the 3TC-resistant variants of HIV-1 reverse transcriptase. Nucleic Acids Res 1997 Aug 15;25(16):3212-7.

(352) Devereux HL, Emery VC, Johnson MA, Loveday C. Replicative fitness in vivo of HIV-1 variants with multiple drug resistance-associated mutations. J Med Virol 2001 Oct;65(2):218-24.

(353) Harrigan PR, Bloor S, Larder BA. Relative replicative fitness of zidovudine-resistant human immunodeficiency virus type 1 isolates in vitro. J Virol 1998 May;72(5):3773-8.

(354) Hsu M, Inouye P, Rezende L, Richard N, Li Z, Prasad VR, et al. Higher fidelity of RNA-dependent DNA mispair extension by M184V drug-resistant than wild-type reverse transcriptase of human immunodeficiency virus type 1. Nucleic Acids Res 1997 Nov 15;25(22):4532-6.

(355) Feng JY, Anderson KS. Mechanistic studies examining the efficiency and fidelity of DNA synthesis by the 3TC-resistant mutant (184V) of HIV-1 reverse transcriptase. Biochemistry 1999 Jul 20;38(29):9440-8.

(356) Rezende LF, Drosopoulos WC, Prasad VR. The influence of 3TC resistance mutation M184I on the fidelity and error specificity of human immunodeficiency virus type 1 reverse transcriptase. Nucleic Acids Res 1998 Jun 15;26(12):3066-72.

(357) Rubinek T, Bakhanashvili M, Taube R, Avidan O, Hizi A. The fidelity of 3' misinsertion and mispair extension during DNA synthesis exhibited by two drug-resistant mutants of the reverse transcriptase of human immunodeficiency virus type 1 with Leu74-->Val and Glu89-->Gly. Eur J Biochem 1997 Jul 1;247(1):238-47.

(358) Wainberg MA, Drosopoulos WC, Salomon H, Hsu M, Borkow G, Parniak M, et al. Enhanced fidelity of 3TC-selected mutant HIV-1 reverse transcriptase. Science 1996 Mar 1;271(5253):1282-5.

(359) Castagna A, Danise A, Menzo S, Galli L, Gianotti N, Carini E, et al. Lamivudine monotherapy in HIV-1-infected patients harbouring a lamivudine-resistant virus: a randomized pilot study (E-184V study). AIDS 2006 Apr 4;20(6):795-803.

(360) Fox Z, Dragsted UB, Gerstoft J, Phillips AN, Kjaer J, Mathiesen L, et al. A randomized trial to evaluate continuation versus discontinuation of lamivudine in individuals failing a lamivudine-containing regimen: the COLATE trial. Antivir Ther 2006;11(6):761-70.

(361) van Maarseveen NM, de JD, Boucher CA, Nijhuis M. An increase in viral replicative capacity drives the evolution of protease inhibitor-resistant human immunodeficiency virus type 1 in the absence of drugs. J Acquir Immune Defic Syndr 2006 Jun;42(2):162-8.

(362) Perez-Bercoff D, Wurtzer S, Compain S, Benech H, Clavel F. Human immunodeficiency virus type 1: resistance to nucleoside analogues and replicative capacity in primary human macrophages. J Virol 2007 May;81(9):4540-50.

(363) Frankel FA, Invernizzi CF, Oliveira M, Wainberg MA. Diminished efficiency of HIV-1 reverse transcriptase containing the K65R and M184V drug resistance mutations. AIDS 2007 Mar 30;21(6):665-75.

(364) Svicher V, Sing T, Santoro MM, Forbici F, Rodriguez-Barrios F, Bertoli A, et al. Involvement of novel human immunodeficiency virus type 1 reverse transcriptase mutations in the regulation of resistance to nucleoside inhibitors. J Virol 2006 Jul;80(14):7186-98.

(365) Villena C, Prado JG, Puertas MC, Martinez MA, Clotet B, Ruiz L, et al. Relative fitness and replication capacity of a multinucleoside analogue-resistant clinical human immunodeficiency virus type 1 isolate with a deletion of codon 69 in the reverse transcriptase coding region. J Virol 2007 May;81(9):4713-21.

(366) Weber J, Rangel HR, Chakraborty B, Marotta ML, Valdez H, Fransen K, et al. Role of Baseline pol Genotype in HIV-1 Fitness Evolution. J Acquir Immune Defic Syndr 2003 Aug 1;33(4):448-60.

(367) de MC, Martin-Carbonero L, Gallego O, Corral A, Gonzalez-Lahoz J, Soriano V. Relationship between drug resistance mutations, plasma viremia, and CD4+ T-cell counts in patients with chronic HIV infection. J Med Virol 2005 May;76(1):1-6.

(368) Fox ZV, Geretti AM, Clotet B, Cozzi-Lepri A, Hill T, Green H, et al. Association between resistance and CD4-count change in patients on ART with ongoing viraemia. 2007 Jun 12; Barbados 2007.

(369) Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. AIDS 1999 Dec 24;13(18):F123-F127.

(370) Carter M. Resistance. http://www aidsmap com/Resistance/page/1327026/ 2009 [cited 2013 Sep 15];Available from: URL: http://www.aidsmap.com/Resistance/page/1327026/

(371) Little SJ, Holte S, Routy JP, Daar ES, Markowitz M, Collier AC, et al. Antiretroviral-drug resistance among patients recently infected with HIV. New England Journal of Medicine 2002 Aug 8;347(6):385-94.

(372) Borroto-Esoda K, Waters JM, Bae AS, Harris JL, Hinkle JE, Quinn JB, et al. Baseline genotype as a predictor of virological failure to emtricitabine or stavudine in combination with didanosine and efavirenz. AIDS Res Hum Retroviruses 2007 Aug;23(8):988-95.

(373) Kuritzkes DR, Lalama CM, Ribaudo HJ, Marcial M, Meyer WA, III, Shikuma C, et al. Preexisting resistance to nonnucleoside reverse-transcriptase inhibitors predicts virologic failure of an efavirenz-based regimen in treatment-naive HIV-1-infected subjects. J Infect Dis 2008 Mar 15;197(6):867-70.

(374) Pozniak AL, Gallant JE, Dejesus E, Arribas JR, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz versus fixed-dose zidovudine/lamivudine and efavirenz in antiretroviral-naive patients: virologic, immunologic, and morphologic changes--a 96-week analysis. J Acquir Immune Defic Syndr 2006 Dec 15;43(5):535-40.

(375) Price MA, Wallis CL, Lakhi S, Karita E, Kamali A, Anzala O, et al. Transmitted HIV Type 1 Drug Resistance Among Individuals with Recent HIV Infection in East and Southern Africa. Aids Research and Human Retroviruses 2011 Jan;27(1):5-12.

(376) Hamers RL, Wallis CL, Kityo C, Siwale M, Mandaliya K, Conradie F, et al. HIV-1 drug resistance in antiretroviral-naive individuals in sub-Saharan Africa after rollout of antiretroviral therapy: a multicentre observational study. Lancet Infectious Diseases 2011 Oct;11(10):750-9.

(377) Hamers RL, Siwale M, Wallis CL, Labib M, van HR, Stevens WS, et al. HIV-1 drug resistance mutations are present in six percent of persons initiating antiretroviral therapy in Lusaka, Zambia. J Acquir Immune Defic Syndr 2010 Sep;55(1):95-101.

(378) Ndembi N, Hamers RL, Sigaloff KCE, Lyagob F, Magambo B, Nanteza B, et al. Transmitted antiretroviral drug resistance among newly HIV-1 diagnosed young individuals in Kampala. AIDS 2011 Apr 24;25(7):905-10.

(379) Yanik EL, Napravnik S, Hurt CB, Dennis A, Quinlivan EB, Sebastian J, et al. Prevalence of transmitted antiretroviral drug resistance differs between acutely and chronically HIV-infected patients. J Acquir Immune Defic Syndr 2012 Oct 1;61(2):258-62.

(380) Agwu AL, Bethel J, Hightow-Weidman LB, Sleasman JW, Wilson CM, Rudy B, et al. Substantial multiclass transmitted drug resistance and drug-relevant polymorphisms among treatment-naive behaviorally HIV-infected youth. AIDS Patient Care STDS 2012 Apr;26(4):193-6.

(381) Castor D, Low A, Evering T, Karmon S, Davis B, Figueroa A, et al. Transmitted drug resistance and phylogenetic relationships among acute and early HIV-1-infected individuals in New York City. J Acquir Immune Defic Syndr 2012 Sep 1;61(1):1-8.

(382) Wheeler WH, Ziebell RA, Zabina H, Pieniazek D, Prejean J, Bodnar UR, et al. Prevalence of transmitted drug resistance associated mutations and HIV-1 subtypes in new HIV-1 diagnoses, U.S.-2006. AIDS 2010 May 15;24(8):1203-12.

(383) Novak RM, Chen L, MacArthur RD, Baxter JD, Huppler HK, Peng G, et al. Prevalence of antiretroviral drug resistance mutations in chronically HIV-infected, treatment-naive patients: implications for routine resistance screening before initiation of antiretroviral therapy. Clin Infect Dis 2005 Feb 1;40(3):468-74.

(384) Little SJ, Frost SD, Wong JK, Smith DM, Pond SL, Ignacio CC, et al. Persistence of transmitted drug resistance among subjects with primary human immunodeficiency virus infection. J Virol 2008 Jun;82(11):5510-8.

(385) Smith DM, Wong JK, Shao H, Hightower GK, Mai SH, Moreno JM, et al. Long-term persistence of transmitted HIV drug resistance in male genital tract secretions: implications for secondary transmission. J Infect Dis 2007 Aug 1;196(3):356-60.

(386) Castro H, Pillay D, Cane P, Asboe D, Cambiano V, Phillips A, et al. Persistence of HIV-1 Transmitted Drug Resistance Mutations. J Infect Dis 2013 Nov;208(9):1459-63.

(387) Johnson JA, Li JF, Wei X, Lipscomb J, Irlbeck D, Craig C, et al. Minority HIV-1 drug resistance mutations are present in antiretroviral treatment-naive populations and associate with reduced treatment efficacy. PLoS Med 2008 Jul 29;5(7):e158.

(388) Paredes R, Lalama CM, Ribaudo HJ, Schackman BR, Shikuma C, Giguel F, et al. Pre-existing minority drug-resistant HIV-1 variants, adherence, and risk of antiretroviral treatment failure. J Infect Dis 2010 Mar;201(5):662-71.

(389) Simen BB, Simons JF, Hullsiek KH, Novak RM, MacArthur RD, Baxter JD, et al. Low-abundance drug-resistant viral variants in chronically HIV-infected, antiretroviral treatment-naive patients significantly impact treatment outcomes. J Infect Dis 2009 Mar 1;199(5):693-701.

(390) Jourdain G, Ngo-Giang-Huong N, Le CS, Bowonwatanuwong C, Kantipong P, Leechanachai P, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. N Engl J Med 2004 Jul 15;351(3):229-40.

(391) Pillay D, Bhaskaran K, Jurriaans S, Prins M, Masquelier B, Dabis F, et al. The impact of transmitted drug resistance on the natural history of HIV infection and response to first-line therapy. AIDS 2006 Jan 2;20(1):21-8.

(392) Saag MS, Cahn P, Raffi F, Wolff M, Pearce D, Molina JM, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. JAMA 2004 Jul 14;292(2):180-9.

(393) Yerly S, Jost S, Monnat M, Telenti A, Cavassini M, Chave JP, et al. HIV-1 co/super-infection in intravenous drug users. AIDS 2004 Jul 2;18(10):1413-21.

(394) Doyle T, Garcia-Diaz AM, Ambrose J, Strang A, Cambiano V, Johnson M, et al. Detecting HIV-1 superinfection by pol gene population sequencing among untreated HIV-1-infected men who experience sudden rises in plasma HIV-1 RNA load. AIDS 2011;25(4):542-4.

(395) Rachinger A, Navis M, van AS, Groeneveld PH, Schuitemaker H. Recovery of viremic control after superinfection with pathogenic HIV type 1 in a long-term elite controller of HIV type 1 infection. Clin Infect Dis 2008 Dec 1;47(11):e86-e89.

(396) Smith DM, Wong JK, Hightower GK, Ignacio CC, Koelsch KK, Daar ES, et al. Incidence of HIV superinfection following primary infection. JAMA 2004 Sep 8;292(10):1177-8.

(397) Gonzales MJ, Delwart E, Rhee SY, Tsui R, Zolopa AR, Taylor J, et al. Lack of detectable human immunodeficiency virus type 1 superinfection during 1072 person-years of observation. J Infect Dis 2003 Aug 1;188(3):397-405.

(398) Hamers RL, Sigaloff KC, Wensing AM, Wallis CL, Kityo C, Siwale M, et al. Patterns of HIV-1 drug resistance after first-line antiretroviral therapy (ART) failure in 6 sub-Saharan African countries: implications for second-line ART strategies. Clin Infect Dis 2012 Jun;54(11):1660-9.

(399) Napravnik S, Edwards D, Stewart P, Stalzer B, Matteson E, Eron JJ, Jr. HIV-1 drug resistance evolution among patients on potent combination antiretroviral therapy with detectable viremia. J Acquir Immune Defic Syndr 2005 Sep 1;40(1):34-40.

(400) Murphy RA, Sunpath H, Lu Z, Chelin N, Losina E, Gordon M, et al. Outcomes after virologic failure of first-line ART in South Africa. AIDS 2010 Apr 24;24(7):1007-12.

(401) van Zyl GU, van der Merwe L, Claassen M, Zeier M, Preiser W. Antiretroviral resistance patterns and factors associated with resistance in adult patients failing NNRTI-based regimens in the Western Cape, South Africa. J Med Virol 2011 Oct;83(10):1764-9.

(402) Cozzi-Lepri A, Phillips AN, Ruiz L, Clotet B, Loveday C, Kjaer J, et al. Evolution of drug resistance in HIV-infected patients remaining on a virologically failing combination antiretroviral therapy regimen. AIDS 2007 Mar 30;21(6):721-32.

(403) Vandamme AM, Sonnerborg A, Ait-Khaled M, Albert J, Asjo B, Bacheler L, et al. Updated European recommendations for the clinical use of HIV drug resistance testing. Antivir Ther 2004 Dec;9(6):829-48.

(404) Baxter JD, Mayers DL, Wentworth DN, Neaton JD, Hoover ML, Winters MA, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy. CPCRA 046 Study Team for the Terry Beirn Community Programs for Clinical Research on AIDS. AIDS 2000 Jun 16;14(9):F83-F93.

(405) Zolopa AR, Shafer RW, Warford A, Montoya JG, Hsu P, Katzenstein D, et al. HIV-1 genotypic resistance patterns predict response to saquinavir-ritonavir therapy in patients in whom previous protease inhibitor therapy had failed. Ann Intern Med 1999 Dec 7;131(11):813-21.

(406) Weinstein MC, Goldie SJ, Losina E, Cohen CJ, Baxter JD, Zhang H, et al. Use of genotypic resistance testing to guide hiv therapy: clinical impact and cost-effectiveness. Ann Intern Med 2001 Mar 20;134(6):440-50.

(407) Durant J, Clevenbergh P, Halfon P, Delgiudice P, Porsin S, Simonet P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. Lancet 1999 Jun 26;353(9171):2195-9.

(408) Mink M, Mosier SM, Janumpalli S, Davison D, Jin L, Melby T, et al. Impact of human immunodeficiency virus type 1 gp41 amino acid substitutions selected during

enfuvirtide treatment on gp41 binding and antiviral potency of enfuvirtide in vitro. J Virol 2005 Oct;79(19):12447-54.

(409) Geretti AM, Easterbrook P. Antiretroviral resistance in clinical practice. Int J STD AIDS 2001 Mar;12(3):145-53.

(410) Bronze M, Steegen K, Wallis CL, De WH, Papathanasopoulos MA, Van HM, et al. HIV-1 phenotypic reverse transcriptase inhibitor drug resistance test interpretation is not dependent on the subtype of the virus backbone. PLoS One 2012;7(4):e34708.

(411) Tang MW, Liu TF, Shafer RW. The HIVdb system for HIV-1 genotypic resistance interpretation. Intervirology 2012;55(2):98-101.

(412) Hirsch MS, Gunthard HF, Schapiro JM, Brun-Vezinet F, Clotet B, Hammer SM, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: 2008 recommendations of an International AIDS Society-USA panel. Clin Infect Dis 2008 Jul 15;47(2):266-85.

(413) Tural C, Ruiz L, Holtzer C, Schapiro J, Viciana P, Gonzalez J, et al. Clinical utility of HIV-1 genotyping and expert advice: the Havana trial. AIDS 2002 Jan 25;16(2):209-18.

(414) Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. Cochrane Database Syst Rev 2002;(1):CD003255.

(415) French PP, Latka M, Gollub EL, Rogers C, Hoover DR, Stein ZA. Use-effectiveness of the female versus male condom in preventing sexually transmitted disease in women. Sex Transm Dis 2003 May;30(5):433-9.

(416) Cameron DW, Simonsen JN, D'Costa LJ, Ronald AR, Maitha GM, Gakinya MN, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet 1989 Aug 19;2(8660):403-7.

(417) Baeten JM, Richardson BA, Lavreys L, Rakwar JP, Mandaliya K, Bwayo JJ, et al. Female-to-male infectivity of HIV-1 among circumcised and uncircumcised Kenyan men. J Infect Dis 2005 Feb 15;191(4):546-53.

(418) Siegfried N, Muller M, Volmink J, Deeks J, Egger M, Low N, et al. Male circumcision for prevention of heterosexual acquisition of HIV in men. Cochrane Database Syst Rev 2003;(3):CD003362.

(419) Weiss HA, Hankins CA, Dickson K. Male circumcision and risk of HIV infection in women: a systematic review and meta-analysis. Lancet Infect Dis 2009 Nov;9(11):669-77.

(420) Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. PLoS Med 2005 Nov;2(11):1112-22.

(421) Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. Lancet 2007 Feb 24;369(9562):643-56.

(422) Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. Lancet 2007 Feb 24;369(9562):657-66.

(423) WHO. Male circumcision for HIV prevention. WHO 2013 June 30 [cited 2013 Jul 14];Available from: URL: http://www.who.int/hiv/topics/malecircumcision/en/index.html

(424) Johnson WD, Diaz RM, Flanders WD, Goodman M, Hill AN, Holtgrave D, et al. Behavioral interventions to reduce risk for sexual transmission of HIV among men who have sex with men. Cochrane Database Syst Rev 2008;(3):CD001230.

(425) Millett GA, Flores SA, Marks G, Reed JB, Herbst JH. Circumcision status and risk of HIV and sexually transmitted infections among men who have sex with men: a meta-analysis. JAMA 2008 Oct 8;300(14):1674-84.

(426) Sanchez J, Sal YR, V, Hughes JP, Baeten JM, Fuchs J, Buchbinder SP, et al. Male circumcision and risk of HIV acquisition among MSM. AIDS 2011 Feb 20;25(4):519-23.

(427) Templeton DJ, Jin F, Mao L, Prestage GP, Donovan B, Imrie J, et al. Circumcision and risk of HIV infection in Australian homosexual men. AIDS 2009 Nov 13;23(17):2347-51.

(428) Montaner JS, Hogg R, Wood E, Kerr T, Tyndall M, Levy AR, et al. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. Lancet 2006 Aug 5;368(9534):531-6.

(429) Attia S, Egger M, Muller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: systematic review and meta-analysis. AIDS 2009 Jul 17;23(11):1397-404.

(430) Castilla J, Del RJ, Hernando V, Marincovich B, Garcia S, Rodriguez C. Effectiveness of highly active antiretroviral therapy in reducing heterosexual transmission of HIV. J Acquir Immune Defic Syndr 2005 Sep 1;40(1):96-101.

(431) Donnell D, Baeten JM, Kiarie J, Thomas KK, Stevens W, Cohen CR, et al. Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis. Lancet 2010;375(9731):2092-8.

(432) Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. N Engl J Med 2011 Aug 11;365(6):493-505.

(433) Statistics South Africa. Mid-year population estimates. Statistics South Africa 2013 May [cited 2014 Mar 3];Available from: URL: http://beta2.statssa.gov.za/publications/P0302/P03022013.pdf

(434) Census 2011; Statistical release (Revised) P0301.4. http://www statssa gov za/publications/P03014/P030142011 pdf 2012 October 30 [cited 2014 Mar 8];Available from: URL: http://www.statssa.gov.za/publications/P03014/P030142011.pdf

(435) Central Intelligence Agency. World Factbook 2011. Central Intelligence Agency 2012 March 20 [cited 2012 Apr 18];Available from: URL: https://www.cia.gov/library/publications/the-world-factbook/geos/sf.html

(436) Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat. World Population Prospects: The 2012 Revision. United Nations 2014 March 8 [cited 2014 Feb 27];Available from: URL: http://esa.un.org/unpd/wpp/index.htm

(437) Anderson B, Phillips HE. Adult mortality (age 15-64) based on death notification data in South Africa: 1997-2004. Statistics South Africa 2006 [cited 2014 Mar 9];**03-09-05 (2006)**Available from: URL: http://www.statssa.gov.za/publications/Report-03-09-05/Report-03-09-052004.pdf

(438) Statistics South Africa. Mortality and causes of death in South Africa, 2010: Findings from death notification. Statistical release P0309.3. Statistics South Africa 2013 April [cited 2014 Mar 8];Available from: URL: http://www.statssa.gov.za/publications/P03093/P030932010.pdf

(439) Central Intelligency Agency. The World Factbook: Death Rate. Central Intelligency Agency 2014 [cited 2014 Mar 8];Available from: URL: https://www.cia.gov/library/publications/the-world-factbook/fields/2066.html#sf

(440) Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Zungu N, et al. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012. HSRC 2014 [cited 2014 Apr 14];Available from: URL: http://www.hsrc.ac.za/en/research-outputs/view/6871

(441) Grabowski MK, Lessler J, Nalugoda F, Reynolds SJ, Ssekubugu R, Kong X, et al. Introduction of HIV into Stable Heterosexual Couples in Rakai, Uganda Before and After ART. 2014 Mar 6; 2014.

(442) Department of Health, Medical Research Council, OrcMacro. South Africa Demographic and Health Survey 2003. Department of Health 2007 [cited 2014 Mar 9];Available from: URL: http://dhsprogram.com/pubs/pdf/FR206/FR206.pdf

(443) Shisana O, Rehle T, Simbayi LC, Parker W, Zuma K, Bhana A, et al. South African national HIV prevalence, incidence, behaviour and communication survey, 2005. HSRC 2005Available from: URL: http://www.wsu.ac.za/hsrc/html/2152-9.pdf

(444) Ras GJ, Simson IW, Anderson R, Prozesky OW, Hamersma T. Acquired immunodeficiency syndrome. A report of 2 South African cases. S Afr Med J 1983 Jul 23;64(4):140-2.

(445) Van der Vliet V. South Africa Divided Against AIDS: a Crisis of Leadership. AIDS and South Africa: The Social Expression of a Pandemic. 2004 ed. Palgrave Macmillan Ltd; 2004.

(446) UNAIDS. South Africa: HIV and AIDS estimates. UNAIDS 2014 [cited 2014 Mar 10];Available from: URL: http://www.unaids.org/en/regionscountries/countries/southafrica/

(447) UNAIDS. AIDS by the numbers. UNAIDS 2013 [cited 2014 Mar 10];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/JC2571_AIDS_by_the_numbers_en.pdf

(448) National Department of Health. The National Antenatal Sentinel HIV and Syphilis Prevalence Survey, South Africa, 2011. National Department of Health 2013 [cited 2014 Mar 10];Available from: URL: http://www.health.gov.za/docs/reports/2013/Antenatal_survey_report_2012_web_optimized.pdf

(449) Zaba B, Gregson S. Measuring the impact of HIV on fertility in Africa. AIDS 1998;12 Suppl 1:S41-S50.

(450) Republic of South Africa. Global AIDS Response Progress Report 2012. UNAIDS 2012 May [cited 2014 Mar 10];Available from: URL: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/ce_ZA_Narrative_Report.pdf

(451) Johnson LF. Access to Antiretroviral Treatment in South Africa, 2004-2011. Southern African Journal of Hiv Medicine 2012 Mar;13(1):22-7.

(452) Shisana O, Rehle T, Simbayi LC, Zuma K, Jooste S, Pillay-van-Wyk V, et al. South African national HIV prevalence, incidence, behaviour and communication survey 2008: A turning tide among teenagers? MRC 2009Available from: URL: http://www.mrc.ac.za/pressreleases/2009/sanat.pdf

(453) Quinn TC, Overbaugh J. HIV/AIDS in women: an expanding epidemic. Science 2005 Jun 10;308(5728):1582-3.

(454) Polis CB, Curtis KM. Use of hormonal contraceptives and HIV acquisition in women: a systematic review of the epidemiological evidence. Lancet Infect Dis 2013 Sep;13(9):797-808.

(455) Low N, Chersich MF, Schmidlin K, Egger M, Francis SC, van de Wijgert JH, et al. Intravaginal practices, bacterial vaginosis, and HIV infection in women: individual participant data meta-analysis. PLoS Med 2011;8(2):e1000416.

(456) South African National AIDS Council. SOUTH AFRICA: HIV Epidemic, Response and Policy Synthesis. SANAC 2011 May 31 [cited 2014 Mar 10];Available from: URL: http://supportservices.ufs.ac.za/dl/userfiles/Documents/00001/1432_eng.pdf

(457) Rehle TM, Hallett TB, Shisana O, Pillay-van W, V, Zuma K, Carrara H, et al. A decline in new HIV infections in South Africa: estimating HIV incidence from three national HIV surveys in 2002, 2005 and 2008. PLoS One 2010;5(6):e11094.

(458) Gregson S, Machekano R, Donnelly CA, Mbizvo MT, Anderson RM, Katzenstein DA. Estimating HIV incidence from age-specific prevalence data: comparison with concurrent cohort estimates in a study of male factory workers, Harare, Zimbabwe. AIDS 1998 Oct 22;12(15):2049-58.

(459) UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance. When and how to use assays for recent infection to estimate HIV incidence at a population

level. http://whqlibdoc who int/publications/2011/9789241501675_eng pdf?ua=1 2011 [cited 2014 Sep 16];Available from: URL: http://whqlibdoc.who.int/publications/2011/9789241501675_eng.pdf?ua=1

(460) Groenewald P, Nannan N, Bourne D, Laubscher R, Bradshaw D. Identifying deaths from AIDS in South Africa. AIDS 2005 Jan 28;19(2):193-201.

(461) WHO. Global tuberculosis report 2013. WHO 2013 [cited 2014 Mar 14];Available from: URL: http://www.who.int/tb/publications/global_report/en/

(462) Statistics South Africa. South African Statistics 2012. Statistics South Africa 2012 [cited 2014 Mar 8];Available from: URL: http://www.statssa.gov.za/publications/SAStatistics/SAStatistics2012.pdf

(463) UNAIDS. South Africa: HIV and AIDS estimates (2012). UNAIDS 2013 [cited 2014 Jan 16];Available from: URL: http://www.unaids.org/en/regionscountries/countries/southafrica/

(464) Heywood M, Cornell M. Human rights and AIDS in South Africa: from right margin to left margin. Health Hum Rights 1998;2(4):60-82.

(465) UNICEF. National Integrated Plan for early childhood development in South Africa. UNICEF 2005 [cited 2014 Mar 11];Available from: URL: http://www.unicef.org/southafrica/SAF_resources_nip.pdf

(466) The National AIDS council. HIV/AIDS/STD Strategic Plan for South Africa 2000-2005. The National AIDS Council 2000 February [cited 2014 Mar 11];Available from: URL: http://hivaidsclearinghouse.unesco.org/search/resources/aidsplan2000.pdf

(467) SANAC. HIV & AIDS and STI Strategic Plan for South Africa 2007-2011. UNAIDS 2006 [cited 2014 Mar 11];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/dataimport/pub/externaldocument/2007/20070604_sa_nsp_final_en.pdf

(468) SANAC Secretariat. The national HIV counselling and testing campaign strategy. SANAC 2010 February [cited 2014 Mar 14];Available from: URL: http://www.westerncape.gov.za/other/2010/6/hct_campaign_strategy_2_3_10_final.pdf

(469) SANAC. National Strategic Plan on HIV, STIs and TB 2012-2016. SANAC 2011 [cited 2014 Mar 11];Available from: URL: http://www.sahivsoc.org/upload/documents/National_Strategic_Plan_2012.pdf

(470) Kharsany AB, Karim QA, Karim SS. Uptake of provider-initiated HIV testing and counseling among women attending an urban sexually transmitted disease clinic in South Africa - missed opportunities for early diagnosis of HIV infection. AIDS Care 2010 May;22(5):533-7.

(471) WHO. Guidance on provider-initiated HIV testing and counselling in health facilities. WHO 2007 [cited 2013 Jul 15];Available from: URL: http://whqlibdoc.who.int/publications/2007/9789241595568_eng.pdf

(472) Dept of Health RoSA. HIV counselling and testing (HCT) policy guidelines. South African National AIDS Council 2010 March [cited 2014 Mar 14];Available from: URL: http://www.sanac.org.za/resources/cat_view/1-resources

(473) SANAC. Global AIDS Response: Progress Report-2013. SANAC 2013 May [cited 2014 Mar 14];Available from: URL: http://dutblogs.dut.ac.za/hivaids/wp-content/uploads/2013/10/South-Africa-Global-AIDS-Response-2013.pdf

(474) WHO. Scaling Up Antiretroviral Therapy in Resource Limited Settings: Treatment Guidelines for a Public Health Approach. WHO 2003 [cited 2014 Mar 15];Available from: URL: http://whqlibdoc.who.int/publications/2004/9241591552.pdf

(475) Department of Health RoSA. The South African antiretroviral treatment guidelines; PMTCT guidelines: revised March 2013. Department of Health,Republic of South Africa 2013 March 13 [cited 2014 Mar 15];Available from: URL: http://web.up.ac.za/sitefiles/file/45/1335/877/PMTCT%20guidelines_March%2013_DoH.pdf

(476) South Africa National Department of Health. Operational plan for comprehensive HIV and AIDS care, management and treatment for South Africa. South Africa National Department of Health 2003 November 19 [cited 2013 Sep 7];Available from: URL: http://www.hst.org.za/uploads/files/aidsplan.pdf

(477) Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS 2004 Apr 9;18(6):887-95.

(478) Bekker LG, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. S Afr Med J 2006 Apr;96(4):315-20.

(479) UNAIDS. New HIV report finds big drop in new HIV infections in South Africa. UNAIDS 2014 January 17 [cited 2014 Mar 10];Available from: URL: http://www.unaids.org/en/resources/presscentre/featurestories/2014/january/20140117southafrica/

(480) Department of Health. Health Information Epidemiology Evaluation and Research. 2010 Nov.

(481) Statistics South Africa. Mid-year population estimates. Statistics South Africa 2011 July 27 [cited 2014 Mar 8];Available from: URL: http://www.statssa.gov.za/publications/P0302/P03022011.pdf

(482) Ojikutu BO, Zheng H, Walensky RP, Lu Z, Losina E, Giddy J, et al. Predictors of mortality in patients initiating antiretroviral therapy in Durban, South Africa. S Afr Med J 2008 Mar;98(3):204-8.

(483) Ahonkhai AA, Noubary F, Munro A, Stark R, Wilke M, Freedberg KA, et al. Not all are lost: interrupted laboratory monitoring, early death, and loss to follow-up (LTFU) in a large South African treatment program. PLoS One 2012;7(3):e32993.

(484) Kranzer K, Lewis JJ, Ford N, Zeinecker J, Orrell C, Lawn SD, et al. Treatment interruption in a primary care antiretroviral therapy program in South Africa:

cohort analysis of trends and risk factors. J Acquir Immune Defic Syndr 2010 Nov;55(3):e17-e23.

(485) Mills EJ, Nachega JB, Buchan I, Orbinski J, Attaran A, Singh S, et al. Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis. JAMA 2006 Aug 9;296(6):679-90.

(486) Malangu N. Self-reported use of traditional, complementary and over-the-counter medicines by HIV-infected patients on antiretroviral therapy in Pretoria, South Africa. African Journal of Traditional, Complementary and Alternative Medicines 2008;4(3):273-8.

(487) Nachega JB, Stein DM, Lehman DA, Hlatshwayo D, Mothopeng R, Chaisson RE, et al. Adherence to antiretroviral therapy in HIV-infected adults in Soweto, South Africa. AIDS Res Hum Retroviruses 2004 Oct;20(10):1053-6.

(488) Darder M, Michaels D, Boulle A, Ncobo N, MacLean E, Goemaere E. Determinants of short and long-term adherence to antiretroviral treatment in resource-poor settings. 2014 Jan 28; Bangkok, Thailand 2004.

(489) Orrell C, Bangsberg DR, Badri M, Wood R. Adherence is not a barrier to successful antiretroviral therapy in South Africa. AIDS 2003 Jun 13;17(9):1369-75.

(490) Dahab M, Hamilton R, Charalambous S, Dube N, Tsimele J, Govender N, et al. A quantitative study of barriers & facilitators to adherence in an antiretroviral therapy programme in South Africa. 2014 Jan 28; Toronto, Canada 2006.

(491) Peltzer K, Friend-du PN, Ramlagan S, Anderson J. Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. BMC Public Health 2010;10:111.

(492) Chaiyachati K, Hirschhorn LR, Tanser F, Newell ML, Barnighausen T. Validating five questions of antiretroviral nonadherence in a public-sector treatment program in rural South Africa. AIDS Patient Care STDS 2011 Mar;25(3):163-70.

(493) Brinkhof MW, Dabis F, Myer L, Bangsberg DR, Boulle A, Nash D, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ 2008 Jul;86(7):559-67.

(494) McMahon JH, Elliott JH, Hong SY, Bertagnolio S, Jordan MR. Effects of physical tracing on estimates of loss to follow-up, mortality and retention in low and middle income country antiretroviral therapy programs: a systematic review. PLoS One 2013;8(2):e56047.

(495) Innes C, Charalambous S, Maraisane M, Senoge S, Seatlanyane P, Fielding K, et al. 24 and 36 month outcomes among HIV-infected individuals starting antiretroviral therapy in a workplace program in South Africa. 2008; Mexico City, Mexico 2008.

(496) Barth RE, van der Meer JT, Hoepelman AI, Schrooders PA, van de Vijver DA, Geelen SP, et al. Effectiveness of highly active antiretroviral therapy administered by general practitioners in rural South Africa. Eur J Clin Microbiol Infect Dis 2008 Oct;27(10):977-84.

(497) Mutevedzi PC, Lessells RJ, Heller T, Barnighausen T, Cooke GS, Newell ML. Scale-up of a decentralized HIV treatment programme in rural KwaZulu-Natal, South Africa: does rapid expansion affect patient outcomes? Bull World Health Organ 2010 Aug 1;88(8):593-600.

(498) Barth RE, Tempelman HA, Moraba R, Hoepelman AI. Long-Term Outcome of an HIV-Treatment Programme in Rural Africa: Viral Suppression despite Early Mortality. AIDS Res Treat 2011;2011:434375.

(499) Fox MP, Cutsem GV, Giddy J, Maskew M, Keiser O, Prozesky H, et al. Rates and predictors of failure of first-line antiretroviral therapy and switch to second-line ART in South Africa. J Acquir Immune Defic Syndr 2012 Aug 1;60(4):428-37.

(500) Johnston V, Fielding KL, Charalambous S, Churchyard G, Phillips A, Grant AD. Outcomes following virological failure and predictors of switching to second-line antiretroviral therapy in a South African treatment program. J Acquir Immune Defic Syndr 2012 Nov 1;61(3):370-80.

(501) Venter F. Median time to switch to second line in Johannesburg General Hospital HIV Clinic. 2013.
Ref Type: Personal Communication

(502) van Zyl GU, van Mens TE, McIlleron H, Zeier M, Nachega JB, Decloedt E, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a resource-limited setting. J Acquir Immune Defic Syndr 2011 Apr;56(4):333-9.

(503) Schoffelen AF, Wensing AM, Tempelman HA, Geelen SP, Hoepelman AI, Barth RE. Sustained virological response on second-line antiretroviral therapy following virological failure in HIV-infected patients in rural South Africa. PLoS One 2013;8(3):e58526.

(504) El-Khatib Z, Ekstrom AM, Ledwaba J, Mohapi L, Laher F, Karstaedt A, et al. Viremia and drug resistance among HIV-1 patients on antiretroviral treatment: a cross-sectional study in Soweto, South Africa. AIDS 2010 Jul 17;24(11):1679-87.

(505) Murphy RA, Sunpath H, Castilla C, Ebrahim S, Court R, Nguyen H, et al. Second-line antiretroviral therapy: long-term outcomes in South Africa. J Acquir Immune Defic Syndr 2012 Oct 1;61(2):158-63.

(506) WHO, UNAIDS. New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications. WHO 2007Available from: URL: http://www.who.int/hiv/pub/malecircumcision/research_implications/en/

(507) WHO/UNAIDS. Joint Strategic Action Framework to Accelerate the Scale-Up of Voluntary Medical Male Circumcision for HIV Prevention in Eastern and Southern Africa. WHO 2011 [cited 2014 Mar 15];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC2251_Action_Framework_circumcision_en.pdf

(508) Johnson S, Kincaid L, Laurence S, Chikwava F, Delate R, Mahlasela L. Second National HIV Communication Survey 2009. John Hopkins 2010 September [cited 2014 Mar 15];Available from: URL:

http://www.uj.ac.za/EN/CorporateServices/ioha/surveys/Documents/ncs_report.pdf

(509) WHO. Progress in scaling up voluntary medical male circumcision for HIV prevention in East and Southern Africa: January-December 2011. WHO 2011 September [cited 2014 Mar 15];Available from: URL: http://www.malecircumcision.org/country_updates/documents/FINAL%20VMMC%20Progress%20Report%20Jan-Dec%202011%20WHO.pdf

(510) Zimbabwe Central Statistics Office. Census 2012: National Report. Zimbabwe Central Statistics Office 2014 [cited 2014 Mar 18];Available from: URL: http://www.zimstat.co.zw/dmdocuments/Census/CensusResults2012/National_Report.pdf

(511) Zimbabwe Central Statistics Office. Census 2002: National Report. Zimbabwe Central Statistics Office 2004 August [cited 2014 Mar 22];Available from: URL: http://www.zimstat.co.zw/dmdocuments/Census/Census.pdf

(512) UNFPA. State of the world population. UNFPA 2011 [cited 2014 Mar 15];Available from: URL: http://foweb.unfpa.org/SWP2011/reports/EN-SWOP2011-FINAL.pdf

(513) Central Intelligence Agency. The World Factbook: Zimbabwe. Central Intelligence Agency 2014 March 11 [cited 2014 Mar 15];Available from: URL: https://www.cia.gov/library/publications/the-world-factbook/geos/zi.html

(514) Gregson S, Gonese E, Hallett TB, Taruberekera N, Hargrove JW, Lopman B, et al. HIV decline in Zimbabwe due to reductions in risky sex? Evidence from a comprehensive epidemiological review. Int J Epidemiol 2010 Apr 20.

(515) Gregson S, Anderson RM, Ndlovu J, Zhuwau T, Chandiwana SK. Recent upturn in mortality in rural Zimbabwe: evidence for an early demographic impact of HIV-1 infection? AIDS 1997 Aug;11(10):1269-80.

(516) Central Statistical Office and Macro International Inc. Zimbabwe Demographic and Health Survey, 1994. Central Statistical Office and Macro International Inc 1995 September [cited 2013 Mar 5];Available from: URL: http://dhsprogram.com/publications/publication-FR62-DHS-Final-Reports.cfm

(517) Central Statistical Office and Macro International Inc. Zimbabwe Demographic and Health Survey, 1999. http://dhsprogram com/pubs/pdf/FR116/FR116 pdf 2000 December [cited 2013 Apr 3];Available from: URL: http://dhsprogram.com/pubs/pdf/FR116/FR116.pdf

(518) Central Statistical Office (CSO) [Zimbabwe], Macro International Inc. Zimbabwe Demographic and Health Survey 2005-06. http://www dhsprogram com/pubs/pdf/FR186/FR186 pdf 2007 [cited 2014 Mar 15];Available from: URL: http://www.dhsprogram.com/pubs/pdf/FR186/FR186.pdf

(519) Zimbabwe National Statistics Agency - Harare Z. Zimbabwe Demographic and Health Survey 2010-11. Zimbabwe National Statistics Agency 2012 March [cited 2012 Apr 4];Available from: URL: http://dhsprogram.com/pubs/pdf/FR254/FR254.pdf

(520) Central Statistical Office and Macro International Inc. Zimbabwe Demographic andHealth Survey, 1988. http://dhsprogram com/publications/publication-fr43-dhs-final-reports cfm 1989 December [cited 2013 Mar 5];Available from: URL: http://dhsprogram.com/publications/publication-fr43-dhs-final-reports.cfm

(521) Zimbabwe National Family Planning Council. Zimbabwe National Youth Reproductive Health Survey 1997. Zimbabwe National Family Planning Council 1999 December [cited 2014 Mar 23];Available from: URL: http://www.dorluk.de/hp/zim_youth.pdf

(522) Ministry of Health and Child Welfare (Zimbabwe), Zimbabwe National Family Planning Council, National AIDS Council (Zimbabwe), U.S.Centers for Disease Control and Prevention. Zimbabwe Young Adult Reproductive Health Survey 2001. Ministry of Health and Child Welfare (Zimbabwe) 2004 [cited 2014 Mar 23];Available from: URL: http://stacks.cdc.gov/view/cdc/8237

(523) Tambashe B, Buzdugan R, Watadzaushe C, Dirawo J, Mundida O, Copas A, et al. Evaluation of Zimbabwe's National Behaviour Change Programme implemented between 2007 and 2011. 2012 Jul 22; Washington,DC 2012.

(524) Cowan FM, Mtetwa S, Davey C, Fearon E, Dirawo J, Wong-Gruenwald R, et al. Engagement with HIV prevention treatment and care among female sex workers in Zimbabwe: a respondent driven sampling survey. PLoS One 2013;8(10):e77080.

(525) Dehne KL, Dhlakama DG, Richter C, Mawadza M, McClean D, Huss R. Herpes zoster as an indicator of HIV infection in Africa. Tropical doctor 1992;22(2):68-70.

(526) UNAIDS. Zimbabwe: HIV and AIDS estimates (2012). UNAIDS 2013 [cited 2014 Mar 23];Available from: URL: http://www.unaids.org/en/regionscountries/countries/zimbabwe/

(527) Mahomva A, Greby S, Dube S, Mugurungi O, Hargrove J, Rosen D, et al. HIV prevalence and trends from data in Zimbabwe, 1997-2004. Sex Transm Infect 2006 Apr;82 Suppl 1:i42-i47.

(528) UNAIDS. Evidence for HIV decline in Zimbabwe: a comprehensive review of the epidemiological data. UNAIDS 2005 November [cited 2013 Mar 7];Available from: URL: http://data.unaids.org/publications/irc-pub06/zimbabwe_epi_report_nov05_en.pdf

(529) Zimbabwe Ministry of Health and Child Welfare. Antenatal Clinic HIV Surveillance Reports 2000–2006. Harare: Zimbabwe Ministry of Health and Child Welfare; 2007.

(530) Global AIDS Response Progress Report 2012. Zimbabwe Country report. Reporting Period: January 2010-December 2011. http://www unaids org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/ce_ZW_Narrative_Report pdf 2012 [cited 2014 Mar 23];Available from: URL: http://www.unaids.org/en/dataanalysis/knowyourresponse/countryprogressreports/2012countries/ce_ZW_Narrative_Report.pdf

(531) Zimbabwe Ministry of Health and Child Welfare. Zimbabwe National HIV Estimates. 2010 Jun.

(532) UNAIDS, WHO. Epidemiological factsheet on HIV and AIDS, 2009: Zimbabwe. UNAIDS 2010 [cited 2014 Mar 24];Available from: URL: http://158.232.15.29/CFS/downloadpdf.htm?country_id=AFRZWE&lng_code=en&pdfoption=epi

(533) Mbizvo MT, Kasule J, Mahomed K, Nathoo K. HIV-1 seroconversion incidence following pregnancy and delivery among women seronegative at recruitment in Harare, Zimbabwe. Cent Afr J Med 2001 May;47(5):115-8.

(534) Humphrey JH, Hargrove JW, Malaba LC, Iliff PJ, Moulton LH, Mutasa K, et al. HIV incidence among post-partum women in Zimbabwe: risk factors and the effect of vitamin A supplementation. AIDS 2006 Jun 26;20(10):1437-46.

(535) Mbizvo MT, Machekano R, McFarland W, Ray S, Bassett M, Latif A, et al. HIV seroincidence and correlates of seroconversion in a cohort of male factory workers in Harare, Zimbabwe. AIDS 1996 Jul;10(8):895-901.

(536) Corbett EL, Makamure B, Cheung YB, Dauya E, Matambo R, Bandason T, et al. HIV incidence during a cluster-randomized trial of two strategies providing voluntary counselling and testing at the workplace, Zimbabwe. AIDS 2007 Feb 19;21(4):483-9.

(537) Chapman G, Hansen KS, Jelsma J, Ndhlovu C, Piotti B, Byskov J, et al. The burden of disease in Zimbabwe in 1997 as measured by disability-adjusted life years lost. Trop Med Int Health 2006 May;11(5):660-71.

(538) Kerina D, Babill SP, Muller F. HIV/AIDS: The Zimbabwean Situation and Trends. American Journal of Clinical Medicine Research 2013;1(1):15-22.

(539) Government of Zimbabwe. National Policy on HIV/AIDS for the Republic of Zimbabwe 1999. Government of Zimbabwe 1999 December [cited 2014 Mar 25];Available from: URL: http://www.hsph.harvard.edu/population/aids/zimbabwe.aids.99.pdf

(540) National AIDS Council. Zimbabwe National HIV and AIDS Strategic Plan (ZNASP) 2006-2010. AIDSTAR-ONE 2006 July [cited 2014 Mar 25];Available from: URL: http://www.aidstar-one.com/sites/default/files/prevention/resources/national_strategic_plans/Zimbabwe_06-10.pdf

(541) Minister of Health and Child Welfare. Zimbabwe National Behavioural Change Strategy 2006-2010. Minister of Health and Child Welfare 2006 [cited 2014 Mar 26];Available from: URL: http://www.nac.org.zw/sites/default/files/BC-strategy(final).pdf

(542) Gibney L, Wade S, Madzime S, Mbizvo M. HIV testing practices of Zimbabwean physicians and their perspectives on the future use of rapid on-site tests. AIDS Care 1999 Dec;11(6):663-73.

(543) Zimbabwe Ministry of Health and Child Welfare. Guidelines for implementation of Provider-Initiated HIV Testing and Counselling. 2007.

(544) Sibanda EL, Hatzold K, Mugurungi O, Ncube G, Dupwa B, Siraha P, et al. An assessment of the Zimbabwe ministry of health and child welfare provider initiated HIV testing and counselling programme. BMC Health Serv Res 2012;12:131.

(545) Mabugu T. Global Fund Report: 2010-2013. 2014.
Ref Type: Personal Communication

(546) Langhaug L, Buzdugan R, Dirawo J, Benedict C, Mundida O, Manyenya S, et al. An evaluation of Zimbabwe's national behaviour change programme: results of the mid-term evaluation survey. 2010 Jul; Vienna, Austria 2010.

(547) Mutasa-Apollo T. Scaling Up Treatment in Zimbabwe: The path to high coverage. WHO 2013 June 30 [cited 2014 Mar 26];Available from: URL: http://www.who.int/hiv/events/2013/2_apollo_scaling_up_zim_ias_v_3_2.pdf

(548) Zimbabwe National Statistical Agency, UNICEF. Zimbabwe Multiple indicator monitoring survey (MIMS) 2009. UNICEF 2010 May [cited 2014 Mar 23];Available from: URL: http://www.childinfo.org/files/MICS3_Zimbabwe_FinalReport_2009_Eng.pdf

(549) Cowan F. Evaluation of National Behavioural Change programme . 2013.
Ref Type: Personal Communication

(550) Ministry of Health and Child Welfare [Zimbabwe], WHO. Zimbabwe National Guidelines on HIV testing and Counselling. WHO 2005 October [cited 2014 Mar 26];Available from: URL: http://www.who.int/hiv/topics/vct/ZIM_HIVTesting%20Guidelines%20Oct2005.pdf

(551) Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. PLoS Med 2011 Jul;8(7):e1001056.

(552) Mugglin C, Estill J, Wandeler G, Bender N, Egger M, Gsponer T, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Trop Med Int Health 2012 Sep 20.

(553) Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc 2012;15(2):17383.

(554) Mutasa-Apollo T, Shiraishi RW, Takarinda KC, Dzangare J, Mugurungi O, Murungu J, et al. Patient retention, clinical outcomes and attrition-associated factors of HIV-infected patients enrolled in Zimbabwe's National Antiretroviral Therapy Programme, 2007-2010. PLoS One 2014;9(1):e86305.

(555) Mugyenyi P, Walker AS, Hakim J, Munderi P, Gibb DM, Kityo C, et al. Routine versus clinically driven laboratory monitoring of HIV antiretroviral therapy in Africa (DART): a randomised non-inferiority trial. Lancet 2010 Jan 9;375(9709):123-31.

(556) Gilks CF, Walker AS, Munderi P, Kityo C, Reid A, Katabira E, et al. A single CD4 test with 250 cells/mm3 threshold predicts viral suppression in HIV-infected adults failing first-line therapy by clinical criteria. PLoS One 2013;8(2):e57580.

(557) Meldrum A. Zimbabwe's health-care system struggles on. Lancet 2008 Mar 29;371(9618):1059-60.

(558) Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. PLoS One 2012;7(12):e52856.

(559) Wandeler G, Keiser O, Pfeiffer K, Pestilli S, Fritz C, Labhardt ND, et al. Outcomes of antiretroviral treatment programs in rural Southern Africa. J Acquir Immune Defic Syndr 2012 Feb 1;59(2):e9-16.

(560) Rasschaert F, Koole O, Zachariah R, Lynen L, Manzi M, Van DW. Short and long term retention in antiretroviral care in health facilities in rural Malawi and Zimbabwe. BMC Health Serv Res 2012;12:444.

(561) Dzangare J, Gonese E, Mugurungi O, Shamu T, Apollo T, Bennett DE, et al. Monitoring of early warning indicators for HIV drug resistance in antiretroviral therapy clinics in Zimbabwe. Clin Infect Dis 2012 May;54 Suppl 4:S313-S316.

(562) AIDS & TB Unit Ministry of Health and Child Care Zimbabwe. Zimbabwe HIV Drug Resistance Early warning indicators: 2013 report. AIDS & TB Unit Ministry of Health and Child Care Zimbabwe 2013 October [cited 2014 Mar 28];Available from: URL: www.nhis.mohcc.gov.zw

(563) Kiwuwa-Muyingo S, Oja H, Walker AS, Ilmonen P, Levin J, Mambule I, et al. Dynamic logistic regression model and population attributable fraction to investigate the association between adherence, missed visits and mortality: a study of HIV-infected adults surviving the first year of ART. BMC Infect Dis 2013 Aug 27;13(1):395.

(564) Kiwuwa-Muyingo S, Walker AS, Oja H, Levin J, Miiro G, Katabira E, et al. The impact of first year adherence to antiretroviral therapy on long-term clinical and immunological outcomes in the DART trial in Uganda and Zimbabwe. Trop Med Int Health 2012 May;17(5):584-94.

(565) Muyingo SK, Walker AS, Reid A, Munderi P, Gibb DM, Ssali F, et al. Patterns of individual and population-level adherence to antiretroviral therapy and risk factors for poor adherence in the first year of the DART trial in Uganda and Zimbabwe. J Acquir Immune Defic Syndr 2008 Aug 1;48(4):468-75.

(566) Rachlis BS, Mills EJ, Cole DC. Livelihood security and adherence to antiretroviral therapy in low and middle income settings: a systematic review. PLoS One 2011;6(5):e18948.

(567) Nakimuli-Mpungu E, Bass JK, Alexandre P, Mills EJ, Musisi S, Ram M, et al. Depression, alcohol use and adherence to antiretroviral therapy in sub-Saharan Africa: a systematic review. AIDS Behav 2012 Nov;16(8):2101-18.

(568) Renaud-Théry F, Duncombe C, Kerr S, Thierry S, Perriens J. Adult antiretroviral therapy in resource limited settings: a systematic review of first-line failure and attrition rates. WHO 2013 [cited 2014 Mar 26];Available from: URL: http://www.who.int/hiv/topics/treatment/First_Line_ART_failure_RLS_metanalysis.pdf

(569) Sigaloff KC, Hamers RL, Wallis CL, Kityo C, Siwale M, Ive P, et al. Second-line antiretroviral treatment successfully resuppresses drug-resistant HIV-1 after first-line failure: prospective cohort in Sub-Saharan Africa. J Infect Dis 2012 Jun;205(11):1739-44.

(570) Phillips AN, Sabin C, Pillay D, Lundgren JD. HIV in the UK 1980-2006: reconstruction using a model of HIV infection and the effect of antiretroviral therapy. HIV Med 2007 Nov;8(8):536-46.

(571) Phillips AN, Pillay D, Garnett G, Bennett D, Vitoria M, Cambiano V, et al. Effect on transmission of HIV-1 resistance of timing of implementation of viral load monitoring to determine switches from first to second-line antiretroviral regimens in resource-limited settings. AIDS 2011;25(6):843-50.

(572) Cambiano V, Bertagnolio S, Jordan MR, Lundgren JD, Phillips A. Transmission of drug resistant HIV and its potential impact on mortality and treatment outcomes in resource-limited settings. J Infect Dis 2013 Jun 15;207 Suppl 2:S57-S62.

(573) Cambiano V, Bertagnolio S, Jordan MR, Pillay D, Perriens JH, Venter F, et al. Predicted levels of HIV drug resistance: potential impact of expanding diagnosis, retention, and eligibility criteria for antiretroviral therapy initiation. AIDS 2014 Jan;28 Suppl 1:S15-S23.

(574) Bansi L, Sabin C, Delpech V, Hill T, Fisher M, Walsh J, et al. Trends over calendar time in antiretroviral treatment success and failure in HIV clinic populations. HIV Med 2010 Aug;11(7):432-8.

(575) Nakagawa F, Lodwick RK, Smith CJ, Smith R, Cambiano V, Lundgren JD, et al. Projected life expectancy of people with HIV according to timing of diagnosis. AIDS 2012 Jan 28;26(3):335-43.

(576) Statistics South Africa. The people of South Africa population census, 1996. Statistics South Africa 1996 [cited 2012 Apr 24];Available from: URL: http://www.statssa.gov.za/census01/Census96/HTML/CIB/CIB1996.pdf

(577) AFRAN Study and Research Institute. Zimbabwe Population Pyramid for 1990. US Census Bureau July 17, 2003 2014 [cited 2014 Apr 16];Available from: URL: http://www.afran.info/modules/publisher/item.php?itemid=66

(578) Statistics South Africa. Census 2001: Achieving a better life for all: Progress between Census '96 and Census 2001. Statistics South Africa 2005 [cited 2011 Oct 27];Available from: URL: http://www.statssa.gov.za/Publications/Report-03-02-16/Report-03-02-16.pdf

(579) Zimbabwe Central Statistics Office. Zimbabwe 1982: Population Census: Main Demographic Features. Harare, Zimbabwe: Zimbabwe Central Statistics Office; 1985.

(580) Statistics South Africa. Census 2001: Primary tables South Africa: Census '96 and 2001 compared. Statistics South Africa 2004 [cited 2014 Mar 30];Available from: URL: http://www.statssa.gov.za/census01/html/RSAPrimary.pdf

(581) Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. Lancet 1998;351 Suppl 3:5-7.

(582) Yang RR, Gui X, Benoit JL, Xiong Y. The comparison of human immunodeficiency virus type 1 transmission between couples through blood or sex in central China. Jpn J Infect Dis 2010 Jul;63(4):283-5.

(583) Nicolosi A, Correa Leite ML, Musicco M, Arici C, Gavazzeni G, Lazzarin A. The efficiency of male-to-female and female-to-male sexual transmission of the human immunodeficiency virus: a study of 730 stable couples. Italian Study Group on HIV Heterosexual Transmission. Epidemiology 1994 Nov;5(6):570-5.

(584) Stekler J, Payant R, Beck I, Maust B, Holte S, Maenza J, et al. Transmitted HIV-1 Drug Resistance Between Partner-Pairs. 2014 Mar 4; 2014.

(585) Wainberg MA, Moisi D, Oliveira M, Toni TD, Brenner BG. Transmission dynamics of the M184V drug resistance mutation in primary HIV infection. J Antimicrob Chemother 2011 Oct;66(10):2346-9.

(586) Corvasce S, Violin M, Romano L, Razzolini F, Vicenti I, Galli A, et al. Evidence of differential selection of HIV-1 variants carrying drug-resistant mutations in seroconverters. Antivir Ther 2006;11(3):329-34.

(587) Powers KA, Ghani AC, Miller WC, Hoffman IF, Pettifor AE, Kamanga G, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. Lancet 2011 Jul 16;378(9787):256-68.

(588) Dunkle KL, Stephenson R, Karita E, Chomba E, Kayitenkore K, Vwalika C, et al. New heterosexually transmitted HIV infections in married or cohabiting couples in urban Zambia and Rwanda: an analysis of survey and clinical data. Lancet 2008 Jun 28;371(9631):2183-91.

(589) Phillips AN, Pillay D, Miners AH, Bennett DE, Gilks CF, Lundgren JD. Outcomes from monitoring of patients on antiretroviral therapy in resource-limited settings with viral load, CD4 cell count, or clinical observation alone: a computer simulation model. Lancet 2008 Apr;371(9622):1443-51.

(590) Koot M, Keet IP, Vos AH, de Goede RE, Roos MT, Coutinho RA, et al. Prognostic value of HIV-1 syncytium-inducing phenotype for rate of CD4+ cell depletion and progression to AIDS. Ann Intern Med 1993 May 1;118(9):681-8.

(591) Pantazis N, Touloumi G. Bivariate modelling of longitudinal measurements of two human immunodeficiency type 1 disease progression markers in the presence of informative drop-outs. Journal of the Royal Statistical Society Series C-Applied Statistics 2005;54:405-23.

(592) Hubert JB, Burgard M, Dussaix E, Tamalet C, Deveau C, Le CJ, et al. Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection. The SEROCO Study Group. AIDS 2000 Jan 28;14(2):123-31.

(593) Henrard DR, Phillips JF, Muenz LR, Blattner WA, Wiesner D, Eyster ME, et al. Natural history of HIV-1 cell-free viremia. JAMA 1995 Aug 16;274(7):554-8.

(594) Lyles RH, Munoz A, Yamashita TE, Bazmi H, Detels R, Rinaldo CR, et al. Natural history of human immunodeficiency virus type 1 viremia after seroconversion and

proximal to AIDS in a large cohort of homosexual men. Multicenter AIDS Cohort Study. J Infect Dis 2000 Mar;181(3):872-80.

(595) Statistics SouthAfrica. Estimation of fertility from the 2007 Community Survey of South Africa. Statistics SouthAfrica 2010Available from: URL: http://www.statssa.gov.za/Publications/Report-03-00-04/Report-03-00-042010.pdf

(596) UNAIDS. Together we will end AIDS. UNAIDS 2012 July [cited 2012 Sep 19];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/20120718_togetherwewillendaids_en.pdf

(597) Hoffmann CJ, Charalambous S, Sim J, Ledwaba J, Schwikkard G, Chaisson RE, et al. Viremia, resuppression, and time to resistance in human immunodeficiency virus (HIV) subtype C during first-line antiretroviral therapy in South Africa. Clin Infect Dis 2009 Dec 15;49(12):1928-35.

(598) Wallis CL, Mellors JW, Venter WD, Sanne I, Stevens W. Varied patterns of HIV-1 drug resistance on failing first-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr 2010 Apr 1;53(4):480-4.

(599) Mackie NE, Phillips AN, Kaye S, Booth C, Geretti AM. Antiretroviral drug resistance in HIV-1-infected patients with low-level viremia. J Infect Dis 2010 May 1;201(9):1303-7.

(600) Cheeseman SH, Hattox SE, McLaughlin MM, Koup RA, Andrews C, Bova CA, et al. Pharmacokinetics of nevirapine: initial single-rising-dose study in humans. Antimicrob Agents Chemother 1993 Feb;37(2):178-82.

(601) Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J, et al. Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. AIDS 2010 Sep 10;24(14):2263-70.

(602) Mabugu T. Proportion on second line ART regimen in Zimbabwe. 2013.
Ref Type: Personal Communication

(603) Anaky MF, Duvignac J, Wemin L, Kouakoussui A, Karcher S, Toure S, et al. Scaling up antiretroviral therapy for HIV-infected children in Cote d'Ivoire: determinants of survival and loss to programme. Bull World Health Organ 2010 Jul 1;88(7):490-9.

(604) Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, et al. Early loss to follow up after enrolment in pre-ART care at a large public clinic in Johannesburg, South Africa. Trop Med Int Health 2010 Jun;15 Suppl 1:43-7.

(605) Charurat M, Oyegunle M, Benjamin R, Habib A, Eze E, Ele P, et al. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors. PLoS One 2010;5(5):e10584.

(606) Lampe FC, Gatell JM, Staszewski S, Johnson MA, Pradier C, Gill MJ, et al. Changes over time in risk of initial virological failure of combination antiretroviral therapy: a multicohort analysis, 1996 to 2002. Arch Intern Med 2006 Mar 13;166(5):521-8.

(607) Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet 1999 Mar 13;353(9156):863-8.

(608) Staszewski S, Miller V, Sabin C, Schlecht C, Gute P, Stamm S, et al. Determinants of sustainable CD4 lymphocyte count increases in response to antiretroviral therapy. AIDS 1999 May 28;13(8):951-6.

(609) Staszewski S, Miller V, Sabin C, Carlebach A, Berger AM, Weidmann E, et al. Virological response to protease inhibitor therapy in an HIV clinic cohort. AIDS 1999 Feb 25;13(3):367-73.

(610) Gallant JE, Staszewski S, Pozniak AL, Dejesus E, Suleiman JMAH, Miller MD, et al. Efficacy and safety of tenofovir DF vs stavuldine in combination therapy in antiretroviral-naive patients - A 3-year randomized trial. Jama-Journal of the American Medical Association 2004 Jul 14;292(2):191-201.

(611) Harrigan PR, Hogg RS, Dong WW, Yip B, Wynhoven B, Woodward J, et al. Predictors of HIV drug-resistance mutations in a large antiretroviral-naive cohort initiating triple antiretroviral therapy. J Infect Dis 2005 Feb 1;191(3):339-47.

(612) Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV viral load response to antiretroviral therapy according to the baseline CD4 cell count and viral load. JAMA 2001 Nov 28;286(20):2560-7.

(613) Johannessen A, Naman E, Kivuyo SL, Kasubi MJ, Holberg-Petersen M, Matee MI, et al. Virological efficacy and emergence of drug resistance in adults on antiretroviral treatment in rural Tanzania. BMC Infect Dis 2009;9:108.

(614) Phillips AN, Dunn D, Sabin C, Pozniak A, Matthias R, Geretti AM, et al. Long term probability of detection of HIV-1 drug resistance after starting antiretroviral therapy in routine clinical practice. AIDS 2005 Mar 25;19(5):487-94.

(615) Mocroft A, Phillips AN, Gatell J, Ledergerber B, Fisher M, Clumeck N, et al. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. Lancet 2007 Aug 4;370(9585):407-13.

(616) Fischer M, Hafner R, Schneider C, Trkola A, Joos B, Joller H, et al. HIV RNA in plasma rebounds within days during structured treatment interruptions. AIDS 2003 Jan 24;17(2):195-9.

(617) Li X, Margolick JB, Conover CS, Badri S, Riddler SA, Witt MD, et al. Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr 2005 Mar 1;38(3):320-8.

(618) Thiebaut R, Pellegrin I, Chene G, Viallard JF, Fleury H, Moreau JF, et al. Immunological markers after long-term treatment interruption in chronically HIV-1 infected patients with CD4 cell count above 400 x 10(6) cells/l. AIDS 2005 Jan 3;19(1):53-61.

(619) Tebas P, Henry K, Mondy K, Deeks S, Valdez H, Cohen C, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4+ T cell decline in

human immunodeficiency virus-infected patients: implications for intermittent therapeutic strategies. J Infect Dis 2002 Sep 15;186(6):851-4.

(620) Wit FW, Blanckenberg DH, Brinkman K, Prins JM, van der Ende ME, Schneider MM, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. AIDS 2005 Feb 18;19(3):345-8.

(621) Youle M, Janossy G, Turnbull W, Tilling R, Loveday C, Mocroft A, et al. Changes in CD4 lymphocyte counts after interruption of therapy in patients with viral failure on protease inhibitor-containing regimens. Royal Free Centre for HIV Medicine. AIDS 2000 Aug 18;14(12):1717-20.

(622) Skiest DJ, Morrow P, Allen B, McKinsey J, Crosby C, Foster B, et al. It is safe to stop antiretroviral therapy in patients with preantiretroviral CD4 cell counts >250 cells/microL. J Acquir Immune Defic Syndr 2004 Nov 1;37(3):1351-7.

(623) d'Arminio MA, Cozzi-Lepri A, Phillips A, De LA, Murri R, Mussini C, et al. Interruption of highly active antiretroviral therapy in HIV clinical practice: results from the Italian Cohort of Antiretroviral-Naive Patients. J Acquir Immune Defic Syndr 2005 Apr 1;38(4):407-16.

(624) Boschi A, Tinelli C, Ortolani P, Moscatelli G, Morigi G, Arlotti M. CD4+ cell-count-guided treatment interruptions in chronic HIV-infected patients with good response to highly active antiretroviral therapy. AIDS 2004 Dec 3;18(18):2381-9.

(625) Achenbach CJ, Till M, Palella FJ, Knoll MD, Terp SM, Kalnins AU, et al. Extended antiretroviral treatment interruption in HIV-infected patients with long-term suppression of plasma HIV RNA. HIV Med 2005 Jan;6(1):7-12.

(626) Johnson VA, Calvez V, Gunthard HF, Paredes R, Pillay D, Shafer RW, et al. Update of the drug resistance mutations in HIV-1: March 2013. Top Antivir Med 2013 Feb;21(1):6-14.

(627) Sigaloff KC, Ramatsebe T, Viana R, de Wit TF, Wallis CL, Stevens WS. Accumulation of HIV drug resistance mutations in patients failing first-line antiretroviral treatment in South Africa. AIDS Res Hum Retroviruses 2012 Feb;28(2):171-5.

(628) Rawizza HE, Chaplin B, Meloni ST, Darin KM, Olaitan O, Scarsi KK, et al. Accumulation of protease mutations among patients failing second-line antiretroviral therapy and response to salvage therapy in Nigeria. PLoS One 2013;8(9):e73582.

(629) Levison JH, Orrell C, Gallien S, Kuritzkes DR, Fu N, Losina E, et al. Virologic failure of protease inhibitor-based second-line antiretroviral therapy without resistance in a large HIV treatment program in South Africa. PLoS One 2012;7(3):e32144.

(630) Arrive E, Newell ML, Ekouevi DK, Chaix ML, Thiebaut R, Masquelier B, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. International Journal of Epidemiology 2007 Oct;36(5):1009-21.

(631) Hauser A, Mugenyi K, Kabasinguzi R, Kuecherer C, Harms G, Kunz A. Emergence and persistence of minor drug-resistant HIV-1 variants in Ugandan women after nevirapine single-dose prophylaxis. PLoS One 2011;6(5):e20357.

(632) Tarwater PM, Parish M, Gallant JE. Prolonged treatment interruption after immunologic response to highly active antiretroviral therapy. Clin Infect Dis 2003 Dec 1;37(11):1541-8.

(633) Deeks SG, Grant RM, Wrin T, Paxinos EE, Liegler T, Hoh R, et al. Persistence of drug-resistant HIV-1 after a structured treatment interruption and its impact on treatment response. AIDS 2003 Feb 14;17(3):361-70.

(634) Birk M, Svedhem V, Sonnerborg A. Kinetics of HIV-1 RNA and resistance-associated mutations after cessation of antiretroviral combination therapy. AIDS 2001 Jul 27;15(11):1359-68.

(635) Hance AJ, Lemiale V, Izopet J, Lecossier D, Joly V, Massip P, et al. Changes in human immunodeficiency virus type 1 populations after treatment interruption in patients failing antiretroviral therapy. J Virol 2001 Jul;75(14):6410-7.

(636) Walter H, Low P, Harrer T, Schmitt M, Schwingel E, Tschochner M, et al. No evidence for persistence of multidrug-resistant viral strains after a 7-month treatment interruption in an HIV-1-infected individual. J Acquir Immune Defic Syndr 2002 Oct 1;31(2):137-46.

(637) Liu H, Miller LG, Hays RD, Golin CE, Wu T, Wenger NS, et al. Repeated measures longitudinal analyses of HIV virologic response as a function of percent adherence, dose timing, genotypic sensitivity, and other factors. J Acquir Immune Defic Syndr 2006 Mar;41(3):315-22.

(638) Liu TF, Shafer RW. Web resources for HIV type 1 genotypic-resistance test interpretation. Clin Infect Dis 2006 Jun 1;42(11):1608-18.

(639) Meynard JL, Vray M, Morand-Joubert L, Race E, Descamps D, Peytavin G, et al. Phenotypic or genotypic resistance testing for choosing antiretroviral therapy after treatment failure: a randomized trial. AIDS 2002 Mar 29;16(5):727-36.

(640) Van LK, De LA, Antinori A, Cingolani A, Perna CF, Vandamme AM. A genotypic drug resistance interpretation algorithm that significantly predicts therapy response in HIV-1-infected patients. Antivir Ther 2002 Jun;7(2):123-9.

(641) Clumeck N, Rieger A, Banhegyi D, Schmidt W, Hill A, van DY, et al. 96 week results from the MONET trial: a randomized comparison of darunavir/ritonavir with versus without nucleoside analogues, for patients with HIV RNA <50 copies/mL at baseline. J Antimicrob Chemother 2011 Aug;66(8):1878-85.

(642) Valantin MA, Lambert-Niclot S, Flandre P, Morand-Joubert L, Cabie A, Meynard JL, et al. Long-term efficacy of darunavir/ritonavir monotherapy in patients with HIV-1 viral suppression: week 96 results from the MONOI ANRS 136 study. J Antimicrob Chemother 2012 Mar;67(3):691-5.

(643) Bygrave H, Ford N, Van CG, Hilderbrand K, Jouquet G, Goemaere E, et al. Implementing a tenofovir-based first-line regimen in rural Lesotho: clinical outcomes and toxicities after two years. J Acquir Immune Defic Syndr 2011 Mar 1;56(3):e75-e78.

(644) Calmy A, Hirschel B, Cooper DA, Carr A. A new era of antiretroviral drug toxicity. Antivir Ther 2009;14(2):165-79.

(645) Boulle A, Orrel C, Kaplan R, Van CG, McNally M, Hilderbrand K, et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. Antivir Ther 2007;12(5):753-60.

(646) Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. BMC Infect Dis 2011;11:244.

(647) Zhou J, Jaquet A, Bissagnene E, Musick B, Wools-Kaloustian K, Maxwell N, et al. Short-term risk of anaemia following initiation of combination antiretroviral treatment in HIV-infected patients in countries in sub-Saharan Africa, Asia-Pacific, and central and South America. J Int AIDS Soc 2012;15(1):5.

(648) Ssali F, Stohr W, Munderi P, Reid A, Walker AS, Gibb DM, et al. Prevalence, incidence and predictors of severe anaemia with zidovudine-containing regimens in African adults with HIV infection within the DART trial. Antivir Ther 2006;11(6):741-9.

(649) UK Collaborative Group on HIV Drug Resistance, UK CHIC study group. Long-term probability of detecting drug-resistant HIV in treatment-naive patients initiating combination antiretroviral therapy. Clinical Infectious Diseases 2010;50(9):1275-85.

(650) Mallolas J, Zamora L, Gatell JM, Miro JM, Vernet E, Valls ME, et al. Primary prophylaxis for Pneumocystis carinii pneumonia: a randomized trial comparing cotrimoxazole, aerosolized pentamidine and dapsone plus pyrimethamine. AIDS 1993 Jan;7(1):59-64.

(651) Phillips AN, Elford J, Sabin C, Bofill M, Janossy G, Lee CA. Immunodeficiency and the risk of death in HIV infection. JAMA 1992 Nov 18;268(19):2662-6.

(652) Touloumi G, Karafoulidou A, Gialeraki A, Katsarou O, Milona I, Kapsimali V, et al. Determinants of progression of HIV infection in a Greek hemophilia cohort followed for up to 16 years after seroconversion. J Acquir Immune Defic Syndr Hum Retrovirol 1998 Sep 1;19(1):89-97.

(653) Lundgren JD, Pedersen C, Clumeck N, Gatell JM, Johnson AM, Ledergerber B, et al. Survival differences in European patients with AIDS, 1979-89. The AIDS in Europe Study Group. BMJ 1994 Apr 23;308(6936):1068-73.

(654) Beaumont MA, Zhang W, Balding DJ. Approximate Bayesian computation in population genetics. Genetics 2002 Dec;162(4):2025-35.

(655) Adam MA, Johnson LF. Estimation of adult antiretroviral treatment coverage in South Africa. Samj South African Medical Journal 2009;99(9):661-7.

(656) HIV Modelling Consortium. Coordinating Research activities in mathematical modelling. HIV Modelling Consortium 2014 [cited 2014 Apr 18];Available from: URL: http://www.hivmodelling.org/

(657) Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. Lancet 2002 Jul 13;360(9327):119-29.

(658) May MT, Sterne JA, Costagliola D, Sabin CA, Phillips AN, Justice AC, et al. HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. Lancet 2006 Aug 5;368(9534):451-8.

(659) Del Romero J, Castilla J, Hernando V, Rodriguez C, Garcia S. Combined antiretroviral treatment and heterosexual transmission of HIV-1: cross sectional and prospective cohort study. British Medical Journal 2010;340:c2205.

(660) Vernazza P, Hirschel B, Bernasconi E, Flepp M. Les personnes seropositives ne souffrant d'aucune autre MST et suivant untraitment antiretroviral efficace ne transmettent pas le VIH par voiesexuelle. Bulletin des Médecins Suisses 2008;89:165-9.

(661) European Centre for Disease Prevention and Control. Evaluating HIV treatment as prevention in the European context. European Centre for Disease Prevention and Control 2012 June [cited 2013 Nov 19];Available from: URL: http://ecdc.europa.eu/en/publications/publications/hiv-treatment-as-prevention.pdf

(662) Cambiano V, Connor O, Phillips A, Rodger A, Lodwick R, Pharris A, et al. Antiretroviral therapy for prevention of HIV transmission: implications for Europe. Euro Surveill 2013;18(48).

(663) Tovanabutra S, Robison V, Wongtrakul J, Sennum S, Suriyanon V, Kingkeow D, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. J Acquir Immune Defic Syndr 2002 Mar 1;29(3):275-83.

(664) Melo MG, Santos BR, De Cassia LR, Varella IS, Turella ML, Rocha TM, et al. Sexual transmission of HIV-1 among serodiscordant couples in Porto Alegre, southern Brazil. Sex Transm Dis 2008 Nov;35(11):912-5.

(665) Reynolds SJ, Makumbi F, Nakigozi G, Kagaayi J, Gray RH, Wawer M, et al. HIV-1 transmission among HIV-1 discordant couples before and after the introduction of antiretroviral therapy. AIDS 2011 Feb 20;25(4):473-7.

(666) Sullivan P, Kayitenkore K, Chomba E, Karita E, Mwananyanda L, Vwalika C, et al. Is the reduction of HIV transmission risk while prescribed antiretroviral therapy (ARVT) different for men and women? Results from discordant couples in Rwanda and Zambia. 2009; Cape Town, South Africa 2009.

(667) Jia Z, Mao Y, Zhang F, Ruan Y, Ma Y, Li J, et al. Antiretroviral therapy to prevent HIV transmission in serodiscordant couples in China (2003-11): a national observational cohort study. Lancet 2013;382(9899):1195-203.

(668) Birungi J, Wang H, Ngolobe M, Muldoon K, Khanakwa S, King R, et al. Lack of effectiveness of antiretroviral therapy (ART) as an HIV prevention tool for serodiscordant couples in a rural ART program without viral load monitoring in Uganda. Journal of the International Aids Society 2012;15:144-5.

(669) Wang L, Ge Z, Luo J, Shan D, Gao X, Ding GW, et al. HIV Transmission Risk Among Serodiscordant Couples: A Retrospective Study of Former Plasma Donors in Henan, China. Jaids-Journal of Acquired Immune Deficiency Syndromes 2010;55(2):232-8.

(670) Tanser F, Barnighausen T, Grapsa E, Zaidi J, Newell ML. High coverage of ART associated with decline in risk of HIV acquisition in rural KwaZulu-Natal, South Africa. Science 2013 Feb 22;339(6122):966-71.

(671) Anglemyer A, Rutherford G, Baggaley R, Egger M, Siegfried N. Antiretroviral therapy for prevention of HIV transmission in HIV-discordant couples: a systematic review of the observational literature. Journal of the International Aids Society 2012;15:145-6.

(672) Anglemyer A, Horvath T, Rutherford G. Antiretroviral Therapy for Prevention of HIV Transmission in HIV-Discordant Couples. Jama-Journal of the American Medical Association 2013;310(15):1619-20.

(673) Baggaley RF, White RG, Hollingsworth TD, Boily MC. Heterosexual HIV-1 infectiousness and antiretroviral use: systematic review of prospective studies of discordant couples. Epidemiology 2013 Jan;24(1):110-21.

(674) Loutfy MR, Wu W, Letchumanan M, Bondy L, Antoniou T, Margolese S, et al. Systematic Review of HIV Transmission between Heterosexual Serodiscordant Couples where the HIV-Positive Partner Is Fully Suppressed on Antiretroviral Therapy. PLoS One 2013;8(2).

(675) Das M, Chu PL, Santos GM, Scheer S, Vittinghoff E, McFarland W, et al. Decreases in community viral load are accompanied by reductions in new HIV infections in San Francisco. PLoS One 2010;5(6).

(676) Fang CT, Hsu HM, Twu SJ, Chen MY, Chang YY, Hwang JS, et al. Decreased HIV transmission after a policy of providing free access to highly active antiretroviral therapy in Taiwan. J Infect Dis 2004 Sep 1;190(5):879-85.

(677) Montaner JS, Lima VD, Barrios R, Yip B, Wood E, Kerr T, et al. Association of highly active antiretroviral therapy coverage, population viral load, and yearly new HIV diagnoses in British Columbia, Canada: a population-based study. The Lancet 2010 Aug 14;376(9740):532-9.

(678) Fisher M, Pao D, Murphy G, Dean G, McElborough D, Homer G, et al. Serological testing algorithm shows rising HIV incidence in a UK cohort of men who have sex with men: 10 years application. AIDS 2007 Nov 12;21(17):2309-14.

(679) Dukers NH, Spaargaren J, Geskus RB, Beijnen J, Coutinho RA, Fennema HS. HIV incidence on the increase among homosexual men attending an Amsterdam sexually transmitted disease clinic: using a novel approach for detecting recent infections. AIDS 2002 Jul 5;16(10):F19-F24.

(680) Grulich AE, Kaldor JM. Trends in HIV incidence in homosexual men in developed countries. Sex Health 2008 Jun;5(2):113-8.

(681) Ping LH, Jabara CB, Rodrigo AG, Hudelson SE, Piwowar-Manning E, Wang L, et al. HIV-1 Transmission during Early Antiretroviral Therapy: Evaluation of Two HIV-1 Transmission Events in the HPTN 052 Prevention Study. PLoS One 2013;8(9):e71557.

(682) Muessig KE, Smith MK, Powers KA, Lo YR, Burns DN, Grulich AE, et al. Does ART prevent HIV transmission among MSM? AIDS 2012 Nov 28;26(18):2267-73.

(683) Wilson DP, Jin FY, Jansson J, Zablotska I, Grulich AE. Infectiousness of HIV-infected men who have sex with men in the era of highly active antiretroviral therapy. AIDS 2010 Sep 24;24(15):2420-1.

(684) Rodger A, Bruun T, Weait M, Vernazza P, Collins S, Estrada V, et al. Partners of people on ART - a New Evaluation of the Risks (The PARTNER study): design and methods. BMC Public Health 2012;12.

(685) Eaton JW, Johnson LF, Salomon JA, Baernighausen T, Bendavid E, Bershteyn A, et al. HIV Treatment as Prevention: Systematic Comparison of Mathematical Models of the Potential Impact of Antiretroviral Therapy on HIV Incidence in South Africa. Plos Medicine 2012;9(7).

(686) Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. Lancet 2009 Jan 3;373(9657):48-57.

(687) Abbas UL, Anderson RM, Mellors JW. Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings. Jaids-Journal of Acquired Immune Deficiency Syndromes 2006;41(5):632-41.

(688) Baggaley RF, Garnett GP, Ferguson NM. Modelling the impact of antiretroviral use in resource-poor settings. PLoS Med 2006 Apr;3(4):e124.

(689) Bendavid E, Brandeau ML, Wood R, Owens DK. Comparative Effectiveness of HIV Testing and Treatment in Highly Endemic Regions. Archives of Internal Medicine 2010;170(15):1347-54.

(690) Andrews JR, Wood R, Bekker LG, Middelkoop K, Walensky RP. Projecting the benefits of antiretroviral therapy for HIV prevention: the impact of population mobility and linkage to care. J Infect Dis 2012 Aug 15;206(4):543-51.

(691) Granich R, Kahn JG, Bennett R, Holmes CB, Garg N, Serenata C, et al. Expanding ART for Treatment and Prevention of HIV in South Africa: Estimated Cost and Cost-Effectiveness 2011-2050. PLoS One 2012;7(2).

(692) Eaton JW, Menzies NA, Stover J, Cambiano V, Chindelevitch L, Cori A, et al. Health benefits, costs, and cost-effectiveness of earlier eligibility for adult antiretroviral therapy and expanded treatment coverage: a combined analysis of 12 mathematical models. Lancet Global Health 2014 Jan;2(1):e23-e34.

(693) Wilson DP, Law MG, Grulich AE, Cooper DA, Kaldor JM. Relation between HIV viral load and infectiousness: a model-based analysis (vol 372, pg 314, 2008). Lancet 2008;372(9652):314-20.

(694) Anglaret X, Scott CA, Walensky RP, Ouattara E, Losina E, Moh R, et al. Could early antiretroviral therapy entail more risks than benefits in sub-Saharan African HIV-infected adults? A model-based analysis. Antiviral Therapy 2013;18(1):45-55.

(695) Kretzschmar ME, van der Loeff MF, Birrell PJ, De Angelis D, Coutinho RA. Prospects of elimination of HIV with test-and-treat strategy. Proceedings of the National Academy of Sciences of the United States of America 2013;110(39):15538-43.

(696) Hontelez JA, Lurie MN, Barnighausen T, Bakker R, Baltussen R, Tanser F, et al. Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. PLoS Med 2013 Oct;10(10):e1001534.

(697) Palombi L, Bernava GM, Nucita A, Giglio P, Liotta G, Nielsen-Saines K, et al. Predicting Trends in HIV-1 Sexual Transmission in Sub-Saharan Africa Through the Drug Resource Enhancement Against AIDS and Malnutrition Model: Antiretrovirals for Reduction of Population Infectivity, Incidence and Prevalence at the District Level. Clinical Infectious Diseases 2012;55(2):268-75.

(698) Klein DJ, Bershteyn A, Eckhoff PA. Dropout and re-enrollment: implications for epidemiological projections of treatment programs. AIDS 2014 Jan;28 Suppl 1:S47-S59.

(699) Wagner BG, Blower S. Universal Access to HIV Treatment versus Universal 'Test and Treat': Transmission, Drug Resistance & Treatment Costs. PLoS One 2012 Sep 5;7(9).

(700) Johnson LF, Hallett TB, Rehle TM, Dorrington RE. The effect of changes in condom usage and antiretroviral treatment coverage on human immunodeficiency virus incidence in South Africa: a model-based analysis. Journal of the Royal Society Interface 2012;9(72):1544-54.

(701) Yusuf TT, Benyah F. Optimal strategy for controlling the spread of HIV/AIDS disease: a case study of South Africa. Journal of Biological Dynamics 2012;6(2):475-94.

(702) Alsallaq RA, Baeten JM, Celum CL, Hughes JP, Abu-Raddad LJ, Barnabas RV, et al. Understanding the Potential Impact of a Combination HIV Prevention Intervention in a Hyper-Endemic Community. PLoS One 2013;8(1).

(703) Cremin I, Alsallaq R, Dybul M, Piot P, Garnett G, Hallett TB. The new role of antiretrovirals in combination HIV prevention: a mathematical modelling analysis. AIDS 2013 Jan 28;27(3):447-58.

(704) Baernighausen T, Bloom DE, Humair S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. Proceedings of the National Academy of Sciences of the United States of America 2012;109(52):21271-6.

(705) Hallett TB, Baeten JM, Heffron R, Barnabas R, de BG, Cremin I, et al. Optimal uses of antiretrovirals for prevention in HIV-1 serodiscordant heterosexual couples in South Africa: a modelling study. PLoS Med 2011 Nov;8(11):e1001123.

(706) Alistar SS, Grant PM, Bendavid E. Comparative effectiveness and cost-effectiveness of antiretroviral therapy and pre-exposure prophylaxis for HIV prevention in South Africa. BMC Med 2014;12:46.

(707) Murnane PM, Hughes JP, Celum C, Lingappa JR, Mugo N, Farquhar C, et al. Using Plasma Viral Load to Guide Antiretroviral Therapy Initiation to Prevent HIV-1 Transmission. PLoS One 2012;7(11).

(708) Walensky RP, Ross EL, Kumarasamy N, Wood R, Noubary F, Paltiel AD, et al. Cost-effectiveness of HIV treatment as prevention in serodiscordant couples. The New England journal of medicine 2013;369(18):1715-25.

(709) El-Sadr WM, Coburn BJ, Blower S. Modeling the impact on the HIV epidemic of treating discordant couples with antiretrovirals to prevent transmission. AIDS 2011 Nov 28;25(18):2295-9.

(710) Sabin CA, Cooper DA, Collins S, Schechter M. Rating evidence in treatment guidelines: a case example of when to initiate combination antiretroviral therapy (cART) in HIV-positive asymptomatic persons. AIDS 2013 Jul 31;27(12):1839-46.

(711) Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, Eron J, Chen YQ, et al. Effects of early versus delayed initiation of antiretroviral treatment on clinical outcomes of HIV-1 infection: results from the phase 3 HPTN 052 randomised controlled trial. Lancet Infect Dis 2014 Apr;14(4):281-90.

(712) Emery S, Neuhaus JA, Phillips AN, Babiker A, Cohen CJ, Gatell JM, et al. Major clinical outcomes in antiretroviral therapy (ART)-naive participants and in those not receiving ART at baseline in the SMART study. J Infect Dis 2008 Apr 15;197(8):1133-44.

(713) Cohen MS, Smith MK, Muessig KE, Hallett TB, Powers KA, Kashuba AD. Antiretroviral treatment of HIV-1 prevents transmission of HIV-1: where do we go from here? Lancet 2013 Nov 2;382(9903):1515-24.

(714) El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, et al. CD4+ count-guided interruption of antiretroviral treatment. N Engl J Med 2006 Nov 30;355(22):2283-96.

(715) WHO. Guidance on couples HIV testing and counselling, including antiretroviral therapy for treatment and prevention in serodiscordant couples. Recommendations for a public health approach. WHO 2012 [cited 2012 Apr 20];Available from: URL: http://www.who.int/hiv/pub/guidelines/9789241501972/en/index.html

(716) HIV Prevention Trials Network. Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART). HIV Prevention Trials Network 2013 July 26 [cited 2013 Nov 19];Available from: URL: http://www.clinicaltrials.gov/ct2/show/NCT01900977

(717) Impact of Immediate Versus WHO Recommendations Guided ART Initiation on HIV Incidence - Feasibility Phase (TasP). French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis (Inserm-ANRS) 2013 July 16 [cited 2013 Nov 19];Available from: URL: http://www.clinicaltrials.gov/ct2/show/NCT01509508?term=Tasp&rank=1

(718) An HIV Prevention Program for Mochudi, Botswana. http://www labome org/grant/r01/ai/an/hiv/an-hiv-prevention-program-for-mochudi--botswana-7680502 html 2012 [cited 2012 Apr 16];Available from: URL: http://www.labome.org/grant/r01/ai/an/hiv/an-hiv-prevention-program-for-mochudi--botswana-7680502.html

(719) WHO, UNAIDS, UNICEF. Global update on HIV treatment 2013: results, impact and opportunities. WHO 2013 June [cited 2013 Dec 21];Available from: URL: http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf

(720) May M, Boulle A, Phiri S, Messou E, Myer L, Wood R, et al. Prognosis of patients with HIV-1 infection starting antiretroviral therapy in sub-Saharan Africa: a collaborative analysis of scale-up programmes. Lancet 2010 Aug 7;376(9739):449-57.

(721) Drain PK, Losina E, Parker G, Giddy J, Ross D, Katz JN, et al. Risk factors for late-stage HIV disease presentation at initial HIV diagnosis in Durban, South Africa. PLoS One 2013;8(1):e55305.

(722) Bongaarts J, Over M. Public health. Global HIV/AIDS policy in transition. Science 2010 Jun 11;328(5984):1359-60.

(723) Garnett GP, Cousens S, Hallett TB, Steketee R, Walker N. Mathematical models in the evaluation of health programmes. Lancet 2011 Aug 6;378(9790):515-25.

(724) Hecht R, Stover J, Bollinger L, Muhib F, Case K, de FD. Financing of HIV/AIDS programme scale-up in low-income and middle-income countries, 2009-31. Lancet 2010 Oct 9;376(9748):1254-60.

(725) Schwartlander B, Stover J, Hallett T, Atun R, Avila C, Gouws E, et al. Towards an improved investment approach for an effective response to HIV/AIDS. Lancet 2011 Jun 11;377(9782):2031-41.

(726) Blower S, Bodine E, Kahn J, McFarland W. The antiretroviral rollout and drug-resistant HIV in Africa: insights from empirical data and theoretical models. AIDS 2005 Jan 3;19(1):1-14.

(727) Salomon JA, Hogan DR. Evaluating the impact of antiretroviral therapy on HIV transmission. AIDS 2008 Jul;22 Suppl 1:S149-S159.

(728) Williams BG, Granich R, De Cock KM, Glaziou P, Sharma A, Dye C. Antiretroviral therapy for tuberculosis control in nine African countries. Proc Natl Acad Sci U S A 2010 Nov 9;107(45):19485-9.

(729) Edejer T-T, Baltussen R, Hutubessy HR, Acharya A, Evans DB, Murray CJL. Making Choices In Health: Who Guide To Cost Effectiveness Analysis. WHO 2003 [cited 2013 Oct 15];Available from: URL: http://www.who.int/choice/publications/p_2003_generalised_cea.pdf

(730) Drummond MF. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press; 2005.

(731) The World Bank. World Development Indicators 2012. The World Bank 2013 [cited 2013 Dec 23];Available from: URL: http://data.worldbank.org/indicator/NY.GDP.MKTP.CD

(732) claxton K, Martin S, Soares M, Rice N, Spackman E, Hinde S, et al. Methods for the Estimation of the NICE Cost Effectiveness Threshold. Revised Report Following Referees Comments. 2013 Jun 10.

(733) Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012 Dec 15;380(9859):2129-43.

(734) Hontelez JA, de Vlas SJ, Tanser F, Bakker R, Barnighausen T, Newell ML, et al. The impact of the new WHO antiretroviral treatment guidelines on HIV epidemic dynamics and cost in South Africa. PLoS One 2011;6(7):e21919.

(735) Boily MC, Masse B, Alsallaq R, Padian NS, Eaton JW, Vesga JF, et al. HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention. PLoS Med 2012;9(7):e1001250.

(736) Jean K, Gabillard D, Moh R, Danel C, Fassassi R, Desgrees-du-Lou A, et al. Effect of Early Antiretroviral Therapy on Sexual Behaviors and HIV-1 Transmission Risk Among Adults With Diverse Heterosexual Partnership Statuses in Cote d'Ivoire. J Infect Dis 2013 Sep 24.

(737) Menzies NA, Berruti AA, Blandford JM. The determinants of HIV treatment costs in resource limited settings. PLoS One 2012;7(11):e48726.

(738) Menzies NA, Berruti AA, Berzon R, Filler S, Ferris R, Ellerbrock TV, et al. The cost of providing comprehensive HIV treatment in PEPFAR-supported programs. AIDS 2011 Sep 10;25(14):1753-60.

(739) Barnighausen T, Bloom DE, Humair S. Economics of antiretroviral treatment vs. circumcision for HIV prevention. Proc Natl Acad Sci U S A 2012 Dec 26;109(52):21271-6.

(740) Njeuhmeli E, Forsythe S, Reed J, Opuni M, Bollinger L, Heard N, et al. Voluntary medical male circumcision: modeling the impact and cost of expanding male circumcision for HIV prevention in eastern and southern Africa. PLoS Med 2011 Nov;8(11):e1001132.

(741) Marconi VC, Sunpath H, Lu Z, Gordon M, Koranteng-Apeagyei K, Hampton J, et al. Prevalence of HIV-1 drug resistance after failure of a first highly active antiretroviral therapy regimen in KwaZulu Natal, South Africa. Clin Infect Dis 2008 May 15;46(10):1589-97.

(742) Orrell C, Walensky RP, Losina E, Pitt J, Freedberg KA, Wood R. HIV type-1 clade C resistance genotypes in treatment-naive patients and after first virological failure in a large community antiretroviral therapy programme. Antivir Ther 2009;14(4):523-31.

(743) Gupta R, Hill A, Sawyer AW, Pillay D. Emergence of drug resistance in HIV type 1-infected patients after receipt of first-line highly active antiretroviral therapy: a systematic review of clinical trials. Clin Infect Dis 2008 Sep 1;47(5):712-22.

(744) Hill A, McBride A, Sawyer AW, Clumeck N, Gupta RK. Resistance at virological failure using boosted protease inhibitors versus nonnucleoside reverse transcriptase inhibitors as first-line antiretroviral therapy--implications for sustained efficacy of ART in resource-limited settings. J Infect Dis 2013 Jun 15;207 Suppl 2:S78-S84.

(745) Gupta RK, Hill A, Sawyer AW, Cozzi-Lepri A, von W, V, Yerly S, et al. Virological monitoring and resistance to first-line highly active antiretroviral therapy in adults infected with HIV-1 treated under WHO guidelines: a systematic review and meta-analysis. Lancet Infect Dis 2009 Jul;9(7):409-17.

(746) Gupta RK, Jordan MR, Sultan BJ, Hill A, Davis DHJ, Gregson J, et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet 2012 Oct 6;380(9849):1250-8.

(747) Pillay V, Ledwaba J, Hunt G, Rakgotho M, Singh B, Makubalo L, et al. Antiretroviral drug resistance surveillance among drug-naive HIV-1-infected individuals in Gauteng Province, South Africa in 2002 and 2004. Antivir Ther 2008;13 Suppl 2:101-7.

(748) Hunt GM, Ledwaba J, Basson AE, Moyes J, Cohen C, Singh B, et al. Surveillance of transmitted HIV-1 drug resistance in Gauteng and KwaZulu-Natal Provinces, South Africa, 2005-2009. Clin Infect Dis 2012 May;54 Suppl 4:S334-S338.

(749) Manasa J, Katzenstein D, Cassol S, Newell ML, de OT. Primary drug resistance in South Africa: data from 10 years of surveys. AIDS Res Hum Retroviruses 2012 Jun;28(6):558-65.

(750) Parikh UM, Kiepiela P, Ganesh S, Gomez K, Horn S, Eskay K, et al. Prevalence of HIV-1 drug resistance among women screening for HIV prevention trials in KwaZulu-Natal, South Africa (MTN-009). PLoS One 2013;8(4):e59787.

(751) Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006 Mar 11;367(9513):817-24.

(752) Clouse K, Pettifor A, Shearer K, Maskew M, Bassett J, Larson B, et al. Loss to follow-up before and after delivery among women testing HIV positive during pregnancy in Johannesburg, South Africa. Trop Med Int Health 2013 Apr;18(4):451-60.

(753) Boyles TH, Wilkinson LS, Leisegang R, Maartens G. Factors influencing retention in care after starting antiretroviral therapy in a rural South African programme. PLoS One 2011;6(5):e19201.

(754) Sabapathy K, Van den Bergh R, Fidler S, Hayes R, Ford N. Uptake of Home-Based Voluntary HIV Testing in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. Plos Medicine 2012 Dec;9(12).

(755) MacPherson P, Lalloo D, Choko A, van Oosterhout J, Thindwa D, Webb E, et al. Home Assessment and Initiation of ART following HIV Self-Testing: A Cluster-Randomised trial to Improve Linkage to ART in Blantyre, Malawi. 2013 Mar 3; 2013.

(756) Sweat M, Morin S, Celentano D, Mulawa M, Singh B, Mbwambo J, et al. Community-based intervention to increase HIV testing and case detection in people aged 16-32 years in Tanzania, Zimbabwe, and Thailand (NIMH Project Accept, HPTN 043): a randomised study. Lancet Infect Dis 2011 Jul;11(7):525-32.

(757) Jani IV, Sitoe NE, Alfai ER, Chongo PL, Quevedo JI, Rocha BM, et al. Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: an observational cohort study. Lancet 2011 Oct 29;378(9802):1572-9.

(758) Burtle D, Welfare W, Elden S, Mamvura C, Vandelanotte J, Petherick E, et al. Introduction and evaluation of a 'pre-ART care' service in Swaziland: an operational research study. BMJ Open 2012;2(2):e000195.

(759) Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antiviral Therapy 2008;13:25-36.

(760) Blower S, Ma L, Farmer P, Koenig S. Predicting the impact of antiretrovirals in resource-poor settings: preventing HIV infections whilst controlling drug resistance. Curr Drug Targets Infect Disord 2003 Dec;3(4):345-53.

(761) Tobias RL. The President's Emergency Plan for AIDS Relief: US Five-Year Global HIV/AIDS Strategy. 2004 Feb 23; 2004.

(762) Nichols BE, Sigaloff KC, Kityo C, Mandaliya K, Hamers RL, Bertagnolio S, et al. Averted HIV infections due to expanded antiretroviral treatment eligibility offsets risk of transmitted drug resistance: a modeling study. AIDS 2014 Jan 2;28(1):73-83.

(763) Fox Z, Phillips A, Cohen C, Neuhaus J, Baxter J, Emery S, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. AIDS 2008;22(17):2279-89.

(764) UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2013. UNAIDS 2013 November [cited 2013 Dec 26];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2013/gr2013/UNAIDS_Global_Report_2013_en.pdf

(765) Paquet AC, Baxter J, Weidler J, Lie Y, Lawrence J, Kim R, et al. Differences in reversion of resistance mutations to wild-type under structured treatment interruption and related increase in replication capacity. PLoS One 2011;6(1):e14638.

(766) Geretti AM, Fox Z, Johnson JA, Booth C, Lipscomb J, Stuyver LJ, et al. Sensitive assessment of the virologic outcomes of stopping and restarting non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy. PLoS One 2013;8(7):e69266.

(767) Kranzer K, Ford N. Unstructured treatment interruption of antiretroviral therapy in clinical practice: a systematic review. Trop Med Int Health 2011 Oct;16(10):1297-313.

(768) Hill T, Bansi L, Sabin C, Phillips A, Dunn D, Anderson J, et al. Data linkage reduces loss to follow-up in an observational HIV cohort study. J Clin Epidemiol 2010 Oct;63(10):1101-9.

(769) Bansi LK, Benzie AA, Phillips AN, Portsmouth S, Hill T, Leen C, et al. Are previous treatment interruptions associated with higher viral rebound rates in patients with viral suppression? AIDS 2008 Jan 30;22(3):349-56.

(770) Holkmann OC, Mocroft A, Kirk O, Vella S, Blaxhult A, Clumeck N, et al. Interruption of combination antiretroviral therapy and risk of clinical disease progression to AIDS or death. HIV Med 2007 Mar;8(2):96-104.

(771) Ruiz L, Paredes R, Gomez G, Romeu J, Domingo P, Perez-Alvarez N, et al. Antiretroviral therapy interruption guided by CD4 cell counts and plasma HIV-1 RNA levels in chronically HIV-1-infected patients. AIDS 2007 Jan 11;21(2):169-78.

(772) Ananworanich J, Gayet-Ageron A, Le BM, Prasithsirikul W, Chetchotisakd P, Kiertiburanakul S, et al. CD4-guided scheduled treatment interruptions compared with continuous therapy for patients infected with HIV-1: results of the Staccato randomised trial. Lancet 2006 Aug 5;368(9534):459-65.

(773) Danel C, Moh R, Chaix ML, Gabillard D, Gnokoro J, Diby CJ, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. J Infect Dis 2009 Jan 1;199(1):66-76.

(774) Ananworanich J, Nuesch R, Le BM, Chetchotisakd P, Vibhagool A, Wicharuk S, et al. Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial. AIDS 2003 Oct 17;17(15):F33-F37.

(775) Pai NP, Tulsky JP, Lawrence J, Colford JM, Jr., Reingold AL. Structured treatment interruptions (STI) in chronic suppressed HIV infection in adults. Cochrane Database Syst Rev 2005;(4):CD005482.

(776) Pai NP, Lawrence J, Reingold AL, Tulsky JP. Structured treatment interruptions (STI) in chronic unsuppressed HIV infection in adults. Cochrane Database Syst Rev 2006;(3):CD006148.

(777) Taylor S, Boffito M, Khoo S, Smit E, Back D. Stopping antiretroviral therapy. AIDS 2007 Aug 20;21(13):1673-82.

(778) Deeks SG, Gange SJ, Kitahata MM, Saag MS, Justice AC, Hogg RS, et al. Trends in multidrug treatment failure and subsequent mortality among antiretroviral therapy-experienced patients with HIV infection in North America. Clin Infect Dis 2009 Nov 15;49(10):1582-90.

(779) Boucher CA, van LR, Kellam P, Schipper P, Tijnagel J, Lange JM, et al. Effects of discontinuation of zidovudine treatment on zidovudine sensitivity of human immunodeficiency virus type 1 isolates. Antimicrob Agents Chemother 1993 Jul;37(7):1525-30.

(780) Falkensammer B, El AR, Mullauer B, Sarcletti M, Parson W, Dierich MP, et al. Loss of zidovudine related mutations in the reverse transscriptase gene of HIV after switching therapy. Eur J Med Res 2002 Sep 30;7(9):379-86.

(781) Batisse D, Karmochkine M, Si MA, Piketty C, Kazatchkine MD, Belec L. Persistence of HIV-1 variants harbouring the zidovudine resistance mutation at pol codon 215 in patients who respond to triple combination therapy. AIDS 1998 May 7;12(7):824-5.

(782) Smith MS, Koerber KL, Pagano JS. Long-term persistence of zidovudine resistance mutations in plasma isolates of human immunodeficiency virus type 1 of dideoxyinosine-treated patients removed from zidovudine therapy. J Infect Dis 1994 Jan;169(1):184-8.

(783) Verhofstede C, Wanzeele FV, Van Der Gucht B, De CN, Plum J. Interruption of reverse transcriptase inhibitors or a switch from reverse transcriptase to protease inhibitors resulted in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. AIDS 1999 Dec 24;13(18):2541-6.

(784) Izopet J, Massip P, Souyris C, Sandres K, Puissant B, Obadia M, et al. Shift in HIV resistance genotype after treatment interruption and short-term antiviral effect following a new salvage regimen. AIDS 2000 Oct 20;14(15):2247-55.

(785) Miller V, Sabin C, Hertogs K, Bloor S, Martinez-Picado J, D'Aquila R, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. AIDS 2000 Dec 22;14(18):2857-67.

(786) Delaugerre C, Valantin MA, Mouroux M, Bonmarchand M, Carcelain G, Duvivier C, et al. Re-occurrence of HIV-1 drug mutations after treatment re-initiation following interruption in patients with multiple treatment failure. AIDS 2001 Nov 9;15(16):2189-91.

(787) Trignetti M, Sing T, Svicher V, Santoro MM, Forbici F, D'Arrigo R, et al. Dynamics of NRTI resistance mutations during therapy interruption. AIDS Res Hum Retroviruses 2009 Jan;25(1):57-64.

(788) Bi X, Gatanaga H, Koike K, Kimura S, Oka S. Reversal periods and patterns from drug-resistant to wild-type HIV type 1 after cessation of anti-HIV therapy. AIDS Res Hum Retroviruses 2007 Jan;23(1):43-50.

(789) Ruiz L, Ribera E, Bonjoch A, Romeu J, Martinez-Picado J, Paredes R, et al. Role of structured treatment interruption before a 5-drug salvage antiretroviral regimen: the Retrogene Study. J Infect Dis 2003 Oct 1;188(7):977-85.

(790) Benson CA, Vaida F, Havlir DV, Downey GF, Lederman MM, Gulick RM, et al. A randomized trial of treatment interruption before optimized antiretroviral therapy for persons with drug-resistant HIV: 48-week virologic results of ACTG A5086. J Infect Dis 2006 Nov 1;194(9):1309-18.

(791) Balduin M, Sierra S, Daumer MP, Rockstroh JK, Oette M, Fatkenheuer G, et al. Evolution of HIV resistance during treatment interruption in experienced patients and after restarting a new therapy. J Clin Virol 2005 Dec;34(4):277-87.

(792) Halfon P, Durant J, Clevenbergh P, Carsenti H, Celis L, Khiri H, et al. Kinetics of disappearance of resistance mutations and reappearance of wild-type during structured treatment interruptions. AIDS 2003 Jun 13;17(9):1351-61.

(793) Mackie NE, Fidler S, Tamm N, Clarke JR, Back D, Weber JN, et al. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. HIV Med 2004 May;5(3):180-4.

(794) Muro E, Droste JA, Hofstede HT, Bosch M, Dolmans W, Burger DM. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies. J Acquir Immune Defic Syndr 2005 Aug 1;39(4):419-21.

(795) Sadiq ST, Fredericks S, Khoo SH, Rice P, Holt DW. Efavirenz detectable in plasma 8 weeks after stopping therapy and subsequent development of non-nucleoside reverse transcriptase inhibitor-associated resistance. AIDS 2005 Oct 14;19(15):1716-7.

(796) Arduino R. CD4 cell count-guided treatment interruption: be smart and wait for more evidence. Clin Infect Dis 2005 Mar 1;40(5):735-7.

(797) Palmer S, Boltz V, Maldarelli F, Kearney M, Halvas EK, Rock D, et al. Selection and persistence of non-nucleoside reverse transcriptase inhibitor-resistant HIV-1 in patients starting and stopping non-nucleoside therapy. AIDS 2006 Mar 21;20(5):701-10.

(798) Marchou B, Tangre P, Charreau I, Izopet J, Girard PM, May T, et al. Intermittent antiretroviral therapy in patients with controlled HIV infection. AIDS 2007 Feb 19;21(4):457-66.

(799) Schweighardt B, Ortiz GM, Grant RM, Wellons M, Miralles GD, Kostrikis LG, et al. Emergence of drug-resistant HIV-1 variants in patients undergoing structured treatment interruptions. AIDS 2002 Nov 22;16(17):2342-4.

(800) Ribaudo HJ, Haas DW, Tierney C, Kim RB, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. Clin Infect Dis 2006 Feb 1;42(3):401-7.

(801) Burger D, van dH, I, la PC, van der Ende M, Groeneveld P, Richter C, et al. Interpatient variability in the pharmacokinetics of the HIV non-nucleoside reverse transcriptase inhibitor efavirenz: the effect of gender, race, and CYP2B6 polymorphism. Br J Clin Pharmacol 2006 Feb;61(2):148-54.

(802) Kikaire B, Khoo S, Walker AS, Ssali F, Munderi P, Namale L, et al. Nevirapine clearance from plasma in African adults stopping therapy: a pharmacokinetic substudy. AIDS 2007 Mar 30;21(6):733-7.

(803) Hare CB, Mellors J, Krambrink A, Su Z, Skiest D, Margolis DM, et al. Detection of nonnucleoside reverse-transcriptase inhibitor-resistant HIV-1 after discontinuation of virologically suppressive antiretroviral therapy. Clin Infect Dis 2008 Aug 1;47(3):421-4.

(804) Izopet J, Marchou B, Charreau I, Saune K, Tangre P, Molina JM, et al. HIV-1-resistant strains during 8-week on 8-week off intermittent therapy and their effect on CD4+ T-cell counts and antiviral response. Antivir Ther 2008;13(4):537-45.

(805) Arnedo-Valero M, Garcia F, Gil C, Guila T, Fumero E, Castro P, et al. Risk of selecting de novo drug-resistance mutations during structured treatment interruptions in patients with chronic HIV infection. Clin Infect Dis 2005 Sep 15;41(6):883-90.

(806) Yerly S, Fagard C, Gunthard HF, Hirschel B, Perrin L. Drug resistance mutations during structured treatment interruptions. Antivir Ther 2003 Oct;8(5):411-5.

(807) Metzner KJ, Bonhoeffer S, Fischer M, Karanicolas R, Allers K, Joos B, et al. Emergence of minor populations of human immunodeficiency virus type 1 carrying

the M184V and L90M mutations in subjects undergoing structured treatment interruptions. J Infect Dis 2003 Nov 15;188(10):1433-43.

(808) Daniel N, Schneider V, Pialoux G, Krivine A, Grabar S, Nguyen TH, et al. Emergence of HIV-1 mutated strains after interruption of highly active antiretroviral therapy in chronically infected patients. AIDS 2003 Sep 26;17(14):2126-9.

(809) Dybul M, Nies-Kraske E, Daucher M, Hertogs K, Hallahan CW, Csako G, et al. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. J Infect Dis 2003 Aug 1;188(3):388-96.

(810) Palmisano L, Giuliano M, Bucciardini R, Fragola V, Andreotti M, Galluzzo C, et al. Determinants of virologic and immunologic outcomes in chronically HIV-infected subjects undergoing repeated treatment interruptions: the Istituto Superiore di Sanita-Pulsed Antiretroviral Therapy (ISS-PART) study. J Acquir Immune Defic Syndr 2007 Sep 1;46(1):39-47.

(811) Parienti JJ, Massari V, Descamps D, Vabret A, Bouvet E, Larouze B, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 2004 May 1;38(9):1311-6.

(812) Sanchez R, Portilla J, Gimeno A, Boix V, Llopis C, Sanchez-Paya J, et al. Immunovirologic consequences and safety of short, non-structured interruptions of successful antiretroviral treatment. J Infect 2007 Feb;54(2):159-66.

(813) Oyugi JH, Byakika-Tusiime J, Ragland K, Laeyendecker O, Mugerwa R, Kityo C, et al. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS 2007 May 11;21(8):965-71.

(814) Spacek LA, Shihab HM, Kamya MR, Mwesigire D, Ronald A, Mayanja H, et al. Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda. Clin Infect Dis 2006 Jan 15;42(2):252-9.

(815) First report from the UK HIV Drug Resistance Database. HPA CDR Weekly 2003 Oct;13(43).

(816) Johnson VA, Calvez V, Günthard HF, Paredes R, Pillay D, Shafer R, et al. 2011 update of the drug resistance mutations in HIV-1. Topics in Antiviral Medicine 2011;19(4):156-64.

(817) Deeks SG, Hoh R, Neilands TB, Liegler T, Aweeka F, Petropoulos CJ, et al. Interruption of treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. J Infect Dis 2005 Nov 1;192(9):1537-44.

(818) Martinez-Picado J, Morales-Lopetegi K, Wrin T, Prado JG, Frost SD, Petropoulos CJ, et al. Selection of drug-resistant HIV-1 mutants in response to repeated structured treatment interruptions. AIDS 2002 Apr 12;16(6):895-9.

(819) Metzner KJ, Allers K, Rauch P, Harrer T. Rapid selection of drug-resistant HIV-1 during the first months of suppressive ART in treatment-naive patients. AIDS 2007 Mar 30;21(6):703-11.

(820) Hallett TB, Eaton JW. A side door into care cascade for HIV-infected patients? J Acquir Immune Defic Syndr 2013 Jul;63 Suppl 2:S228-S232.

(821) Makadzange AT, Ndhlovu CE, Takarinda K, Reid M, Kurangwa M, Gona P, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. Clin Infect Dis 2010 Jun 1;50(11):1532-8.

(822) Kigozi IM, Dobkin LM, Martin JN, Geng EH, Muyindike W, Emenyonu NI, et al. Late-disease stage at presentation to an HIV clinic in the era of free antiretroviral therapy in Sub-Saharan Africa. J Acquir Immune Defic Syndr 2009 Oct 1;52(2):280-9.

(823) McNairy ML, El-Sadr WM. The HIV care continuum: no partial credit given. AIDS 2012 Sep 10;26(14):1735-8.

(824) Fox MP, Larson B, Rosen S. Defining retention and attrition in pre-antiretroviral HIV care: proposals based on experience in Africa. Trop Med Int Health 2012 Oct;17(10):1235-44.

(825) Micek MA, Gimbel-Sherr K, Baptista AJ, Matediana E, Montoya P, Pfeiffer J, et al. Loss to follow-up of adults in public HIV care systems in central Mozambique: identifying obstacles to treatment. J Acquir Immune Defic Syndr 2009 Nov 1;52(3):397-405.

(826) Lahuerta M, Lima J, Nuwagaba-Biribonwoha H, Okamura M, Alvim MF, Fernandes R, et al. Factors associated with late antiretroviral therapy initiation among adults in Mozambique. PLoS One 2012;7(5):e37125.

(827) Lahuerta M, Ue F, Hoffman S, Elul B, Kulkarni SG, Wu Y, et al. The problem of late ART initiation in Sub-Saharan Africa: a transient aspect of scale-up or a long-term phenomenon? J Health Care Poor Underserved 2013 Feb;24(1):359-83.

(828) Geng EH, Nash D, Kambugu A, Zhang Y, Braitstein P, Christopoulos KA, et al. Retention in care among HIV-infected patients in resource-limited settings: emerging insights and new directions. Curr HIV/AIDS Rep 2010 Nov;7(4):234-44.

(829) Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C, et al. Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med 2011 Oct;8(10):e1001111.

(830) Li MS, Musonda P, Gartland M, Mulenga PL, Mwango A, Stringer JS, et al. Predictors of patient attrition according to different definitions for loss to follow-up: a comparative analysis from Lusaka, Zambia. J Acquir Immune Defic Syndr 2013 Jul 1;63(3):e116-e119.

(831) Chi BH, Cantrell RA, Mwango A, Westfall AO, Mutale W, Limbada M, et al. An empirical approach to defining loss to follow-up among patients enrolled in antiretroviral treatment programs. Am J Epidemiol 2010 Apr 15;171(8):924-31.

(832) WHO. Operations manual for delivery of HIV prevention, care and treatment at primary health centres in high-prevalence, resource-constrained settings. Edition 1 for field testing and country adaptation. WHO 2008 December 2 [cited 2014 Apr

20];Available from: URL: http://www.who.int/hiv/pub/imai/operations_manual/en/

(833) Calmy A, Pinoges L, Szumilin E, Zachariah R, Ford N, Ferradini L. Generic fixed-dose combination antiretroviral treatment in resource-poor settings: multicentric observational cohort. AIDS 2006 May 12;20(8):1163-9.

(834) Ferradini L, Jeannin A, Pinoges L, Izopet J, Odhiambo D, Mankhambo L, et al. Scaling up of highly active antiretroviral therapy in a rural district of Malawi: an effectiveness assessment. Lancet 2006 Apr 22;367(9519):1335-42.

(835) Yu JK, Chen SC, Wang KY, Chang CS, Makombe SD, Schouten EJ, et al. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. Bull World Health Organ 2007 Jul;85(7):550-4.

(836) Chi BH, Cantrell RA, Zulu I, Mulenga LB, Levy JW, Tambatamba BC, et al. Adherence to first-line antiretroviral therapy affects non-virologic outcomes among patients on treatment for more than 12 months in Lusaka, Zambia. Int J Epidemiol 2009 Jun;38(3):746-56.

(837) Bisson GP, Gaolathe T, Gross R, Rollins C, Bellamy S, Mogorosi M, et al. Overestimates of survival after HAART: implications for global scale-up efforts. PLoS One 2008;3(3):e1725.

(838) Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA 2008 Aug 6;300(5):506-7.

(839) Wools-Kaloustian K, Kimaiyo S, Diero L, Siika A, Sidle J, Yiannoutsos CT, et al. Viability and effectiveness of large-scale HIV treatment initiatives in sub-Saharan Africa: experience from western Kenya. AIDS 2006 Jan 2;20(1):41-8.

(840) Shepherd BE, Blevins M, Vaz LM, Moon TD, Kipp AM, Jose E, et al. Impact of definitions of loss to follow-up on estimates of retention, disease progression, and mortality: application to an HIV program in Mozambique. Am J Epidemiol 2013 Sep 1;178(5):819-28.

(841) Bassett IV, Wang B, Chetty S, Mazibuko M, Bearnot B, Giddy J, et al. Loss to care and death before antiretroviral therapy in Durban, South Africa. J Acquir Immune Defic Syndr 2009 Jun 1;51(2):135-9.

(842) Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One 2009;4(6):e5790.

(843) Bedelu M, Ford N, Hilderbrand K, Reuter H. Implementing antiretroviral therapy in rural communities: the Lusikisiki model of decentralized HIV/AIDS care. J Infect Dis 2007 Dec 1;196 Suppl 3:S464-S468.

(844) Chan AK, Mateyu G, Jahn A, Schouten E, Arora P, Mlotha W, et al. Outcome assessment of decentralization of antiretroviral therapy provision in a rural district of Malawi using an integrated primary care model. Trop Med Int Health 2010 Jun;15 Suppl 1:90-7.

(845) Rosen S, Ketlhapile M, Sanne I, DeSilva MB. Cost to patients of obtaining treatment for HIV/AIDS in South Africa. S Afr Med J 2007 Jul;97(7):524-9.

(846) Mills EJ, Nachega JB, Bangsberg DR, Singh S, Rachlis B, Wu P, et al. Adherence to HAART: a systematic review of developed and developing nation patient-reported barriers and facilitators. PLoS Med 2006 Nov;3(11):e438.

(847) Aspeling HE, van Wyk NC. Factors associated with adherence to antiretroviral therapy for the treatment of HIV-infected women attending an urban care facility. Int J Nurs Pract 2008 Feb;14(1):3-10.

(848) Heunis JC, Wouters E, Norton WE, Engelbrecht MC, Kigozi NG, Sharma A, et al. Patient- and delivery-level factors related to acceptance of HIV counseling and testing services among tuberculosis patients in South Africa: a qualitative study with community health workers and program managers. Implement Sci 2011;6:27.

(849) Weiser SD, Heisler M, Leiter K, Percy-de KF, Tlou S, DeMonner S, et al. Routine HIV testing in Botswana: a population-based study on attitudes, practices, and human rights concerns. PLoS Med 2006 Jul;3(7):e261.

(850) Odhiambo J, Kizito W, Njoroge A, Wambua N, Nganga L, Mburu M, et al. Provider-initiated HIV testing and counselling for TB patients and suspects in Nairobi, Kenya. Int J Tuberc Lung Dis 2008 Mar;12(3 Suppl 1):63-8.

(851) Hensen B, Baggaley R, Wong VJ, Grabbe KL, Shaffer N, Lo YR, et al. Universal voluntary HIV testing in antenatal care settings: a review of the contribution of provider-initiated testing & counselling. Trop Med Int Health 2012 Jan;17(1):59-70.

(852) Wanyenze RK, Hahn JA, Liechty CA, Ragland K, Ronald A, Mayanja-Kizza H, et al. Linkage to HIV care and survival following inpatient HIV counseling and testing. AIDS Behav 2011 May;15(4):751-60.

(853) Becker S, Mlay R, Schwandt HM, Lyamuya E. Comparing couples' and individual voluntary counseling and testing for HIV at antenatal clinics in Tanzania: a randomized trial. AIDS Behav 2010 Jun;14(3):558-66.

(854) Ditekemena J, Matendo R, Koole O, Colebunders R, Kashamuka M, Tshefu A, et al. Male partner voluntary counselling and testing associated with the antenatal services in Kinshasa, Democratic Republic of Congo: a randomized controlled trial. Int J STD AIDS 2011 Mar;22(3):165-70.

(855) Mohlala BK, Boily MC, Gregson S. The forgotten half of the equation: randomized controlled trial of a male invitation to attend couple voluntary counselling and testing. AIDS 2011 Jul 31;25(12):1535-41.

(856) Helleringer S, Kohler HP, Frimpong JA, Mkandawire J. Increasing uptake of HIV testing and counseling among the poorest in sub-Saharan countries through home-based service provision. J Acquir Immune Defic Syndr 2009 Jun 1;51(2):185-93.

(857) Wachira J, Kimaiyo S, Ndege S, Mamlin J, Braitstein P. What is the impact of home-based HIV counseling and testing on the clinical status of newly enrolled adults in a large HIV care program in Western Kenya? Clin Infect Dis 2012 Jan 15;54(2):275-81.

(858) Fylkesnes K, Siziya S. A randomized trial on acceptability of voluntary HIV counselling and testing. Trop Med Int Health 2004 May;9(5):566-72.

(859) Were WA, Mermin JH, Wamai N, Awor AC, Bechange S, Moss S, et al. Undiagnosed HIV infection and couple HIV discordance among household members of HIV-infected people receiving antiretroviral therapy in Uganda. J Acquir Immune Defic Syndr 2006 Sep;43(1):91-5.

(860) Menzies N, Abang B, Wanyenze R, Nuwaha F, Mugisha B, Coutinho A, et al. The costs and effectiveness of four HIV counseling and testing strategies in Uganda. AIDS 2009 Jan 28;23(3):395-401.

(861) Lugada E, Levin J, Abang B, Mermin J, Mugalanzi E, Namara G, et al. Comparison of home and clinic-based HIV testing among household members of persons taking antiretroviral therapy in Uganda: results from a randomized trial. J Acquir Immune Defic Syndr 2010 Oct;55(2):245-52.

(862) Suthar AB, Ford N, Bachanas PJ, Wong VJ, Rajan JS, Saltzman AK, et al. Towards universal voluntary HIV testing and counselling: a systematic review and meta-analysis of community-based approaches. PLoS Med 2013 Aug;10(8):e1001496.

(863) Wolff B, Nyanzi B, Katongole G, Ssesanga D, Ruberantwari A, Whitworth J. Evaluation of a home-based voluntary counselling and testing intervention in rural Uganda. Health Policy Plan 2005 Mar;20(2):109-16.

(864) van RH, Barnabas RV, Baeten JM, Phakathi Z, Joseph P, Krows M, et al. High HIV testing uptake and linkage to care in a novel program of home-based HIV counseling and testing with facilitated referral in KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr 2013 Sep 1;64(1):e1-e8.

(865) Corbett EL, Dauya E, Matambo R, Cheung YB, Makamure B, Bassett MT, et al. Uptake of workplace HIV counselling and testing: a cluster-randomised trial in Zimbabwe. PLoS Med 2006 Jul;3(7):e238.

(866) Efuntoye M, Okonkwo O, Omorgeie G, Musa G. Increasing access to HIV counselling and testing: A demonstration project trialling the greater involvement of people living with HIV/AIDS (GIPA) in the workplace. Mexico 2008.

(867) Chirawu P, Langhaug L, Mavhu W, Pascoe S, Dirawo J, Cowan F. Acceptability and challenges of implementing voluntary counselling and testing (VCT) in rural Zimbabwe: evidence from the Regai Dzive Shiri Project. AIDS Care 2010 Jan;22(1):81-8.

(868) Granich R, Muraguri N, Doyen A, Garg N, Williams BG. Achieving universal access for human immunodeficiency virus and tuberculosis: potential prevention impact of an integrated multi-disease prevention campaign in kenya. AIDS Res Treat 2012;2012:412643.

(869) Kharsany AB, Mlotshwa M, Frohlich JA, Yende ZN, Samsunder N, Abdool Karim SS, et al. HIV prevalence among high school learners - opportunities for schools-based HIV testing programmes and sexual reproductive health services. BMC Public Health 2012;12:231.

(870) Report on the first international symposium on self-testing for HIV: The legal,ethical, gender, human rights and public health implications of HIV self-testing scale-up. WHO 2013 April 9 [cited 2013 Nov 12];Available from: URL: http://www.who.int/hiv/pub/vct/self_test/en/

(871) Choko AT, Desmond N, Webb EL, Chavula K, Napierala-Mavedzenge S, Gaydos CA, et al. The uptake and accuracy of oral kits for HIV self-testing in high HIV prevalence setting: a cross-sectional feasibility study in Blantyre, Malawi. PLoS Med 2011 Oct;8(10):e1001102.

(872) Choko AT, MacPherson P, Webb EL, Ball H, Sambakunsi R, Mdolo A, et al. One Year Outcomes Following Community-Based HIV Self-Testing: A Prospective Study in Malawi. 2014 Mar 3; 2014.

(873) Kalibala SWTWMPCEOaP. 'Knowing myself first': Feasibility of self-testing among health workers in Kenya.". Population Council Kenya 2011 [cited 2013 Apr 5];Available from: URL: http://www.popcouncil.org/pdfs/2011HIV_KenyaHWSelfTesting.pdf

(874) Pant Pai N, Behlim T, Abrahams L, Vadnais C, Shivkumar S, Pillay S, et al. Will an unsupervised self-testing strategy for HIV work in health care workers of South Africa? A cross sectional pilot feasibility study. PLoS One 2013;8(11):e79772.

(875) Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care: a systematic review. AIDS 2012 Oct 23;26(16):2059-67.

(876) Hatcher AM, Turan JM, Leslie HH, Kanya LW, Kwena Z, Johnson MO, et al. Predictors of linkage to care following community-based HIV counseling and testing in rural Kenya. AIDS Behav 2012 Jul;16(5):1295-307.

(877) MacPherson P, MacPherson EE, Mwale D, Bertel SS, Makombe SD, Corbett EL, et al. Barriers and facilitators to linkage to ART in primary care: a qualitative study of patients and providers in Blantyre, Malawi. J Int AIDS Soc 2012;15(2):18020.

(878) Nsigaye R, Wringe A, Roura M, Kalluvya S, Urassa M, Busza J, et al. From HIV diagnosis to treatment: evaluation of a referral system to promote and monitor access to antiretroviral therapy in rural Tanzania. J Int AIDS Soc 2009;12(1):31.

(879) Wynberg E, Cooke G, Shroufi A, Reid SD, Ford N. Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review. J Int AIDS Soc 2014 Jan 20;17(1):18809.

(880) Corbett EL. Uptake, accuracy and linkage into care following access to community-based self-testing for HIV in Malawi. 10-4-2013. *The legal, ethical, gender, human rights and public health implications of self-testing scale-up.*
Ref Type: Generic

(881) Emenyonu N, Muyindike W, Habyarimana J, Pop-Eleches C, Thirumurthy H, Ragland K, et al. Cash transfers to cover clinic transportation costs improve retention in care in a HIV treatment program in rural Uganda. 2010 Feb 19; 2010.

(882) Ivers LC, Chang Y, Gregory JJ, Freedberg KA. Food assistance is associated with improved body mass index, food security and attendance at clinic in an HIV program in central Haiti: a prospective observational cohort study. AIDS Res Ther 2010;7:33.

(883) Kohler PK, Chung MH, McGrath CJ, Benki-Nugent SF, Thiga JW, John-Stewart GC. Implementation of free cotrimoxazole prophylaxis improves clinic retention among antiretroviral therapy-ineligible clients in Kenya. AIDS 2011 Aug 24;25(13):1657-61.

(884) Muhamadi L, Tumwesigye NM, Kadobera D, Marrone G, Wabwire-Mangen F, Pariyo G, et al. A single-blind randomized controlled trial to evaluate the effect of extended counseling on uptake of pre-antiretroviral care in Eastern Uganda. Trials 2011;12:184.

(885) Kumwenda M, Tom S, Chan AK, Mwinjiwa E, Sodhi S, Joshua M, et al. Reasons for accepting or refusing HIV services among tuberculosis patients at a TB-HIV integration clinic in Malawi. Int J Tuberc Lung Dis 2011 Dec;15(12):1663-9.

(886) Katz IT, Essien T, Marinda ET, Gray GE, Bangsberg DR, Martinson NA, et al. Antiretroviral therapy refusal among newly diagnosed HIV-infected adults. AIDS 2011 Nov 13;25(17):2177-81.

(887) Faal M, Naidoo N, Glencross DK, Venter WDF, Osih R. Providing Immediate CD4 Count Results at HIV Testing Improves ART Initiation. Jaids-Journal of Acquired Immune Deficiency Syndromes 2011 Nov 1;58(3):E54-E59.

(888) Siedner MJ, Lankowski A, Haberer JE, Kembabazi A, Emenyonu N, Tsai AC, et al. Rethinking the "pre" in pre-therapy counseling: no benefit of additional visits prior to therapy on adherence or viremia in Ugandans initiating ARVs. PLoS One 2012;7(6):e39894.

(889) Ware NC, Wyatt MA, Geng EH, Kaaya SF, Agbaji OO, Muyindike WR, et al. Toward an understanding of disengagement from HIV treatment and care in sub-Saharan Africa: a qualitative study. PLoS Med 2013;10(1):e1001369.

(890) Mitchell SK, Kelly KJ, Potgieter FE, Moon MW. Assessing social preparedness for antiretroviral therapy in a generalized AIDS epidemic: a diffusion of innovations approach. AIDS Behav 2009 Feb;13(1):76-84.

(891) Nachega JB, Knowlton AR, Deluca A, Schoeman JH, Watkinson L, Efron A, et al. Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults. A qualitative study. J Acquir Immune Defic Syndr 2006 Dec 1;43 Suppl 1:S127-S133.

(892) Maskew M, MacPhail P, Menezez C, Rubel D. Lost to follow up: contributing factors and challenges in South African patients on antiretroviral therapy. South African Medical Journal 2007;97(9):853-7.

(893) Ive P, Conradie F, Xaba S, Sanne I. Causes of loss to follow-up in patients taking antiretroviral therapy in the national rollout program of South Africa. 2005; Rio De Janeiro 2005.

(894) Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic

population in southwestern Uganda: a qualitative study. AIDS Behav 2010 Aug;14(4):778-84.

(895) Nel A, Kagee A. The relationship between depression, anxiety and medication adherence among patients receiving antiretroviral treatment in South Africa. Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv 2013;25(8):948-55.

(896) Selin A, Mills EJ, Nachega JB. Barriers to highly active antiretroviral therapy adherence in sub-Saharan Africa. Future Medicine 2007;1(3):331-9.

(897) Rosen S, Ketlhapile M. Cost of using a patient tracer to reduce loss to follow-up and ascertain patient status in a large antiretroviral therapy program in Johannesburg, South Africa. Trop Med Int Health 2010 Jun;15 Suppl 1:98-104.

(898) Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard GJ, et al. "That is why I stopped the ART": patients' & providers' perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme. BMC Public Health 2008;8:63.

(899) Golooba-Mutebi F, Tollman SM. Confronting HIV/AIDS in a South African village: the impact of health-seeking behaviour. Scand J Public Health Suppl 2007 Aug;69:175-80.

(900) Gilbert L, Walker L. "They (ARVs) are my life, without them I'm nothing"--experiences of patients attending a HIV/AIDS clinic in Johannesburg, South Africa. Health Place 2009 Dec;15(4):1123-9.

(901) Cooper D, Harries J, Myer L, Orner P, Bracken H, Zweigenthal V. "Life is still going on": reproductive intentions among HIV-positive women and men in South Africa. Soc Sci Med 2007 Jul;65(2):274-83.

(902) Kaplan R, Orrell C, Zwane E, Bekker LG, Wood R. Loss to follow-up and mortality among pregnant women referred to a community clinic for antiretroviral treatment. AIDS 2008 Aug 20;22(13):1679-81.

(903) Wang B, Losina E, Stark R, Munro A, Walensky RP, Wilke M, et al. Loss to follow-up in a community clinic in South Africa--roles of gender, pregnancy and CD4 count. S Afr Med J 2011 Apr;101(4):253-7.

(904) Ford N, Kranzer K, Hilderbrand K, Jouquet G, Goemaere E, Vlahakis N, et al. Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho. AIDS 2010 Nov 13;24(17):2645-50.

(905) Leisegang R, Cleary S, Hislop M, Davidse A, Regensberg L, Little F, et al. Early and late direct costs in a Southern African antiretroviral treatment programme: a retrospective cohort analysis. PLoS Med 2009 Dec;6(12):e1000189.

(906) Leisegang R, Maartens G, Hislop M, Regensberg L, Cleary S. Improving the evidence base of Markov models used to estimate the costs of scaling up antiretroviral programmes in resource-limited settings. BMC Health Serv Res 2010;10 Suppl 1:S3.

(907) Al-Dakkak I, Patel S, McCann E, Gadkari A, Prajapati G, Maiese EM. The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis. AIDS Care 2013;25(4):400-14.

(908) Tessema B, Biadglegne F, Mulu A, Getachew A, Emmrich F, Sack U. Magnitude and determinants of nonadherence and nonreadiness to highly active antiretroviral therapy among people living with HIV/AIDS in Northwest Ethiopia: a cross-sectional study. AIDS Res Ther 2010;7:2.

(909) Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, Bangsberg DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. Int J STD AIDS 2005 Jan;16(1):38-41.

(910) Tadios Y, Davey G. Antiretroviral treatment adherence and its correlates in Addis Ababa, Ethiopia. Ethiop Med J 2006 Jul;44(3):237-44.

(911) Berhe N, Tegabu D, Alemayehu M. Effect of nutritional factors on adherence to antiretroviral therapy among HIV-infected adults: a case control study in Northern Ethiopia. BMC Infect Dis 2013;13:233.

(912) Lamb MR, El-Sadr WM, Geng E, Nash D. Association of adherence support and outreach services with total attrition, loss to follow-up, and death among ART patients in sub-Saharan Africa. PLoS One 2012;7(6):e38443.

(913) Decroo T, Rasschaert F, Telfer B, Remartinez D, Laga M, Ford N. Community-based antiretroviral therapy programs can overcome barriers to retention of patients and decongest health services in sub-Saharan Africa: a systematic review. Int Health 2013 Sep;5(3):169-79.

(914) Jaffar S, Amuron B, Foster S, Birungi J, Levin J, Namara G, et al. Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. Lancet 2009 Dec 19;374(9707):2080-9.

(915) Luque-Fernandez MA, Van CG, Goemaere E, Hilderbrand K, Schomaker M, Mantangana N, et al. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. PLoS One 2013;8(2):e56088.

(916) Amuron B, Levin J, Birunghi J, Namara G, Coutinho A, Grosskurth H, et al. Mortality in an antiretroviral therapy programme in Jinja, south-east Uganda: a prospective cohort study. AIDS Res Ther 2011;8:39.

(917) Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Results of a community-based antiretroviral treatment program for HIV-1 infection in Western Uganda. Curr HIV Res 2010 Mar;8(2):179-85.

(918) Kipp W, Konde-Lule J, Saunders LD, Alibhai A, Houston S, Rubaale T, et al. Antiretroviral treatment for HIV in rural Uganda: two-year treatment outcomes of a prospective health centre/community-based and hospital-based cohort. PLoS One 2012;7(7):e40902.

(919) Selke HM, Kimaiyo S, Sidle JE, Vedanthan R, Tierney WM, Shen C, et al. Task-shifting of antiretroviral delivery from health care workers to persons living with

HIV/AIDS: clinical outcomes of a community-based program in Kenya. J Acquir Immune Defic Syndr 2010 Dec;55(4):483-90.

(920) Franke MF, Kaigamba F, Socci AR, Hakizamungu M, Patel A, Bagiruwigize E, et al. Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda. Clin Infect Dis 2013 May;56(9):1319-26.

(921) Braitstein P, Einterz RM, Sidle JE, Kimaiyo S, Tierney W. "Talkin' about a revolution": How electronic health records can facilitate the scale-up of HIV care and treatment and catalyze primary care in resource-constrained settings. J Acquir Immune Defic Syndr 2009 Nov;52 Suppl 1:S54-S57.

(922) Talisuna-Alamo S, Colebunders R, Ouma J, Sunday P, Ekoru K, Laga M, et al. Socioeconomic support reduces nonretention in a comprehensive, community-based antiretroviral therapy program in Uganda. J Acquir Immune Defic Syndr 2012 Apr 1;59(4):e52-e59.

(923) Pop-Eleches C, Thirumurthy H, Habyarimana JP, Zivin JG, Goldstein MP, de WD, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders. AIDS 2011 Mar 27;25(6):825-34.

(924) Lester RT, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet 2010 Nov 27;376(9755):1838-45.

(925) Chung MH, Richardson BA, Tapia K, Benki-Nugent S, Kiarie JN, Simoni JM, et al. A randomized controlled trial comparing the effects of counseling and alarm device on HAART adherence and virologic outcomes. PLoS Med 2011 Mar;8(3):e1000422.

(926) Sarna A, Luchters S, Geibel S, Chersich MF, Munyao P, Kaai S, et al. Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial. J Acquir Immune Defic Syndr 2008 Aug 15;48(5):611-9.

(927) Barnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. Lancet Infect Dis 2011 Dec;11(12):942-51.

(928) Kunutsor S, Walley J, Katabira E, Muchuro S, Balidawa H, Namagala E, et al. Improving clinic attendance and adherence to antiretroviral therapy through a treatment supporter intervention in Uganda: a randomized controlled trial. AIDS Behav 2011 Nov;15(8):1795-802.

(929) Chang LW, Kagaayi J, Nakigozi G, Ssempijja V, Packer AH, Serwadda D, et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. PLoS One 2010;5(6):e10923.

(930) Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. J Acquir Immune Defic Syndr 2010 Jun;54(2):167-79.

(931) Pearson CR, Micek MA, Simoni JM, Hoff PD, Matediana E, Martin DP, et al. Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique. J Acquir Immune Defic Syndr 2007 Oct 1;46(2):238-44.

(932) Nachega JB, Chaisson RE, Goliath R, Efron A, Chaudhary MA, Ram M, et al. Randomized controlled trial of trained patient-nominated treatment supporters providing partial directly observed antiretroviral therapy. AIDS 2010 Jun 1;24(9):1273-80.

(933) Mugusi F, Mugusi S, Bakari M, Hejdemann B, Josiah R, Janabi M, et al. Enhancing adherence to antiretroviral therapy at the HIV clinic in resource constrained countries; the Tanzanian experience. Trop Med Int Health 2009 Oct;14(10):1226-32.

(934) Cantrell RA, Sinkala M, Megazinni K, Lawson-Marriott S, Washington S, Chi BH, et al. A pilot study of food supplementation to improve adherence to antiretroviral therapy among food-insecure adults in Lusaka, Zambia. J Acquir Immune Defic Syndr 2008 Oct 1;49(2):190-5.

(935) Tirivayi N, Koethe JR, Groot W. Clinic-Based Food Assistance is Associated with Increased Medication Adherence among HIV-Infected Adults on Long-Term Antiretroviral Therapy in Zambia. J AIDS Clin Res 2012;3(7):171.

(936) Serrano C, Laporte R, Ide M, Nouhou Y, De TP, Rouveix E, et al. Family nutritional support improves survival, immune restoration and adherence in HIV patients receiving ART in developing country. Asia Pac J Clin Nutr 2010;19(1):68-75.

(937) Ndekha MJ, van Oosterhout JJ, Zijlstra EE, Manary M, Saloojee H, Manary MJ. Supplementary feeding with either ready-to-use fortified spread or corn-soy blend in wasted adults starting antiretroviral therapy in Malawi: randomised, investigator blinded, controlled trial. BMJ 2009;338:b1867.

(938) Posse M, Baltussen R. Costs of providing food assistance to HIV/AIDS patients in Sofala province, Mozambique: a retrospective analysis. Cost Eff Resour Alloc 2013;11(1):20.

(939) Bemelmans M, van den Akker T, Ford N, Philips M, Zachariah R, Harries A, et al. Providing universal access to antiretroviral therapy in Thyolo, Malawi through task shifting and decentralization of HIV/AIDS care. Trop Med Int Health 2010 Dec;15(12):1413-20.

(940) Callaghan M, Ford N, Schneider H. Review A systematic review of task-shifting for HIV treatment and care in Africa. Human Resources for Health 2010;8:8-16.

(941) McGuire M, Goossens S, Kukasha W, Ahoua L, Le Paih M, Munger A, et al. Nurses and medical assistants taking charge: task-shifting HIV care and HAART initiation in resource-constrained and rural Malawi. 2014 Jan 30; 2008.

(942) Torpey KE, Kabaso ME, Mutale LN, Kamanga MK, Mwango AJ, Simpungwe J, et al. Adherence support workers: a way to address human resource constraints in antiretroviral treatment programs in the public health setting in Zambia. PLoS One 2008;3(5):e2204.

(943) Braitstein P, Siika A, Hogan J, Kosgei R, Sang E, Sidle J, et al. A clinician-nurse model to reduce early mortality and increase clinic retention among high-risk HIV-infected patients initiating combination antiretroviral treatment. J Int AIDS Soc 2012;15(1):7.

(944) Udegboka N, Moses John H. Reduction of client waiting time through task shifting in Northern Nigeria. 2014 Jan 30; 2009.

(945) Sanne I, Orrell C, Fox MP, Conradie F, Ive P, Zeinecker J, et al. Nurse versus doctor management of HIV-infected patients receiving antiretroviral therapy (CIPRA-SA): a randomised non-inferiority trial. Lancet 2010 Jul 3;376(9734):33-40.

(946) Boyer S, Eboko F, Camara M, Abe C, Nguini ME, Koulla-Shiro S, et al. Scaling up access to antiretroviral treatment for HIV infection: the impact of decentralization of healthcare delivery in Cameroon. AIDS 2010 Jan;24 Suppl 1:S5-15.

(947) World Health Organization. Treat train retain. Task shifting: Global recommendations and guidelines. WHO 2007 [cited 2014 Jan 24];Available from: URL: http://www.who.int/healthsystems/task_shifting/en/

(948) Friedland G, Harries A, Coetzee D. Implementation issues in tuberculosis/HIV program collaboration and integration: 3 case studies. J Infect Dis 2007 Aug 15;196 Suppl 1:S114-S123.

(949) Topp SM, Chipukuma JM, Giganti M, Mwango LK, Chiko LM, Tambatamba-Chapula B, et al. Strengthening health systems at facility-level: feasibility of integrating antiretroviral therapy into primary health care services in lusaka, zambia. PLoS One 2010;5(7):e11522.

(950) Killam WP, Tambatamba BC, Chintu N, Rouse D, Stringer E, Bweupe M, et al. Antiretroviral therapy in antenatal care to increase treatment initiation in HIV-infected pregnant women: a stepped-wedge evaluation. AIDS 2010 Jan 2;24(1):85-91.

(951) Pfeiffer J, Montoya P, Baptista AJ, Karagianis M, Pugas MM, Micek M, et al. Integration of HIV/AIDS services into African primary health care: lessons learned for health system strengthening in Mozambique - a case study. J Int AIDS Soc 2010;13:3.

(952) Tsague L, Tsiouris FO, Carter RJ, Mugisha V, Tene G, Nyankesha E, et al. Comparing two service delivery models for the prevention of mother-to-child transmission (PMTCT) of HIV during transition from single-dose nevirapine to multi-drug antiretroviral regimens. BMC Public Health 2010;10:753.

(953) Suthar AB, Hoos D, Beqiri A, Lorenz-Dehne K, McClure C, Duncombe C. Integrating antiretroviral therapy into antenatal care and maternal and child health settings: a systematic review and meta-analysis. Bull World Health Organ 2013 Jan 1;91(1):46-56.

(954) Stinson K, Jennings K, Myer L. Integration of antiretroviral therapy services into antenatal care increases treatment initiation during pregnancy: a cohort study. PLoS One 2013;8(5):e63328.

(955) Alamo ST, Wagner GJ, Sunday P, Wanyenze RK, Ouma J, Kamya M, et al. Electronic medical records and same day patient tracing improves clinic efficiency and adherence to appointments in a community based HIV/AIDS care program, in Uganda. AIDS Behav 2012 Feb;16(2):368-74.

(956) Govindasamy D, van SN, Kranzer K, Wood R, Mathews C, Bekker LG. Linkage to HIV care from a mobile testing unit in South Africa by different CD4 count strata. J Acquir Immune Defic Syndr 2011 Nov 1;58(3):344-52.

(957) Larson BA, Brennan A, McNamara L, Long L, Rosen S, Sanne I, et al. Lost opportunities to complete CD4+ lymphocyte testing among patients who tested positive for HIV in South Africa. Bull World Health Organ 2010 Sep 1;88(9):675-80.

(958) April MD, Walensky RP, Chang YC, Pitt J, Freedberg KA, Losina E, et al. HIV Testing Rates and Outcomes in a South African Community, 2001-2006: Implications for Expanded Screening Policies. Jaids-Journal of Acquired Immune Deficiency Syndromes 2009 Jul 1;51(3):310-6.

(959) Clouse K, Pettifor AE, Maskew M, Bassett J, Van RA, Behets F, et al. Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary health care clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr 2013 Feb 1;62(2):e39-e46.

(960) Dalal RP, Macphail C, Mqhayi M, Wing J, Feldman C, Chersich MF, et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa. J Acquir Immune Defic Syndr 2008 Jan 1;47(1):101-7.

(961) Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. J Acquir Immune Defic Syndr 2010 Mar;53(3):405-11.

(962) Tweya H, Feldacker C, Estill J, Jahn A, Ng'ambi W, Ben-Smith A, et al. Are They Really Lost? "True" Status and Reasons for Treatment Discontinuation among HIV Infected Patients on Antiretroviral Therapy Considered Lost to Follow Up in Urban Malawi. PLoS One 2013;8(9):e75761.

(963) Bassett IV, Regan S, Chetty S, Giddy J, Uhler LM, Holst H, et al. Who starts antiretroviral therapy in Durban, South Africa? ... not everyone who should. AIDS 2010 Jan;24:S37-S44.

(964) Rosen S, Long L, Sanne I. The outcomes and outpatient costs of different models of antiretroviral treatment delivery in South Africa. Trop Med Int Health 2008 Aug;13(8):1005-15.

(965) O'Connor C, Osih R, Jaffer A. Loss to follow-up of stable antiretroviral therapy patients in a decentralized down-referral model of care in Johannesburg, South Africa. J Acquir Immune Defic Syndr 2011 Dec 1;58(4):429-32.

(966) Hamers RL, Schuurman R, Sigaloff KCE, Wallis CL, Kityo C, Siwale M, et al. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a multicentre cohort study. Lancet Infectious Diseases 2012 Apr;12(4):307-17.

(967) Kranzer K, Zeinecker J, Ginsberg P, Orrell C, Kalawe NN, Lawn SD, et al. Linkage to HIV Care and Antiretroviral Therapy in Cape Town, South Africa. PLoS One 2010 Nov 2;5(11).

(968) Salomon JA, Vos T, Hogan DR, Gagnon M, Naghavi M, Mokdad A, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. Lancet 2012 Dec 15;380(9859):2129-43.

(969) Medicines Sans Frontier. Untangling the Web of Antiretroviral Price Reductions: 16th Edition. Medicines Sand Frontier 2013 July [cited 2013 Aug 10];Available from: URL: http://msfaccess.org/sites/default/files/AIDS_Report_UTW16_ENG_2013.pdf

(970) Keebler D, Revill P, Braithwaite S, Phillips A, Blaser N, Borquez A, et al. Cost-effectiveness of different strategies to monitor adults on antiretroviral treatment: a combined analysis of three mathematical models. The Lancet Global Health 2014;2(1):e35-e43.

(971) Central Intelligence Agency. The World Factbook: GDP per capita (PPP). Central Intelligence Agency 2014 [cited 2014 Mar 2];Available from: URL: https://www.cia.gov/library/publications/the-world-factbook/fields/2004.html

(972) Sweat M, Gregorich S, Sangiwa G, Furlonge C, Balmer D, Kamenga C, et al. Cost-effectiveness of voluntary HIV-1 counselling and testing in reducing sexual transmission of HIV-1 in Kenya and Tanzania. Lancet 2000 Jul 8;356(9224):113-21.

(973) Waters RC, Ostermann J, Reeves TD, Masnick MF, Thielman NM, Bartlett JA, et al. A Cost-Effectiveness Analysis of Alternative HIV Retesting Strategies in Sub-Saharan Africa. Jaids-Journal of Acquired Immune Deficiency Syndromes 2011;56(5):443-52.

(974) Venkatesh KK, Becker JE, Kumarasamy N, Nakamura YM, Mayer KH, Losina E, et al. Clinical impact and cost-effectiveness of expanded voluntary HIV testing in India. PLoS One 2013;8(5):e64604.

(975) Negin J, Wariero J, Mutuo P, Jan S, Pronyk P. Feasibility, acceptability and cost of home-based HIV testing in rural Kenya. Trop Med Int Health 2009 Aug;14(8):849-55.

(976) Thielman NM, Chu HY, Ostermann J, Itemba DK, Mgonja A, Mtweve S, et al. Cost-effectiveness of free HIV voluntary counseling and testing through a community-based AIDS service organization in Northern Tanzania. Am J Public Health 2006 Jan;96(1):114-9.

(977) Losina E, Toure H, Uhler LM, Anglaret X, Paltiel AD, Balestre E, et al. Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal. PLoS Med 2009 Oct;6(10):e1000173.

(978) Estill J, Tweya H, Egger M, Wandeler G, Feldacker C, Johnson LF, et al. Tracing of patients lost to follow-up and HIV transmission: Mathematical modelling study based on two large ART programmes in Malawi. J Acquir Immune Defic Syndr 2013 Dec 8.

(979) Walensky RP, Wood R, Fofana MO, Martinson NA, Losina E, April MD, et al. The Clinical Impact and Cost-Effectiveness of Routine, Voluntary HIV Screening in South Africa. J Acquir Immune Defic Syndr 2011 Jan 1;56(1):26-35.

(980) Hoffmann CJ, Lewis JJ, Dowdy DW, Fielding KL, Grant AD, Martinson NA, et al. Mortality associated with delays between clinic entry and ART initiation in resource-limited settings: results of a transition-state model. J Acquir Immune Defic Syndr 2013 May 1;63(1):105-11.

(981) Badri M, Lawn SD, Wood R. Short-term risk of AIDS or death in people infected with HIV-1 before antiretroviral therapy in South Africa: a longitudinal study. Lancet 2006 Oct 7;368(9543):1254-9.

(982) WHO. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector Progress report June 2008. WHO 2008 June [cited 2013 Aug 10];Available from: URL: http://www.who.int/hiv/pub/towards_universal_access_report_2008.pdf

(983) UNAIDS. UNAIDS World AIDS Day report 2012. UNAIDS 2012 November 20 [cited 2012 Dec 10];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/documents/epidemiology/2012/gr2012/JC2434_WorldAIDSday_results_en.pdf

(984) Staveteig S, Wang S, Head SK, Bradley SEK, Nybro E. Demographic patterns of HIV testing uptake in Sub-Saharan Africa. DHS comparative report 30. Demographic Health Survey 2013 April [cited 2013 Sep 16];

(985) U.S.Food and Drug administration. First Rapid Home-Use HIV Kit Approved for Self-Testing. U S Food and Drug Administration 2013 [cited 2013 Mar 5];Available from: URL: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm310545.htm

(986) Zachary D, Mwenge L, Muyoyeta M, Shanaube K, Schaap A, Bond V, et al. Field comparison of OraQuick ADVANCE Rapid HIV-1/2 antibody test and two blood-based rapid HIV antibody tests in Zambia. BMC Infect Dis 2012;12:183.

(987) van Dyk AC. Self-testing as strategy to increase the uptake of HIV testing in South Africa. African Journal of AIDS Research 2013;12(1):41-8.

(988) Napierala MS, Baggaley R, Corbett EL. A review of self-testing for HIV: research and policy priorities in a new era of HIV prevention. Clin Infect Dis 2013 Jul;57(1):126-38.

(989) Wright AA, Katz IT. Home testing for HIV. N Engl J Med 2006 Feb 2;354(5):437-40.

(990) Pant Pai N, Balram B, Shivkumar S, Martinez-Cajas JL, Claessens C, Lambert G, et al. Head-to-head comparison of accuracy of a rapid point-of-care HIV test with oral versus whole-blood specimens: a systematic review and meta-analysis. Lancet Infect Dis 2012 May;12(5):373-80.

(991) Ng OT, Chow AL, Lee VJ, Chen MI, Win MK, Tan HH, et al. Accuracy and user-acceptability of HIV self-testing using an oral fluid-based HIV rapid test. PLoS One 2012;7(9):e45168.

(992) Gaydos CA, Hsieh YH, Harvey L, Burah A, Won H, Jett-Goheen M, et al. Will patients "opt in" to perform their own rapid HIV test in the emergency department? Ann Emerg Med 2011 Jul;58(1 Suppl 1):S74-S78.

(993) International Initiative for Impact Evaluation. Thematic Window 2: HIV Oral Self-testing, Phase I Request for Applications. International Initiative for Impact Evaluation 2014 [cited 2013 Nov 13];Available from: URL: http://www.3ieimpact.org/media/filer/2013/02/06/thematic_window_2_hiv_phase_i_rfa_1.pdf

(994) Lucas A, Armbruster B. The cost-effectiveness of expanded HIV screening in the United States. AIDS 2013 Mar 13;27(5):795-801.

(995) Paltiel AD, Weinstein MC, Kimmel AD, Seage GR, Losina E, Zhang H, et al. Expanded screening for HIV in the United States - An analysis of cost-effectiveness. New England Journal of Medicine 2005 Feb 10;352(6):586-95.

(996) Sanders GD, Bayoumi AM, Sundaram V, Bilir SP, Neukermans CP, Rydzak CE, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. N Engl J Med 2005 Feb 10;352(6):570-85.

(997) Sanders GD, Anaya HD, Asch S, Hoang T, Golden JF, Bayoumi AM, et al. Cost-Effectiveness of Strategies to Improve HIV Testing and Receipt of Results: Economic Analysis of a Randomized Controlled Trial. Journal of General Internal Medicine 2010;25(6):556-63.

(998) Yazdanpanah Y, Sloan CE, Charlois-Ou C, Le Vu S, Semaille C, Costagliola D, et al. Routine HIV Screening in France: Clinical Impact and Cost-Effectiveness. PLoS One 2010;5(10).

(999) Walensky RP, Weinstein MC, Kimmel AD, Seage GR, III, Losina E, Sax PE, et al. Routine human immunodeficiency virus testing: an economic evaluation of current guidelines. Am J Med 2005 Mar;118(3):292-300.

(1000) Wilson DP, Hoare A, Regan DG, Law MG. Importance of promoting HIV testing for preventing secondary transmissions: modelling the Australian HIV epidemic among men who have sex with men. Sex Health 2009 Mar;6(1):19-33.

(1001) Bassett IV, Giddy J, Nkera J, Wang B, Losina E, Lu Z, et al. Routine voluntary HIV testing in Durban, South Africa - The experience from an outpatient department. Jaids-Journal of Acquired Immune Deficiency Syndromes 2007 Oct 1;46(2):181-6.

(1002) Alemnji GA, Ngulefac GA, Ndumbe PM, Asonganyi T. Field evaluation of Calypte's AWARE blood serum plasma (BSP) and oral mucosal transudate (OMT) rapid tests for detecting antibodies to HIV-1 and 2 in plasma and oral fluid. Open AIDS J 2009;3:14-8.

(1003) Ingole NA, Mehta PR, Bande RN, Paranjpe SM, Wanjare SW. Evaluation of Calypte AWARE HIV-1/2 OMT antibody test as a screening test in an Indian setting. Indian J Med Microbiol 2010 Oct;28(4):295-8.

(1004) Lee VJ, Tan SC, Earnest A, Seong PS, Tan HH, Leo YS. User acceptability and feasibility of self-testing with HIV rapid tests. J Acquir Immune Defic Syndr 2007 Aug 1;45(4):449-53.

(1005) Mayhood MK, Afwamba IA, Odhiambo CO, Ndanu E, Thielman NM, Morrissey AB, et al. Validation, performance under field conditions, and cost-effectiveness of Capillus HIV-1/HIV-2 and determine HIV-1/2 rapid human immunodeficiency virus antibody assays using sequential and parallel testing algorithms in Tanzania. J Clin Microbiol 2008 Dec;46(12):3946-51.

(1006) de la Fuente L, Rosales-Statkus ME, Hoyos J, Pulido J, Santos S, Bravo MJ, et al. Are participants in a street-based HIV testing program able to perform their own rapid test and interpret the results? PLoS One 2012;7(10):e46555.

(1007) Cremin I, Nyamukapa C, Sherr L, Hallett TB, Chawira G, Cauchemez S, et al. Patterns of Self-reported Behaviour Change Associated with Receiving Voluntary Counselling and Testing in a Longitudinal Study from Manicaland, Zimbabwe. Aids and Behavior 2010;14(3):708-15.

(1008) Muller O, Sarangbin S, Ruxrungtham K, Sittitrai W, Phanuphak P. Sexual Risk Behavior Reduction Associated with Voluntary Hiv Counseling and Testing in Hiv-Infected Patients in Thailand. Aids Care-Psychological and Socio-Medical Aspects of Aids/Hiv 1995;7(5):567-72.

(1009) Carballo-Dieguez A, Frasca T, Balan I, Ibitoye M, Dolezal C. Use of a rapid HIV home test prevents HIV exposure in a high risk sample of men who have sex with men. AIDS Behav 2012 Oct;16(7):1753-60.

(1010) Ng OT, Tan MT. HIV self-testing: money matters. Clin Infect Dis 2013 Sep;57(5):771-2.

(1011) Katz DA, Golden MR, Hughes JP, Farquhar C, Stekler JD. Acceptability and ease of use of home self-testing for HIV among MSM. 2012 Mar 5; 2012.

(1012) UNITAID W. HIV/AIDS Diagnostic Technology Landscape - 2nd edition. UNITAID 2012 June 25Available from: URL: http://www.unitaid.eu/images/marketdynamics/publications/UNITAID-HIV_Diagnostics_Landscape-2nd_edition.pdf

(1013) Joint United Nations Programme on HIV AIDS, Medicines Sans Frontier, United Nations Children's Fund, WHO Headquarters in Geneva. Sources and prices of selected medicines and diagnostics for people living with HIV/AIDS / a joint UNICEF, UNAIDS, WHO,MSF project. - 6th ed. UNAIDS 2005 [cited 2013 Oct 25];Available from: URL: http://www.unaids.org/en/media/unaids/contentassets/dataimport/publications/irc-pub02/jc645-sources_prices_en.pdf

(1014) Bavinton BR, Brown G, Hurley M, Bradley J, Keen P, Conway DP, et al. Which gay men would increase their frequency of HIV testing with home self-testing? AIDS Behav 2013 Jul;17(6):2084-92.

(1015) Hoyos J, Belza MJ, Fernandez-Balbuena S, Rosales-Statkus ME, Pulido J, de la Fuente L. Preferred HIV testing services and programme characteristics among clients of a rapid HIV testing programme. BMC Public Health 2013 Aug 30;13(1):791.

(1016) Spielberg F, Camp S, Ramachandra E. HIV home self-testing: can it work? 2003.

(1017) Spielberg F, Bill and Melinda Gates Foundation. Acceptability of self-testing for STIs in India. 2010.

(1018) Gaydos CA, Solis M, Hsieh YH, Jett-Goheen M, Nour S, Rothman RE. Use of tablet-based kiosks in the emergency department to guide patient HIV self-testing with a point-of-care oral fluid test. Int J STD AIDS 2013 Sep;24(9):716-21.

(1019) Zimbabwe Economy Profile 2013. CIA World Factobook 2013 February 21 [cited 2013 Sep 10];Available from: URL: http://www.indexmundi.com/zimbabwe/economy_profile.html

(1020) Medicines Control Council. Antiretrovirals registered by the Medicines Control Council for the period 1989-2004. Medicines Control Council 2004 July 13 [cited 2013 Sep 7];Available from: URL: http://www.mccza.com/genericDocuments/9.01_Registration_of_antiretroviral_medicines_89-04_Jul04v1.doc

(1021) Clayden P, Harrington M. Seven Ways to Speed Up the Pipeline. Clayden 2013 [cited 2013 Sep 7];Available from: URL: http://www.pipelinereport.org/sites/pipelinereport.drupalgardens.com/files/201306/7%20ways.pdf

(1022) Medicines Control Authority of Zimbabwe. Register for approved human medicines February 2014 update. Medicines Control Authority of Zimbabwe 2014 February [cited 2014 Apr 10];Available from: URL: http://www.mcaz.co.zw/images/regis_h.pdf

(1023) Noguera M, Alt D, Hirschhorn L, Maponga C, Osewe P, Sam-Abbenyi A. Zimbabwe: Antiretroviral Therapy Program—Issues and Opportunities for Initiation and Expansion. WHO 2003 [cited 2014 Apr 10];Available from: URL: http://www.who.int/hiv/amds/countries/zwe_ARVTherapProgJSIDELIVER.pdf

(1024) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Jul 2010. Medicines Control Council 2010 July [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.54_Notification_of_Registration_Jul10_v1.doc

(1025) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Oct 2013. Medicines Control Council 2013 November [cited 2014 Apr 10];Available from: URL: http://www.mccza.com/genericDocuments/12.75_Notification_of_Registration_Oct13_v1.pdf

(1026) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Aug 2011. Medicines Control Council 2011 December [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.60_Notification_of_Registration_Aug11v1.pdf

(1027) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Mar 2013. Medicines Control Council 2013 July [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.71_Notification_of_Registration_Mar13_v1.pdf

(1028) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Feb 2011. Medicines Control Council 2011 April [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.57_Notification_of_Registration_Feb11v1.doc

(1029) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Oct 2012. 2013. 8-9-2013.
Ref Type: Online Source

(1030) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Sept 2012. Medicines Control Council 2012 October [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.68_Notification_of_Registration_Sep12_v1.pdf

(1031) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Oct 2010. Medicines Control Council 2010 October [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.55_Notification_of_Registration_Oct10_v1.doc

(1032) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Jun 2012. Medicines Control Council 2012 July [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.66_Notification_of_Registration_Jun12_v1.pdf

(1033) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Nov 2010. Medicines Control Council 2010 November [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.56_Notification_of_Registration_Nov10_v1.doc

(1034) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Apr 2011. Medicines Control Council 2011 May [cited 2013 Sep 8];Available from: URL: http://www.mccza.com/genericDocuments/12.58_Notification_of_Registration_Apr11v1.doc

(1035) Medicines Control Council. NOTIFICATION OF REGISTRATION OF MEDICINES BY THE REGISTRAR IN TERMS OF SECTION 17 OF THE MEDICINES AND RELATED SUBSTANCES ACT, 1965 (ACT 101 OF 1965) - Aug 2013. Medicines Control Council 2013 September [cited 2014 Apr 10];Available from: URL: http://www.mccza.com/genericDocuments/12.74_Notification_of_Registration_Aug13_v1.pdf

(1036) Petersen EA, Ramirez-Ronda CH, Hardy WD, Schwartz R, Sacks HS, Follansbee S, et al. Dose-related activity of stavudine in patients infected with human immunodeficiency virus. J Infect Dis 1995 Mar;171 Suppl 2:S131-S139.

(1037) Phan V, Thai S, Choun K, Lynen L, van GJ. Incidence of treatment-limiting toxicity with stavudine-based antiretroviral therapy in Cambodia: a retrospective cohort study. PLoS One 2012;7(1):e30647.

(1038) van GJ, De NL, Mushi T, Ubarijoro S, Gashumba D, Gazille C, et al. High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda. Trans R Soc Trop Med Hyg 2007 Aug;101(8):793-8.

(1039) Haubrich RH, Riddler SA, DiRienzo AG, Komarow L, Powderly WG, Klingman K, et al. Metabolic outcomes in a randomized trial of nucleoside, nonnucleoside and protease inhibitor-sparing regimens for initial HIV treatment. AIDS 2009 Jun 1;23(9):1109-18.

(1040) Pujari SN, Dravid A, Naik E, Bhagat S, Tash K, Nadler JP, et al. Lipodystrophy and dyslipidemia among patients taking first-line, World Health Organization-recommended highly active antiretroviral therapy regimens in Western India. J Acquir Immune Defic Syndr 2005 Jun 1;39(2):199-202.

(1041) Crane HM, Grunfeld C, Harrington RD, Uldall KK, Ciechanowski PS, Kitahata MM. Lipoatrophy among HIV-infected patients is associated with higher levels of depression than lipohypertrophy. HIV Med 2008 Oct;9(9):780-6.

(1042) Wohl D, Scherzer R, Heymsfield S, Simberkoff M, Sidney S, Bacchetti P, et al. The associations of regional adipose tissue with lipid and lipoprotein levels in HIV-infected men. J Acquir Immune Defic Syndr 2008 May 1;48(1):44-52.

(1043) De Socio GV, Parruti G, Quirino T, Ricci E, Schillaci G, Adriani B, et al. Identifying HIV patients with an unfavorable cardiovascular risk profile in the clinical practice: results from the SIMONE study. J Infect 2008 Jul;57(1):33-40.

(1044) de WS, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, et al. Incidence and risk factors for new-onset diabetes in HIV-infected patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. Diabetes Care 2008 Jun;31(6):1224-9.

(1045) Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. Lancet 2008 Apr 26;371(9622):1417-26.

(1046) Milinkovic A, Martinez E, Lopez S, De LE, Miro O, Vidal S, et al. The impact of reducing stavudine dose versus switching to tenofovir on plasma lipids, body

composition and mitochondrial function in HIV-infected patients. Antivir Ther 2007;12(3):407-15.

(1047) John M, McKinnon EJ, James IR, Nolan DA, Herrmann SE, Moore CB, et al. Randomized, controlled, 48-week study of switching stavudine and/or protease inhibitors to combivir/abacavir to prevent or reverse lipoatrophy in HIV-infected patients. J Acquir Immune Defic Syndr 2003 May 1;33(1):29-33.

(1048) Martin A, Smith DE, Carr A, Ringland C, Amin J, Emery S, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS 2004 Apr 30;18(7):1029-36.

(1049) Moyle GJ, Sabin CA, Cartledge J, Johnson M, Wilkins E, Churchill D, et al. A randomized comparative trial of tenofovir DF or abacavir as replacement for a thymidine analogue in persons with lipoatrophy. AIDS 2006 Oct 24;20(16):2043-50.

(1050) Carr A, Workman C, Smith DE, Hoy J, Hudson J, Doong N, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipoatrophy: a randomized trial. JAMA 2002 Jul 10;288(2):207-15.

(1051) Tebas P, Zhang J, Hafner R, Tashima K, Shevitz A, Yarasheski K, et al. Peripheral and visceral fat changes following a treatment switch to a non-thymidine analogue or a nucleoside-sparing regimen in HIV-infected subjects with peripheral lipoatrophy: results of ACTG A5110. J Antimicrob Chemother 2009 May;63(5):998-1005.

(1052) Grunfeld C, Saag M, Cofrancesco J, Jr., Lewis CE, Kronmal R, Heymsfield S, et al. Regional adipose tissue measured by MRI over 5 years in HIV-infected and control participants indicates persistence of HIV-associated lipoatrophy. AIDS 2010 Jul 17;24(11):1717-26.

(1053) Lonergan JT, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. Clin Infect Dis 2000 Jul;31(1):162-6.

(1054) Bonnet F, Bonarek M, Abrij A, Beylot J, Morlat P. Metabolic acidosis in HIV-infected patients. Clin Infect Dis 2002 May 1;34(9):1289-90.

(1055) Bonnet F, Bonarek M, Morlat P, Mercie P, Dupon M, Gemain MC, et al. Risk factors for lactic acidosis in HIV-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. Clin Infect Dis 2003 May 15;36(10):1324-8.

(1056) Vrouenraets SM, Treskes M, Regez RM, Troost N, Smulders YM, Weigel HM, et al. Hyperlactataemia in HIV-infected patients: the role of NRTI-treatment. Antivir Ther 2002 Dec;7(4):239-44.

(1057) Wester CW, Okezie OA, Thomas AM, Bussmann H, Moyo S, Muzenda T, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. J Acquir Immune Defic Syndr 2007 Nov 1;46(3):318-22.

(1058) Jouquet G, Bygrave H, Kranzer K, Ford N, Gadot L, Lee J, et al. Cost and cost-effectiveness of switching from d4T or AZT to a TDF-based first-line regimen in a resource-limited setting in rural Lesotho. J Acquir Immune Defic Syndr 2011 Nov 1;58(3):e68-e74.

(1059) Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. Clin Infect Dis 2007 Jul 15;45(2):254-60.

(1060) Boubaker K, Flepp M, Sudre P, Furrer H, Haensel A, Hirschel B, et al. Hyperlactatemia and antiretroviral therapy: the Swiss HIV Cohort Study. Clin Infect Dis 2001 Dec 1;33(11):1931-7.

(1061) Marceau G, Sapin V, Jacomet C, Ughetto S, Cormerais L, Regagnon C, et al. Frequency, risk factors, and outcome of hyperlactatemia in HIV-positive persons: implications for the management of treated patients. Clin Chem 2003 Jul;49(7):1154-62.

(1062) WHO. Antiretroviral therapy for HIV infection in adults and adolescents : recommendations for a public health approach. - 2006 rev. 2006 Jan.

(1063) WHO, UNAIDS, UNICEF. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector : progress report 2009. UNAIDS 2009 [cited 2013 Jul 15];Available from: URL: http://data.unaids.org/pub/Report/2009/20090930_tuapr_2009_en.pdf

(1064) Wits Reproductive Health and HIV Institute. D4T Study. Wits Reproductive Health and HIV Institute 2012 [cited 2014 Apr 11];Available from: URL: http://www.wrhi.ac.za/Pages/ClinicalTrials.aspx

(1065) Hammond E, McKinnon E, Nolan D. Human immunodeficiency virus treatment-induced adipose tissue pathology and lipoatrophy: prevalence and metabolic consequences. Clin Infect Dis 2010 Sep 1;51(5):591-9.

(1066) Fisher M, Moyle GJ, Shahmanesh M, Orkin C, Kingston M, Wilkins E, et al. A randomized comparative trial of continued zidovudine/lamivudine or replacement with tenofovir disoproxil fumarate/emtricitabine in efavirenz-treated HIV-1-infected individuals. J Acquir Immune Defic Syndr 2009 Aug 15;51(5):562-8.

(1067) Semba RD, Martin BK, Kempen JH, Thorne JE, Wu AW. The impact of anemia on energy and physical functioning in individuals with AIDS. Arch Intern Med 2005 Oct 24;165(19):2229-36.

(1068) Volberding PA, Levine AM, Dieterich D, Mildvan D, Mitsuyasu R, Saag M. Anemia in HIV infection: clinical impact and evidence-based management strategies. Clin Infect Dis 2004 May 15;38(10):1454-63.

(1069) O'Brien ME, Kupka R, Msamanga GI, Saathoff E, Hunter DJ, Fawzi WW. Anemia is an independent predictor of mortality and immunologic progression of disease among women with HIV in Tanzania. J Acquir Immune Defic Syndr 2005 Oct 1;40(2):219-25.

(1070) Mugisha JO, Shafer LA, Van der Paal L, Mayanja BN, Eotu H, Hughes P, et al. Anaemia in a rural Ugandan HIV cohort: prevalence at enrolment, incidence, diagnosis and associated factors. Trop Med Int Health 2008 Jun;13(6):788-94.

(1071) Firnhaber C, Smeaton L, Saukila N, Flanigan T, Gangakhedkar R, Kumwenda J, et al. Comparisons of anemia, thrombocytopenia, and neutropenia at initiation of HIV antiretroviral therapy in Africa, Asia, and the Americas. Int J Infect Dis 2010 Dec;14(12):e1088-e1092.

(1072) Moore RD, Forney D. Anemia in HIV-infected patients receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2002 Jan 1;29(1):54-7.

(1073) Semba RD, Shah N, Klein RS, Mayer KH, Schuman P, Gardner LI, et al. Highly active antiretroviral therapy associated with improved anemia among HIV-infected women. AIDS Patient Care STDS 2001 Sep;15(9):473-80.

(1074) Semba RD, Shah N, Vlahov D. Improvement of anemia among HIV-infected injection drug users receiving highly active antiretroviral therapy. J Acquir Immune Defic Syndr 2001 Apr 1;26(4):315-9.

(1075) Huffam SE, Srasuebkul P, Zhou J, Calmy A, Saphonn V, Kaldor JM, et al. Prior antiretroviral therapy experience protects against zidovudine-related anaemia. HIV Med 2007 Oct;8(7):465-71.

(1076) Bussmann H, Wester CW, Thomas A, Novitsky V, Okezie R, Muzenda T, et al. Response to zidovudine/didanosine-containing combination antiretroviral therapy among HIV-1 subtype C-infected adults in Botswana: two-year outcomes from a randomized clinical trial. J Acquir Immune Defic Syndr 2009 May 1;51(1):37-46.

(1077) Semba RD, Shah N, Klein RS, Mayer KH, Schuman P, Vlahov D. Prevalence and cumulative incidence of and risk factors for anemia in a multicenter cohort study of human immunodeficiency virus-infected and -uninfected women. Clin Infect Dis 2002 Jan 15;34(2):260-6.

(1078) Moore RD, Keruly JC, Chaisson RE. Neutropenia and bacterial infection in acquired immunodeficiency syndrome. Arch Intern Med 1995 Oct 9;155(18):1965-70.

(1079) Moore DA, Benepal T, Portsmouth S, Gill J, Gazzard BG. Etiology and natural history of neutropenia in human immunodeficiency virus disease: a prospective study. Clin Infect Dis 2001 Feb 1;32(3):469-75.

(1080) Moyle G, Sawyer W, Law M, Amin J, Hill A. Changes in hematologic parameters and efficacy of thymidine analogue-based, highly active antiretroviral therapy: a meta-analysis of six prospective, randomized, comparative studies. Clin Ther 2004 Jan;26(1):92-7.

(1081) Shaunak S, Bartlett JA. Zidovudine-induced neutropenia: are we too cautious? Lancet 1989 Jul 8;2(8654):91-2.

(1082) Maxson CJ, Greenfield SM, Turner JL. Acute pancreatitis as a common complication of 2',3'-dideoxyinosine therapy in the acquired immunodeficiency syndrome. Am J Gastroenterol 1992 Jun;87(6):708-13.

(1083) Nguyen BY, Yarchoan R, Wyvill KM, Venzon DJ, Pluda JM, Mitsuya H, et al. Five-year follow-up of a phase I study of didanosine in patients with advanced human immunodeficiency virus infection. J Infect Dis 1995 May;171(5):1180-9.

(1084) Seidlin M, Lambert JS, Dolin R, Valentine FT. Pancreatitis and pancreatic dysfunction in patients taking dideoxyinosine. AIDS 1992 Aug;6(8):831-5.

(1085) Lankisch PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. Gut 1995 Oct;37(4):565-7.

(1086) Moyle GJ, Datta D, Mandalia S, Morlese J, Asboe D, Gazzard BG. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. AIDS 2002 Jul 5;16(10):1341-9.

(1087) K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002 Feb;39(2 Suppl 1):S1-266.

(1088) Schmid S, Opravil M, Moddel M, Huber M, Pfammatter R, Keusch G, et al. Acute interstitial nephritis of HIV-positive patients under atazanavir and tenofovir therapy in a retrospective analysis of kidney biopsies. Virchows Arch 2007 Jun;450(6):665-70.

(1089) Fine DM, Perazella MA, Lucas GM, Atta MG. Renal disease in patients with HIV infection: epidemiology, pathogenesis and management. Drugs 2008;68(7):963-80.

(1090) Brennan A, Evans D, Maskew M, Naicker S, Ive P, Sanne I, et al. Relationship between renal dysfunction, nephrotoxicity and death among HIV adults on tenofovir. AIDS 2011 Aug 24;25(13):1603-9.

(1091) Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005 Apr 15;40(8):1194-8.

(1092) Reid A, Stohr W, Walker AS, Williams IG, Kityo C, Hughes P, et al. Severe renal dysfunction and risk factors associated with renal impairment in HIV-infected adults in Africa initiating antiretroviral therapy. Clin Infect Dis 2008 Apr 15;46(8):1271-81.

(1093) Woodward CL, Hall AM, Williams IG, Madge S, Copas A, Nair D, et al. Tenofovir-associated renal and bone toxicity. HIV Med 2009 Sep;10(8):482-7.

(1094) Zimmermann AE, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. Clin Infect Dis 2006 Jan 15;42(2):283-90.

(1095) Islam FM, Wu J, Jansson J, Wilson DP. Relative risk of renal disease among people living with HIV: a systematic review and meta-analysis. BMC Public Health 2012;12.

(1096) Naicker S. End-stage renal disease in sub-Saharan Africa. Ethn Dis 2009;19(1 Suppl 1):S1-S5.

(1097) Pollak MR. Kidney disease and African ancestry. Nat Genet 2008 Oct;40(10):1145-6.

(1098) Reynes J, Cournil A, Peyriere H, Psomas C, Guiller E, Chatron M, et al. Tubular and glomerular proteinuria in HIV-infected adults with estimated glomerular filtration rate >/= 60 ml/min per 1.73 m2. AIDS 2013 May 15;27(8):1295-302.

(1099) Stohr W, Reid A, Walker AS, Ssali F, Munderi P, Mambule I, et al. Glomerular dysfunction and associated risk factors over 4-5 years following antiretroviral therapy initiation in Africa. Antivir Ther 2011;16(7):1011-20.

(1100) Fabian J, Naicker S. HIV and kidney disease in sub-Saharan Africa. Nat Rev Nephrol 2009 Oct;5(10):591-8.

(1101) Mulenga LB, Kruse G, Lakhi S, Cantrell RA, Reid SE, Zulu I, et al. Baseline renal insufficiency and risk of death among HIV-infected adults on antiretroviral therapy in Lusaka, Zambia. AIDS 2008;22(14):1821-7.

(1102) Arribas JR, Pozniak AL, Gallant JE, Dejesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. J Acquir Immune Defic Syndr 2008 Jan 1;47(1):74-8.

(1103) Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis 2003 Apr 15;36(8):1070-3.

(1104) Gallant JE, Winston JA, Dejesus E, Pozniak AL, Chen SS, Cheng AK, et al. The 3-year renal safety of a tenofovir disoproxil fumarate vs. a thymidine analogue-containing regimen in antiretroviral-naive patients. AIDS 2008 Oct 18;22(16):2155-63.

(1105) Mocroft A, Kirk O, Reiss P, de WS, Sedlacek D, Beniowski M, et al. Estimated glomerular filtration rate, chronic kidney disease and antiretroviral drug use in HIV-positive patients. AIDS 2010 Jul 17;24(11):1667-78.

(1106) Scherzer R, Estrella M, Li Y, Choi AI, Deeks SG, Grunfeld C, et al. Association of tenofovir exposure with kidney disease risk in HIV infection. AIDS 2012;26(7):867-75.

(1107) Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. Clin Infect Dis 2010 Sep 1;51(5):496-505.

(1108) Morse CG, Mican JM, Jones EC, Joe GO, Rick ME, Formentini E, et al. The incidence and natural history of osteonecrosis in HIV-infected adults. Clin Infect Dis 2007 Mar 1;44(5):739-48.

(1109) Brown TT, Qaqish RB. Antiretroviral therapy and the prevalence of osteopenia and osteoporosis: a meta-analytic review. AIDS 2006 Nov 14;20(17):2165-74.

(1110) Puoti M, Torti C, Bruno R, Filice G, Carosi G. Natural history of chronic hepatitis B in co-infected patients. J Hepatol 2006;44(1 Suppl):S65-S70.

(1111) Lim SG, Wai CT, Rajnakova A, Kajiji T, Guan R. Fatal hepatitis B reactivation following discontinuation of nucleoside analogues for chronic hepatitis B. Gut 2002 Oct;51(4):597-9.

(1112) Nuesch R, Ananworanich J, Srasuebkul P, Chetchotisakd P, Prasithsirikul W, Klinbuayam W, et al. Interruptions of tenofovir/emtricitabine-based antiretroviral therapy in patients with HIV/hepatitis B virus co-infection. AIDS 2008 Jan 2;22(1):152-4.

(1113) Rivas P, Polo J, de GM, Fernandez-Guerrero ML. Drug points: Fatal lactic acidosis associated with tenofovir. BMJ 2003 Sep 27;327(7417):711.

(1114) Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS 2001 Jan 5;15(1):71-5.

(1115) Clifford DB, Evans S, Yang Y, Acosta EP, Goodkin K, Tashima K, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. Ann Intern Med 2005 Nov 15;143(10):714-21.

(1116) Hawkins T, Geist C, Young B, Giblin A, Mercier RC, Thornton K, et al. Comparison of neuropsychiatric side effects in an observational cohort of efavirenz- and protease inhibitor-treated patients. HIV Clin Trials 2005 Jul;6(4):187-96.

(1117) Moyle G, Fletcher C, Brown H, Mandalia S, Gazzard B. Changes in sleep quality and brain wave patterns following initiation of an efavirenz-containing triple antiretroviral regimen. HIV Med 2006 May;7(4):243-7.

(1118) Fumaz CR, Munoz-Moreno JA, Molto J, Negredo E, Ferrer MJ, Sirera G, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. J Acquir Immune Defic Syndr 2005 Apr 15;38(5):560-5.

(1119) Barrett JS, Joshi AS, Chai M, Ludden TM, Fiske WD, Pieniaszek HJ, Jr. Population pharmacokinetic meta-analysis with efavirenz. Int J Clin Pharmacol Ther 2002 Nov;40(11):507-19.

(1120) Pfister M, Labbe L, Hammer SM, Mellors J, Bennett KK, Rosenkranz S, et al. Population pharmacokinetics and pharmacodynamics of efavirenz, nelfinavir, and indinavir: Adult AIDS Clinical Trial Group Study 398. Antimicrob Agents Chemother 2003 Jan;47(1):130-7.

(1121) Haas DW, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004 Dec 3;18(18):2391-400.

(1122) Rotger M, Telenti A. Optimizing efavirenz treatment: CYP2B6 genotyping or therapeutic drug monitoring? Eur J Clin Pharmacol 2008 Apr;64(4):335-6.

(1123) Nelson MWAWLHCRMM-PBMAMSYHM&FM. Multicentre Open-label study of switching from Atripla to Eviplera for possible efavirenz associated CNS toxicity. 2013 Sep 10; 2013.

(1124) Albrecht MA, Bosch RJ, Hammer SM, Liou SH, Kessler H, Para MF, et al. Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. N Engl J Med 2001 Aug 9;345(6):398-407.

(1125) Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. Clin Infect Dis 2004 Mar 1;38 Suppl 2:S80-S89.

(1126) U.S.Department of Health and Human Services Food and Drug Administration Center for Biologics Evaluation and Research. Guidance for Industry. Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials. U S Food and Drug Administration 2007 [cited 2013 Nov 4];Available from: URL: http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf

(1127) Chu KM, Manzi M, Zuniga I, Biot M, Ford NP, Rasschaert F, et al. Nevirapine- and efavirenz-associated hepatotoxicity under programmatic conditions in Kenya and Mozambique. International Journal of Std & Aids 2012 Jun;23(6):403-7.

(1128) Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. Hepatology 2002 Jan;35(1):182-9.

(1129) Rockstroh JK, Mocroft A, Soriano V, Tural C, Losso MH, Horban A, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. J Infect Dis 2005 Sep 15;192(6):992-1002.

(1130) Law WP, Dore GJ, Duncombe CJ, Mahanontharit A, Boyd MA, Ruxrungtham K, et al. Risk of severe hepatotoxicity associated with antiretroviral therapy in the HIV-NAT Cohort, Thailand, 1996-2001. AIDS 2003 Oct 17;17(15):2191-9.

(1131) Amin J, Kaye M, Skidmore S, Pillay D, Cooper DA, Dore GJ. HIV and hepatitis C coinfection within the CAESAR study. HIV Med 2004 May;5(3):174-9.

(1132) Agwale SM, Tanimoto L, Womack C, Odama L, Leung K, Duey D, et al. Prevalence of HCV coinfection in HIV-infected individuals in Nigeria and characterization of HCV genotypes. J Clin Virol 2004 Dec;31 Suppl 1:S3-S6.

(1133) De SM, Carducci B, De SL, Cavaliere AF, Straface G. Periconceptional exposure to efavirenz and neural tube defects. Arch Intern Med 2002 Feb 11;162(3):355.

(1134) Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. AIDS 2002 Jan 25;16(2):299-300.

(1135) Lewis-Hall FC. Important Change in SUSTIVA® (efavirenz) Package Insert - Change from Pregnancy Category C to D. Bristol-Myers Squibb Company 2005 February [cited 2013 Nov 3];Available from: URL: http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM164871.pdf

(1136) Ford N, Mofenson L, Kranzer K, Medu L, Frigati L, Mills EJ, et al. Safety of efavirenz in first-trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. AIDS 2010 Jun 19;24(10):1461-70.

(1137) Carr A, Vella S, de Jong MD, Sorice F, Imrie A, Boucher CA, et al. A controlled trial of nevirapine plus zidovudine versus zidovudine alone in p24 antigenaemic HIV-

infected patients. The Dutch-Italian-Australian Nevirapine Study Group. AIDS 1996 Jun;10(6):635-41.

(1138) de Jong MD, Vella S, Carr A, Boucher CA, Imrie A, French M, et al. High-dose nevirapine in previously untreated human immunodeficiency virus type 1-infected persons does not result in sustained suppression of viral replication. J Infect Dis 1997 Apr;175(4):966-70.

(1139) Gathe J, Andrade-Villanueva J, Santiago S, Horban A, Nelson M, Cahn P, et al. Efficacy and safety of nevirapine extended-release once daily versus nevirapine immediate-release twice-daily in treatment-naive HIV-1-infected patients. Antivir Ther 2011;16(5):759-69.

(1140) Anton P, Soriano V, Jimenez-Nacher I, Rodriguez-Rosado R, Dona MC, Barreiro PM, et al. Incidence of rash and discontinuation of nevirapine using two different escalating initial doses. AIDS 1999 Mar 11;13(4):524-5.

(1141) Klein R, Struble K. Important changes to Viramune (nevirapine) oral solution and tablets. U S Food and Drug Administration 2009 June 18 [cited 2013 Nov 3];Available from: URL: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm121680.htm

(1142) Martinez E, Blanco JL, Arnaiz JA, Perez-Cuevas JB, Mocroft A, Cruceta A, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001 Jul 6;15(10):1261-8.

(1143) Taiwo BO. Nevirapine toxicity. Int J STD AIDS 2006 Jun;17(6):364-9.

(1144) Wit FW, Weverling GJ, Weel J, Jurriaans S, Lange JM. Incidence of and risk factors for severe hepatotoxicity associated with antiretroviral combination therapy. J Infect Dis 2002 Jul 1;186(1):23-31.

(1145) Stern JO, Robinson PA, Love J, Lanes S, Imperiale MS, Mayers DL. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. J Acquir Immune Defic Syndr 2003 Sep;34 Suppl 1:S21-S33.

(1146) Palmon R, Koo BC, Shoultz DA, Dieterich DT. Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr 2002 Apr 1;29(4):340-5.

(1147) Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. J Acquir Immune Defic Syndr 2004 Apr 15;35(5):538-9.

(1148) Coffie PA, Tonwe-Gold B, Tanon AK, Amani-Bosse C, Bedikou G, Abrams EJ, et al. Incidence and risk factors of severe adverse events with nevirapine-based antiretroviral therapy in HIV-infected women. MTCT-Plus program, Abidjan, Cote d'Ivoire. BMC Infect Dis 2010;10:188.

(1149) Peters PJ, Stringer J, McConnell MS, Kiarie J, Ratanasuwan W, Intalapaporn P, et al. Nevirapine-associated hepatotoxicity was not predicted by CD4 count >/=250 cells/muL among women in Zambia, Thailand and Kenya. HIV Med 2010 Nov;11(10):650-60.

(1150) De LE, Leon A, Arnaiz JA, Martinez E, Knobel H, Negredo E, et al. Hepatotoxicity of nevirapine in virologically suppressed patients according to gender and CD4 cell counts. HIV Med 2008 Apr;9(4):221-6.

(1151) U.S.Food and Drug administration. FDA Public Health Advisory for Nevirapine (Viramune). U S Food and Drug Administration 2005 January 19 [cited 2013 Oct 15];Available from: URL: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051674.htm

(1152) Kesselring AM, Wit FW, Sabin CA, Lundgren JD, Gill MJ, Gatell JM, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. AIDS 2009 Aug 24;23(13):1689-99.

(1153) Phanuphak N, Apornpong T, Teeratakulpisarn S, Chaithongwongwatthana S, Taweepolcharoen C, Mangclaviraj S, et al. Nevirapine-associated toxicity in HIV-infected Thai men and women, including pregnant women. HIV Med 2007 Sep;8(6):357-66.

(1154) Bera E, Mia R. Safety of nevirapine in HIV-infected pregnant women initiating antiretroviral therapy at higher CD4 counts: a systematic review and meta-analysis. S Afr Med J 2012 Nov;102(11 Pt 1):855-9.

(1155) Abbott Laboratories. Kaletra (lopinavir/ritonavir) tablets and oral solution. Prescribing information. Abbott Laboratories 2014 [cited 2014 Apr 13];Available from: URL: http://www.rxabbvie.com/pdf/kaletratabpi.pdf

(1156) Gathe J, da Silva BA, Cohen DE, Loutfy MR, Podzamczer D, Rubio R, et al. A once-daily lopinavir/ritonavir-based regimen is noninferior to twice-daily dosing and results in similar safety and tolerability in antiretroviral-naive subjects through 48 weeks. J Acquir Immune Defic Syndr 2009 Apr 15;50(5):474-81.

(1157) Johnson MA, Gathe JC, Jr., Podzamczer D, Molina JM, Naylor CT, Chiu YL, et al. A once-daily lopinavir/ritonavir-based regimen provides noninferior antiviral activity compared with a twice-daily regimen. J Acquir Immune Defic Syndr 2006 Oct 1;43(2):153-60.

(1158) Molina JM, Podsadecki TJ, Johnson MA, Wilkin A, Domingo P, Myers R, et al. A lopinavir/ritonavir-based once-daily regimen results in better compliance and is non-inferior to a twice-daily regimen through 96 weeks. AIDS Res Hum Retroviruses 2007 Dec;23(12):1505-14.

(1159) Molina JM, Andrade-Villanueva J, Echevarria J, Chetchotisakd P, Corral J, David N, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. Lancet 2008 Aug 23;372(9639):646-55.

(1160) Pulido F, Estrada V, Baril JG, Logue K, Schewe K, Plettenberg A, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. HIV Clin Trials 2009 Mar;10(2):76-87.

(1161) Mills AM, Nelson M, Jayaweera D, Ruxrungtham K, Cassetti I, Girard PM, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS 2009 Aug 24;23(13):1679-88.

(1162) Eron J, Jr., Yeni P, Gathe J, Jr., Estrada V, Dejesus E, Staszewski S, et al. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. Lancet 2006 Aug 5;368(9534):476-82.

(1163) Johnson M, Grinsztejn B, Rodriguez C, Coco J, Dejesus E, Lazzarin A, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. AIDS 2005 Apr 29;19(7):685-94.

(1164) Johnson M, Grinsztejn B, Rodriguez C, Coco J, Dejesus E, Lazzarin A, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. AIDS 2006 Mar 21;20(5):711-8.

(1165) Madruga JV, Berger D, McMurchie M, Suter F, Banhegyi D, Ruxrungtham K, et al. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. Lancet 2007 Jul 7;370(9581):49-58.

(1166) Cohen C, Nieto-Cisneros L, Zala C, Fessel WJ, Gonzalez-Garcia J, Gladysz A, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. Curr Med Res Opin 2005 Oct;21(10):1683-92.

(1167) Young J, Schafer J, Fux CA, Furrer H, Bernasconi E, Vernazza P, et al. Renal function in patients with HIV starting therapy with tenofovir and either efavirenz, lopinavir or atazanavir. AIDS 2012 Mar 13;26(5):567-75.

(1168) Goicoechea M, Liu S, Best B, Sun S, Jain S, Kemper C, et al. Greater tenofovir-associated renal function decline with protease inhibitor-based versus nonnucleoside reverse-transcriptase inhibitor-based therapy. J Infect Dis 2008 Jan 1;197(1):102-8.

(1169) Rollot F, Nazal EM, Chauvelot-Moachon L, Kelaidi C, Daniel N, Saba M, et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir-ritonavir-didanosine. Clin Infect Dis 2003 Dec 15;37(12):e174-e176.

(1170) Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study. J Infect Dis 2013 May 1;207(9):1359-69.

(1171) Fontas E, van LF, Sabin CA, Friis-Moller N, Rickenbach M, d'Arminio MA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? J Infect Dis 2004 Mar 15;189(6):1056-74.

(1172) Hicks C, King MS, Gulick RM, White AC, Jr., Eron JJ, Jr., Kessler HA, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. AIDS 2004 Mar 26;18(5):775-9.

(1173) Martinez E, Domingo P, Galindo MJ, Milinkovic A, Arroyo JA, Baldovi F, et al. Risk of metabolic abnormalities in patients infected with HIV receiving antiretroviral therapy that contains lopinavir-ritonavir. Clin Infect Dis 2004 Apr 1;38(7):1017-23.

(1174) Montes ML, Pulido F, Barros C, Condes E, Rubio R, Cepeda C, et al. Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors. J Antimicrob Chemother 2005 May;55(5):800-4.

(1175) Valerio L, Fontas E, Pradier C, Lavrut T, Garraffo R, Dunais B, et al. Lopinavir/ritonavir combination and total/HDL cholesterol ratio. J Infect 2005 Apr;50(3):229-35.

(1176) Lafeuillade A, Jolly P, Chadapaud S, Hittinger G, Lambry V, Philip G. Evolution of lipid abnormalities in patients switched from stavudine- to tenofovir-containing regimens. J Acquir Immune Defic Syndr 2003 Aug 1;33(4):544-6.

(1177) Bongiovanni M, Chiesa E, Di BA, Meraviglia P, Capetti A, Tordato F, et al. Use of lopinavir/ritonavir in HIV-infected patients failing a first-line protease-inhibitor-containing HAART. J Antimicrob Chemother 2005 Jun;55(6):1003-7.

(1178) Shafran SD, Mashinter LD, Roberts SE. The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations. HIV Med 2005 Nov;6(6):421-5.

(1179) Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. Lancet 2002 Nov 30;360(9347):1747-8.

(1180) Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS 2003 Nov 21;17(17):2479-86.

(1181) Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med 2007 Apr 26;356(17):1723-35.

(1182) Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis 2010 Feb 1;201(3):318-30.

(1183) Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, et al. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. Arch Intern Med 2010 Jul 26;170(14):1228-38.

(1184) Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, et al. Risk of cardiovascular disease from antiretroviral therapy for HIV: a systematic review. PLoS One 2013;8(3):e59551.

(1185) Coplan PM, Nikas A, Japour A, Cormier K, Maradit-Kremers H, Lewis R, et al. Incidence of myocardial infarction in randomized clinical trials of protease

inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. AIDS Res Hum Retroviruses 2003 Jun;19(6):449-55.

(1186) Sanne I, Piliero P, Squires K, Thiry A, Schnittman S. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. J Acquir Immune Defic Syndr 2003 Jan 1;32(1):18-29.

(1187) Squires K, Lazzarin A, Gatell JM, Powderly WG, Pokrovskiy V, Delfraissy JF, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. J Acquir Immune Defic Syndr 2004 Aug 15;36(5):1011-9.

(1188) Brystol Myers Squibb Company. Reyataz (atazanavir sulfate) package insert. 2013.

(1189) Busti AJ, Tsikouris JP, Peeters MJ, Das SR, Canham RM, Abdullah SM, et al. A prospective evaluation of the effect of atazanavir on the QTc interval and QTc dispersion in HIV-positive patients. HIV Med 2006 Jul;7(5):317-22.

(1190) Gianotti N, Guffanti M, Galli L, Margonato A, Chiaravalli G, Bigoloni A, et al. Electrocardiographic changes in HIV-infected, drug-experienced patients being treated with atazanavir. AIDS 2007 Jul 31;21(12):1648-51.

(1191) Albini L, Cesana BM, Motta D, Foca E, Gotti D, Calabresi A, et al. A randomized, pilot trial to evaluate glomerular filtration rate by creatinine or cystatin C in naive HIV-infected patients after tenofovir/emtricitabine in combination with atazanavir/ritonavir or efavirenz. J Acquir Immune Defic Syndr 2012 Jan 1;59(1):18-30.

(1192) Brewster UC, Perazella MA. Acute interstitial nephritis associated with atazanavir, a new protease inhibitor. Am J Kidney Dis 2004 Nov;44(5):e81-e84.

(1193) Dauchy FA, Lawson-Ayayi S, de La FR, Bonnet F, Rigothier C, Mehsen N, et al. Increased risk of abnormal proximal renal tubular function with HIV infection and antiretroviral therapy. Kidney Int 2011 Aug;80(3):302-9.

(1194) Rockwood N, Mandalia S, Bower M, Gazzard B, Nelson M. Ritonavir-boosted atazanavir exposure is associated with an increased rate of renal stones compared with efavirenz, ritonavir-boosted lopinavir and ritonavir-boosted darunavir. AIDS 2011 Aug 24;25(13):1671-3.

(1195) Chang HR, Pella PM. Atazanavir urolithiasis. N Engl J Med 2006 Nov 16;355(20):2158-9.

(1196) Pacanowski J, Poirier JM, Petit I, Meynard JL, Girard PM. Atazanavir urinary stones in an HIV-infected patient. AIDS 2006 Oct 24;20(16):2131.

(1197) Moriyama Y, Minamidate Y, Yasuda M, Ehara H, Kikuchi M, Tsuchiya T, et al. Acute renal failure due to bilateral ureteral stone impaction in an HIV-positive patient. Urol Res 2008 Oct;36(5):275-7.

(1198) The World Bank. Fertility rate, total (births per woman). The World Bank 2014 [cited 2014 Mar 8];Available from: URL: http://data.worldbank.org/indicator/SP.DYN.TFRT.IN

(1199) Barron P, Pillay Y, Doherty T, Sherman G, Jackson D, Bhardwaj S, et al. Eliminating mother-to-child HIV transmission in South Africa. Bull World Health Organ 2013 Jan 1;91(1):70-4.

(1200) National Department of Health. Policy and guidelines for the implementation of the PMTCT programme. National Department of Health 2008 February 11 [cited 2014 Mar 14];Available from: URL: http://southafrica.usembassy.gov/root/pdfs/2008-pmtct.pdf

(1201) National Department of Health SA, SANAC. Clinical Guidelines: PMTCT (Prevention of Mother to Child Transmission). SANAC 2010 [cited 2014 Mar 15];Available from: URL: http://www.fidssa.co.za/images/PMTCT_Guidelines.pdf

(1202) Wouters E, Van DW, van RD, Meulemans H. Impact of baseline health and community support on antiretroviral treatment outcomes in HIV patients in South Africa. AIDS 2008 Nov 30;22(18):2545-8.

(1203) Badri M, Lawn SD, Wood R. Utility of CD4 cell counts for early prediction of virological failure during antiretroviral therapy in a resource-limited setting. BMC Infect Dis 2008;8:89.

(1204) Boulle A, Van CG, Cohen K, Hilderbrand K, Mathee S, Abrahams M, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. JAMA 2008 Aug 6;300(5):530-9.

(1205) Gandhi NR, Moll AP, Lalloo U, Pawinski R, Zeller K, Moodley P, et al. Successful integration of tuberculosis and HIV treatment in rural South Africa: the Sizonq'oba study. J Acquir Immune Defic Syndr 2009 Jan 1;50(1):37-43.

(1206) Fatti G, Grimwood A, Bock P. Better antiretroviral therapy outcomes at primary healthcare facilities: an evaluation of three tiers of ART services in four South African provinces. PLoS One 2010;5(9):e12888.

(1207) Sanne IM, Westreich D, Macphail AP, Rubel D, Majuba P, Van RA. Long term outcomes of antiretroviral therapy in a large HIV/AIDS care clinic in urban South Africa: a prospective cohort study. J Int AIDS Soc 2009;12:38.

(1208) Fatti G, Meintjes G, Shea J, Eley B, Grimwood A. Improved survival and antiretroviral treatment outcomes in adults receiving community-based adherence support: 5-year results from a multicentre cohort study in South Africa. J Acquir Immune Defic Syndr 2012 Dec 1;61(4):e50-e58.

(1209) Bisson GP, Gross R, Bellamy S, Chittams J, Hislop M, Regensberg L, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med 2008 May 20;5(5):e109.

(1210) Johnston V, Fielding K, Charalambous S, Mampho M, Churchyard G, Phillips A, et al. Second-line antiretroviral therapy in a workplace and community-based treatment programme in South Africa: determinants of virological outcome. PLoS One 2012;7(5):e36997.

(1211) Johnston V, Cohen K, Wiesner L, Morris L, Ledwaba J, Fielding KL, et al. Viral Suppression Following Switch to Second-line Antiretroviral Therapy: Associations

With Nucleoside Reverse Transcriptase Inhibitor Resistance and Subtherapeutic Drug Concentrations Prior to Switch. J Infect Dis 2014 Mar;209(5):711-20.

(1212) Fox MP, Ive P, Long L, Maskew M, Sanne I. High rates of survival, immune reconstitution, and virologic suppression on second-line antiretroviral therapy in South Africa. J Acquir Immune Defic Syndr 2010 Apr 1;53(4):500-6.

(1213) Levison JH, Orrell C, Losina E, Lu Z, Freedberg KA, Wood R. Early outcomes and the virological effect of delayed treatment switching to second-line therapy in an antiretroviral roll-out programme in South Africa. Antivir Ther 2011;16(6):853-61.

(1214) Republic of Zimbabwe. Births and Deaths Registration Act [Chapter 5:02]. Republic of Zimbabwe 2001 [cited 2014 Mar 22];Available from: URL: http://www.parlzim.gov.zw/attachments/article/89/BIRTHS_AND_DEATHS_REGISTRATION_ACT_5_02.pdf

(1215) WHO Regional Office for Africa. Civil registration and vital statistics systems. WHO 2014 [cited 2014 Mar 22];Available from: URL: http://www.aho.afro.who.int/profiles_information/index.php/AFRO:Civil_registration_and_vital_statistics_systems

(1216) World Health Organization. Coverage of selected health services for HIV/AIDS prevention and care in less developed countries in 2001. WHO 2002 November [cited 2014 Mar 28];Available from: URL: http://www.who.int/hiv/pub/prev_care/isbn9241590319.pdf

(1217) Perez F, Orne-Gliemann J, Mukotekwa T, Miller A, Glenshaw M, Mahomva A, et al. Prevention of mother to child transmission of HIV: evaluation of a pilot programme in a district hospital in rural Zimbabwe. BMJ 2004 Nov 13;329(7475):1147-50.

(1218) Holmes CB, Wood R, Badri M, Zilber S, Wang B, Maartens G, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. J Acquir Immune Defic Syndr 2006 Aug 1;42(4):464-9.

(1219) Lopez AD, Salomon J, Ahmad O, Murray CJL, Mafat D. Life tables for 191 countries: data, methods and results. WHO 2000 [cited 2014 Jan 21];Available from: URL: http://www.who.int/healthinfo/paper09.pdf

(1220) Losina E, Yazdanpanah Y, Deuffic-Burban S, Wang B, Wolf LL, Messou E, et al. The independent effect of highly active antiretroviral therapy on severe opportunistic disease incidence and mortality in HIV-infected adults in Cote d'Ivoire. Antivir Ther 2007;12(4):543-51.

(1221) Losina E, Anglaret X, Yazdanpanah Y, Wang B, Toure S, Seage GR, III, et al. Impact of opportunistic diseases on chronic mortality in HIV-infected adults in Cote d'Ivoire. S Afr Med J 2006 Jun;96(6):526-9.

(1222) Apondi R, Bunnell R, Ekwaru JP, Moore D, Bechange S, Khana K, et al. Sexual behavior and HIV transmission risk of Ugandan adults taking antiretroviral therapy: 3 year follow-up. AIDS 2011 Jun 19;25(10):1317-27.

(1223) Baggaley RF, White RG, Boily MC. Infectiousness of HIV-infected homosexual men in the era of highly active antiretroviral therapy. AIDS 2010 Sep 24;24(15):2418-20.

(1224) Jin FY, Jansson J, Law M, Prestage GP, Zablotska I, Imrie JCG, et al. Per-contact probability of HIV transmission in homosexual men in Sydney in the era of HAART. AIDS 2010;24(6):907-13.

(1225) Zou G. A modified poisson regression approach to prospective studies with binary data. Am J Epidemiol 2004 Apr 1;159(7):702-6.

(1226) Fetene NW, Feleke AD. Missed opportunities for earlier HIV testing and diagnosis at the health facilities of Dessie town, North East Ethiopia. BMC Public Health 2010;10:362.

(1227) Scott V, Chopra M, Azevedo V, Caldwell J, Naidoo P, Smuts B. Scaling up integration: development and results of a participatory assessment of HIV/TB services, South Africa. Health Res Policy Syst 2010;8:23.

(1228) Dalal S, Lee CW, Farirai T, Schilsky A, Goldman T, Moore J, et al. Provider-initiated HIV testing and counseling: increased uptake in two public community health centers in South Africa and implications for scale-up. PLoS One 2011;6(11):e27293.

(1229) Roura M, Watson-Jones D, Kahawita TM, Ferguson L, Ross DA. Provider-initiated testing and counselling programmes in sub-Saharan Africa: a systematic review of their operational implementation. AIDS 2013 Feb 20;27(4):617-26.

(1230) Van der Borght SF, Schim van der Loeff MF, Clevenbergh P, Kabarega JP, Kamo E, van CK, et al. Long-term voluntary counseling and testing (VCT) uptake dynamics in a multicountry HIV workplace program in sub-Saharan Africa. AIDS Care 2010 Feb;22(2):195-205.

(1231) Kwena ZA, Camlin CS, Shisanya CA, Mwanzo I, Bukusi EA. Short-term mobility and the risk of HIV infection among married couples in the fishing communities along Lake Victoria, Kenya. PLoS One 2013;8(1):e54523.

(1232) Khumalo-Sakutukwa G, Morin SF, Fritz K, Charlebois ED, van RH, Chingono A, et al. Project Accept (HPTN 043): a community-based intervention to reduce HIV incidence in populations at risk for HIV in sub-Saharan Africa and Thailand. J Acquir Immune Defic Syndr 2008 Dec 1;49(4):422-31.

(1233) Kundu CK, Samanta M, Sarkar M, Bhattacharyya S, Chatterjee S. Food supplementation as an incentive to improve pre-antiretroviral therapy clinic adherence in HIV-positive children--experience from eastern India. J Trop Pediatr 2012 Feb;58(1):31-7.

(1234) Govindasamy D, Kranzer K, Ford N. Strengthening the HIV cascade to ensure an effective future ART response in sub-Saharan Africa. Transactions of the Royal Society of Tropical Medicine and Hygiene 2014;108(1):1-+.

(1235) Ware NC, Idoko J, Kaaya S, Biraro IA, Wyatt MA, Agbaji O, et al. Explaining adherence success in sub-Saharan Africa: an ethnographic study. PLoS Med 2009 Jan 27;6(1):e11.

(1236) Toro PL, Katyal M, Carter RJ, Myer L, El-Sadr WM, Nash D, et al. Initiation of antiretroviral therapy among pregnant women in resource-limited countries: CD4+ cell count response and program retention. AIDS 2010 Feb 20;24(4):515-24.

(1237) Decroo T, Telfer B, Biot M, Ma+»k+®r+® J, Dezembro S, Cumba LI, et al. Distribution of antiretroviral treatment through self-forming groups of patients in Tete province, Mozambique. JAIDS Journal of Acquired Immune Deficiency Syndromes 2011;56(2):e39-e44.

(1238) Horvath T, Azman H, Kennedy GE, Rutherford GW. Mobile phone text messaging for promoting adherence to antiretroviral therapy in patients with HIV infection. Cochrane Database Syst Rev 2012;3.

(1239) Taiwo BO, Idoko JA, Welty LJ, Otoh I, Job G, Iyaji PG, et al. Assessing the viorologic and adherence benefits of patient-selected HIV treatment partners in a resource-limited setting. J Acquir Immune Defic Syndr 2010 May 1;54(1):85-92.

(1240) Ndekha M, van Oosterhout JJ, Saloojee H, Pettifor J, Manary M. Nutritional status of Malawian adults on antiretroviral therapy 1 year after supplementary feeding in the first 3 months of therapy. Trop Med Int Health 2009 Sep;14(9):1059-63.

(1241) Labhardt ND, Keiser O, Sello M, Lejone TI, Pfeiffer K, Davies MA, et al. Outcomes of antiretroviral treatment programmes in rural Lesotho: health centres and hospitals compared. J Int AIDS Soc 2013;16:18616.

(1242) Turan JM, Steinfeld RL, Onono M, Bukusi EA, Woods M, Shade SB, et al. The study of HIV and antenatal care integration in pregnancy in Kenya: design, methods, and baseline results of a cluster-randomized controlled trial. PLoS One 2012;7(9):e44181.

(1243) Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. Lancet Infect Dis 2011 Nov;11(11):855-67.

(1244) Harris JB, Hatwiinda SM, Randels KM, Chi BH, Kancheya NG, Jham MA, et al. Early lessons from the integration of tuberculosis and HIV services in primary care centers in Lusaka, Zambia. Int J Tuberc Lung Dis 2008 Jul;12(7):773-9.

(1245) van der Kop ML, Ojakaa DI, Patel A, Thabane L, Kinagwi K, Ekstrom AM, et al. The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain). BMJ Open 2013;3(6).

(1246) Ingle SM, May M, Uebel K, Timmerman V, Kotze E, Bachmann M, et al. Outcomes in patients waiting for antiretroviral treatment in the Free State Province, South Africa: prospective linkage study. AIDS 2010 Nov 13;24(17):2717-25.

(1247) Losina E, Bassett IV, Giddy J, Chetty S, Regan S, Walensky RP, et al. The "ART" of linkage: pre-treatment loss to care after HIV diagnosis at two PEPFAR sites in Durban, South Africa. PLoS One 2010;5(3):e9538.

(1248) Luseno W, echsberg W, Middlesteadt-Ellerson R, Gumula W. Linkages and barriers to care for high-risk South African women testing positive for HIV. 2008 Aug 3; 2008.

(1249) Naidoo NP, Faal M, Venter F, Osih R. Patient retention - reasons why patients do or do not come back for care after HIV testing. 2010; Vienna, Austria 2010.

(1250) Lessells RJ, Mutevedzi PC, Cooke GS, Newell ML. Retention in HIV care for individuals not yet eligible for antiretroviral therapy: rural KwaZulu-Natal, South Africa. J Acquir Immune Defic Syndr 2011 Mar 1;56(3):e79-e86.

(1251) Lawn SD, Myer L, Harling G, Orrell C, Bekker LG, Wood R. Determinants of mortality and nondeath losses from an antiretroviral treatment service in South Africa: implications for program evaluation. Clin Infect Dis 2006 Sep 15;43(6):770-6.

(1252) Murphy RA, Sunpath H, Taha B, Kappagoda S, Maphasa KT, Kuritzkes DR, et al. Low uptake of antiretroviral therapy after admission with human immunodeficiency virus and tuberculosis in KwaZulu-Natal, South Africa. Int J Tuberc Lung Dis 2010 Jul;14(7):903-8.

(1253) Pepper DJ, Marais S, Wilkinson RJ, Bhaijee F, De A, V, Meintjes G. Barriers to initiation of antiretrovirals during antituberculosis therapy in Africa. PLoS One 2011;6(5):e19484.

(1254) Nachega JB, Hislop M, Dowdy DW, Gallant JE, Chaisson RE, Regensberg L, et al. Efavirenz versus nevirapine-based initial treatment of HIV infection: clinical and virological outcomes in Southern African adults. AIDS 2008 Oct 18;22(16):2117-25.

(1255) Nachega JB, Hislop M, Dowdy DW, Lo M, Omer SB, Regensberg L, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr 2006 Sep;43(1):78-84.

(1256) Charalambous S, Innes C, Muirhead D, Kumaranayake L, Fielding K, Pemba L, et al. Evaluation of a workplace HIV treatment programme in South Africa. AIDS 2007 Jul;21 Suppl 3:S73-S78.

(1257) Grimwood A, Magege A, Scheepers E. Public-private partnership achieves long-term ARV adherence in South Africa [abstract CDB0221]. 2008.

(1258) MacPherson P, Moshabela M, Martinson N, Pronyk P. Mortality and loss to follow-up among HAART initiators in rural South Africa. Trans R Soc Trop Med Hyg 2009 Jun;103(6):588-93.

(1259) Nglazi MD, Lawn SD, Kaplan R, Kranzer K, Orrell C, Wood R, et al. Changes in programmatic outcomes during 7 years of scale-up at a community-based antiretroviral treatment service in South Africa. J Acquir Immune Defic Syndr 2011 Jan 1;56(1):e1-e8.

(1260) Fairall LR, Bachmann MO, Louwagie GM, van VC, Chikobvu P, Steyn D, et al. Effectiveness of antiretroviral treatment in a South African program: a cohort study. Arch Intern Med 2008 Jan 14;168(1):86-93.

(1261) Khan MSH. Retention and attrition of patients commenced on HAART at Ladysmith Provincial Hospital in South Africa. South Africa 2009.

(1262) Ford N, Reuter H, Bedelu M, Schneider H, Reuter H. Sustainability of long-term treatment in a rural district: the Lusikisiki model of decentralised HIV/AIDS care: HIV management. Southern African Journal of Hiv Medicine 2006;(25):p-17.

(1263) Cornell M, Myer L, Kaplan R, Bekker LG, Wood R. The impact of gender and income on survival and retention in a South African antiretroviral therapy programme. Trop Med Int Health 2009 Jul;14(7):722-31.

(1264) Dahab M, Charalambous S, Karstaedt A, Hamilton R, Makoa Z. Off the radar screen: comparing reasons for treatment default in a workplace ART programme and a public sector clinic in South Africa [abstract THPE0123]. AIDS 2008.

(1265) Peltzer K, Ramlagan S, Khan MS, Gaede B. The social and clinical characteristics of patients on antiretroviral therapy who are 'lost to follow-up' in KwaZulu-Natal, South Africa: a prospective study. SAHARA J 2011;8(4):179-86.

(1266) Fatti G, Grimwood A, Mothibi E, Shea J. The effect of patient load on antiretroviral treatment programmatic outcomes at primary health care facilities in South Africa: a multicohort study. J Acquir Immune Defic Syndr 2011 Sep 1;58(1):e17-e19.

(1267) Mutevedzi PC, Lessells RJ, Newell ML. Disengagement from care in a decentralised primary health care antiretroviral treatment programme: cohort study in rural South Africa. Trop Med Int Health 2013 Aug;18(8):934-41.