Understanding the acceptability and utility of early antiretroviral therapy to reduce transmission of HIV amongst men who have sex with men in the UK

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Declaration

"I, Victoria Parsons, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis."

Signed:

Abbreviations

Ab	Antibody
AHI	Acute HIV infection
AI	Anal intercourse
aOR	Adjusted odds ratio
ART	Antiretroviral therapy
AZT	Zidovudine
BASHH	British Association of Sexual Health and HIV Research
bDNA	Branched DNA
BDSM	Bondage, discipline, sadism and masochism
BHIVA	British HIV Association
CI	Confidence interval
CROI	Conference on Retroviruses and Opportunistic Infections
CTU	Clinical Trials Unit
DNA	Deoxyribonucleic acid
EHI	Early HIV infection
HAART	Highly active antiretroviral therapy
GRO	General Registrar Office
GUM	Genitourinary medicine
HIV	Human Immunodeficiency Virus
HPA	Health Protection Agency
HPA	Health Protection Scotland
HR	Hazard ratio
FDA	Food and Drug Administration
IAS	International AIDS Society
IDU	Injecting drug use
IQR	Interquartile Range
IWHOD	International Workshop of HIV Observational Databases
LGV	Lymphogranuloma venereum
LREC	Local Research Ethics Committee
MRC	Medical Research Council
MREC	Multicentre Research Ethics Committee
MSM	Men who have sex with men

MSW	Sex between men and women
NASBA	Nucleic acid sequence based amplification
NATSAL	National Survey of Sexual Attitudes and Lifestyles
NHS	National Health Service
NIH	National Institute of Health
NNRTI	Non-nucleoside reverse transcriptase inhibitors
NRTI	Nucleoside reverse transcriptase inhibitors
ONS	Office of National Statistics
OR	Odds ratio
PCP	Pneumocystis pneumonia
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PHE	Public Health England
PHI	Primary HIV infection
PI	Protease inhibitors
PopART	Population Effects of Antiretroviral Therapy to reduce HIV Transmission
PrEP	Pre-exposure prophylaxis
PLWH	People living with HIV
R&D	NHS research and development
RCS	Restricted cubic splines
RCT	Randomised controlled trial
RITA	Recent infection testing algorithm
RNA	Ribonucleic acid
SPARTAC	Short Pulse Antiretroviral Therapy at Seroconversion
STARHS	Serological Testing Algorithm for Recent HIV Seroconversion
START	Strategic Timing of Antiretroviral Therapy
STI	Sexually transmitted infection
THT	Terrence Higgins Trust
UAI	Unprotected (condomless) anal intercourse
UCL	University College London
UK	United Kingdom
UK Register	UK Register of HIV Seroconverters
USA	United States of America
VIF	Variance inflation factor

Glossary

Acute HIV infection (AHI)	The first 30 days following HIV infection. Clinically identified by a HIV test interval ≤30 days or by laboratory evidence of AHI (absence of HIV antibody with either detectable p24 antigen, or HIV RNA).
Agency	Defined by Bandura as "the capacity to exercise control over nature and the quality of one's life" [1].
Casual partner	A partner with whom the index has had sex with once only.
ChemSex	The use of specific illegal substances immediately before or during sex to increase the pleasure, duration and intensity of sex. The exact illegal substances included in the definition vary according to the study but almost always include the following three drugs: methamphetamine (crystal/crystal meth/meth/ice/glass/Tina), mephedrone (meph/drone/meow meow/plant food/MCAT) and GHB (Gammahydroxybutyrate) or GBL (Gammabutyrolactone).
Early ART	Initiation of ART during early HIV infection; either as short-course ART initiated during PHI or long term ART at CD4 count>350.
Early HIV infection (EHI)	The first 12 months of HIV infection.
Enacted stigma	Defined by Scambler as the experience of discrimination from others based on a personal characteristic[2], for example being HIV positive. Also known as external stigma or discrimination.

Felt stigma	Defined by Scambler as the experience of feelings of shame due to a personal characteristic, or the fear of experiencing enacted stigma [2]. Also known as internal stigma or self-stigmatisation.
HIV test interval	The time interval elapsed between HIV antibody negative and positive tests. This is 0 if the patient presents with laboratory evidence of AHI (absence of HIV antibody with either detectable p24 antigen, or HIV RNA) or is RITA incident.
HIV treatment optimism	The belief that HIV is less serious due to the availability of ART. It can be further categorised into health optimism, the belief that ART improves personal health, and transmission optimism, the belief that ART reduces risk of HIV transmission[3].
Primary HIV infection (PHI)	The first 6 months following HIV infection.
Regular partner	A partner with whom the index has had sex with more than once.
Risk compensation	Increased engagement in sexual behaviours that carry a high risk of HIV transmission, due to a perceived lower risk of HIV acquisition or transmission.
Self-efficacy	Defined by Bandura as "the belief in one's capabilities to organize and execute the courses of action required to manage prospective situations."[1].

Sero-adaptive behaviours	Modification of sexual practices to reduce HIV transmission, based on the known HIV status of one's sexual partner. Examples include serosorting and strategic positioning.
Seroconcordant sex	Sex with a partner who is known to have the same HIV status as oneself.
Seroconversion date	Estimated as the midpoint date in the HIV test interval (see definition above), or the date RITA incident, or the date tested p24/HIV RNA positive and antibody negative. Seroconversion date is commonly used as a proxy for date of HIV infection.
Serodiscordant sex	Sex with a partner who is known to have the opposite HIV status as the index partner. In the analyses included in this thesis serodiscordant sex is also considered to have occurred if the partner's HIV status was unknown.
Serosorting	Intentional selection of sexual partners known to have the same HIV-status as the index, for example, an HIV-positive MSM practises exclusive serosorting if he only has sex with men he knows to be HIV positive.
Short-course ART	ART initiated in PHI with the intention of stopping at some point in the future, usually, but not exclusively, after 3-12 months.
Strategic positioning	Intentional selection of sexual positioning to minimise HIV transmission risk with partners who are known to be serodiscordant, or have unknown HIV status as the index.

Transient ART See short-course ART.

Abstract

High viraemia in early HIV infection (EHI) may contribute disproportionately to onward transmission in men who have sex with men (MSM) but early antiretroviral therapy (ART) could minimise risk of transmission. The effectiveness of this strategy depends on viral load (VL) at presentation, sexual behaviour and ART acceptability, which are unknown. This thesis combines quantitative and qualitative methods to understand the acceptability and utility of early ART to reduce HIV transmission in UK MSM.

Using UK Register of HIV Seroconverters data I examined temporal trends in ART initiation and VL at presentation, using Kaplan-Meier and logistic regression. An in-depth interview and cross-sectional survey explored and quantified men's attitudes, beliefs and acceptability of early ART and sexual behaviour. Using logistic regression I examined factors associated with early ART initiation and high-risk sex post diagnosis.

VL peaked in men presenting ~30 days post-seroconversion, plateauing ~day 100. Median(95% CI) time from seroconversion to ART initiation decreased, from 3.7(3.2,4.9) years pre-2000 to 1.4(1.3,1.7) in 2010-11. Early ART was acceptable; 67%(76/114) would have accepted it at diagnosis and 47%(55/116) had initiated it. ART initiation was more likely if men believed it had health benefits or their clinician recommended it. It was perceived to reduce transmission anxiety and provide holistic health benefits, but fear of toxicities and stigma were potential barriers to initiation. Transmission risk was low post-diagnosis; 32%(37/117) abstained from sex and 21%(24/117) exclusively used condoms. However, 35%(41/117) reported high-risk sex, associated with treatment optimism, ChemSex and higher partner numbers pre-diagnosis.

Early ART was acceptable to MSM to prevent transmission, and for perceived holistic health benefits. It is unlikely, however, to be effective in reducing transmission risk during peak viraemia given the low proportion presenting at that stage. Expansion of HIV testing is required to identify MSM during that stage.

Thesis Overview

This multidisciplinary mixed-methods PhD sought to use a combination of epidemiological and social science approaches to answer the overarching research question:

> *"Is early antiretroviral therapy acceptable to men who have sex with men (MSM) with early HIV infection attending UK HIV clinics, and could it be used in this population to reduce HIV transmission?"*

In chapter 1, I provide a background to the thesis by first situating the research idea in the context of the state of knowledge about treatment as prevention (TasP) when I embarked on the PhD. I then give an outline of the global and UK HIV epidemic and describe the natural history and life cycle of HIV. I discuss the virological and immunological events which occur in early HIV infection (EHI) in more detail and outline the methods used to identify recent seroconverters. Finally, I provide an overview of the factors important in determining onward transmission of HIV.

Chapter 2 contains the results from two scoping literature reviews, designed to answer the following questions: "What role does EHI play in the secondary transmission of HIV?" and "What is the rationale for initiation of ART in EHI?". For this part of the thesis I designed the search strategies, reviewed the identified article titles and abstracts for inclusion, charted the data and wrote the reviews. The first literature review presents data published up until the end of 2009, when I finalised my research question, to illustrate the role that recent HIV seroconverters may play in onward transmission of HIV. The second presents a scoping review of literature outlining the rationale for initiation of early ART, including literature published , or presented at key conferences, up until the end of 2010 when I upgraded from MPhil to PhD. Relevant literature published after these dates are included in the discussion, chapter 7. At the end of this chapter I outline the rationale for my thesis and present the overarching research question.

In chapter 3 I outline the methodology and methods I employed during my PhD. A brief description of mixed methods research is presented with a rationale for the selection of this approach to answer the overarching research question. I outline the study design and present the overall aims and research questions for each part of the PhD: workstream 1, which involved statistical analysis of UK Register of HIV Seroconverters (UK Register) data; and workstream 2, comprising of both phase A, the in-depth interview study; and phase B,

the cross-sectional survey. I then provide the full methods for these three parts which combine to address the overarching research question.

In chapter 4 I provide the results of workstream 1, the statistical analysis of data from the UK Register. Here I aimed to examine how high viral load is when HIV seroconverters present to clinic in the UK, what the median time to ART initiation is and whether these have changed over time. For these analyses I was responsible for determining and refining the research questions, downloading and cleaning the data from the UK Register database and operationalising the dependent, and independent, variables of interest. I designed and conducted the statistical analyses and interpreted the results. I presented this work as a poster at the British HIV Association (BHIVA) Spring conference, Liverpool, in April 2009 (appendix 1), at the Conference on Retroviruses and Opportunistic Infections (CROI), Boston in March 2014 (appendix 2), and as an oral presentation at the BHIVA Spring conference, Liverpool, in April 2014 (appendix 3). Selected results were also published in a review article by Hamlyn et al, of which I was a co-author [4].

In chapter 5 I provide the results from workstream 2, phase A, the in-depth interview study. The aim of this part of the PhD was to explore the experience of MSM with EHI around the time of HIV infection and diagnosis, to understand their priorities at this time and their attitudes and beliefs in relation to early ART. I was responsible for designing the study, writing the protocol, developing the topic guide and applying for NHS permission to conduct the study. I liaised with staff at the recruitment clinic to initiate the study and recruited the men for the study. I co-ordinated the study for the duration and conducted all of the in-depth interviews. I then coded and analysed the data using a framework approach, facilitated through use of NVivo, interpreted the results, and developed attitude and belief statements and questions for the cross-sectional survey questionnaire in phase B, the cross-sectional survey. I presented the findings from this qualitative work as a poster at the HIV Therapy conference, Glasgow, in November 2014 (appendix 4).

In chapter 6 I present the results from the cross-sectional survey of MSM recruited to the UK Register. This study aimed to estimate the prevalence of certain attitudes and beliefs towards early ART in a UK-wide population of MSM with EHI and was informed by the qualitative study presented in the previous chapter. It also aimed to examine ART acceptability and uptake in this population and the factors associated with early ART initiation, along with sexual behaviour after HIV diagnosis, and factors associated with

behaviours which carried a high risk of HIV transmission. For this phase, I was responsible for designing the sub-study and refining the research questions. I designed and developed the questionnaire using a combination of previously validated questions from other questionnaires designed for use by HIV-positive MSM and newly-developed questions, and newly developed items based on findings from my in-depth interview study. I then piloted the questionnaire and validated the questions and statements through conducting cognitive interviews with MSM with EHI. I refined the questionnaire design and item wording based on the results of those interviews. I designed and formatted the layout of the final questionnaire using Microsoft Word and co-ordinated the professional printing of the questionnaires. I completed the necessary paperwork to gain NHS ethics approval to conduct the survey as a sub-study, and worked with the UK Register study manager Louise Walker-Nthenda, to obtain NHS research and development (R&D) approval for each of the participating HIV clinics. I liaised with participating centres, presenting the study in person to clinic staff and investigators where necessary, and co-ordinated the running of the survey for its duration. I designed a Microsoft Access database in which to enter the data from the questionnaires and performed the data entry. I cleaned the final dataset, merged it with clinical and demographic data downloaded from the UK Register database, determined eligible respondents, then cleaned and recoded the final dataset ready for analysis. I designed and performed the statistical analyses of the survey data and interpreted the results. I presented this work as a poster at the International Workshop of HIV Observational Databases (IWHOD), Catania, in March 2015 (appendix 5) and BHIVA Spring conference, Brighton, in April 2015 (appendix 6).

Chapter 7 contains the overall discussion for the thesis. Here, I discuss the overall findings from the two workstreams in relation to the overall research question, highlighting where they complement and contrast each other, and in the context of work which was published from 2010 onwards, i.e. (after my literature review and research question were finalised). Whilst the strengths and limitations of the individual workstreams and phases of the study are discussed at the end of the individual results chapters (4, 5 and 6), here I provide an overview of the strengths and limitations of adopting a mixed-methods approach, along with some of the difficulties encountered during the process. Finally, I highlight areas in need of future research and provide implications for policy.

1 Background

This chapter forms a background to the thesis, first giving a flavour of the research focus on TasP when I first started this PhD, in October 2008. I then give an overview of the global and UK epidemiology of HIV infection, the natural history of HIV and AIDS, the life-cycle of the HIV virion and how it interacts with the host's immune system, and how ART interrupts this life-cycle. I then focus on early HIV infection (EHI), defined here as the first year following infection, and the immunological events which occur at this time, outlining the various methods of identifying EHI. Finally, I provide an overview of the factors influencing HIV transmission.

1.1 A bold statement

In January 2008, the Swiss National AIDS Commission released a statement written in French and German by four prominent doctors in Swiss HIV medicine for circulation to Swiss clinicians. This statement has since become so internationally renowned now it is now known simply as "The Swiss Statement". It stated that:

> *"An HIV-infected person on antiretroviral therapy with completely suppressed viraemia ("effective ART") is not sexually infectious, i.e. cannot transmit HIV through sexual contact.".*
>
> Vernazza et al (2008) [5]

With a further qualification that the statement was valid as long as all of the following three circumstances held true;

1. *"The person adheres to antiretroviral therapy, the effects of which must be evaluated regularly by the treating physician."*
2. *"The viral load has been suppressed below the limits of detection (i.e. below 40 copies/mL) for at least six months."*
3. *"There are no other sexually transmitted infections."*

Vernazza et al (2008) [5]

By releasing the statement authors wished for as many as possible of the 17,000 people living with HIV (PLWH) in Switzerland to have a "normal sexual life". In short, the paper was intended to guide the management of individual risk of HIV transmission between serodiscordant monogamous partners. However, global circulation of the paper over the

internet meant it swiftly became one of the most hotly debated topics in HIV research, as it had major implications for public health [6,7]. Did the reduced transmission risk afforded by effective ART, have the potential to reduce the global pandemic if rolled out at a population level?

Whilst few healthcare professionals and researchers doubted that undetectable viral load meant less chance of transmission, many were reticent to claim zero risk of transmission [7]. At this time the HPTN-052 trial was under way to address whether ART can reduce the risk of HIV transmission in serodiscordant couples, though the results were not expected for a number of years. Further questions were asked about the relevance of the Swiss Statement to MSM, as the scientific evidence underlying the statement was largely from studies conducted with heterosexual couples. Some HIV advocacy and prevention groups insisted that the three stipulations that needed to be met for an individual to be classed as "uninfectious" were too nuanced and complicated to be communicated to people living with HIV PLWH in a way that could be understood and incorporated into everyday life. Furthermore, there were concerns that risk compensation may occur (whereby high-risk sexual behaviour increases due to a perceived lower risk of HIV transmission), enacted primarily by abandonment of condom use. On the other hand, other groups welcomed the statement as liberating, citing the stigma reduction, the potential effect on HIV criminalisation laws and the addition of a new method risk-reduction for men to use as major benefits [7].

At the time of the Swiss Statement's release, ART was being recommended by BHIVA for PLWH before CD4 count fell below 350 cells/mm^3, or specifically in primary HIV infection (PHI) if they had an AIDS defining illness or neurological involvement. Under these guidelines any potential public health benefit of TasP would be limited to partners of these individuals, unless expansion of the number of PLWH on ART occurred through earlier initiation. As yet, there was no randomised clinical trial evidence of additional clinical benefit afforded by earlier ART initiation (specifically in PHI or at higher CD4 counts), although trials to rectify this were already underway. The International Network for Strategic Initiatives in Global HIV Trials (INSIGHT) study group were planning the Strategic Timing for Antiretroviral Therapy (START) trial which would compare clinical outcomes between individuals randomised to initiate ART at CD4≥500 cells/mm^3 and those randomised to defer therapy to CD4≤350. For some years there had been research investigating the use of immediate short-course ART during PHI, with the UK-run Short-

Course Antiretroviral Therapy in Primary HIV Infection (SPARTAC) trial underway to address the question as to whether it could delay disease progression.

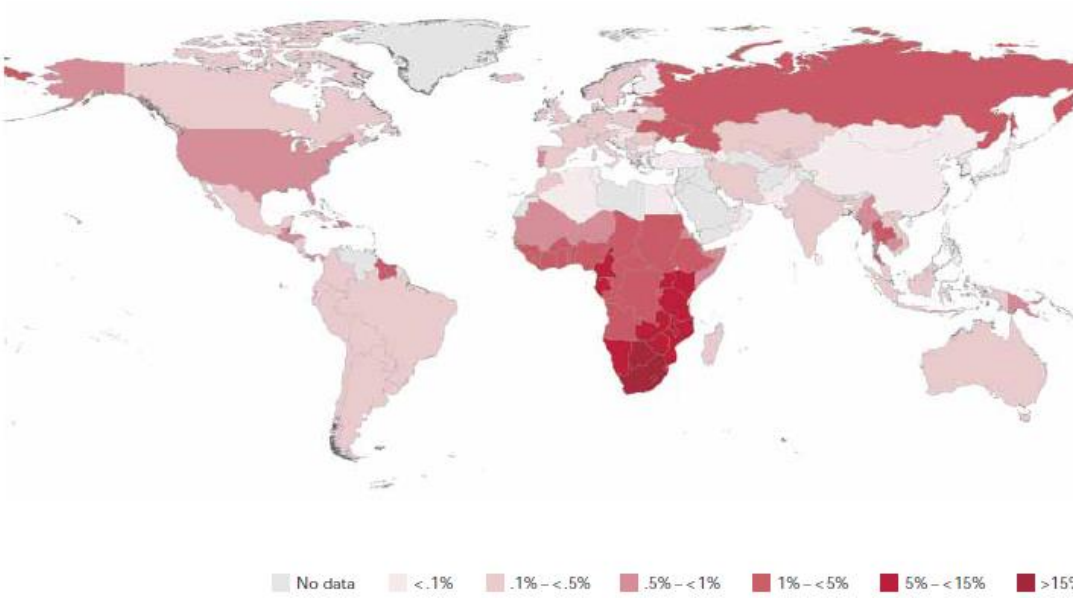
In October 2008, amid international research focus on both the potential public health impact of TasP and the health benefits of early HIV treatment, I started this PhD. I had been awarded a Medical Research Council studentship to investigate the acceptability of early ART amongst recent HIV seroconverters in the UK, by using a mixed methods approach and existing data from the UK Register of HIV seroconverters.

1.2 Epidemiology of HIV

Since the first cases of AIDS were described in the USA in 1981, HIV has spread rapidly across the world so that at the time of embarking on this thesis, an estimated 33.3 million people were living with HIV worldwide [8]. As can be seen in figure 1.1, the largest burden of HIV is in sub-Saharan Africa, where 68% of all PLWH reside, equating to a prevalence of 5% of the adult population (15-49 years). In sub-Saharan countries, the HIV epidemic is largely generalised with the main route of transmission through heterosexual sex. Comparatively, Western Europe has a much lower burden of HIV with 820,000 cases estimated in 2009, equating to a prevalence of 0.2% in the adult population. The epidemic in Western Europe is more diverse than that of sub-Saharan Africa, with a large proportion of transmissions attributable to unprotected sex between men and, to a lesser extent, injecting drug use (IDU), as well as sex between men and women [8].

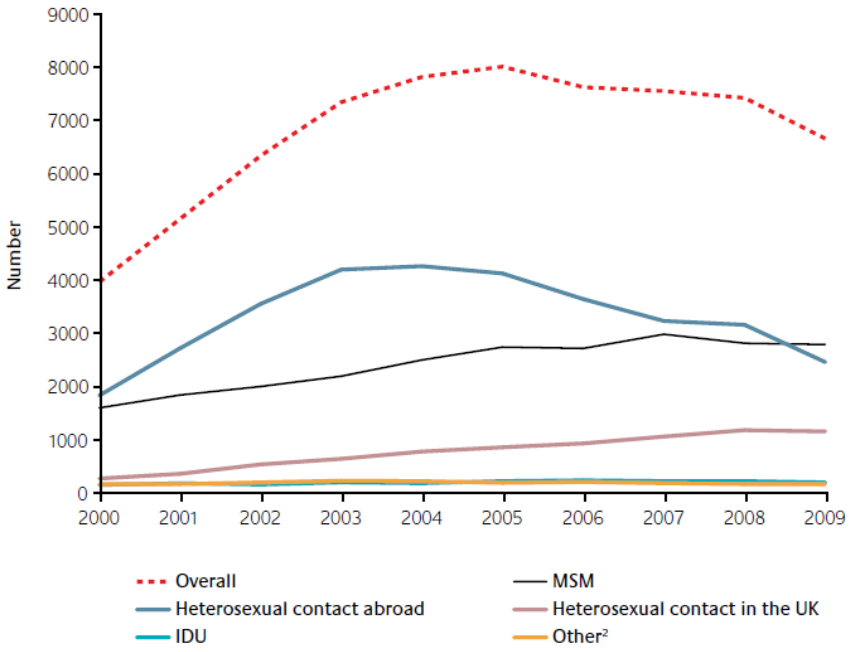
In the UK in 2009, the estimated number of people living with HIV was 86,500 with a disproportionate number of MSM represented in these statistics [9]. Of 6,630 individuals newly diagnosed in 2009, 2,760 (41.6%) were within this risk group (see figure 1.2). Whilst a year on year decline in the number of newly diagnosed PLWH have been observed in the UK since 2005, this is largely due to the decline in heterosexually acquired infections abroad with no comparable decrease observed amongst MSM [9]. Furthermore, a higher proportion of recent infections in 2009 was also observed amongst MSM, compared to heterosexuals, with 1 in 6 infections identified as probably contracted in the last 4-5 months amongst MSM compared to 1 in 16 for heterosexual PLWH [9].

Figure 1.1 Global HIV prevalence in 2009



Source: UNAIDS (2009) [8]

Figure 1.2 Number of new HIV diagnoses in the UK by prevention group: 2000-2009



Source: Health Protection Agency (2009) [9]

1.3 HIV and ART

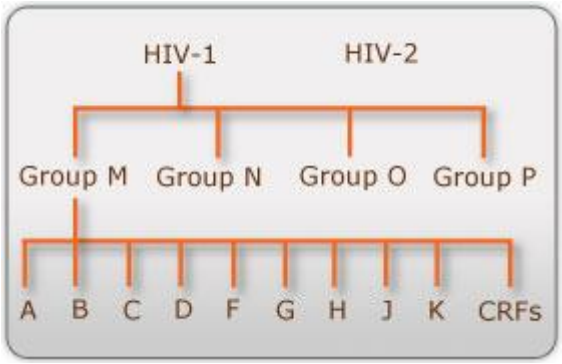
HIV is a retrovirus [10–12] which is transmitted between humans through sexual intercourse [13–15], contact between broken skin or mucosa and blood or other bodily secretions for example through the sharing of contaminated needles [16], blood or organ transfusion [17], and through mother to child (vertical) transmission in the womb, during birth [18,19] or through breastfeeding [20,21]. Without treatment, HIV eventually depletes the host's immune system leaving them susceptible to a range of opportunistic infections and AIDS-defining conditions, followed by death.

HIV can be categorised into two types HIV-1 and HIV-2 [22,23], with HIV-1 being the predominant virus globally and HIV-2 accounting for comparably few infections which are mostly geographically limited to West Africa [8]. Within HIV-1, the virus can be arranged into four groups (see figure 1.3) which are thought to correspond to four isolated introductions of simian immunodeficiency virus into the human population. The majority of HIV infections globally are group "M" viruses, though there are nine subtypes within this group: A, B, C, D, F, G, H, J, K, as well as numerous hybrid combinations of subtypes, known as CRFs (circulating recombinant forms), a product of viral reproduction in the cells of a host infected with two subtypes [24]. Whilst the original distribution of subtypes showed distinct patterns by risk group and geographic region, immigration and sexual mixing have now blended these somewhat [25,26]. The predominant subtype found in the UK remains subtype B, accounting for around 40% of all HIV infections acquired in the UK [27]. Whilst historically this subtype was associated solely with MSM, a recent analysis reported that heterosexual HIV exposures now accounted for 22% of subtype B infections in the UK [27].

1.3.1 The natural course of HIV infection and its clinical manifestations

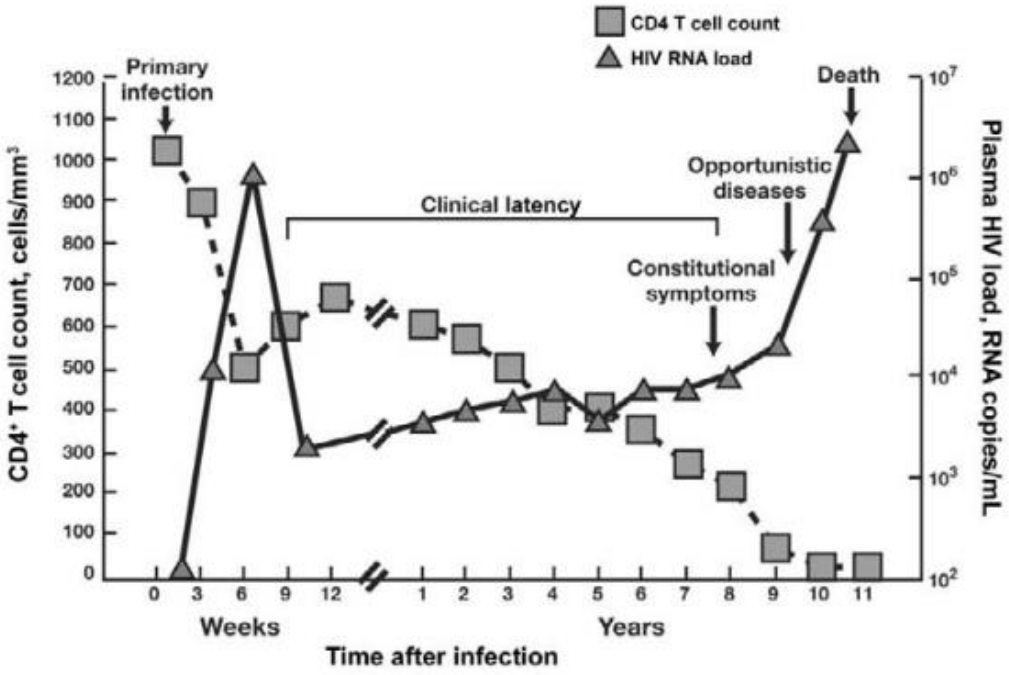
A schematic overview of the full natural history of HIV infection is depicted in figure 1.4, which shows HIV viral dynamics alongside the host's immunological changes over the course of infection, as measured by CD4 count. Broadly speaking, HIV infection is typically described as having three phases: the acute phase, comprising the first month of infection; the latent phase, which is sometimes described as asymptomatic infection; and AIDS, or late stage disease, when the immune system is too damaged to function efficiently.

Figure 1.3 HIV types, groups and subtypes



Source: http://www.aids.info/symptomstypes/HIV-types-groups-and-subtypes [28]

Figure 1.4 Schematic representation of the natural history of HIV infection



Source: Fauci (2007) [29]

HIV, identified in the form of HIV-RNA most commonly through polymerase chain reaction (PCR), but also branched DNA (B-DNA) or nucleic acid sequence based amplification (NASBA) assays, is detectable in blood plasma on average between 4 and 11 days following infection [30]. Viral replication occurs at a very rapid rate at this time with blood plasma viral load documented to rise to over 1 million (6 $\log_{10}$) copies/mL whilst the virus remains largely unrecognised by the host's immune system [31], see figure 1.4. A rapid decline in plasma viraemia occurs around the same time as seroconversion as the immune system mounts a full scale attack on the virus. Eventually, viral load falls to a point where it reaches a plateau; this is termed the viral "set point" or "steady state".

Much variation in the timing and titre of peak viral load and set point has been demonstrated between individuals. Using a mathematical modelling approach Pilcher et al estimated peak viraemia was reached at approximately day 20 after infection with set point occurring around day 54 [32]. Conversely, set point has been demonstrated to occur much later when estimated using data from large epidemiological cohorts; the CASCADE collaboration estimated set point to be reached at around 10 months post-seroconversion [33]. The titre at which viral set-point occurs varies between individuals and has been linked to disease progression rates, with those at higher risk of rapid progression if viral set point is higher [34,35]. After reaching set-point, viral load increases gradually and is accompanied by a corresponding decrease in the host's CD4 count which eventually, reduces the capacity of the immune system to such a level the host becomes susceptible to AIDS defining conditions.

Shortly after infection, an immune response is mounted by the host. This involves activation of CD4+ CCR5+ T cells (CD4 cells), before the development of HIV specific antibody. The development of HIV-specific antibodies is termed seroconversion. These antibodies have been shown to be detectable a median of 2.4 months following the appearance of HIV-DNA in the blood plasma [36]. Some individuals exhibit symptoms around the time of seroconversion, termed acute retroviral syndrome or seroconversion illness, though many remain asymptomatic. It is currently unknown whether acute retroviral syndrome is caused by the high viraemia experienced at this time or the actual immune response to infection. The proportion of newly infected individuals who report experiencing acute retroviral syndrome varies considerably and has been documented to be between 40-85% amongst cohorts of recently infected individuals [30,37,38]. If acute retroviral syndrome develops, symptoms are usually non-specific and vary considerably between individuals,

the most commonly reported symptoms being fever, fatigue and a macro-papular rash [30,39]. Of note, the majority of the work performed examining acute retroviral syndrome has been amongst cohorts of recent seroconverters diagnosed early in infection and the lack of control data in these studies, in addition to potentially long recall periods, introduces the possibility of bias in the estimation of the proportion of individuals who experience symptoms.

In the absence of HIV-treatment, over time the host's CD4 cells are depleted to such a low level that the immune system can no longer fulfil its function to protect from opportunistic infections and illnesses. Advanced HIV infection occurs when CD4 count falls below 200 cells/mm3, and may be accompanied by an AIDS diagnosis if one or more AIDS defining illnesses are also present. The average time elapsed between exposure to HIV and the diagnosis of AIDS is known as the incubation period, and the has been estimated to last around 9 years; ranging between 8.3 years to 9.8 years [40,41]. Individual variation is vast, however, and incubation period duration has been demonstrated to decrease with increasing age at HIV infection [42–44].

In the absence of ART, median survival time following AIDS diagnosis has been estimated at 11 months [45]. Older age at AIDS diagnosis has been shown to be associated with shorter survival and higher CD4 counts at AIDS diagnosis predict longer survival [45]. Estimated survival post-AIDS diagnosis also depends on AIDS defining conditions; ranging from 3 months for HIV neurological AIDS defining conditions to 31 months for candidiasis [46]. In developed countries where ART is available and accessible, these survival estimates are largely irrelevant as intervention with ART increases survival markedly. In the UK, Ewings et al [47] described a 97% reduction in the risk of death amongst those seroconverting in 2004-6 (the HAART era) compared to prior to 1996 (the pre-HAART era); over this time the proportion of seroconverters surviving for 10 years after their estimated date of seroconversion increased from 50% prior to 1996 to 94% in 2004-2006.

Preventing disease progression to AIDS is not the only goal of ART; analysis of data from the Strategic Management of Antiretroviral Therapy (SMART) study also highlighted a high risk of death from non-AIDS defining renal, hepatic and cardiovascular conditions [48]. Associations have subsequently been found between uncontrolled viraemia and biomarkers of coagulation and inflammation [49], underlining the importance of virological control through use of ART.

1.3.2 HIV life cycle and the influence of ART

Whilst it is important to understand the typical disease course of HIV and progression to AIDS the availability of sensitive and specific diagnostic tests for HIV, coupled with the widespread availability of effective ART, has altered the typical course of HIV progression in treated individuals. ART has dramatically decreased the morbidity and mortality caused by HIV/AIDS [35,50–52] and extended life expectancy for PLWH to near that of their HIV negative counterparts [53]. As the focus of my PhD is on MSM with recent HIV infection in the UK, where PLWH currently have access to ART free at the point of use, the next section details the natural life cycle of a HIV virion including how and when the different ART classes disrupt viral reproduction (see figure 1.5).

Since the US Food and Drug Administration (FDA) approved the use of the first antiretroviral agent Zidovudine (AZT) in 1987, there have been a multitude of new drugs licensed to treat HIV. These can be grouped into different drug classes according to which part of the HIV life cycle they affect. There are currently six therapeutic classes of anti-HIV medication available: CCR5 inhibitors, fusion inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI), integrase inhibitors and protease inhibitors.

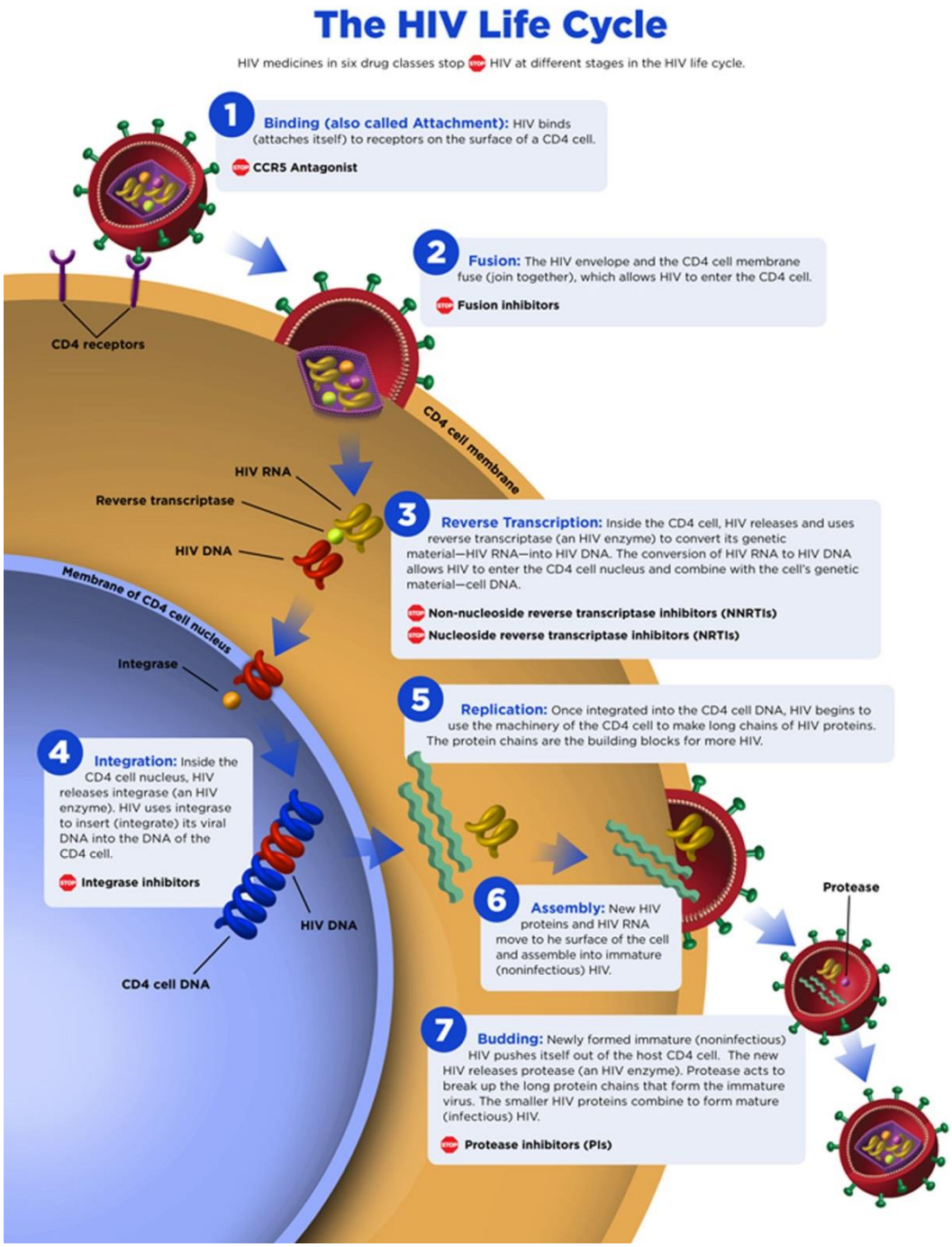
After permeating the mucosa and entering the host organism, a HIV virion will bind with the CCR5 receptors on the surface of a CD4+ T-lymphocytes (CD4) cells. The viral envelope and the CD4 cell membrane fuse and allow the viral RNA and reverse transcriptase to enter the CD4 cell cytoplasm. Two drug classes act at this point of the life cycle: CCR5 inhibitors act by effectively blocking the CCR5 receptor, so that the virion may not bind with the CD4 cell to begin with [54]; and fusion inhibitors prevent a bound virion from fusing to the CD4 cell and permeating the cell membrane [55].

In the absence of any therapy, the reverse transcriptase in the virion's cytoplasm is used by the virus to convert HIV RNA to HIV DNA. The NRTI and NNRTI drug classes act at this point to interrupt the conversion of HIV RNA to DNA. In the absence of these drugs however the newly created HIV DNA passes through the CD4 cell nucleus membrane and, once inside, integrase is used by HIV to integrate viral DNA into the CD4 cell DNA thus allowing use of the protein creating capabilities of the CD4 cell to make HIV protein chains. The fifth drug class integrase inhibitors act here to prevent the integration of CD4 and HIV DNA. HIV

infected CD4 cells where the HIV DNA has successfully fused with the cell DNA are called proviral cells, and these cells can lie dormant for weeks and even years.

The HIV protein chains and HIV RNA created in the CD4 cytoplasm migrate to the cell surface membrane where they assemble and prepare to exit the CD4 cell as immature and uninfectious HIV. Protease is then released within the immature viral particle which serves to break up the long protein chains to smaller proteins. These proteins combine to form mature, and now infectious, HIV which bind with further CD4 cells so that the process repeats. The final class of anti-HIV medication are the protease inhibitors and these act to block the effect of the protease enzyme, which prevents the immature HIV virion from maturing and becoming infectious.

Figure 1.5 HIV virion life cycle including target areas for antiretroviral therapy



Source: https://aidsinfo.nih.gov/education-materials/fact-sheets/19/73/the-hiv-life-cycle [56]

1.4 Early HIV infection

So far I have presented a brief overview of the natural course of HIV infection, however as the population under focus in this thesis are individuals with EHI, it is important to delve deeper into the events occurring over this initial period. In order to do this, it is necessary to clarify the nomenclature of this early period of HIV infection as the terms "early infection", "primary infection" and "acute infection" are often used inter-changeably in the literature. For the purpose of this thesis I will define early infection as the first year following HIV infection, primary infection as the 6 month period following infection and acute infection as the first 30 days following HIV infection. The main focus of this thesis is early infection, the one-year period following infection, which encompasses both the acute and primary infection phases. Where I reference literature which adopts different nomenclature to that outlined above I will report the author's definitions.

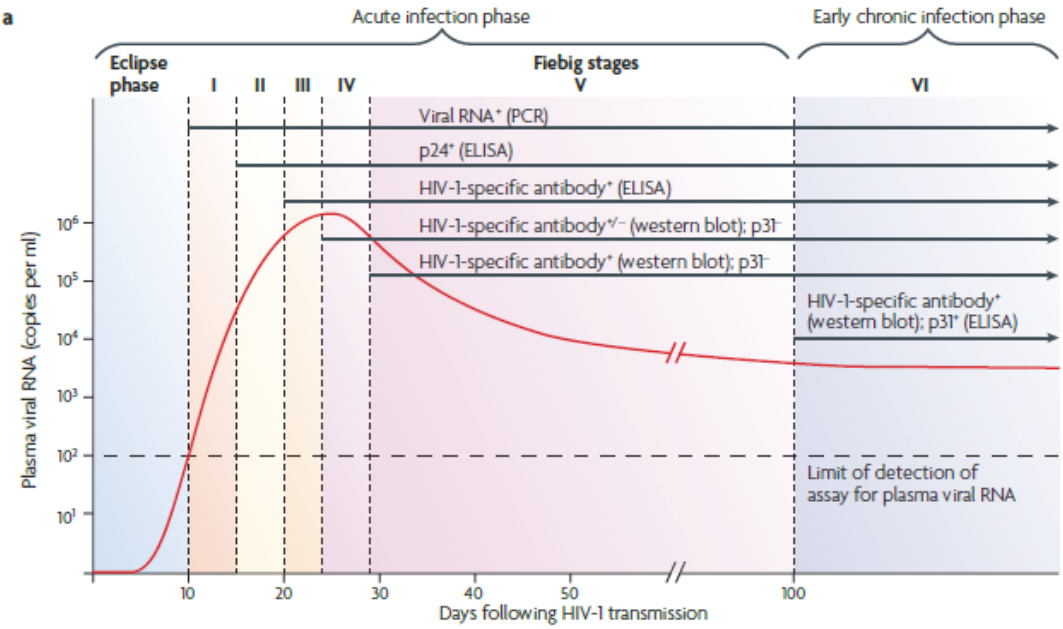
1.4.1 The stages of early HIV infection

Early HIV infection (the first year of infection) can be sub-divided into 7 stages: the eclipse phase; which is then followed by the 6 Fiebig stages sequentially, Fiebig I-VI, see figure 1.6. In this section I present an overview of these stages of EHI as presented by Fiebig et al [57], outlining in detail the immunological and virological changes that occur over this period.

Fiebig et al illustrate that the eclipse phase spans from the point of infection to the time HIV-RNA first becomes detectable by laboratory assays [57]. During this phase it is not possible to identify whether an individual is infected with HIV. The Fiebig stages I-VI are laboratory stages of EHI defined by the emergence of viral and immunological markers which occur in a consistent sequence following HIV infection. As illustrated in figure 1.6, Fiebig stage I corresponds to the appearance of HIV in blood samples as detected by HIV RNA assays and typically spans 5 days (95% CI 3-8) [57]. The authors estimate HIV RNA levels on average increase by 2.0 $\log_{10}$ copies/mL between Fiebig stages I to II ($p<0.001$). In stage II p24 antigen first becomes detectable alongside HIV RNA, typically occurring 10 days following infection (95% CI 7-14). Stage III typically occurs 14 days after infection (95% CI 10-17) and corresponds with the detectability of HIV RNA, p24 antigen and HIV antibody on IgM sensitive enzyme immunoassays (3rd generation EIA) and no HIV-specific bands are present on Western Blot. HIV RNA is known to peak during stage III, around the time of HIV seroconversion. Stage IV is defined by detectability of HIV RNA and HIV antibody on 3rd generation EIA, though p24 antigen may no longer be observed and an indeterminate

Western Blot. The typical duration of each of the first 4 Fiebig stages is very short at 3-5 days each, amounting to a cumulative duration of 19 days (95% CI 15-23). By stage V, HIV RNA and HIV antibody is detectable on 3rd and potentially 2nd generation EIA and Western Blot is reactive but without p31 reactivity. HIV RNA decline is observable by this stage which typically occurs 89 days after infection (95% CI 47-130 days). These phases typically comprise the period of primary infection.

Figure 1.6 Detailed schematic representation of the period of "acute" and "early chronic" HIV infection



Source: McMichael et al (2010) [58].

The final Fiebig stage VI, sometimes termed "early chronic infection", corresponds with HIV RNA and antibody detection (on 2nd, 3rd and 4th generation EIA) and full Western Blot reactivity (including p31). This stage can be further sub-divided according to the detectability of antibody using low and high sensitivity EIAs compared using recent testing algorithms. Laboratory techniques collectively known RITA (Recent Infection Testing Algorithm) or STARHS (Serological Testing Algorithm for Recent HIV Seroconversion) have been developed to identify these early infections. RITA approaches exploit the properties of evolving HIV antibody responses by measuring the avidity, isotype, concentration or proportion of antibodies and are predominantly used for the calculation of incidence

estimates in large populations. Since 2008, PHE (formerly the Health Protection Agency) have been phasing in the use of RITA assays to their routine surveillance programme to estimate HIV incidence in the UK [9]. In addition to allowing incidence calculations the assays facilitate the identification of recent seroconverters for research into acquisition and onward transmission in EHI.

Concerns have been expressed over the sensitivity and specificity of some of the RITA assays, however. In a systematic review of serological assays for detection of recent infection Guy et al [59] reported the median sensitivity across 13 RITA assays to be 89% (ranging from 42%-100% depending on the assay). The median specificity across all 13 assays for detecting established infection was 86.8%, though this ranged from 49.5% to 100%. The window period for identifying recent infection using any given RITA technique varies greatly across individuals and assays, so misclassifications are inevitable. The window periods are estimated as means, which by definition results in a large proportion of the sample being above and below the exact window period cut off. These types of misclassifications tend to cancel each other out in overall incidence calculations, or can be adjusted for by the use of correcting factors. They are more problematic however when RITA assays are used as a diagnostic tool in identifying individuals with recent infection as it is not possible to use a correcting factor. In addition to individual variation in window periods, misclassification can also occur with some of the assays when RITA is applied to patients with advanced disease stage, AIDS or in those who are taking or have taken ART. Currently, the majority of RITA assays are designed to detect recent HIV-1 subtype B infection, so may not apply to HIV-2 or other HIV-1 subtypes.

Whilst the Fiebig stages are useful in identifying the key events of early infection, it should be noted that identification of earlier Fiebig stages is highly dependent on the sensitivity of laboratory assays used, with older less sensitive assays detecting markers at a later time point than their newer counterparts. More recently, the development of fourth generation EIA assays (which detect p24 antigen as well as HIV antibody) has led to proposed modifications to the Fiebig staging system to incorporate the increased sensitivity provided by these assays and the reduced window period of HIV detection [60]. Perhaps the most limiting factor of the use of the Fiebig staging system, however, is the typical delay between HIV infection and presentation to medical services observed amongst recently infected individuals resulting in only a small minority of patients presenting before Fiebig stage III.

1.5 Transmission of HIV

Whilst it is important to understand the natural history of HIV and how the virus interacts with the host on an individual level, it is the transmission dynamics of the virus which dictate the spread of the disease throughout a population. In this section I present a simple model of transmission, proposed by May and Anderson [61] which can be used to assess the rate at which HIV will persist in a susceptible population.

$$R_0=\beta cD$$

This equation facilitates the prediction of the average number of secondary cases of HIV originating from a single infection in a totally susceptible population (R_0) and is a product of the following three parameters:

- the transmission co-efficient or per-contact transmission probability (β),
- the average rate of acquisition of new sexual partners (c),
- the duration of infectiousness (D).

Whilst May and Anderson's model provides a useful starting point from which to understand transmission dynamics, a number of limitations exist in its application to HIV epidemics in general populations. Firstly, R_0 relates to the average number of secondary cases amongst a totally susceptible population, which does not apply in the case of a mature epidemic like that under study in this thesis, where a proportion of the population has HIV and a proportion is susceptible. In this scenario the net reproductive number (R_n) is used to describe the number of new cases arising from an infectious population, and is equal to R_0 multiplied by the proportion of the population susceptible [62]. Secondly, it is problematic to assume homogenous rates of acquisition of new sexual partners; mathematical modelling studies of HIV and other STIs have demonstrated that heterogeneity in the rate of acquisition of sexual partners between sub-populations can affect the overall population rate of secondary transmission, and that rates of mixing between these sub-populations also affects epidemic spread [63,64].

Building on May and Anderson's simple model of transmission, Boerma and Weir deconstructed the three biological parameters βcd into a theoretical framework outlining the proximate determinants of HIV transmission, with the proximate determinants acting as an interface between the underlying social determinants of HIV transmission and the

biological determinants which make up the transmission model as described above [65]. It is notable that Boerma and Weir's framework broadens the c parameter from "the average rate of acquisition of new partners" in May and Anderson's model to "exposure of susceptible to infected persons". In doing this, they implicitly incorporate the proportion susceptible, in addition to the rate of new sexual partner acquisition, into the biological parameter. To acknowledge the importance of sexual mixing and background prevalence, in addition to the rate of partner acquisition, on the c parameter I will henceforth adopt Boerma and Weir's terminology and refer to the c parameter as "exposure of susceptible to infected persons" for the remainder of the thesis. The proximate determinants that influence β, c and d are demonstrated in figure 1.7 and those relevant to this thesis are described in more detail in the following section.

Figure 1.7 Boerma and Weir's conceptual framework of the proximate determinants of sexual transmission of HIV

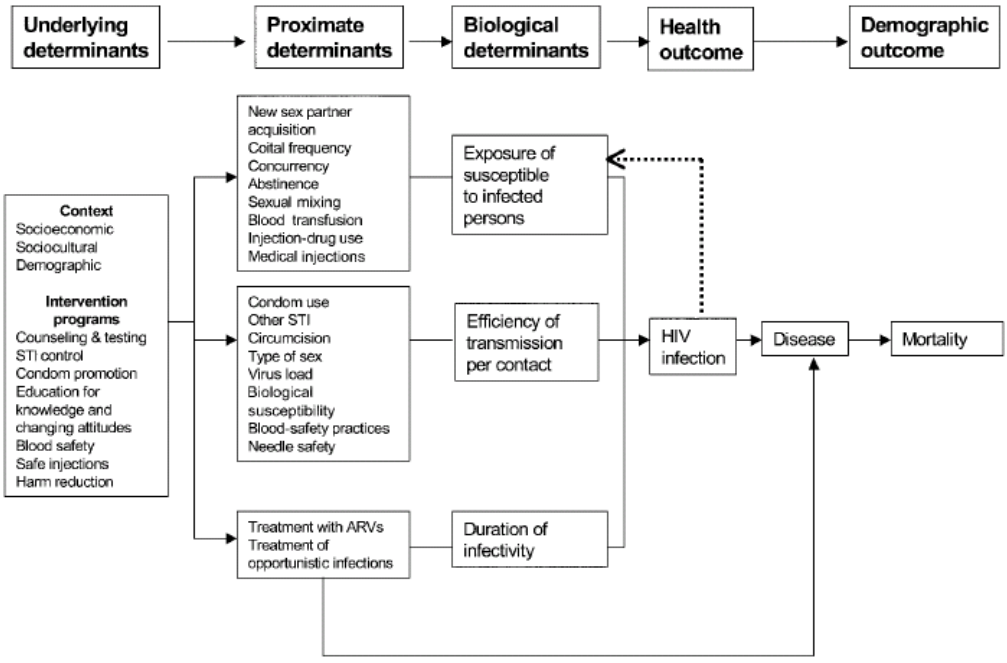


Figure 1. Proximate-determinants conceptual framework for factors affecting the risk of sexual transmission of HIV. ARVs, antiretrovirals; STI, sexually transmitted infection.

Source: Boerma and Weir (2005) [65]

1.5.1 Factors affecting the transmission coefficient (β)

The transmission coefficient (β) is defined as the per-contact transmission probability and is dependent on both the infectiousness of the host individual and the susceptibility of the uninfected partner to HIV [61]. Factors that have been shown to be associated with the infectiousness of an individual include: HIV viral load, typically measured as plasma viral load; the presence of a sexually transmitted infection (STI); HIV type and subtype; and the type of sexual act. Though not so integral to this thesis, factors associated with HIV susceptibility have also been identified as: mucosal integrity, presence of STI, as well as innate and acquired natural resistance to HIV infection. An overview of these factors now follows.

1.5.1.1 HIV viral load

The period of elevated viraemia during acute infection is thought to translate to a period of increased infectiousness in the individual as blood serum viral load has been shown to be highly correlated with HIV transmission. In a seminal piece of research, Quinn et al [66] followed up 415 monogamous couples from Rakai Uganda, who were initially serodiscordant for HIV. Biological and behavioural factors were studied in relation to incident infection in the susceptible partner. Overall HIV incidence was estimated as 11.88 per 100 person years, with no significant differences between male-to-female and female-to-male transmission rates. A strong dose-response effect was found between log-transformed blood serum HIV-1 RNA levels and transmission rates leading the authors to conclude that viral load is a key predictor of heterosexual transmission of HIV-1. Figure 1.8 shows the changes in transmission rates with increasing blood viral load. Also of interest was the finding that no transmission events were observed amongst persons with viral load less than 1500 copies/mL. The same data from the Rakai Project were also used by Gray et al [67] to highlight differences in HIV transmission probability per coital act at varying HIV viral load quantities. The probability of transmission per sexual act was 0.0001, 0.0013, 0.0014 and 0.0023 at viral loads of <1700, 1700-12499, 12500-38500 and >38500 copies/mL, respectively.

The reduction in blood plasma viral load afforded by ART effectively prevents mother-to-child transmission [68], and led researchers to speculate there is a decreased transmission risk from individuals with undetectable viral load [5]. The HTPN-052 trial was under way at the

time of writing to establish whether ART can reduce the risk of HIV transmission in serodiscordant couples.

Figure 1.8 Transmission rate per 100 person years by blood HIV-1 RNA level and sex and of the index partner

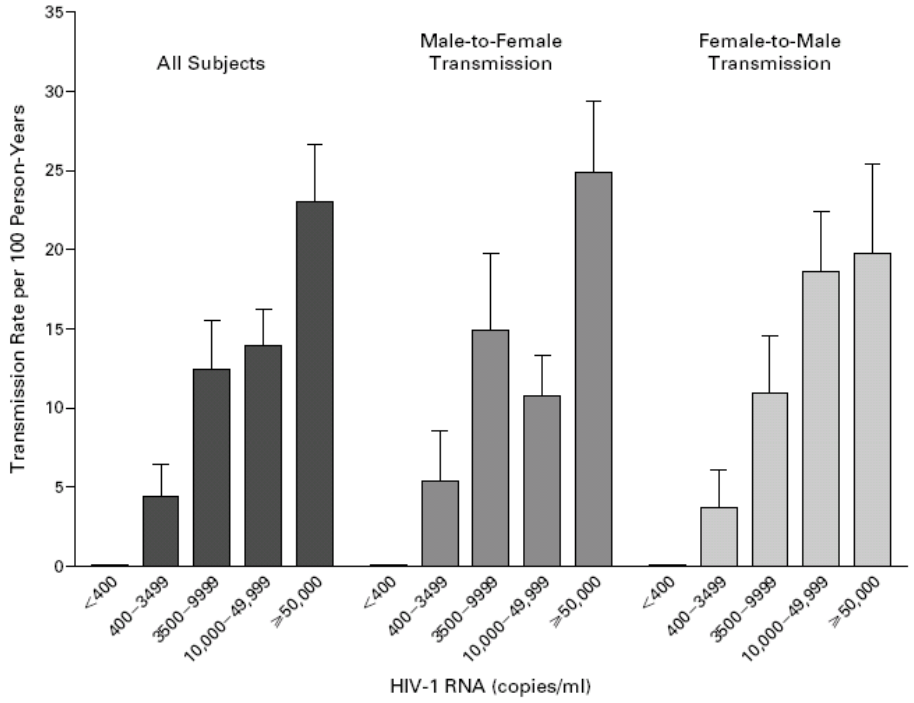


Figure 1. Mean (+SE) Rate of Heterosexual Transmission of HIV-1 among 415 Couples, According to the Sex and the Serum HIV-1 RNA Level of the HIV-1–Positive Partner.

At base line, among the 415 couples, 228 male partners and 187 female partners were HIV-1–positive. The limit of detection of the assay was 400 HIV-1 RNA copies per milliliter. For partners with fewer than 400 HIV-1 RNA copies per milliliter, there were zero transmissions.

Source: Quinn et al (2000) [66]

Although blood plasma viraemia is unlikely to be directly responsible for sexual transmission of HIV in the majority of cases, it has been shown to be highly correlated to HIV-RNA in the genital fluids. Pilcher et al [69] prospectively studied HIV RNA titre in different body fluids amongst 17 people with primary HIV infection (defined as 8-70 days following onset of acute retroviral syndrome symptoms). The authors found that HIV-RNA levels in semen and saliva were statistically correlated with that of blood plasma amongst individuals with primary infection, though both at a lower titre than blood plasma. Longitudinal analysis of blood and plasma samples provided by men recently infected with HIV attending the University of Washington Primary Infection Clinic between 1993 and

2005 has also shown a moderate correlation between levels of HIV-1 RNA in seminal plasma and in blood plasma, with a lower concentration in seminal plasma [70]. Evidence of a correlation between seminal viral load and HIV transmission has also been demonstrated by Chakraborty et al by using epidemiological data fitted to a probabilistic empiric model to examine male-to-female transmission risk per sexual contact at different seminal viral loads [71].

1.5.1.2 Co-infection with STI

For an HIV-positive individual, genital tract infections have been shown to be associated with spikes in genital viral load. Pilcher et al [69] observed genital viral loads exceeding that of their blood plasma in three individuals of 17 with primary infection, all of whom presented with at least one other STI. More recently, Fisher et al [72] used phylogenetic sequencing of the pol gene to establish transmission clusters amongst 859 men recruited from an HIV clinic in Brighton. The rate of transmission in men diagnosed with an STI in the past 3 months was 5.64 times that of those not diagnosed with an STI [72]. Whilst these studies indicate higher transmission probabilities from individuals with STI co-infection and not on ART, Kelley et al found no evidence of an association between rectal HIV shedding and presence of a rectal STI amongst MSM on ART with an undetectable viral load [73].

1.5.1.3 HIV type and subtype

The variation of HIV subtypes in different HIV risk groups observed early in the epidemic led to speculation that different subtypes were more infectious than others or more suited to transmission via certain routes. For example, the high prevalence of subtype B amongst MSM in Northern Europe, US and Australia led to speculation that this clade was more suited to transmission via the rectal lining [74]. Whilst this theory has not been disproven, recent data indicating a growing proportion of non-B subtypes circulating in MSM in the UK may indicate the dominance of certain subtypes amongst particular risk groups in early infection may in fact have been due to assortative sexual mixing [27]. Evidence of higher transmissibility has been observed, however, for subtype A compared to D amongst heterosexual serodiscordant couples in Rakai [75], and compared to C in an in vitro study in India [76]. Conversely, no evidence was found in the risk of vertical transmission between subtypes B and C in Brazil [77]. Differences in infectivity between HIV strains are also hypothesised, with HIV-1 believed to be more infectious than HIV-2 due to higher viral load concentrations in the blood and semen of HIV-1 infected individuals [78]. HIV-1 subtype has

been shown to significantly influence CD4 count at seroconversion with the rate of CD4 decline slowest in subtypes A, C, and CRF02_AG [79].

1.5.1.4 Type of sex

The fact that some sexual acts result in a higher transmission coefficient was established fairly early on in the epidemic. The range of average per-contact risk of transmission for other sexual acts reported in the literature to date may be found in table 1.1. Receptive anal intercourse (AI) with an HIV-positive partner with ejaculation and without a condom carries by far the largest risk of transmission at all disease stages. In the UK, a recent case-control study showed MSM attending HIV testing clinics in London, Manchester and Brighton who seroconverted in the last 18 months to have 3.9 times the odds of engaging in receptive condomless anal intercourse (UAI) since their last HIV negative test than those who did not seroconvert [80]. Higher still was the risk of engaging in receptive UAI with MSM not known to be HIV negative; OR 5.6 (95% CI 2.88-10.81). Seroconverters were also more likely to report insertive UAI with an HIV-positive or unknown status partner than non-seroconverters, OR 2.1 (95% CI 1.1-3.8), though this was less of a risk factor for HIV acquisition.

Table 1.1 Average per-contact probability of HIV transmission for different sexual acts

Study population	Transmission route	Transmission probability (95% CI)	Reference
Heterosexual – Europe	Male to female	0.0005 (0.0003-0.0007)	Downs et al (1996) [81]
Heterosexual - Europe	Female to male	0.0003 (0.0002-0.0005)	Downs et al (1996) [81]
MSM	Unprotected insertive anal intercourse	0.0006	Vittinghoff et al (1999) [82]
MSM - US	Unprotected receptive anal intercourse	0.005-0.03	De-Gruttola et al (1989) [83]
MSW & MSM	Receptive oral intercourse	0.0004	Vittinghoff et al (1999) [82]

Alongside condom use, several risk-reduction strategies have been adopted by MSM to reduce the transmission probability, including engagement in condomless oral sex only, withdrawal prior to ejaculation and “strategic positioning” (defined as taking the receptive position if HIV-positive, and the insertive position if HIV-negative) [84].

1.5.1.5 Factors affecting susceptibility to HIV

The factors above affect the efficiency of transmission from the HIV-positive partner, however a number of factors can influence the potential to acquire HIV infection. As these are of less interest in the context of this thesis they will be briefly outlined in this section below.

The presence of STIs especially ulcerative STIs such as Herpes Simplex Virus (HSV), have been demonstrated to increase the probability of HIV acquisition. Modelling studies have indicated that genital ulceration has been a key co-factor in the spread of HIV throughout sub-Saharan Africa [85]. This is proposed to be due to mechanical and immunological reasons; the presence of ulcerative STIs is thought to increase immune system activation at the point of infection therefore increasing the number of cells present in the genital tract for the virus to bind to [86]. In addition to mucosal compromise through presence of ulcerative STIs, rough sex without adequate lubrication has also been hypothesised to increase the risk of HIV acquisition as it may cause small rips in the mucosa which would allow the virus to pass more easily through the membrane.

The study of individuals who have been repeatedly exposed to HIV but yet remain sero-negative has led to the discovery of mechanisms for natural protection to HIV. Such individuals have been identified amongst high-risk cohorts of commercial sex workers, serodiscordant couples who engage in condomless sex and infants of women living with HIV and have resulted in the identification of both innate genetic and acquired immunological mechanisms of protection [87]. Genetic mutations are known to exist within chemokine receptors, and homozygosity for Δ32 in the CCR5 co-receptor gene has been linked to a decreased susceptibility to HIV, as the receptor is not expressed on the cell surface [88]. Heterozygosity for the Δ32 allele appears to provide less HIV-1 resistance but is associated with significantly slower disease progression [89]. In addition to these mechanisms of innate genetic immunity, a number of immunological changes, postulated to be acquired after repeated exposure to HIV-1, have been shown to be present in people with natural resistance to HIV infection. These changes include cytotoxic T cell responses, helper T-cell responses, humoral immune responses and soluble inhibitory factors, though definitive data to prove these immune changes are responsible for the resistance to HIV acquisition are lacking [87].

Most recently, evidence of the efficacy of pre-exposure prophylaxis (PrEP) to prevent HIV acquisition has increased interest in a biomedical method with which to prevent HIV acquisition [90].

1.5.2 Factors affecting the exposure of infected to susceptible individuals (c)

The second parameter important in determining R_0,as described by May and Anderson, is the average rate of acquisition of new partners (c) [61]. As mentioned in the introduction of section 1.5, whilst the c parameter is often cited as the most important factor influencing R_0 in a totally susceptible population [61,91,92], in a general population where some individuals are not susceptible as they have HIV, background prevalence must also be considered. In addition, heterogeneous rates of partner change between population sub-groups, and importantly the interaction between rate of partner change and sexual mixing, can also lead to substantial variation in epidemic patterns [93]. For these reasons, Boerma and Weir adopt the term "exposure of susceptible to infected partners" instead of "average rate of acquisition of new partners" to describe the c parameter in their proximal determinants framework [65]. They proposed several proximal determinants which influence this parameter, namely the rate of new partner acquisition, sexual mixing, concurrency, and coital frequency.

1.5.2.1 Rate of new partner acquisition

Sexual transmission of HIV prevails in populations where there is a high rate of partner change, though the background prevalence of HIV within the population will dictate the spread of infection [61]. For individuals infected with HIV, higher rate of partner change means coming into contact with a larger number of susceptible individuals, certainly at the beginning of the epidemic when the majority are susceptible to the virus. As background prevalence increases in a fixed population, however, the number individuals who are susceptible decreases and so does the influence of rate of partner change.

1.5.2.2 Sexual mixing

Any population can be divided into different sub-groups by demographic factors, such as ethnicity, age and gender; as well as by risk behaviours, such as the annual number of sex partners or engagement in condomless sex. In a given population, mixing between these sub-groups can occur in different ways and to different extents. Sexual mixing can be categorised into three extreme types: assortative (often called like with like), disassortative

(exclusive between group mixing) and random mixing. Variations in the type of sexual mixing in a population can alter transmission dynamics considerably and lead to different patterns of HIV spread throughout a population. Mixing patterns are dynamic and interchangeable, with different patterns dominating in different social settings and at different stages of an epidemic. Epidemic growth in a predominantly disassortative mixing framework will be slower but will eventually reach a much higher prevalence across all populations [94]. An epidemic in a population exhibiting assortative mixing, results in a rapid increase in prevalence in one risk group, as individuals from different populations do not tend to mix. Assortative mixing of MSM in the highest sexual risk class was observed to be one of the important drivers of the early HIV epidemic in the US [94].

One concept arising from the study of sexual mixing, is that of core groups, which can be defined as a subpopulation with a high rate of partner change and high background prevalence. It is proposed that core-groups have a vital role in the persistence of HIV, especially in situations where HIV prevalence in the general population is relatively low [95]. In these situations core-groups serve to maintain a high reproductive number through the many "bridges" between the core-groups and general population in which there is a larger number of susceptible individuals.

1.5.2.3 Sexual networks, concurrency and partnership type

A social network is defined by Morris et al [96] as "a set of relations (links) among persons (nodes) where the relations can range from kinship and exchange, to affection or physical contact". A sexual network will constitute only a small subset of an individual's social network. In a sexual network it is not only the behaviour of an individual that determines transmission risk but also the behaviour of their partners. Within a sexual network many partnership types will prevail, though most sexual behaviour studies tend to dichotomise partnership types into regular and casual. Gorbach et al [97] outline seven different sexual partner types from qualitative data in their analysis of sexual behaviour in MSM recently diagnosed with HIV in California, USA (see table 1.2). Different partnership types are associated with different sexual behaviour, as factors such as trust, power balance and communication between partners will dictate the level of intimacy and ability to negotiate the use of risk reduction strategies.

Table 1.2 Seven types of sexual partner, as defined by Gorbach et al (2006)[97]

Partner type	Description
Unknown	Someone you have never met before you had sexual contact and never plan to see again
1-time	Someone you had sexual contact with only 1 time, but could find again if necessary
Acquaintance	Someone you have had sexual contact with more than once but not on a regular basis and who you don't socialise with
Friend	Someone you have had sexual contact with more than once but not on a regular basis and who you normally socialise with
Regular	Someone who you have sex with on a regular basis
Main	Someone who is your primary sexual partner
Trade	Someone who you gave sex to for money or other goods, or someone who gave you sex for money or other goods.

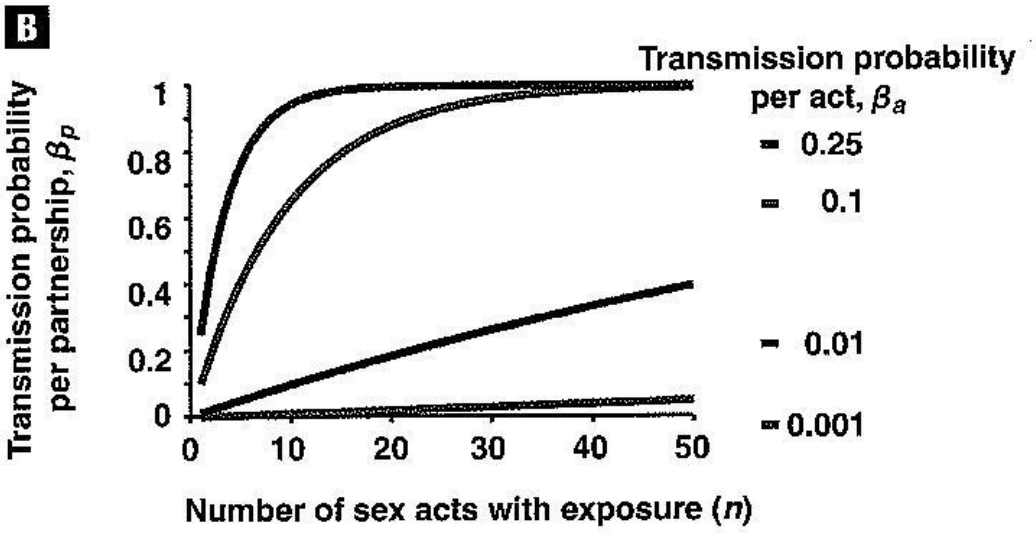
Monogamy and concurrency both describe the timing of relationships within a network. Serial monogamy is when an individual has multiple partners but none of the relationships overlap temporally. Concurrent partnerships are less easily defined, most likely due to the many possible nuances of concurrency. For example, Gorbach and Holmes defined concurrency as "a sexual partnership in which one or more of the partnership members have other partners whilst continuing sexual activity with the original partner" [98] but Koumans et al expanded this definition to someone who "had sex with two or more partners during 1 week in the previous month, [or] has overlapping partners if she/he had partners with overlapping dates of sexual exposure" [99].

Mathematical modelling has indicated that longer monogamous partnerships result in slow progression of the epidemic and lower peak prevalence [96]. Serial monogamous relationships also follow a "protective" sequence, meaning that earlier partners of the index case are not placed at risk from infection acquired in a later partnership. Conversely, concurrency was highlighted early on in the epidemic as a potential driver of epidemic growth, and has subsequently been demonstrated to increase the growth of an epidemic exponentially by acting as a bridge across sexual networks [100]. It places any given concurrent partner of the index case at direct risk of infection from the index, but also, at indirect risk of infection from the other concurrent sexual partners of the index [96].

1.5.2.4 Coital frequency

In a serodiscordant partnership, the probability of transmission from an index case to a susceptible partner increases with the number of sex acts between partners. This pattern of increase follows a binomial distribution, with the probability increasing to a maximum of 1. Variation in the per sex act probability will dictate the trajectory of the transmission probability per partnership curve, with sex acts which carry a high risk of transmission warranting a steeper trajectory over the course of a partnership [101], see figure 1.9. Hence, individuals may mediate the risk of HIV acquisition or transmission by reducing the number of sexual exposures within a partnership, or adopting risk reduction techniques to reduce the probability of transmission (β) per exposure, by using the methods outlined in section 1.5.1.4.

Figure 1.9 Changes in per partnership transmission probability with increasing number of sex acts, and variable per contact transmission probabilities



Source: Garnett (2008) [101]

1.5.3 Duration of infectiousness (D)

The third parameter which influences secondary transmission of HIV is duration of infectiousness. Estimates of the duration of HIV infection vary dramatically and depend on the population under study and whether ART is initiated. As will be reviewed in detail in the next chapter, infectiousness is unlikely to be constant over the course of HIV infection with the elevated viraemia of primary infection and again during end-stage HIV/AIDS, likely resulting in increased transmission potential. The average life course of HIV infection in the UK is estimated to be 8-10 years in the absence of ART [102]. The duration of infection is vastly increased however for those treated with ART [47], and in some cases the estimated life expectancy is likely to be the same as their uninfected equivalent [53]. This increased life expectancy for PLWH on ART has resulted in a longer duration of HIV infection during which time a higher number of sexual partners and larger number of sex acts can be accumulated. However, the goal of ART is to achieve undetectable viral load which likely renders the individual less infectious for the duration viral load remains undetectable [66].

2 Literature review

In this chapter I present the results of the two scoping literature reviews I conducted. Due to the multidisciplinary, mixed methods nature of this thesis conducting a systematic review of the literature was neither appropriate, nor possible given the time constraints. Instead multiple scoping reviews were conducted, using systematic searches to identify potentially relevant literature. The first review examines the role that individuals with EHI play in secondary transmission, and includes research published or presented at conferences up to April 2009. The second review covers literature published or presented at conferences up to March 2010, assessing the rationale for initiation of ART in EHI, focussing on short-course ART in PHI, ART initiation at CD4>350cells/mm^3 and TasP. All relevant research published after these reviews were conducted are included in the thesis discussion, chapter 7. At the end of this chapter I outline the rationale for my thesis and present the overarching research question.

2.1 What role does early HIV infection play in the secondary transmission of HIV?

The simple model for HIV transmission ($R_0=\beta cD$) as presented in section 1.5, is typically applied over the whole duration of HIV infection but equally can be applied to each stage of infection if the parameters β (the per-contact risk of transmission), c (rate of exposure of susceptible to infected individuals) and D (the duration of infectiousness) are thought to vary enough by disease stage to impact on R_0 (the basic reproductive number). Whether recent seroconverters contribute disproportionally to secondary transmission can therefore be assessed by examining changes in the parameters β, c, and D between HIV stages and the corresponding impact of such changes on R_0. In this section I use the simple model of HIV transmission as a framework to help summarise the research performed to date examining secondary transmission from individuals with EHI.

2.1.1 Literature review scope and search strategy

This review aimed to examine the literature to establish the role individuals with EHI play in the onward sexual transmission of HIV. To do this I searched PubMed (which includes Medline) and Ovid (which includes PsychINFO, EMBASE), for English language articles published up until April 2009, using the search terms in table 2.1, in this case formatted for Ovid. I reviewed all identified article titles and abstracts to identify any studies which

estimated either the per-contact risk of transmission, the proportion of HIV transmissions by HIV disease stage, or sexual behaviour over EHI. In line with the scoping review methods outlined by Arksey and O'Malley [103], no a-priori restrictions were placed on the methods used in studies or the quality of the studies as the aim was to summarise the full range of published information to enable the identification of gaps in knowledge. I first reviewed the abstracts and then the full papers or conference proceedings for studies identified as potentially relevant, charting their findings according to outcome (estimated per-contact HIV transmission, the proportion of infections attributable to each disease stage or sexual behaviour during EHI) as well as the study design (mathematical models, phylogenetic studies or observational studies). The reference lists of relevant articles were manually checked for publications which met the above criteria and may not have been picked up in the database searches.

Table 2.1 Database search strategy formatted for Ovid

Boolean operator	Search term	Field
	"HIV" OR "Human immunodeficiency" OR "Human immuno-deficiency" OR "AIDS" OR "Acquired immunodeficiency"	Title/abstract
AND	"seroconver*" or "early" or "primary" or "acute" OR "HIV stage" OR "disease stage" OR "HIV phase" OR "HIV stage"	Title/abstract
AND	"infecti*" OR "transmi*" OR "spread"	Title/abstract
AND	"probabilit*" OR "risk" OR "rate" OR "proportion"	Any
AND	"sex*" OR "men who have sex with men" OR "MSM" OR "gay" OR "homosexual" OR "heterosexual" OR "MSW" OR "partner*"	Any
AND NOT	"perinatal" or "mother to child" or "mother-to-child" or "vertical"	Title/abstract

2.1.2 Transmission probability per sexual contact (β) by HIV disease stage

As presented in the background chapter, the association between blood plasma viral load and HIV transmission [66], in conjunction with the high viraemia demonstrated in EHI [31,32,57], has led researchers to postulate that people with recent HIV infection contribute disproportionally to onward transmission of HIV. Cohen used the term "amplified transmission" to describe the likely increase in probability of transmission from individuals with EHI [104].

The majority of research conducted amongst heterosexuals in this area has used empirical data collected from partner studies where the date of infection of the index partner is known or can be well estimated, and follow-up of the susceptible partner occurs to establish whether a transmission event has occurred. In some studies, behavioural data collected at these follow-up visits is then used to estimate the average risk of transmission per contact through the use of mathematical models. A summary of per-contact transmission probabilities by disease stage can be found in table 2.2.

Table 2.2 Estimates of the transmission probability per sexual contact acquired from the literature

			HIV stage:		
Author (year)	**Risk group (sexual act)**	**Location**	**Early**	**Asymptomatic**	**Symptomatic**
Ahlgren et al (1990) [105]	MSM (any penile-anal)	San Francisco	0.0323[a]	0.000578	
Jacquez et al (1994) [106]	MSM (any penile-anal)	US	0.1-0.3[b]	0.0001-0.001	0.001-0.01
Leynaert et al (1998) [107]	MSW (any penile-anal)	Europe	0.1261[c]	0.0167	0.3213
Leynaert et al (1998) [107]	MSW (all)	Europe	0.0029[c]	0.0009	0.0013
Wawer et al (2005) [108]	MSW/WSM (all)	Rakai	0.0082[d]	0.0015	0.0007
Rapatski et al (2005) [109]	MSM and MSW (insertive penile sex)	San Francisco	0.024[e]	0.002	0.299
Pinkerton (2008) [110]	MSW/WSM (all)	Rakai	0.03604[f]	0.00084	
Boily et al (2009) [111]	MSW/WSM (all)	Various	0.0066[g]	0.0007	0.0055

a=early infection duration 11-19 weeks; b=early infection duration 2 months; c=early infection duration 3 months; d=early infection duration 2.5 months; e=early infection duration 6 months; f=early infection duration 49 days ;g=estimated from a meta-analysis including studies with differing definitions of early infection

Leynaert et al [107] fitted data from the European Study of Heterosexual Transmission of HIV, a retrospective study of 499 serodiscordant partners conducted in 9 European countries between 1987 and 1992, to their probabilistic model to estimate per-contact transmission risk. They assumed a 3 month duration of PHI (modelling it also as 2 and 6 months in a sensitivity analysis), after which time the infected individual entered the second "asymptomatic" period where they stayed until clinical signs of HIV infection manifested or CD4 count fell below 200 cells/mm^3 and they moved into the third stage. The authors categorised sexual contacts into two risk groups: type 1, male-female penile-vaginal sex and sex outside of menstruation; and type 2, penile-anal sex when the male partner was HIV-positive and sex during menses when the female was the HIV-positive partner. There was no variation in the male-female penile-vaginal transmission probability over the three disease stages, however penile-anal transmission risks were higher in primary and symptomatic stages when compared to the asymptomatic stage, with probabilities of 0.1261, 0.3213 and 0.0167, respectively. There was no significant variation across stages when data from the two risk strata were combined with probabilities of 0.0029, 0.0009 and 0.0013 in primary, asymptomatic and symptomatic phases. Calculation of an estimate for female-male risk of transmission in primary infection was not possible due to lack of data, however transmission risks were highest at 0.0063 when the index partner was menstruating and had symptomatic HIV infection, and lowest at 0.0003 when not menstruating and in the asymptomatic stage. The lack of certainty around the date of infection and seroconversion is one potential weakness of this study. For each individual with unknown infection date, the probability of infection at each possible date was estimated using a continuous-time Markov process based on CD4 count at presentation compared to empirical CD4 decline from seroconversion to AIDS, whilst controlling for country-specific population prevalence. The authors did not seem to assess the accuracy of this method in estimating infection dates. Given the short 3-month duration of primary infection used in the final model, any loss of accuracy around the estimate may have resulted in under or over-estimation of transmission probabilities.

Evidence in support of the concept of amplified transmission probability in primary infection amongst heterosexual couples was found by Wawer et al [108]. The authors used data from monogamous serodiscordant and seroconcordant negative couples identified retrospectively from the Rakai study, Uganda, estimating and comparing the risk of HIV acquisition per coital act for different stages of HIV infection. Importantly, none of the study participants reported anal intercourse, blood transfusion, IDU, or sex between men,

and in all couples the initially uninfected partner reported monogamy for the duration of follow-up. In couples where both members were initially HIV negative and both went on to seroconvert within a single 10 month follow-up period, the index case was defined as the partner who reported extra-marital sexual activity. The risk of transmission per coital act at each stage of infection was 0.0082 (95% CI 0.0039-0.0150), 0.0015 (95% CI 0.0002-0.0055), 0.0007 (95% CI 0.0006-0.0011) and 0.0028 (95% CI 0.0015-0.0041) approximately 2.5 months after seroconversion, 6-15 months after seroconversion, during chronic infection and 6-25 months before death, respectively. The adjusted risk ratio for HIV transmission per coital act after controlling for covariates (presence of genital ulcer disease and age group) remained highest during incident infection at 7.25 (3.05-17.25) times the risk in the chronic stage.

Pinkerton [110] performed a secondary analysis on Rakai project data, estimating per coital act and per partnership transmission probabilities in 23 couples where both members seroconverted during follow-up. Couples were grouped into early and chronic groups depending on the 10 month follow-up period in which the non-index couple seroconverted, i.e. early transmission occurred if both couples seroconverted within the same 10 month period, middle in the period after the period the index-partner seroconverted and late transmission 2 to 3 periods after the index couple. Per coital act transmission probabilities were estimated as 0.03604 and 0.00084 for early and chronic transmission groups amongst the incident couples, respectively.

A sub-analysis of transmission probabilities by disease stage was performed by Boily et al [111] in a meta-analysis of risk of heterosexual HIV-1 transmission per sexual act. The pooled HIV-1 transmission probability in early infection was estimated to be 0.658% (95% CI 0.283-1.152%), in the asymptomatic stage 0.072% (0.053-0.097%) and in the late stage 0.553% (0.200-1.525%). The final per-act transmission risk ratios compared to the asymptomatic stage were 9.17 (4.47-18.81) in early infection and 7.27 (4.45-11.88) in late stage infection.

In contrast to models of transmission amongst heterosexuals, those estimating per contact transmission by disease stage amongst MSM have little empirical data on transmission events upon which to base model parameter estimates [105,106,109]. In these studies, observed epidemic curves are modelled in addition to behavioural data, if available, with the transmission parameters β and D permitted to vary and maximum likelihood used to

establish the best fit to epidemic data. Nonetheless, these studies also conclude that transmission probabilities are amplified in early infection, ranging from 0.024-0.3 in EHI, compared to 0.0001-0.002 in the asymptomatic stage (see table 2.2).

2.1.3 Proportion of infections attributable to each disease stage

The studies presented above provide support for the concept of amplified transmission in EHI, however increased per-contact transmission probabilities alone cannot predict the extent to which it contributes to onward transmission. To assess this it is also necessary to account for the duration of primary infection (D) and rate and nature of sexual partner formation over this time (c). As presented in the background, the duration of elevated viraemia seen in EHI is relatively short, lasting weeks to months in comparison to the asymptomatic stage HIV [32,33]. Logically, the number of sexual partners experienced over the short duration of early infection is likely to be smaller than that of the asymptomatic stage which lasts for a number of years and this may mediate the increased infectivity over this time. Two methods have been used in the literature to estimate which stage of disease dominates transmission dynamics: mathematical modelling and phylogenetic analysis.

2.1.3.1 Mathematical modelling of HIV transmission by disease stage

With certain assumptions, deterministic models can be fitted to clinical, epidemiological and behavioural data from observational studies, and population surveillance data, to elucidate whether a particular disease stage is responsible for a greater proportion of onward transmissions. Early mathematical models were somewhat simplistic due to a lack of empiric data available for use as parameter values and limitations in computing power, they also predominantly modelled MSM. More recently a shift towards studies modelling heterosexual transmission has occurred largely due to the availability of extensive transmission data collected as part of the previously mentioned Rakai study in Uganda. Table 2.3 summarises the proportion of secondary HIV infections as estimated from mathematical modelling studies.

One of the first models to investigate secondary transmission by stage of infection was reported by Koopman et al [112]. They used two compartmental deterministic models to estimate the proportion of infections transmitted during EHI in a hypothetical population of MSM in the early stages of an HIV epidemic. The authors used “hypothesised” transmission probabilities per partner of 0.2, 0.001 and 0.076 for early infection (defined as the first 1.5 months after infection), middle stage (duration 104 months) and late stage (duration 14.5

Table 2.3 Mathematical modelling studies estimating the proportion of HIV infections attributable to early HIV infection

Authors (year)	Risk group (assumptions)	Population	EHI duration	Proportion of infections attributable to: Early HIV	Asymptomatic HIV	Symptomatic HIV	Not early HIV
Abu-Raddad & Longini (2008) [113]	MSW/WSM (generalised epidemic)	Rakai	2.5 months	25.0%	44.0%	31.0%	0.0%
Abu-Raddad & Longini (2008) [113]	MSW/WSM (hyper-endemic situation)	Rakai	2.5 months	13.0%	51.0%	32.0%	0.0%
Coutinho et al (2001) [114]	Unspecified (modelling VL, age mixing in 1 year increments, age-declining sexual activity in 5 year increments, peak sexual activity at 20 years)	Hypothetical	6-7 weeks	88.5%	9.0%	2.5%	0.0%
Coutinho et al (2001) [114]	Unspecified (modelling VL, age mixing in 10 year increments, age-declining sexual activity in 15 year increments, peak sexual activity at 25 years)	Hypothetical	6-7 weeks	32.5%	12.8%	54.8%	0.0%
Coutinho et al (2001) [114]	Unspecified (modelling VL, no age mixing, no age-declining sexual activity, no age defined peak sexual activity)	Hypothetical	6-7 weeks	21.4%	7.1%	71.5%	0.0%
Coutinho et al (2001) [114]	Unspecified (modelling log 10 VL, age mixing in 1 year increments, age-declining sexual activity in 5 year increments, peak sexual activity at 20 years)	Hypothetical	6-7 weeks	13.4%	86.2%	0.5%	0.0%
Coutinho et al (2001) [114]	Unspecified (modelling log 10 VL, age mixing in 10 year increments, age-declining sexual activity in 15 year increments, peak sexual activity at 25 years)	Hypothetical	6-7 weeks	3.8%	78.5%	17.7%	0.0%

EHI= Early HIV infection

Table 2.3 (continued)

Authors (year)	Risk group (assumptions)	Population	Proportion of infections attributable to: EHI duration	EHI	Asymptomatic HIV	Symptomatic HIV	Not early HIV
Coutinho et al (2001) [114]	Unspecified (modelling log 10 VL, no age mixing, no age-declining sexual activity, no age defined peak sexual activity)	Hypothetical	6-7 weeks	2.0%	81.6%	16.4%	0.0%
Hollingsworth (2006) [115]	MSW/WSM (random mixing)	Rakai	2.9 months	31.0%	42.0%	27.0%	0.0%
Hollingsworth (2006) [115]	MSW/WSM (serial monogamy)	Rakai	2.9 months	9.0%	71.0%	20.0%	0.0%
Koopman et al (1997) [112]	MSM (assortative age mixing)	Hypothetical	1.5 months	20.0%	7.0%	73.0%	0.0%
Koopman et al (1997) [112]	MSM (assortative age mixing & transient high-risk behaviour)	Hypothetical	1.5 months	10.0%	40.0%	50.0%	0.0%
Pinkerton (2008) [110]	MSW/WSM	Rakai	49 days	46.5%	0.0%	0.0%	53.5%
Rapatski et al (2005) [109]	MSM	San Francisco	2-6 months	1.3%	2.0%	97.2%	0.0%
Xiridou et al (2004) [116]	MSM	Amsterdam	1-5 months	11.2%	0.0%	0.0%	88.8%

EHI= Early HIV infection

months), respectively. They then adapted the model to include a homogenous contact rate of two partners per month, age-preferred sexual mixing where 80% of partnerships are formed within the partner's own age-group (a figure derived from US wide survey data), and age-peaked sexual contact forming. The proportion of cumulative transmissions accountable to the early, mid and late infection were: 20.0%, 6.7% and 73.3%, in the crude model; 36%, 8% and 56% in the model incorporating ageing, homogenous contact patterns and proportionate mixing; and 47.4%, 8.4% and 44.2% in the model incorporating ageing, age-peaked contact rates and proportionate mixing. The second model presented in this paper [112], compared mid and late infection to early infection, modelled as a 6 month stage stratified into 3 periods: latent, primary and post-primary, lasting 0.5, 0.5 and 5 months, respectively. The transmission probabilities used in this model were 0.0, 0.2, 0.04, 0.012 and 0.1 for each respective stage with the corresponding proportion of transmission assigned to each stage estimated at 0.0% 3.3%, 6.7%, 40% and 50%, respectively.

Xiridou et al [116] also estimated the proportion of HIV transmissions occurring during primary HIV infection amongst MSM in Amsterdam. Unlike previous models which modelled behaviour using very simplistic assumptions, their model included detailed sexual behaviour data collected from the Amsterdam cohort study of young MSM. In addition to incorporating acquisition rate of both steady and casual partnerships, and frequency of receptive and insertive UAI, the authors included more comprehensive behavioural parameters such as percentage reduction in risky behaviour by use of negotiated safety methods and percentage reduction in risky behaviour due to HIV diagnosis in chronic infection. Uncertainty analysis with a sample of values selected from probability density distributions of each parameter were used where parameter estimates were unclear, for example PHI duration and infectivity in PHI relative to chronic HIV infection. In total, the percentage of new infections estimated as attributable to transmission in PHI was 11.21%. Transmission in casual partnerships where the index partner had PHI was higher than in steady partnerships, 6.42% compared to 4.79%. Increasing the level of risky behaviour by 50% amongst casual partnerships in the model resulted in an estimated 25% of new infections transmitted during PHI. When risky behaviour was doubled amongst steady partners the estimated contribution of PHI to onward transmission reduced to 10%. The results led the authors to conclude that in Amsterdam, where the epidemic has matured and the majority of transmission events are between regular partners, the proportion of transmission events attributable to PHI is very small in comparison to the chronic and late stages. The explanation given for this finding is that the average duration of a steady

relationship is longer than the duration of primary HIV infection; therefore, fewer contacts are exposed to infection in PHI in communities where steady relationships dominate.

Rapatski et al [109] modelled data from the San Francisco Clinic Cohorts Study to demonstrate that late stage disease is responsible for driving the HIV epidemic amongst MSM in San Francisco between 1978 and 1984. The duration of the primary, asymptomatic and symptomatic stages were modelled as 6 months, 7 years and 3 years, respectively. The authors fitted retrospectively ascertained antibody prevalence and sexual behaviour data to their deterministic model. They modelled behaviour in six risk groups depending on the number of contacts per year, ranging from 231 in group 1 to 0 in group 6. All contacts were assumed to be casual and promiscuous under what the authors term "the bathhouse assumption" and sexual behaviour was said to be constant over time. Under these assumptions, they estimated per contact transmission risks at 0.024, 0.002 and 0.299 for primary, asymptomatic and symptomatic stages, respectively. This translated to 1.3%, 1.5% and 97.2% of infections observed in the study period occurring in primary, asymptomatic and symptomatic infection. The authors conceded that the initial wave of the epidemic was likely to have been driven by men in the highest risk group with primary HIV infection. Over the full course of the epidemic and in the later stages when equilibrium is reached, it is the symptomatic stage that accounts for the majority of transmissions.

The large proportion of infections attributable to the symptomatic disease stage proposed by Rapatski et al has led to criticism over the behavioural assumptions incorporated into the model. Koopman and Simon questioned how representative the San Francisco City Clinic Cohort was of the wider MSM population, adding that the partnership formation assumptions of random mixing, no clustering of partnerships and no ongoing partnerships were unfeasible within this population [117]. Finally, they queried the assumption that partnership formation rates remain constant over the study period, and do not fluctuate with illness, death or any other social factors [117].

2.1.3.2 Heterosexual populations

As was the case with studies estimating transmission probability per sexual act (β), the majority of the work to date in heterosexual populations is based on data from the Rakai study. Hollingsworth et al fitted a probabilistic model to the Rakai study data and estimated the likely stage duration and probability of transmission in a monogamous relationship for each HIV stage (primary, asymptomatic and late) [118]. PHI and late-stage infection were

estimated to be 26 and 7 times more infectious, respectively, than asymptomatic infection, with an estimated 276 (95% CI 131-509) transmissions per 100 person years for PHI and 76 (41.3-128) in late stage, and 10.6 (7.61-13.3) in asymptomatic infection. A number of methodological improvements were made on the model used by Wawer et al to estimate per contact risk of transmission by disease stage [108]. Instead of using the midpoint of each 10 month follow-up period in the estimations when a seroconversion or death occurred, they assumed there was an equal probability that these events could occur on any day in the follow-up period. In addition, the model used by Hollingsworth et al made no assumption regarding the duration of each HIV stage, instead they allowed the durations to vary to achieve the best fit to the Rakai data using maximum likelihood. The duration of PHI using this method was estimated as 2.90 months (95% CI 1.23-6.00) and the duration of high transmission risk before death (late HIV stage) was 9.00 months (95% CI 4.81-14.00). The authors went on to use the estimated rates and stage durations to model the likely proportion of new infections amongst two hypothetical populations with extremes of sexual behaviours: those who practised serial monogamy and those who practised random mixing. The percentage of new infections attributable to PHI in serial monogamous scenario was estimated at 9% in comparison to 31% in a situation of random mixing. In both populations, the majority of infections were estimated to have occurred in the asymptomatic stage due to its long duration (71% in the serial monogamy model and 42% in the random mixing).

The HIV stage-specific transmission risks presented by Wawer et al [108] were also incorporated by Abu-Raddad and Longini [113] in a deterministic compartmental model to ascertain the proportion of infections between 1980 and 2007 that were attributable to index cases in each HIV stage. Data from two different Sub-Saharan African populations were modelled separately representing the hyper-endemic situation in Kisumu, Kenya and the generalised but non-hyper-endemic epidemic in Yaounde, Cameroon. Adopting the same definition of acute, latent and late disease stages as Wawer et al, and including non-random population mixing between four sexual-risk classes they estimated that acute infection was responsible for 13% of all infections acquired between 1980 and 2007 in Kisumu, with 51% attributed to latent stage and 32% to late stage. In Yaounde, the cumulative proportion of infections was 25%, 44% and 31% in the acute, latent and late stages, respectively. The authors conclude that, in both epidemic scenarios, acute infection contributes disproportionally to onward transmission in the early stages of an epidemic only, when transmission occurs predominantly amongst high-risk sexual behaviour groups.

The latent stage accounted for the largest proportion of incident infections despite having the lowest transmission risk per coital act. This was likely due to the long duration of the latent stage and the potential increased number of sexual contacts during this period.

Pinkerton [110] also estimated the proportion of all infections transmitted during the acute phase using data from the Rakai study. An average number of transmission events were estimated from the first and second follow-up periods by calculating the mean number of transmission events in each 10 month period. Adjusting for a latent period of 9 days, during which no transmission events could occur, and using an estimated acute infection period of 49 days, Pinkerton's model predicted 46.5% of the 23 incident infections observed in this cohort were transmitted in the acute stage of infection.

2.1.3.3 Influence of behavioural assumptions on mathematical models

Models that predict HIV transmission in different disease stages can assume homogenous behaviours in the population regardless of infection status. Coutinho et al (2001) [119] neatly demonstrated the effect of different assumptions regarding sexual behaviour on transmission models predicting the proportion of infections attributable to primary, asymptomatic and symptomatic disease stages. The authors developed two transmission models: the first was based on a directly proportional increase in transmissibility with increased viraemia; the second on a directly proportional increase in transmissibility with increase in log-viraemia. The primary, asymptomatic and symptomatic stage durations were held constant across all simulations at 6 weeks, 10 years and 2 years. The age at which an individual became sexually active was also held constant at 15 years. The authors varied the following parameters: preferences in the acquisition of new partners from no age-preference to within 1 or 10 years of the individual's age, age-declining sexual activity from none exhibited to 5 or 15 years post peak, and the age of peak sexual activity at 20 or 25 years. The results vary markedly as can be seen in table 2.3. In the model where increased transmissibility is directly proportional to increased log-viraemia the dominant stage of infection is typically the asymptomatic stage no matter how behavioural parameters are varied. Due to a lack of epidemiological data it is unknown as to whether the normal or log viraemia model is more representative of the actual relationship between transmissibility and viraemia.

2.1.3.4 Caveats surrounding modelling estimates

Mathematical models are heavily dependent on generalising assumptions governing partnership formation rates, relationship durations, risk-taking behaviour, sexual mixing and partnership concurrency. Thus they may predict transmission probabilities and rates in populations where these assumptions hold true, but may not be generalisable to different populations. For example Rapatski et al's [109] model was formed using data from the early San Francisco epidemic amongst MSM and is most likely not generalisable to the situation in Sub-Saharan Africa where the epidemic is generalised. Extrapolation from a modelling study using data from one population can only be done with caution and an appreciation that assumptions which hold in one population may not be true in another.

To date, the majority of models comparing HIV transmission probability by stage of HIV infection model Rakai study data. These models are based entirely on transmission probabilities from monogamous heterosexual couples in a developing country. Rapatski et al [120] argue that a partial immunity can be acquired through multiple contacts with an HIV-positive partner, and this may help to explain the higher transmission probabilities observed during primary infection in comparison to late-stage infection. This acquired immunity would result in reduced susceptibility to HIV infection over time and could explain why more infections were estimated to be attributable to primary infection in models using Rakai study data. The monogamous heterosexual couples enrolled in the Rakai study are likely not representative of the individuals driving the epidemic in Western countries. This serves to highlight the importance of modelling behavioural assumptions specific to the population under study, and where basing these assumptions on empiric data.

2.1.3.5 Phylogenetic studies estimating the proportion of infections attributable to each disease stage

Phylogenetic studies use molecular and epidemiological techniques to determine transmission clusters amongst HIV-positive individuals. They typically involve sequencing of the pol region of the HIV genome from plasma virus or pro-viral DNA. These sequences are then matched across samples collected from other HIV-positive individuals to form clusters of individuals who share statistically similar sequences. Using the estimated date of HIV infection amongst individuals in these clusters it is possible to construct likely chains of transmission where, due to the timing of infection, one person is likely to have transmitted

to another. With various assumptions, estimation of the proportion of HIV infections attributable to individuals with EHI is then possible.

In the UK, Pao et al identified 103 recently HIV-positive individuals presenting to a genitourinary medicine (GUM) clinic during PHI between 1999 and 2003 [121]. Recruited individuals were predominantly male and MSM. PHI was diagnosed if the individual had a HIV test interval of 18 months or less, an evolving Western Blot or antibody response, or tested incident using a RITA assay. Fifteen transmission clusters were found, with 34% of the 103 PHI infections falling into these clusters. The authors found that individuals in 11 out of 15 clusters had PHI diagnosis within 12 months of each other; possibly showing enhanced transmission during PHI when viral load is elevated. They found younger age, higher CD4 count and higher number of sexual contacts in the 3 months preceding seroconversion to be associated with being in a PHI cluster. The presence of an STI at time of PHI diagnosis was not found to be significantly associated with clustering, though the risk of STI infection was higher amongst individuals within a cluster. Interestingly plasma viral load at diagnosis was not found to be predictive of clustering. The authors suggested that transmission amongst MSM may be more correlated with seminal viral load rather than blood plasma viral load.

More recently, Fisher et al [72] isolated the Pol sequence from samples of 859 MSM recruited from a large cohort attending an HIV treatment centre in Brighton. Of these 859, 159 (19%) were found to have been recently infected, defined in this study as a negative HIV antibody test in the past 6 months, laboratory evidence of seroconversion or testing incident with RITA if subtype B. From these 159 recently infected individuals, 47(29.6%) fell into transmission clusters, with a single likely transmitter identified for 41 (26%) individuals. Likely transmitters had to share a cluster with a recently infected individual, and be diagnosed HIV positive prior to them. Of these likely transmitters it was estimated that 24% had recent infection at the time of transmission (as per the above definition), with the remaining 76% in chronic stage of infection.

Brenner et al also used phylogenetic linking to assess the proportion of individuals with primary HIV infection (defined as seroconversion within the 6 months before genotyping) in Quebec who fell into clustered transmission groups [122]. The authors found that 49.4% of the sequences from individuals with PHI fell into 75 chains of transmission, however, within these chains the mean transmission interval (time between HIV acquisition and

transmission) was 15.2 months (standard deviation 9.5 months; range 1-37 months) so whilst those diagnosed in PHI were likely involved in more transmission events, a number of these events would have occurred outside the period of PHI.

2.1.3.6 Caveats surrounding phylogenetic studies

Phylogenetic linkage studies are useful as they assess actual transmission events amongst known contacts in a sexual network. One problem with phylogenetic linking however is the assumption that people within a cluster have directly infected each other. In reality, there may be an individual outside of the study population who is responsible for infecting some or all of the people in the cluster but who was not included in the study themselves. Brown et al [123] also highlighted the importance of the use of full and adequate definitions as well as known dates of seroconversion when performing phylogenetic reconstructions of transmissions to demonstrate amplified transmission in acutely infected individuals. Using 165 individuals with well estimated infection dates from the CASCADE Collaboration of recent seroconverters they conducted a phylogenetic analysis on the HIV pol sequence. Nine phylogenetic clusters were found amongst the sequences, containing 11% of the 165 sequences. Only two of the nine clusters could have occurred during acute infection though due to the timing of infections exceeding the duration of PHI. The authors concluded that individuals with transmission intervals which exceed the duration of PHI should be excluded from force of infection calculations for those in that HIV stage.

2.1.4 Factors affecting exposure of susceptible to infected individuals (c) across HIV stages

As infection with HIV is asymptomatic or, in the case of acute retroviral syndrome, very non-specific, it can remain undiagnosed for long periods in the absence of routine HIV testing. A key concept in the hypothesis that individuals with recent HIV infection account for a disproportionate number of sexual HIV transmissions is that any risky sexual behaviour that may have led to primary infection of the index case continues until that individual is diagnosed with HIV. Awareness of HIV status is therefore of great importance, and may act as an important pivot point for behaviour change in PLWH.

A meta-analysis conducted by Marks et al showed that knowledge of HIV-positive status was associated with a reduction of 53% (95% CI 45-60%) in the prevalence of unprotected vaginal or anal intercourse with any partner [124]. After adjusting for the proportion of sexual partners who were at risk of HIV, the effect of awareness of personal HIV-positive status on

prevalence on UVAI reduced by 68% (95% CI 59-76%) [124]. In a subsequent paper, the authors went on to use the relative reduction in UVAI afforded by awareness of HIV status estimated from the above meta-analysis in a model assessing the number of new HIV infections attributable to those unaware of their HIV status [125]. This model accounted for undetectable/low viral loads and subsequent low biological risk of transmission amongst aware HIV-positive people but no adjustment was made for unaware individuals due to them not being on ART to control viraemia. As an estimate of the ratio of HIV-positive to HIV-negative sex partners that unaware HIV-positive individuals have was unavailable, the authors used three arbitrary values (1:1, 1.5:1 and 2:1) modelling each of the three ratios. They concluded that even when the number of partners was equal between aware and unaware individuals, secondary sexual transmission from the unaware group accounted for 54% of the new infections. When the number of susceptible partners was double that of the aware individuals, transmission from those unaware of their positive status accounted for 70% of new infections [125].

Pinkerton also investigated the role that awareness of HIV status has on secondary transmission across all disease stages and, specifically, in the acute stage using epidemiological data from the USA [126]. Acute infection in this model was assumed to last for 49 days, ranging between 42 and 56 days in sensitivity analysis. The model used estimates of transmission probability ratios for acute to asymptomatic infection derived from studies in different risk populations; these ranged from 4.2 (representative of male-female transmission) to 12.0 (calculated from male-male transmission). A 3.7 risk ratio for transmission from individuals unaware of their HIV status compared to those who were aware was modelled, as estimated from the Marks et al meta-analysis [124]. The final model predicted 8.6% of 32,000 annual infections sexually acquired in the USA were attributable to acute infection. However, 48.5% of the remaining infections were attributable to individuals with undiagnosed chronic infection, indicating a markedly higher contribution of undiagnosed infection to onward transmission compared to acute infection.

To date, three studies have examined behaviour change following HIV diagnosis amongst cohorts of recently infected MSM in the US and UK. Gorbach et al [97] studied transmission behaviours in 106 MSM from Southern California who were infected with HIV in the last 12 months. They conducted baseline and 3 month follow-up interviews to determine sexual behaviour in the 3 months prior to interview and found that 46.9% of the sexually active MSM reported a reduction in number of partners between baseline and follow-up. A

significant reduction in the mean number of all, one-time and acquaintance partners was also observed from 7.9 to 5.2, 1.9 to 0.8, and 1.1 to 0.5 between baseline and follow-up, respectively. There was also a significant reduction in UAI with reported HIV negative or status unknown partners from 82% at baseline to 48% at follow-up. Unfortunately no further rounds of follow up data were collected to examine whether observed changes persisted.

Colfax et al [127] also observed a reduction in risky sexual behaviour amongst 66 MSM recruited to the HIVNET vaccine cohort who seroconverted within a 6 month test window. Baseline data were collected prior to positive result notification, and follow-up interviews were conducted at 1, 3, 6, 9 and 12 months after positive test. A reduction in the proportion of MSM reporting insertive UAI with HIV negative or unknown status partners was observed between baseline and one month follow up from 39% to 2%. Unfortunately, this proportion then steadily increased to 8%, 6%, 13% and 12% at 3, 6, 9 and 12 months following the positive test. The authors also observed that MSM who continued to engage in UAI after HIV diagnosis were significantly more likely to continue to do so at 6 and 9 months post diagnosis but not 12 months.

Most recently, Fox et al [128] followed up a cohort of 98 MSM diagnosed with primary HIV infection enrolled in an ART intervention study to assess changes in sexual behaviour after HIV diagnosis. Men completed a survey at diagnosis enquiring about sexual behaviour in the 12 weeks prior to diagnosis and at 12 week follow-up. Recreational drug use was high amongst study participants at 71% pre diagnosis, and 62% reported UAI with a casual male partner. By 12 weeks after diagnosis, prevalence of drug use had fallen to 25% and condom use had increased amongst men reporting sex with casual partners. Notably, 76% of the men had eliminated any transmission risk over the follow-up period, defined as UAI with a regular partner of unknown or negative HIV status, UAI with casual male partners or incident STI. Even amongst men presenting with continued transmission risk, the median number of partners in the 12 weeks since diagnosis was significantly lower. The 22 men who continued to pose a transmission risk after PHI diagnosis reported more sexual partners in the 12 weeks prior to their diagnosis than those who posed no apparent risk. They also had almost 3 times the odds of reporting ketamine use and 2.7 times the odds of having an STI at diagnosis.

One factor which may also mediate sexual behaviour during early infection is the presence of acute retroviral syndrome which, if experienced, coincides with the time of peak infectivity and may lower libido. Celum et al found that 70 out of the 103 seroconverters in their cohort reported changes in their usual activities because of acute retroviral illness lasting for 3 days or more; moreover 59/103 took time off work over this period [37]. The severity and number of acute retroviral syndrome symptoms experienced in PHI has been shown to be positively correlated with viral load at this time [129]. Gray et al [67] observed from the Rakai data that sex was most frequent amongst couples where the infected partner had a HIV viral load <1700 copies/mL at 10.4 acts per month, and less frequent amongst couples where the infected partner had a HIV viral load >38500 copies/mL at 7.91 acts per month. The true extent to which individuals engage in unsafe sexual behaviour at this time of peak viraemia is currently unknown.

The duration of the high viraemia in EHI is much shorter in comparison to the asymptomatic and symptomatic stages; estimated to be weeks or months in EHI [32,57], as opposed to years for asymptomatic and symptomatic stages [40,41,45]. In a hypothetical situation, when the rate of sexual contact formation and transmission probability stays constant throughout infection, the shorter duration of elevated infectiousness seen in primary infection should result in fewer sexual contacts and therefore fewer transmission events in comparison to the long asymptomatic period which lasts for years. The assumption of a constant rate of sexual contact formation over this time period may not be valid however. One view is that partner formation rates and risky behaviour are higher throughout early infection, as any risky behaviour that may have led to the primary infection may remain unmodified whilst the individuals is unaware of their positive status. In high-risk populations where partner formation rates are high and UAI remains frequent over early infection, primary infection likely plays an important role as the high number of contacts achieved in the short period would be ample to transmit the virus. In this period, concurrency of partners will also fuel a faster growing epidemic. However, in populations where relationships are long lasting and monogamous in nature, the duration of the primary infection plays less of a role as relationships are likely to last longer than the short duration of primary infection, therefore only exposing one partner to the high infectivity over that time period.

2.1.5 Conclusions

Partner studies and indirect estimates from mathematical models have unilaterally shown the HIV transmission coefficient (β) to be elevated in early infection, a finding which supports the theory of increased infectiousness as a result of the elevated viraemia during this period. Deterministic models combine these stage-specific transmission coefficients with data summarising sexual behaviour (c) in the population and disease stage durations (D) to provide estimates of the proportion of infections attributable to early infection, however the resulting estimates are varied ranging from 1% to 89%. This variation is due primarily to differences in model assumptions across study settings, mainly involving sexual behaviour parameters, which can undermine the validity and generalisability of model findings. Phylogenetic studies have the advantage of tracking actual transmission events in real sexual networks but must be performed with rigorous definitions. Though phylogenetic analyses have provided evidence that EHI may contribute to a large proportion of secondary transmissions the most recent study in the UK demonstrated that undiagnosed infection across all disease stages contributes to a larger proportion of transmission events than recent infection. To date, there is limited data on the sexual behaviour of MSM diagnosed during with EHI in the UK from which to understand their role in secondary transmission in this country. Empiric estimates of the number of sexual partners accrued over EHI, alongside their HIV status is crucial to facilitate modelling of the role of recent seroconverters in onward transmission of HIV in the UK.

2.2 What is the rationale for initiation of ART in early HIV infection?

2.2.1 Literature review methods

This scoping literature review aimed to summarise the literature published up until March 2010 examining the rationale for initiation of ART in early ART, specifically:

1. The clinical benefit of initiating ART in EHI in terms of:
    - immunological benefits of ART in PHI
    - virological benefits of ART in PHI
    - clinical benefits of ART initiation at CD4>350 cells/mm^3
2. The role of early ART in reducing HIV transmission
3. Acceptability and potential barriers towards early ART.

The scoping review approach as outlined by Arksey and O'Malley [103], and used for the previous review, was adopted for this scoping review, with one change. Due to the wider range of topics to be covered in this review, it was necessary to perform a number of searches on the online bibliographic databases PubMed and Ovid (see appendix 7 for search strategies). Studies were charted according to the three themes listed above, and according to the research methods each employed. In addition to searching bibliographic databases, the reference lists of articles found to be relevant were hand checked and conference abstracts of UK and international HIV conferences between 2008 and 2010 were also checked to ensure inclusion of relevant recent studies that were not likely to be published yet.

2.2.2 Does initiating ART in early HIV infection confer clinical benefit?

At the time of writing this literature review, the optimum time to start ART in asymptomatic HIV-positive individuals was unknown. Historically the perceived optimum time to start ART has varied over the years. The "hit hard and early" approach, advocated soon after the advent of ART [130], was followed by a more cautious "deferred therapy" approach resulting in recommendations of ART for those with CD4 counts of 200 cells/mm^3 or less [131]. In recent years, the recommendations have shifted back towards starting ART earlier in infection, with UK guidelines changed from CD4 count of 200 to 350 cells/mm^3 in 2008 [132].

HIV treatment initiation in the UK is currently predominantly guided by immune deficiency as measured by CD4 count, though specific guidelines also exist for PHI. At the time of

writing, BHIVA guidelines recommended commencement of HIV treatment in PHI if the patient had neurological involvement, CD4≤350 cells/mm^3 or AIDS diagnosis, and in asymptomatic HIV-positive patients at CD4≤350 cells/mm^3 [132]. However, there is a rationale to start treatment earlier in infection than current BHIVA guidelines recommend, as aside from possibly conferring clinical benefits, earlier initiation of ART could also reduce infectiousness and hence the extent of onward transmission. If HIV treatment were to be used to reduce onward HIV transmission the largest reduction in infectiousness would be amongst individuals who have high viral loads, which is particularly the case in EHI. In addition to the reduction in infectiousness, individuals with high CD4 counts, and/or PHI, may also benefit clinically from initiation of ART at this time point. This section of the literature review outlines the rationale for early initiation of ART from a clinical and public health perspective.

Over the years, several clinical rationales have been proposed for ART in EHI. Before investigating these further it is important to clarify the definition of early ART as there are separate rationales to treat primary HIV infection (usually defined as the first 6 months of HIV infection) and early-chronic infection (where CD4 count is likely still >350 cells/mm^3 but patients are still asymptomatic). Both of these scenarios apply to the population under study in this thesis, individuals with EHI, as the vast majority still have CD4 count >500 within a year of seroconversion [133]. In this section, I provide an overview of the research performed to date and where possible synthesise the evidence for and against early initiation of ART, focussing foremost on those with PHI and secondly individuals with chronic asymptomatic infection and high CD4 count.

2.2.2.1 Immunological benefits of ART in PHI

Several studies have investigated the effectiveness of ART initiated specifically in PHI, the majority of which are observational, or clinical, cohorts of individuals with laboratory confirmed dates of seroconversion. As recent seroconverters are identified and recruited to studies in the very early stages of HIV infection, it is expensive and impractical to follow up large cohorts until AIDS events or death. Instead, measures of viral load and CD4 counts, which are known to be predictive of disease progression and AIDS [134], are used to reduce the necessary study follow-up duration. Uncertainty exists, however, in whether the apparent short term improvements in these surrogate markers, as demonstrated in studies investigating transient ART in PHI, translate into clinical benefits in later infection.

There is a rationale for starting treatment specifically in PHI to lessen the extent of immune depletion that occurs in the weeks following HIV infection. T-cell activation is very high in acute infection, and the extent of activation has been shown to be associated with CD4+ T-cell depletion [135]. ART initiated in PHI, ideally as early as possible after infection, has been shown to reduce the duration of T-cell activation and lessen the extent of depletion of CD8+ and CD4+ T-cells [136–143], and preserves a higher level of immune function for longer than individuals not treated in PHI [144,145].

It is important to note, however, that it may be possible to initiate ART too soon. Younes et al [146] demonstrated that in individuals who start ART within 1 month of seroconversion, the short exposure to HIV does not allow the generation of significant detectable frequencies of HIV-specific CD4+ memory T-cells. The authors suggest balance must therefore be reached between initiating ART in PHI late enough that HIV-specific immunity can first be developed but early enough to avoid the depletion of CD4+ T-cell numbers and functionality observed in chronic infection.

2.2.2.2 Virological benefits of ART in PHI

Viral load "set point", the point at which blood viral load levels off after the initial rise and fall following HIV infection, has been shown to be a strong predictor of long term disease progression with a higher set point associated with faster disease progression [34,35]. This makes it an ideal surrogate marker to use as an outcome in the assessment of virological benefits of ART in PHI. There have been conflicting results to date from studies assessing the effect of ART in EHI on viral set point following drug cessation, with six studies having shown a significant difference between individuals treated in EHI versus their controls [140,147–151] and three studies showing no difference [143,152,153]. The lack of agreement of these studies is likely due to variation between the observational studies in the key variables of interest such as the definition of EHI, the timing, duration and formulation of ART and importantly the way viral set point has been defined, which has no standard definition. What is evident from these studies however, is that any viral control achieved through early ART is very rarely attenuated for any length of time following cessation of treatment. This is due to the re-emergence of the virus post-treatment from a latent reservoir of HIV-infected CD4 cells, which is established in EHI [154] and this is known to persist even amongst individuals on ART whose blood plasma viral load is undetectable [155]. There is however some evidence that initiation of immediate ART in acute infection, results in a significantly smaller latent viral reservoir compared to individuals who initiated therapy

in chronic infection [156] and even compared to those initiating later in EHI (over 180 days following infection) [157]. The small reservoir size reported by Pires et al was comparable to that found in the cohort of long term non-progressors, prompting cautious speculation that an early ART strategy could be used to provide a functional cure [156].

At the time of writing, only data from observational studies were available to assess whether initiation of combination ART earlier in infection benefits the individual in terms of preservation of immune function, delaying onset of opportunistic infections or death and these have found no consensus. In addition, observational studies, whilst logistically and financially more convenient to conduct, are prone to unmeasured confounding. Well designed, adequately powered, randomised controlled clinical trials provide the highest quality evidence of the clinical efficacy of ART initiated in PHI. The SPARTAC (Short Pulse Anti-Retroviral Therapy At Seroconversion) trial is one such trial and was in the follow up phase at the time of writing. The aim of SPARTAC was to elucidate whether a transient short (12-week) or longer (48-week) course of ART given to individuals with PHI can delay the time taken for CD4 count to fall below 350 cells/mm^3 on two consecutive occasions, or time to clinically indicated initiation of ART [158]. The findings of SPARTAC apply specifically to individuals with PHI and, as they were reported in 2013, are not included in this literature review but are included in the thesis discussion, chapter 7.

Even if the existence of immunological or virological benefits through use of transient ART in PHI are demonstrated, it would not necessarily result in an immediate change in BHIVA recommendations. Results from the SMART (Strategies for Management of Antiretroviral Therapy) study, a large clinical trial examining structured treatment interruptions in chronically infected individuals, have shown that CD4 guided ART interruptions resulted in higher risk of AIDS and death from any cause [48]. Whilst those initiating ART in early infection may be a sufficiently different population from those enrolled in the SMART study there may still be an underlying risk associated with transient treatment in PHI. The act of starting ART in PHI, stopping, then restarting it later in the disease course when clinically indicated could increase the risk of cardiovascular events, AIDS and/or death as demonstrated in the SMART study [48].

2.2.2.3 Earlier CD4-guided ART initiation for clinical benefit

Two very large cohort collaborations have recently reported findings from studies assessing higher CD4 guided ART start points, than the current recommended threshold of 350

cells/mm^3. The first was run by NA-ACCORD (North American AIDS Cohort Collaboration on Research and Design), a collaboration of 22 research groups in North America [159]. Data from 17,517 asymptomatic patients were used to run two comparison analyses. The first used data from 8,362 patients to compare mortality between those who initiated ART at CD4 351 to 500 cells/mm^3 (n=2084) to those who had deferred treatment until their CD4 was 350 cells/mm^3 or less. After controlling for differences in calendar year, demographic factors and clinical characteristics between the two groups, the findings showed an increased risk of death in the deferred treatment group of 69% compared to the earlier treatment group (risk ratio: 1.69, 95% CI: 1.26-2.26). The second analysis presented used data from 9,155 patients to show an increase in mortality of 94% (RR=1.94; 95% CI=1.37-2.79) amongst the group that deferred ART until CD4 count was less than 500 cells/mm^3 (n=6,935) when compared to those who started at CD4>500 cells/mm^3 [159].

The second large cohort study addressing the issue of earlier commencement of ART is the When to Start Consortium of HIV Cohort Studies [160]. By combining data on 21,247 AIDS-free, non-IDU, patients from 15 cohort studies across North America and Europe and using novel statistical methods to account for unobserved events in the deferred treatment arm the ART-CC (Antiretroviral Treatment Cohort Collaboration) compared deferring ART across a range of different CD4 counts, to initiating it at those counts. They found that deferring ART until CD4 was less than 350 cells/mm^3 resulted in a 28% (HR=1.28, 95% CI=1.04-1.57) increase in AIDS or death when compared to starting it at CD4 351-450 cells/mm^3. No significant differences in mortality or AIDS events were observed between those who started and those who deferred.

The findings from the observational analyses above are not directly comparable due to the different end points used, and study populations. In addition, results from any cohort study must be treated with caution as the nature of the methodology makes the results susceptible to confounding from unmeasured factors though efforts were made to control for bias and potential confounders. ART-CC used novel statistical techniques to estimate distributions of lead-time and unseen events prior to the deferred group starting ART by using pre-ART data. This method relies on the assumption that the course of infection in the pre-ART era is representative of the current course of infection, i.e. that the rate of disease progression in the absence of ART has not increased. NA-ACCORD controlled for demographic and clinical confounders in their analyses, though unmeasured confounders may have persisted.

Despite the lack of randomised evidence indicating clinical benefit of initiation of ART at CD4>350, the US DHHS released new guidelines in December 2009 recommending ART initiation amongst asymptomatic individuals diagnosed with HIV and who have a CD4 between 350 and 500 cells/mm^3 [161]. The START (Strategic Timing of Anti-Retroviral Treatment) clinical trial, which at the time of writing was recruiting, aims to examine whether starting HIV treatment at CD4 of 500 cells/mm^3 delays progression to AIDS and reduces mortality, compared to deferring it until CD4 count reaches 350 cells/mm^3. Whilst the study population is not specifically recent seroconverters, the findings will apply to the majority of recent seroconverters by default given that the high CD4 counts that determine eligibility are typically observed in EHI.

2.2.3 Early ART to reduce transmission

Antiretroviral therapy has long been known to be effective at reducing blood viral load in PLWH. This has led researchers to hypothesise that the reduction of viral load in the blood brought about by ART may also reduce sexual transmission at the individual level [5]. A recent systematic review and meta-analysis of studies examining transmission amongst serodiscordant heterosexual couples appeared to confirm this hypothesis showing transmission rate to be 0.46 per 100 person-years in studies where the HIV-positive partner was on ART compared to 5.64 per 100 person-years [162]. Furthermore, no transmission events were identified amongst couples where the HIV-positive partner's viral load was <400 copies/mL in the studies included in the meta-analysis.

Most recently, results from the "Partners in Prevention" study, the primary objective of which was to assess whether treatment of herpes with acyclovir reduced HIV transmission, aimed to assess the effect of ART on HIV transmission amongst 3381 serodiscordant couples as a secondary objective [163]. The study team observed a far lower rate of HIV transmission amongst couples where the HIV-positive partner self-reported taking ART: 0.39 (95% CI 0.09-2.18) per 100 person years, compared to 2.23 (1.84-2.70) per 100 person years in those who were not on ART. This equated to a 92% reduction in HIV transmission afforded by ART, after controlling for CD4 count at initiation and the time enrolled in the study. One transmission event occurred in the ART cohort, however in this case it was plausible that the transmission event had occurred prior to the index partner initiating ART.

In North America, Central and Western Europe the dominant mode of HIV transmission is between sex between men [8], however, there is a notable lack of published partner studies

examining transmission in this population. As a result, concern exists over the extent to which findings from heterosexual studies can be extrapolated to MSM. Also though observational evidence exists that ART decreases transmission risk, transient ART during PHI carries the possibility of a delay in the hyper-viraemia observed during AHI until after treatment discontinuation, as demonstrated by Rieder et al [164]. The authors carried out phylogenetic analyses of the sequences from the *env* and *pol* region of the HIV genome sampled from 111 MSM enrolled in the Zurich Primary HIV Infection study who were diagnosed with acute or primary infection revealed and 18% to be involved in 6 transmission clusters with other MSM in this study and the Swiss HIV Cohort Study. The 111 MSM were followed up for a median of 3.3 years, during which time 93 MSM initiated early ART (with 47 stopping treatment after a year of viral load being suppressed to below 50copies/mL). Within the 6 transmission clusters, only 1 transmission was likely to have occurred in the acute period, 1 in the recent infection period and 5 transmissions were likely to have occurred in the period following cessation of transient ART. The corresponding rate of transmission prior to early ART initiation was 3.5 transmissions per person-year (95% CI 0.9-13.5) compared to 1.8 for the period after treatment cessation (95% CI 0.5-5.8). Interestingly, one cluster contained a potential transmission from an index patient stable on ART with an undetectable viral load at the time, however the authors dismissed this as highly unlikely as upon updating the analysis it appeared there were another possible 3 transmitters in the cluster [164].

Whilst the observational evidence to date appears to indicate transmission whilst undetectable on ART is unlikely, these studies are susceptible to unmeasured confounders. At the time of writing the randomised HPTN-052 trial was ongoing with the primary objective of assessing the effectiveness of ART in preventing HIV transmission amongst 1,750 serodiscordant couples [165]. Both heterosexual and MSM couples are eligible, with the index (HIV-positive partner) of each couple randomised to one of two arms: to receive immediate ART, or defer ART initiation to when CD4 count falls below 200-250 cells/mm^3.

At a population level, the impact of ART on HIV transmission has been assessed through mathematical modelling and ecological studies. Ecological analyses of HIV incidence amongst MSM following the widespread rollout of ART in Amsterdam, San Francisco, Taiwan and British Columbia have yielded mixed results. Dukers et al used unlinked anonymous samples from 3090 MSM attending an Amsterdam STI clinic, to estimate HIV incidence between 1991-2001 [166]. The authors observed an increase in HIV incidence, and

concurrent STI infection over time which was particularly evident amongst MSM aged >34 years. Katz et al used routine surveillance data from San Francisco to demonstrate that HIV incidence has remained stable between 1996 and 1999, despite rapidly increasing uptake of ART over this time period [167]. Both of these studies concluded that any decrease in infectiousness afforded by increased ART use was likely mediated by population-wide increases in unprotected sex. Conversely, Porco et al observed a 60% reduction in HIV incidence following the widespread use of ART amongst MSM enrolled in the Young Men's Health Study between 1994-1999 [168], the same period as the study by Katz et al [167]. Fang et al conducted an ecological analysis of national surveillance data in Taiwan and demonstrated a 53% decrease in HIV transmission rate following the introduction of a national policy of free ART access to all HIV-positive individuals [169]. Notably there was no observed increase in the incidence of syphilis over the same time period, inferring no increase in high-risk sexual behaviour.

Recent analysis of routine data from San Francisco by Das et al used estimates of community viral load (calculated as the mean or the total of the most recent viral load test for all HIV-positive individuals in a given geographical population) as a proxy of population infectiousness, instead of the previously used proxy of ART uptake [170]. These data suggest an association between decreasing community viral load over time and decreasing incidence between 2006 and 2007, following the introduction of an expanded test and treat strategy in 2006 [170]. In British Columbia, Canada, the increase in ART rollout at a population level has also been associated with a decrease in the annual number of new HIV diagnoses between 1999 and 2009 following a concentrated effort to expand testing and access to ART [171]. This was delivered alongside several other community strategies which aimed to: improve linkage to care; promote condom use; distribute free condoms; and provide free ART to those who are HIV-positive and have no health insurance. Whilst these more recent studies appear to indicate decreasing incidence occurring in combination with expanded test and treat strategies, it is important to acknowledge the risk of ecological fallacy; as the outcomes and risk factors are measured as an aggregate across the entire population, any decreases in HIV incidence cannot be directly attributed to test and treat initiatives.

Mathematical modelling studies have also provided insight into the role ART can play in reducing transmission at a population level, though opinions on its potential efficacy are divided. Months after the release of the Swiss statement, Wilson et al published a paper highlighting the potentially negative public health impact the Swiss Statement could have if

condoms were subsequently abandoned and ART solely relied upon to reduce transmission in serodiscordant partnerships [172]. The authors' model estimated the cumulative risk of HIV transmission from HIV-positive individuals undetectable on ART (viral load <10 copies/mL) and in monogamous serodiscordant partnerships. Using the correlation between viral load and per contact transmission risk estimated in the Rakai study [66], Wilson et al modelled male-to-female, female-to-male and male-male transmission, estimating annual cumulative risk of transmission to be 0.0043, 0.0022 and 0.043, respectively, assuming couples engage in 100 sexual acts per year. This translated to 10 year cumulative number of seroconversions of 425 from male-female transmission, 215 from female-male and 3524 amongst MSM, in hypothetical populations of 10,000 partnerships over a 10 year period in the total absence of condom use. Applying the assumption of 80% condom use, with a 95% efficacy per act, in addition to ART, decreased the number of seroconversions substantially to 104, 52, and 990, respectively. Central to the model were the assumptions that the log-linear association between viral load and per contact transmission risk was applicable in different transmission scenarios (male-to-female, female-male and male-male), that the correlation held even at undetectable viral loads and in the presence of ART. There is no evidence published to date to confirm or refute these assumptions, and it is conceivable that a threshold effect operates, rendering transmission below a particular viral titre unfeasible.

Several other models have endorsed the use of TasP at a population level. Granich et al predicted that the prevalence of HIV in South Africa could be reduced to less than 1% within 50 years if universal HIV testing followed by immediate HIV treatment initiation was implemented [173]. This estimated decrease in prevalence is caused by the reduction in population viral load afforded by early HIV treatment, along with a decrease in the proportion of HIV-positive individuals who remain unaware of their HIV infection. However, the study has faced criticism for its "utopian" assumptions of very optimistic ART rollout, uptake and adherence rates [174]; 90% of South Africans were assumed to have ART and follow-up care accessible to them within the next 8 years, and adherence was assumed to remain high after ART initiation.

Other modelling studies have corroborated the idea that TasP can be used to reduce HIV incidence. Dodd et al used a more detailed deterministic model, acknowledging that epidemiological variations in epidemic stage, survival rates, stage of infection and sexual behaviour can vastly influence model predictions [175]. They found that in certain epidemic

situations, for example in a population with homogenous risk distribution testing 80% of the population every 2-3 years could generate an 95% reduction in incidence over 30 years, however this reduces to 85% reduction in epidemics where sexual mixing is random and risk is heterogeneous. They conclude that test and treat models should be fitted to specific populations, and ideally include local sexual behaviour data to enable the most accurate prediction of TasP impact. Similarly, Lima et al modelled the effect of varying ART coverage, adherence, recommended CD4 initiation thresholds in British Columbia, Canada [176]. The authors concluded a decrease in HIV incidence would be seen if a minimum of 75% of individuals who were clinically eligible for ART were treated, and that this can be optimised by recommending ART at higher CD4 counts as well as achieving high rates of coverage and maintaining high adherence amongst those who are clinically eligible.

At the time of writing this literature review, the Population effects of Antiretroviral Therapy (PopART) trial was being developed to examine whether universal testing and treatment for all HIV-positive individuals, irrespective of CD4 count, would reduce HIV incidence at a population level in a real world setting [177]. The study aims to estimate HIV incidence amongst 21 community clusters, each recruiting a random selection of 2500 adults, in South Africa and Zambia. Communities will be randomised to one of three arms: arm 1 will receive the combination prevention package comprised of annual home testing with immediate ART for all testing HIV positive, and promotion of male circumcision for HIV-negative men; arm 2 will receive the package but with HIV treatment as per current national guidelines; arm 3 will receive standard of care.

2.2.4 Barriers to early ART

If ART were to be offered earlier in infection to those with EHI in the UK to reduce transmission, there is no guarantee that it would be taken up. There has been no work published to date on the acceptability of early ART initiation amongst individuals with EHI. With no RCT evidence indicating clinical benefit of early ART, individuals would be asked to initiate purely to reduce transmission, almost as an altruistic act. No published literature was available on the concept of altruism in relation to ART use, though the broader concept of HIV "prevention altruism" had been explored. Nimmons defined the term "prevention altruism" as the values, motivations and practices of caretaking towards one's sexual partners to avoid the transmission of HIV [178]. O'Dell et al observed high levels of prevention altruism, as measured on a seven-item likert scale, in a cross-sectional survey of HIV-positive MSM in the US [179]. Univariate analysis showed MSM in the highest tertile of

prevention altruism were half as likely to report serodiscordant UAI than those in the lowest. However, when disinhibitive factors such as crystal meth or Viagra use were adjusted for the association did not remain statistically significant [179].

Even if the trials do show a clinical benefit of earlier ART, taking medication in the absence of symptoms or illness may introduce adherence problems. Drug resistance, both transmitted and acquired, is also of major concern when considering the drawbacks of expanding ART for prevention. The reported decrease in the detection of drug resistance in British Columbia where the "Seek and Treat" strategy is currently in place, from a rate of 1.73 to 0.13 cases per 100 person-months of therapy between 1997 and 2008 is encouraging though [180]. This decrease has occurred alongside an increase in the proportion of HIV-positive individuals with suppressed viraemia (<50 copies/mL) of 65% in 2000, to 87% in 2008. Though causal associations cannot be made from observational studies, it is encouraging that at a time of expanded access in this population, detected drug resistance appears to have decreased [180].

Risk compensation, is also a very real possibility should early ART be widely adopted to prevent transmission in the absence of condom use. Mathematical modelling has estimated that a 50% increase in condomless sex amongst Australian MSM will completely offset any decrease in infectiousness afforded by ART, and result in increased incidence in the population [181]. An increase in high-risk sexual behaviour during EHI may also occur if individuals on ART feel better. A population wide increase in condomless sex could not only directly increase HIV incidence, but also facilitate the spread of other STIs. Any increase in the prevalence of STIs amongst HIV-positive individuals could in turn indirectly facilitate transmission as viral load in the genital fluids of HIV-positive people is known to increase with the presence of another STI [69].

At the time of writing this review, there were no published data to indicate whether initiation of treatment in EHI results in risk compensation; however, data do exist from studies investigating the relationship between attitudes to treatment, viral load and sexual behaviour in MSM who were not recently infected. Crepaz et al performed a meta-analytic review of studies examining the relationship between ART and sexual risk behaviour [182]. Their review included studies amongst heterosexuals, MSM and IDU. Their random effects model included 21 effect estimates form 16 studies and concluded that there was no significant difference in unprotected sexual intercourse between HIV-positive people who

were on ART and those who were not (OR, 0.92; 95% CI, 0.65-1.31). Their random effects model of data from 12 studies examining whether undetectable viral load was associated with unprotected sex also showed no evidence of an association (OR, 0.99; 95% CI, 0.82-1.21). Interestingly, meta-analysis of the 18 effect sizes from the 10 studies investigating beliefs about ART or viral load and unprotected sex amongst HIV-positive, negative and unknown individuals showed the likelihood of unprotected sexual behaviour was significantly higher in people who believed ART reduces HIV transmission or who were less concerned about unsafe sex because of the availability of ART (OR, 1.82; 95% CI, 1.52-2.17). It is important to note that this meta-analysis covered studies published up until 2003 only. Since then, improvements in drug technology and subsequent reduction in pill burden and toxicities, in addition to the increased publicity given to the effect of ART on infectiousness may have resulted in shifts in attitudes and beliefs associated with ART and resulted in higher treatment optimism and reduced concern about transmission.

Finally, perhaps the biggest factor to limit the utility of early ART to reduce HIV transmission will be the rate of HIV testing [173,175]. For this reason, many of the population-based programmes assessing the impact of early ART involve plans to scale up HIV testing, for example the previously mentioned "Test and Treat" programme in San Francisco [170] and "Seek and Treat" in British Columbia [180] as well as the PopART trial [177]. The benefits of increasing HIV-testing are two-fold; it decreases the number of individuals unaware of their HIV status and increases the number who may initiate early ART and achieve undetectable viral load. In the UK at the time of writing, BHIVA recommended annual HIV testing for MSM, or more regularly if HIV symptoms are present or individuals engage in high risk sexual behaviour [132]. Surveillance data collected from sexual health clinics has indicated an increase in HIV testing over time across the UK [183] with UK national surveillance figures estimating that 93% of GUM clinic attendees received an HIV test in 2008 [9]. Whilst testing amongst sexual health clinic attenders may be high, data from the second National Survey of Sexual Attitudes and Lifestyles, a weighted probability sample survey conducted in the general population, found only 44% of MSM to have ever tested for HIV, out of whom only 1 in 3 had tested in the last year [184]. Increasing the proportion of MSM who have ever tested for HIV, and encouraging MSM to test regularly thereafter, is a crucial precursor to any role early treatment could play in curbing onward transmission.

2.2.5 Conclusion

At the time of writing this review, there was clinical equipoise over whether early ART, both when initiated at high CD4 counts (>350 cells/mm^3) and when given as short-course therapy in PHI, conferred significant clinical benefits to the individual. Whilst, in both cases, observational studies to date have reported potential benefits to earlier initiation, they are subject to bias and the effect of unmeasured confounders. Large randomised controlled trials are currently underway to address these gaps in the evidence: START to assess whether initiation of ART at CD4>500 cells/mm^3 confers clinical benefit compared to starting at ≤350; and SPARTAC to assess whether short-course ART of 12 or 48-week duration initiated in PHI could delay the time to treatment re-initiation, compared to no ART in PHI. Meanwhile, there is mounting evidence from observational and mathematical modelling studies that ART, often in combination with expanded HIV testing, can play a role in reducing HIV transmission at both the individual and population level. The HPTN-052 trial is currently underway and aims to address whether ART can reduce risk of HIV transmission amongst serodiscordant partners, whilst the PopART cluster randomised trial is currently in planning phase and seeks to assess whether a universal test and treat policy can reduce HIV incidence at the population level.

The success of the widespread rollout of TasP depends not only on the efficacy of ART in the prevention of transmission, but also the identification of undiagnosed individuals at an early stage of infection, good linkage to care to enable ART initiation and retention in care for monitoring of adherence and viral load. There are also concerns as to whether risk compensation may occur if TasP were to be adopted as a prevention strategy, whereby high-risk sexual behaviour increases due to a perceived decrease in the risk of transmitting or acquiring HIV. In addition, there is no research to date on the acceptability of early ART to reduce transmission, particularly in the current scenario where there is no randomised evidence of clinical benefit to the individual.

2.3 PhD Rationale and research question

In this chapter I have summarised the findings from the literature showing that the elevated viral load during EHI likely results in disproportionally high transmission risk over this disease stage. This has been shown in several modelling and phylogenetic studies, though the proportion of infections attributable to EHI varies greatly (from 1.3 to 88.5%) according to the populations under study, stage of the epidemic, model assumptions and

definitions adopted by the researchers. Sexual behaviour studies have also indicated that lack of awareness of HIV infection and subsequent continued high-risk sexual behaviours over EHI, may also be responsible for high transmission potential during this stage.

Individuals with EHI are likely to present with high CD4 counts, most likely above the current BHIVA recommended threshold for treatment initiation of 350 cells/mm^3 [132]. Evidence from observational studies indicates that initiation of life-long therapy at CD4>350 cells/mm^3, or specifically in PHI, may confer clinical benefit, though randomised evidence is currently lacking. There is also a growing body of observational evidence supporting the use of ART as a method of reducing sexual transmission of HIV, at the individual and public health level, though again, randomised trial data are still awaited.

MSM in the UK carry a disproportionate burden of HIV, with 2760 newly diagnosed with HIV in 2009, comprising 42% of all new diagnoses in the UK [185]. As 1 in 6 MSM presented with evidence of a recent infection, and 4 out of 5 were likely to have contracted HIV in the UK [185], it is evident that TasP could play a role in reducing transmission amongst this risk group. As MSM with EHI are known to have higher viral loads than those with chronic infection, early initiation of ART in this population could reduce the high infectivity associated with elevated viral loads, help reduce community viral load, and may also provide clinical benefits to the individual. The rollout of TasP in the UK would result in HIV-positive MSM being offered ART at a much earlier time point in the course of HIV infection than they are under the current guidelines. However, at the time of this literature review, there was no work to date investigating the acceptability of early ART to prevent HIV transmission amongst MSM with EHI. Whether MSM would accept early ART to prevent transmission is a particularly salient question, given the absence of randomised evidence of individual clinical benefit.

Due to the short duration of elevated infectiousness in early infection, early presentation to health services for HIV diagnosis at peak viraemia is crucial in dictating the utility of TasP. However, currently no data exist characterising viral load at clinic presentation amongst MSM with EHI in the UK. Similarly, the success of TasP in reducing secondary transmission during EHI is dependent on sexual behaviour over this time period. Studies from the US, and one study conducted in a central London HIV clinic, indicated attenuation of HIV-transmission risk-behaviours after HIV diagnosis amongst MSM with EHI, but no recent data exist to address this question amongst a wider population of MSM in the UK.

This thesis attempts to bridge the gaps in the knowledge and understanding of acceptability of early ART amongst MSM with EHI in the UK, and how TasP could be used in this population to reduce HIV transmission. The overarching research question this thesis seeks to address is:

> *"Is early antiretroviral therapy acceptable to MSM with early HIV infection attending UK HIV clinics, and could it be used in this population to reduce HIV transmission risk?"*

3 Methodology and methods

In this chapter I first give a brief introduction to mixed methods research, outlining its origin and underlying methodology. I then provide my rationale for selecting this approach, framing this decision within the context of my worldview and philosophical assumptions on the nature of research. The study design is then outlined in full, with the aims and objectives of the two PhD workstreams presented, and the methods for each of their comprising phases described in detail.

3.1 The mixed methods approach

Mixed methods research has been defined by Tashakkori and Creswell as "research in which the investigator collects and analyses data, integrates the findings, and draws inferences using both qualitative and quantitative approaches or methods in a single study or programme of inquiry" [186]. Greene went on to add a further layer to this definition by stating that mixed methods research invites us "to participate in dialogue about multiple ways of seeing and hearing, multiple ways of making sense of the social world, and multiple standpoints on what is important and to be valued and cherished" [187].

The first studies demonstrating the use of mixed methods, by merging qualitative and quantitative data using data triangulation techniques, can be traced back to 1970's psychology. However, mixed methods research in its current guise, as a methodology in its own right, is a far more recent development, dating from the late 1980s and early 1990s. Researchers in the UK, US and Canada from very different backgrounds in sociology, psychology, management, evaluation, education and nursing began by independently, then collaboratively, refining the definition of mixed methods and developing a typology of different mixed methods approaches. The culmination was a formal classification of mixed methods design types defined by a number of factors including: the sequence in which the qualitative and quantitative components are conducted, the relative weight, emphasis and aim of each component and how, and at what point in the study, the results are integrated [188].

Mixed methods research can be employed for many reasons. Greene et al defined a typology of five reasons for using a mixed methods approach, namely: triangulation, complementarity, development, initiation and expansion [189]. Triangulation enables

corroboration of results between the methods, whilst complementarity seeks enhancement and clarification of findings. Development refers to the use of one method to inform the other, either from a sampling, data capture or implementation perspective. Initiation refers to the discovery of contradictions in findings between the methods, and expansion is the ability of mixed methods to reveal a greater depth and breadth of a subject using different study components. By combining qualitative and quantitative methods, it is possible to capitalise on the benefits of both approaches, whilst minimising the bias and limitations each approach is renowned for.

Arguably, the most dominant worldview in health research today is the positivist perspective, which assumes that an external reality exists in a fixed state, all phenomena can be measured objectively and that knowledge can be gained through hypothesis testing. The positivist worldview derives from the natural sciences and generally assumes the researcher is independent from the phenomenon under study. Interpretivism on the other hand is deeply rooted in the social sciences and recognises that the researcher and the phenomenon under study can influence each other. It is for this reason that qualitative research findings are often regarded as subjective. From an interpretivist perspective, social reality is viewed as being less constant as it is based on human thoughts and behaviour, which are not governed by the "law-like" regularities seen in the natural world [190]. The integration of qualitative and quantitative methods, with their fundamentally distinct ontology, axiology and epistemology, into a mixed methods approach has led to resistance from methodological purists over the years. However, the development of mixed methods methodology brought with it a new research paradigm in the shape of a pragmatist worldview, which is generally now regarded as the "paradigm of choice" amongst mixed methods researchers. Pragmatism in this context is defined by Creswell and Plano Clark as focussing on "the consequences of research, on the primary importance of the question asked rather than the methods, and on the use of multiple methods of data collection to inform problems under study whilst valuing both objective and subjective knowledge" [191].

Despite the opposition to mixed methods research from positivist and interpretivist purists, it is hard to argue that there is no place for it in today's research world. In health research, where research questions are often complex and multifaceted, the use of mixed methods has risen exponentially and funding calls now often specify the need for a qualitative component in the study design. This is reflected in the observed increase in US National

Institute of Health funded projects with mixed methods designs which increased from 1 in 1997 to 60 in 2007 [192].

3.2 Philosophical assumptions and personal characteristics

Whilst quantitative research lends itself to a positivist worldview, qualitative research is reflexive in nature with the researcher playing an integral part in the research process. As such, an appreciation of my philosophical assumptions is important to assist in understanding my position and how this affects my chosen study design and interpretation of the resulting data.

I have a very multidisciplinary background as a researcher and have worked on a number of studies over the years, ranging from clinical observational cohorts and a randomised trial of computer aided sexual health interviewing techniques for clinicians, to an international longitudinal study on health, and various cross-sectional sexual behaviour surveys in between. The majority of my work to date, has involved a combination of epidemiology and social epidemiology. I believe that there is a difference between the fixed state of the natural world and the ever-changing landscape of the social world. As such, I hold a pragmatic worldview and believe that whilst a positivist approach to research may be acceptable in certain basic science circumstances where elements can be artificially controlled, such as in a laboratory context, the nature of the social world is far more complex and difficult to control. I believe the close interaction between the researcher and the participants in a face-to-face in-depth interview situation means that, while a social reality may exist outside of the interview context for the participant, the relationship between the researcher and participant will dictate how much of that reality is presented to the researcher within the interview context. Furthermore, my philosophical assumptions, research motivations and personal characteristics are entwined within the research itself, and may be enacted subconsciously.

3.3 The mixed methods study design of the thesis

3.3.1 Rationale for using mixed methods approach for this thesis

As demonstrated in the background chapter by May and Anderson's simple model of HIV transmission, the global HIV epidemic is a product of the relationship between the virus, the host and a range of psychological and societal factors which dictate human

behaviour [61]. As such, immunology, virology, epidemiology, sociology and psychology all have a play a part in assessing, and attenuating, onward transmission of HIV. We live in world where dependence on biomedical intervention is high, and as such, clinical practice has a propensity to focus on clinical outcomes, sometimes to the detriment of psychological and social factors which are often also important. After all, a biomedical intervention is of no use if it is not accepted, adopted and used as intended by those whom it was designed to help. The decision that an intervention is acceptable, and the subsequent adoption of it, are dependent on an individual's attitudes and beliefs about the intervention which are moulded by psychological and societal factors.

In this thesis, where the goal is to understand how useful early ART could be in reducing transmission amongst MSM with EHI, assessing the acceptability of the intervention, and understanding the underlying attitudes, beliefs, and experiences of the men who would take it, is as crucial a step as examining the biological factors changes in infectiousness over EHI. By adopting a multi-disciplinary mixed-methods approach, I hope to provide a comprehensive understanding of where early ART fits into the lives of MSM with EHI, how acceptable it is and whether it could be useful in preventing secondary transmission in this group.

3.3.2 Study design

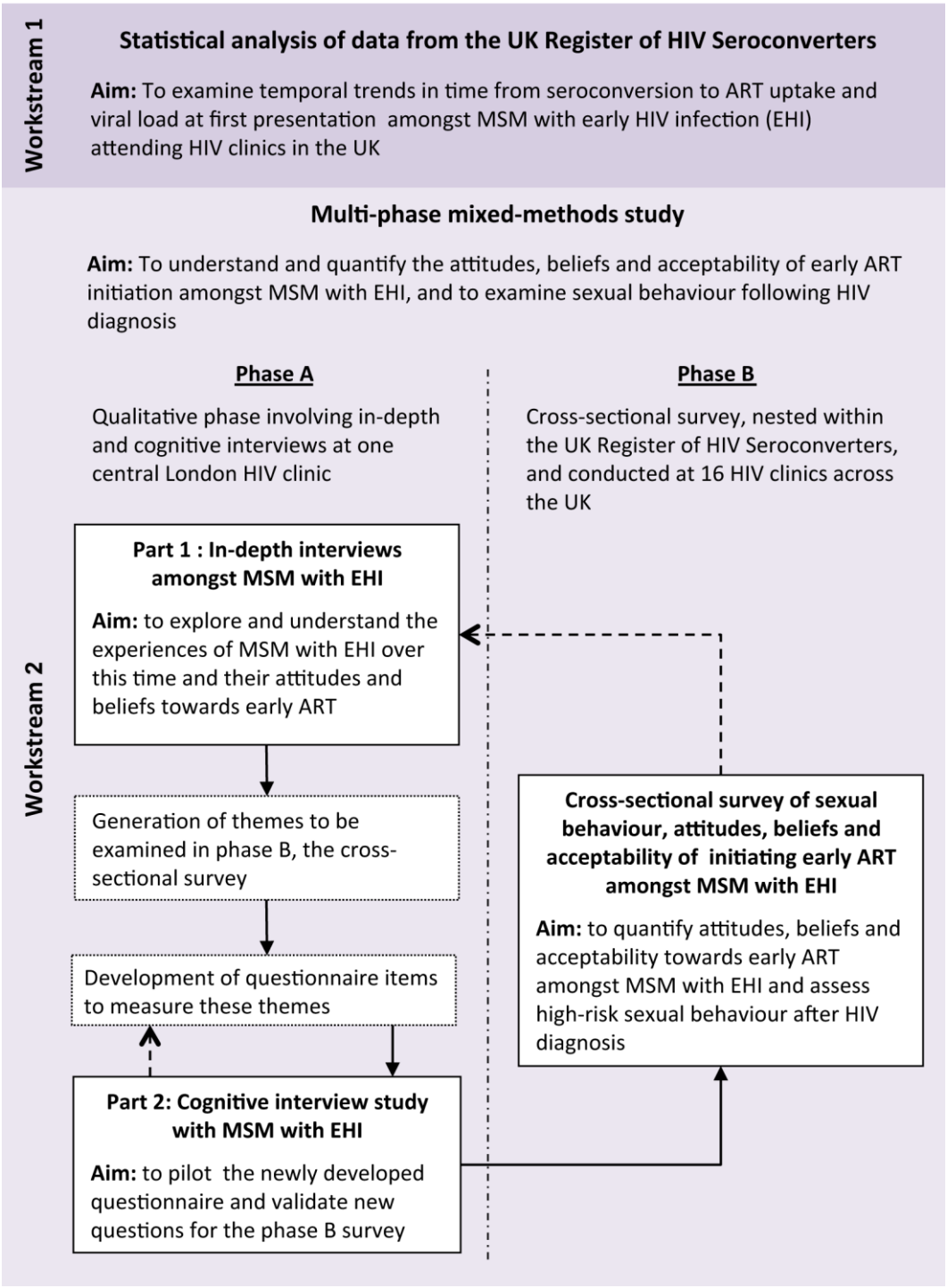
In this thesis, I describe the use of a multi-phase mixed-methods study design which combines 2 concurrent workstreams, as illustrated in figure 3.1, to answer the overarching research question:

> *"Is early antiretroviral therapy acceptable to MSM with early HIV infection attending UK HIV clinics, and could it be used in this population to reduce HIV transmission risk?"*

As an overview: workstream 1 involved secondary analysis of data from the UK Register of HIV Seroconverters to examine temporal changes in ART uptake amongst individuals with EHI and viral load at first clinic presentation amongst MSM with EHI. In workstream 2, I designed and conducted an exploratory sequential mixed methods study [191], also known as the quantitative follow-up design [193]. This involved a qualitative component (phase A), an in-depth interview study to explore attitudes and beliefs towards early ART amongst MSM with EHI attending a central London HIV clinic. This was followed by a multi-site cross-

Figure 3.1 PhD study design

"Is early antiretroviral therapy acceptable to MSM with early HIV infection attending UK HIV clinics, and could it be used in this population to reduce HIV transmission?"



sectional survey (phase B) to obtain an estimate of the prevalence of the views identified in the qualitative component amongst a wider population of MSM recruited across the UK, and identify factors associated with uptake of early ART, as well as high HIV transmission-risk behaviours. The first and second workstreams ran concurrently, and phases A and B of workstream 2 ran sequentially.

The rationale for taking this sequential approach to workstream 2 was that by conducting the exploratory qualitative work first, it was possible to identify themes in the men's attitudes and beliefs to early ART, which I may not have identified myself. At the time of starting this study, there were no data published on attitudes, beliefs and acceptability of ART amongst men with EHI. I wanted to avoid a dictatorial "top-down" method of designing a questionnaire without consultation with the men who would complete it, which would have led to a survey which established the level of agreement with my attitudes and beliefs. Conducting the qualitative work first allowed me to develop the questionnaire based on the attitudes, beliefs and themes derived from the seroconverters themselves, from the "bottom up". A full overview of the two work streams now follows.

3.3.3 Workstream 1: Analysis of data from the UK Register of HIV Seroconverters

This part of the PhD was quantitative in nature and used data from the UK Register of HIV Seroconverters to epidemiologically characterise the time from seroconversion to ART initiation and viral load at first clinic presentation. I examined temporal trends in time from seroconversion to, and CD4 count at, ART initiation to investigate whether patterns of ART uptake had changed over time amongst individuals diagnosed in EHI. I also examined viral load at first clinic presentation amongst MSM with EHI, to understand how early an intervention with ART would be required to maximise its impact on HIV transmission. The specific research questions this workstream sought to answer were:

- Has time from seroconversion to ART initiation changed over time amongst people with EHI?
- When do MSM with EHI first present to HIV clinic and what is their viral load at first presentation?
- Has viral load at first clinic presentation changed over time?

3.3.4 Workstream 2: Exploring and quantifying attitudes, beliefs and acceptability towards early ART and changes in sexual behaviour after HIV diagnosis

3.3.4.1 Workstream 2 phase A: Qualitative component

This qualitative phase comprised of two parts. The first was an in-depth interview study with 14 MSM with EHI presenting to a central London HIV clinic. I conducted the interviews with the aim of exploring the attitudes, beliefs, and acceptability of early ART amongst this population. The specific research questions this phase aimed to address were:

- How does being diagnosed with recent HIV infection affect men's lives?
- How do MSM with EHI feel about early ART?

In the second part of phase A, I drew on the themes identified during the in-depth interviews to develop new survey items measuring the newly identified attitudes and beliefs towards HIV treatment. In an iterative process I piloted and refined the resulting questionnaire using cognitive interviewing techniques amongst MSM with EHI recruited from the same London HIV clinic.

3.3.4.2 Workstream 2 phase B: Cross-sectional survey of MSM seroconverters

This phase was quantitative and involved conducting a cross-sectional pen and paper survey in 16 HIV clinics across the UK to quantify the sexual behaviour, attitudes, beliefs and acceptability of early ART amongst MSM with EHI. I undertook this phase as a sub-study of the existing multi-site MRC-funded UK Register of HIV Seroconverters. This phase aimed to answer the following research questions:

- How widely held are the attitudes and beliefs identified in workstream 2 phase A amongst MSM with EHI in the UK?
- What proportion of MSM with EHI regarded early ART as acceptable?
- What proportion of MSM initiated early ART, and what factors are associated with this?
- Amongst MSM who initiated early ART, what were the predominant reasons for initiation?
- What proportion of MSM engaged in high-risk sex after HIV diagnosis, and what factors are associated with this?

3.3.5 Conceptual framework of the thesis

Figure 3.2 outlines my conceptual framework for the thesis, which I developed based on my background reading and the findings from my scoping review of the literature presented in chapter 2. It illustrates how the research questions addressed in workstream 1, and in phase A and B of workstream 2, relate to one another and assist in examining the specific aspects of the overarching research question.

Boerma and Weir's proximate-determinants framework of HIV transmission is influenced by the three biological parameters adapted from May and Anderson's simple model of transmission: per contact risk of transmission (β), exposure of susceptible to infected individuals (c) and the duration of infectiousness (D) [61,65]. In order to reduce secondary transmission of HIV, early ART would have to influence the proximal determinants of these three parameters as outlined in section 1.5. Assessment of the extent to which this is currently possible amongst MSM with EHI comprises the utility element to the research question.

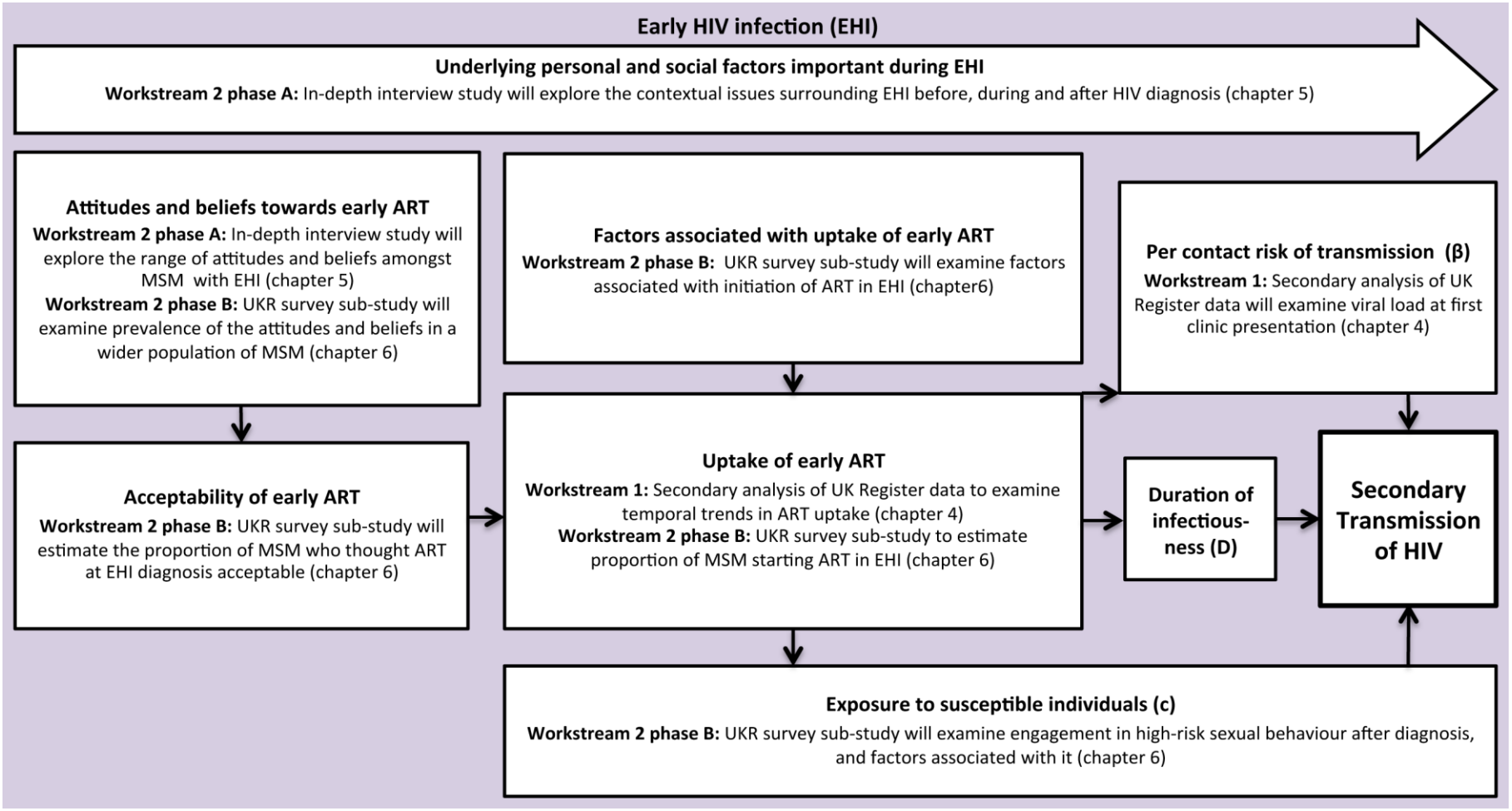
Workstream 1 aims to elucidate whether MSM with EHI present to clinic early enough that initiating ART immediately could mediate elevated viraemia observed in early infection and reduce the per contact risk of transmission. Focussing on another biological determinant of transmission as proposed by Boerma and Weir, exposure of susceptible to infected individuals [65], phase B of workstream 2 aims to assess the proportion of MSM who engage in sex which carries a high risk of HIV-transmission after receiving their HIV diagnosis. By investigating the factors associated with engagement in high-risk sex after diagnosis it may be possible to identify men most at risk of transmitting HIV after HIV diagnosis.

Workstream 1 also aims to provide an estimate of ART uptake by describing trends in ART initiation over time amongst HIV seroconverters. A further estimate of early ART uptake, specifically amongst MSM with EHI will be provided by phase B of workstream 2, which will also identify demographic, clinical, attitudinal and behavioural factors independently associated with early ART initiation in this group.

As mentioned previously, uptake of ART is partially dictated by the acceptability amongst those who would use it, and estimates of this will be provided by the cross-sectional survey data (phase B of workstream 2). Underlying the acceptability of early ART are men's attitudes and beliefs towards it, which will be explored in detail the in-depth interview

study (phase A of workstream 2), as well as empirically described in the cross-sectional survey (phase B of workstream 2). Importantly, men's attitudes and beliefs towards ART are a product of men's experiences over their life, and perhaps most acutely, in their experience of being diagnosed with HIV and the aftermath. The in-depth interview study (phase A of workstream 2) aims to elucidate men's experiences over this time, and how these may relate to their attitudes and beliefs around early ART.

Figure 3.2 Conceptual framework of the interrelationship of factors influencing the acceptability and utility of early ART to reduce HIV transmission amongst MSM with EHI in the UK



3.4 Workstream 1 methods: Analysis of data from the UK Register of HIV Seroconverters

Risk of HIV transmission is known to increase with blood plasma HIV viral load [66], with the high viraemia observed around the time of seroconversion likely resulting in increased transmission risk [105–110], and both mathematical modelling and phylogenetic studies suggesting individuals with EHI contribute disproportionately to the HIV epidemic [72,110,112,113,116,118,121,122]. The timing of presentation to clinic services and the corresponding viral load amongst individuals with EHI may provide some insight as to whether initiation of ART could be useful in preventing secondary transmission form this population. In addition to this elevated viraemia during EHI, there are also conflicting reports from Europe and the US on changes in initial viral load and set point over time, a proxy of HIV virulence[194,195]. At the time of initiating this thesis, there were no published data characterising viral load at first clinic presentation, and examining temporal trends amongst ART-naïve seroconverters in the UK. Secondly, it is important to contextualise the rest of the PhD by describing the temporal trends in ART initiation amongst UK seroconverters.

I therefore undertook analyses using data from the UK Register of HIV Seroconverters with the aim of characterising viral load at first clinic presentation. I also examined temporal trends in time from HIV seroconversion to initiation of ART amongst the same cohort.

The specific objectives were:

- To examine temporal trends in time from seroconversion to, and CD4 count at, ART initiation amongst people diagnosed in EHI
- To establish when MSM with EHI first present to HIV clinic and their viral load at first clinic presentation
- To examine temporal trends in viral load at first clinic presentation amongst MSM with EHI.

3.4.1 Overview of the UK Register of HIV Seroconverters

The UK Register of HIV Seroconverters is a cohort of individuals whose time of HIV seroconversion can be reliably estimated. The study was started in 1994 with the primary aim of estimating the time from HIV seroconversion to AIDS and death and to examine

related factors. Full details of the methodology of the study can be found elsewhere [196–198], so a brief overview is presented here.

Individuals are eligible to join the UK Register if they meet at least one of the following criteria for having confirmed laboratory evidence of HIV seroconversion:

1. An HIV antibody negative test followed by an HIV antibody positive test within 12 months (prior to 2004 the maximum window between negative and positive tests was 3 years and those recruited using this definition continue to be followed up in the UK Register)
2. Test "incident" at low level using a RITA assay
3. HIV antibody negative with positive reverse transcription polymerase chain reaction (RT-PCR)
4. Equivocal HIV antibody test supported by a repeat test within a 2 week period showing a rising optical density.
5. Have clinical manifestations of symptomatic HIV seroconversion illness supported by antigen positivity and <4 bands on Western Blot.

In addition, individuals infected through mother-to-child transmission are eligible when they are 16 years of age. All patients provide written informed consent to enrol in the study.

Recruitment of individuals to the UK Register can be prospective and retrospective. Individuals enrolling to the study provide consent for all their HIV clinical data, both historical and future, to be extracted and collated by the UK Register study team. Once an individual is enrolled in the study, a case registration form, see appendix 8, is completed by the clinic staff. This collects the following information: initials, soundex, date of birth, sex, ethnicity, probable route of HIV acquisition, country of infection, dates of the laboratory evidence of seroconversion, dates and values for previous CD4 counts, dates and values of previous viral loads including the assay type and cut-off, ART status (including previous treatment, pre- and post-exposure prophylaxis [PrEP and PEP]), dates and details of AIDS defining conditions, other serious medical conditions, Hepatitis B and C testing history, date and causes of death, and date last seen in clinic. A 10ml EDTA blood sample is requested as close to first positive test as possible, and thereafter annual bloods are requested. It is possible to enrol to the UK Register and consent to making clinical data available without providing a blood sample.

Annual follow up data are provided by the study clinics through the UK Register follow-up proforma, although some of the larger clinics provide viral load, CD4 and ART data as electronic downloads. Data on date last seen at clinic, CD4 and viral load measures performed since last follow-up, date of last follow-up blood sample, ART status changes, pneumocystis pneumonia (PCP) prophylaxis status, any AIDS diagnosis, other life threatening events, Hepatitis B and C testing since last follow-up are collected via a patient specific follow-up proforma generated through the UK Register database and sent out to clinics annually.

HIV infections are reported on a voluntary basis to national surveillance centres: PHE, Public Health Wales and Health Protection Scotland (HPS). Through collaboration with these organisations and cross-checking of databases, the UK Register study team endeavours to identify all seroconverters in the UK for enrolment to the study. Cross-checking the UK Register database with HIV/AIDS databases held at PHE and HPS also enables tracing of individuals who have been lost to follow-up. In addition to these surveillance centres, the UK Register team cross-check information on those who become lost to follow-up with the Office of National Statistics (ONS) in England, Wales and Northern Ireland and the General Registrar Office (GRO) in Scotland to check for deaths. In addition, HIV subtypes are identified through FASTA files obtained from clinics and by cross-checking patients enrolled on the UK Register with the MRC hosted UK HIV Resistance Database. Matching records with the above mentioned organisations and databases is always performed using initials, date of birth, sex and soundex code.

The UK Register has ethics approval from South Birmingham Research Ethics Committee, REC reference number: 04/Q2707/155 (see appendix 9).

3.4.2 Analysis of temporal trends in ART initiation

3.4.2.1 Study population

The data used in the ART initiation analysis were downloaded from the UK Register database on 2nd January 2014. Data were restricted to individuals aged 16 or more seroconverting on or after 1st January 1998, when ART first became routinely available in UK clinics, to 31st December 2011, to allow adequate follow-up time. Only individuals who acquired HIV sexually or through injecting drugs were included in the analysis.

3.4.2.2 Variable definitions

Date of HIV diagnosis was defined as the earlier of either first antibody positive or first detectable viral load. Date of HIV seroconversion was estimated as the midpoint between HIV antibody negative and positive tests in those meeting UK Register inclusion criteria 1, (see section 3.4.1). In individuals who present with evidence of AHI (inclusion criteria 3-5) or a RITA incident test (inclusion criteria 2) the date first HIV-positive was used as the date of HIV seroconversion. HIV test interval is defined as the time interval between HIV antibody positive and negative antibody test dates for individuals meeting inclusion criteria 1. For individuals who present to clinic with evidence of AHI, or who are RITA incident (UK Register seroconversion eligibility criteria 2-5), the HIV test interval was coded as 0.

ART start date was defined as the earliest date any ART drug was initiated, providing it was after, or in the 7 days prior to, the date of HIV diagnosis. Where ART was both commenced and ended prior to date of HIV diagnosis it was deemed to be PEP or PrEP. For patients identified as having taken PrEP or PEP, their date of ART start was the first date of ART after HIV diagnosis.

CD4 count at ART initiation was calculated as the mean of the last two measurements taken in the 6 months prior to ART initiation, where only one measure was available this was used (18.8% of sample).

Diagnosis in PHI was defined as having an HIV test window <180 days, and initiation of ART in PHI was defined as having an ART start date within 180 of estimated date of seroconversion. Interruption of ART amongst those initiating in PHI was defined as terminating ART for 2 weeks or longer.

3.4.2.3 Statistical analysis

I used time to event analyses to examine the effect of calendar year of seroconversion on time from HIV seroconversion to ART initiation. Follow-up was censored at date last assessed or date of death. Kaplan-Meier plots were produced to visually describe time from seroconversion to ART initiation by the independent variable of interest year of HIV seroconversion (modelled as seven categories: pre-2000, 2000-1, 2002-3, 2004-5, 2006-7, 2008-9, 2010-11).

Cox proportional hazards models were used to assess changes over calendar time, adjusting for age at seroconversion (continuous, in 10 year increments), sex (male, female), HIV exposure category (sex between men, sex between men and women, injecting drug user) and HIV test interval (<30 days, ≥30 days). HIV test interval was regarded as an a-priori confounder; shorter HIV test intervals have been shown to be associated with both presence and severity of seroconversion symptoms, faster disease progression and shorter time to AIDS[199,200]. Data on ethnicity were available but not included in the models due to the large proportion of white ethnicity individuals (87.1%) and the limited prognostic value of combining non-white ethnicities.

Temporal trends in CD4 count at ART initiation were assessed using ordinary least squares regression, modelling square root transformed CD4 count, year of seroconversion as a continuous variable (per 10 years) and adjusting for the above mentioned covariates.

Logistic regression was used to assess temporal trends in the proportion of individuals diagnosed in PHI (defined as having an HIV test interval of less than 180 days), who initiated ART within 6 months of seroconversion. Amongst individuals who initiated ART in PHI, I used time to event analysis to determine time from ART initiation to interruption, censoring at date of death or date last assessed.

All data management and statistical analyses were performed using STATA 13 [201].

3.4.2.4 Sensitivity analyses

Three separate sensitivity analyses were conducted:

1. To account for the fact that some clinicians' prescribe short-course ART in PHI, I performed a sensitivity analysis excluding individuals diagnosed in PHI from the main time to ART initiation analysis;
2. For the same reason I also excluded those known to have started ART within PHI in a sensitivity analysis of CD4 count at ART initiation;
3. Finally, I excluded individuals known to be recruited to SPARTAC trial from the analyses of ART in PHI.

3.4.3 Analysis of viral load at first clinic presentation

3.4.3.1 Study population

Data used in the following analyses were downloaded on the 15th August 2013 from the UK Register of HIV Seroconverters database. Data were restricted to individuals who reported their likely route of HIV infection as through sex between men as the main focus of this thesis is MSM with EHI, and as differences in viral load between males and females, amongst different exposure groups and ethnicities have been previously documented [79,202,203]. Data were restricted to individuals diagnosed with HIV on or after 1st January 1997, when viral load testing became routine in UK clinical practice.

3.4.3.2 Variable definitions

Date of HIV diagnosis, HIV seroconversion, HIV test interval and ART start date were defined as in the time to ART initiation analysis as outlined above (see section 3.4.2.2). AHI was defined as presentation with an HIV test interval of <30 days.

Viral load at first clinic presentation was defined as the first viral load measure taken for each patient. Men were excluded from the analysis if they started ART prior to their first viral load measure being taken. Where two or more viral load measures were taken on the same date, the mean of available measurements was used. The midpoint of the lower limit of detectability was used for viral load measures that were undetectable, e.g. 20 copies/mL if the lower limit was 40 copies/mL. For viral load beyond the upper detection limit of the assay, the upper limit of detection was used as an estimate of viral load. Viral load was $\log^{10}$ transformed to normalise the distribution. Log transformed viral load was grouped into the five categories according to risk of transmission established by Quinn et al [66]: undetectable (<2.7 $\log_{10}$ copies/mL), 2.7-3.9 $\log_{10}$ copies/mL, 4.0-4.69 $\log_{10}$ copies/mL, 4.7-4.99 $\log_{10}$ copies/mL and >5.0 $\log_{10}$ copies/mL.

CD4 count at diagnosis was estimated as the mean of the first two CD4 counts following HIV diagnosis (measured within 6 months of diagnosis) where two or more were taken, or else the first measure was used. Likewise, CD4 at ART commencement was defined as the mean of the last two CD4 counts measured within the 6 months prior to ART start date (up to 2 weeks after ART initiation) where two counts were available, or else the single measure was used.

The following variables were re-categorised into binary variables due to the small number in the dataset: ethnicity (white/non-white), and HIV subtype (B and non-B). Time from seroconversion to first viral load measure was grouped into the following 6 categories: 0-7 days, >7 days-30 days, >30 days-90 days, >90 days-180 days, >180 days-365 days, >365 days. Year of seroconversion was grouped into the following year groups: 1997-99, 2000-1, 2002-3, 2004-5, 2006-7, 2008-9 and 2010-12.

Over the years there have been a variety of different assays used to measure plasma HIV viral load in UK clinics. To adjust for viral load assay type in sensitivity analyses these were grouped into 3 main types of assay: branch DNA (bDNA), polymerase chain reaction (PCR) and nucleic acid sequence-based amplification (NASBA). Individual assays recorded on the UK Register were classified into assay type by a clinical virologist (Dr Eleni Nastouli) at UCLH Virology laboratory. I used the data from the UK Register of HIV Seroconverters database to create a variable categorising assays according to their upper limit of detection >100,000, >500,000, >750,000 and >10,000,000 copies/mL. Table 3.1 outlines the assays used in the UK Register of HIV Seroconverters and lists assay type and upper detection limit allocated to each assay.

3.4.3.3 Statistical analysis

Median viral load at presentation was calculated with interquartile range (IQR). The proportion of individuals within each viral load category was calculated according to the time from seroconversion to first viral load measure.

To examine changes in initial viral load by time since seroconversion, data were restricted to individuals with a viral load measure within one year of seroconversion. Log transformed continuous viral load measures were plotted against time from seroconversion to initial viral load (modelled as a continuous variable in days) in a scatterplot, with ordinary least squares (OLS) simple linear regression model used to check for evidence of any temporal trend. This model was compared to a model fitting time from seroconversion to first viral load as a 5 group categorical variable, and a likelihood ratio test was used to assess for evidence of departure from linearity.

Table 3.1 Coding table for HIV-1 RNA assays

Assay name	Assay type	Upper range of detection (copies/mL)
Abbott U-S	PCR	>10,000,000
Chiron/Bayer 2.0	bDNA	>500,000
Chiron/Bayer 3.0	bDNA	>500,000
Chiron/Bayer unspecified	bDNA	>500,000
Cobas 1.5 (<400)	PCR	>750,000
Cobas 1.5 U-S (<50)	PCR	>100,000
Cobas Taq Man	PCR	>10,000,000
Cobas Unspecified	PCR	>750,000
NASBA (<1000/<400)	NASBA	>6,000,000
NASBA U-S (<50/<150)	NASBA	>100,000
NASBA Unspecified	NASBA	>6,000,000
Nuclisens Easy Q	NASBA	>10,000,000
Nuclisens US (<50)	NASBA	>100,000
Nuclisens Unspecified	NASBA	>6,000,000
Other	Unknown	>100,000
Roche 1.0 (<400)	PCR	>750,000
Roche 1.5 (<400)	PCR	>750,000
Roche 1.5 US (<50)	PCR	>100,000
Roche Taq Man	PCR	>10,000,000
Roche Unspecified (<400)	PCR	>750,000
Roche(<40)	PCR	>10,000,000

PCR=polymerase chain reaction; bDNA=branched DNA; NASBA=nucleic acid sequence based amplification

To examine trends in initial viral load over calendar time the log transformed continuous viral load measures were plotted by date of seroconversion in a scatterplot. Viral load at first presentation was modelled with year group of diagnosis fitted as a continuous variable using ordinary least squares (OLS) simple linear regression model to check for evidence of any temporal trend. This model was compared to a model fitting calendar year of seroconversion as a 7 group categorical variable, and a likelihood ratio test was used to assess for evidence of departure from linearity.

Trends in viral load at first presentation by both time since seroconversion and over calendar time were assessed using the same multivariate model. The following independent variables were considered as potential confounders: ethnicity, age at seroconversion, HIV subtype, HIV test interval, evidence of acute infection, time from

diagnosis to first viral load measurement, viral load assay type and viral load assay upper range of detection. Associations between these variable and viral load at first presentation were tested first by modelling each independent variable in an OLS simple regression models and using a likelihood ratio test to assess goodness of fit. Variables found to be associated at the $p<0.10$ level were put forward for multivariate analyses.

Multiple regression OLS models were then built using independent variables found to be associated in the univariate regression models to the $p<0.10$ level. A forward stepwise approach to model building was used with independent variables added one by one and likelihood ratio test used to assess goodness of fit. The variables found to be most strongly associated with viral load at presentation were added first to the model. A p-value of <0.10 meant that the variable remained in the model and the next was added. Independent variables were checked for possible interactions with one another by fitting interaction terms and using the likelihood ratio test to assess goodness of fit.

Collinearity and multicollinearity were checked by examining the variance inflation factor (VIF) for each independent variable in the final multiple regression models using the "collin" command in STATA 12 [204], using a VIF cut off of 10.

HIV subtype, viral load assay type and viral load assay cut-off all had a substantial amount of missing data but were found to be associated with initial viral load in simple OLS regression model. I elected to exclude them from the full model to maximise power and instead assessed their influence on the observed associations in sensitivity analyses.

Restricted cubic spline (RCS) functions of seroconversion date were introduced to the univariate and final multivariate model to examine the evidence of non-linearity in the relationship between viral load at first presentation and time from seroconversion to ART initiation. Using RCS to split a continuous independent variable into splines by defining knots in the data, either by the predetermined values as proposed by Harrell [205] or at values of choice, allows for an almost limitless graphical representation of the shape of the association between x and y [206]. Knots for the RCS were created at 5, 25, 50, 75 and 95th percentiles in this analyses, though I also conducted sensitivity analyses modelling seroconversion date using 3 and 7 knot splines, and comparing the 3 or 7 spline model to the 5 spline model using likelihood ratio tests.

Predicted initial viral load was graphed by time from HIV seroconversion to initial viral load, with 95% confidence intervals for both the unadjusted and adjusted models, fitting time as a RCS function with 5 splines. Restricted cubic spline functions of seroconversion date were introduced to the final univariate and multivariate models to examine the evidence of non-linearity in the relationship between viral load at first presentation and calendar time. Predicted initial viral load was graphed by year of seroconversion with 95% confidence intervals for both the unadjusted and adjusted models, fitting time as a RCS function with 5 splines. The final OLS models were checked for evidence of violation of the assumptions underlying linear regression.

All data management and statistical analyses were carried out using STATA 12 [204].

3.4.3.4 Sensitivity analyses

The following sensitivity analyses were planned for the final OLS multiple regression model assessing temporal trends in viral load at first clinic presentation:

- Data were restricted to MSM with an HIV test interval of ≤180 days
- Data were restricted to a more homogenous sample of white ethnicity MSM
- Viral load at presentation was right truncated at 5.0 $\log_{10}$ copies/mL
- HIV subtype was added in the multiple regression model.

3.5 Workstream 2 phase A methods: In-depth interview study

This phase of workstream 2 involved in-depth interviews with MSM diagnosed in EHI attending a central London HIV clinic, with the aim of exploring the range of attitudes and beliefs towards early ART and understanding the experiences of men diagnosed with recent HIV infection.

This phase of workstream 2 aimed to answer the following research questions:

- How does being diagnosed with recent HIV infection affect men's lives?
- How do MSM with EHI feel about early ART?

The standalone qualitative findings to answer the research questions above are presented in full in chapter 5. In addition, the themes identified in these interviews were used to develop questionnaire items for the cross-sectional survey (workstream 2 phase B). These were piloted using cognitive interviewing and the process is outlined in section 3.6.

Ethics approval was granted for the qualitative study and cognitive interview piloting by Camden and Islington Research Ethics Committee (ref. 09/H0722/92), see appendix 10.

3.5.1 Data collection

The target population for this qualitative study were men aged ≥16 years of age, attending a central London HIV Clinic with laboratory evidence of HIV seroconversion in the past 12 months, and whose reported route of HIV transmission was through sex with men. The initial timeline allocated for me to recruit the men was six months, based on an average of 25-30 new HIV diagnoses a month at the clinic. PHE estimates that 20% of newly diagnosed infections are incident [9] meaning a total of 5-6 new diagnoses a month would be eligible for the study. Assuming the response rate would be 50-65%, six months was calculated to be sufficient to recruit the desired number of individuals.

3.5.2 Sampling strategy

Using purposive sampling to fulfil an age-based quota, I aimed to recruit 3 men from each of the following age categories (16-25 years, 26-30, 31-35, 36-40, 41+). This quota was chosen to try to ensure the range of opinions reflected the views of men over a wide age distribution. There were many other factors likely to be associated with attitudes and

acceptability towards early ART, for example ethnicity, educational level, historical risk behaviour and geographic area, however due to the limited target size of the IDI study, the fact that recruitment was from a single clinic in London and the challenges in recruiting men with early HIV infection, I elected to purposively sample based only on age.

3.5.3 Eligibility criteria

Individuals were eligible for the study if they met **all** of the following criteria:

- Primary route of exposure to HIV was through sex with men
- Were eligible for the UK Register of HIV Seroconverters (as outlined in section 3.4.1)

Individuals were not eligible for the study if they meet **any** the following criteria:

- Inability to provide full informed consent for their participation
- Experience of a severe psychological reaction to their HIV diagnosis
- Inability to speak and read English

Initially men had to be interviewed within 6 months of their HIV diagnosis, however due to slow recruitment within the first 3 months of the study a pragmatic decision was made to increase this to 12 months after diagnosis.

As the eligibility criteria for this study matched that of the UK Register of HIV Seroconverters, for which the central London HIV clinic was a participating site, the invitation for this qualitative study piggybacked the invitation to participate in the UK Register. As I was not a member of the patient clinical care team I was not permitted to make contact with the patient without an introduction from clinic staff.

3.5.4 Data collection

A topic guide (see appendix 11) was developed in conjunction with the research team: Professor Graham Hart, Professor Kholoud Porter and Dr Richard Gilson. As the IDI study was intended to be exploratory in nature, no pre-existing social or psychological theory was used to underpin its development. Whilst there was no patient and public involvement (PPI) group created for this study, I did meet with the HIV clinic patient representatives to seek and include their opinions on the study design and the topic guide and built in suggestions where possible. In addition, Simon Collins from HIV-iBase, an HIV treatment

activist group, was involved throughout the PhD as a member of the UK Register of HIV Seroconverters Steering Committee.

Prior to initiation of the study, I conducted a practice face-to-face in-depth interview with a colleague highly experienced with qualitative research methods in order to practise using the topic guide and receive feedback on my interviewing style. As the study population was very small, I made the pragmatic decision not to pilot the topic guide within the population, but to start recruitment with a view to amending the topic guide as the study progressed.

Prior to commencing the interview all patients were given the patient information sheet to read (appendix 12), had the study aims and any risks of participation discussed, and written informed consent was obtained (appendix 13). Interviews were digitally audio recorded unless the patient declined when asked prior to the interview commencing. I took notes on the topic guide during each the interview to assist with probing and immediately after the interview I wrote up a summary of my experience of the interview, the key themes that emerged from memory and any thoughts relating to the interview or topic guide.

When all the interviews had been conducted, the audio recordings were transcribed verbatim by an external agency experienced in transcribing sensitive data for similar studies. The agency had been recommended by other members of the Department and held a full confidentiality agreement with UCL.

3.5.5 Development of the topic guide

The topic guide underwent several revisions after the interviews commenced, as was originally planned. One of the first changes to make to the topic guide was to add in two statements to gather respondents' views on whether HIV transmission was possible whilst virologically suppressed on ART and whether it was necessary to disclose HIV status if somebody was virologically suppressed on ART. I initially found discussions around ART, transmission and disclosure challenging as individuals had differing levels of knowledge about treatment and I felt I was in danger of leading those who had less knowledge by asking specific questions about transmission. To make the process less open to this problem, I added two statements to the interview process and asked individuals their opinions on the statements, whether they agreed or disagreed with them, and why they felt that way.

I also included a question about previous experiences of PEP. This topic came up during the second interview and it became obvious that any attitudes to ART may well be coloured by previous experience with PEP, whether good or bad. Since then, respondents were asked about their knowledge and experiences with PEP. In addition to this, I asked about their experiences in taking other medications for long periods of time or for other chronic conditions as this may have had some bearings on beliefs and attitudes towards long term commitment to ART.

3.5.6 Data analysis

I carried out thematic analysis of the data using the Framework approach as developed by the National Centre for Social Research. Framework analysis is a systematic technique which uses matrices to chart the cases, themes and sub-themes that emerge in your dataset [190].

Verbatim transcripts were checked through by me in Microsoft Word to remove any identifiable information. I then read through each transcript whilst listening to the audio recording of the interview to mark the transcripts where any strong emotions were present as well as checking the transcripts were verbatim. Whilst reviewing the transcripts I kept a log of all of the themes and sub-themes that emerged from the data.

In consultation with the CI, Professor Graham Hart, I constructed a thematic framework (see table 3.2) based on the study topic guide and the list of themes that had emerged from reviewing the transcripts.

At this point I imported the transcripts into NVivo [207], and applied the thematic framework to three interviews at random to test and refine it, indexing the transcripts on each occurrence of a sub-theme. NVivo was then used to automatically generate framework matrices for each of the themes, plotting the cases (participants) along the rows and the sub-themes in columns. NVivo automatically populated each matrix cell with quotations coded with the case specific sub themes. I then reviewed the content of each cell, condensing the information whilst retaining the context and language used by the participant as much as possible (see appendix 14 for an example). NVivo maintains links in each of the matrix cells to the original quotes in the transcripts which facilitated the analysis process.

From the summarised frameworks, I then identified overarching phenomenon acting across themes and sub-themes and pertaining to the research questions. The data were then examined for linkages between the phenomenon and possible explanations.

Table 3.2 Thematic framework for qualitative study

Theme	Subthemes			
Life experiences	Alcohol and drug use	Housing	Socialising	Other
	Coming out	Looks and attractiveness	Stresses	
	Family	Sexual relationships	Work and study	
HIV Diagnosis	Co-infections & complications	Feelings	Previous testing experience	Stigma
	Disclosure	GP or hospital	Reasons for testing	Other
	Effect on life	Illness or symptoms	Receipt of diagnosis	
Sexual Behaviour	Discussing HIV status	Meeting partners	Relationships	Type of sex
	Feelings about sex	Post-diagnosis	Risk perception	
	HIV transmission	Pre-diagnosis	Risk reduction	
HIV Treatment	Concerns about treatment	When to start treatment	Role of clinician	Trials and evidence
	Early treatment	Health	Short-course	Other
	Effects of treatment	PEP	Treatment and transmission	
	Expectations	Reasons for starting	Treatment knowledge	
Other issues	Abandoning responsibilities	Health	Mental health	Visibility of HIV
	Exercise	Health service related	Personal struggles	
	Guilt	Homophobia	Pornography	
	HCV co-infection	Law and prosecution	THT	

3.6 Workstream 2 phase B methods: Cross-sectional survey

This section describes in detail the methods used in the development of sexual behaviour and attitudes to early ART survey sub-study of the UK Register. Here I outline the overall survey design, the development of the questionnaire tool, the methods of data collection and data analysis used. The survey sought to describe and quantify the prevalence of the attitudes and beliefs towards early ART uncovered in the in-depth interview study. It also aimed to identify factors associated with uptake of early ART and with engaging in high-risk (defined as behaviours which are most likely to lead to onward transmission of HIV) sexual behaviour after HIV diagnosis.

Specifically, the research questions workstream 2 phase B aimed to address were:

- How widely held are the attitudes and beliefs identified in workstream 2 phase A amongst MSM with EHI in the UK?
- What proportion of MSM with EHI regarded early ART as acceptable?
- What proportion of men initiated early ART, and what factors are associated with this?
- Amongst MSM who initiated early ART, what were the predominant reasons for initiation?
- What proportion of MSM present a heightened HIV transmission-risk after HIV diagnosis and what factors are associated with this?

3.6.1 Survey and questionnaire design

For logistical and financial reasons a cross-sectional pen and paper survey design was selected. Computer-aided self-interview methods were considered but dismissed as being prohibitively expensive and difficult to implement across multiple sites. During the study design phase the members of the UK Register Steering Committee were consulted, with their feedback incorporated into the final survey design.

From the outset, I intended to keep the questionnaire as short as possible whilst capturing as much information as possible. The questionnaire was divided into separate sections to capture data on respondent demographics, socio-economic status, HIV testing history and seroconversion experience, sexual behaviour including substance use in the six months prior to HIV diagnosis, sexual behaviour in the time since diagnosis including substance use

and status disclosure, ART experience (including PEP), and acceptability, barriers and attitudes towards early ART.

Nesting the survey in the UK Register allowed for a shorter questionnaire as much of the key demographic and clinical data were collected through the UK Register already. It also increased the accuracy of clinical measures which would otherwise have been captured using self-report methods.

The questions used in the final questionnaire are a combination of questions developed from the in-depth interview study (phase A of workstream 2), and questions which have been previously used in other cross-sectional surveys including: the Gay Men's Sexual Health Survey (GMSHS), the ASTRA (Antiretrovirals, Sexual Transmission Risk and Attitudes) study and the SHARPN (Sex, Health, Antiretrovirals and Partner Notification) studies, all undertaken at UCL Research Department of Infection and Population Health. I decided to utilise questions and attitude statements from these questionnaires where possible as they all had been previously used within the population of interest (HIV-positive MSM recruited in sexual health clinics or, in the case of GMSHS, in the community) and undergone previous validity checks. The sexual behaviour questions were adapted from those used in the UCL and PHE run Gay Men's Sexual Health Survey. This survey ran annually, from 1997 to 2006, then repeated in 2008, 2011 and 2013 in gay community venues and has so been validated in a similar population as the target population in this study [208,209]. One strength of the sexual behaviour question format from this study is that they require numeric answers and can be combined to assess the number of serodiscordant/status unknown UAI partners, which is a key outcome of interest as the behaviour most-likely to lead to onward transmission of HIV. Several attitude and belief statements were taken from the ASTRA study, which allows the possibility of cross-comparison of attitudes to ART between ASTRA respondents with chronic HIV and our survey respondents with recent HIV infection. In addition, the questions on substance use before and during sex were taken from the SHARPN study.

3.6.2 Development of new survey questions

One advantage of adopting a sequential mixed methods approach to workstream 2 was that it permitted the development of new questions based on the themes which emerged from the in-depth interview study in phase A. Though the original plan to conduct all the in-depth interviews prior to designing the survey was not possible due to slow recruitment

and time constraints, data were available from the eight interviews conducted before questionnaire piloting began. Several themes emerged from the in-depth interview study, which had not been considered previously, and which were subsequently included in the survey questionnaire.

In the qualitative study it became apparent that some men expected HIV treatment to be given in the same manner as other diseases, and so expect ART to be prescribed immediately upon diagnosis. Also many of the men interviewed believed there were health benefits to starting ART early, despite a lack of randomised trial evidence indicating this. Men also appeared to delineate between the altruistic ideal of starting treatment to protect your HIV negative partner and starting treatment to reduce anxiety of transmission. Interestingly one man went on to suggest that being on ART made it easier to disclose his HIV status to sexual partners. Specific attitude and belief statements were designed by me to assess the prevalence of these viewpoints in the wider population of MSM recruited to the UK Register. For simplicity and due to lack of time to fully pilot the questionnaire, the attitudes and belief statements were written as individual standalone statements, and not as constructs made up of multiple items.

3.6.3 Questionnaire piloting and validation

I conducted piloting of the questionnaire by using cognitive interview techniques with 4 MSM attending a central London HIV clinic. By using cognitive interviewing it was possible to identify questions that were difficult for respondents to understand and answer. Most importantly, it permitted identification of the elements that make them difficult to answer and allowed respondents to suggest possible solutions.

The cognitive interview questions are designed to establish the methods employed by the respondents to:

- Understand and interpret the questionnaire questions
- Recall information needed to answer questionnaire questions
- Judge what information is relevant in answering questionnaire questions.

Men were invited to participate in the cognitive interviews as per the qualitative interview eligibility criteria and recruitment methods, the information sheet and consent form can be found in appendix 15 and 16. I conducted one-to-one face-to-face interviews in a private

room at the study site. The men were given the pilot questionnaire and asked to complete it one section at a time. At the end of every questionnaire section, I asked them to talk me through how they went about answering the questions. Particular focus was given to understanding, interpretation and recall of information for all newly developed questions, the calculation and ability to recall the number of partners for the sexual behaviour study. In addition, the overall appearance, ordering, routing and flow of the questionnaire were also assessed in these interviews. During the interviews I took comprehensive paper notes which I subsequently assessed after each interview. I also timed how long it took participants to complete each section of the questionnaire which enabled me to calculate a guide time for completion. The aim was to keep the questionnaire short enough to complete in 15 minutes, and all of the men took 15-20 minutes to complete it during the cognitive interviews.

I found the cognitive interview process to be highly insightful and useful; not only were the issues highlighted in real time by the men as they completed the questionnaire but many men went on to provide assistance in finding a solution to problems. From this perspective, piloting became a two way process whereby a problem was raised by the respondent, for example the wording of a question, I could then seek immediate feedback from them on potential alternative wordings, with the men themselves sometimes suggesting more appropriate wording.

As a result of the pilot study, many changes were made to the questionnaire from the original to the final version (see appendix 17 for a log of the changes). One example of a major change following piloting using cognitive interviews, was the way the respondents conceptualised “early ART”. It became evident that men had different expectations as to when treatment would normally be started; what then constituted “early”, and whether it was a CD4 based definition or a time based decision. To alleviate this issue and remove the confusion of the CD4 guided definition of early, I reworded the attitude and belief statements to use the term “now” as opposed to “early”; i.e. “I would start ART now if there was a proven health benefit to me”. This made it conceptually clearer and by definition, as all respondents were only eligible for the survey within the first year of diagnosis and were seroconverters, the majority of respondents would have a CD4 count >350 at the time of completion.

The final version of the questionnaire was designed by me using MS Word and 500 were professionally printed as stapled booklets for distribution across participating HIV centres. A PDF version can be found in appendix 18.

3.6.4 Sample size and power estimation

The plan for this survey was to recruit 120 individuals in the 12 month recruitment period allocated to the sub-study. This number was based on the following calculation: 247 seroconverters were recruited to the UK Register in 2012-2013 overall, of these 220 met eligibility criteria for this sub-study (were MSM recruited to the UK Register within 12 months of their HIV diagnosis and aged ≥16 years at seroconversion). Assuming a 55% response rate for the survey resulted in a likely number of 120 men recruited over a 12 month period.

Assuming a 40% uptake of early ART, a sample size of 120 gives 80% power to detect this prevalence to within 13%, at the 5% significance level. Given this assumption, a sample size of 120 would provide 80% power to detect as significant at the 5% significance level an association between early ART uptake and a given risk factor that increases the prevalence by 1.5 times (e.g. from 31% to 49%).

3.6.5 Selection of study centres

I emailed all UK Register principal investigators at the HIV centres who actively recruited to the UK Register in 2012-13 enquiring whether they would be interested in recruiting to the survey sub-study and giving a brief 1 page outline of the proposed research. All responses of interest were followed up by a further email upon receipt of ethics approval and the process of seeking R&D approval was initiated for these centres. Once R&D approval was granted for a clinic the survey questionnaires and envelopes were sent out to the research team and recruitment could begin.

3.6.6 Ethics

Ethics permission was sought for this section of the PhD by means of a substantial amendment to the UK Register of HIV Seroconverters protocol adding the survey as a sub-study. Permission was granted by the National Research Ethics Service Committee West Midlands, South Birmingham on the 7th May 2013, REC ref. 04/Q2707/155 amendment ref: Protocol v3.1 (appendix 19).

R&D approval for the sub-study was obtained at each of the HIV centres participating in the survey prior to commencement of survey recruitment. This involved the UK Register study manager, Louise Walker-Nthenda, and I liaising with the study PIs at each centre to notify the relevant R&D Departments of the substantial amendment to use the new protocol. Due to the number of research studies conducted at St Mary's Hospital and Chelsea and Westminster Hospital, a request was made for me to present the study to a panel of clinicians for internal study approval prior to the R&D application. I did so and on both occasions the study was approved both by the internal review committee and by the R&D departments.

3.6.7 Data protection and patient anonymity

I designed the questionnaire to be anonymous and contain no uniquely identifiable information if intercepted in transit. Questionnaires were linked to their corresponding UK Register database record by a combination of the HIV clinic recruiting the patient, the last 4 digits of the patient's clinic number, date of birth and, if necessary, date first HIV positive; a combination of variables I successfully piloted within the UK Register database to be able to generate a one-to-one match.

Once questionnaires were received at the MRC CTU, they were stored in a locked cupboard in a secure area. The sub-study database was encrypted and stored on the MRC secure network and was password protected for extra security.

3.6.8 Eligibility and recruitment

Men were eligible for the survey if they were aged 16 years or over at HIV diagnosis, their likely route of HIV exposure was sex with another man, and they were recruited to the UK Register of HIV Seroconverters prior to or at the same time as recruitment to this survey. The survey questionnaire had to be completed by the patient within one year of their date of HIV diagnosis. Men who were considered by their clinical care team to be experiencing psychological difficulties in coming to terms with their diagnosis were not eligible for the sub-study. It was the responsibility of research staff at each clinic to assess and enforce all eligibility criteria. Men who were recruited and completed the questionnaire outside of the one year eligibility period were identified and excluded by me from the final study population.

Eligible men were given a participant information sheet (appendix 20) and informed that participation in the survey sub-study was optional and they were permitted to enrol in the UK Register without participating in the survey. For those agreeing to participate in the survey, written informed consent was required for both the UK Register and the survey (appendix 21). This was taken by clinic staff with separate consent forms and information sheets for the UK Register and survey sub-study.

Prior to the commencement of survey recruitment in each clinic, I provided a list of patients recruited to the UK Register in the past 12 months, as these patients were eligible for the survey up until one year after their diagnosis. The idea was that clinic staff could recruit these eligible patients if they happened to attend before a year after their HIV diagnosis (so-called retrospective recruitment). The majority of clinics operated their own system for identifying seroconverters eligible for the survey, however, and retrospective recruitment was not implemented by the majority of the clinics. Instead, they favoured a process of prospective recruitment where newly identified eligible seroconverters were recruited to both the UK Register and the Survey at the same time.

Once the participant had consented to the survey, the nurse or researcher completed the questionnaire front cover and handed it to the participant with a pen and an envelope. Men were instructed to complete the questionnaire in the clinic, place it into the envelope provided, seal it for confidentiality and give it back to the research staff. The research staff then returned the questionnaire to MRC CTU data manager in the sealed envelope.

3.6.9 Study period

Ethics permission for this study was granted in May 2013 however the long process of obtaining R&D permission from each participating site resulted in a lengthy delay in some cases between ethics approval and recruitment commencement. All centres operated a continuous recruitment period, with the exception of Brighton and Guy's and St Thomas' hospital who conducted recruitment in two phases. Recruitment to this study continued until December 2014.

3.6.10 Data entry

I entered the questionnaire data into a Microsoft Access database designed and built by me for this study. Upon completion of data entry I randomly selected 30 questionnaires and double checked the database entry with the questionnaire booklet to ensure data

consistency. The data were exported from Access using .csv files and imported into STATA where they were merged with the corresponding UK Register record using the last 4 digits of the respondent clinic numbers and the name of the HIV centre the patient was recruited from. After using this method of matching there were a number of questionnaires which remained unmatched. For these I manually matched the records using HIV centre, patient date of birth and/or date first HIV positive allowing for typographic errors in the above. If, after manual matching, a questionnaire remained unmatched the relevant clinic was informed, as this was usually indicative that the clinic had not returned the corresponding UK Register case report form for that patient. In all but a few cases the clinic then forwarded the patient's UK Register form for entry to the database and a match could then be made.

3.6.11 Data analyses

3.6.11.1 Data management

The distributions of ordinal and continuous variables were checked for normality, with relevant transformations applied to them in the presence of notable skewness and/or kurtosis. For this reason viral load at diagnosis was log transformed, and CD4 at diagnosis was square root transformed for logistic regression models.

The attitude and belief statements were originally measured using a 5-point likert scale. For the purposes of calculating a binary outcome for each attitude and belief statement the 5-point scales were recoded into binary outcomes in the following way: respondents who answered "Agree" or "Strongly agree" to each statement were recoded as "Agree"; all those answering "Strongly disagree", "Disagree", "Neither agree or disagree" or "Don't know" were coded as "Did not agree".

As both descriptive and risk factor analyses were planned using the survey data I have split the statistical methods into descriptive and analytic sections.

3.6.11.2 Variable definitions

The majority of variables included in the final analyses were derived directly from individual survey questions and presented as continuous data, binary or categorical variables. Several of the sexual behaviour variables were however derived from the responses to two or more

questions, and involved various assumptions. The definitions of these variables are given below.

Unprotected anal intercourse (UAI)

Reporting insertive or receptive anal sex, with one or more partners and without a condom in the recall period.

Serodiscordant UAI status partners before HIV diagnosis

Reporting insertive or receptive anal sex, with one or more partners without a condom in the recall period, where the partner's HIV status was not known to be HIV negative.

This variable was derived from the answers to the following two questions:

> *"C8a In the 6 months prior receiving your HIV diagnosis, with how many men have you had anal intercourse (active or passive) without a condom?"*

and

> *"D9a: Since receiving your HIV diagnosis, how many of the men have you had anal intercourse (active or passive) without a condom did you know were HIV positive?".*

Serodiscordant UAI after HIV diagnosis

This was defined as reporting insertive or receptive anal sex with one or more partners without a condom in the recall period, where the partner's HIV status was not known to be HIV-positive.

This variable was derived from the answers to the following two questions:

> *"D8a Since receiving your HIV diagnosis, with how many men have you had anal intercourse (active or passive) without a condom?*
>
> *D8b Of these, how many were once only partners?"*

and

"D9a: Since receiving your HIV diagnosis, how many of the men have you had anal intercourse (active or passive) without a condom did you know were HIV positive?

D9b Of these, how many were once only partners?"

The total number of serodiscordant (HIV negative or status unknown) UAI partners after diagnosis was calculated as the number of reported UAI partners post-diagnosis (answered in D8a) minus the number of HIV-positive UAI partners post-diagnosis (answered in D9a). The binary variable engagement in serodiscordant UAI post-diagnosis was calculated from the number of serodiscordant UAI partners and coded as follows: 0, if no serodiscordant partners were reported; and 1, if >0 partners were reported.

The same methods were used to derive the number of casual serodiscordant UAI partners but using the answers to questions D8b and D9b.

Exclusive condom use since HIV diagnosis

This was defined as reporting AI with one or more partners since receiving HIV diagnosis, when the number of reported UAI partners was 0.

Exclusive serosorting since HIV diagnosis

This was defined as reporting UAI with 1 or more partners since diagnosis but the number of reported serodiscordant UAI partners was 0.

ChemSex (before or after diagnosis)

ChemSex (measured in the time before and since diagnosis) was defined as reporting the use of any of the following drugs before or during sex: liquid ecstasy (GHB/GBL), methedrone, methamphetamine, piperazines or ketamine. The substances included in the definition were decided in November 2014 in consultation with the following members of the UK Register of HIV Seroconverters Steering Committee; Prof Kholoud Porter, Prof Andrew Phillips, Dr Sarah Fidler, Dr Richard Gilson, Dr Julie Fox and Simon Collins. Notably the inclusion of piperazines and ketamine in the definition above means that the chemsex definition used in this thesis, differs from the now "standard" chemsex definition developed by 56 Dean Street and ReShape, and published on the iBase website in December 2014 [210]. According to this official definition, chemsex is defined as the use of three "chems" (GHB/GBL, methedrone and/or methamphetamine) in a sexual context.

3.6.11.3 Descriptive analyses

The descriptive research questions under study were:

- How acceptable is ART at diagnosis to MSM seroconverters?
- What proportion of ART-naïve MSM would start early ART for TasP in the absence of clinical benefit?
- What are the main barriers to early ART initiation amongst ART-naïve MSM?
- What are the main reasons for early ART initiation amongst MSM on ART?
- What proportion of MSM reported sexual behaviour that could lead to HIV transmission after HIV diagnosis?

Descriptive statistics were calculated for all explanatory and outcome variables with proportions calculated for binary and categorical outcomes. Ordinal and continuous data were described using medians and interquartile ranges (IQR) or means and standard deviations (SD).

3.6.11.4 Exploratory risk factor analyses

Two risk factor analyses were conducted using the survey data. These were designed to answer the following research questions:

- What factors are associated with initiation of early ART?
- What factors are associated with engaging in high-risk sexual behaviour which could lead to onward transmission after HIV diagnosis?

"Early ART" was defined as having self-reported taking ART since receipt of their HIV diagnosis. By definition of survey eligibility, this had to have been within 1 year of HIV diagnosis. The denominator was all men responding to the question "Have you taken ART since receiving your HIV diagnosis?".

"High-risk" sex post-diagnosis was a composite outcome and was defined as reporting either of the following behaviours:

- UAI with one or more HIV-negative or status unknown partners since HIV diagnosis
- ChemSex and AI with one or more partners since HIV diagnosis.

The denominator was all men who answered whether they had had oral or anal sex since HIV diagnosis.

3.6.11.5 Univariate risk factor analyses

Descriptive statistics were calculated for all explanatory and outcome variables. Ordinal and continuous data were described using medians and interquartile ranges (IQR), and categorical variables were described using proportions.

Chi squared tests were first used to test for associations between binary/categorical and binary outcomes and t-tests were used to compare independent means. Time from HIV diagnosis to questionnaire completion was considered an a-priori confounder and was adjusted for in all regression models. This is because it is known to be associated with the outcomes of interest, ART uptake and high-risk sex, and likely to be associated with many of the explanatory variables too. The relationship between time from diagnosis to questionnaire completion and the outcomes of interest were modelled as a continuous and categorical, with likelihood ratio test used to compare models and assess for departure from linearity. Each explanatory variable was modelled with the outcome early ART uptake, controlling for time from HIV diagnosis to questionnaire completion as a continuous variable.

All continuous explanatory variables were modelled first as linear terms, and secondly as categorical variables with likelihood ratio test used to assess departure from linearity. In the event of evidence of departure from linearity (at the $p<0.05$ level), continuous variables were modelled as categorical terms, otherwise they remained in the model as continuous terms.

3.6.11.6 Multivariate analysis of factors associated with early ART

All explanatory variables found to be associated with the outcome at the $p<0.2$ level in univariate analysis, after adjusting for time from diagnosis to survey completion, were put forward for inclusion in the multivariate models. The dataset for analysis was small with data from 117 men available for analysis, and the low number of men with the event of interest (n=55) limited the number of variables it was possible to adjust for in multivariate analysis. I made the pragmatic decision to use a conceptual framework approach to multivariate modelling, in order to restrict the number of variables included in the model at any one time and maximise power.

A multi-level conceptual framework was developed (see table 3.3). The base level included factors that were known a-priori to be associated with the outcome of interest (early ART initiation). Each subsequent level contained first socio-demographic, then clinical, next attitudinal and finally behavioural variables.

First, all variables in the base level that were found to be associated at the $p<0.2$ level in univariate analysis, were added to the multiple logistic regression model adjusting for time from diagnosis to survey completion. Variables found not to be associated at the $p<0.1$ level in the multivariate model were then dropped from the model individually (starting with factors with the highest p-values), with a likelihood ratio test performed to ascertain goodness of fit. This created a final "base model" which featured time to survey completion as well as all variables from level 1 of the framework which were associated in multivariate logistic regression at the $p<0.1$ level. The more severe cut-off of $p<0.1$ was used for selecting the variables for the final base model due to the small dataset size and number of men initiating ART. This translated to a lack of power to adjust for many factors at any one time in multivariate analysis.

For each of the subsequent levels of the conceptual framework, all variables within the level under study were first examined individually in the univariate time-adjusted analysis. In multivariate analysis all factors within the level found to be significant at $p<0.2$ level in time-adjusted analysis were added to the final base model. Backward elimination was then used to drop factors within that framework level which were not associated at the $p<0.1$ level after adjusting for all the other variables in the level and the final base model. This process was repeated for each of the hierarchical levels outlined in table 3.4.

Finally, a composite model including all variables from all levels of the conceptual framework which were found to be associated with early ART at the $p<0.1$ level after adjusting for variables in the final base model and within each level.

Collinearity and multicollinearity were checked by examining the variance inflation factor (VIF) for each independent variable in the final multiple regression models using the "collin" command in STATA 13 [201], using a VIF cut off of 10.

Table 3.3 Hierarchical conceptual framework of variables under study for multivariate analysis of factors associated with early ART initiation

Conceptual framework level	Variable(s) of interest		
A-priori confounders	Time from diagnosis to survey completion		
1. Base model (factors known to be associated with starting early ART)	Year first HIV positive HIV test interval – months	Age at HIV seroconversion Square root CD4 count at diagnosis	Recruited from an HIV centre with PHI interests Dr advised starting ART
2. Socio-demographic factors	Ethnicity Years full time education after 16 years of age Currently employed	Home owner Current living arrangements Sexual orientation	Current regular male partner Recruited from London HIV centre
3. Clinical/seroconversion factors	Diagnosed in acute infection (seroconversion interval <30 days) Log_{10} viral load at diagnosis Seroconversion symptoms self-reported	Individual seroconversion symptoms: rash/ headache/sore throat/fever/body aches/vomiting or diarrhoea/ night sweats	Seroconversion symptoms affected daily routine STI co-infection at HIV diagnosis Ever taken PEP
4. Attitudes to ART	Surprised at HIV-positive result Expected to start ART within 1 month of HIV diagnosis Would have accepted ART at diagnosis if offered	"Being on ART and having an undetectable vial load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom" "It is not necessary to disclose your HIV status to a sexual partner if you are on ART and have an undetectable viral load"	"Better HIV treatment means that people are less worried about catching HIV" "It is better for my health to start ART earlier rather than later"
5. Behavioural factors	Had AI in 6 months before HIV diagnosis Had casual AI in 6 months before HIV diagnosis Had UAI in 6 months before HIV diagnosis Had casual UAI in 6 months before HIV diagnosis Had non-concordant UAI in 6 months before HIV diagnosis Had casual non-concordant UAI in 6 months before HIV diagnosis	Met partners in sex on premises venue in 6 months before diagnosis Had ChemSex in 6 months before diagnosis Had AI since diagnosis Had casual AI since diagnosis Had UAI since diagnosis Had casual UAI since diagnosis	Had non-concordant UAI since HIV diagnosis Had casual non-concordant UAI since HIV diagnosis Had ChemSex since diagnosis Disclosed status to: Nobody/GP/HIV-positive friend/HIV-negative friend/family/regular partner/work

3.6.11.1 Multivariate analysis of factors associated with high-risk sex after HIV diagnosis

Due to the high levels of collinearity between the sexual behaviour risk factors, I felt it was inappropriate to conduct multivariate analyses for this outcome. Instead, only the time from HIV diagnosis to questionnaire completion adjusted data are presented.

All data management and statistical analyses were carried out using STATA 13 [201].

4 Workstream 1 results: trends in ART initiation and viral load at first clinic presentation

In this chapter I present the results from workstream 1; the secondary analysis of data from the UK Register of HIV Seroconverters, the methods of which can be found in chapter 3, section 3.4. This workstream aimed to use data from the UK Register of HIV seroconverters to examine temporal trends in the uptake of ART amongst individuals with EHI and to describe viral load at first clinic presentation amongst MSM with EHI.

Specifically, it aimed to answer the following research questions:

1 When do individuals with EHI initiate ART in the UK, and has this changed over time?
2 How high is viral load when MSM with EHI first present to clinic in the UK?
3 Has initial viral load changed over time amongst MSM with EHI in the UK?

4.1 Temporal trends in ART initiation amongst HIV seroconverters

The analyses presented in this section (4.1) were presented at BHIVA Spring conference in 2014, and were therefore conducted amongst seroconverters whose route of exposure was through heterosexual sex and IDU, in addition to MSM.

4.1.1 Eligibility and cohort characteristics

Of the 3619 individuals enrolled in the UK Register as of 1st January 2014 and aged ≥16 years at the time of seroconversion, 1885 were excluded from the analysis for the following reasons: 1834 seroconverted before 1st January 1998 and after 31st December 2011, 22 initiated ART before their HIV diagnosis, and 22 had an unknown route of transmission (see figure 4.1). Of the 1734 remaining, the median year of seroconversion was 2005 (IQR 2001, 2009) and the cohort was largely male (94%), exposed to HIV through sex between men (90%), of white ethnicity (87%) and of median (IQR) age 32.8 years (27.2, 40.3), see table 4.1. These demographic variables remained stable over time.

Figure 4.1 Eligibility flowchart for analyses assessing time to, and CD4 count at, ART initiation amongst a UK cohort of HIV seroconverters

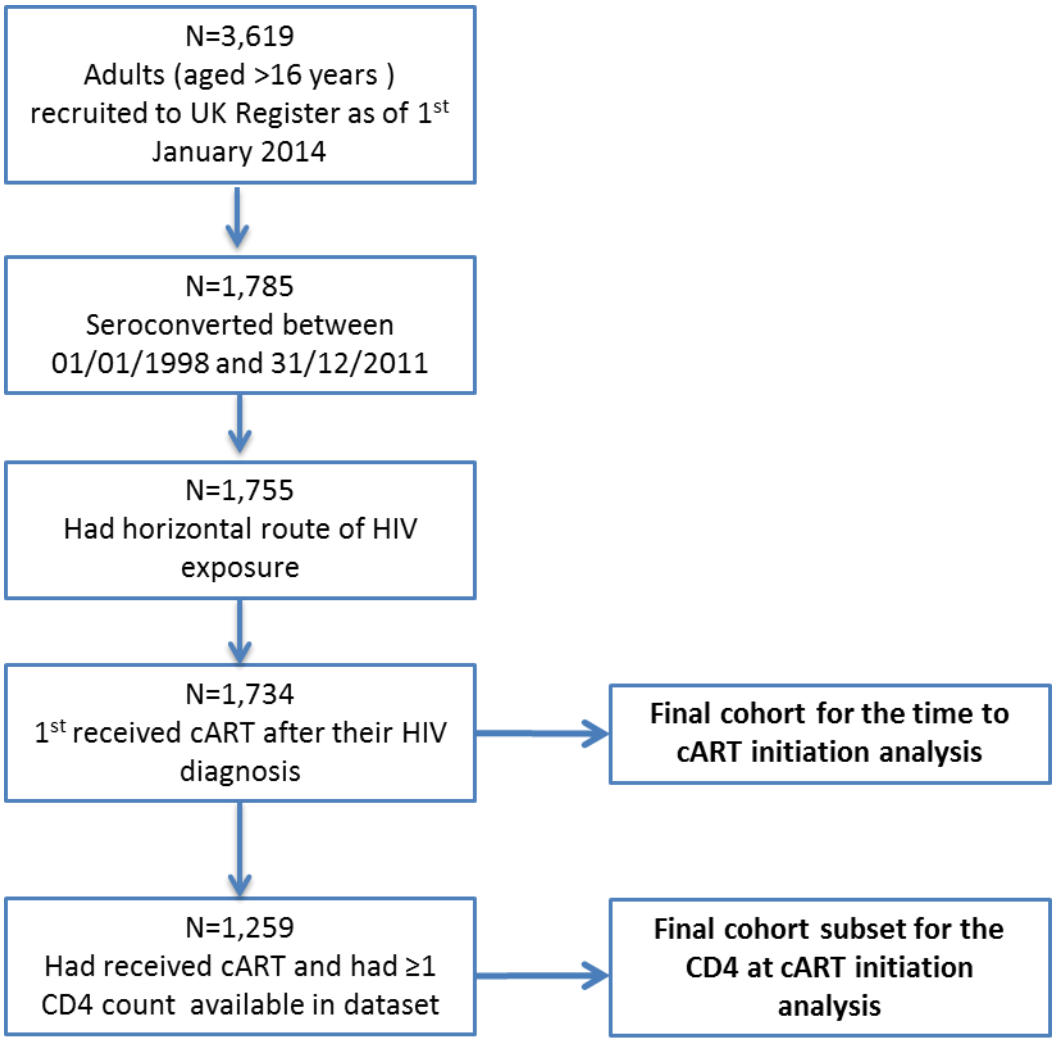


Table 4.1 Demographics and clinical characteristics of UK seroconverters eligible for time to ART initiation analysis, by calendar year of seroconversion

			Calendar year of seroconversion						
		Overall	**1998-1999**	**2000-01**	**2002-03**	**2004-05**	**2006-07**	**2008-09**	**2010-11**
N		1,734	194	244	246	254	224	225	347
Median (IQR) age at seroconversion – years		32.8 (27.2, 40.3)	31.9 (28.1, 37.4)	32.5 (27.6, 38.1)	33.3 (27.6, 39.4)	34.0 (27.3, 41.1)	33.4 (25.8, 40.8)	31.8 (27.0, 41.6)	32.7 (26.6, 41.3)
Sex (%)	Male	94.1	94.9	93.4	89.8	94.1	97.8	92.9	95.7
Exposure (%)	MSM	89.9	92.3	88.9	85.4	87.0	94.6	90.2	91.1
	IDU	0.5	2.1	0.4	0.8	0.4	0.0	0.0	0.0
	MSW	9.7	5.7	10.7	13.8	12.6	5.4	9.8	8.9
HIV test interval[a] (%)	<30 days	23.1	12.4	17.6	16.3	32.3	23.7	22.7	30.8
Ethnicity (%)	White	87.1	88.1	83.2	88.2	86.6	90.2	84.4	88.5
	Non-white	7.2	6.2	8.2	9.4	9.5	4.0	7.6	5.5
	Missing	5.8	5.7	8.6	2.4	3.9	5.8	8.0	6.1

IQR=interquartile range; MSM=sex between men; MSW=sex between men and women; IDU=injecting drug use; a=interval between HIV antibody negative and positive tests. a=HIV test interval is the interval between HIV antibody negative and positive tests.

4.1.2 Temporal trends in time from seroconversion to ART initiation

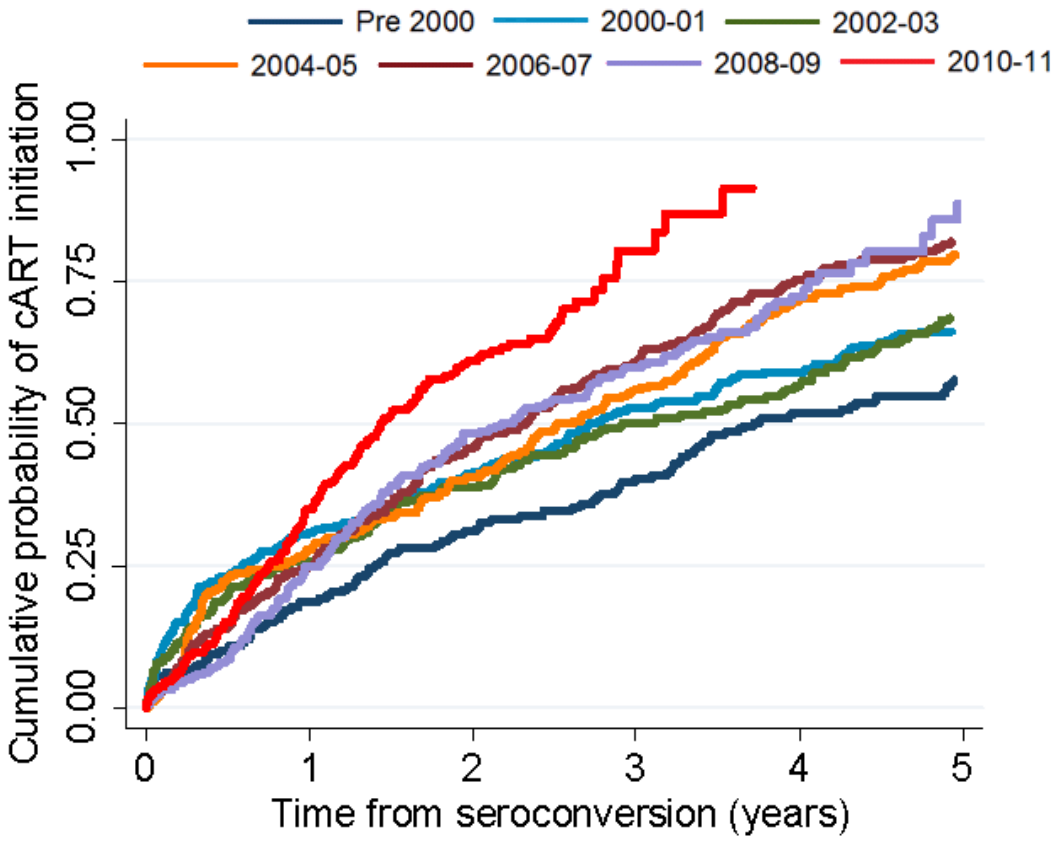
Of the 1734 individuals, contributing 4634 years of follow-up, 1337 (77.1%) started ART. The Kaplan Meier graph in figure 4.2, illustrates the time to ART initiation by calendar year of seroconversion split into 7 year groups. Whilst there is little difference in ART uptake within the first year of infection by year of seroconversion, ART initiation in the first 6 months was most rapid in 2000-03. There was a decrease over time in the median time from seroconversion to ART initiation from 3.7 (95%CI 3.2, 4.9) years pre-2000 to 2.8 (2.2, 3.5), 2.9 (2.3, 4.0), 2.6 (2.2, 3.0), 2.3 (1.8, 2.7), 2.2 (1.8, 2.7) and 1.4 (1.3, 1.7) years in 2000-1, 2002-3, 2004-5, 2006-7, 2008-9 and 2010-11, respectively (p-trend <0.001). There was strong evidence of a linear decrease in time to ART initiation over calendar time which remained after adjusting for covariates, with the risk of ART initiation increasing by 6% every calendar year (95% CI 4-7%; p<0.001), see table 4.2. Older age at seroconversion and shorter HIV test interval were also associated with ART initiation in the adjusted model.

ART can be prescribed by clinicians in short-course form during primary infection, defined as the first 6 months following seroconversion. To avoid the influence of trends in short-course ART in PHI on overall ART temporal trends I performed a sensitivity analysis excluding those diagnosed in PHI (HIV test interval <180 days). The upwards trend in risk of ART initiation over calendar time remained highly significant and increased to 9% per calendar year (95% CI 7-12%; p<0.001) in the fully-adjusted model (data presented in appendix 22). Controlling for CD4 count at HIV diagnosis in the Cox model also produced limited change to the risk of ART initiation (data presented in appendix 23).

4.1.3 Temporal trends in CD4 count at ART initiation in UK seroconverters

Of the 1734 individuals eligible for the analysis, 1259 had at least one CD4 count available at ART initiation. There was strong evidence of an upward linear increase in CD4 at initiation over calendar time from median 284 cells/mm^3 (IQR 190, 378) pre-2000 to 280 (221, 410), 297 (227, 380), 314 (241, 450), 330 (272, 412), 337 (282, 437), 375 (296, 511) in 2000-1, 2002-3, 2004-5, 2006-7, 2008-9, 2010-11, respectively (p-trend<0.001), see figure 4.3. After adjusting for sex, age at seroconversion, exposure category and HIV test interval the temporal increase in CD4 count at ART initiation remained significant (p<0.001), see table 4.3. This upward trend in CD4 at initiation over time remained in the sensitivity analysis excluding individuals who started ART in PHI, with an increase seen from median 275 cells/mm^3 (IQR 187, 352) pre-2000 to 375 (301, 500) in 2010-11 (p-trend<0.001).

Figure 4.2 Kaplan Meier plot of time from seroconversion to ART initiation amongst UK seroconverters, by calendar year of seroconversion



Number at risk

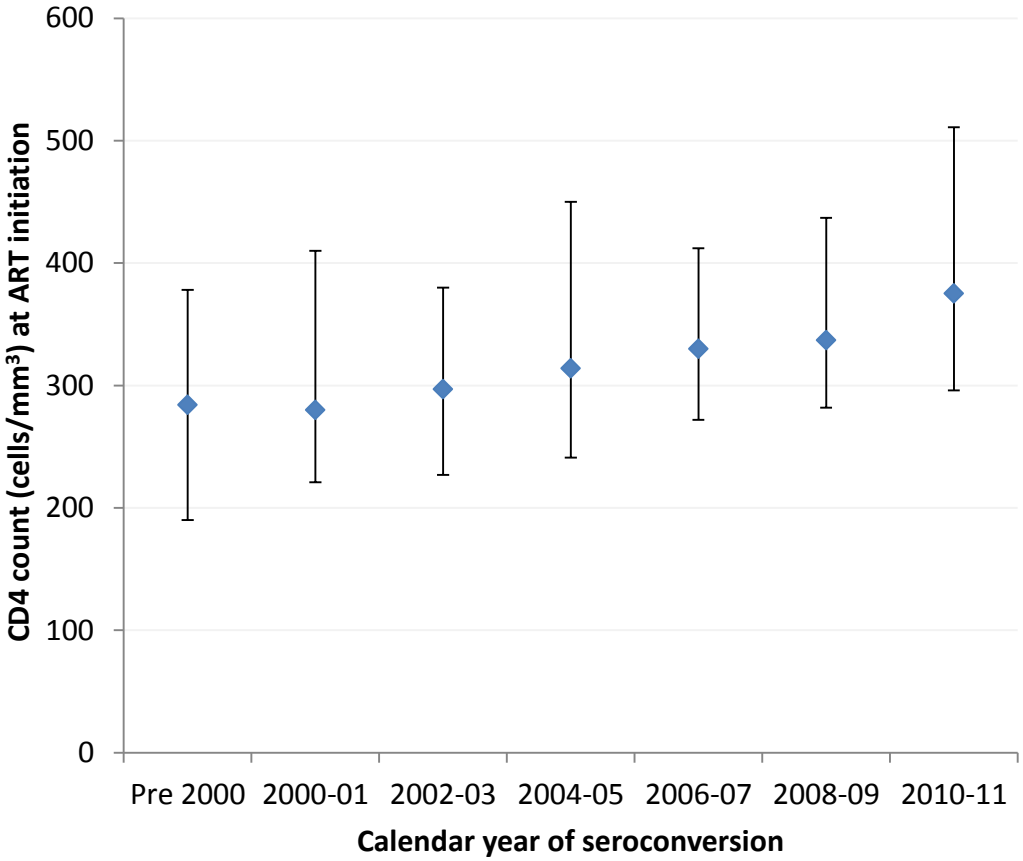
Pre-2000	194	153	128	109	85	70
2000-1	244	167	134	106	87	70
2002-3	246	181	142	110	94	67
2004-5	254	179	144	105	64	43
2006-7	224	162	116	81	49	31
2008-9	225	162	107	73	24	4
2010-11	347	202	70	7	0	0

Table 4.2 Factors associated with risk of ART initiation amongst HIV seroconverters in the UK

	Unadjusted HR	95% CI	p	Adjusted HR[a]	95% CI	p
Calendar year of seroconversion (per year increase)	1.06	(1.04, 1.08)	<0.001	1.06	(1.04, 1.07)	<0.001
Age at seroconversion (per 10 year increase)	1.14	(1.08, 1.21)	<0.001	1.13	(1.07, 1.19)	<0.001
HIV test interval[b]						
30 days or more	1	-	<0.001	1	-	<0.001
<30 days	1.59	(1.40, 1.80)		1.42	(1.24, 1.62)	
Sex						
Male	1	-	0.357	1	-	0.682
Female	1.11	(0.89, 1.40)		1.08	(0.76, 1.52)	
HIV exposure category						
MSM	1	-	0.291	1	-	0.940
MSW	1.16	(0.97, 1.40)		1.02	(0.77, 1.34)	
IDU	0.97	(0.46, 2.03)		1.15	(0.53, 2.51)	

Analyses based on 1743 individuals, contributing 4633 person years at risk, of whom 1337 initiated ART. HR= Hazard ratio; CI=confidence interval; MSM=sex between men; MSW=sex between men and women; IDU=injecting drug use. a=adjusted for all other variables in the table; b=interval between HIV antibody negative and positive tests

Figure 4.3 Temporal trend in median CD4 count at ART initiation



Note: Error bars denote interquartile range

Table 4.3 Factors associated with CD4 count (square root transformed cells/mm^3) at ART initiation

	Unadjusted coefficient	95% CI	p-value	Adjusted[a] coefficient	95% CI	p-value
Calendar year of seroconversion (per 10 year increase)	2.05	1.43, 2.67	<0.001	1.98	1.36, 2.61	<0.001
Age at seroconversion (per 10 year increase)	-0.04	-0.30, 0.21	0.735	-0.07	-0.32, 0.19	0.619
HIV test interval[b]						
30 days or more	0.00	-	0.012	0.00	-	
<30 days	0.76	0.17, 1.35		0.68	0.09, 1.27	0.024
Sex						
Male	0.00	-	0.192	0.00	-	0.002
Female	0.71	-0.36, 1.79		2.57	0.93, 4.21	
Exposure group						
MSM	0.00	-	0.596	0.00	-	0.012
MSW	-0.23	-1.10, 0.66		-1.93	-3.25, -0.61	
IDU	-1.66	-5.29, 1.98		-2.71	-6.44, 1.01	

Analyses based on 1259 individuals with one or two CD4 counts within the 6 months prior to ART initiation. CI=confidence interval; MSM=sex between men; MSW=sex between men and women; IDU=injecting drug use. a=Adjusted for all other variables in the table; b=interval between HIV antibody negative and positive tests.

4.1.4 Temporal trends in ART initiation in PHI

Of the 1734 seroconverters, 967 presented in PHI (with a HIV test interval of ≤6 months) and, of these, 251 (26%) initiated ART within 6 months of seroconversion. The proportion starting ART in PHI fluctuated over calendar time; increasing from 27.9% pre-2000 to a peak of 50.0% in 2000-1, and decreasing to the lowest values in more recent years to 12.9% in 2008-9 and 19.8% in 2010-11, see table 4.4. Those starting ART in PHI, were most likely to initiate with a non-nucleoside reverse transcriptase inhibitor (NNRTI) based combination, or a protease inhibitor (PI) based combination, though between 2004 and 2007 PI-based combinations were substantially more popular than NNRTI with around 83% starting them as opposed to 13%.

The 251 individuals initiating ART in PHI contributed 478 person-years of follow-up, during which time 168 (66.9%) stopped therapy. There was strong evidence of temporal variation in time from PHI ART initiation to stopping, with individuals seroconverting from 2008 onwards far less likely to stop therapy within the first year, after adjusting for prognostic factors, ($p<0.001$), see table 4.4.

After conducting sensitivity analyses excluding individuals known to be enrolled on the SPARTAC trial (a trial of short-course ART initiated in PHI which ran from 2003-2007), there remained strong evidence of heterogeneity in the proportion starting ART in PHI over calendar year of seroconversion in adjusted models ($p<0.001$), with a notable decrease in uptake observed after 2004 (see appendix 24). The temporal effect on time from ART initiation in PHI to stopping after excluding SPARTAC patients remained highly significant ($p<0.001$) with the proportion stopping within 12 months decreasing substantially after 2008 (see appendix 24).

Table 4.4 Temporal trends in ART initiation, starting combinations and time to stopping ART in patients with primary HIV infection

	Calendar year of seroconversion[a]							
	1998-99	**2000-01**	**2002-03**	**2004-05**	**2006-07**	**2008-09**	**2010-11**	**p-value**
N	61	98	114	175	148	139	232	
% (95% CI) initiating ART in PHI	27.9 (18.0, 40.4)	50.0 (40.2, 59.8)	35.1 (26.9, 44.3)	29.1 (22.9, 36.3)	20.3 (14.5, 27.6)	12.9 (8.3, 19.7)	19.8 (15.2,25.5)	p<0.001[b]
% (95% CI) ART starting classes								
NRTI+NNRTI	29.4 (12.4,55.1)	75.5 (61.4,85.7)	57.5 (41.7,71.9)	15.7 (8.0,28.6)	16.7 (7.0,34.8)	44.4 (23.4,67.7)	47.8 (33.7,62.3)	
NRTI+PI	64.7 (39.6,83.7)	16.3 (8.3,29.6)	42.5 (28.1,58.3)	84.3 (71.4,92.0)	83.3 (65.2,93.0)	38.9 (19.3,62.9)	47.8 (33.7,62.3)	
NRTI only	5.9 (0.8,33.6)	8.2 (3.1,20.1)	0 (0,0)	0 (0,0)	0 (0,0)	11.1 (2.7,36.4)	4.3 (1.1,16.1)	
Other	0 (0,0)	0 (0,0)	0 (0,0)	5.6 (0.7,32.1)	0 (0,0)	0 (0,0)	0 (0,0)	
% (95% CI) of those starting ART in PHI who stop within 12 months[c]	52.9 (32.0, 77.0)	62.9 (49.4, 76.4)	72.5 (58.3, 85.1)	82.4 (70.8, 91.3)	86.7 (72.2, 95.8)	11.1 (2.9, 37.6)	11.3 (4.9, 25.1)	P<0.001[d]

ART= antiretroviral therapy; PHI=primary HIV infection; CI=confidence interval; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.
a=Calendar year of seroconversion modelled as categorical year groups; b=p-value for heterogeneity from logistic regression model of effect of year group of seroconversion (categorical) adjusting for sex, exposure group (MSM, MSW, IDU), age at seroconversion (continuous, per 10 years) and HIV test interval (30 days or more, < 30 days); c=time to event analysis assessing time from ART initiation in PHI to stopping ART; based on 251 individuals starting ART in PHI, contributing 478 person-years at risk, of whom 168 stopped therapy; d p-value for heterogeneity in Cox proportional hazards model, modelling year group of seroconversion (categorical) and adjusting for sex, exposure group (MSM, MSW, IDU), age at seroconversion (continuous, per 10 years) and HIV test interval (30 days or more, < 30 days)

4.2 Viral load at first clinic presentation amongst MSM with early HIV infection in the UK

As a reminder this part of workstream 1 sought to establish viral load at first clinic presentation amongst MSM with EHI enrolled in the UK Register, and to examine temporal trends in viral load at first clinic presentation. The methods for this analysis can be found in section 3.4.3.

4.2.1 Eligibility and data availability

As of 1st January 2013, 3,552 individuals were enrolled in the UK Register, with the median year of seroconversion 1999 (IQR 1992, 2006). The predominant route of exposure was sex between men (83.6%), with heterosexual contact, IDU and vertical transmission accounting for 9.1%, 5.9% and 0.1%, respectively. As expected, with a high prevalence of MSM, the majority of the cohort is male at 92%. The median age at seroconversion is 30.7 years (IQR 25.5, 37.4). The majority were eligible for the study because they had a previous negative test in the last 3 years 88.5%; and for these the median HIV test interval 198 days (IQR 79, 383). 7.5% presented with laboratory evidence of acute HIV infection.

A total of 84,534 viral load measurements were taken between 1988 and 2013 with a clearly visible increase in the annual number of tests from 526 in 1996 to 2,342 in 1997.. This coincides with reports from the clinic laboratories of when viral load testing became routine. Due to the sparse viral load data before 1997 I limited inclusion criteria to those first testing positive with HIV from 1997 onwards.

Of the 3,552 people enrolled to the UK Register, 2,102 were diagnosed with HIV on or after 1st January 1997. As my thesis focusses specifically on MSM with primary HIV infection, data for this analysis were restricted to men who reported their likely route of HIV infection to be through sex with other men (n=1,845). Of these, 1,543 had an HIV test interval 1 year or less and 1,500 had one or more ART-naïve viral load measure available.

4.2.2 Cohort characteristics

The characteristics of the 1,500 MSM enrolled to the UK Register with one or more viral load measure available for analysis are outlined in table 4.5. In summary, the median year of seroconversion was 2006 (IQR 2003, 2010) and median HIV test interval was 3.8 months, (IQR 0.7, 7.4). 18.1% of the men were diagnosed during acute infection. Both the HIV test interval and the proportion presenting during acute infection fluctuated over the years but no systematic pattern was observed overall.

Men were a median of 32.7 years old at the time of seroconversion (IQR 27.1, 40.0), this varied slightly over the study years between 30.7 years in 1997-9 to 34.3 in 2002-5 but there was no clear trend over time. The vast majority of the men in the cohort were of white ethnicity (91%). The proportion of non-white ethnicity MSM fluctuated over calendar time and was highest in 2008-9 at 13% and lowest in 2002-3 at 4.8%. HIV subtype data were not available for the majority of the cohort; only 37.3% had a subtype available overall and in 2010-12 only 1.9% had been sub-typed. Overall, 75% of men had their first viral load within 2 weeks of the date of HIV diagnosis, at a median of 6 days after. This interval was longest in 1997-9 at 12 days, but was stable at between 5 and 9 days otherwise.

Over 95% of the cohort had information available on the type of the viral load assay used to measure first viral load. Overall the most common assay type was PCR-based accounting for over 78% of measures. Unsurprisingly, there was a shift in the use of assays over time, with the popularity of bDNA-based assays waning in favour of PCR assays over time, from 40% in 1997-99 to 1.3% in 2010-12. NASBA assays were used infrequently across all years at 4.9% overall; their use peaked in 2002-3 and again in 2008-09 when they accounted for 11.5% of first viral load measures.

4.2.3 Characterising viral load at first presentation amongst UK MSM with early HIV infection

Overall, the median (IQR) viral load at first presentation was 5.0 (4.4, 5.7) $\log_{10}$ copies/mL, taken a median of 75 (20, 132) days after seroconversion. There was strong evidence ($p<0.001$) of a linear trend with viral load at first presentation decreasing by 0.09 $\log_{10}$ copies/mL (95% CI -0.11, -0.07) for every month between seroconversion to first viral load

measure, see figure 4.4 and table 4.6. There was significant evidence of departure from linearity ($p<0.001$) in the association between time from seroconversion to viral load, so it was modelled as a 5 group categorical variable (<1 week, ≥1 week and <1 month, ≥1 month and <3 months, ≥3 and <6 months and ≥6 months). In the unadjusted model including time from seroconversion to viral load as a categorical variable, there was significant evidence of differences in viral load at first presentation over time ($p<0.001$). A small increase in viral load of 0.06 $\log_{10}$ copies/mL was seen between <1 week and 1 week-1 month categories, then from 1 month after seroconversion a decrease in viral load becomes apparent, which slows from 6 months onwards.

Table 4.5 Demographic and clinical characteristics of MSM HIV seroconverters eligible for viral load analysis, by calendar year of seroconversion

		Calendar year of seroconversion						
	Total	**1997-99**	**2000-01**	**2002-03**	**2004-05**	**2006-07**	**2008-09**	**2010-12**
N	1500	143	133	166	205	204	192	457
Median (IQR) age at seroconversion - years	32.7 (27.1, 40.0)	30.7 (26.9, 35.0)	32.3 (27.4, 36.3)	34.3 (27.5, 41.1)	34.3 (27.2, 41.6)	33.8 (27.2, 41.6)	31.7 (26.8, 41.0)	32.4 (26.3, 40.2)
Median (IQR) HIV test interval - months	3.8 (0.7, 7.4)	5.6 (2.2, 8.7)	3.5 (0.7, 8.1)	5.0 (2.4, 8.9)	3.3 (0.2,6.1)	3.7 (1.0, 7.0)	4.1 (1.3, 7.2)	3.2 (0, 6.9)
Median (IQR) time from seroconversion to first VL measure - days	70.5 (20, 132)	94 (57, 167)	67 (19, 134)	100.5 (42, 147)	70 (14, 113)	74 (27, 135)	75 (22, 122)	53 (7, 117)
Median (IQR) time from diagnosis to first VL measure - days	6 (1, 15)	12 (2, 27)	7 (0, 14)	9 (1, 18)	7 (1, 15)	7 (2, 19)	5 (1, 13)	5 (0, 11)
Evidence of acute infection (%)								
No	81.9	81.1	75.2	83.1	77.6	86.3	83.3	82.9
Yes	18.1	18.9	24.8	16.9	22.4	13.7	16.7	17.1
Ethnicity (%)								
White	90.9	89.5	90.2	94.6	92.2	92.7	87.0	90.6
Non-white	7.6	5.6	6.0	4.8	7.3	5.9	13.0	8.3
Missing	1.5	4.9	3.8	0.6	0.5	1.5	0.0	1.1

IQR=interquartile range; HIV test interval= interval between HIV antibody negative and positive tests; VL=viral load; PCR=polymerase chain reaction; bDNA=branched DNA; NASBA=nucleic acid sequence based amplification

Table 4.5 (continued)

	Total	Year of seroconversion						
		1997-99	2000-01	2002-03	2004-05	2006-07	2008-09	2010-12
HIV Subtype (%)								
B	34.9	48.3	51.9	57.2	51.7	47.1	42.2	1.7
Non-B	2.3	0.0	4.5	3.6	3.9	2.5	4.7	0.2
Missing	62.7	51.8	43.6	39.2	44.4	50.5	53.1	98.0
Viral load assay type (%)								
PCR	77.9	49.7	66.9	54.2	75.6	87.3	81.3	93.9
bDNA	12.6	39.9	30.1	28.9	13.2	4.9	0.5	1.3
NASBA	4.9	4.9	0.8	11.5	2.4	5.9	11.5	1.5
Unknown	4.7	5.6	2.3	5.4	8.8	2.0	6.8	3.3
Assay cut off in copies/mL (%)								
>100,000	11.2	10.5	13.5	19.9	32.2	6.9	5.7	2.4
>500,000	12.6	39.9	30.1	28.9	13.2	4.9	0.5	1.3
>750,000	25.6	39.2	52.6	32.5	35.1	32.8	21.9	5.0
>6,000,000	3.6	4.9	0.8	8.4	1.5	5.4	7.8	0.7
>10,000,000	42.3	0.0	0.8	4.8	9.3	48.0	57.3	87.3
Missing	4.7	5.6	2.3	5.4	8.8	2.0	6.8	3.3

IQR=interquartile range; HIV test interval= interval between HIV antibody negative and positive tests; VL=viral load; PCR=polymerase chain reaction; bDNA=branched DNA; NASBA=nucleic acid sequence based amplification

There was also evidence of an association between calendar time and initial viral load, with an increase in initial viral load of 0.18 $\log_{10}$ copies/mL per decade. There was evidence of departure from linearity however (p=0.027), and so calendar year of seroconversion was included in the adjusted model as a 7 group categorical to improve model fit. Initial viral load was also found to be higher by 0.07 $\log_{10}$ copies/mL with every 10 year increase in age at seroconversion (p=0.023), lower by -0.44 $\log_{10}$ copies/mL for non-white MSM (p<0.001) and higher by 0.71 $\log_{10}$ copies/mL for those presenting with laboratory evidence of acute infection (p<0.001). HIV test interval was inversely associated with first viral load, with a -0.06 $\log_{10}$ copies/mL decrease in viral load measure observed per 1 month increase in HIV test interval (95% CI -0.07, -0.04; p<0.001). Similarly, first viral load measure decreased as time from diagnosis to first viral load measure increased by -0.02 $\log_{10}$ copies/mL per month (95% CI -0.03, -0.01, p<0.001).

The association between time to initial viral load from seroconversion with first viral load measure remained strong in the fully-adjusted model (p<0.001), after controlling for ethnicity, age at seroconversion, presentation during acute infection, and calendar year of seroconversion.

Figures 4.5a and b illustrate the unadjusted and fully-adjusted ordinary least squares regression prediction of viral load at first presentation by time from seroconversion modelled as a 5 knot restricted cubic splines (RCS) anchored at the 5^{th}, 25^{th}, 50^{th} 75^{th} and 95^{th} percentiles. Figure 4.5a clearly illustrates the much higher viral load in those presenting to clinic within the first 30 days of seroconversion at around 5.3 $\log_{10}$ copies/mL and the rapid decline seen thereafter until the plateau is reached at around 100 days post seroconversion at about 4.7 $\log_{10}$ copies/mL.

In the model adjusting for ethnicity, age at seroconversion, evidence of acute infection and calendar year of seroconversion, the peak viral load seen at first presentation and the value at which viral load plateaued was similar at around 5.2 $\log_{10}$ copies/mL and 4.8 $\log_{10}$ copies/mL, respectively (see figure 4.5b).

Figure 4.4 Scatterplot of HIV viral load at presentation by time since seoroconversion amongst MSM seroconverters in the UK, with OLS line of best fit

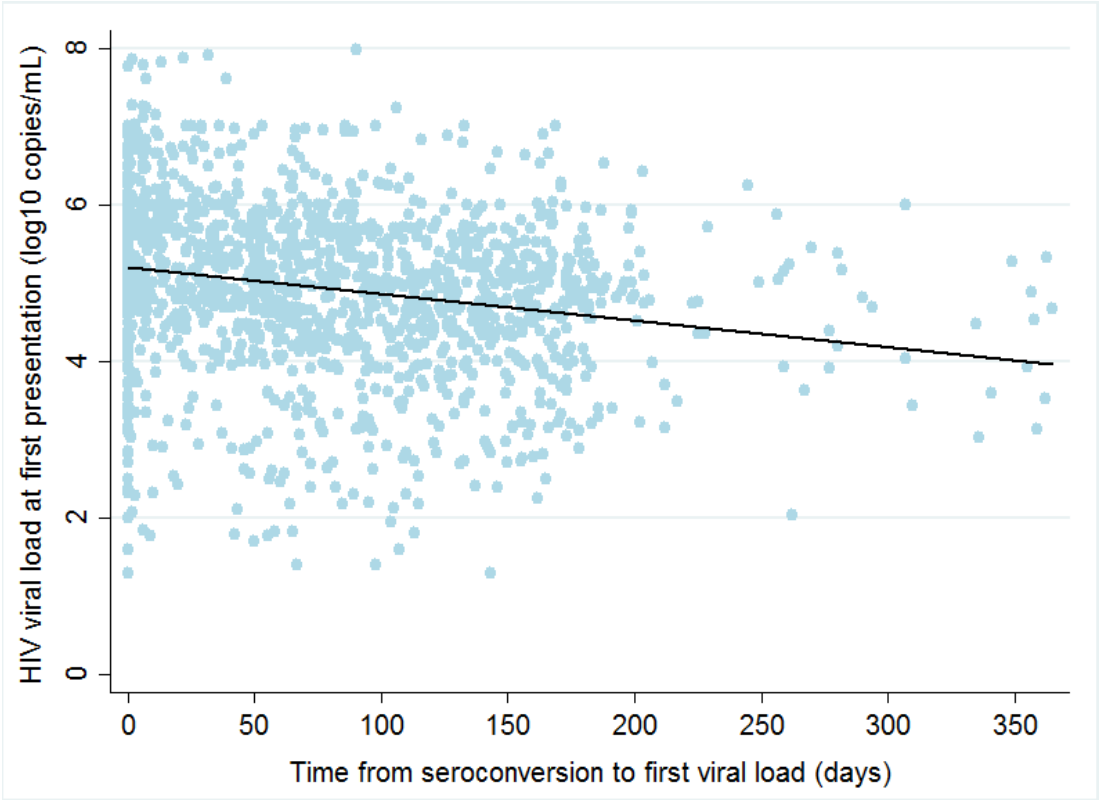


Table 4.6 Factors associated with HIV viral load at first clinic presentation (log_{10} copies/mL) amongst MSM with early HIV infection in the UK

		Unadjusted coefficient	95% CI	p-value	Adjusted coefficient[d]	95% CI	p-value
Time from seroconversion to first VL (per month increase)[a]		-0.09	-0.11, -0.07	<0.001	-	-	-
Time from seroconversion	<7 days	0	-	<0.001	0	-	<0.001
to first VL	1 week- 1 month	0.06	-0.14, 0.27		0.07	-0.13, 0.27	
	>1 month - 3 months	-0.33	-0.48, -0.17		-0.02	-0.20, 0.16	
	>3 months-6 months	-0.61	-0.76, -0.46		-0.28	-0.46, -0.10	
	>6 months	-0.75	-0.98, -0.53		-0.37	-0.62, -0.13	
Year of seroconversion (per 10 year increase) [b]		0.18	0.06, 0.30	0.004	-	-	-
Year of seroconversion	1997-99	0	-	0.002	0	-	0.020
	2000-01	0.28	0.03, 0.54		0.20	-0.04, 0.45	
	2002-03	0.21	-0.02, 0.45		0.19	-0.04, 0.42	
	2004-05	0.3	0.08, 0.53		0.22	0.00, 0.45	
	2006-07	0.21	-0.02, 0.44		0.19	-0.03, 0.42	
	2008-09	0.1	-0.13, 0.33		0.09	-0.14, 0.32	
	2010-12	0.39	0.19, 0.59		0.33	0.13, 0.53	
Age at seroconversion (per 10 year increase)		0.07	0.01, 0.12	0.023	0.03	-0.02, 0.09	0.278
Ethnicity	White	0	-		0	-	
	Non-white	-0.44	-0.65, -0.24	<0.001	-0.44	-0.64, -0.24	<0.001

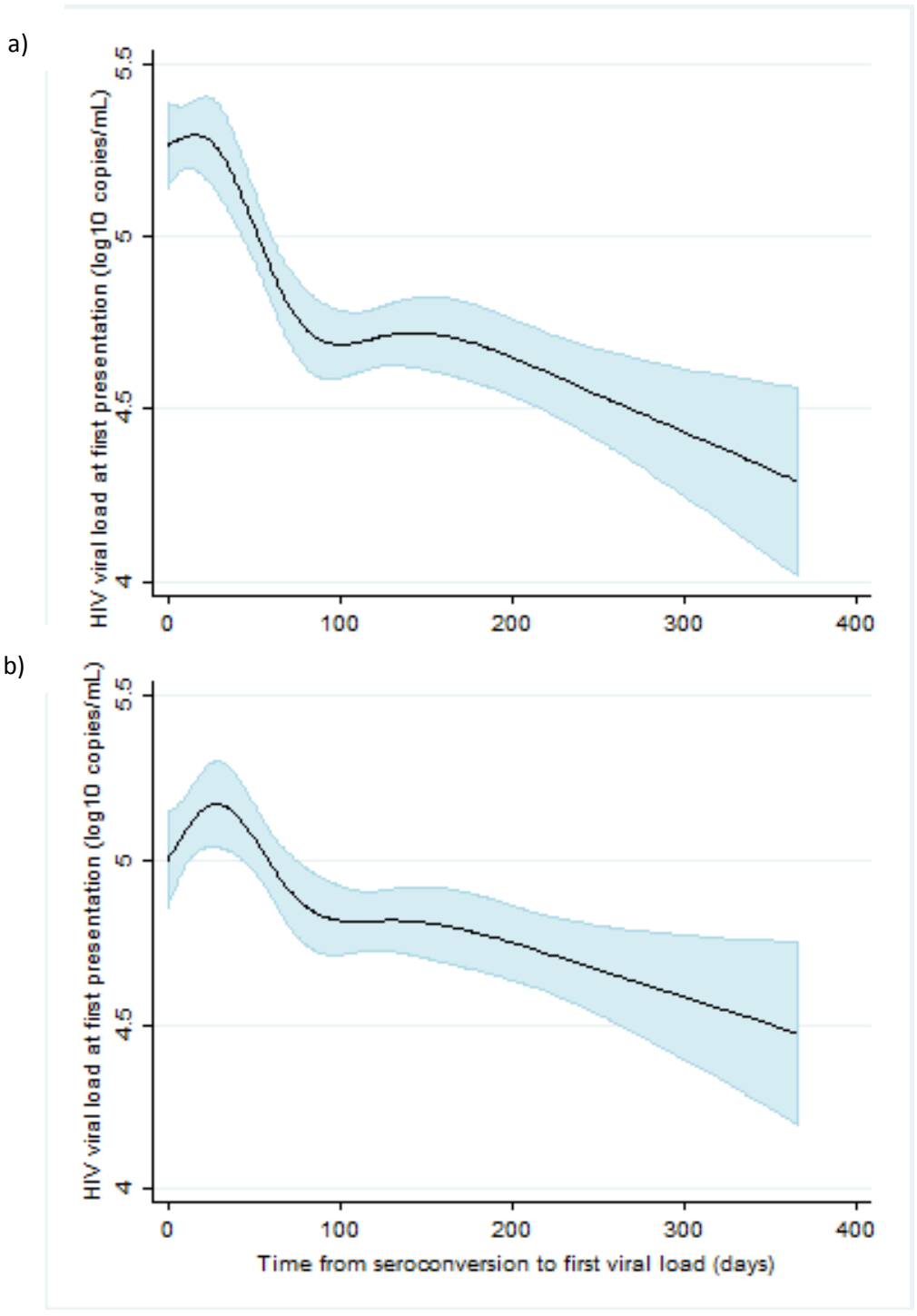
CI=confidence interval; VL=viral load. a= likelihood ratio test showed evidence departure from linearity (p<0.001) time since seroconversion modelled as categorical variable in adjusted model. b=likelihood ratio test showed evidence departure from linearity (p=0.027) so year of seroconversion modelled as categorical variable in adjusted model. c=HIV test interval and time from diagnosis to first VL measure excluded from multivariate model due to collinearity with time from seroconversion to first VL measure. d=Adjusted for year of seroconversion (categorical), evidence of acute infection, age at seroconversion (per 10 year increase) and ethnicity.

Table 4.6 (continued)

		Unadjusted coefficient	95% CI	p-value	Adjusted coefficient[d]	95% CI	p-value
Laboratory evidence of acute infection	No	0	-	<0.001	0	-	<0.001
	Yes	0.71	0.58, 0.85		0.56	0.38, 0.74	
HIV test interval (per month increase)[c]		-0.06	-0.07, -0.05	<0.001	-	-	-
Time from diagnosis to 1st VL (per month increase)[c]		-0.19	-0.03, -0.01	<0.001	-	-	-

CI=confidence interval; VL=viral load. a= likelihood ratio test showed evidence departure from linearity (p<0.001) time since seroconversion modelled as categorical variable in adjusted model. b=likelihood ratio test showed evidence departure from linearity (p=0.027) so year of seroconversion modelled as categorical variable in adjusted model. c=HIV test interval and time from diagnosis to first VL measure excluded from multivariate model due to collinearity with time from seroconversion to first VL measure. d=Adjusted for year of seroconversion (categorical), evidence of acute infection, age at seroconversion (per 10 year increase) and ethnicity.

Figure 4.5 Estimated mean HIV viral load at first clinic presentation amongst MSM with recent HIV infection by time since seroconversion, modelled using restricted cubic splines



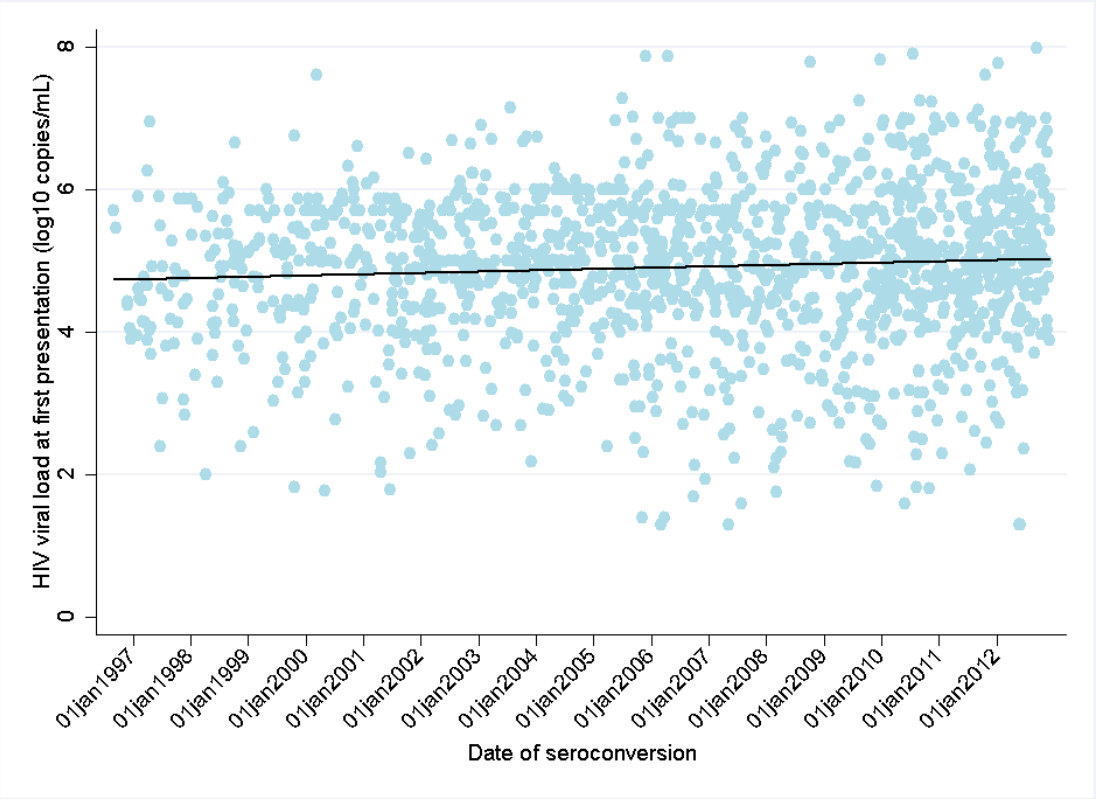
a) Simple linear regression model; b) Multiple regression model adjusting for calendar year of seroconversion, age at seroconversion, ethnicity, laboratory evidence of acute infection.

Note: Black line denotes mean and blue shaded area denotes 95% confidence interval. Time from seroconversion to first viral load measure modelled using restricted cubic splines anchored at the 5th, 25th, 50th, 75th and 95th percentiles.

4.2.4 Temporal trends in viral load at first clinic presentation

Median viral load at initial presentation increased from the lowest value 4.75 log_{10} copies/mL in 1997-99 to the highest value of 5.11 in 2000-01, then remained relatively stable at around 5.00 until 2006-7 before decreasing to 4.86 in 2008-09 and increasing again to 5.07 in 2010-12. A scatterplot of the raw data fitted with an OLS line of best fit, showed no notable linear increase in initial viral load over time (see figure 4.6).

Figure 4.6 Scatterplot of HIV viral load at first clinic presentation amongst MSM seroconverters in the UK by date of seroconversion, with OLS line of best fit



As presented in table 4.6, there was a positive correlation between seroconversion year and initial viral load, with an increase of 0.18 log_{10} copies/mL per 10 year increase in seroconversion year (95% CI 0.06, 0.30; p=0.004). When seroconversion year was modelled as a 7 group categorical variable there was evidence of heterogeneity in the effect of year of seroconversion on initial viral load (p=0.002) with fluctuations in viral load over time peaking twice: in 2004-2005, at 0.30 log_{10} copies/mL above the reference year 1997-99; and

again in 2010-12, at 0.39 above the reference year. A likelihood ratio test confirmed departure from linearity (p=0.027) so seroconversion year was modelled in adjusted models as a categorical variable. Ethnicity, age at seroconversion, acute infection, HIV test interval, time from diagnosis to first viral load and time from seroconversion to first viral load were all found to be associated with first viral load in unadjusted analysis. These variables were therefore included in the multivariate analysis as they were potential confounders of the association between calendar year of seroconversion and initial viral load. After adjusting for all the potential confounding variables , the temporal association between year of seroconversion and initial viral load weakened slightly but remained significant (p=0.020). The pattern of fluctuations in viral load over time remained unchanged, though their magnitude decreased slightly. Initial viral load in the most recent year group 2010-12 remained the highest out of all the other years at 0.33 $\log_{10}$ copies/mL higher than the reference group 1997-99.

Graphical depictions of the unadjusted and adjusted temporal trends in initial viral load are shown in figures 4.7a and b, allowing non-linearity by modelling date of seroconversion as RCS with knots at 5, 25, 50, 75 and 95th percentiles. An increase in viral load at first presentation is observed from around 4.6 $\log_{10}$ copies/mL those seroconverting in 1997 to over 4.9 in 2003. It then plateaued at around this level until 2009, after which initial viral load increased to 5.2 $\log_{10}$ copies/mL. The shape of the curve remained after adjusting for ethnicity, age at seroconversion, acute infection and time from seroconversion to initial viral load, though the magnitude of initial viral load across all years was slightly lower, the plateau was flatter, and the peak initial viral load in 2012 was lower at just under 5.1 $\log_{10}$ copies/mL (see figure 4.7b).

Figure 4.7 Predicted temporal trend in mean viral load at first presentation amongst MSM in the UK

Figure a) Unadjusted simple linear regression estimates; figure b) Multiple regression estimates, adjusting for time from seroconversion to first viral load, age at seroconversion, ethnicity and acute infection.

Note: Black line denotes mean and blue shaded area denotes 95% confidence interval. Time from seroconversion to first viral load measure modelled using restricted cubic splines anchored at the 5th, 25th, 50th, 75th and 95th percentiles.

4.2.5 Sensitivity analyses

I conducted several sensitivity analyses to ascertain the robustness of the temporal variation in initial viral load, most of which are displayed in table 4.7 and figures 4.8a-d. To reduce the uncertainty around date of seroconversion, I restricted the analysis to MSM with a shorter HIV test window of ≤180 days. Interestingly this resulted in a stronger association (p=0.010) and an increase in all the year group effects as compared to the reference category. Figure 4.8b illustrates the resulting graph, which follows the same pattern of variation as the final adjusted model as shown in figure 4.8a, with slightly lower estimated viral load in both 1997 and 2012. Initial viral load in 2012 remains the highest of all years.

After restricting the dataset to white MSM (N=1364), there remained weak evidence of an association between year of seroconversion and initial viral load (p=0.065), though the coefficients and shape of the curve remain relatively unchanged and initial viral load remains highest in most recent years (figure 4.8c).

Finally, after right truncating viral load at 5.0 $\log_{10}$ copies/mL (the lowest upper limit of detection used across the assays), the temporal pattern remained as did the association (p=0.030) (figure 4.8d).

Additional sensitivity analysis was planned to be performed on the final multivariate model by adjusting for HIV subtype, however the high proportion of missing subtype data overall (62.7%), and in particular the near total lack of sub-type data in those seroconverting in 2010-12 (98.0%), rendered this unfeasible.

Table 4.7 Sensitivity analyses of calendar trends in viral load at first clinic presentation amongst MSM with EHI

	Model a)Final adjusted multivariate model (N=1478)			Model b) MSM with HIV test interval ≤180 days (N=976)			Model c) white MSM only (N=1364)			Model d) Right truncating VL at 5.0 log_{10} copies/mL (N=1478)		
	Coefficient	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**	**Coefficient**	**95% CI**	**p-value**
1997-99	0	-	0.020	0.00	-	0.010	0.00	-	0.065	0.00	-	0.030
2000-01	0.20	-0.04, 0.45		0.35	0.03, 0.68		0.19	-0.07, 0.44		0.11	-0.06, 0.28	
2002-03	0.19	-0.04, 0.42		0.35	0.04, 0.66		0.21	-0.03, 0.45		0.12	-0.04, 0.28	
2004-05	0.22	0.00, 0.45		0.34	0.06, 0.63		0.25	0.02, 0.45		0.13	-0.03, 0.28	
2006-07	0.19	-0.03, 0.42		0.36	0.06, 0.65		0.21	-0.02, 0.44		0.04	-0.11, 0.20	
2008-09	0.09	-0.14, 0.32		0.21	-0.09, 0.51		0.18	-0.06, 0.41		-0.06	-0.21, 0.10	
2010-12	0.33	0.13, 0.53		0.49	0.23, 0.76		0.34	0.13, 0.54		0.14	0.00, 0.28	

VL=viral load; MSM=men who have sex with men. a=Final model adjusting for time from seroconversion to first VL, age at seroconversion, ethnicity and acute infection. b=Model a but restricting to MSM with HIV test interval of ≤180 days. c=Model a but restricting to white ethnicity MSM. d=Model a but right truncating viral load at 5.0 log_{10} copies/mL.

Figure 4.8 Sensitivity analyses of temporal trends in HIV viral load at first presentation amongst MSM with EHI

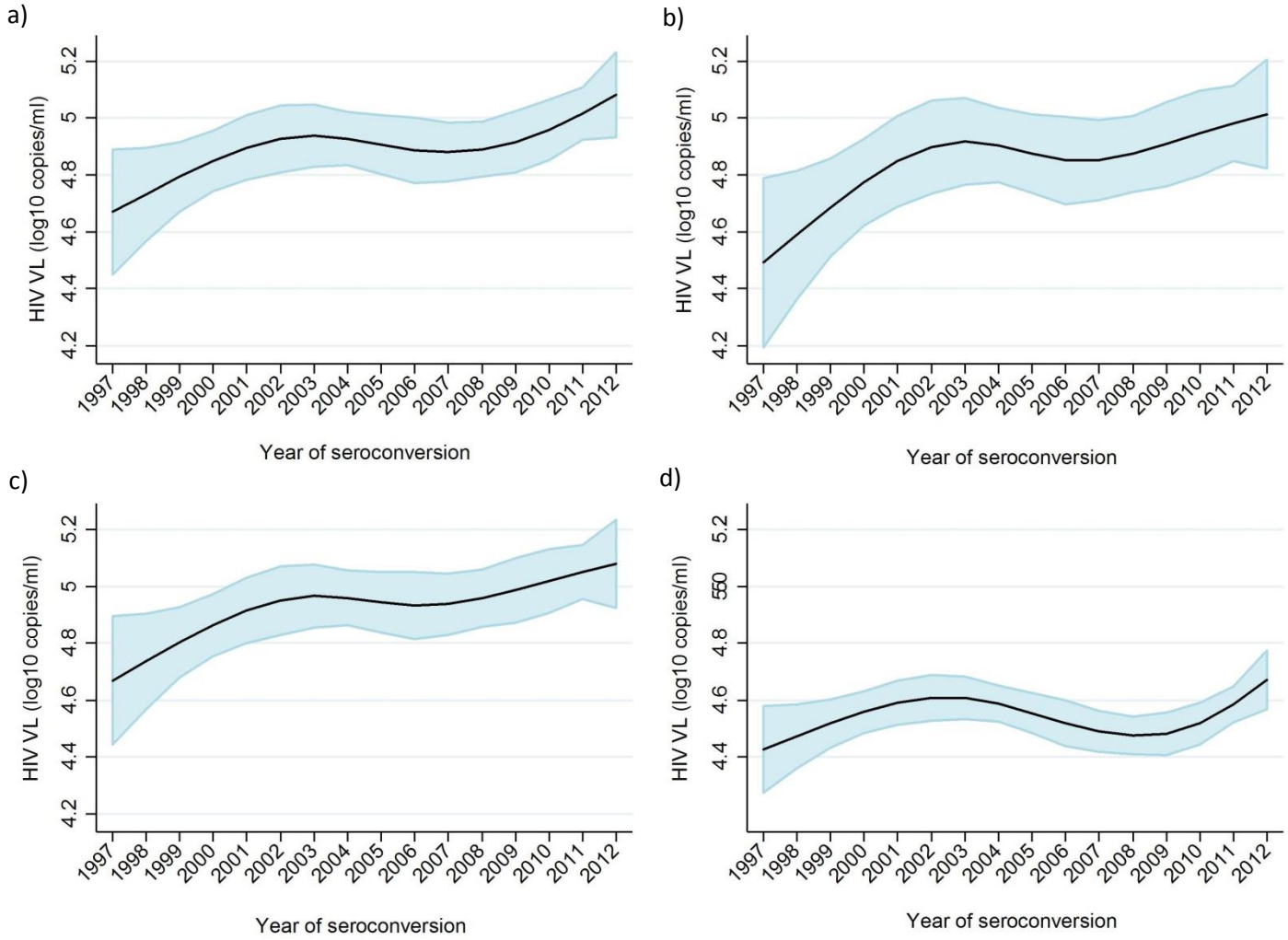


Figure a) Final adjusted model (n=1,478).

Figure b) restricts to MSM ethnicity with an HIV test interval <=180 days (n=976).

Figure c) restricting to white MSM (n=1,364).

Figure d) right truncating viral load at presentation at 5.0 $\log_{10}$ copies/mL (n=1,478).

Note: Black line denotes mean and blue shaded area denotes 95% confidence interval. Time from seroconversion to first viral load measure modelled using restricted cubic splines anchored at the 5th, 25th, 50th, 75th and 95th percentiles.

4.3 Summary discussion

These data from a UK cohort of recent HIV seroconverters show that time from seroconversion to initiation of ART has decreased over time, from a median of 3.7 years in 1998-99 to 1.4 years in 2010-11. This has been accompanied by an increase in CD4 count at ART initiation; over a quarter of individuals who seroconverted in 2010-11 and started therapy, did so with a CD4 count greater than 500 cells/mm^3. As time to ART initiation has crept nearer to seroconversion overall, there has been an apparent decrease in the proportion initiating ART in PHI in more recent years. Whilst these findings may appear to contrast, it is possible for both to co-exist, through a shift away from specific short-course treatment of primary infection and an overall decrease in the time to initiation of 'lifelong' ART. From 2008 onwards, notably more of the individuals who started ART in PHI appeared to remain on treatment as opposed to using the short-course approach. These results appear to indicate a general movement towards earlier initiation of 'lifelong' ART in the UK amongst those identified in EHI, independent of the strategy of treating PHI with short-course ART.

The viral load data presented in this chapter indicate that the peak viraemia in EHI is observed in MSM presenting to clinic at around 30 days post seroconversion, though it remains elevated in men presenting at up to 100 days after seroconversion. In order for TasP to have the maximal effect of reducing transmission potential in MSM with PHI it would need to be started within one month of seroconversion, though there may still be some added benefit from early ART in reducing the observed elevated viraemia up until 100 days post seroconversion. Currently only 24% of MSM enrolled in the UK Register cohort presented to clinic within 30 days of seroconversion. In order to increase the proportion of men diagnosed before peak viraemia, men would have to test more frequently than the current PHE recommendation of every three-months [211], perhaps a regularly as monthly or every 6 weeks.

The relationship between ethnicity and viral load is highlighted in these findings also, with non-white MSM having consistently lower initial viral loads than their white counterparts. Conversely, older age was associated with higher initial viral load in univariate analysis, however the relationship did not persist in multivariate models. Whether the observed lower plasma viral load amongst non-white ethnicity, and to a lesser extent younger MSM, corresponds to a reduced transmission risk warrants further investigation.

These data also indicate evidence of a possible increase in viral load at first presentation over time amongst MSM seroconverters. The increase in initial viral load from 4.68 log_{10} copies/mL in 1997 to 5.12 log_{10} copies/mL in 2012 as predicted by the adjusted RCS model equates to an increase on the linear scale from 47,863 to 131,826 copies/mL; an increase of 83,963 copies/mL over the 15 year period. It is highly possible that these estimates are overly inflated, due to the increased use of more sensitive viral load assays in recent years with higher upper limits of detection, but even when right truncating viral load measures at 5.0 log_{10} copies/mL in sensitivity analyses, a significant increase in initial viral load over time persisted, albeit at a lower threshold.

4.3.1 Strengths and limitations

By using data from a seroconverter cohort, it was possible to characterise ART initiation and initial viral load amongst individuals identified at the earliest point in infection without the bias of late presentation to services. The use of laboratory confirmation of seroconversion date in the UK Register adds strength to this data, as dates are estimated with a strong degree of confidence. It also allowed us to examine trends in treatment during primary HIV infection, which, in the UK, has separate initiation guidelines.

There are drawbacks to using a seroconverter cohort however. By definition of eligibility, seroconverters may display more health seeking traits than those presenting later [212]; most are regular testers and perhaps recognise their HIV risk or know the symptoms of seroconversion. It may also be that disease progression in those experiencing symptomatic acute infection is accelerated compared to those asymptomatic in early infection, resulting in presentation because of ill health due to rapid progression [213]. The results arising from this study population may therefore not be representative to recent seroconverters who do not present to clinic for diagnosis during in EHI.

4.3.1.1 Time to ART initiation analysis

More rapid disease progression and CD4 decline in those seroconverting in more recent years has been reported [79] and could also cause the apparent temporal trend to initiate closer to seroconversion. The upward trend observed in CD4 at ART initiation hints that this is unlikely in this population, however, and including CD4 at seroconversion in sensitivity analysis in the adjusted Cox model examining temporal trends in ART initiation did not affect the estimate. However, the analysis of CD4 count at initiation is based only upon individuals who have already started ART, and it is impossible to predict the CD4 count that

others will start at in the future. Whilst median CD4 count at initiation is likely to decrease as individuals initiate therapy later in infection, the high proportion of seroconverters in the most recent years who had started therapy within the follow-up period means that this is likely to affect the estimate less.

Prescribing patterns in UK clinics can vary; certain centres may have a reputation to be more proactive in treating early, or hold research interests in ART in PHI. I was unable to control for recruitment centre as there are numerous small centres across the UK who provide only a few patients to the UK Register of HIV Seroconverters, so I can only acknowledge this as a limitation. The other potential source of bias comes from trials of treatment in PHI; the SPARTAC trial is one such example and recruited from August 2003-July 2007, likely increasing the proportion of MSM initiating ART in PHI over this time period. Whilst I was able to run sensitivity analysis excluding individuals enrolled in SPARTAC, by virtue of a link between the UK Register and SPARTAC databases, there may have been other locally managed trials which I was unaware of. In the UK, treatment in PHI is recommended for individuals with persistently low CD4 count (for 3 or more months), neurological involvement or AIDS defining illness [132]. I assumed it unlikely that the prevalence of these conditions would change over time, and so did not adjust for these factors in our model.

4.3.1.2 Viral load at first clinic presentation analysis

Viral load assay technologies have developed considerably since their introduction leading to an exponential increase in the linear range of the assays, from <500 to 500,000 copies/mL pre-2006, to between <50 and 10,000,000 in those most commonly used from 2006 onwards. As use of different assay type is strongly associated with time, significant collinearity exists between assay type, upper limit of detection and calendar time, making it difficult to control for assay type in multiple regression models assessing temporal trends. To attempt to account for changes in the upper linear range of detection I performed sensitivity analyses by right truncating viral load data at 5.0 $\log_{10}$ copies/mL (500,000 copies/mL) and rerunning the multiple regression models.

The finding that the initial viral load was highest amongst those presenting in most recent years could be due to a possible selection bias. It is possible that symptomatic people are more likely to be recruited to the UK Register earlier compared to those who are asymptomatic. Compared to asymptomatic seroconverters, those who are symptomatic are

likely to have higher viral loads during early infection[129]. This may lead to greater engagement with their HIV clinic during the first few months of HIV infection due to ill health, thus providing more opportunity for recruitment to the study. Conversely, asymptomatic seroconverters may be more likely to disengage with an HIV clinic temporarily until later in their infection, and hence may have less chance of being invited and recruited to the UK Register until later on in the course of infection when they re-engage with care. For seroconverters recruited in earlier year groups, this bias is less of a problem as these "asymptomatic seroconverters" are likely to be recruited retrospectively a few years after their seroconversion date. For more recent years however, less time has elapsed in which to retrospectively recruit these seroconverters. Currently the date of recruitment to the UK Register is not captured in the study database so there is no way of systematically assessing the extent of this bias, or adjusting for it. It is however important to acknowledge that if found to be problematic, it could cause an overestimation in viral load at first presentation in the most recent year groups.

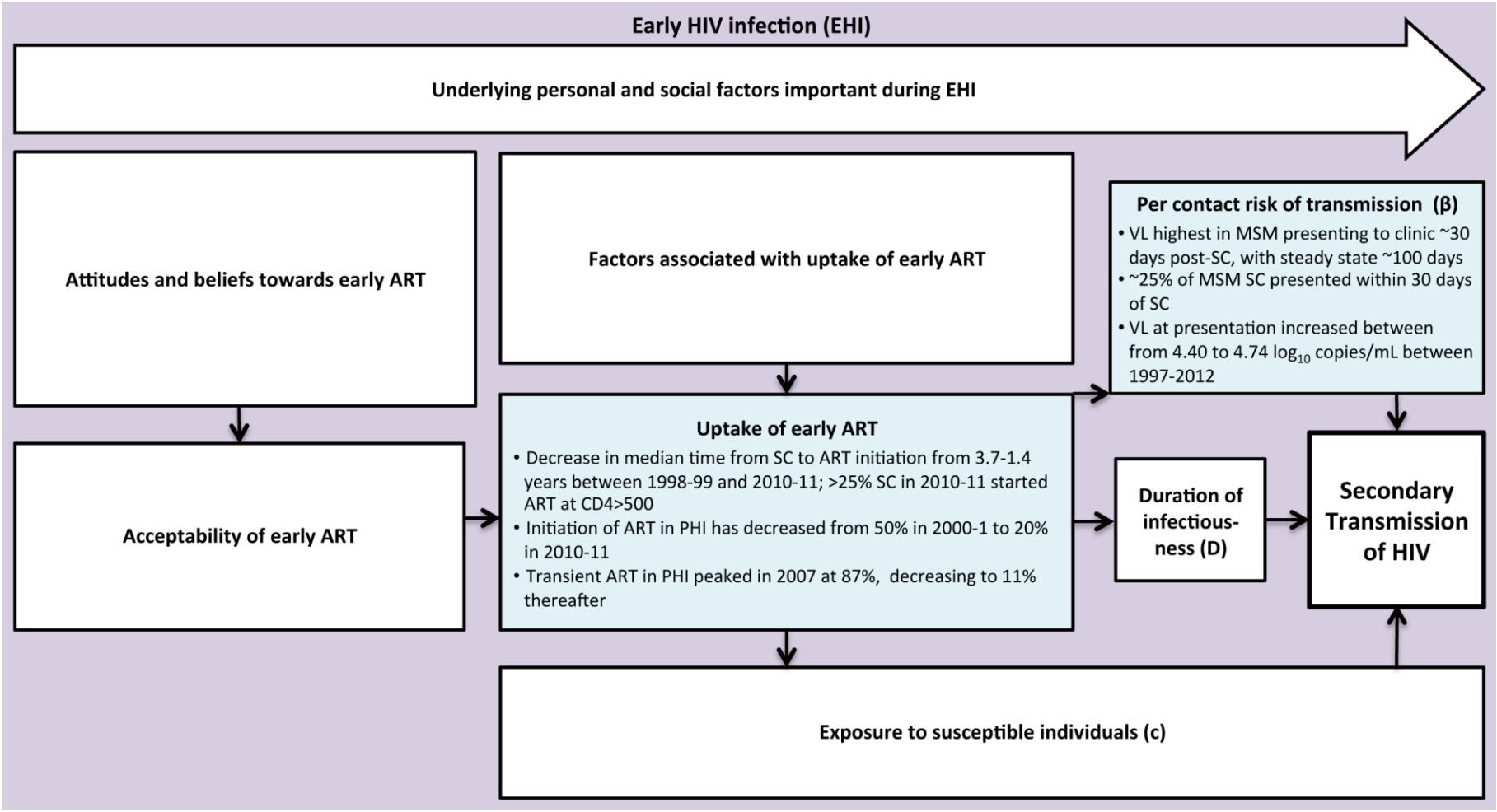
4.4 Chapter summary

The key results of this chapter are highlighted in blue in the thesis schematic presented overleaf (figure 4.9). In this chapter I provided evidence of more rapid uptake of ART over time amongst HIV seroconverters in the UK; half of those most recently diagnosed started ART within 1.4 years of seroconversion. In line with these findings, there was also an increase in the CD4 count at which seroconverters initiated ART; over 25% did so with a CD4>500 in the most recent years. The reasons for this tendency to initiate earlier in infection in more recent years are unclear. Possible reasons may include the influence of international guidelines recommending initiation at CD4>500 or test and treat approach, a greater acceptability of treatment amongst patients or increased use of TasP. The next section of the PhD aims to investigate the acceptability of early ART amongst MSM seroconverters using mixed methods approach.

The data presented in this chapter indicate that to maximize the impact of TasP on peak viraemia amongst MSM seroconverters in the UK, it would need to be initiated within 30 days of seroconversion. Currently, only one in four of the MSM seroconverters who enrol in the UK Register present this early in their infection, and would have the opportunity to initiate this early. After the first 30 days of infection, viraemia amongst those presenting appears to decrease reaching a plateau at around 100 days post seroconversion. From a

public health perspective if considering risk of HIV transmission for a single sexual act, these results indicate that the benefit of immediate TasP in UK MSM presenting from 30 days post seroconversion wanes over time, and by 100 days post seroconversion, becomes no more than it would be for those presenting in chronic infection. There may still be a benefit to ART initiation after the initial 100 days if cumulative transmission risk is considered, however, as the earlier ART is successfully initiated, the shorter the duration of infectiousness is, and so more potential transmission occurrences could potentially be averted. This is particularly the case for those individuals who present with very high viraemia after 100 days post-seroconversion; around 1 in 3 seroconverters who presented to clinic 3-12 months after seroconversion had an initial viral load >5.0 $\log_{10}$ copies/mL, corresponding with a very high transmission risk and so would benefit from TasP.

Figure 4.9 Conceptual framework of the thesis including results from workstream 1



5 Workstream 2 phase A results: How do MSM with recently acquired HIV infection feel about early ART?

In the previous chapter I presented data from the first workstream of my PhD. Using data from the UK Register I demonstrated that there had been a shift towards earlier initiation of ART over time amongst recent seroconverters in the UK. In this chapter I present the findings of phase A of workstream 2, the qualitative in-depth interview study, the methods of which can be found in chapter 3, section 3.5. The aims of this workstream were to understand the attitudes and beliefs of MSM with EHI towards early ART, and how early ART may sit in the context of recent diagnosis of EHI.

Specifically, the workstream aimed to answer two research questions:

- How does being diagnosed with recent HIV infection affect men's lives?
- How do MSM with early HIV infection feel about early ART?

In this chapter I first present an overview of the demographic makeup of the respondents. I then describe the men's experience of being diagnosed with HIV, its effect on their lives and how they adjusted to the diagnosis. Next the men's knowledge and expectations around ART are described along with the themes that emerged from the data whilst focusing on the research question "How do MSM with early HIV infection feel about early ART?".

5.1 Respondent demographics

Fourteen MSM attending one inner-London HIV clinic were interviewed over the course of this study which ran from 2010-2013 (see table 5.1). All MSM had laboratory confirmed evidence of seroconversion and most were interviewed within 6 months of their date of HIV diagnosis. The majority of men were ART-naïve at the time of interview, 3 were on ART and one man had picked up his prescription on the day of the interview but had not yet started, so was subsequently classed as not on ART. Notably, all of the men who were on ART, as well as the man who had just collected his first dose of ART, were interviewed in late 2012 and 2013.

The majority of respondents were aged between 31-35 years of age, and of white British ethnicity, though there a range of ethnicities were represented. Men were well-educated on

the whole, and all were employed, except the current student. Five of the 14 men were in a relationship at the time of HIV diagnosis, three with a HIV-negative partner, one with a known positive partner, and, one with a partner who was diagnosed HIV positive at the same time as the respondent. At the time of interview, only two men remained in their relationship (one with an HIV negative partner, and one with a positive one).

Table 5.1 Characteristics of in-depth interview respondents (n=14)

		n
Year of interview	2010	5
	2011	3
	2012	2
	2013	4
Age at diagnosis (years)	<25	2
	26-30	2
	31-35	6
	36-40	2
	41+	2
Seroconversion identification method	Ab- then + within 12 months	10
	Ab- and PCR +	2
	RITA incident	2
Experienced seroconversion symptoms	No	4
	Yes	9
	Don't know	1
Time form HIV diagnosis to interview	<3 months	5
	3-6 months	7
	>6 months	2
On ART at time of interview	No	11
	Yes	3
PEP ever	No	11
	Yes	2
	Don't know	1
HCV co-infection	No	13
	Yes	1
Ethnicity/nationality	White British	8
	White African	2
	White European	1
	White North American	1
	Black Latin American	1
	White Latin American	1

Ab-=HIV antibody negative; Ab+=HIV antibody positive; PCR+=viral load detectable on polymerase chain reaction; RITA=recent infection testing algorithm; PEP=post-exposure prophylaxis; HIV+=HIV antibody positive; HIV-=HIV antibody negative.

Table 5.1 (continued): Characteristics of in-depth interview respondents (n=14)

		n
Partnership status at diagnosis	Single	9
	In relationship with HIV+ partner	2
	In relationship with HIV- partner	3
Partnership status at interview	Single	12
	In relationship with HIV+ partner	1
	In relationship with HIV- partner	1
Education status	University level	12
	Below university level	2
Employment status	Employed	12
	Self-employed	1
	Student	1
Housing status	Home owner	3
	Rented accommodation	10
	Unknown	1

Ab-=HIV antibody negative; Ab+=HIV antibody positive; PCR+=viral load detectable on polymerase chain reaction; RITA=recent infection testing algorithm; PEP=post-exposure prophylaxis; HIV+=HIV antibody positive; HIV-=HIV antibody negative.

5.2 The impact of HIV diagnosis

To understand how men felt about early HIV treatment it was important to first understand how they felt about their HIV diagnosis, and how it had impacted their lives.

The men interviewed received their HIV diagnoses either in a primary care setting or after presenting for HIV testing at the sexual health clinic. The men who reported experiencing ill health in the lead up to their HIV diagnosis all presented to their GP at the time they were ill, one respondent even registered with a GP for the first time in 10 years as he felt so sick. Of the men who presented to the GP, most reported flu-like symptoms, swollen glands, rash and fever and in two cases extreme diarrhoea and weight-loss. All but one of these men were sent home without an HIV test. The others were told they likely had a virus, and should "take some paracetamol", or were diagnosed with a range of conditions by their GP, including impetigo, pharyngitis, glandular fever, vertigo, bacterial stomach-bug and an ear infection and given antibiotics or other forms of treatment. The one respondent who was HIV tested by his GP at the first visit was diagnosed in Spain and the doctor did not inform him he was being tested for HIV. It therefore came as a huge shock when he returned for the test results to be told by another doctor he was HIV-positive. Men presented several times to their GP before an HIV test was offered or recommended, if it was at all. One patient who suffered with a rash, flu-like symptoms and chronic diarrhoea also presented to A&E whilst experiencing these symptoms after fainting several times at work but was not offered an HIV test. Men who were diagnosed with HIV by UK GPs were all referred to the HIV clinic for further care, with the respondent based in Spain self-referring himself and travelling home to the UK for appointments.

Of the men who tested HIV-positive through the sexual health clinic, two went to be tested because of a specific sexual incident which was causing them worry. The others went either because it was time for their routine six monthly or annual test, or because they had other STI symptoms. For the men who had a blood test for HIV they said they knew then that they were going to be told they had HIV when they received a phone call from the health advisors at the clinic asking to come into the clinic to discuss the results. One man even asked to be told over the phone then and there to avoid lengthening the experience. This was largely due to previous experience of receiving text messages for other STI results, and hearing friends' stories of receiving a call from the clinic which led to a positive HIV diagnosis.

Whilst all of the men had very different backgrounds and lifestyles, it was striking how similar their reaction to HIV diagnosis was. Men generally appeared to report two phases in the process of coming to terms with their HIV diagnosis, though the duration of these phases varied by individual. The two phases could be divided into the immediate aftermath of being diagnosed which was characterised by shock, numbness and intense negative feelings which commonly lasted days or weeks. In the interviews men notably did not reflect on what was discussed with the clinic staff at the diagnosis appointment, or the level of support they had been offered. Upon reflecting on this initial period, the men universally described the raw intrinsic emotions experienced at this time instead. This was followed by a longer phase of re-adjustment in which extrinsic forces came into play through talking to others, seeking further information and rationalising the situation. This two-phase period of coming to terms with HIV is very neatly conceptualized by the two respondents below.

> *"I did think three days afterwards, I remember sat [at work]. I remember sitting there and thinking will I ever think of anything else? Because at … on that day I was doing my job and then went and sat for 20 minutes and that was all I was thinking about. And I walked to say I don't know, for example, Marks & Spencers to get a sandwich. And that was all I was thinking about. And I did the … and that was all. It was literally 24/7. That was all I was thinking about. But I have to say, a week later. It had changed. And I wasn't thinking about it so much. Um, I think because as I said the [stutter] sexual partner had he said well, I had it for seven years. I was like, wow, okay. Um, and I'd known him for about 3 or 4 years and he'd never mentioned it. And whatever. So I thought oh, okay perhaps life's not completely over at this point. And it [stutter] took about three or four days to it not to become the most important thing in my head."*
>
> **White British man, age 31-35, single, >6 months since diagnosis, not on ART**

> *"I mean, the first couple of weeks was, yeah, it was just, like, a surviving situation. And then after that, I suppose, I don't know, I was gradually starting to kind of think about the implications of it and find out about them. Because you assume, initially, that, you know, kind of, "That's it. My life's over." Certainly as it was before I knew about this. But then, I don't know, I think in a way, like, some of the changes – although, I'm not saying it's a good thing, or anything like that – but some of the changes that have*

happened or that mentally that I've felt differently, some of it has been good."

White British, age 26-30, in relationship, 3-6 months since diagnosis, not on ART

In the following sections, I describe how men felt upon receipt of their HIV diagnosis, their methods of adjusting to life with HIV, and the impact it had on their life and relationship, which provides the context for the thematic analysis of the research question "How do MSM with recent HIV infection feel about early ART?".

5.2.1 The immediate reaction: shock and a maelstrom of negative feelings

The reporting of one or more of negative emotional reactions upon receipt of diagnosis was universal, as was shock. Negative feelings of disappointment, anger, blame, sadness, hopelessness, panic and feeling "dirty" were reported by the men upon receiving their diagnosis. These feelings were most acute in the hours and days immediately following diagnosis, and then gradually ebbed with time. In the two men with a self-reported predisposition to depression however, these feelings remained at an overwhelming level for months, and were still felt to some extent at the time of the interview.

"I cried for months and months and I used to say to myself, I'm screaming and dragging at home on my own saying I'm so disappointed, disappointed, this was still hammers in my mind I was so disappointed"

Black South American, age 36-40, single, 3-6 months since diagnosis, not on ART

Negative emotions could be directed internally and/or externally. The feelings of anger and disappointment were commonly directed both internally and externally. Men reported feeling very angry and disappointed with the sexual partner that gave them HIV, but also at themselves for putting themselves at risk of acquiring HIV.

Feelings of panic were reported by the men and appeared to have three sources: fear of having transmitted to a partner; fear of being ill, or being in pain; and fear that others will find out about the diagnosis. Panic was most acute in men who worried they had transmitted HIV to somebody else, especially in the men who had an HIV negative regular partner at the time of

diagnosis. This feeling was exacerbated and mingled with paranoia and guilt where HIV had been acquired outside of the agreed parameters of the relationship.

Reflecting on the moments following his HIV diagnosis, having suspecting he contracted HIV in a sauna whilst "cheating" on his partner, the respondent below described himself as feeling like "scum of the earth" and "horrible" that he could have passed it to "the person you love". In this circumstance, the negative feelings experienced at the time of diagnosis were centred around the effect of his cheating on his relationship and the chance his partner may now have HIV, rather than any personal implications of having HIV himself.

> *"it wasn't so much being positive that I was worried about I was so focussed on the relationship I was so focussed on that and that was what was causing the hurt, yes, there was the HIV as well. But again I have friends who are HIV positive and who have and lead very fruitful lives, a bit of a cliché but, so there was a worry there but I was more worried how this was going to affect my relationship with my partner and then about 10 days after my diagnosis I felt really down, I almost, I suppose it's as close to suicidal as I have ever been and I don't have it in me, and I don't think there was ever any real danger of doing it and I got in touch with a woman who is a life coach and I dropped her an email and said this is what has happened can you help me, and I've been seeing her since, and talking to her a lot.. I got a lot of value in terms of trying to give some meaning as to why I caught it, how I caught it, the types of behaviour that led me to it and how I can change it and how I can break it and how I have broken it since then."*
>
> **White European, age 31-35, single, 3-6 months since diagnosis, on ART**

5.2.2 Adjustment to the diagnosis

Men found different ways to get them through this initial bleak period, amongst the coping mechanisms mentioned were meditating, appointing a life-coach and exercising. However, the most recurrent theme was that of distracting oneself during this time. Men talked about the importance of having something to focus on other than HIV; most commonly a relationship, work, a job interview or just being with people. Idleness or lack of preoccupation might result in the return of negative thoughts about HIV. For the respondent below, being with his friends was crucial over that time period to stop him tormenting himself and to help him deal with his biggest fear of being lonely.

"The week from when I found out, that whole week, every night, I was going to friends' houses because I couldn't bear to be on my own. If I was on my own my head, my thoughts would start to spiral and I would think more about it and I would kind of torment myself in terms of, "Oh my God," you know, and feeling scared and lonely. That was, my biggest thing was being lonely. And so I had to be around friends. And when I was around them, I wasn't around them so much even really talking about it, we were just having time together, eating dinner, watching TV and stuff. But just to be with somebody, it took my mind off of it. And that really helped, having those friends around me. And that was really the only way that I dealt with it, just to tell a few people close to me and talk to them about …"

White British, age 26-30, single, <3 months since diagnosis, not on ART

HIV diagnosis appeared to have less of an effect on men's life if they had experienced other traumatic life events. Men who found themselves in this situation tended to have a more pragmatic view of life in which HIV was perceived as not such a big deal.

"Erm, it's not had an enormous effect. Erm, in a sense that, you know, I still go out and see friends, still you know, go to work and same old job, still looking to buy a flat and do all those other things the same … same old, same old. Erm, I still, you know, do … take my exercise, all the rest of it, I'm, you know, exactly the same. Erm, so I don't think it's had a major erm, effect. I mean I've, I've been through a couple of erm, fairly major things before where I had a erm, a to… completely unprovoked erm, erm, homophobic attack in 2004, I was stabbed five times. So that was, yeah, so that was just, you know, a random nutter basically. So, I've been … you know, I've already sort of come through a few things, I'm a bit more sort of philosophical about these kind of knocks that come along because actually, you know, what … I'm still here. Still, still the same as I was yesterday more or less. So erm, so yeah I don't, I don't have too much of a problem there."

White British, age 36-40, single, <3 months since diagnosis, not on ART

Men sometimes attempted to put their HIV into context by comparing their situation to others they perceived as worse off, for example somebody who was "dying of cancer" or had no money to buy food. This comparison appeared to be a way to maintain perspective on the situation, to refocus on the positives and remind them that they are relatively fortunate. HIV diagnosis could be easier to deal with if it was followed by an event perceived to be comparably worse. One respondent was diagnosed with Hepatitis C very shortly after his HIV

diagnosis, which in his opinion made his HIV diagnosis almost inconsequential, as he explains below.

> *"Erm, no, no in some ways, it's kind of almost reinforced, it's almost reinforced in my head how the HIV seems like not a problem at all. Whereas the Hep it seems like the major problem at the moment and that's probably a bit, because like when I told my brother, I told him about, I was doing it in chronological order, there's something I should have told you before but I didn't want to, I'm HIV, and he was like wow and sat down and goes oh, and then you know it was obviously the second one, and I told him about the Hep C, and similarly when I told my boss, she said well Hep C, that's not too bad and it's like well actually I think it's a hell of a lot worse than the HIV personally yeah, but maybe that's again how I am thinking now but yeah, the majority of people I know say that you know you see so many people living normal lives, people just saying I take a pill a day it's fine, and you hear some people say oh god I had this treatment and I couldn't sleep and it's like yeah but you've got some choices here, whereas at the moment in the Hep C there isn't really any choice and that's what you've got to get and people say it's awful and they have to have time off work and all the rest of it so that's really in my mind at the moment."*
>
> **White British, age 31-35, single, 3-6 months since diagnosis, not on ART**

For some, the process of re-adjustment involved the men educating themselves about HIV often through internet research and sometimes by making contact with other HIV-positive people. Sharing experiences with other positive men was perceived as a great way for men to educate themselves about HIV from people who had been through the same feelings as themselves and helped the men face their fears and worries. However, self-guided research and learning about HIV was avoided by some men who were keen to avoid scare stories and untrustworthy sources of information.

5.2.3 Diagnosis as an impetus for self-reflection and self-improvement

Whilst already having a positive or pragmatic worldview before HIV diagnosis appeared to make it easier to accept an HIV diagnosis, some men adopted a more positive outlook on life after being diagnosed with HIV. In these men the time following diagnosis was used to self-reflect and create a plan for self-improvement in all aspects of life, be it work, fitness or sexual behaviour. This process could be self-conducted or, in the case of two of the men, facilitated by a therapist or a life coach.

"It hasn't affected my life but it has affected it. So it's hard. I feel … it certainly makes you assess your life, and I've done a lot of self-assessment recently. And that can sometimes be a good thing and sometimes a bad thing. And I've talked to my friends about this and they say, "You can go through a time when you beat yourself up," not just because of HIV but I've started, you know, "What am I doing with my life? Where am I going with my life?" you know. "Who am I? What am I trying to be? Why am I not achieving the goals that I set myself when I was younger?" And you, all of that stuff. And I think that that, for me, I'd be worried about getting into depression and things like that if I let myself go down that route. So I try not to. But it does make you assess your life a lot, and about who you are as a person and where you want to be. And some of my friends, that's been a really positive thing, it's made them want to go to the gym more, it's made them want to look after themselves more and be healthy and fit, and not go out partying all the time, you know. So it can have a good effect on your life as well."

White British, age 26-30, single, <3 months since diagnosis, not on ART

One man, who reported experiencing a severe bout of depression following his diagnosis, related the moment he decided he had to take some action. For him, setting a strict gym routine allowed him to feel better about himself and combat the depression. It put him in a better mental place to turn his life around and start his own business.

"I was so depressed and I was crying every single day, how sad is it, since September every single day I was crying, I wasn't even talking, the sound of my voice was irritating me. If you get to this point, I tell you what, you have only one way or you get up and do something or you barricade yourself because of, what is the point to be like ... I wasn't even a vegetable, I was like rotting, so and I then looked at the cigarette and said I'm going to finish you and you're going to be the last cigarette I smoke. So I throw the cigarette, I throw the weed, on the sanitary and I flush it, because I knew that if I would put it in the bin, after I had a few sweets and probably some snacks from the fridge I would definitely searched for the weed in the bin, for the weed. And then I put the alarm on, I put my two alarms, my two mobile phones I put the alarm on, I woke up at 6.30, by 7.30 I was at the gym and then I started to go the gym since early February for 5, it varied between 3-6 days a week. Then later on in the morning before I go to work, and that's how I, you know made me like ... I think probably the ... it also makes you feel healthy, it makes you feel part of that group that you would like to be and you work hard and then you go to the mirror before you get changed

and then you take your wet shirt off and you look at your tummy and your chest and you feel good, you go to work with a different attitude. ”

Black South American, age 36-40, single, 3-6 months since diagnosis, not on ART

5.2.4 Effect on relationships

Men described how their HIV diagnosis put strain on relationships with family, friends and at work, as well as their sexual relationships. The urge to talk about the HIV diagnosis straight after receiving it was strong in many of the men. Of the men interviewed all but one had disclosed their status to someone outside of the clinic, be it friends, family or work. The one man who had not disclosed felt it was unnecessary as he did not want people to “treat him differently” or “feel sorry” for him. He did, however, disclose his status to casual sexual partners he met online. In his mind there was a clear distinction from people he had sex with, and would not see again, to the people he cared about and had meaningful relationship with.

5.2.4.1 Friends and family

There was a need to be selective about who could be told about the diagnosis. Most men told one or two of their closest friends shortly after diagnosis, and only ever the people they could totally trust. Pragmatic decisions had to be made as telling the wrong people could result in a loss of control over who knew, or a change in the relationship dynamic because they felt pity towards them. In the worst case scenario men feared rejection from their friends. One man had a particularly bad experience with his best friend who shut off contact after he disclosed his HIV status, resulting in deepening feelings of despair and isolation at a time of already heightened stress.

Telling another HIV-positive friend brought the benefit of having a shared experience and being able to relate to each other, without the pity. Men who disclosed to HIV-positive friends talked of being able to “talk science” together, of their shared understanding of the situation and the ability to support each other in confidence without the risk of judgement. In many cases this resulted in a closer friendship.

“My first instinct was I need to tell someone, I need to share this with someone because I felt it was so hard to just be myself, and so I, I told a

good friend of mine who is also HIV and I knew that he was HIV and we were open, and in a way it was good because it makes our friendship really strong, so we can support each other."

White South American, age 41+, single, <3 months since diagnosis, not on ART

"RES: "I've subsequently met one person through the internet who is also positive … who I kind of knew from the gym about six years ago. And having him has been really helpful, because he's been kind of a stranger but a friend, do you know, I've only just met him… through finding out, and that's, to talk to him has been really helpful. He's been very kind.

INT: And is he at a similar kind of phase?

RES: No, he's been positive for four years. He's on medication now. He's kind of, I think he's dealt with it a lot. But he had no-one, when he found out he didn't tell anyone. He didn't know anyone else that was in the same situation, so it was quite lonely for him, and I think that he's met me and he wants to kind of be the person that he didn't have. Which is really sweet of him.

And he's been really supportive, phoning me a lot, coming round to see me, talking to me about his situation, I've been talking to him about mine and the problems that I've had. And that's been a huge help. I think me talking to other people that are HIV-positive is the biggest help. Talking to people that are not HIV-positive doesn't really help, to be honest, because they don't understand what, they don't really understand what it's like. They can feel sorry for you and talk to you about it but it's a big help to have someone who you can say, "What's your CD4? What's your viral load? How did you feel? Who did you tell? Did you get sick? Did you not get sick? Do you know who it was?" All of those questions, to have something in common with someone helps massively."

White British, age 26-30, single, <3 months since diagnosis, not on ART

A common theme amongst the men was the unwillingness to disclose their HIV status to their family. Oftentimes men explained that their parents just would not understand and that they "did not cope" or "struggled to come to terms" with them being gay so telling their parents they were HIV positive was out of the question.

"RES: I absolutely can't tell my family, they're bananas so ... my mother's quite mentally ill, she's bipolar so she's not going to deal with it. And my sister won't keep her mouth shut and so if I'm not telling them, I'm just not going to tell any of them, they don't need to know.

INT: So do they know that you're gay?

RES: Yeah, they do and they're sort of fine with all of that, in their sort of Daily Mail reading way. You know they're fine with it as long as I've got some nice clean cut guy and I'm going steady with him and they're not fine if they think anything vaguely progressive is happening. You know, parents ... as long as I don't get my ear pierced they'd be very understanding, because that's what they think being gay is, you know and that's what they'll think HIV is, they'll think it's all grubbing around in seedy nightclubs they just won't understand anything."

White British, age 31-35, <3 months since diagnosis, not on ART

Other times, non-disclosure was a way of protecting their family from extra stress when it wasn't necessary. Disclosure to family tended to occur with siblings rather than parents as they were often perceived to be more worldly. Some of the negative feelings experienced at diagnosis centred on the idea of "letting people down" by catching HIV; two men explicitly mentioned that their parents had told them not to catch HIV when they first came out as being gay. Other men "felt bad" for not telling their friends and family but hoped they would understand the reasons why, if or when they did choose to disclose in the future.

5.2.4.2 At work

The men interviewed came from a broad range of occupations and whilst many men notified work because of the time they would need off for appointments, for a few men, being diagnosed with HIV created a crisis over whether they would be able to continue in their current job or career. One respondent was in the medical profession and knew that he had to notify occupational health immediately, but was unsure how it would influence his career. Another man was a teacher who was worried about the "inbuilt ignorance" amongst parents towards HIV-positive gay men working with children. For him, being diagnosed with HIV meant he wanted to take a job in a university and get away from the risk of encountering stigma at work.

5.2.4.3 Long term partners

For the men who had an HIV negative partner at the time of HIV diagnosis, the period immediately following diagnosis was regarded as particularly stressful. This was due to the added worry that they may have transmitted HIV to their partner. Men related their tales of calling their partners to the clinic to be tested and the anxious wait for the result.

> *"I can talk about it now because I've done a lot of work around this, but it wasn't and then the horrible thing was I did have unprotected sex with my boyfriend was the fear that I had infected him and that horrible window period between you know and me obviously feeling like I'm the scum of the earth so yeah ... it was horrible, I mean he was in complete shock but oddly enough we still couldn't keep our hands off each other if you see what I mean, like literally days later it was really. It was really awkward and horrible because I then went to, the day I got diagnosed, he came over, he got tested straightaway and that was negative, he then came with me to the other clinic just next door and then I had a chat with the nurse or doctor I can't even remember and then we sort of parted ways, and it was like erm okay I'm completely on my own now, so a) I had to deal with the fact that I was HIV positive and I lost my boyfriend, in the space of 2 hours and then erm there was still contact going in him sending messages and me sending messages and then we met again a couple of days later and it was really a very intense conversation and somehow we ended up in a hotel in Kings Cross having a drink and then ended up booking a room there and sleeping with each other because it was just like so, we couldn't let go of each other and it was so much to. And that continued for weeks on end, he disappeared for a while then we sort of got back together I suppose erm and you know gradually I think he sort of accepted it, about 6 weeks later he had his final result back saying that he was negative so that helped and erm throughout we were still seeing each other."*
>
> **White European, age 31-35, single, 3-6 months since diagnosis, on ART**

Maintaining a serodiscordant partnership was testing when barebacking was a feature of the relationship prior to HIV diagnosis. Men could be put under pressure by their negative partner to continue to bareback despite the risk of transmission and refusal to do so invariably led to stress on the relationship. Interestingly, one man perceived his HIV negative partner's insistence to abandon condoms as a loving gesture, as their partner still wanted the same level of intimacy despite the risks involved.

"Yeah, well obviously I got back with my ex that night and that was, yeah, yeah it was weird, it was very weird to start with, erm I kind of wore a condom and whatever, but I was kind of nervous about kissing him too much and things like that, erm ... and then but then he piped up with the idea of let's not use condoms which I was really unhappy about and I said why? And I refused point blank then for at least a month, but then at the same time, every time I insisted on using a condom he was like looking at me like it was, he was really annoyed and so in the end we started, you know, so, it's your choice and in some ways that's really sweet if that's the case"

White British, age 31-35, single, 3-6 months since diagnosis, not on ART

Men reported experiencing very intense emotional feelings of desire and love for their partners after receiving their HIV diagnosis, and it even appeared to reignite one relationship. These feelings could be short lived, however with the practicalities of navigating through the emotional upheaval of receiving an HIV diagnosis and the stress and worry of transmission. For two respondents, being diagnosed resulted in a closening of the relationship with their long term partners: one whose partner was, and remained HIV negative; and one whose partner was diagnosed HIV positive at the same time. Common to both of these couples was the concept that HIV was a collective journey that both members of the partnership took together, from educating oneself about HIV to attending appointments together, even in the case of the serodiscordant couple.

5.2.5 Finding a new sexual identity

Sexual behaviour could change significantly following HIV diagnosis, for a variety of reasons. Amongst men who did not have long term partner at the time of diagnosis, conscious abstinence was adopted by some, this was called different things by different men from acting like a "nun", a "virgin" or a "priest" to taking a "year of cleansing". Men reported a range of reasons underlying the decision to remain abstinent. Some experienced a total lack of interest in sex, linked in some cases to a depression following HIV diagnosis or the feeling of being "dirty" or "infected". This was usually acknowledged as a temporary state, that these feelings will probably change given time.

"INT: So, would you say that the diagnosis has had an effect on your sex life?

RES: Well I mean it's just completely obliterated any notion of it. You know I'm not really part of that big sexual gay scene anyway. You know secretly I'm quite middle class and I just want a Labrador and a husband, I don't really, I've never really been part of that scene and I'm, I've no interest in the grubbiness of it, you know. I think, but I do feel quite dirty, I'm told I'm ill, it's odd, you know I might buy shares in hibbiscrub or something, I'm sure it will pass but you know, but effectively one ought to be less infectious if there's any way to do it."

White British, age 31-35, <3 months since diagnosis, not on ART

For other men, a feeling of sexual desire was still present but the actual practicalities of having sex were off-putting. Sex minus all the social and emotional factors was perceived as just a mechanical act.

"I've been a virgin…it's just I find it really, really hard at the moment to come to someone and say look I'm HIV positive would you like to have sex with me [laughs]… It is not a very easy thing to do , and I need to tell people and obviously they have to know and so they can take all the preparations[sic]…It's not that I don't feel horny or anything like that, I do, it's just that it's not the same… For the time being, I know it will come back, I know things will probably change but it's just like having sex for the sake of having sex…Maybe I should become a priest or something,"

White South American, age >40, <3 months since diagnosis, not on ART

Men described a huge fear of rejection from sexual partners. Experiencing stigma in the most intimate part of their life at a time where confidence and self-esteem were already low was too much for some men to cope with. In these cases, abstinence became a mechanism to protect from further negative feelings and emotions such as worry and anger.

"I think the fear of rejection is quite strong, even though when you think about it actually if people knew 20% of London and gay men are HIV positive a lot of them are not on medication, the amount of people I must have slept with who had HIV that I didn't know, and didn't tell me, didn't even know themselves, so somebody telling you that they have it but they're on medication should actually reassure them to some extent but it's a really tricky one and I don't know, and that's part of the reason why actually I don't want to worry about it at the moment, that's why I want this cleansing

I don't want to have to tell people and deal with the rejection because I get very angry."

White European, age 31-35, single, 3-6 months since diagnosis, on ART

Serosorting for positive partners was another strategy which was adopted by men keen to avoid experiencing stigma after diagnosis. Men who had met HIV-positive casual partners before they were diagnosed, often contacted these partners after diagnosis as it was perceived as "safer" and a way to avoid "getting hurt" by rejection.

"I was, at first, terrified of having sex. And I have had sex since I found out. I've had sex mostly with other people that are HIV-positive that I have known about or known of, or whatever. As I said, I've always been quite open, I'm not, when I was negative I wasn't the sort of person that would not have sex with someone that was positive. So I had met people that I'd known over the years who had, perhaps, been casual sexual partners that I knew were HIV-positive. So I kind of contacted them, and spoke to them, a) someone to talk to and, b) because I knew that they were in the same position as me and I could have sex with them without, with the guarantee of not having that question of, "Are you positive?" and then you have to say, "Yes," and they're not. And I'm not ready for that stress right now of someone freaking out that I'm positive and they're negative. So for me, it's a safer option to have sex with someone that's positive right now."

White British, age 26-30, single, <3 months since diagnosis, not on ART

The internet was another method used to meet positive partners. By updating their Gaydar or Grindr profile to include a reference to their HIV-positive status, men felt that their partners would know what they were getting into before they even make contact. This was not a fool proof strategy however, as one of the respondents pointed out he often met guys online who didn't bother to read the profile and only looked at the pictures. Men who used the internet to source partners before tended to report less of an impact of diagnosis on sexual behaviour.

"It's not really changed much to be honest. Just, erm I'm just meeting more people that are also positive or on treatment. I don't know ... we can ... you know we don't need to, erm pass that hurdle of telling each other. It's not so much of a shock."

White African, age 31-35, single, 3-6 months since diagnosis, on ART

Being diagnosed with HIV could bring with it a sexual liberation, and could result in a more lax attitude to using condoms. However this did not necessarily reflect a carefree attitude to sex as there was a notable degree of coquettishness or even shame in the narratives of the men, who often described their barebacking as a "bad" thing or something to be regretted.

> *"I think my attitude to unprotected sex has actually got worse since the diagnosis. It's also worse at times but I also switch between moods very easily, I've got it, doesn't matter now, other times, like I said, don't be ridiculous, so I don't know. That's bad because I consider myself quite educated on the subject but I considered myself educated on the subject before. And if I'm thinking these sort of things then people who don't know as much about it and aren't as aware, are really going to get screwed over."*
>
> **White British, age <25, single, <3 months since diagnosis, on ART**

Men who had actively sought HIV-positive partners since receiving their diagnosis, either on the internet or out and about in bars, clubs or saunas, reported an external social pressure to bareback now they were HIV positive. This could be hard to resist in different situations, especially where recreational drugs such as crystal methamphetamine were involved and senses were dampened.

> *"It goes back to the whole bare backing thing that I'm still now, I'm now really struggling to get to terms with because when you're negative and you say no I'm negative I only play safe people understand. But now that I'm positive, kind of people look at you weirdly if you say I only play safe. And it's like well you're positive, so yeah in the last few months I started playing not quite safe and look where it's got me so [a Hep C infection]"*
>
> **White British, age 31-35, single, 3-6 months since diagnosis, not on ART**

Amongst the men not so involved in the London gay scene, serosorting for HIV-positive partners was described as a very strange process. Having spent their adult lives avoiding HIV they would not have considered a positive partner prior to diagnosis because of the potential risk of contracting HIV. To go against these lifelong practices took some getting used to and also resulted in some guilt now the shoe was on the other foot.

"INT: I was going to ask has it changed your sex life since having the diagnosis?

RES: Oh yes, yeah definitely.

INT: Have you had any sexual partners since ... ?

RES: I have but that was, but that ... I knew they were HIV positive which was kind of ... which was a bit strange. But, yeah.

INT: Just out of interest, how did you meet them?

RES: So when I was at university I was, erm, I kind of did some training to kind of be in a, kind of like ... not a counsellor, that's the wrong word, but some kind of training to support other people that were in the college that I was in. And there were some people there that I have picked up, I was kind of like friends with who they'd ... we were kind of sort of advertised at the college for the people to come to talk to you if they had issues they needed to. And one of the things that somebody came to talk to me about was they had been diagnosed with HIV. So that was the first ... that same person was the first person that I spoke to on the day of the diagnosis and it was through him that I met other people that he knew and then ... Yeah.

INT: And so, you said it was weird, can you kind of expand on that a little bit?

RES: Well weird just because, err, erm, it's odd because it's not something that I would have done if I'd have been HIV negative…

Well because I would have made every precaution to avoid it. Like when I went to Ethiopia, I got all my own needles in case I ever need any operation. I did everything to avoid the risks of it, so I wouldn't have had sex with somebody who's HIV positive knowingly beforehand. Erm, knowing so much more about it now ... I did ... I was fairly informed six months ago but I know a lot more now because the amount of reading I have done. And kind of now understanding that the risks involved from somebody who is on medication and who does have undetectable viral loads and all the rest of it, I probably would have had a relationship with somebody who was. But, not have ... it's kind of a lot of education that I've had to have to be able ... to have thought that in hindsight."

White British, age <25, single, 3-6 months since diagnosis, not on ART

Men engaging in casual sex often strove to select seroconcordant partners and use condoms, but this was not always achievable. Serosorting was often acknowledged as particularly difficult

when recreational drugs were being used and in group sex scenarios. Two respondents who regularly engaged in group sex using crystal methamphetamine acknowledged the lack of control they experienced whilst high, and how they often could not remember what had happened after the event. The respondent below relates the importance of crystal meth to his enjoyment of group sex and in particular fisting, along with the hazards of not being totally in control. This incident occurred at a party after his HIV diagnosis and just prior to his diagnosis with Hepatitis C.

> *"I'm fully aware that they probably do make you take risks that you wouldn't normally take, you know, any risks that I took were, again, well yes, making you less aware of what's happening around you, so yeah like the time before, I remember just someone had been inside someone else and then he put his hand straight in me, and it was like oh, oh well, it's happened now I can't, there's no point in ... but kind of said make sure you wash your hands next time, but yeah it kind of it sort of dampens things down but it kind of maybe ... yeah it takes a few hours to get ready for fisting and then if you haven't got any drugs it kind of, it seems you spend more time getting ready than actually enjoying yourself which kind of then seems a bit wrong so the drugs are maybe drag the thing out and it's quite sociable and chatting and whatever"*
>
> **White British, age 31-35, single, 3-6 months since diagnosis, not on ART**

5.3 ART knowledge and expectations of when to start

Knowledge about ART was varied amongst the respondents but in general, men were relatively well informed about HIV and treatment. The most commonly cited sources of information about HIV and ART were their HIV clinicians, HIV-positive friends and partners/ex-partners, the internet and previous GUM clinic visits. After receiving their HIV diagnosis, a few men attended a newly diagnosed course which ran at the clinic and recommended the experience highly.

The internet was used prolifically for information gathering after diagnosis with Terrence Higgins Trust (THT) and NAM, in addition to HIV-positive and gay forums, being accessed to understand more about the course of HIV and people's experiences with ART. For some men though, seeking information on the internet was seen as a hazardous activity as it was difficult to avoid opinion pieces and sift out the "scare stories" from the real facts. HIV forums in particular divided the men, with some men using them profusely, and others just not being able to "identify" with the men who post on the forums.

When asking men to recall their expectations about starting ART when they were first diagnosed, a few respondents demonstrated a very low level of knowledge about HIV and the typical course of infection. Amongst these men, the delay to starting treatment after their HIV diagnosis was a big surprise. HIV was such a big deal to them that they could not fathom the idea that somebody diagnosed with HIV would do nothing after diagnosis for potentially a number of years. They assumed that they would be starting straight after diagnosis. As one man elaborated:

> *"I'm coming from a point of absolute ignorance, all I know about AIDS is how not to get it, I don't know anything about what happens now. I just assumed that the second you got diagnosed there would be this flurry of medical activity and you would end up on lots of tablets and I'd feel like shit for a few weeks and then things would go back to normal… But I didn't really, it didn't register, it never occurred to me that you wouldn't be starting treatment instantly anyway."*
>
> **White British man, age 31-35, single, interview <3 months of diagnosis**

At the opposite end of the spectrum, I interviewed men who were incredibly knowledgeable about HIV treatment and knew about some of the key clinical trials and research studies, for example SMART, START and VISCONTI (Virological and Immunological Studies in Controllers after Treatment Interruption), a cohort study of 14 seroconverters who maintained virological control for at least 24 months after stopping treatment initiated in PHI [214]. This knowledge was usually, though not always acquired after HIV diagnosis, through the leaflets that were given to the men upon diagnosis, websites such as NAM, the THT, and through discussions with their HIV clinician as well as other HIV-positive men. Men who were more knowledgeable on ART appeared to be more likely to be aware of the difference in national treatment guidelines between the US and UK.

An interesting finding from the interviews, was that a strong expectation to start ART shortly after diagnosis was observed in those who were at polar opposites on the treatment knowledge spectrum. Men who had very limited knowledge of HIV were as likely to report the expectation or desire to start immediately as those who demonstrated the fullest understanding of the potential benefits of early ART and differing treatment guidelines worldwide. Those less knowledgeable appeared to be willing to try it, so long as there were no

huge health risks, and those more knowledgeable tended to believe that there were health benefits associated with early ART initiation and this neutralised any risks of starting earlier.

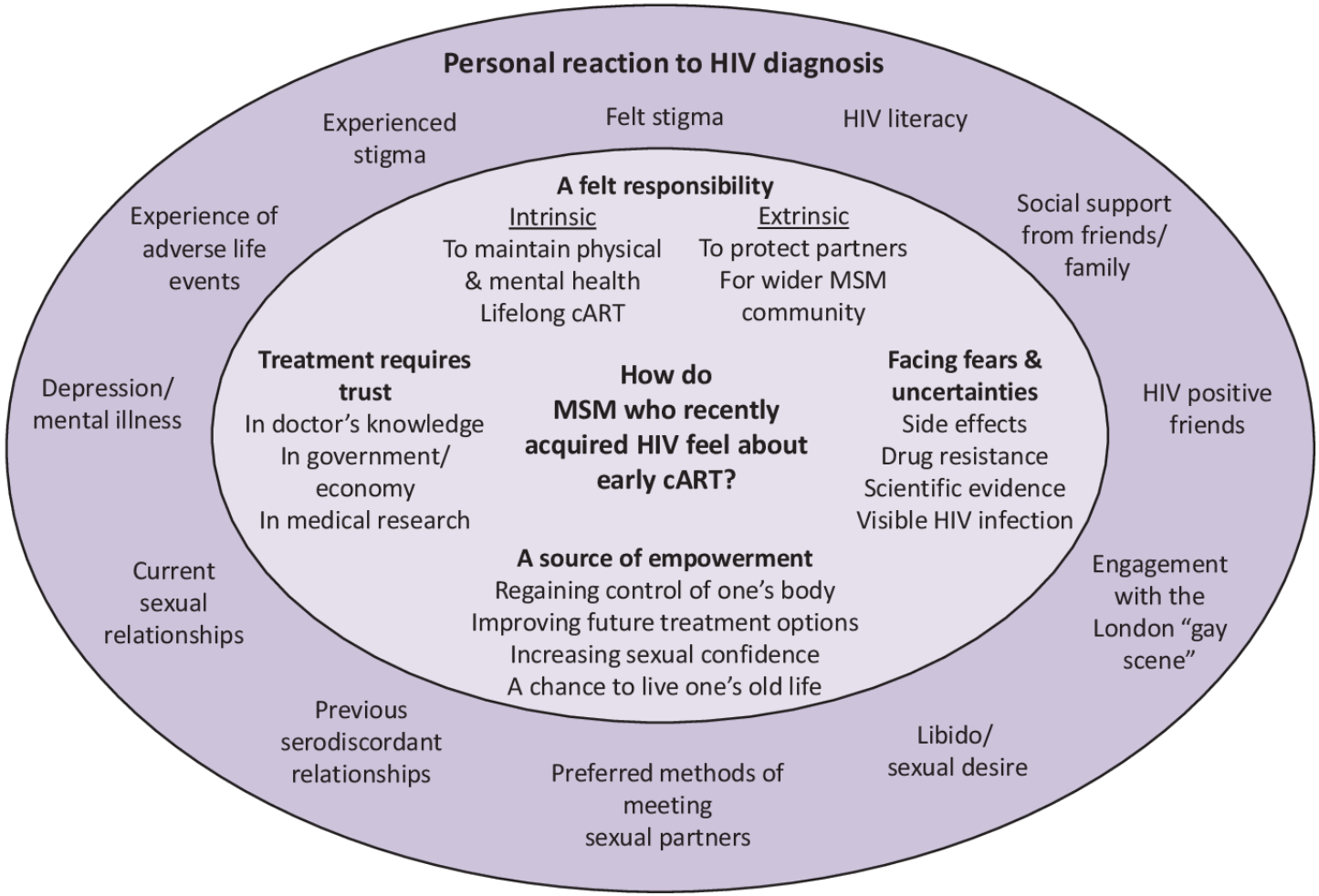
5.4 How do MSM with recent HIV infection feel about early ART?

As outlined in section 5.2 and 5.3, HIV diagnosis can be a highly emotional time for men with recent HIV infection, with their reaction to the diagnosis dependent on many personal and social factors. The experience of HIV diagnosis and the social and personal context it occurs in may partially dictate men's feelings towards ART. Thematic analysis of the transcripts to answer the research question "How do MSM with recent HIV infection feel about early ART?" revealed four overarching themes:

- Treatment as a responsibility
- Treatment as a source of fear and uncertainty
- Treatment as an empowering force
- Trust before treatment.

These four themes encapsulate the men's underlying attitudes, beliefs, assumptions and knowledge about HIV and treatment. Figure 5.1 is a diagrammatic representation of how men's feelings towards early ART sit within the broader landscape of their personal reaction to HIV diagnosis. A multitude of personal, social and environmental factors influenced men's reaction and adjustment to their HIV diagnosis and are presented in the outer circle of figure 5.1. These factors in turn also held influence over how men felt about early ART, as explained in the identified in the next section.

Figure 5.1 Conceptual diagram of MSM's feelings towards early ART in the context of factors which influence their personal reaction to being diagnosed with recent HV infection



5.4.1 ART as a responsibility

The decision to start ART was perceived by men to come with a great deal of responsibility. This responsibility could be further categorised into both internal responsibility (a personal responsibility to themselves and their own health) and external responsibility (a responsibility to partners).

5.4.1.1 The internal responsibility to protect one's health

Health was often presented by the men as a holistic concept, with going to the gym, exercising, giving up smoking, eating healthily, sleeping more, not "partying" too hard and not taking so many recreational drugs were all mentioned as things that should be done to improve individual health alongside HIV treatment. Men spoke of a responsibility to look after their own health, with starting HIV treatment at the right time an integral part of this concept.

Respondents could be generally categorized into those who believed treatment was to be initiated when CD4 count dropped to 350 or when the doctor tells them that they need to start, and those men who saw starting treatment as their own decision to make. Early treatment did not necessarily feature in a health context as a positive thing. Some men mentioned their concerns about the side effects of treatment and worries about resistance in the long term having a potentially negative impact on their health. In these cases, men leaned towards putting off treatment until such time as they felt they needed it or, were told they needed to start by their doctor.

Amongst the men, there was a feeling of responsibility to maintain good mental health as well as physical health. The avoidance of the additional stress and worry of transmitting to sexual partners, if undetectable on treatment, was perceived as a big advantage to starting treatment early. However, starting treatment very soon after diagnosis could add another source of stress whilst men were already not in a very good mental position whilst still assimilating the HIV-positive diagnosis.

> *"But I think, with HIV, there's two big hurdles: there's finding out that you've got it and then there's going on some tablets for the rest of your life. A big hurdle. And that's something I don't feel I'm ready for just yet… It would be too much of a – a head fuck, sorry… I couldn't think of a better word for it. I'm only one month diagnosed. I need to absorb that, become happy with that, before I can then, in my mind do the next*

hurdle which is medication. But if I had to, because of my health was terrible, I would do it right now."

White British, age 26-30, single, <3 months since diagnosis, not on ART

This reaction appeared to most affect men who had strong beliefs that side effects were inevitable, and seemed linked to their fears about ART.

"What a lot of people know about the treatment is what it was like maybe ten years ago. I mean, it was very sort of, you know, toxic, and that's what I imagined anyway. So I think that that would have been in my mind, that, "Oh God, that's it then." It would have brought it home much quicker and much … and also, the fact of having to take a tablet every day and kind of having those side-effects early on, when you're not in a very good mental position, I think wouldn't necessarily be positive if it's not absolutely necessary."

White British man, age 26-30, in relationship, 3-6months since diagnosis, not on ART

Taking personal responsibility for the decision of when to start ART was not universally embraced; some men perceived the decision when to start as their clinician's job and they would do whatever is recommended by them. Amongst the men interviewed, this total deference to medical expertise appeared to have two underlying explanations. Firstly, the clinicians were seen by some men to be the ultimate experts with many years training and expertise in HIV. This perceived wealth of knowledge and understanding held by the clinician was enough for men to accept the clinician's advice, sometimes with little input from themselves. Secondly, a total deferral to medical opinion could also reflect a personal indecisiveness about whether early ART was a good or bad idea. The men below recount their desires to avoid uncertainty and to be told by the clinician when to start, instead of being asked their opinion.

"I would have followed medical advice, so in a way I wouldn't have wanted to be asked if I want to, it's more we recommend that you do or we recommend that you wait until then, so yeah. I don't want the uncertainty in a way, there is that grey area that's not understood yet…

But in a way I don't want to have to make that decision myself, I want to be told what's the best thing to do and I don't ... well that's the thing the science doesn't know exactly, erm. So that, that's ... basically I want to do the best thing but the science isn't sure, and some of the tests have been misleading because of the cross sections they've used to come up

with the results. So it's hard for me to make my mind up if I want to start or not or if it matters when I start."

White British, aged 21-25, single, 3-6 months since diagnosis

Maintaining quality of life was mentioned by most men as the ideal end goal in the decision as to when to start treatment. This was commonly framed as a compromise between starting treatment sooner rather than later to give their health the best chance, and avoiding the medication as long as possible to avoid the possible side effects. Men placed great emphasis on being able to enjoy life to the full now, with what will happen in the 20-40 years' time something very "abstract" to them.

"I don't really think long-term so I'm not sure. Erm, I just think about now so I want a better life now. I'm not too bothered about living until I'm 70, so. You know, I don't even know if I want to but, erm I just don't ... I want to have a good life in the now, not ... you know. And I still want to be healthy, I want to be healthy."

White African, age 31-35, single, 3-6 months since diagnosis, on ART

Taking tablets every day for the rest of their life could be a huge responsibility in itself, and put some men off starting early. Age seemed to be an important factor here, with younger men in particular struggling with the responsibility of committing to something so long term. The older men, on the other hand, appeared more able to deal with this, possibly because were likely to be on other medication by this point in their lives. As one man put it, he was already taking daily tablet for blood pressure so it is not such a problem to take one for HIV at the same time.

5.4.1.2 External responsibility

There was much discussion around the responsibility to protect sexual partners from the virus and how early HIV treatment could be used to this end. Protecting partners, like health, was largely presented as a holistic theme, with TasP was just one of many strategies discussed by the men. Men largely understood and believed the reduction of transmission risk afforded by TasP, however, a diverse range of opinions were offered over the personal responsibility to protect partners.

Two motivations for using ART to reduce transmission risk appeared in the data. The first was based on the concept of altruism. Men reported situations in which they might feel a

"sense of duty" to protect their partners from HIV, though this was mainly framed in the context of long term HIV negative partners. For these men, the potential personal health sacrifices of starting early could be offset by the desire to protect their long term partner from all the stress, worry and lifestyle changes that they were experiencing.

> *"I knew that once you're undetectable it's very, well I don't know this, but I have been told that it's very unlikely that you'll pass it on, and still seeing [name of HIV negative long term partner] I thought that was the least I could do, to reduce the risk for him."*
>
> **White European, aged 31-35, single, 3-6 months since diagnosis, on ART**

> *"I know a friend that started because he was seeing someone who was negative and he did that, and I suppose that would be a point on an altruistic but on a very visible scale because that's the person you love and you're with"*
>
> **White British, aged 31-35, single, 3-6 months since diagnosis, not on ART**

But using treatment to reduce transmission to others was not always presented as an entirely altruistic ideal. One individual neatly expressed two intrinsic benefits to starting ART to reduce transmission: namely avoiding the guilt of transmission, and increasing sexual confidence.

> *"I don't think it is entirely an altruistic reason. I mean, it's like, you do want to protect the person that you're with, and whatever. And also, like, if I were to pass it on to someone else I would feel guilty and, you know, that would be … And also, just knowing that the chances of, even if there was, you know, an accident, or whatever, that it wouldn't, that the chances would still be very low of you passing it on. I think that would just, like, make me feel more kind of confident about having sex, and things like that. And, you know, reassuring other people as well… that there's, you know, not much risk"*
>
> **White British, aged 26-30, in relationship, 3-6 months since diagnosis, not on ART**

The responsibility to protect sexual partners was not universally felt, particularly in men who were still angry about contracting HIV. These men tended to feel that "it takes two to tango" and that HIV negative partners should take equal responsibility to protect themselves from HIV. When asked whether he would consider starting treatment early

purely to reduce the chances of transmission, if there were no proven health benefits to himself, one respondent answered:

> *"It's hard, it's a very ... God you could have a debate about and ... Because I would say well no one did it for me and you know whatever at the time same point I was trying to play safe and so I managed to get it and so yeah I suppose catch me on the right day"*
>
> **White British, aged 31-35, single, 3-6 months since diagnosis, not on ART**

When discussing TasP use in the wider MSM population, many men held strong beliefs that reducing the population viral load could create a "healthier society" and was as a good idea.

> *"I know that they offer the treatment once you get to a certain point on your CD4 count which is 350 below ... erm and they are thinking about to do from 500 below because of the fact that if the people get an undetectable virus then obviously there's less chance for them to pass to other people, so if everybody gets undetected virus on their body, so ... it would much, much, it would be a way it's putting the virus to other people and it would be a much healthier society actually which I think is quite a good idea, because if everybody is undetectable so why erm if you keep on having sex because I've seen loads of people having unprotected sex, they don't care."*
>
> **Latin American, aged >41, single, <3 months since diagnosis, not on ART**

However, whilst public health benefits of TasP were acknowledged, the perceived personal sacrifice of experiencing side effects and long term toxicities could put men off until such a time as it was needed for their own personal health.

> *"I know there some talk of moving up to 500 which in my opinion then makes me wonder whether it's actually treating the population rather than necessarily treating the individual because obviously then that's good to stop infecting other people which I can understand, but from a purely selfish point of view, the side effects, there will always be some side effects and I think they're getting better all the time and they're saying the cardiovascular side effects, so from a selfish point of view I would rather stay off treatment as long as I can, but then I'm not scared of, you know when I need it, I obviously need it."*
>
> **White British, aged 31-35, single, 3-6 months since diagnosis, not on ART**

Whilst TasP was seen as a great option, it was not always perceived as a reason to give up having protected sex. For some men, any risk of transmitting, no matter how small, placed too much worry or stress on them so men talked of the necessity of continued condom use in conjunction with TasP.

> *"I know of stories about people that have had unprotected sex, you know, a negative person having unprotected sex with a positive person who's undetectable, and thinking that that's okay. I do know that the chances are much more reduced. I think that that is true. I wouldn't personally want to do that because… I've said to my friend, "I would hate for someone to say that I've given this to them." I don't ever want to be that person. Because I know, as a, although I don't hate the person that I'm pretty sure gave it to me, he will always be in my head, I will always remember him. And I don't want to be that person in someone else's mind. I'm quite a genuine, honest person and I don't, I couldn't cope with that myself."*
>
> **White British, age 26-30, single, <3 months since diagnosis, not on ART**

Interestingly a few men felt a responsibility to help others who find themselves in their situation in the future by engaging in HIV treatment research, be it interviews like this or clinical trials. The feeling that they were benefitting from those who had engaged in the past made men feel like part of a community, and it was their duty to do the same for the next generation.

> *"I understand that the only way that so much is known now about it is because people have gone through trials of different kinds, and stuff like that. So, I think, I do feel like I'm part of, I don't know, a community I suppose and, like, whatever. So I think, in order to increase knowledge about it as well."*
>
> **White British, aged 26-30, in relationship, 3-6 months since diagnosis, not on ART**

> *"I've told myself, as soon as I found out about this, that I want to help as much as I can. Hence, why I'm here now. I will take an hour out of my week, every week, to do something like this if someone wants me to, because it really is important to me, you know. I want to help people and I want to get as much understanding of this as possible. So I understand the value of research."*
>
> **White British, aged 26-30, single, <3months since diagnosis, not on ART**

5.4.2 ART as a source of fear and uncertainty

Receiving an HIV diagnosis was a very stressful time for the men interviewed, with many emotions to deal with and uncertainties to face as outlined in section 5.3. These newly diagnosed men experienced many worries over the unknown entities in the weeks following diagnosis, with a multitude of questions arising about what to expect in the future and how HIV would affect their quality of life. The prospect of starting ART brought with it an additional set of unknowns and uncertainties in the form of fear of side effects and toxicities, drug resistance, treatment duration, uncertainty of scientific evidence and ART as a marker for attracting HIV stigma.

5.4.2.1 Fear of side effects

Concerns over the potential side effects of ART were universally mentioned by participants as a source of worry and potential barrier to initiation. Side effects – as described by the respondents - fell into those experienced in the short term when they start taking therapy (for example diarrhoea, vomiting, night sweats, dizziness) and long term side effects (cardiovascular, liver related, neurological) commonly referred to in medical literature as toxicities. Interestingly, long term side effects brought with them their own set of uncertainties as they were perceived to be less well researched, so more of an unknown entity.

> *"Yeah. I mean, I still, one thing that I still don't feel I is fully been answered but, is sort of what the long-term effects of the treatment are. And I mean, I don't know if that's because it's not completely known, because these treatments haven't been, you know, used for that long, I mean, relatively. So I think I'd want to know a bit more about that before I decided. Because obviously, once I start, that's it then, you have to keep taking them. So yeah, I'd want to know a bit more about that, effects on my liver and so on, and whatever."*
>
> **White British, aged 26-30, in relationship, 3-6 months since diagnosis, not on ART**

Whilst most men appreciated that they were in no way guaranteed to experience side effects, this did not detract from the fear of them. For some men the fear of side effects was based on previous experiences with PEP, for others it came from the experiences of HIV-positive friends or partners. Interestingly, the men's views of ART were often acknowledged by themselves as being "old fashioned" or based on outdated information, but despite this acknowledgement the fear remained.

"My view on treatment was a little bit old-fashioned, I think, because of my experience ten years ago. My ex used to take, I would guess at around 20 big tablets a day, that he used to take twice a day, and they used to make him ill and give him diarrhoea and no appetite. And they used to make you lose weight and kind of you have that stereotypical image of, you know, looking really gaunt. And it was … so that was, I was a bit scared about treatment. Even my ex I had five years ago, the treatment he was on was better, but still he had to take a few tablets and it'd make him a bit ill, sometimes."

White British, aged 26-30, single, <3months since diagnosis, not on ART

Though side effects featured heavily in the discourse around barriers to starting ART, it was not always the acute illness brought on by side effects that were the source of the fear. Some of the lesser side effects like drowsiness and inability to concentrate particularly concerned individuals, especially from a work perspective. This was very apparent in jobs where the safety and security of members of the public were at risk from symptoms of drowsiness.

Whilst side effects were universally talked about, some men held a very pragmatic opinion of when to start ART. The benefit of ART on quality of life could be worth the risk of side effects, if the time was right to start. Though it came down to personal opinion as to whether that time was right so soon after diagnosis.

5.4.2.2 Drug resistance

Another fear that emerged from the interviews was drug resistance, though notably fewer men mentioned it. Uncertainty arose around whether choosing to start ART earlier would restrict drug choices in the future. The idea of drug resistance was acknowledged by respondents as complex and somewhat confusing, however. It was interesting to hear the way one man understood the balance between resistance and time on ART, as he explains below.

"I don't know to a certain extent there are advantages of taking the medicine very early but I think there are certain things because then your body gets used to it and then you have to take another medicine and then your body gets used to it again and then it takes another one and then how long will you keep taking different medicine, so perhaps the longer you leave then you take it, the longer your expectancy for your life and things go on, because there is medicines available, I don't know."

Latin American, aged 41+, single, <3months since diagnosis, not on ART

The short-course treatment approach to PHI appeared to cause some confusion amongst several of the men as they were under the impression that treatment was for life. Stopping ART after a short-course of a year or so of treatment was perceived to increase the risk of drug resistance and these men could not understand why anyone would want to do that.

5.4.2.3 Permanence of treatment

The permanence of treatment could be a scary prospect, for younger men in particular, with the thought of having to do something for the rest of their life deemed "abstract". One man, who picked up his first tablets on the day of the interview, likened his feelings towards starting ART for life to the horror he felt when he had dermatitis as a child.

> *"I remember as a kid I had eczema and um, uh, sorry not eczema, dermatitis in my hair. And I was given this solution to put in and I remember like at the age of 12 going to bed and thinking. Oh my god am I going to be putting this solution in my hair when I'm 65. Oh my god. Uh, within a few months it had gone and I stopped the treatment. Um, so yeah, I imagine when I take that tablet tonight, I'm going to be like, okay this is every day now for … the … for the rest of my life."*
>
> **White British, aged 31-35, single, >6 months since diagnosis, not on ART**

Amongst the men aged over 35, this appeared to be less of a problem as it was likely that they would be put on some other permanent medication for something else at some point soon anyway.

> *"I said to, to my ex, when he started taking treatment, I said, 'Well okay, erm, most … not most people, an awful lot of people when you get to forty or beyond are having some sort of tablet for something'. Blood pressure or, you know, they've got inhaler or they're got this, that and the rest of it, so, you know, picking up a pill off the table in the morning is, is not that drastic is it really, you know, everybody does it really at some stage or another so erm, as long as … as long as the result of that is that you're fit and well then I don't see any point in dwelling on what the pill's actually there for too much"*
>
> **White British, aged 36-40, single, <3 months since diagnosis, not on ART**

Short-course treatment was perceived by some men as a more acceptable way to start ART, as the tangible end date, whether 3 or 12 months in the future, was easier to get to grips

with than the unknown entity of life-long treatment. One man even thought that he would most likely stay on ART if he started short-course therapy.

5.4.2.4 Treatment as a marker of HIV positivity

As discussed in section 5.3, men commonly felt stigmatised for being HIV positive and were very selective about who they disclosed their status to in order to avoid unwanted social situations. Face to face disclosure of positive status was typically undertaken by men on a case-by-case basis, in a pragmatic and controlled way. One negative aspect of starting ART, was that men would have to carry it with them and that this would physically mark them out as being different, possibly resulting in attention and unwanted questions. It was particularly notable amongst men who travelled with work or who worked unusual hours.

> *"Well it was funny actually because um, today, I picked up. I've picked up the tablets. And when she handed them to me I was like oh, okay. They're in that sort … they're in that little container. I don't know what I was expecting. I don't know because it was 4 weeks I was being given. I didn't know whether I was expecting a big box. Because I was going okay, oh god, you know. Um, you know in a few weekends' time, I'm going to Poland for three days. And funny enough that was in the back of my head and also I want to go to New York. For a … for a week, I've got a friend that lives there. And now being on treatment. It's like okay so if I'm going through security. Would the security guard sort of like say okay, you know, what's this. And if my … if a work colleague is next to me, am I going to have to justify what it is."*
>
> **White British, aged 31-35, single, >6 months since diagnosis, not on ART**

> *"I was thinking how am I going to do if I have to take my medication now, how am I going to do in terms of taking that medication if it, would I ... especially with the time difference at work and I know that, and would I take in front of the people, would I go to toilet quickly and take the medication, because I don't want people to ask questions"*
>
> **Latin American, aged 41+, single, <3months since diagnosis, not on ART**

This was not just a problem for travelling but also could be influences by living arrangements, as one man explained that he was so grateful he owned his own house so that if he started he would not have to hide medication from housemates.

> *"I'm so blessed and I thank to God and touch wood that I have a property and I wouldn't have a problem with medication in there instead of being sharing with someone who doesn't know my background and I think I*

have to keep hiding medications and doctors prescriptions and you know, because very unfortunately we still live in this world that people do sort of have a discrimination but yes, I don't have any problem."

Latin American, aged 36-40, single, 3-6 months post diagnosis, not on ART

5.4.2.5 Uncertainty in scientific evidence

The uncertainty in the scientific and medical community around whether there were individual health benefits in starting ART earlier was a source of consternation for some men trying to decide whether early treatment was for them. The evidence base supporting early treatment was often described as "unclear" or as a "grey area". On one hand, this was an important factor for some men, who reported a need for good evidence that starting early was better for their health to override the recommendation to delay starting until CD4≤350 cells/mm^3.

"When I know I need it because my CD4 is plummeting and I'm becoming ill or whatever, like that then yes I'll happily start, then prior to that I would have to be shown some very convincing argument to make me"

White British, age 31-35, single, 3-6 months since diagnosis, not on ART

"So if the doctor tells me I need to, or if there was good evidence of starting early was better, then I would."

White British, aged 26-30, single, <3months since diagnosis, not on ART

For other men scientific uncertainty surrounding health benefits of early treatment was not such a big problem, with the evidence from cohort studies and the hope of a cure and being able to stop the drugs in the future enough to consider early ART.

"Erm, I suppose I just do have a hope that there would be something within my lifetime that would mean that I would be able to stop at some point and there would be possibly a cure."

White British, aged 21-25, single, 3-6 months since diagnosis, not on ART

Near the end of the in-depth interview study, the VISCONTI (Virological and Immunological Studies in CONtrollers after Treatment Interruption) study reported findings of post-treatment control amongst 14 seroconverters in France who initiated ART soon after

infection for an average of 3 years. These results were widely reported by the national media, and appeared to influence men's decision to start early in two cases.

> *"Mainly because this Visconti trial [sic] was, a huge thing, erm, so 14 patients out of 70 odd, I'd say you know to maintain viral expression [sic]. Erm, there was a tiny little bit of time pressure there because you had to start within ... if I was going to start it needed to be in those few weeks, otherwise, you know there was no evidence in starting after that. Erm that was mainly it and the hope that in a few years I'd be able to come off them, or try to coming off them and see what happened."*
>
> **White British, aged 21-25, single, <3 months since diagnosis, on ART**

5.4.3 ART as a source of empowerment

HIV treatment was perceived as an empowering force by some respondents, which was an important olive branch at a time which was characterized by a loss of control over their life. Treatment was a way of regaining control of their body after losing control to the virus, improving sexual confidence, a chance to live their old life and a way to futureproof themselves.

5.4.3.1 Regaining control of one's body

Men talked about a period of feeling out of control of their body when they first found out they are HIV positive. Some men even visualised the virus invading their cells whilst another referred to HIV as being like "gremlins". Early treatment was a way of restoring some control on the situation by "fighting" this tangible image of HIV.

> *"And also I'm from [European country] originally, when you're ill you get a pill, you take antibiotics for everything, I still have that mindset, it was like a control thing, I wanted to control it straight away I did not want to wait for two years to 5 years and hopefully it would go down and need to be told at some point you need to start taking it. I wanted to get the virus down straightaway I wanted to attack it, I had this fear that the longer I waited the more my cells would be penetrated, I know it's probably not how it happens it but that's how I visualised it."*
>
> **White European, aged 31-35, single, 3-6 months since diagnosis, on ART**

Early treatment was also perceived as a way of being pro-active by not letting the virus dominate them and make them more ill. This pro-activity helped men feel more in control

and contributed to a more positive mental state. Men believed ART would prevent further illness and help them regain control of their own body again.

As described in section 5.3 above, feelings of powerlessness, self-blame and loss of self-esteem were commonly felt at diagnosis. Sitting back and doing nothing for potentially years was seen by some men as compounding these feelings. The ability to control the situation using treatment assisted with combatting feelings of helplessness and was perceived as a conscious step towards restricting the damage to their immune system, keeping options open and "future proofing" themselves by keeping the virus in check form a very early time point.

5.4.3.2 Increasing sexual confidence

Starting treatment was, for some, a way of increasing sexual confidence lost after diagnosis as outlined in section 5.3. Being "infectious" was associated with feelings of "grubbiness" and being "dirty", but treatment was a possible way to help reduce this stigma. The label of being "infectious" could be downgraded or removed totally if they were on treatment with undetectable viral load which reduced the worry of transmission to partners and the risk of criminal prosecution. Men also mentioned the idea that being undetectable on treatment could facilitate status disclosure with sexual partners as they could say they were highly unlikely to transmit the virus even if something went wrong.

> *"And so glad I have now because as I say, the conversation you can have about it now, you're undetectable with risk of transmission and the chances of you transmitting are very, very low."*
>
> **White British, aged 21-25, single, <3 months since diagnosis, on ART**

Though not all men agreed that it was necessary to disclose HIV status to sexual partners and TasP could be perceived as a reason not to disclose to partners. Being undetectable on ART made them effectively uninfectious, which meant their risk of transmission was so negligible that it was not worth discussing. In this case, not disclosing was a potential way to reduce the chance of rejection by sexual partners based on HIV status, and avoid subjecting themselves to stigma.

> *"If the risks are miniscule… the one kind of part of my reading which did kind of help me a bit was knowing that if you have sex with somebody who has an undetectable viral load, there's less chance of you getting HIV, than somebody who believes they're negative… so knowing that the*

chances of me passing it on is less than just somebody who thinks they're negative. That makes it justifiable not to have to disclose it straight away…"

White British, aged 21-25, single, 3-6 months post diagnosis, not on ART

5.4.3.3 A chance to live their old life

Interestingly, there was a perception that HIV treatment could give them a lease of life that was lost after contracting HIV. Some men mentioned that they felt they could not live their desired lifestyle working and/or socialising as they used to and felt really drained. Going on treatment was a potential way to extend their energy and allow them to live the lifestyle they lived before contracting HIV. The respondent below describes his dwindling energy levels and an assumption that it was HIV that was doing this to his body.

"It was becoming really hard because I was just always tired, just exhausted the whole time and, erm I go to the gym every second day and you can sort of tell, you've just got no motivation to do it. You're forcing yourself and you're like ... you're doing weights that are like much lighter than before and you're doing less because you just don't have the energy. Erm, and I didn't ... I thought it must be the HIV doing that so I wanted to get rid of that to be honest. I'm feeling a lot healthier so. You know, I've got more energy in the evenings. So it's good that I'm on treatment I think."

White African, aged 31-35, single, 3-6 months since diagnosis, on ART

"Yeah, yeah he'd [respondents' HIV-positive partner] a really bad week, the week before last um, we'd actually … actually had a party … party at our house. Um and it was a dinner party and we ended up taking some drugs and then we kind of stayed up until uh, this was on Saturday night, stayed up until Sunday night. Just carrying on. But that week he really struggled and he was like oh, do you want … because … if he was going to feel like this then he wants to take … start taking the drugs[ART]… like sooner."

White African, aged 31-35, in relationship, 3-6 months since diagnosis, not on ART

5.4.3.4 Improving future treatment options

Early ART was also perceived as giving men more control of their future treatment options, at a time where much research was being conducted. This feeling was particularly evident in those who were hopeful of a future cure, be it functional (where HIV remains in the body

but is rendered uninfectious and does no damage) or sterilising (a complete eradication of HIV). Notably this sub-theme featured more heavily in the more recent interviews, and was perhaps related to media coverage of the VISCONTI study and talk of a functional cure at the time.

> *"I've got to remain hopeful and the idea of starting treatment early was that, erm I would be protecting myself and there's always research coming out saying if you start earlier, your chances are better, you know. And there was one that came out the other day, I think saying that if you've started early that they're the people who will be most likely to benefit from a functional cure."*
>
> **White British, aged 21-25, single, <3 months since diagnosis, on ART**

5.4.3.5 Loss of control

The prospect of starting ART led to a perception of a loss of control in some individuals, which provided a stark contrast to the proactive views outlined above. Common amongst those reporting feelings of disempowerment associated with ART initiation, were two sub-themes both very much linked to the fear/uncertainty theme described above in section 5.5.2. The first was the belief that by starting ART men would be handing over control of their body to the drugs themselves, with no knowledge as to what side effects, if any at all, would be experienced and how long they would last. The second was the concept that the physical presence of the tablets themselves, whether in a cupboard at home, or when men carried them on their person, was a visual indicator of being HIV positive, there for anybody to see. These men felt they currently had a fair amount of control over who knew about their status or not; they had disclosed only to select people, or in some cases, nobody at all. The decision to start ART required careful consideration of what would be the sacrifice of control over who knew about their status, as there was always a risk somebody (not necessarily a partner, but a family member or housemate) would see the tablets and find out they are HIV positive. As mentioned in the fear/uncertainty theme, the underlying factor common to fear of some side-effects and fear of people knowing men's HIV status was stigma.

5.4.4 Trust and ART

The theme of trust emerged many times over the course of the interviews, though was seldom mentioned explicitly. Starting ART involved placing trust in not just the clinical care providers, but in the economy and government and in science and research.

5.4.4.1 Trust in medical opinion

Respondents demonstrated an implicit trust in their HIV clinician's medical opinion as to the best time to start ART. This trust was often unequivocal, given that often the men had met the doctor only one or two times. It appeared that trust in the clinician could be granted by default through previous positive experiences with the GUM clinic in the same building.

> *"INT: If you were kind of asked at your first appointment, not when you were diagnosed, but your first [HIV clinic name] appointment, erm, how would you have felt about taking HIV treatment? What would your response have been?*
>
> *RES: … so after the diagnosis?*
>
> *INT: Yes, after the diagnosis*
>
> *RES: If they'd said to me, 'Do … we'd like you to start treatment now' how would I have felt about that?*
>
> *INT: Yeah.*
>
> *RES: I would've felt fine about that. Erm, because erm, like I say, I've been going there for quite a few years, erm, so I'm reasonably familiar with them and I absolutely trust their advice so if that was their advice then I would take it"*
>
> **White British, age 36-40, single, <3 months since diagnosis, not on ART**

Men talked about consulting with their doctors about whether they need to start ART and in some cases totally deferred the decision making to their clinician, who was perceived to be the "expert". Whilst some men displayed an implicit expectation that HIV clinicians would present all treatment options to their patients, it became apparent that not all of the respondents had received a discussion about the possibility of early treatment. From this perspective, the clinician was the "gatekeeper" of early treatment and, in some cases, their attitudes and beliefs precluded the discussion or offer or early treatment to patients.

Not all respondents followed medical advice without question, however. There were scenarios where the men's viewpoints differed from those of the healthcare provider team as to when to start ART, and this could lead to suspicions that providers were saying things to make men feel better about their diagnosis.

"I think it's interesting that when you get diagnosed and you come and see the health advisor they go oh it's the ... I don't know if they say it's the average or something is about 7 or 8 years and then virtually everyone I know seems to start within 2 or 3, so I wonder if that is what, you know maybe it's the 19 year old outliers that jack that average up and what is that, is that the mean, the median or the mode, who knows or ... you know but I wonder if they also do that just to lessen the blow of your diagnosis and make you think that it's going to be a while so you don't need to worry about it yet and life is going to be normal for now."

White British, aged 31-35, single, 3-6 months since diagnosis, not on ART

Two of the respondents made a personal decision very early after infection, and without consulting their clinician, that they would like to start early treatment. Both were very well informed about UK and international treatment guidelines and current research. It was clear they both expected some resistance to their request for early treatment, as they perceived it to be against the BHIVA guidelines [although it was not] and that the clinician would adhere to the guidelines. Their expectations manifested in different ways, resulting in very different feelings going into their first consultations. One assumed he would have to fight to be allowed to start, but would not have taken no for an answer.

"And I thought I was going to be up for a battle I thought they wouldn't let me but then the doctor was actually quite, well if that's what you wanted, you can do, but she didn't actively advise me to do it… I was 100% confident that I was going to start straight away, if the doctors here wouldn't have let me I would have found one who would have."

White European, aged 31-35, single, 3-6 months since diagnosis, on ART

The other man professed to feeling very "awkward" about asking for treatment early. This was not helped in the consultation itself by the doctor apparently being quite dismissive of it.

"Okay, so ... but then I'd spoken to [doctor's name] and he was, not negative about the idea of starting treatment but he was quite like dismissive of it. He's trained in Epidemiology as well. So the numbers aren't good enough to show, not either way, it's just like START [sic] trial, that didn't really show anything unless you were on it for 96 weeks and then only a small reduction in the reservoir and better HIV immune response. And he was just like, erm, I'm not sure, it's a big decision to go

on treatment, I've got guys who ... the last thing they want to do is be on treatment, they beg not to be on treatment."

White British, aged 21-25, single, <3 months since diagnosis, on ART

In this second scenario, the patient ended up rethinking after this initial consultation and deciding against early treatment, only to be advised by the same doctor on his next appointment that he now believed the patient should start early and recommended him to do so. This case demonstrated how instrumental the clinician's underlying attitude to early treatment can be in decision to start, particularly in patients who may be nervous about asking for treatment as they think it is an out of the ordinary request.

5.4.4.2 Trust in the government and economy

Questions were raised by some participants over the long term free provision of ART in such an economically and politically uncertain environment. A lack of trust in the current government led to feelings that NHS budget cuts may extend to ART in the future and a fear of not being able to personally afford treatment costs.

"I read somewhere about the different points at which people in different countries start treatment. And that in America it's kind of, it's recently changed to 500, in Britain it's 350. So I mean, it seems like … and then I just think, you know, "Well, why is that?" you know, "Is it for sort of, is it because of money constraints, like it's expensive to start treatment early?" In which case, it's, I don't know, like, feeling a slight feeling of suspicion towards the motives of, like, you know, the Government or the NHS, or whatever."

White British, aged 26-30, in relationship, 3-6 months since diagnosis, not on ART

Interestingly, one man considered starting ART sooner for this reason, as he would then be on it for life and thought the NHS could not then cut his supply as this would be damaging to his health.

"You know, but that's the other thing that I've been a bit concerned about, because the government is getting worse, because the government cuts, the UK cuts, who knows that in a few years' time, they're going to say that okay all the people who are on the treatment now, they can carry on having treatment, but the people who have not

been treated so far, they have to pay for the medication and you can't afford to do that."

Latin American, aged 41+, single, <3months since diagnosis, not on ART

5.4.4.3 Trust in scientific research and medicine

Trust in science and medicine was an important underlying factor in the decision to start early. On the whole men held a lot of faith in medical research, and were excited about future treatment developments. Research reported in the mainstream media was very influential, with many men relaying evidence for a future cure for HIV from newspaper articles they had read or documentaries aired on television.

Conflicting evidence from different research studies focusing on early treatment published over the interview period provided some consternation in men who were heavily engaged with treatment literature. In particular, the stark differences between the US "test and treat" approach and BHIVA treatment guidelines caused confusion and suspicion. The idea that two panels of experts could review the same evidence base and come up with different conclusions was troubling, possibly because of the tendency to believe medicine is based on hard facts and not opinion. Some men also reported a lack of trust in the safety of clinical trials for early treatment, as they had seen trials go wrong on the news, or heard about misreporting of results.

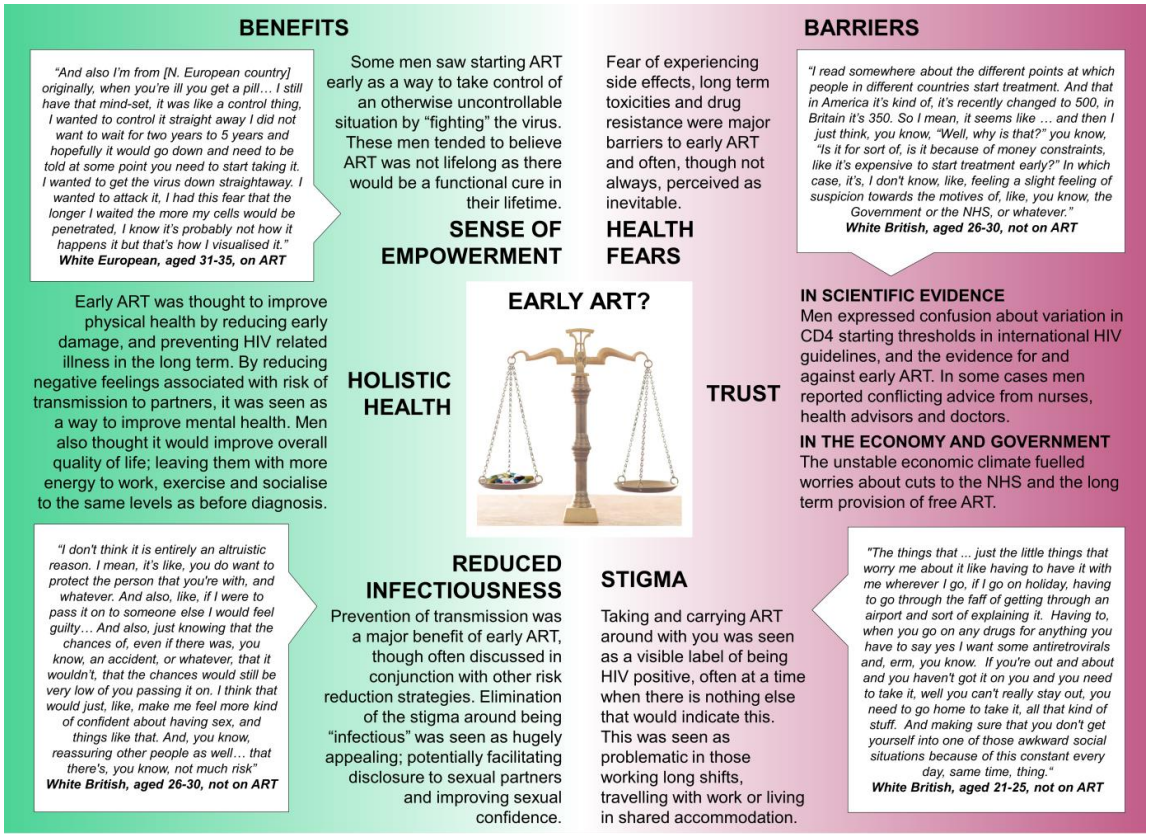
5.5 Summary discussion

5.5.1 Key findings

Using qualitative data from my in-depth interview study I have demonstrated that MSM with EHI view the decision to start ART early as a balancing act involving a trade-off between the perceived benefits of starting ART early and managing the fears and uncertainties surrounding its initiation (see figure 5.2). The potentially empowering effects of early treatment such as the reduction of infectiousness and its associated stigma, as well as perceptions of improved physical and mental health were pitted against the fears surrounding side effects, toxicity, drug resistance, increased visibility of HIV leading to stigma and economic and scientific uncertainty. The conundrum of early treatment is further complicated as it is posed within the emotionally charged backdrop of a recent HIV diagnosis, which for many of the men involved facing a great deal of uncertainty and a period of adjustment (see figure 5.1).

The decision to start early ART was perceived by men as part of a responsibility to maintain their own health and that of their partners. Seeking clinical advice from the doctor as well as gathering knowledge from several other sources, namely NAM, THT, mainstream media, newly diagnosed courses, patient representatives, HIV-positive forums and friends, was crucial to the decision making process for proactive men. Trust in the patient-doctor relationship was also crucial, and differences in opinion over the value of early ART could undermine this relationship. Men who totally deferred the decision to start to the clinician tended to do so as they were undecided on the merits of early treatment, or felt they could never match the knowledge levels and clinical expertise of their HIV physician.

Figure 5.2 Benefits and barriers to initiation of ART amongst MSM with early HIV infection attending an HIV clinic in central London



Some respondents entered a period of celibacy following their HIV diagnosis, reported to last from weeks to a planned "year of cleansing". Whilst initiation of ART exclusively to prevent transmission would be rendered useless amongst these individuals, an argument remains to initiate early to achieve undetectable viraemia and lessen the stigma of being "infectious" and associated feelings of "dirtiness". Men reported both felt and enacted stigma associated with being HIV positive in the interviews. Having an undetectable viral

load, could lessen the emotional burden of being infectious even if sex is not actively being sought at the time. Good sexual relationships are an integral part of a healthy lifestyle, and many of the men interviewed led very active sex lives prior to diagnosis. Achieving undetectability through TasP was perceived as a way to normalise meeting sexual partners again face-to-face, with less fear of rejection anticipated in this scenario. Notably, TasP was not trusted entirely to prevent transmission and was often talked about as a risk-reduction strategy in combination with continued condom use and serosorting for HIV-positive partners.

Early treatment could be an empowering force which could help immensely with the process of adjusting to life as an HIV-positive MSM by eliminating the stigma and worry of being infectious. For those who believed in a future cure, largely stoked by regular news reports in the mainstream media, the hope this would come in their lifetime, made it more appealing to start early. For these men ART was unlikely to be for life. In some cases starting ART soon after seroconversion was seen by men as a way to put themselves in the best position to benefit from a functional cure.

At the time of HIV diagnosis worry and uncertainty were rife amongst the men interviewed. Some men struggled to come to terms with HIV diagnosis, and were overwhelmed by the idea of initiating treatment straight away due to the myriad of other uncertainties it would bring. For these men, losing their quality of life through looking and feeling ill or not being able to perform at work were often regarded as unavoidable side effects of treatment and the reason to delay starting as long as possible. Subscribing to lifelong treatment was also a very difficult concept to deal with for younger men in particular. Short-course treatment could make early ART more appealing because of the tangible end date, with the option of then staying on ART if the much anticipated side effects were not experienced. However short-course treatment was believed to be hazardous by some men as they had read that starting ART after stopping is bad for your health.

5.5.2 Strengths and limitations

This study is the first to examine how MSM with EHI in the UK feel about early initiation of ART. Previous studies have assessed attitudes and beliefs in people living with HIV but not recent seroconverters. Whilst recent seroconverters currently only form a small subpopulation of HIV diagnoses a year, the current push for more regular testing, along with the routine application of RITA, will likely result increasing proportion of newly

diagnosed men being identified during EHI. The fact that seroconverters do not necessarily have the same "clinical need" for starting ART as those diagnosed later in infection may alter their way of thinking about ART so findings from interviews with men with chronic infection may not translate to seroconverters.

Using in-depth interviews allowed the men to describe, in their own words, their experiences and feelings about diagnosis and early ART in a neutral setting without judgement. The two-way process of the interviews allowed me to probe respondents further and develop explanations of some of the mechanisms underlying the observations. The purpose of the in-depth interviews are not to measure the number of men who hold a particular view, but to explore the depth and complexity of men's views on early treatment. From this perspective, this dataset was rich and varied covering a range of ethnicities and backgrounds.

5.5.2.1 Selection bias

There were however, some limitations to the study. As only one clinic was used to recruit patients, there was a risk of selection bias in the participants. Some HIV clinics have different ART policies, or may hold research interests in early treatment. The clinic used for this study did not hold research interest in early treatment, but men may select their HIV clinic by whether they are likely to have early treatment prescribed or not. If I had conducted the study at a pro-early treatment clinic I may well have recruited men with very different perspectives of early treatment, and this should be considered when interpreting the findings.

I experienced ongoing recruitment problems to this study, which were caused both by clinic logistics hampering the meeting of patients, and a reluctance to enrol in the study once men were invited to take part. The small study population, lack of engagement in the study from the clinic staff, complex eligibility criteria and the absence of a research nurse dedicated to the UK Register for a substantial proportion of the study period hampered my initial introduction to patients. Interestingly, a few of the health advisors thought it was inappropriate to invite any individuals who had been recently diagnosed to engage in research and refused to refer to the study based on their moral preference. To negate these problems, I met several times with the HIV nursing team and the health advisor team to discuss the study and to field any questions or concerns individuals had. However, even after contact had been made with an eligible patient to explain the study and I had invited

them to participate, the qualitative nature of the study deterred some men from participating. In contrast, of the men who agreed to be interviewed many professed it was an enjoyable experience and some even said they found it quite therapeutic talking about lots of things they felt they couldn't talk to anyone else about. Any differences between respondents and non-respondents in terms of social demographic factors, knowledge and or sexual behaviour will have led to bias in the views represented in these findings, and this should be considered as a study weakness.

To add to this, the result of the slow and erratic recruitment to this study was the failure to meet the age quota for this study. Whilst this means data from a narrower age range is represented here, I feel that the results are likely representative of the majority of MSM diagnosed with recent infection in the UK, whose median age is 33 years (IQR 27-40), as reported in section 4.2. I had also hoped to be able to develop typologies of seroconverters dependent on their attitudes to early treatment, but slow recruitment led to me curtailing the study to focus on other parts of the PhD and I did not have a sufficient number of interviews to fulfil this objective.

5.5.2.2 Information bias

As with any study researching sensitive subject matter, there is always a risk of respondents giving socially desirable answers. This study is no exception, and the effects of social desirability may well be exacerbated in the in-depth interview scenario as it involves talking face-to-face with the interviewer. On the whole I felt that there was good rapport between myself and the respondents. Nevertheless, there were moments of inconsistency in two of the men's narratives, which may reflect a censoring of information; however, the majority of men appeared happy to talk about their sexual behaviour in depth and provided consistent accounts.

Recall bias may also have been introduced by the study design. Men were asked to recount their feelings at the time of diagnosis, which may have been influenced by factors arising since diagnosis. In an ideal situation, a baseline interview would have been conducted at diagnosis followed by a follow-up interview 3-6 months later, however time and financial constraints made this approach impractical. The result was a large range in the time from diagnosis to interview, from 2 weeks after diagnosis up to 9 months post-diagnosis, and whilst this resulted in a wide range of perspectives, it also made direct comparisons between respondents difficult and enhanced the possibility of recall bias.

The crucial role of healthcare providers in the process of deciding to start treatment must also be acknowledged, with the HIV clinician the gatekeeper to accessing early ART in many cases. Their underlying attitudes and beliefs towards early ART are an implicit step in the decision making process as they dictate when, or whether, the patient is first offered early ART, and their personal opinion is often sought as to whether early therapy is a good idea. One limitation of this study is the one-sided nature of assessing the role of the clinician in the decision to start. A future qualitative study should be conducted to better understand clinician's perspectives on treatment in early infection, and the factors involved in the decision to offer or recommend early ART.

5.5.2.3 Representativeness

The slow and erratic recruitment to this study resulted in a long study period (2010-2013), which likely introduced issues with the representativeness of findings due to changes in the study context over time. HIV clinicians in the UK tend to use the BHIVA treatment guidelines to inform clinical practice which, over the study period, recommended ART on clinical grounds for patients who presented with a CD4 count ≤350cells/mm^3, an AIDS defining illness, or with evidence of primary HIV infection and neurological involvement. However, the degree to which clinicians' maintain an up-to-date knowledge of recent research findings published after the last set of guidelines varies, and a number of key studies focusing on early ART as TasP [215] or in primary infection [214,216] were published over the study period. Although the BHIVA guidelines recommending initiation at CD4≤350 cells/mm^3 remained unchanged over the study period, a position statement in response to the HPTN-052 was released by BHIVA in January 2013 [217]. This stated that there should be discussion between healthcare providers and all HIV-positive adults about the effect of ART on transmission, and that the possibility of starting ART to reduce transmission should be discussed with ART-naïve individuals who wish to start to reduce transmission.

The results from these studies and the subsequent guideline changes may have impacted on attitudes and beliefs towards early ART amongst clinicians, as well as patients. Certainly it was notable that prior to late 2012 none of the men interviewed had started ART, whereas in 2013 three out of the four men interviewed had started. A full discussion of how these studies and subsequent guideline changes affected attitudes towards ART can be found in the discussion, in chapter 7. Whilst I cannot be certain that the greater proportion of the men on ART interviewed in more recent years was directly due to these study results, it is a very plausible explanation. It would also serve to highlight the transient nature of

people's attitudes and beliefs, highlighting how they may change over time and with shifts in evidence.

5.5.2.4 Interviewer bias

Throughout the interview process I was aware of the fact that as a female, I was very different from the men being interviewed, and that this may have a bearing on the results of the qualitative study. In addition, there was a possible power imbalance as men recruited to the study were all known by me to be HIV positive and MSM, whereas as the researcher my HIV status and my sexuality was unknown to the participant. Whilst it is impossible to judge the effect of these factors on the data generated from the interviews, these personal characteristics at least were stable throughout the interview process, so were a constant potential source of bias.

More of an issue was the fact that five of the in-depth interviews were conducted whilst I was pregnant; three of which when I could no longer hide this fact. This was of particular concern to me as it was a very visible change to my personal characteristics which carried with it a host of social expectations. In the interviews I conducted before and after I was pregnant, some men discussed difficult encounters with their parents around coming out and disclosure of HIV status. I was concerned that during the interviews conducted when I was visibly pregnant, men may not be so honest about these situations or may be more concerned about upsetting or shocking me given my impending motherhood. It is difficult to know the exact effect of my pregnancy on the relationship between the respondents and myself in the interviews and impossible to account for It, but I feel it is important to acknowledge it.

Only one patient declined to have their interview audio recorded; he was in the legal profession and for reasons of confidentiality did not want to be on record talking about his sexual behaviour and his HIV status. For this individual I resorted to taking notes with pen and paper during the interview but I found this experience very difficult and felt that the extra concentration required to note-take detracted from that required to follow the topic guide and probe efficiently. As a result the interview felt stilted, shallow and did not flow as well as the other interviews.

Whilst I had no experience of conducting qualitative research prior to this study, I did attend several courses: namely "Conducting in-depth interviews", by the Social Research

Association; “Analysing Qualitative Data” and “Using Framework Analysis”, both run by the National Centre for Social Research (NatCen); and an NVivo course, run by UCL. On designing and conducting the study and analysis I liaised closely with my secondary supervisor and the study CI, Professor Graham Hart, who has many years of experience in conducting qualitative research and advised me throughout the research process. Despite this however, there was inevitably a period of learning on the job for me. My confidence as an interviewer, my ability to actively listen and to probe effectively developed markedly over the course of this qualitative study, and as a result the later interviews were significantly longer and contained much richer data.

Finally, the transcripts were only coded by me as there was no funding to employ somebody to double code. Whilst I employed the Framework approach in the qualitative analysis, which has been noted to be systematic and reproducible [190], it is possible that other individuals may have interpreted the men’s words and sentiments in a different manner to me. Whilst I strove for objectivity in all aspects of the research process, by documenting the themes and subthemes, and discussing the frameworks in detail with Prof. Hart, the lack of external validation of my transcript coding inevitably leaves the results open to any unintended subjectivity in my opinions.

5.6 Chapter summary

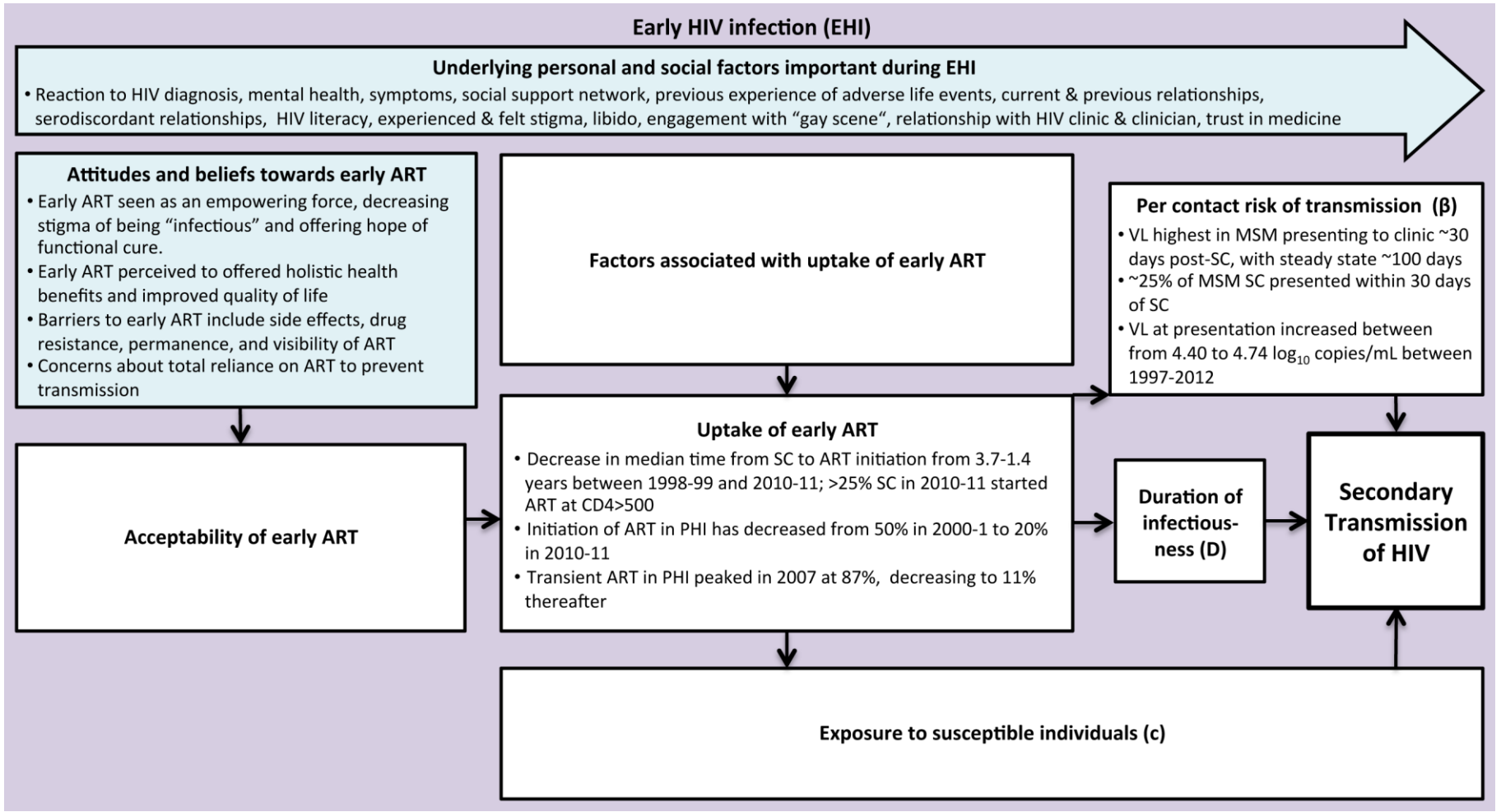
A summary of the findings of this chapter are presented in the conceptual framework in figure 5.3. In this chapter I have demonstrated that the decision to start early ART is highly personal and depends on a myriad of social and personal factors. It involves a complicated balancing act of assessing benefits and risks, presented at a highly emotional time in men’s lives in the aftermath of HIV diagnosis. The perceived benefits and barriers to treatment differ between individuals, depending on many social and personal factors which also influence how men cope with the HIV diagnosis itself.

Whilst the decision to start early ART can be perceived as a further burden at a time of already heightened stress, for some men the initiation of early treatment may assist with the coming to terms with HIV positivity through the removal or reduction of the stigmatizing label of being “infectious”. The mental relief of achieving undetectable viral load through early treatment, with the subsequent reduction/removal of the stigma of being “infectious”, was apparent in these men but has been largely overlooked in the literature as a reason to start early therapy. Early treatment can be perceived as a

normalising influence, allowing men to live life like they did before their HIV diagnosis, to meet partners as they used to and to increase sexual confidence at a time when self-esteem and self-confidence would normally be low.

Early treatment to prevent transmission was regarded as a welcome addition to the armoury of risk reduction strategies currently used by the men, which included abstinence, serosorting, and using condoms. Whilst TasP was seen as a great idea for public health, it was not regarded as a panacea; on a personal level not all men had enough confidence in TasP to abandon condom use altogether. In addition, many of the men interviewed reported a period of sexual abstinence following HIV diagnosis and depending on the prevalence and duration of this abstinence, early ART to prevent transmission may have less of an impact on onward transmission than predicted. However, amongst men who engaged in high-risk sexual activities after diagnosis, for example group sex, fisting and recreational drug use, there is a strong rationale to initiate early ART for TasP reasons due to the reported lack of control when engaging in these sexual practices.

Figure 5.3 Conceptual framework of the thesis including results from workstream 1, and phase A of workstream 2



6 Workstream 2 phase B results: Survey of sexual behaviour, attitudes, beliefs and acceptability to early ART amongst MSM with early HIV infection

In this chapter I present the results of the survey of sexual behaviour, attitudes, beliefs and acceptability to early ART, which was nested in the UK Register of HIV Seroconverters. The aim of this workstream was to estimate the prevalence of acceptability towards early ART as well as some of the attitudes and beliefs which arose from these in-depth interviews. The survey also sought to describe sexual behaviour over EHI, and assess risk factors for engaging in HIV transmission risk-behaviours after HIV diagnosis. The specific objectives were to:

- Describe the prevalence of the attitudes and beliefs to early ART identified in the in-depth interview study
- Estimate the proportion of MSM with EHI who regarded early ART as acceptable
- Examine the predominant reasons for early ART initiation amongst MSM who started ART in EHI
- Estimate proportion of MSM who initiated early ART, and examine what factors were associated with this
- Estimate the proportion of MSM who present a heightened HIV transmission-risk after HIV diagnosis and examine what factors are associated with this.

The full methods can be found in chapter 3, section 3.6, but as a brief reminder MSM were eligible for the survey if they were recruited to the UK Register (i.e. had laboratory evidence of recent seroconversion) and were aged ≥16 years. Participation involved one-off self-completion of a pen-and-paper questionnaire within 12 months of HIV diagnosis.

6.1 Eligibility, survey completion and non-response

This survey ran from July 2013 to December 2014 in 16 UK Register centres. Overall, 141 questionnaires were returned, of which 134 were successfully matched to a corresponding record in the UK Register database. Of these, 17 were ineligible: 2 had never had sex with another man and 15 completed the questionnaire >12 months after date of HIV diagnosis. Data from 117 respondents were included in this analysis. It was not possible to calculate a

survey response rate as despite staff recruiting at the centres being asked to keep count of the number of men refusing to participate, none actually did so. Instead it was possible to calculate the proportion of survey-eligible men recruited to the UK Register who were also recruited to the survey at participating centres. Table 6.1 illustrates the number of survey participants recruited from each centre, and the number of survey-eligible UK Register participants enrolled over the survey study period. The majority of men were recruited from 3 London HIV centres: 29.1% from St Mary's Hospital, 12.8% from Guy's and St Thomas', and 10.3% from Mortimer Market Centre. Overall, the proportion of all survey eligible men recruited to the UK Register who were recruited to the survey was 45.7%, though this varied substantially between centres. It is important to note however that this is likely to be a conservative estimate due to the way the survey was carried out in each centre; some men classified as "non-responders" in the above calculations may not have actually been invited to participate in the survey.

Comparisons were made between survey participants and those enrolled to the UK Register during the survey period but not participating in the survey. Overall, there were no observed differences in key demographic and clinical characteristics, see table 6.2.

Table 6.1 Proportion of UK Register recruits who were eligible and recruited to the survey sub-study by HIV centre: July 2013-December 2014

HIV Centre	No. of survey eligible MSM recruited to UK Register	No. of eligible MSM recruited to the survey	% UK register recruits completing the survey	% of survey recruits from each centre
London, Guy's & St. Thomas' Hospital	74	15	20.3	12.8
London, St. Mary's Hospital	70	34	48.6	29.1
Brighton, Brighton General Hospital	16	11	68.8	9.4
Liverpool, Royal Liverpool University Hospital	14	10	71.4	8.5
Manchester, Withington Hospital	14	5	35.7	4.3
London, Mortimer Market Centre	13	12	92.3	10.3
London, 56 Dean Street - Sexual Health Clinic	10	8	80.0	6.8
Birmingham, Selly Oak Hospital	10	6	60.0	5.1
London, Charing Cross Hospital	10	3	30.0	2.6
Bradford, St. Luke's Hospital	6	2	33.3	1.7
London, Homerton Hospital	5	5	100.0	4.3
Bristol, Southmead Hospital	5	2	40.0	1.7
London, Chelsea & Westminster Hospital	3	1	33.3	0.9
Sutton-in-Ashfield, King's Mill Centre	3	1	33.3	0.9
London, Kings College Hospital	2	1	50.0	0.9
Leeds, St. James University Hospital	1	1	100.0	0.9
Total	**256**	**117**	**45.7**	**100**

Table 6.2 Comparison of characteristics of survey respondents and MSM enrolled in the UK Register but not recruited to the survey

Variable		Not recruited to survey n	Not recruited to survey Median (IQR) or %	Survey respondent n	Survey respondent Median (IQR) or %	p-value[a]
Age at seroconversion (years)						
	Median (IQR)	165	33 (28, 41)	117	33 (28, 39)	0.206
HIV test interval (months)[b]						
	Median (IQR)	165	2.1 (0, 5.0)	117	2.7 (0, 5.5)	0.606
CD4 at seroconversion (cells/mm^3)						
	Median (IQR)	158	555 (428, 696)	112	518 (403, 667)	0.408[c]
Viral load at seroconversion (log_{10} copies/mL)						
	Median (IQR)	154	5.2 (4.6, 6.0)	112	4.8 (4.3, 5.8)	0.235
Ethnicity						
	White	134	81.2	98	83.8	0.581
	Non-white	31	18.8	19	16.2	
Seroconversion identification method						
	HIV Ab- then HIV Ab+ ≤12 months	103	62.4	82	70.1	0.540
	HIV Ab- and PCR+	34	20.6	17	14.5	
	RITA	26	15.8	17	14.5	
	Equivocal Ab then Ab+	2	1.2	1	0.9	

Cross-sectional survey study recruitment period July 2013-December 2014. IQR=interquartile range; Ab-=antibody negative; Ab+=antibody positive; PCR=polymerase chain reaction; RITA=recent infection testing algorithm. a=p-value obtained using t–test for continuous variables and chi2 for categorical variables; b=interval between HIV Ab negative and positive tests; c= t-test performed on square root CD4 to normalise distribution

6.2 Demographic and clinical characteristics of the respondents

Table 6.3 outlines the demographic and clinical characteristics of the 117 eligible survey respondents. They were mostly of white ethnicity (83.8%) with a median (IQR) age at seroconversion of 33 years (28, 39). The median year of seroconversion was 2013 (2013, 2014), the HIV test interval (the time between negative and positive antibody tests) was 81 days (0, 168) and 35.9% (42/117) had a HIV test interval of less than 30 days. The median time from diagnosis to questionnaire completion was 76 days (29, 191). Median CD4 count and log HIV viral load at seroconversion was 518 (403, 671) cells/mm^3 and 4.8 (4.3, 5.8) log_{10} copies/mL, respectively. Most were recruited from London HIV centres (67.5%; 79/117) and around half (51.3%; 60/117) were recruited from three UK centres known to have a research interest in primary HIV infection, namely: Brighton and Sussex University Hospital in Brighton, St Mary's Hospital and Guy's and St Thomas' Hospital, both in London.

Most respondents were in current employment (82.1%; 96/117), had three or more years of full-time education after the age of 16 (84.6%; 99/117), and nearly a third (32.5%; 38/117) were home owners. Most men self-identified as gay/homosexual 89.7% (105/117), though 9.4% (11/117) identified as bisexual and one man as heterosexual with an interest in transgender men. 52 men (44.8%) had a regular male partner at the time of questionnaire completion, and of these over half (51.9%; 30/52) reported their partner's HIV status as positive, 42.3% (22/52) as negative and 5.8% (3/52) did not know their partner's status.

The most common reasons given for seeking the last HIV test were that it was a routine test (41.0%; 48/117) or because they felt unwell (35.0%; 41/117). Over two thirds (68.4%; 80/117) of men reported being surprised by their HIV positive result, though 21.4% (25/117) were not. A notable proportion, 23.3% (27/116) of men reported previously taking PEP, with the median number of times 1 (IQR 1, 2; max 6).

Nearly two thirds of men (65.5%; 76/116) reported feeling unwell in the run up to their HIV diagnosis, with 38.8% (45/116) reporting that these symptoms affected their daily routine. The median (IQR) duration of symptoms was 14 days (7, 21), with the median duration of routine disruption being of 7 days (5, 14). The most commonly reported symptoms were fever (53.4%; 62/116), night sweats (50.0%; 58/116), body aches (40.5%; 47/116) and sore throat (36.2%; 42/116), see figure 6.1.

Table 6.3 Demographic and clinical characteristics of MSM seroconverters recruited to the survey

Variable	Level	n	Median (IQR) or %
Time from diagnosis to questionnaire completion (days)	Median(IQR)	117	76 (29, 191)
Year of seroconversion	Median(IQR)	117	2013 (2013, 2014)
Age at seroconversion (years)	Median(IQR)	117	33 (28, 39)
Ethnicity	White	98	83.8
	Non-white	19	16.2
HIV test interval (days)	Median(IQR)	117	81 (0, 168)
CD4 at seroconversion (cells/mm$^{3)}$	Median(IQR)	112	518 (403, 667)
HIV viral load at seroconversion (log_{10} copies/mL)	Median(IQR)	112	4.8 (4.3, 5.8)
Years of full time education >16 years of age	<3 years	18	15.4
	≥3 years	99	84.6
Currently employed	No	21	17.9
	Yes	96	82.1
Own or rent accommodation	Own outright	38	32.5
	Rent - private landlord	64	54.7
	Rent - council/HA/other	15	12.8
Current living arrangements	Alone	30	25.6
	Partner	31	26.5
	Friends/tenants/lodgers	43	36.8
	Family/guardians	13	11.1
Sexual orientation	Gay/homosexual	105	89.7
	Bisexual	11	9.4
	Other	1	0.9
Regular male partner	No	64	55.2
	Yes	52	44.8
HIV status of regular male partner	Negative	27	51.9
	Positive	22	42.3
	Don't know	3	5.8
Recruited from HIV centre with PHI interests	No	57	48.7
	Yes	60	51.3
Evidence of acute HIV infection	No	75	64.1
	Yes	42	35.9
Recruited from a London HIV centre	No	38	32.5
	Yes	79	67.5

Table 6.3 (continued)

Variable	Level	n	Median (IQR) or %
Reason for last HIV test	Routine test	48	41.0
	Condom failed	6	5.1
	UAI with HIV+ partner	7	6.0
	UAI with HIV unknown status partner	19	16.2
	UAI with HIV- partner	20	17.1
	Felt unwell	41	35.0
	GP/hospital recommend	10	8.5
Seroconversion symptoms experienced	No	40	34.5
	Yes	76	65.5
Number of days symptoms lasted	Median(IQR)	76	14 (7, 21)
Symptoms affected daily routine	No	26	33.8
	Yes	45	58.4
	Don't know	6	7.8
Number of days daily routine was disrupted	Median(IQR)	48	7 (5, 14)
Surprised at HIV positive result	No	25	21.4
	Yes	80	68.4
	Don't know	12	10.3
STI diagnosed at HIV diagnosis	No	64	55.7
	Yes	51	44.3

IQR=interquartile range; HIV test interval=time interval between HIV Ab negative and positive tests; HA=Housing Association; PHI=primary HIV infection; UAI=unprotected anal intercourse; STI=sexually transmitted infection

Of the 115 men who responded to the question, 44.3% (n=51) reported being diagnosed with an STI at the time of HIV diagnosis. Figure 6.2 illustrates the STIs diagnosed at the time of HIV diagnosis. The most prevalent STI was gonorrhoea which was reported by 28.7% of men (33/115), the second most common STI was chlamydia reported by 15.7% (18/115) men with the other STI's prevalence all under 10%.

Figure 6.1 Prevalence of reported HIV seroconversion symptoms

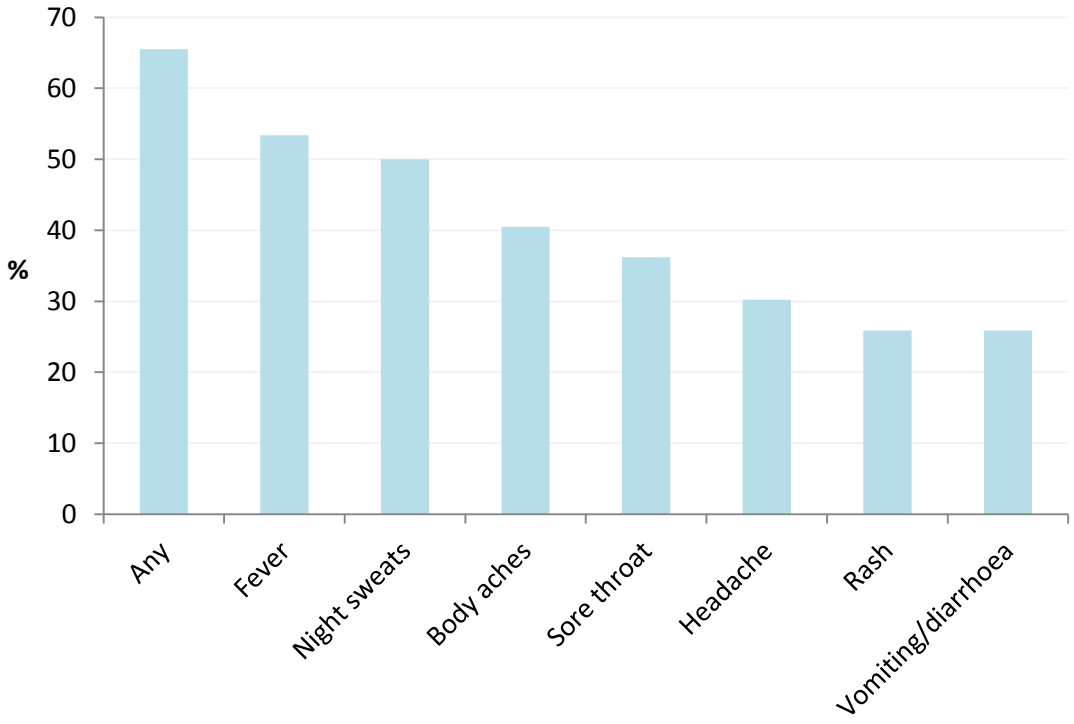
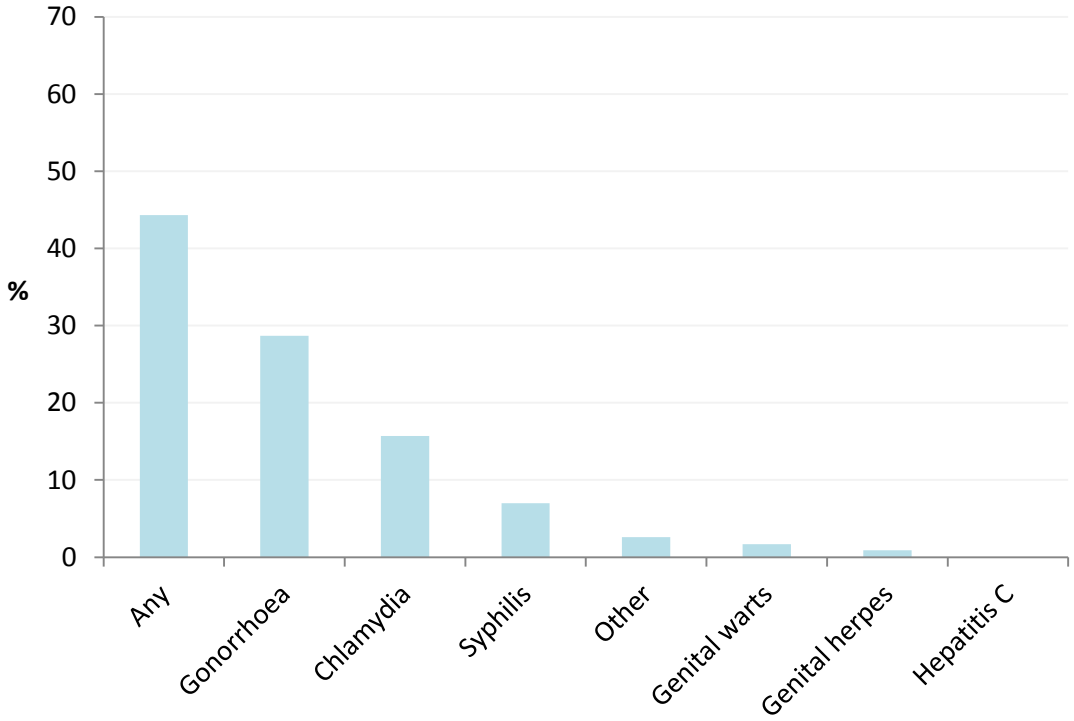


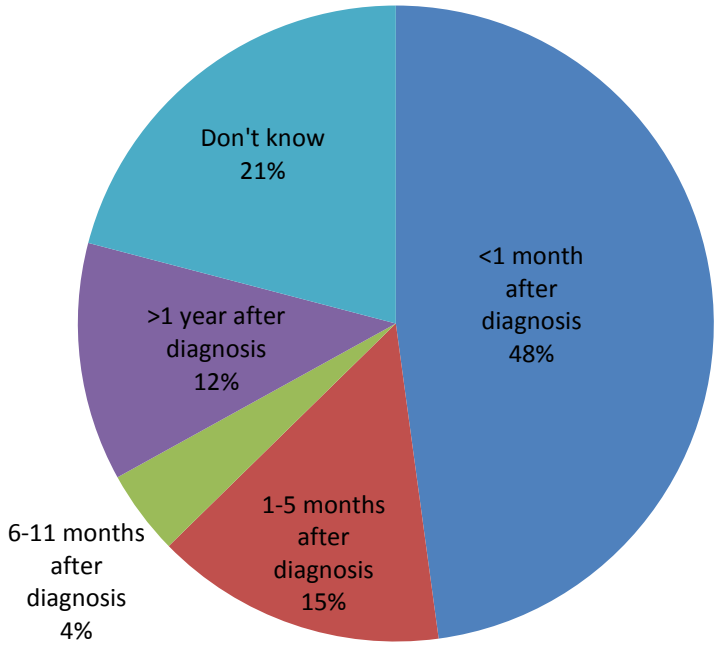
Figure 6.2 Prevalence of STI co-infections at time of HIV diagnosis



6.3 Acceptability, attitudes and uptake of ART

Early ART appeared to be acceptable to men at the point of diagnosis; when asked to think back to their HIV diagnosis, nearly half the men (47.8%; 55/115) reported that they had expected to start ART within 1 month of their HIV diagnosis, see figure 6.3. Furthermore, two thirds of men (66.7%; 76/114) stated they would have accepted ART at diagnosis if they had been offered it, with 24.6% (28/114) reporting they may have, and 8.8% (10/114) saying that they would not have accepted. Overall, 58.9% (63/107) of men reported their doctor had advised them to start ART and 47.4% (55/116) had initiated ART at the time of questionnaire completion.

Figure 6.3 When asked to think back to their HIV diagnosis, how soon after HIV diagnosis did MSM expect to start ART? (n=115)



6.3.1 Amongst ART-naïve MSM

Of the men who had not taken ART since their diagnosis, 74.6% (44/59) said they had considered starting ART since their HIV diagnosis and 46.7% (28/60) expected to start ART within the next month, see figure 6.4.

Figure 6.4 How long in the future, from the date of questionnaire completion, did ART-naïve MSM expect to start ART? (n=60)

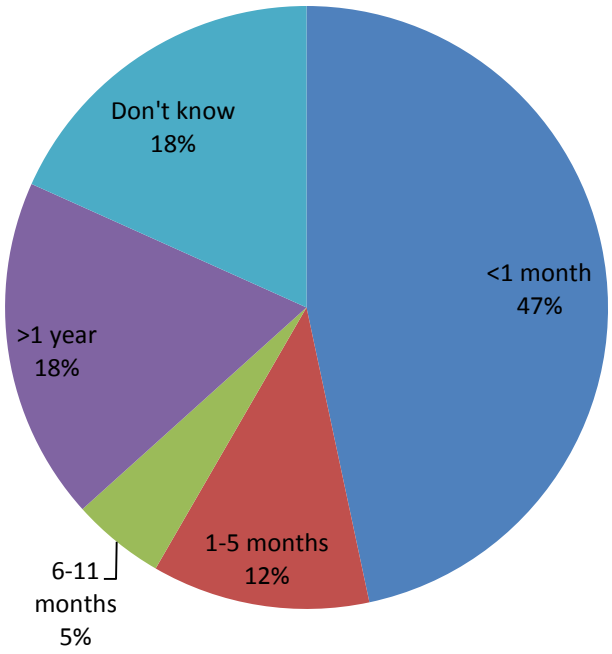
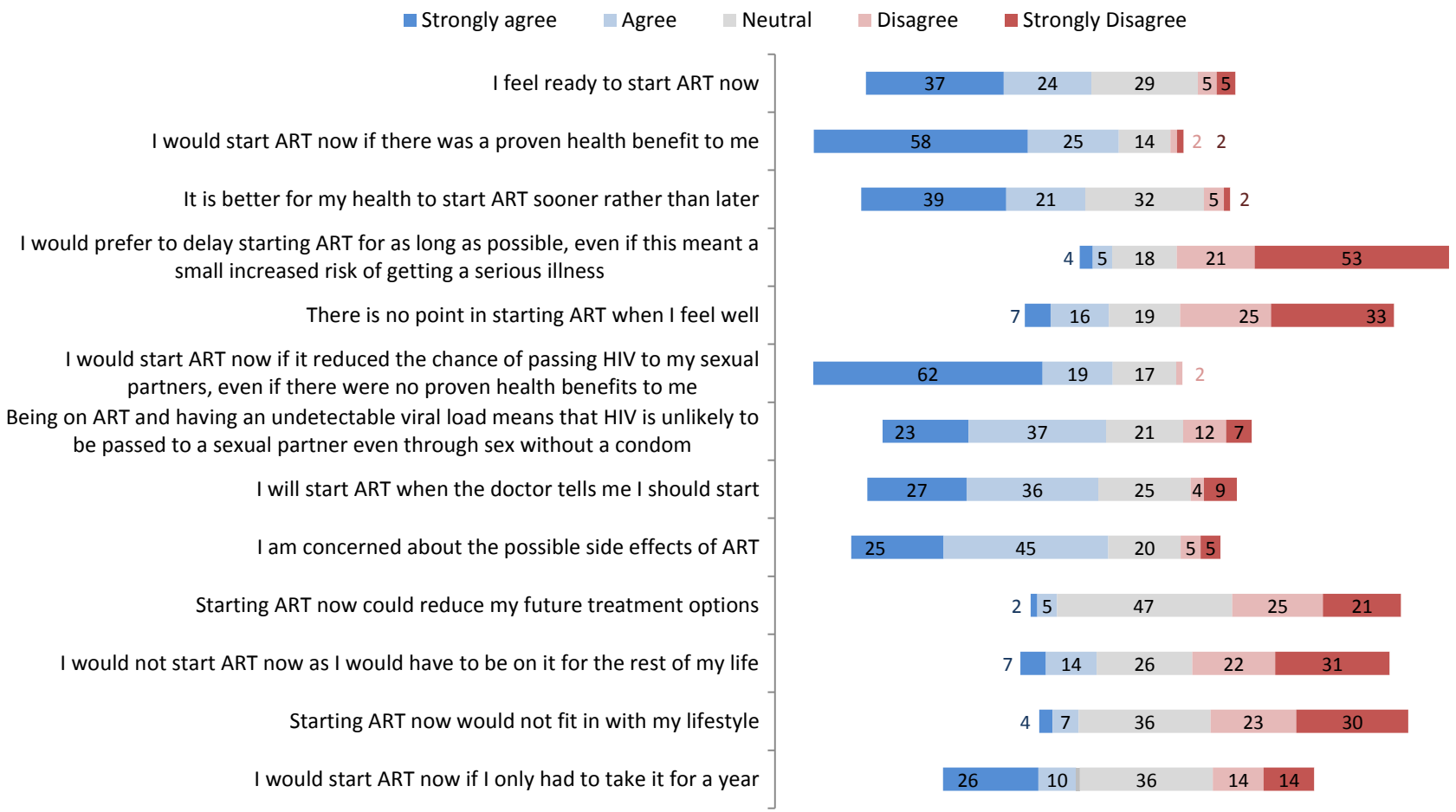


Figure 6.5 illustrates ART-naïve men's attitudes and beliefs towards ART. Overall, 61.0% (36/61) of ART-naïve men agreed with the statement "I am ready to start ART now", and 10.2% (6/59) disagreeing. 82.5% (47/57) agreed they "would start ART now if there was a proven health benefit to me", however there appeared to be some doubt about whether evidence of health benefit existed as 59.6% (34/57) agreed with the statement "It is better for my health to start ART earlier rather than later". Whilst the majority of men (73.7%; 42/57) did not agree with the statement "I would prefer to delay starting ART for as long as possible, even if this meant a small increased risk of getting a serious illness", 8.8% (5/57) did agree with the statement. Also of note were the 22.8% (13/57) who agreed with the statement "There was no point in starting ART when I feel well".

Figure 6.5 Attitudes and beliefs of ART-naïve MSM towards early ART (numbers denote percentages)



81.0% (47/58) of men agreed with the statement "I would start ART now if it reduced the chance of passing HIV to sexual partners, even if there were no proven health benefits to me". However fewer ART-naïve men (60.5%; 26/43) agreed with the statement "Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through sex without a condom". Ultimately, many men appeared to be guided by their doctors' advice on whether to start, with 62.5% (35/56) agreeing they would "start ART when the doctor tells me I should start" and 12.5**%** (7/56) disagreeing with the statement.

Side effects were a concern for many ART-naïve men with 69.6% (39/56) agreeing with the statement "I am concerned about the possible side effects of ART". Fewer men perceived drug resistance to be a problem, with 7% (4/57) agreeing with the statement "Starting ART now could reduce my future treatment options", though nearly half the men (47.4%, 27/57) neither agreed or disagreed, or did not know the answer to this statement. The permanence of treatment appeared to put a fifth of ART-naïve men off the idea of starting ART now; 20.7% (12/58) agreed with the statement "I would not start ART now because I would have to be on it for the rest of my life", and 10.7% (6/56) of men agreed with the statement "Starting ART now would not fit in with my lifestyle". Short-course ART did not seem appealing to respondents, with 36.8% (21/57) of men agreeing with the statement "I would start ART now if I only had to take it for a year".

6.3.2 Amongst men on ART

Of the 55 men who had started ART since their diagnosis, 94.5% (52/55) were still on ART at the time of questionnaire completion, see table 6.4. Whilst respondents were asked why they stopped ART, the 3 respondents not currently on ART did not give a reason for stopping. Most men (69.1%, 38/55) started ART within 1 month of their diagnosis and 94.5% (52/55) within 6 months. The majority (75.6%; 41/55) also self-reported starting when their CD4 count was >350 cells/mL: 29.1% (16/55) at CD4 351-500, and 45.5% (25/55) at CD4>500. The self-reported last viral load of men on ART was mostly "detectable" at >50 copies/mL (55.6% 30/54), whilst 31.5% (17/54) had an undetectable viral load and the rest were unsure.

Figure 6.6 illustrates the attitudes, beliefs and reasons for starting ART amongst men who had started early ART. The most common reasons to start ART appeared to be health-related: 96.3% (52/54) said they started "to control the spread of HIV in my body", and

96.3% (52/54) “to reduce the damage HIV was doing to my body”. In addition, 85.2% (46/54) started to “improve my quality of life” and “to increase my life expectancy”. Overall, 90.7% (49/54) of the men on ART agreed “It is better for my health to start ART earlier rather than later”.

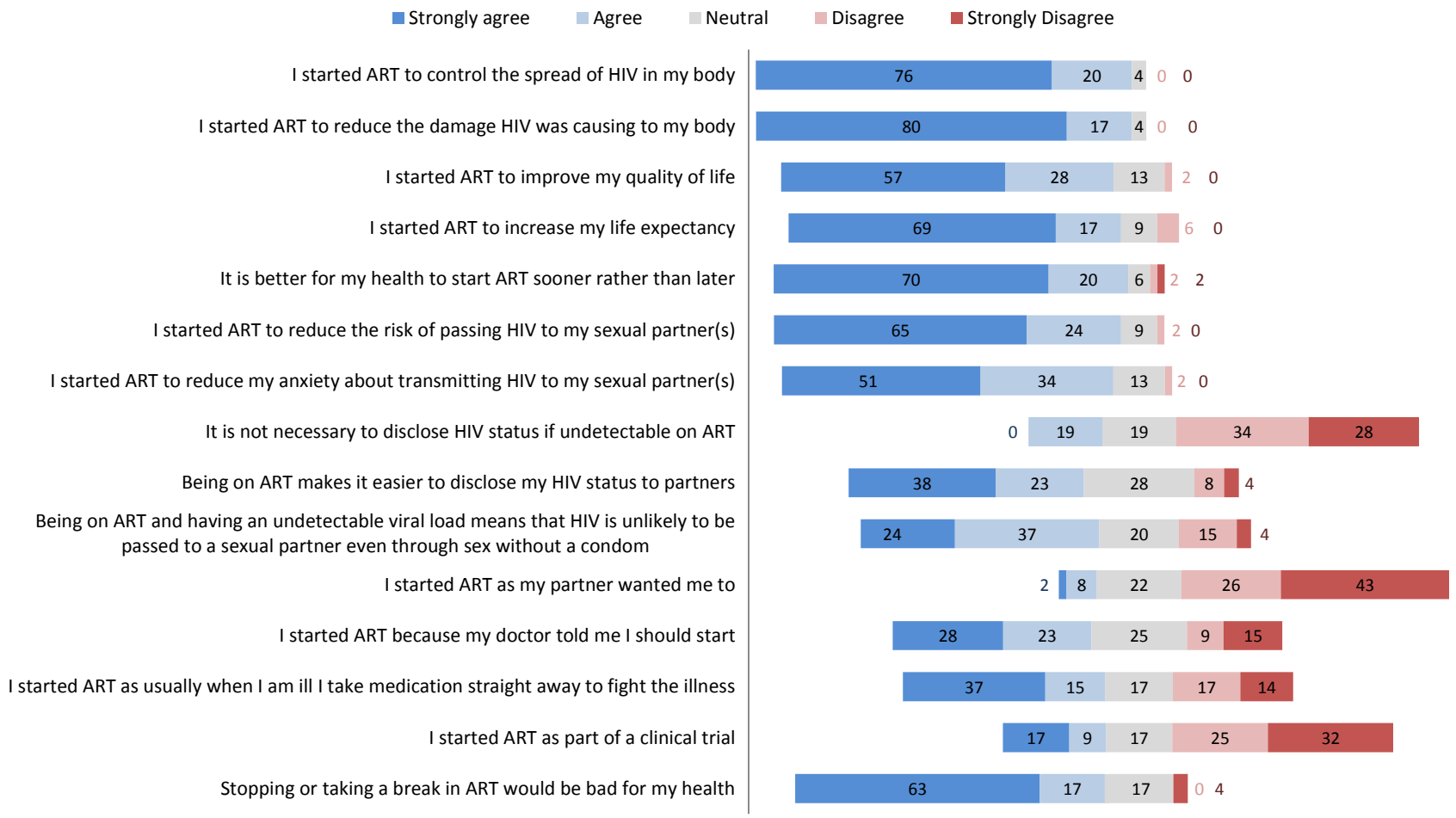
Protecting partners from HIV was also important though, with 88.9% (48/54) agreeing they “started ART to reduce the risk of passing HIV to my sexual partner(s)”, though this may not have been wholly altruistic as 84.9% agreed with the statement “I started ART to reduce my anxiety about transmitting HIV to my sexual partner(s)”. 60.4% (32/53) of men agreed “Being on ART makes it easier to disclose my HIV status to sexual partners”. Around 1 in 10 men (9.8%; 5/51) agreed with the statement “I started ART because my partner wanted me to”.

Just over half (50.9%, 27/53) started as their doctor advised them to, and a similar proportion (51.9%, 27/52) agreed with the statement “When I am ill I take medication straight away to fight the illness”. 26.4% (14/53) of the men started ART early as part of a clinical trial. Treatment interruption was seen negatively by most men; 79.6% (43/54) agreed with the statement “Stopping or having a break in ART will be bad for my health”.

Table 6.4 Attitudes to early ART and reasons for starting amongst MSM initiating ART in early HIV infection

Variable	Level	N	Percentage
How soon after diagnosis did you start ART?	<1 month	38	69.1
	≥1 & <6 months	14	25.5
	≥ 6months	3	5.5
Are you still on ART?	No	3	5.5
	Yes	52	94.5
What was your main reason for starting?	Only for own health	8	14.5
	Mostly own health, a little to prevent transmission	13	23.6
	Equal mix of both	29	52.7
	Mostly to reduce transmission, but little for own health	2	3.6
	Only to reduce transmission	2	3.6
	Don't know	1	1.8
Last CD4 before starting - self-reported	≤200	1	1.8
	201-350	6	10.9
	351-500	16	29.1
	>500	25	45.5
	Can't remember/don't know	7	12.7
Last viral load measure - self-reported	<50 copies/mL	17	31.5
	≥50 copies/mL	30	55.6
	Can't remember/don't know	7	13

Figure 6.6 Attitudes towards early ART and reasons for starting early amongst MSM who started early ART (numbers denote percentages)



6.4 Factors associated with early ART initiation in MSM with early HIV infection

6.4.1 Time-adjusted analysis

Time from HIV diagnosis to questionnaire completion was considered to be an a-priori confounder and all models were adjusted for this. In addition, year of HIV diagnosis, HIV test interval, age at HIV seroconversion, CD4 count at diagnosis, recruitment from a centre with PHI interests and doctor advising the patient to start were all identified as factors likely to be associated with early ART initiation based on results of the qualitative study and the literature, and so comprised the "base model".

Table 6.5 highlights that after adjusting for time from diagnosis to questionnaire completion, only the doctor advising initiation of ART was significantly associated with early ART uptake (OR 7.34; 95% CI 2.76, 19.50; p<0.001). There was also a tendency that men on ART had a lower CD4 count at HIV diagnosis, median 520 (IQR 411, 718) in those not on ART compared to 491 (390, 629) in those on ART, though this was not significant at the p<0.05 level in the regression model.

Table 6.6 illustrates the association between various clinical factors and early ART initiation after adjusting for time from HIV diagnosis to questionnaire completion. Though there was no significant difference in the reporting of one or more seroconversion symptoms between those who had and hard not started early ART, men who reported a rash in the months preceding HIV diagnosis were more likely to have started ART to those who had not experienced a rash (OR 2.49; 1.06, 6.02; p=0.043). Men who had taken PEP in the past had 3.15 times the odds of having started ART (95% CI 1.22, 8.09, p=0.017) compared to those who had not. Men who were diagnosed with another STI at the time of HIV diagnosis were less likely to have started ART (OR 0.28; 95% CI 0.13, 0.63; p=0.002); though when examining individual STIs only gonorrhoea co-infection was associated at the p<0.05 level (OR 0.29; 0.12, 0.71; p=0.007, data not shown).

The associations between sexual behaviours, both before and after HIV diagnosis, and early ART initiation (after adjusting for time from HIV diagnosis to questionnaire completion) are presented in table 6.7. None of the sexual behaviour risk factors were found to be associated with initiation of early ART, though there was a tendency that men on ART were less likely to report engaging in casual serodiscordant UAI before HIV diagnosis (OR 0.49; 95% CI 0.22, 1.11; p=0.086).

Table 6.5 Base model and demographic factors associated with early ART initiation, adjusting for time from diagnosis to questionnaire completion

		ART naïve		On ART					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
Time from diagnosis to survey completion	Per month	61	1.4 (0.7, 5.5)	55	3.7 (1.6, 8.0)	116	1.14	1.02, 1.27	0.019
Year first HIV positive	Per year	61	2013 (2013, 2014)	55	2013 (2013, 2014)	116	1.55	0.85, 2.83	0.156
HIV test interval[b]	Per month	61	2.8 (0, 5.9)	55	2.5 (0, 5.5)	116	0.95	0.83, 1.07	0.396
Age at HIV seroconversion	Per year	61	32.5 (27.3, 38.2)	55	33.4 (27.9, 41.3)	116	1.01	0.97, 1.06	0.55
CD4 count at diagnosis[c]	Cells/mm^3	58	520 (411, 718)	53	491 (390, 629)	111	0.92	0.84, 1.02	0.103
Recruited from an HIV centre with PHI interests	No	31	50.8	25	45.5	116	1	-	0.188
	Yes	30	49.2	30	54.5		1.71	0.77, 3.81	
Doctor advised starting ART	No	32	58.2	12	23.1	107	1	-	<0.001
	Yes	23	41.8	40	76.9		7.34	2.76, 19.50	
Ethnicity	White	49	80.3	48	87.3	116	1	-	0.331
	Non-white	12	19.7	7	12.7		0.6	0.21, 1.69	
Years full time education >16 years of age	<3 years	7	11.5	10	18.2	116	1	-	0.383
	3 years or more	54	88.5	45	81.8		0.62	0.21, 1.81	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; HIV test interval=time between HIV antibody negative and positive tests.

a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term; b=interval between HIV antibody negative and positive tests; c=modelled as square root transformed cells/mm3

Table 6.5 (continued)

Factor of interest	Level	ART naïve n	ART naïve Median (IQR) or %	On ART n	On ART Median (IQR) or %	N	OR[a]	95% CI	p-value
Currently employed	No	8	13.1	13	23.6	116	1	-	0.176
	Yes	53	86.9	42	76.4		0.5	0.19, 1.36	
Own or rent accommodation	Own	21	34.4	17	30.9	116	1	-	0.651
	Rent - private landlord	34	55.7	29	52.7		1.01	0.44, 2.31	
	Rent - other	6	9.8	9	16.4		1.71	0.50, 5.91	
Current living arrangements	Alone	18	29.5	11	20	116	1	-	0.562
	Partner	17	27.9	14	25.5		1.03	0.35, 3.03	
	Friends/tenants/lodgers	20	32.8	23	41.8		1.69	0.63, 4.52	
	Family/guardians	6	9.8	7	12.7		1.97	0.51, 7.59	
Sexual orientation	Gay/homosexual	54	88.5	50	90.9	115	1	-	0.842
	Bisexual	6	9.8	5	9.1		1.14	0.31, 4.14	
	Other	1	1.6	0	0		1.14	1.02, 1.27	
Current regular male partner	No	31	51.7	32	58.2	115	1	-	0.364
	Yes, HIV+	14	23.3	8	14.5		0.48	0.17, 1.36	
	Yes, HIV-/unknown status	15	25	15	27.3		0.99	0.40, 2.41	
Recruited from London HIV centre	No	16	26.2	21	38.2	116	1	-	0.453
	Yes	45	73.8	34	61.8		0.73	0.32, 1.67	

IQR=interquartile range; OR=odds ratio; CI=confidence interval

a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term; b=interval between HIV antibody negative and positive tests; c=modelled as square root transformed cells/mm3

Table 6.6 Association between clinical factors and early ART initiation, after adjusting for time from diagnosis to questionnaire completion

		ART naïve		On ART					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
Diagnosed in acute infection	No	37	60.7	37	67.3	116	1	-	0.840
	Yes	24	39.3	18	32.7		0.92	0.42, 2.04	
HIV viral load at diagnosis	Log_{10} copies per mL	57	4.85 (4.26, 5.83)	54	4.82 (4.30, 5.79)	111	1.12	0.81, 1.53	0.495
Experienced seroconversion symptoms	No	20	33.3	20	36.4	115	1	-	0.877
	Yes	40	66.7	35	63.6		0.94	0.43, 2.07	
Experienced rash at seroconversion	No	49	81.7	36	65.4	115	1	-	0.043
	Yes	11	18.3	19	34.6		2.49	1.06, 6.02	
Experienced headache at seroconversion	No	44	73.3	36	65.5	115	1	-	0.160
	Yes	16	26.7	19	34.6		1.83	0.79, 4.24	
Experienced sore throat at seroconversion	No	39	65.0	34	61.8	115	1	-	0.584
	Yes	21	35.0	21	38.2		1.24	0.57, 2.72	
Experienced fever at seroconversion	No	30	50.0	24	43.6	115	1	-	0.350
	Yes	30	50.0	31	56.4		1.44	0.67, 3.08	
Experienced body aches at seroconversion	No	39	65.0	30	54.5	115	1	-	0.197
	Yes	21	35.0	25	45.5		1.66	0.77, 3.60	

IQR=interquartile range; OR=odds ratio; CI=confidence interval

a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

Table 6.6 (continued)

Factor of interest	Level	ART naïve n	ART naïve Median (IQR) or %	On ART n	On ART Median (IQR) or %	N	OR[a]	95% CI	p-value
Experienced vomiting & diarrhoea at seroconversion	No	43	71.7	42	76.4	115	1	-	0.704
	Yes	17	28.3	13	23.6		0.85	0.36, 1.99	
Experienced night sweats at seroconversion	No	31	51.7	27	49.1	115	1	-	0.662
	Yes	29	48.3	28	50.9		1.18	0.56, 2.51	
Seroconversion symptoms affected daily routine	No	38	63.3	32	58.2	115	1	-	0.484
	Yes	22	36.7	23	41.8		1.32	0.61, 2.85	
STI co-infection at diagnosis	No	25	41.7	38	70.4	114	1	-	0.002
	Yes	35	58.3	16	29.6		0.28	0.13, 0.63	
Ever taken PEP	No	52	86.7	36	65.5		1	-	0.017
	Yes	8	13.3	19	34.5	115	3.15	1.22, 8.09	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; STI=sexually transmitted infection; PEP=post exposure prophylaxis

a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

Table 6.7 Association between behavioural and attitudinal factors and early ART initiation, adjusting for time from diagnosis to questionnaire completion

Factor of interest	Level	ART naïve		On ART		N	OR[a]	95% CI	p-value
		n	Median (IQR) or %	n	Median (IQR) or %				
Had AI pre-diagnosis	No	2	3.3	1	1.8	116	1	-	0.668
	Yes	59	96.7	54	98.2		1.73	0.14, 21.33	
Had casual AI pre-diagnosis	No	10	16.4	10	18.2	116	1	-	0.867
	Yes	51	83.6	45	81.8		0.92	0.34, 2.47	
Had UAI pre-diagnosis	No	9	15.0	9	16.7	114	1	-	0.514
	Yes	51	85.0	45	83.3		0.63	0.29, 1.35	
Had casual UAI pre-diagnosis	No	23	38.3	26	49.1	113	1	-	0.235
	Yes	37	61.7	27	50.9		0.63	0.28, 1.42	
Had SD UAI pre-diagnosis	No	18	31.0	21	38.9	112	1	-	0.268
	Yes	40	69.0	33	61.1		0.63	0.28, 1.42	
Had casual serodiscordant UAI pre-diagnosis	No	30	53.6	36	67.9	109	1	-	0.086
	Yes	26	46.4	17	32.1		0.49	0.22, 1.11	
ChemSex pre-diagnosis	No	31	53.5	27	50.9	111	1	-	0.824
	Yes	27	46.6	26	49.1		1.09	0.51, 2.34	
Met partners in a sex on premises venue pre-diagnosis	No	42	68.9	30	54.5	116	1	-	0.657
	Yes	19	31.1	25	45.5		1.19	0.56, 2.52	
Had AI post-diagnosis	No	26	42.6	15	27.3	116	1	-	0.545
	Yes	35	57.4	40	72.7		1.32	0.54, 3.26	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI=condomless anal intercourse; SD=serodiscordant

a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

Table 6.7 (continued)

Factor of interest	Level	ART naïve n	ART naïve Median (IQR) or %	On ART n	On ART Median (IQR) or %	N	OR[a]	95% CI	p-value
Had casual AI post-diagnosis	No	37	61.7	30	54.6	115	1	-	0.802
	Yes	23	38.3	25	45.5		0.90	0.39, 2.10	
Had UAI post-diagnosis	No	46	75.4	33	60.0	116	1	-	0.296
	Yes	15	24.6	22	40.0		1.53	0.67, 3.66	
Had casual UAI post-diagnosis	No	49	80.3	45	81.8	116	1	-	0.309
	Yes	12	19.7	10	18.2		0.60	0.22, 1.66	
Had serodiscordant UAI post-diagnosis	No	56	91.8	49	89.1	116	1	-	0.739
	Yes	5	8.2	6	10.9		0.80	0.20, 3.11	
Had casual serodiscordant UAI post-diagnosis	No	57	93.4	51	92.7	116	1	-	0.617
	Yes	4	6.6	4	7.3		0.68	0.14, 3.16	
ChemSex post diagnosis	No	41	70.7	32	61.5	110	1	-	0.645
	Yes	17	29.3	20	38.5		1.22	0.53, 2.80	
Expected to start ART within a month of diagnosis	No	33	55.0	26	48.2	114	1	-	0.210
	Yes	27	45.0	28	51.8		1.66	0.75, 3.64	
Would have taken ART at diagnosis if offered	No/unsure	31	51.7	6	11.3	113	1	-	<0.001
	Yes	29	48.3	47	88.7		15.6	4.61, 52.85	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI=condomless anal intercourse; SD=serodiscordant; a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

Table 6.7 (continued)

Factor of interest	Level	ART naïve n	ART naïve Median (IQR) or %	On ART n	On ART Median (IQR) or %	N	OR[a]	95% CI	p-value
"Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom"	Don't agree	17	39.5	21	38.9	97	1	-	0.849
	Agree	26	60.5	33	61.1		1.08	0.47, 2.51	
"It is not necessary to disclose your HIV status if you are on ART and have an undetectable viral load"	Don't agree	36	83.7	43	81.1	96	1	-	0.821
	Agree	7	16.3	10	18.9		1.13	0.38, 3.38	
"Better treatment means people are less worried about HIV"	Don't agree	22	51.2	22	40.7		1	-	0.135
	Agree	21	48.8	32	59.3	97	1.93	0.82, 4.56	
"It is better for my health to start ART earlier rather than later"	Don't agree	22	39.3	5	9.3		1	-	<0.001
	Agree	34	60.7	49	90.7	110	13.10	3.60, 47.3	
Disclosed HIV status to nobody	No	52	86.7	54	98.2		1	-	0.079
	Yes	8	13.3	1	1.8	115	0.15	0.02, 1.25	
Disclosed HIV status to GP	No	44	73.3	28	50.9		1	-	0.030
	Yes	16	26.7	27	49.1	115	2.41	1.09, 5.34	
Disclosed HIV status to a HIV positive friend	No	45	75.0	28	50.9			-	0.012
	Yes	15	25.0	27	49.1	115	2.81	1.26, 6.28	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

Table 6.7 (continued)

Factor of interest	Level	ART naïve n	ART naïve Median (IQR) or %	On ART n	On ART Median (IQR) or %	N	OR[a]	95% CI	p-value
Disclosed HIV status to a HIV negative friend	No	38	63.3	15	27.3			-	<0.001
	Yes	22	36.7	40	72.7	115	4.48	2.00, 10.06	
Disclosed HIV status to family	No	45	75.0	34	61.8			-	0.275
	Yes	15	25.0	21	38.2	115	1.58	0.69, 3.61	
Disclosed HIV status to work	No	52	86.7	44	80.0			-	0.391
	Yes	8	13.3	11	20.0	115	1.56	0.56, 4.31	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; a=OR adjusting for time from HIV diagnosis to survey completion modelled as a continuous term

There was a tendency that men who had disclosed their positive status to a friend were more likely to have initiated early ART (OR 2.18; 95% CI 1.26, 6.28; p=0.066); be it an HIV-positive friend (OR 2.81; 95% CI 1.26, 6.28; p=0.012) or an HIV negative friend (OR 4.48; 95% CI 2.00, 10.06; p<0.001). They were also more likely to disclose their HIV positive status to their GP (OR 2.41; 95% CI 1.09, 5.34; p=0.03).

Men who stated they would have accepted ART at diagnosis if they had been offered were much more likely to have started early ART (OR 7.57; 95% CI 1.49, 38.40; p<0.001) than those that would not have or were unsure. Of the attitude statements, starting ART early was associated with agreement with the statement "It is better for my health to start ART earlier rather than later"; those who agreed were more likely to have started ART (OR 13.05; 95% CI 3.60, 47.27; p<0.001).

6.4.2 Multivariate analysis

Factors found to be associated with initiation of early ART in the time from diagnosis to survey completion adjusted model at p<0.20 were considered for multivariate analysis and grouped into a hierarchical conceptual framework outlined in table 6.8. Time from diagnosis to questionnaire completion was considered an a-priori confounder and adjusted for in all analyses. Year of HIV diagnosis, CD4 at seroconversion, the patient's doctor advising to start ART and being recruited from a centre with PHI interests have all been noted to be associated with uptake of early ART in previous research so comprised the base model. All other factors were grouped into clinical/seroconversion factors, attitudes and beliefs, and behavioural factors and modelled in the next stage within their respective groups.

Table 6.9 indicates that after adjusting for all of the base model variables, time from diagnosis to questionnaire completion was highly associated with early ART initiation with a 1.4 increase in the odds of starting early per 1 month increase in time elapse since HIV diagnosis. Men whose doctors had advised early ART were more likely to have initiated ART, with the odds of starting early nearly 6 times higher than those whose doctors did not (aOR 5.98; 95% CI 2.14, 16.68; p=0.001). There was no evidence of any interactions between any of the base model variables.

Table 6.8 Conceptual hierarchical framework for multivariate modelling of factors associated with early ART

Model level	Variables included
A-priori confounders	Time from diagnosis to survey completion
Base model	Year first HIV positive CD4 count at diagnosis[a] Recruited from an HIV centre with PHI interests Dr advised starting ART
Socio-demographic factors	Currently employed
Clinical/seroconversion factors	Seroconversion symptoms – rash Seroconversion symptoms – headache Seroconversion symptoms – body aches STI co-infection at HIV diagnosis Ever taken PEP
Attitudes and beliefs	Would have accepted ART at diagnosis if offered "It is better for my health to start ART earlier rather than later" "Better HIV treatment means that people are less worried about catching HIV"
Behavioural factors	Had casual serodiscordant UAI in 6 months before HIV diagnosis Disclosed status to nobody[b] Disclosed status to GP Disclosed status to HIV+ friend Disclosed status to HIV- friend

Note: all factors included in the table were associated at the p<0.2 level in univariate time-adjusted analysis

a=square-root transformed cells/mm^3

b=whilst this independent variable was associated in the time from HIV diagnosis to questionnaire completion adjusted analysis, small numbers meant it was not possible to include it in multivariate analysis

Table 6.9 Association between base model variables and early ART initiation, after adjusting for all other variables in the table (N=103)

Variable	Level	aOR[a]	95% CI	p-value
Time from HIV diagnosis to survey completion	Per 1 month increase	1.40	1.16, 1.70	<0.001
Year diagnosed HIV positive	Per 1 year increase	2.07	0.93, 4.59	0.074
CD4 count at seroconversion (square root cells/mm^3)	Per 1 unit increase	0.91	0.81, 1.02	0.102
Recruited from a PHI centre	No	1	-	0.123
	Yes	2.25	0.80, 6.36	
Doctor advised starting ART	No	1	-	0.001
	Yes	5.98	2.14, 16.68	

aOR=adjusted OR; CI=confidence interval; PHI=primary HIV infection

a=OR adjusted for all of the other variables present in the table

Table 6.10 shows the association between the demographic and clinical factors found to be associated with initiation of early ART at p<0.2 in the time-adjusted analysis. Model 1 shows the association of each independent variable after adjusting for the base model variables time from HIV diagnosis to questionnaire completion, year of HIV diagnosis and doctor advised starting ART. After adjusting for these, men diagnosed with an STI at HIV diagnosis were less likely to have initiated early ART (aOR 0.28; 95% CI 0.11, 0.72; p=0.009) compared to those who did not have an STI. Men who had reported previous PEP use were more likely to have started early (aOR 3.71; 95%CI 1.22, 11.60; p=0.021), as were those who reported experiencing a rash at seroconversion (aOR 3.01; 95% CI 1.00, 9.08; p=0.051).

Table 6.10 Association between demographic and clinical variables and early ART initiation, adjusted for base model and other covariates

		Model 1			Model 2		
Variable	**Level**	**aOR**	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
Currently employed	No	1	-	0.149		N/A	
	Yes	0.40	0.12, 1.39				
Self-reported rash	No	1	-	0.051	1	-	0.050
	Yes	3.01	1.00, 9.08		3.22	1.00, 10.37	
Self-reported headaches	No	1	-	0.225		N/A	
	Yes	1.87	0.68, 5.15				
Self-reported body aches	No	1	-	0.264		N/A	
	Yes	1.70	0.67, 4.32				
STI coinfection at HIV	No	1	-	0.009	1	-	0.023
	Yes	0.28	0.11, 0.72		0.31	0.12, 0.85	
Previous PEP	No	1	-	0.021	1	-	0.021
	Yes	3.76	1.22, 11.60		4.14	1.24, 13.81	

aOR=adjusted odds ratio; CI=confidence interval; STI=sexually transmitted infection; PEP=post exposure prophylaxis

Model 1= adjusted for time from HIV diagnosis to questionnaire completion, year of HIV diagnosis, doctor advised starting ART;

Model 2= adjusted for time from HIV diagnosis to questionnaire completion, year of HIV diagnosis, doctor advised starting ART, experienced rash at seroconversion, STI coinfection

Model 2 in table 6.10 shows the association of those variables associated with early ART initiation in model 1 at the p<0.10 level, after adjusting for associated base model variables, as well as all other independent variables in the table associated at p<0.1 in model 1. The odds ratios remained largely unchanged for all three of these associated variables, after

adjusting for the other variables in the table associated at p<0.1, as well as associated base level variables.

Table 6.11 outlines the association between early ART initiation and the attitudes and behavioural variables which were found to be associated at p<0.2 in the time-adjusted analysis. Model 1 shows that, after adjusting for the base model variables, there was very strong evidence that men were more likely to have initiated early ART if they reported they would have accepted ART at diagnosis (aOR 21.87; 95% CI 4.50, 106.26; p<0.001) and if they agreed with the statement "It is better for my health to start ART earlier rather than later" (aOR 50.88; 95% CI 6.49, 399.07; p<0.001). Men who had initiated ART in EHI were more likely to have disclosed their HIV status to their friends, be it HIV-positive friends (aOR 3.41; 95% CI 1.29, 9.07; p=0.013) or HIV negative friends (aOR 3.69; 95% CI 1.42, 9.58; p=0.007). After adjusting for all the other associated variables at p<0.10 in model 1 as well as base model variables, disclosure to a HIV-positive friend was no longer associated with early ART initiation. The odds ratio dramatically dropped for agreement with the statement "It is better for my health to start ART earlier rather than later" (aOR 28.06; 95% CI 2.05, 383.71; p=0.012) though it remained significant. The other associated variables changed very little.

Table 6.12 shows the final model of factors associated with initiation of early ART, adjusted for all over variables in the model. After adjusting for all of the other variables associated at the p<0.10 level at each level of the conceptual framework, time from HIV diagnosis to survey completion was still strongly associated with early ART initiation, with the odds of starting ART increasing by 1.53 per month elapsed between HIV diagnosis and questionnaire completion (95% CI 1.14, 2.05; p=0.004). Men who reported that they would have accepted ART at diagnosis if offered were also significantly more likely to have started early ART after adjusting for all other variables (aOR 15.50; 95% CI 2.66, 90.27; p=0.002) as were men who held positive health beliefs around early ART by agreeing with the statement "It is better for my health to start ART earlier rather than later" (aOR 17.36; 95% CI 1.57, 192.18; p=0.020). Independently of all other factors, those men whose clinician had recommended starting ART had 5.03 times the odds of having initiated early ART (95% CI 1.15, 22.03; p=0.015). There was also evidence that men who had disclosed their HIV status to an HIV negative friend were more likely to have initiated early ART (aOR 6.96; 95% CI 1.44, 33.75; p=0.016). None of the other factors remained significant in the fully-adjusted model.

Table 6.11 Association between attitudes and behavioural variables and early ART initiation, adjusting for base model and other covariates

		Model 1			Model 2		
Variable	**Level**	**aOR**	**95% CI**	**p-value**	**aOR**	**95% CI**	**p-value**
Would have accepted ART at diagnosis if offered	No	1	-	<0.001	1	-	0.001
	Yes	21.87	4.50, 106.26		20.61	3.40, 124.90	
"Better HIV treatment means that people are less worried about catching HIV"	No	1	-	0.171		N/A	
	Yes	2.02	0.74, 5.56				
"It is better for my health to start ART earlier rather than later"	No	1	-	<0.001	1	-	0.012
	Yes	50.88	6.49, 399.07		28.06	2.05, 383.71	
Reported casual SD UAI in 6 months before HIV diagnosis	No	1	-	0.282		N/A	
	Yes	0.57	0.20, 1.59				
Disclosed HIV status to GP	No	1	-	0.117		N/A	
	Yes	2.16	0.82, 5.66				
Disclosed HIV status to HIV-positive friend	No	1	-	0.013	1	-	0.131
	Yes	3.41	1.29, 9.07		3.20	0.71, 14.48	
Disclosed HIV status to HIV negative friend	No	1	-	0.007	1	-	0.048
	Yes	3.69	1.42, 9.58		4.49	1.01, 19.96	

aOR=adjusted odds ratio; CI=confidence interval; SD=serodiscordant/status unknown; UAI=condomless anal intercourse.

Model 1= adjusted for time from HIV diagnosis to questionnaire completion, year of HIV diagnosis, doctor advised starting ART;

Model 2=adjusted for time from HIV diagnosis to questionnaire completion, year of HIV diagnosis, doctor advised starting ART and all variables associated at p<0.01 in model 1.

Table 6.12 Final adjusted model of factors associated with initiation of early ART (N=94)

	Level	aOR[a]	95% CI	p-value
Time from HIV diagnosis to survey completion	Continuous per month increase	1.53	1.14, 2.05	0.004
Year diagnosed HIV positive	Continuous per year increase	2.38	0.62, 9.15	0.207
Square root CD4 at seroconversion (cells/mm^3)	Continuous per 1 unit increase	0.94	0.79, 1.13	0.524
Clinician recommended starting ART	No	1	-	0.015
	Yes	5.03	1.15, 22.03	
Experienced a rash at seroconversion	No	1	-	0.861
	Yes	0.87	0.19, 4.09	
STI co-infection at HIV diagnosis	No	1	-	0.312
	Yes	0.51	0.14, 1.88	
Previously taken PEP	No	1	-	0.372
	Yes	2.13	0.41, 11.13	
Would have accepted ART at diagnosis if offered	No	1	-	0.002
	Yes	15.50	2.66, 90.27	
"It is better for my health to start ART earlier rather than later"	No	1	-	0.020
	Yes	17.36	1.57, 192.18	
Disclosed HIV status to HIV negative friend	No	1	-	0.016
	Yes	6.96	1.44, 33.75	

aOR=adjusted odds ratio; CI=confidence interval; STI=sexually transmitted infection; PEP=post exposure prophylaxis.
a=model adjusted for all other variables in the table

6.5 Sexual behaviour amongst MSM recent seroconverters

6.5.1 Sexual behaviour in the six months prior to, and time since, HIV diagnosis

Table 6.13 shows the prevalence of various sexual behaviours reported by the men in the survey during the 6 months before HIV diagnosis, and the time between HIV diagnosis and questionnaire completion. All men reported having any type of sex (either anal or oral) with another man in the six months prior to diagnosis, and nearly all men (97.4%, 114/117) reported having any AI during that time, the median number of partners being 6 (3, 15). 82.9% (97/117) reported AI with a casual (once only) male partner over this time, median number of casual partners 4 (1, 9). Condomless AI (UAI) was reported by 84.3% (97/115) and condomless UAI with a casual partner by 58.1% (65/114), median overall and casual UAI partner numbers were 2 (1, 5) and 1 (0, 3). UAI with serodiscordant/unknown status men in (serodiscordant UAI) the six months prior to HIV diagnosis was reported by 65.5% (74/113), and with casual partners by 40.0% (44/110). The median number of overall serodiscordant UAI partners was 1 (0, 3) and casual serodiscordant UAI partners was 0 (0, 2).

Of note, 21.1% (16/76) of the 76 men who reported experiencing seroconversion symptoms also reported having UAI whilst experiencing these symptoms. Men experiencing seroconversion-like symptoms reported UAI with more regular partners over the symptomatic period median (IQR) of 1 (1, 2.5) compared to 0 (0, 2) casual partners.

As expected, there was a decrease in the proportion of men reporting any sexual activity after diagnosis with 31.6% (37/117) of men reporting having had no sex (either OI or AI) since their HIV diagnosis. Though it is important to note that the recall period post-diagnosis varied between individuals and was much less than the 6 month recall period pre-diagnosis (median 76 days; IQR 29-191). The proportion of men reporting any AI since diagnosis was 64.1% (75/117), with reported median partner numbers of 1 (0, 3). 41.4% (48/116) reported AI with a casual partner, median partner number 0 (0, 2). Less than a third of men (31.6%, 37/117) reported UAI and 18.8% (22/117) casual UAI. Around 1 in 10 of the men (9.6%, 11/117) reported having UAI with serodiscordant/status unknown partners since their diagnosis. 6.8% (8/117) reported serodiscordant UAI with casual partners.

Table 6.13 Prevalence of reported sexual behaviours before and after HIV diagnosis amongst MSM seroconverters attending UK clinics

		In 6 months before HIV diagnosis		In time interval since HIV diagnosis	
Variable		**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**
Had any sex (AI or OI)	No	0	0	37	31.6
	Yes	117	100	80	68.4
Any AI	No	3	2.6	42	35.9
	Yes	114	97.4	75	64.1
No. of AI partners		117	6 (3, 15)	117	1 (0, 3)
Any casual AI	No	20	17.1	68	58.6
	Yes	97	82.9	48	41.4
No. of casual AI partners		117	4 (1, 9)	116	0 (0,2)
Any UAI	No	18	15.7	80	68.4
	Yes	97	84.3	37	31.6
No. of UAI partners		115	2 (1, 5)	117	0 (0,1)
Any casual UAI	No	49	43	95	81.2
	Yes	65	57	22	18.8
No. of casual UAI partners		114	1 (0, 3)	117	0 (0, 0)
Any SD UAI	No	39	34.5	106	90.6
	Yes	74	65.5	11	9.4
No. of SD UAI partners		113	1 (0, 3)	117	0 (0, 0)
Any casual SD UAI	No	66	60	109	93.2
	Yes	44	40	8	6.8
No. of casual SD UAI partners		110	0 (0, 2)	117	0 (0, 0)
Illegal drug use before or during sex	No	54	48.2	69	62.7
	Yes	58	51.8	41	37.3
Injected drugs before or during sex	No	110	94.8	106	93.8
	Yes	6	5.2	7	6.2
Engaged in "ChemSex"	No	59	52.7	74	66.7
	Yes	53	47.3	37	33.3
Engaged in high-risk sex (either SD UAI or ChemSex and AI)	No	29	24.8	76	65.0
	Yes	88	75.2	41	35.0

IQR=interquartile range; AI=anal intercourse; OI=oral intercourse; UAI=condomless anal intercourse; SD UAI=serodiscordant/status unknown condomless anal intercourse.

6.5.2 Recreational drug use before and during sex

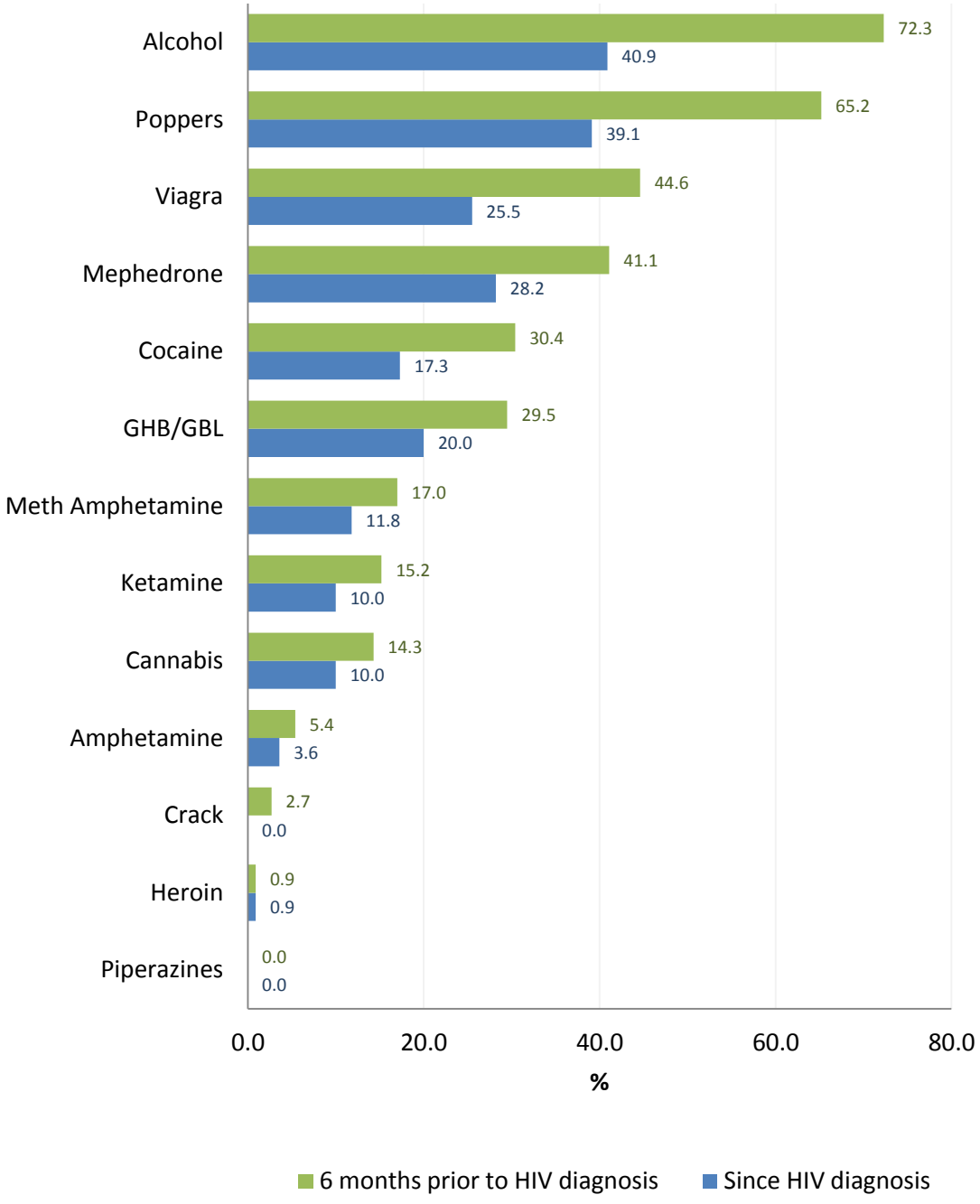
Table 6.13 shows that there were high levels of recreational drug use amongst respondents; in the six months prior to diagnosis, 51.8%, (58/112) of men reported using illegal drugs immediately before or during sex but this proportion dropped markedly after diagnosis to 37.3% (41/110), though fewer men had resumed sexual activity after diagnosis. The proportion of men reporting injecting drugs before or during sex was low though at 5.2% (6/116) prior to diagnosis and 6.2% (7/113) after diagnosis. 47.3% of men (53/112) had participated in "ChemSex" (defined as the use of any of any the following drugs before or during sex: GHB/GBL, methedrone, methamphetamine, piperazines or ketamine) in the 6 months prior to diagnosis, compared to 33.3% (37/111) in the time since diagnosis.

Figure 6.7 shows that in the six months prior to HIV diagnosis, the most commonly-used stimulants before and during sex were alcohol and poppers with 72.3% (81/112) and 65.2% (73/112) of men, respectively reporting their use. These remained the most commonly used stimulants in the period after HIV diagnosis, though the proportion of men who reported using them decreased markedly to 40.9% (45/110) for alcohol and 39.1% (43/110) for poppers. The most popular illegal drugs used before and during sex were the same both before and after HIV diagnosis, though the proportion using them decreased after diagnosis in all cases.

6.5.3 Meeting sexual partners

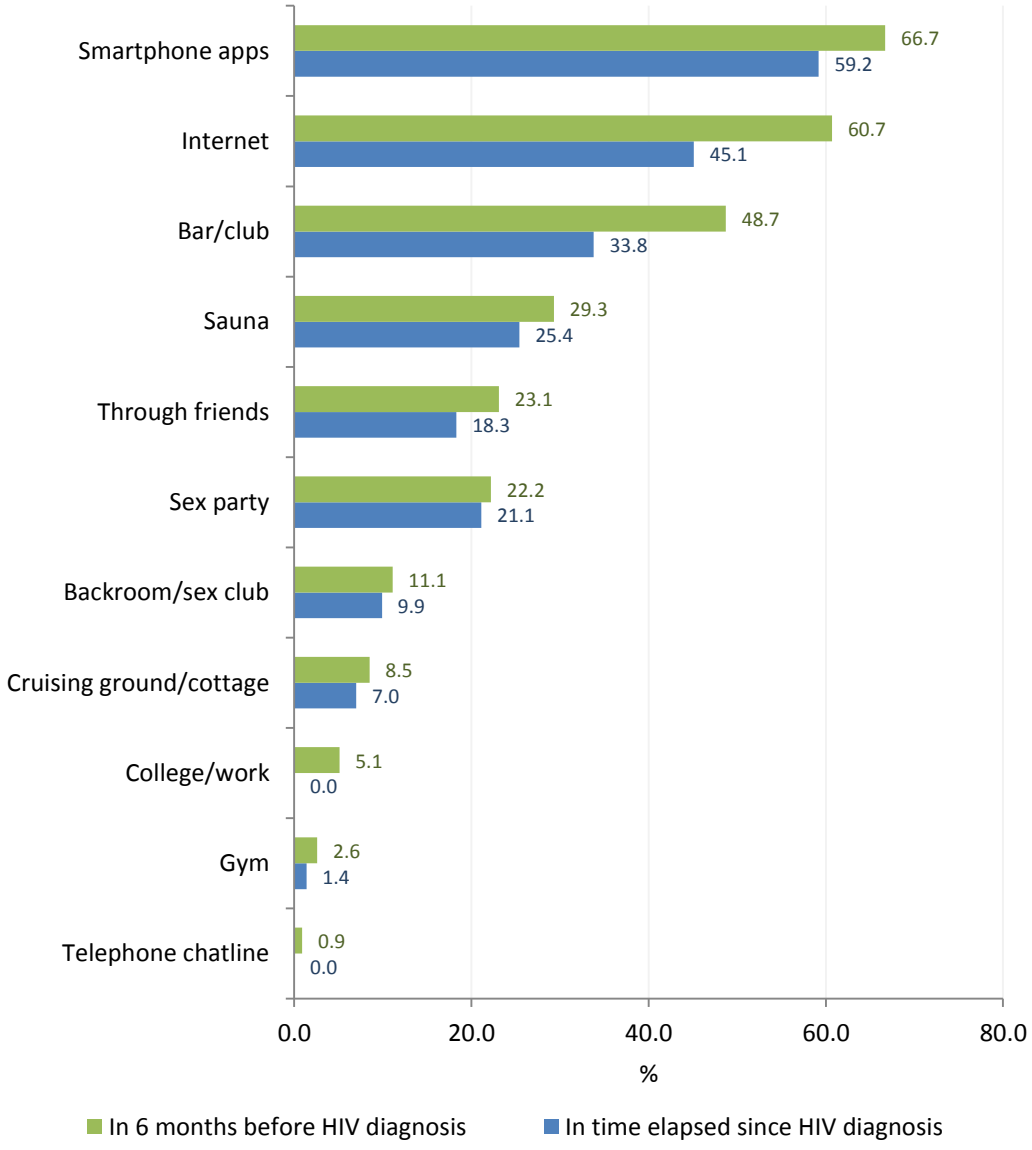
Figure 6.8 shows the most commonly reported methods of meeting sexual partners in the six months prior to diagnosis was through smartphone apps (66.7%, 78/117), the internet (60.7%, 71/117), in bars/clubs (48.7%, 57/117) and in saunas (29.3%, 34/117) with men using a median(IQR) of 3 (2, 4) methods to meet partners. After diagnosis, the four most common methods for meeting partners remained the same, though the popularity of their use amongst those men who were sexually active was lower. Meeting partners on the internet and in bars and clubs were notably less popular after HIV diagnosis. Men reported using a fewer number of methods of meeting new partners after diagnosis of median 2 (1, 3).

Figure 6.7 Reported alcohol and drug use during sex amongst MSM before and after HIV diagnosis



Of note, in the six months prior to diagnosis, the proportion of sexually active men who met new partners at a sex-on-premises (SOP) venue (sauna/backroom or sex club/cruising ground or cottage) was 38.5% (45/117), and this remained similar at 31.0% (22/71) after diagnosis. Of the men who met new partners in a SOP venue after their HIV diagnosis, all but one (95.5% 21/22) had met partners in an SOP venue before their diagnosis.

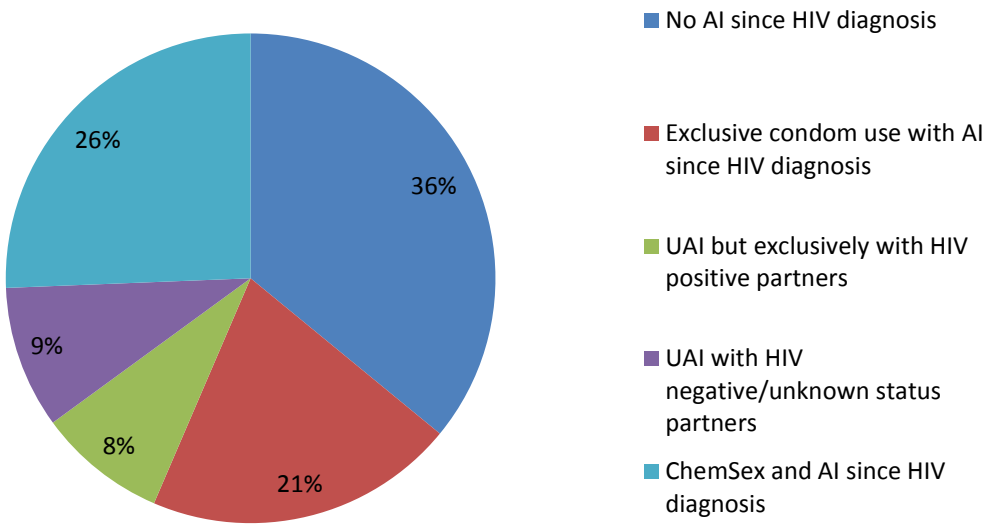
Figure 6.8 Reported methods of meeting new sexual partners reported by sexually active MSM seroconverters before and after their HIV diagnosis



6.5.4 Factors associated with engagement in high-risk sex after HIV diagnosis

Figure 6.9 outlines sexual behaviour by transmission risk. It is clear that 57% of survey respondents engaged only in behaviour which carried very little risk of transmitting HIV to sexual partners either by having not engaging in AI since diagnosis (36%) or exclusively using condoms for AI (21%). A further 8% of men did engage in UAI but reduced their risk of transmitting HIV by exclusively serosorting for HIV-positive partners. The highest risk of onward transmission comes from the 10% who engaged in UAI with serodiscordant or status unknown partners and the 26% who reported having AI since HIV diagnosis and engaging in ChemSex, due to the lack of control over safe sex practices under the influence of ChemSex drugs.

Figure 6.9 Prevalence of sexual behaviours amongst MSM after receiving HIV diagnosis (n=117)



Men were defined as being at high-risk of transmitting HIV after their diagnosis if they reported having UAI with 1 or more partners of serodiscordant or unknown HIV status since receiving their HIV diagnosis, or reported having 1 or more AI partners and having engaged in ChemSex since HIV diagnosis. The denominator for the prevalence estimate, was all men who had answered the question “How many men have you had anal intercourse (active or passive) with

since receiving your HIV diagnosis?". Overall, 35.0% (41/117) of men had engaged in sex that could have led to onward transmission of HIV: 30 had engaged in ChemSex and AI since diagnosis, 5 had engaged in serodiscordant UAI, and 6 had engaged in both serodiscordant UAI and ChemSex.

Table 6.14, illustrates the association between demographic factors and engagement in high-risk sex, post diagnosis. As expected, time from HIV diagnosis to questionnaire completion was strongly associated the odds of engaging in high-risk sex after HIV diagnosis; the odds increasing by 1.21 for every month since diagnosis (95% CI 1.08, 1.35; p=0.001). All associations between independent variables are adjusted for time from HIV diagnosis to questionnaire completion. Of note, a larger proportion of men who engaged in high-risk sex after HIV diagnosis did not have a regular male partner, compared to men not engaging in high-risk sex, 65.9% and 49.3%, respectively, however there was only very weak evidence of an association after adjusting for time from diagnosis to questionnaire completion (p=0.093). None of the other demographic factors were associated with engaging in high-risk sex after HIV diagnosis after adjusting for time from HIV diagnosis to questionnaire completion.

Table 6.15 shows the association between clinical factors and engagement in high-risk sex after HIV diagnosis. After adjusting for time from HIV diagnosis to questionnaire completion, there was weak evidence that men recruited from centres with a PHI research interest were more likely to have engaged in risky sex since their HIV diagnosis (OR 2.32; 95% CI 0.95, 5.63; p=0.064). There was also weak evidence that men who reported experiencing seroconversion like symptoms were less likely to have engaged in high-risk sex since diagnosis (OR 0.34; 95% CI 0.20, 1.05; p=0.066). Specifically, men who reported a rash were significantly less likely to report high-risk sex after diagnosis (OR 0.34; 95% CI 0.12, 0.97; p=0.043), as were those who reported having a sore throat (OR 0.37; 95% CI 0.15, 0.91; p=0.031) or body aches (OR 0.24; 95% CI 0.10, 0.62; p=0.003). The odds of engaging in high-risk sex after HIV diagnosis were 4.73 times higher for men who reported previously taking PEP, compared to those who had never taken PEP (95% CI 1.81, 12.33; p=0.001). Although more of the men who had engaged in high-risk sex had initiated ART than men who did not (58.5% vs 41.3%), there was no significant association after adjusting for time from HIV diagnosis to questionnaire completion.

Table 6.14 Demographic and social factors associated with engagement in high-risk sex after HIV diagnosis, adjusting for time from HIV diagnosis to questionnaire completion

		Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
Time from diagnosis to survey completion[b]	Per month increase (continuous)	76	1.5 (0.7, 4.8)	41	5.0 (2.1, 8.0)	117	1.21	1.08, 1.35	0.001
Year of HIV diagnosis	Per year increase (continuous)	76	2014 (2013, 2014)	41	2013 (2013, 2014)	117	0.68	0.35, 1.33	0.259
Age at HIV seroconversion	Per year increase (continuous)	76	32.6 (27.4, 40.2)	41	32.8 (28.4, 37.4)	117	0.97	0.92, 1.02	0.232
Ethnicity	White	61	80.3	37	90.2	117	1	-	0.169
	Non-white	15	19.7	4	9.8		0.42	0.12, 1.45	
Recruited from London HIV centre	No	24	34.6	14	34.1	117	1	-	0.463
	Yes	52	68.4	27	65.9		1.38	0.57, 3.41	
Years full time education after 16 years of age	<3 years	11	14.5	7	17.1	117	1	-	0.994
	3 years or more	65	85.5	34	82.9		1.00	0.33, 2.99	
Currently employed	No	16	21.1	5	12.2	117	1	-	0.162
	Yes	60	79.0	36	87.8		2.28	0.72, 7.22	
Own or rent accommodation	Own	25	32.8	13	31.7	117	1	-	0.955
	Rent - private landlord	41	54.0	23	56.1		0.98	0.40, 2.37	
	Rent - other	10	13.2	5	12.2		0.82	0.22, 3.09	

IQR=interquartile range; OR=odds ratio (adjusted for time from HIV diagnosis to questionnaire completion); CI= confidence interval

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion; b=likelihood ratio test for departure from linearity modelling time from diagnosis to questionnaire completion as a linear versus a 4 group categorical variable p=0.588.

Table 6.14 (continued)

Factor of interest	Level	Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis		N	OR[a]	95% CI	p-value
		n	Median (IQR) or %	n	Median (IQR) or %				
Current living arrangements	Alone	20	26.3	10	24.4	117	1	-	0.244
	Partner	21	27.6	10	24.4		0.66	0.21, 2.10	
	Friends/tenants/lodgers	24	31.6	19	46.3		1.44	0.52, 4.00	
	Family/guardians	11	14.5	2	4.9		0.37	0.06, 2.11	
Sexual orientation	Gay/homosexual	66	86.8	39	95.1	117	1	-	0.350
	Bisexual/Other	10	13.2	2	4.9		0.46	0.09, 2.35	
Current regular male partner (RMP)	No RMP	37	49.3	27	65.9	116	1	-	0.093
	HIV+ RMP	14	18.7	8	19.5		0.68	0.23, 1.96	
	HIV-/unknown RMP	24	32.0	6	14.6		0.32	0.11, 0.94	

IQR=interquartile range; OR=odds ratio; CI= confidence interval

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion

Table 6.15 Clinical factors associated with engagement in high-risk sex after HIV diagnosis, adjusting for time from HIV diagnosis to questionnaire completion

		Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
HIV test interval	Per month increase (continuous)	76	3.0 (0.0, 5.4)	41	2.5 (0.2, 5.9)	117	0.91	0.80, 1.05	0.185
Diagnosed in acute infection	No	60	79.0	32	78.1	117	1	-	0.324
	Yes	16	21.0	9	21.9		1.66	0.61, 4.56	
CD4 count at diagnosis (square root transformed cells/mm3)	Per unit increase (continuous)	72	458.3 (398.3, 672.5)	40	579.8 (418.0, 648.3)	112	1.03	0.93, 1.13	0.592
HIV viral load at seroconversion	Per $\log_{10}$ increase (continuous)	73	4.9 (4.4, 5.8)	39	4.5 (4.1, 5.6)	112	0.93	0.66, 1.31	0.671
Recruited from an HIV centre with PHI interests	No	39	51.3	18	43.9		1	-	0.064
	Yes	37	48.7	23	56.1	117	2.32	0.95, 5.63	
Doctor advised starting ART	No	29	42.0	15	39.5		1	-	0.652
	Yes	40	57.0	23	60.5	107	1.59	0.65, 3.87	
Experienced seroconversion symptoms	No	21	28.0	19	46.3		1	-	0.066
	Yes	54	72.0	22	53.7	116	0.46	0.20, 1.05	
Experienced rash at seroconversion	No	51	68.0	35	85.4		1	-	0.043
	Yes	24	32.0	6	14.6	116	0.34	0.12, 0.97	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; STI=sexually transmitted infection; HIV test interval=time between HIV Ab negative and positive tests

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion

Table 6.15 (continued)

Factor of interest	Level	Not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
		n	Median (IQR) or %	n	Median (IQR) or %	N	OR[a]	95% CI	p-value
Experienced headache at seroconversion	No	48	64.0	33	80.5	116	1	-	0.197
	Yes	27	36.0	8	19.5		0.54	0.21, 1.38	
Experienced sore throat at seroconversion	No	42	56.0	32	78.1	116	1	-	0.031
	Yes	33	44.0	9	21.9		0.37	0.15, 0.91	
Experienced fever at seroconversion	No	32	42.7	22	53.7	116	1	-	0.358
	Yes	43	57.3	19	46.3		0.69	0.31, 1.53	
Experienced body aches at seroconversion	No	37	49.3	32	78.1	116	1	-	0.003
	Yes	38	50.7	9	21.9		0.24	0.10, 0.62	
Experienced vomiting & diarrhoea at seroconversion	No	56	74.7	30	73.2	116	1	-	0.579
	Yes	19	25.3	11	26.8		1.29	0.52, 3.21	
Experienced night sweats at seroconversion	No	34	45.3	24	58.5	116	1	-	0.206
	Yes	41	54.7	17	41.5		0.59	0.26, 1.33	
Seroconversion symptoms affected daily routine	No	42	56.0	29	70.7	116	1	-	0.159
	Yes	33	44.0	12	29.3		0.54	0.23, 1.27	
STI co-infection at diagnosis	No	43	56.6	21	53.9	115	1	-	0.720
	Yes	33	43.4	18	46.1		1.16	0.51, 2.64	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; STI=sexually transmitted infection

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion

Table 6.15 (continued)

Factor of interest	Level	Not engaged in high-risk sex since HIV diagnosis n	Not engaged in high-risk sex since HIV diagnosis Median (IQR) or %	Engaged in high-risk sex since HIV diagnosis n	Engaged in high-risk sex since HIV diagnosis Median (IQR) or %	N	OR[a]	95% CI	p-value
Ever taken PEP	No	66	86.8	23	57.5	116	1	-	0.001
	Yes	10	13.2	17	42.5		4.73	1.81, 12.33	
Currently taking ART	No	44	58.7	17	41.5	116	1	-	0.287
	Yes	31	41.3	24	58.5		1.56	0.69, 3.56	

IQR=interquartile range; OR=odds ratio; CI= confidence interval; PEP=post exposure prophylaxis; ART=antiretroviral therapy

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion

Table 6.16 shows the association between sexual behaviour in the six months prior to diagnosis and engagement in high risk sex since HIV diagnosis, after adjusting for time from HIV diagnosis to questionnaire completion. The odds of engaging in risky sex post-diagnosis were higher for men who reported casual AI prior to HIV diagnosis (OR 4.37; 95% CI 1.13, 16.93; p=0.033) and casual condomless AI prior to diagnosis (OR 3.41; 95% CI 1.39, 8.42; p=0.008). There was very strong evidence that engagement in ChemSex prior to diagnosis was a risk factor for engagement in high-risk sex after HIV diagnosis (OR 26.95; 95% CI 7.39, 98.30; p<0.001). In addition, men who engaged in high-risk sex after diagnosis were more likely to have met partners in a sex on premises venue prior to diagnosis (OR 3.17; 95% CI 1.38, 7.29; p=0.007).

As is illustrated in table 6.16, men who reported having high-risk sex after HIV diagnosis also reported significantly higher numbers of regular and casual AI partners compared to those who did not. This was true also of regular and casual UAI partners, and serodiscordant UAI partners. As the distribution for sexual partner count variables were skewed, I conducted sensitivity analyses where observations in the tail (>99th percentile) were removed to check for leverage. The odds ratios and confidence intervals remained unchanged for all partner count variables.

Table 6.17 shows the association between various sexual behaviours after diagnosis and engaging in high-risk sex, after adjusting for time from HIV diagnosis to questionnaire completion. Men who had engaged in high-risk sex were significantly more likely to have had higher AI partner numbers since diagnosis, both regular (OR 1.41; 95% CI 1.16, 1.71; p=0.001) and casual partners (OR 1.69; 95% CI 1.24, 2.29; p=0.001). They were also much more likely to report having condomless AI (OR 10.40; 95% CI 4.01, 26.80; p<0.001) and condomless AI with one or more casual partners (OR 16.90; 95% CI 4.47, 63.82; p<0.001). Serodiscordant UAI and ChemSex after HIV diagnosis were not included as risk-factors in the model as they comprised the definition of the outcome under study, high-risk sex.

Table 6.16 Association between pre-diagnosis sexual behaviours and engagement in high-risk sex HIV after diagnosis, adjusting for time from HIV diagnosis to questionnaire completion

		Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
Any AI pre-diagnosis	No	3	3.9	0	0.0				
	Yes	73	96.1	41	100.0	117	N/A	N/A	N/A
Median number of AI partners pre-diagnosis	Per 1 partner increase (continuous)	76	4(2, 8.5)	41	12 (6, 20)	117	1.09	1.04, 1.14	0.001
Any casual AI pre-diagnosis	No	17	22.4	3	7.3		1	-	0.033
	Yes	59	77.6	38	92.7	117	4.37	1.13, 16.93	
Median number of casual AI partners pre-diagnosis	Per 1 partner increase (continuous)	76	2(1, 5.5)	41	8 (3, 15)	117	1.09	1.03, 1.15	0.003
Any UAI pre-diagnosis	No	16	21.3	2	5.0		1	-	0.070
	Yes	59	78.7	38	95.0	115	4.25	0.89, 20.31	
Median number of UAI partners pre-diagnosis	Per 1 partner increase (continuous)	75	2 (1, 3)	40	3.5 (2, 12)	115	1.18	1.06, 1.31	0.002
Any casual UAI pre-diagnosis	No	39	52.0	10	25.6		1	-	0.008
	Yes	36	48.0	29	74.4	114	3.41	1.39, 8.42	
Median number of casual UAI partners pre-diagnosis	Per 1 partner increase (continuous)	75	0 (0, 2)	39	2 (0, 8)	114	1.22	1.06, 1.36	0.004

IQR=interquartile range; OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI= condomless anal intercourse; N/A=conducting a logistic regression was not possible due to lack of observations or collinearity.

a=adjusted for time from HIV diagnosis to questionnaire completion modelled as a linear term

Table 6.16 (continued)

Factor of interest	Level	Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
		n	Median (IQR) or %	n	Median (IQR) or %	N	OR[a]	95% CI	p-value
Any SD UAI pre-diagnosis	No	29	39.2	10	25.6	113	1	-	0.238
	Yes	45	60.8	29	74.4		1.72	0.70, 4.24	
Median number of SD UAI partners pre-diagnosis	Per 1 partner increase (continuous)	74	1 (0, 2)	39	1 (0, 6)	113		N/A	
Any casual SD UAI pre-diagnosis	No	48	66.7	18	47.4	110	1	-	0.084
	Yes	24	33.3	20	52.6		2.10	0.91, 4.89	
Median number of casual SD UAI partners pre-diagnosis	Per 1 partner increase (continuous)	72	0 (0, 1.5)	38	1 (0, 3)	110		N/A	
ChemSex pre-diagnosis	No	52	73.2	7	17.1	112	1	-	<0.001
	Yes	19	26.8	34	82.9		26.95	7.39, 98.30	
Met partners in a sex on premises venue pre-diagnosis	No	55	72.4	17	41.5	117	1	-	0.007
	Yes	21	27.6	24	58.5		3.17	1.38, 7.29	

IQR=interquartile range; OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI= condomless anal intercourse; SD=serodiscordant/status unknown

a=adjusted for time from HIV diagnosis to questionnaire completion modelled as a linear term

Table 6.17 Association between sexual behaviours after diagnosis and engagement in high-risk sex HIV after diagnosis, adjusting from time from HIV diagnosis to questionnaire completion

		Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
Factor of interest	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
Any AI post-diagnosis	No	42	55.3	0	0.0	117		N/A	
	Yes	34	44.7	41	100.0				
Number of AI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 1)	41	5 (2, 15)	117		N/A	
Any casual AI post-diagnosis	No	60	78.9	8	20.0	116	1	-	<0.001
	Yes	16	21.1	32	80.0		12.2	4.58, 32.64	
Number of casual AI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 0)	40	2 (1, 7.5)	116		N/A	
Any UAI post-diagnosis	No	66	86.8	14	34.2	117	1	-	<0.001
	Yes	10	13.2	27	65.8		10.40	4.01, 26.80	
Number of UAI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 0)	41	1 (0, 5)	117		N/A	
Any casual UAI post-diagnosis	No	73	96.1	22	53.7	117	1	-	<0.001
	Yes	3	3.9	19	46.3		16.90	4.47, 63.82	
Number of casual UAI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 0)	41	0 (0, 4)	117		N/A	

OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI= condomless anal intercourse; N/A=conducting a logistic regression was not possible due to lack of observations or collinearity. a=adjusted for time from HIV diagnosis to questionnaire completion modelled as a linear term

Table 6.17 (continued)

Factor of interest	Level	Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis		N	OR[a]	95% CI	p-value
		n	Median (IQR) or %	n	Median (IQR) or %				
Any SD UAI post-diagnosis	No	76	100.0	30	73.2	117		N/A	
	Yes	0	0.0	11	26.8				
Median number of SD UAI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 0)	41	0 (0, 1)	117		N/A	
Any casual SD UAI post-diagnosis	No	76	100.00	33	80.5	117		N/A	
	Yes	0	0.0	8	19.5				
Median number of casual SD UAI partners post-diagnosis	Per 1 partner increase (continuous)	76	0 (0, 0)	41	0 (0, 0)	117		N/A	
ChemSex post-diagnosis	No	69	98.6	5	12.2	111		N/A	
	Yes	1*	1.4	36	87.8				

OR=odds ratio; CI=confidence interval; AI=anal intercourse; UAI= condomless anal intercourse; SD=serodiscordant/status unknown; N/A=conducting a logistic regression was not possible due to lack of observations or collinearity.

a=adjusted for time from HIV diagnosis to questionnaire completion modelled as a linear term; *individual reported engaging in ChemSex but no AI.

The association between four attitudes and engagement in high-risk sex after HIV diagnosis are presented in table 6.18. After adjusting for time from diagnosis to questionnaire completion, there was evidence that men who agreed with the statement “Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom” were more likely to have engaged in high-risk sex compared to those who did not (OR 2.72; 95% CI 1.03, 7.21; p=0.044). In addition, men who agreed with the statement “Better treatment means people are less worried about HIV” were more likely to have engaged in high-risk sex after diagnosis than those who did not agree (OR 2.71; 95% CI 1.01, 7.31; p=0.049).

Due to the multi-collinearity of the sexual behaviour variables, and the very small number of other variables found to be associated with the outcome after adjusting for time from diagnosis to questionnaire completion, there was little benefit from fitting a multivariate model.

Table 6.18 Association between attitudes towards ART and engagement in high-risk sex after HIV diagnosis, adjusting from time from HIV diagnosis to questionnaire completion

		Has not engaged in high-risk sex since HIV diagnosis		Engaged in high-risk sex since HIV diagnosis					
Variable	**Level**	**n**	**Median (IQR) or %**	**n**	**Median (IQR) or %**	**N**	**OR[a]**	**95% CI**	**p-value**
"Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom"	Don't agree	29	45.3	9	26.5	98	1	-	0.044
	Agree	35	54.7	25	73.5		2.72	1.03, 7.21	
"It is not necessary to disclose your HIV status if you are on ART and have an undetectable viral load"	Don't agree	54	85.7	26	76.5	97	1	-	0.294
	Agree	9	14.3	8	23.5		1.82	0.59, 5.61	
"Better treatment means people are less worried about HIV"	Don't agree	32	50.0	13	38.2	98	1	-	0.049
	Agree	32	50.0	21	61.8		2.71	1.01, 7.31	
"It is better for my health to start ART earlier rather than later"	Don't agree	19	26.4	9	23.1	111	1	-	0.203
	Agree	53	73.6	30	76.9		1.94	0.70, 5.38	

IQR=interquartile range; OR=odds ratio; CI=confidence interval

a=odds ratio adjusting for time from HIV diagnosis to questionnaire completion.

6.6 Summary discussion

Early ART, offered at the point of diagnosis was acceptable to the majority of MSM with EHI recruited to this study. Two thirds (95% CI 58.1-73.4%) would have accepted ART at diagnosis if they were offered it and a further 25% (95% CI 16.7-32.5%) would have considered it. Not only was it acceptable but it appeared to be expected; nearly half of the respondents had expected to start ART within a month of diagnosis, and 47% (95% CI 38.3-56.5%) of respondents had already started ART by the time of questionnaire completion. Of the men who had not yet started ART, 61% (95% CI 48.8-73.2%) agreed with the statement "I am ready to start ART now".

Most respondents who had initiated ART by the time of questionnaire completion believed in the health benefits of early treatment: 97% (95% CI 91.3-100.0%) reported starting to reduce the damage HIV was causing and to control the spread of HIV and 90% (95% CI 83.0-98.5%) agreed with the statement "It is better for my health to start ART earlier rather than later". In fact, nearly 40% of men who were on ART at the time of completing the questionnaire said they had started ART mostly, or only, for health reasons. Protecting partners from HIV was also important though, with 89% (95% CI 80.5-97.3%) starting to reduce the risk transmission, though this may not have been wholly altruistic as 85% (95% CI 75.5-94.5%) reported starting to reduce the anxiety of transmission. 60% (95% CI 47.2-73.6%) of men believed that being on ART made it easier to disclose their HIV status to sexual partners.

Whilst the majority of men surveyed had not engaged in sex which carries a high-risk of HIV transmission since their HIV diagnosis, nearly 1 in 10 men reported engaging in UAI with a serodiscordant/unknown status partner since receiving their diagnosis. In addition, a quarter of MSM surveyed had reported engaging in ChemSex and having AI since receiving their diagnosis. Given the documented loss of control under the influence of ChemSex drugs, it is likely that there is an increased risk of transmitting HIV in this setting. Engagement in these two high-risk sex practices after diagnosis was associated with higher partner numbers prior to diagnosis, engaging in ChemSex prior to diagnosis and having ever taken PEP. There was also evidence men were more likely to agree with a variation of the Swiss Statement if they had engaged in high-risk sex since diagnosis and were more likely to display treatment optimism beliefs by agreeing with the statement "Better treatment means people are less worried about HIV".

Whilst the proportion of men engaging in high risk sex was higher amongst those on ART, this was not found to be statistically significant at the $p<0.05$ level, though it is not possible to rule out that this finding may have been due to a lack of power to detect small differences.

6.7 Strengths and limitations

6.7.1 Selection bias

The proportion of UK Register recruits who completed this survey was not particularly high, at 45% of eligible MSM. It is important to note though that this is likely to be a conservative estimate as clinics did not have the resources to record invitations and refusals, although asked to do so. The result was that some of the men classed as non-respondents in this thesis were likely not invited to participate by the clinic. Importantly, the number of men who were invited and refused to participate in the UK Register itself was not available and no data exist which compare UK Register respondents to seroconverters not enrolled in the UK Register, so we are unable to assess whether any selection bias exists. It is conceivable that men who are more health-conscious maybe more likely to know about possible benefits of early treatment and be more interested in taking part in medical research, at which point this study may over-emphasise the acceptability of early ART. In some circumstances, it is possible to weight survey data by key characteristics to account for differences between the population and the study sample. However, no suitable population-based parameters exist for recent seroconverters in the UK on which to base such a weighting scheme.

Whilst it is impossible to assess whether there was selection bias to the UK Register as a whole, it is important to acknowledge that HIV centres differ in their clinical or research focus and, crucially for this study, some clinics or doctors become known amongst patients as ”specialists” in PHI. Therefore, it is plausible that differences in ART acceptability exist amongst men recruited from different HIV centres. The fact that those centres with an interest in PHI tend to recruit more seroconverters to the UK Register, and over half of the patients surveyed were recruited from the three centres with PHI interests, may also have led to selection bias. Whilst it was not possible to adjust for the individual HIV centre of recruitment due to the small study numbers and the fact that many HIV centres contributed very small numbers of patients, I did examine the effect of recruitment from centres known to have PHI interests. Interestingly, whilst there was a tendency of MSM recruited from PHI centres to have started ART early, this

was not statistically significant after adjusting for other factors. One plausible explanation is that any effect of attending a PHI centre on early ART initiation, was most likely enacted through the doctors at the centre being more likely to advise the patient to start early ART; a factor which was strongly independently associated with early ART initiation with men 5 times more likely to start if they have been recommended to by their clinician.

Such bias could have been minimised through use of a sampling strategy to select participating UK centres, stratified by geographic area and perhaps by the probability of ART initiation in EHI, however financial and logistical issues prohibited this. The necessity to maximise survey response amongst a relatively small population over the course of a short time period of 1 year, meant that any clinic willing to recruit to the study was permitted to do so. Even with this approach, we did not recruit the required sample size and found recruitment rates to be generally low amongst participating centres. Overall recruitment to the study was slow and sometimes erratic. The main reason for this was the lack of funding for the survey sub-study meant that no extra financial incentive could be offered to clinics to recruit to this study, over and above what is already paid for recruitment to the UK Register. Research teams at the larger centres in particular reported being stretched by the number of ongoing research projects, and understandably had to prioritise recruitment according to financial incentives.

6.7.2 Information bias

A strength of this study was that the survey questions were validated through use of cognitive interview techniques. This enabled me to refine the language, make the questions more understandable to the respondents, and provided a level of confidence that questions were measuring the construct we intended to measure. Unfortunately due to lack of time and the small study population, it was not possible to pilot the questionnaire in a representative population large enough to assess the reliability of the questions using test-retest methods, or to conduct principle component analysis to refine and collate the attitude statements.

Item response was generally good with the exception of three attitude questions at the end of the questionnaire which nearly 15% of the men did not answer. This item non-response was most likely a by-product of the questionnaire booklet design with a notable number of men who were ART-naïve not following the questionnaire routing to the end of the booklet. This

meant that, compared to men who had started early ART, a larger proportion of ART-naïve men had missing data for the statements assessing agreement with a version of the "Swiss statement", whether disclosure of HIV status was necessary if undetectable or ART and the statement assessing treatment optimism (questions H1, H2 and H3 in appendix 18). Whilst it is an unlikely scenario, any systematic difference in the attitudes or beliefs of the men who overlooked these questions to those who responded may have impacted on the final findings of the factors associated with early ART initiation, especially given the small numbers involved in the analyses.

Whilst every effort was made to recruit as many men as possible, the target sample size was not reached. Though recruitment was extended for 6 months, the lack of time and funding available made it unfeasible to run the survey for longer, or in more HIV centres. As a consequence, the small number of respondents resulted in low power to detect associations, and a subsequent increased chance of type II error. This was particularly problematic in the multivariate risk factor analyses, where there were only enough numbers to assess for 4 or 5 independent variables in models and it was necessary to construct a conceptual framework for multivariate analysis for this reason. Independent variables found to have very strong associations with outcomes of interest (i.e. had very high odds ratios) were unlikely to be greatly affected by low power, however some of the more subtle associations may not be apparent in the data due to the low number of respondents. It is important to therefore acknowledge that a lack of association at the $p<0.05$ level may mean there truly is no association in the population, or may mean that there is but it was unlikely to be detected with this small sample size. In addition to high risk of type II error, the high number of independent variables modelled in the risk factor analyses may have resulted in type I error, whereby the null hypothesis is incorrectly rejected due to chance. The statistical cut off of $p<0.05$ was used in this study resulting in a 1 in 20 chance of incorrectly rejecting the null hypothesis for any given test. The multiple testing involved in the risk factor analyses (for ART initiation and high risk sex), and in-particular through use of the stepwise model building and conceptual framework has likely resulted in an increased probability of type I error in these results.

One major limitation of a cross-sectional design, is the inability to establish the temporal sequence of the independent factors of interest and the outcomes under study, for example whether the positive attitudes to ART preceded early ART initiation or whether they were part

of a post-hoc rationalisation after starting ART early. It is, therefore, important to acknowledge, as with any cross-sectional study, that the findings of this study show only associations and not necessarily causation.

Serodiscordant UAI pre-diagnosis was defined as condomless sex with somebody known to be HIV-positive or with unknown HIV-status in the 6 months before diagnosis. This may have introduced misclassification error in the reporting of serodiscordant UAI pre-diagnosis, as it was not possible to ascertain whether the respondent was HIV-positive or negative when serodiscordant UAI partners were reported in the 6 months pre-diagnosis. It is conceivable that some of the serodiscordant partners reported pre-diagnosis were actually concordant. Similarly, the limitations of using serodiscordant UAI as a proxy for transmission risk should be acknowledged. Serodiscordant UAI has many variations, and can be undertaken in combination with other risk-reduction methods which were not ascertained in this survey; such as strategic positioning (where the HIV-positive partner assumes the receptive role) and withdrawal (where the HIV-positive partner withdraws before ejaculation), along with undetectable viral load [218]. Indeed, amongst the men who engaged in high-risk sex and were on ART, it was not possible to determine whether risky sexual behaviour was undertaken whilst undetectable on ART as there was no temporal sequence data for sexual behaviour in relation to ART initiation. The median time to achieve undetectability has been estimated at 12 weeks [219] and the BHIVA TasP Position Statement specifies that viral load should sustained at <50 copies/mL for 6 months prior to being classed as uninfectious [217]. Given these stipulations, it is likely that many of the men on ART in this study did not meet BHIVA criteria for being classed as "uninfectious". Whilst it would have been possible to extend the questionnaire length and enquire in more depth about resumption of sexual behaviour and timing of sex especially in relation to initiation of ART, keeping the survey as short as possible was crucial to maximise participation. In addition, a cross-sectional design is a sub-optimal approach to understanding resumption of sexual behaviour as it is subject to recall bias, and it was not possible to ascertain exactly when sexual behaviour resumed. An observational cohort approach, including repeat surveys at regular follow-up intervals alongside clinical measures of viraemia would be the best approach for understanding resumption of sexual behaviour following diagnosis in EHI.

This survey included questions which may be regarded as sensitive by some people and may not be answered truthfully. Providing-socially desirable responses to questions, especially for

sexual behaviours known to be high risk is a known problem and, whilst there is no way to prevent it, steps were taken to minimize its occurrence. To minimise the influence of interviewer bias, the questionnaire was designed to be self-completed and all study documentation assured anonymity of the data. Clinic staff were asked to reassure participants of the anonymous nature of the study and respondents were provided with a sealable envelope to put the questionnaire into after completion. Nonetheless, survey completion in the clinic setting may have resulted in reports of lower partner numbers and fewer high-risk behaviours, which would underestimate the prevalence of high-risk behaviours linked to secondary transmission of HIV.

The possibility of recall bias is also introduced with this study design. Men were asked to recall numbers of sexual partners in the six months prior to HIV diagnosis and in the time between HIV diagnosis and questionnaire completion. Recall of events is likely to be easier for those who are less sexually active, and over shorter durations. During the questionnaire piloting men were asked to use the "walk through" method to describe how they were answering the partner number questions. It was commonplace for men with larger partner numbers to use logical estimation methods for example, "I averaged two sex partners a week over that period and there are 4 weeks in a month, so that's 8 a month multiplied by 6 months". Some even went so far to include holidays in the estimation, and increase partner numbers accordingly. As the focus on the analyses here was less on partner numbers and more on overall prevalence of sexual behaviour, it is unlikely that recall bias where partner numbers were over or underestimated by a small amount would have affected the overall associations.

Another limitation with the survey design is that men had different recall periods for the sexual behaviour after HIV diagnosis, depending on time elapsed between HIV diagnosis and completing the questionnaire. Unsurprisingly, men were more likely to have resumed having sex the longer the time interval between questionnaire completion and diagnosis. Whilst I adjusted for this interval in all regression analyses, it is likely that a number of the men interviewed within a month of diagnosis may have resumed sexual behaviour if they had been interviewed 2 or 3 months after diagnosis. Once again, this problem could not have been avoided given the financial and logistic constraints of the study, however warrants acknowledgement.

In an ideal world, I would have undertaken a follow-up study with men asked to complete the survey at diagnosis, and then again 3, 6 and 12 months after diagnosis. This approach would have enabled us to establish more of a temporal sequence between independent variables and the outcomes of interest, whilst also standardising recall periods. However, it would have also brought with it another set of challenges. Many clinics were reticent to approach patients for research at the point of diagnosis due to the heightened emotions at this time, and the potential for disengagement from care following diagnosis may have hampered follow-up. Such a study design is also very labour-intensive and would have required selection of a smaller number of large HIV clinics in which to run the study. Given the small population under study and the necessity for 12 months follow-up, this would have to result in a much longer study period. Instigation of a simple cross-sectional design in this case allowed us to achieve a greater geographical spread, with over a third of the respondents recruited from 8 centres outside of London, and is a strength of the study.

One other important caveat of the study findings is that agreement with statements in a survey is not necessarily the same as acting on them. Acceptability and intention does not necessarily translate to behaviour but as evidenced here, the uptake of ART amongst these MSM was high with nearly half of men already on ART by the time they completed the questionnaire.

Invariably with surveys, there are topics it would have been interesting to include in the final questionnaire. With retrospect, including a measure of HIV related stigma and mental health would have been useful in this study, as well as including questions to ascertain ART knowledge, previous PrEP use and sex work. In addition, it would have been useful to use principal component analysis (PCA) to understand the underlying components of the attitudes and beliefs identified in workstream 2 phase A. Unfortunately as attitudes and beliefs around early ART were different according to ART status in the survey, the number of observations were relatively small (n=55 on ART and n=61 ART-naïve), and the number of variables (p) to include in the PCA models were relatively large (p=14 for MSM on ART and p=12 for ART-naïve MSM). The subsequent observation to variable ratios for both MSM on ART and ART-naïve were too small to be able to use PCA reliably [220].

Use of PCA could have also been beneficial in overcoming the observed multicollinearity by reducing the number of covariates in the multivariate sexual behaviour model, however the

observation to variable ratios were even smaller in this analysis than in the factors associated with cART analysis, thus rendering the approach inappropriate in this study context. The only other way of dealing with collinearity is by the removal of variables with evidence of high correlation. This approach was deemed unfeasible due to the very high correlation amongst almost all of the associated covariates; all sexual behaviour covariates, ever taken PEP, and chemsex pre-diagnosis. The removal of all of these collinear measures would have amounted to little more than the univariate models presented.

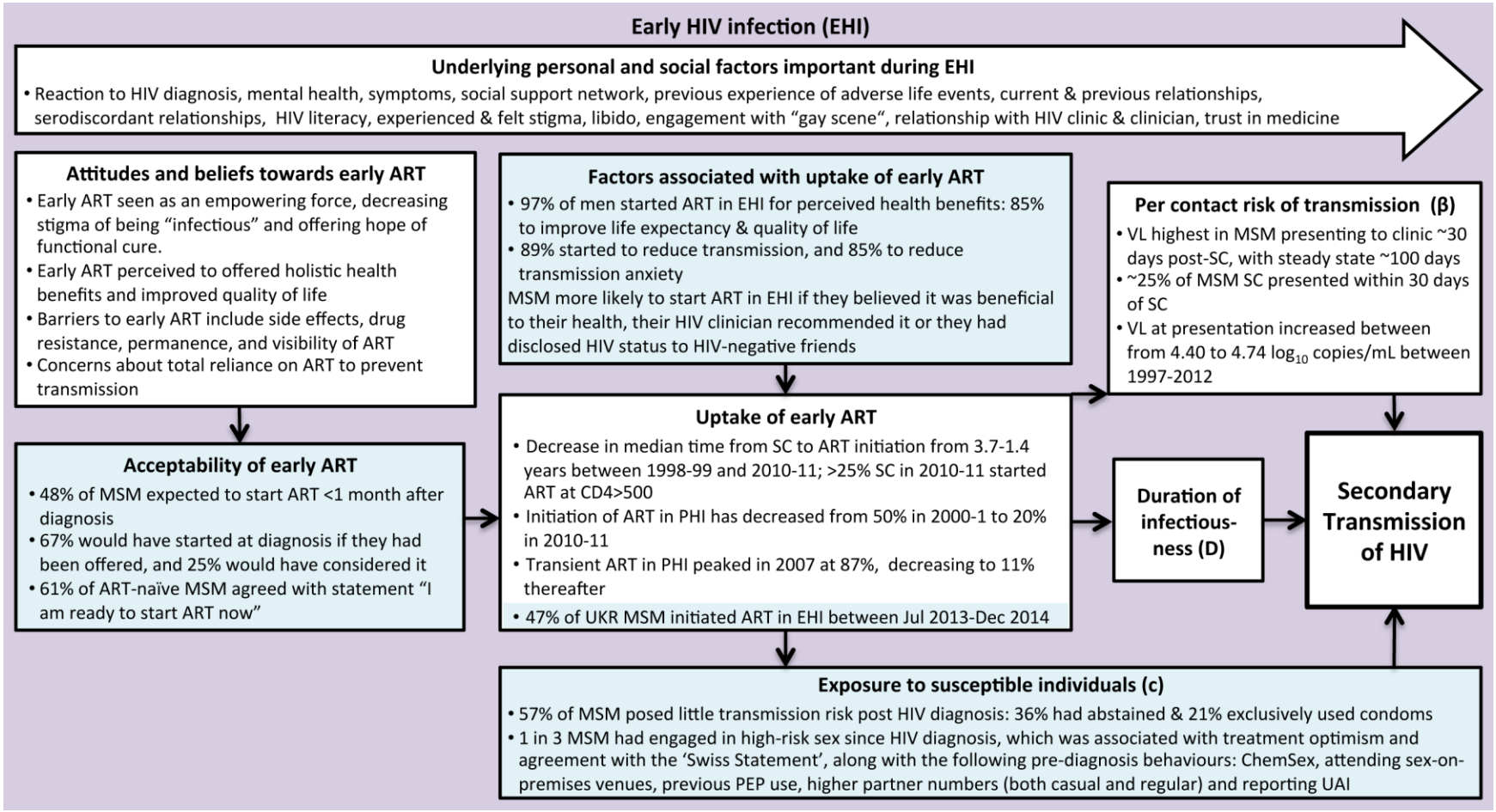
6.8 Chapter summary

The findings presented in this chapter are highlighted in blue overleaf on the theoretical framework (figure 6.10). In this chapter I have shown that offering ART at the point of diagnosis is acceptable to the majority of the MSM with EHI who were surveyed; most would have accepted ART at diagnosis if they had been offered it by their clinician. Almost half of the men surveyed had initiated early ART and, of those who had not, around half expected to start ART in the next month. Men reported starting ART for health reasons in addition to preventing transmission of HIV, an interesting finding due to the lack of randomised clinical trial evidence indicating clinical benefit of earlier treatment at the time of the survey.

Believing that earlier ART is beneficial to health, and being willing to start ART at diagnosis if it had been offered, were most strongly associated with early ART initiation. The role of the clinician was also important, and men were more likely to have initiated early ART if they had been advised to do so by their doctor. It also appeared that men who had initiated ART were more likely to have disclosed their status to HIV negative friends, perhaps reflecting a tighter social network amongst men who were on ART.

From a TasP perspective, I have shown that over a third of men reported engaging in high risk sex that could have led to secondary HIV transmission since receiving their diagnosis. Nearly 1 in 10 of the men surveyed reported having one or more serodiscordant/status unknown UAI partners since their HIV diagnosis, and over a quarter of men surveyed had engaged in ChemSex and AI since their diagnosis. Given the lack of control and loss of inhibitions commonly reported during ChemSex, there is an elevated risk that secondary HIV transmissions may have occurred from these men since HIV diagnosis.

Figure 6.10 Conceptual framework of the thesis including results from workstream 1 and both phases of workstream 2



7 Discussion

In this chapter I present a synthesis of the findings from the two workstreams of this PhD to answer the overarching research question. The key findings from each of the three results chapters, covering the statistical analysis of UK Register data (chapter 4), the qualitative in-depth interview study (chapter 5) and the cross-sectional survey (chapter 6), are presented in the context of work which was published from 2010 onwards, after my literature reviews were completed. Where possible, I triangulate the findings from all three chapters discussing how they contrast and complement each other to deepen our understanding of the mechanisms and reasons behind some of the observations. I then discuss the implications of the thesis findings on clinical practice and policy, and my recommendations for future research.

7.1 Main thesis findings

This multi-disciplinary, mixed-methods PhD sought to answer the following overriding research question:

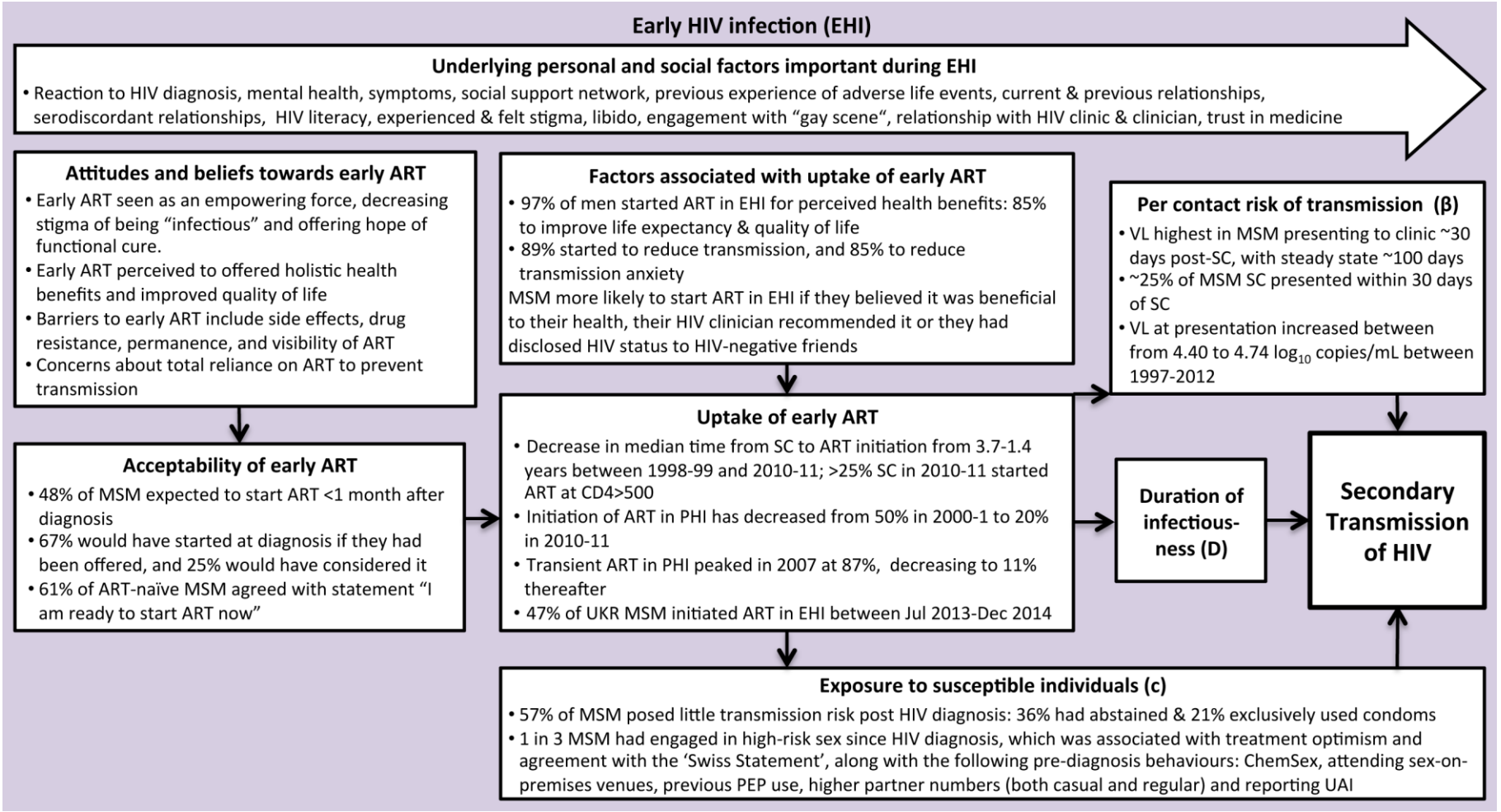
> *"Is early antiretroviral therapy acceptable to MSM with early HIV infection attending UK HIV clinics, and could it be used in this population to reduce HIV transmission risk?"*

The research question is composed of two components: the acceptability of early ART and the potential utility of early ART in the context of the current HIV epidemic amongst MSM in the UK. The main thesis findings are summarised in the conceptual framework in figure 7.1, and a synthesised overview of the key findings now follows.

7.1.1 Early ART is highly acceptable to MSM with early HIV infection

Data from the cross-sectional survey indicated early ART was highly acceptable at the point of HIV diagnosis; 2 in 3 of the men surveyed would have accepted early ART if it had been offered to them, with 24% stating they may have and only 9% stating they would not have. Nearly 50% of respondents expected that they would start ART within a month of diagnosis, and of those men who were still ART-naïve at questionnaire completion, 61% stated they were ready to start ART now.

Figure 7.1 Conceptual framework of the acceptability and utility of early ART to reduce HIV transmission amongst MSM with early HIV infection in the UK



At the time of writing, no studies investigating acceptability of early ART amongst MSM with EHI in the UK had been published with which to directly compare these results. A review of the literature published up until December 2012 investigating acceptability towards TasP identified only three studies in which acceptability towards TasP was measured [221]. Of these studies none were directly applicable to the population under study here: two were conducted amongst of PLWH with chronic infection recruited form HIV clinics in the US [222,223], and one online survey of HIV-positive (11.7% of respondents) and negative MSM in Australia [224]. The article by Kalichman et al, examined the association between belief that undetectable viral load decreases transmission risk and STI infection amongst MSW and MSM using a cross-sectional design, finding that the proportion of respondents with an STI held greater belief in that undetectable meant uninfectious [223]. Dombrowski et al reported that 56% of a random sample of 136 ART-naïve PLWH (MSM and MSW) attending a Seattle clinic expressed interest in initiating ART solely to reduce transmission, and that 61% of them believed that doctors should offer TasP to patients [222]. Holt et al conducted a cross sectional online survey amongst 1,283 MSM in Australia comparing attitudes to PrEP and TasP between HIV-positive and negative MSM [225]. The authors reported similar attitudes to PrEP amongst positive and negative men, though compared to HIV-positive men, HIV-negative men were less likely to believe in there were health benefits to ART, and that undetectable viral load means an individual is uninfectious. In addition to the above studies, a qualitative study was also conducted involving semi-structured interviews with recently diagnosed Australian MSM to elicit their opinions on ART [226]. In this study, conducted between 2011 and 2012, 53 men who were diagnosed with HIV within the last two years were recruited across all Australian states and territories except the Northern Territory, with half of the respondents having started ART. The themes identified in this study were similar to those emerging from the qualitative work presented in this thesis, with the men demonstrating a range of knowledge of ART and TasP and notably seeing ART as a personal balancing act between the benefits and risks of ART.

Perhaps the most appropriate study investigating acceptability of early ART in the UK with which to compare these thesis results is the ASTRA study which was published after the aforementioned review. ASTRA examined the attitudes of 281 ART-naïve PLWH with CD4≥350 recruited from 8 HIV outpatient clinics in the UK, 85% of whom were MSM [227]. ASTRA reported that 63% of respondents stated they would start ART “now” to reduce risk of serious illness, or to make themselves less infectious to a sexual partner. A comparison between findings from this thesis and the ASTRA study is possible in relation to the

statement “I would want to start treatment now if this would make me less infectious to a sexual partner, even if there was no benefit to my own health”, as the same statement was used in both studies. A much higher proportion of ART-naïve MSM with EHI in this thesis (81%) agreed with this statement compared to the ASTRA respondents (45%). Also of note, the proportion undecided over the statement was far lower in this study at 17%, compared to 30% in ASTRA. This difference could be due to the new evidence and extra publicity TasP had received by the time I conducted my survey in July 2013-December 2014, compared to ASTRA which was February 2011-December 2012.

When I embarked on this PhD, only observational evidence existed indicating ART could prevent sexual transmission of HIV, and that initiating earlier ART, whether during PHI or at CD4>350, may be beneficial compared to delaying it. Since then, the evidence base on both TasP and early ART for clinical benefit has grown dramatically with several key studies reporting findings which have resulted in shifts in attitudes towards early ART. Specifically from a TasP perspective, observational evidence from the Partners in Prevention study showed a 92% decrease in risk of transmission amongst heterosexual serodiscordant couples where the HIV-positive partner had started ART [228]. This was corroborated in 2011, with the publication of findings from the landmark HPTN-052 trial which provided randomised evidence of a 96% (95% CI 73%-99%) reduction in transmission amongst serodiscordant couples where the HIV-positive partner received immediate ART treatment, compared to deferring it [215]. In total, 39 transmission events were observed across both treatment arms, four of which occurred in the early therapy group. However comparison of the HIV viral genotype between partners where a transmission event was observed revealed that only one of the four observed transmission events was acquired from the HIV-1 infected partner, indicating that the other three events had occurred outside of the study partnership. Moreover, the single transmission event which remained attributable to the index partner in the early treatment arm occurred within the first three month follow-up period following ART initiation when viral load is unlikely to be totally suppressed. One of the main limitations of this study was that it was conducted in predominantly heterosexual couples in Africa and Asia, and questions remained regarding the generalisability of the results to MSM.

Following publication of HPTN-052, BHIVA guidelines were updated to include TasP guidelines, recommending the evidence that ART lowers transmission is discussed with all patients including an assessment of current risk of transmission to others, and that after

this, if a patient wishes to commence ART with a CD4>350 the decision is respected [229]. In January 2013, after recruitment to ASTRA closed but before my survey began, BHIVA and EAGA released a joint TasP position statement, outlining in detail the specific conditions that should be in place to achieve a low risk of transmission on ART [217]. These conditions were that viral load must be sustained at ≤50 copies/mL for a minimum of 6 months, that both partners be free of other STIs (as verified by STI screens for both partners, and after every occurrence of sex outside the partnership), and that viral load monitoring occurs every 3-4 months.

Also during the course of my survey, in March 2014, the interim analysis from the PARTNER study (a large observational cohort of serodiscordant couples) corroborated the HPTN-052 findings by reporting that the best estimate of risk of sexual transmission of HIV whilst on ART was zero [230]. Crucially, the PARTNER study findings included a substantial proportion of MSM as well as MSW; over half the couples enrolled were MSM with 21,000 of the 44,500 condomless sex events being anal sex. Whilst the rates of transmission for both anal sex (men and women combined) and anal sex with ejaculation were estimated at 0 per 100 couple-years follow-up, the upper 95% confidence intervals for these estimates were 0.96 and 1.97 per 100 couple years, respectively. Phase 1 of the PARTNER study has since been published showing no linked transmission events to have occurred in the study, hence the best estimate of risk of transmission on ART remained zero [231]. This was accompanied by a reduction of the upper confidence interval for the risk of transmission for anal sex (men and women combined) to 0.71 per 100 couple-years of follow-up. Unlike in a clinical trial setting where research conditions are optimised, the observational design of PARTNER means the findings are representative of the real world setting, as is reflected in the reports of inconsistent or total absence of condom use in partnerships.

Further evidence of the effectiveness of TasP amongst MSM serodiscordant couples has also been provided by the Opposites Attract study, a cohort of serodiscordant MSM couples currently under follow-up in Australia, Thailand and Brazil [232]. Though Opposites Attract is not powered to give as precise estimates as PARTNER, the interim findings indicated there were no transmission events in the 90.8 couple years follow up encompassing a total of 5,905 acts of condomless AI across 88 couples. The estimated incidence rate for condomless sex was 0 (95% CI 0-4.06) per 100 couple years follow-up. Given the randomised evidence supporting TasP, and now observational evidence suggesting a low

risk of transmission between serodiscordant MSM, it is unsurprising that acceptability to ART is high amongst the men in this survey.

7.1.2 Uptake of ART in early HIV infection was high

In line with the very high acceptability of early ART found in this thesis, the uptake of early ART was also high amongst MSM in the cross-sectional survey with 47% of MSM having started by the time of questionnaire completion at a median of 76 days (IQR 23, 191) post-diagnosis. To some extent, this corroborated the findings of workstream 1, the analysis of data from the UK Register of HIV Seroconverters, which showed a more rapid rate of uptake of ART over calendar time in 2010-11, resulting in a decrease in median time from seroconversion to ART initiation from 3.7 years pre-2000 to 1.4 years in 2010-2011. These findings of initiation sooner after seroconversion in more recent years and at higher CD4 counts are broadly in line with those previously reported amongst PLWH in the UK [47,233]. However, analysis of UK Register data also revealed a tapering in the proportion of seroconverters initiating ART in PHI from 2004 onwards, with only around 1 in 5 seroconverters presenting in PHI starting ART in PHI in 2010-11. So, whilst the overall time to initiation has decreased, this does not appear to be driven by targeted treatment of PHI.

Using time to event analysis of the UK Register is the optimal way to examine trends in ART uptake as it accounts for loss to follow-up, but it also necessitates a long follow-up period and so I could only include data up until 2010-11 in the analyses. The findings from the cross-sectional survey which ran from 2013-14 suggested that time to initiation may have decreased further after 2011, as 47% of MSM respondents had initiated within 1 year of their diagnosis, and, of those who had, 69% had done so within a month of their HIV diagnosis. Whilst a further decrease in the time to ART initiation is likely due to the mounting evidence for TasP and ART for health benefits, the comparison between the cross-sectional and time to event analysis has some caveats. Firstly, it assumes that the cross-sectional survey sub-population is representative of the wider UK Register population and whilst there were no differences between the respondents and non-respondents in terms of clinical and demographic characteristics, it was not possible to compare their attitudes and beliefs towards early ART. Equally, it may be that the UK Register centres who recruited to the survey had more of an interest in early ART and therefore were more likely to discuss, and/or recommend early ART, than the centres who did not recruit to the survey. Both of these situations could have resulted in a selection bias towards survey

respondents who were more amenable to early ART, and resulted in an overestimation of the proportion of MSM with EHI who start ART early in the UK.

7.1.3 Attitudes and beliefs towards early ART

One of the strengths of using mixed methods research design is that it permits triangulation of qualitative and quantitative findings to facilitate a deeper understanding of mechanisms underlying the observed high acceptability and uptake. In workstream 2 I explored the context of EHI diagnosis through in-depth interviews by asking men about their experiences over this time, along with the way men felt about ART in EHI. I then estimated the prevalence of selected themes identified from the qualitative study in the multi-site cross-sectional survey. The information from this mixed-methods thesis results in both an estimate of the prevalence of attitudes and beliefs towards early ART, along with the depth of understanding of the mechanisms behind the findings.

7.1.3.1 Early ART to prevent transmission: altruism or self-protection?

Nearly 90% of men who started ART in the survey agreed with the statement "I started ART to reduce the risk of transmission to my sexual partner(s)", however, 85% agreed with the statement "I started ART to reduce my anxiety about transmitting HIV to my sexual partners". The in-depth interview study revealed a strong desire and a felt responsibility to protect sexual partners from HIV infection, with TasP regarded as one way to achieve this. These feelings of responsibility to protect partners, both long term and casual, were also widely reported by Down et al, in their semi-structured interviews with recently diagnosed MSM in Australia [226]. In line with previous work by Nimmons et al on prevention altruism [178], this desire to protect partners could at least partially be ascribed to selfless motivations to protect others from experiencing the emotional turmoil of an HIV diagnosis that they were themselves experiencing. However, personal motivations were also present amongst the men interviewed. An extreme anxiety over transmitting HIV to sexual partners was linked to worries around potential prosecution for intentional transmission, dissolution of relationships and the overwhelming feelings of guilt that would accompany a transmission event. The alleviation of stress and anxiety of HIV transmission afforded by TasP, at this time of intense emotional upheaval, was regarded as a major advantage of early ART amongst the men in this thesis.

7.1.3.2 TasP was not the panacea of HIV prevention, but another arrow in the risk reduction quiver

One concern with the widespread rollout of TasP is "risk compensation", the idea that people will come to depend solely on ART to prevent transmission, resulting in reduced use of condoms along with other risk-reduction methods. My survey revealed that 61% of men agreed with the statement "Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom", and 85% of the men who started ART appeared to do so to reduce transmission. But the in-depth interview study indicated that whilst men might believe that ART reduced transmission, this would not automatically result in the abandonment of other risk reduction strategies, predominantly using condoms and serosorting. In fact, despite evidence for the efficacy of TasP, total trust in it to prevent transmission was notably lacking; any risk of transmission was perceived by some as a risk too many. This was especially true of MSM interviewed who were in long term serodiscordant partnerships, where the strong emotional element present in the partnership exacerbated the perceived responsibility to protect their partner form HIV. Even amongst MSM who were not in a serodiscordant relationship, ART was referred to as an additional method of risk reduction to add to their armoury of condom use, serosorting and strategic positioning. This finding amongst HIV-positive MSM, that TasP tends to be viewed as an additional risk reduction methods to complement existing ones, is in line with findings from the qualitative research amongst HIV-negative MSM who use PrEP to reduce transmission [234–236].

One finding of note from the in-depth interview study was that TasP may enable risk reduction via an additional pathway than by solely reducing the probability of transmission due to undetectable viral load. TasP was perceived by the men interviewed to facilitate HIV disclosure, and this was confirmed in the survey data; 60% of men on ART agreed that "Being on ART makes it easier to disclose my HIV status to sexual partners". Discussing HIV status with sex partners is a key component of successful implementation of sero-adaptive risk-reduction behaviours such as strategic positioning and serosorting. This finding appears to reflect the adoption of viral undetectability into safer-sex negotiations, as has been reported amongst MSM in the Netherlands, where 63% of the 120 HIV-positive men who reported UAI since diagnosis had factored undetectable viral load into the decision to engage in UAI with a partner; 44% with HIV-positive partners (to avoid super-infection) and 38% with presumed HIV-negative partners (to prevent transmission) [237].

Findings from the in-depth interviews may shed light on the reasons why ART is perceived to facilitate status disclosure. Despite the medical advances which have made HIV a manageable disease, and no longer a death sentence, the stigma surrounding HIV infection remains, even amongst high prevalence populations like MSM in the UK [238–240]. Stigma can manifest as enacted stigma, defined by Scambler as an episode of discrimination against someone with HIV, and also as felt stigma, which is comprised of two elements: a personal feeling of shame associated with being HIV positive, in addition to the fear of enacted stigma[2]. A systematic review of the literature on social support, stigma and HIV disclosure noted the existence of an inverse relationship between felt stigma and HIV status disclosure [241]. Discussion of HIV status is commonly regarded amongst UK MSM as a "unilateral responsibility" attributed to either the person with HIV (to disclose their positive status voluntarily), or the HIV negative partner (to ask about HIV status), with very few men regarding it as a "shared responsibility" [238].

There was a strong perception of responsibility to disclose HIV status amongst the men interviewed, and this created an anxiety about forming new sexual partnerships. Disclosing their HIV status was perceived to put them at risk of experiencing enacted stigma through sexual rejection by potential partners based on HIV positivity, irrespective of whether this outcome was likely or not. Felt stigma was very evident amongst the men interviewed and when reflecting on their feelings about being HIV positive, men commonly struggled with the concept of being "infectious", describing themselves as "dirty" or "grubby". For the men in my study, this felt stigma caused both by the fear of enacted stigma and the shame of being infectious, and in some cases experience of enacted stigma itself, resulted in problems with forming relationships and sexual abstinence. ART was regarded as a way to reduce this label of being infectious by decreasing the amount of virus in the body, and thus alleviating some of the associated felt stigma. Improved self-efficacy and agency afforded by felt stigma reduction can facilitate negotiation of sexual encounters using the reduction in infectiousness as a way to mediate the risk of encountering enacted stigma.

Despite the positive effect TasP may have in reducing transmission anxiety and facilitating disclosure, it should be noted that the preventive element of ART can be perceived as an additional burden to some individuals. Young et al highlighted that the availability of TasP might result in an external expectation on HIV-positive individuals to take TasP due to the public health benefits which could in turn result in constrained treatment choices and poor mental health [242]. They argue that these feelings may add to the "burden of prevention"

that HIV-positive individuals already carry, due to the addition of ART adherence to the existing social expectations to disclose HIV status and negotiate safer sex.

Ultimately, the ideal scenario is one where the responsibility to negotiate safer sex falls with both HIV negative and positive parties, yet the most recent Gay Men's Sex Survey indicated that 67% of men in England had not discussed HIV status with their last casual sex partner [239]. As the evidence base supporting TasP expands and uptake increases, it is likely that the knowledge about TasP in the MSM community will also improve. Whether an improved knowledge of TasP in the wider MSM community brings with it a reduction in the likelihood of experiencing enacted stigma in the form of sexual rejection based on HIV serostatus, remains to be demonstrated. Recently published data from a cross-sectional internet survey conducted in Australia in 2012, indicated that 1 in 5 HIV-negative and positive MSM reported being willing to have UAI with a serodiscordant partner if the HIV-positive partner was on ART, however this willingness was independently more likely to be reported by HIV-positive MSM [243]. It is likely knowledge and attitudes to TasP amongst MSM have changed since the data were collected in 2012 however, due to recent results from the PARTNER and Opposites Attract studies [230,232,244]. The high efficacy and effectiveness of PrEP in preventing HIV acquisition amongst high-risk MSM [245,246] will also go some way towards achieving a balance in the responsibility to prevent HIV transmission between HIV-positive and negative MSM, by providing a biomedical tool with which HIV negative men can protect themselves from HIV, so long as it becomes widely available in the UK, which at the time of writing is not the case.

7.1.3.3 Men believed there were health benefits to starting ART early

Nearly all of the survey respondents (96%) who had initiated early ART reported that they started "to control the spread of HIV in my body" and "to reduce the damage HIV was doing to my body". In addition, 38% percent of the men who initiated ART by the time of survey completion had chosen to do so solely, or predominantly, for their own health. In multivariate analysis of factors associated with early initiation, men who agreed with the statement "It is better for my health to start ART earlier rather than later" were 17 times more likely to have initiated early ART than those who did not agree. The strong health beliefs in early ART demonstrated by the survey respondents was of particular interest, given the absence of randomised clinical evidence of any health benefit to ART over the study period (2010-2014).

Whilst during the study period the HPTN-052 study provided RCT evidence of the efficacy of TasP [215], no equivalent RCT was published to tip the equipoise regarding clinical benefit of early ART initiation. This remained the case until the findings of the START trial were published in 2015, showing that earlier initiation of ART at CD4>500 improved health outcomes when compared to deferring to CD4≤350 [247]. Several observational studies were however published over the PhD study period to indicate a potential clinical benefit of initiation of ART in chronic infection at higher CD4 counts [215,248–253]. In addition, data from the HTPN-052 trial revealed the early ART arm, who initiated at CD4 350-550 cells/mm^{3,} experienced 41% (HR 0.59; 95% CI 0.40-0.88; p=0.01) fewer clinical events (serious HIV-1 related clinical events or death) than the deferred treatment arm (who initiated at 200-250 cells/mm^3) [215]. Of the 105 events observed, 99% occurred in Africa and Asia, and most were tuberculosis-related but there were no differences between the arms in overall mortality. The findings from these studies, along with the increased evidence on the efficacy of TasP, led to several national and international bodies changing their treatment recommendations over the study period, with IAS-US [254] and France [255] updating their treatment guidelines to recommend universal test and treat approach. The US-DHHS [256] and WHO [257] switched to recommending treatment initiation for asymptomatic PLWH at CD4≤500 cells/mm^3 and EACS recommended clinicians to "consider" treatment in asymptomatic HIV infection [258], though they maintained the recommended threshold at ≤CD4 350 cells/mm^3. Over this same period BHIVA maintained their recommendation to initiation ART at CD4 ≤350 cells/mm^3 in those with chronic asymptomatic infection [229].

The release of the START trial results in May 2015, after recruitment to the UK Register survey sub-study had ended, resulted in a global change to HIV guidelines with a universal recommendation of immediate ART initiation after HIV diagnosis. START randomised 4685 individuals with CD4>500 from 35 countries to receive immediate ART (n=2326), or to the deferred treatment arm to receive treatment when CD4 count fell to 350, or the patient developed an AIDS-related event [247]. Patients were followed up for a median of 2.8 years (IQR 2.1-3.9 years), over which time 138 primary end-point events (a composite of serious AIDS-related events, serious non-AIDS events or death) were reported. Despite the rate of AIDS and non-AIDS events being lower than expected, the trial was stopped early as the rate of the primary end point was 57% lower in the early treatment arm, compared to the deferred arm (hazard ratio [HR] 0.43; 95% CI 0.30-0.62; p<0.001). These findings were consistent across age, sex, race, geographic region, baseline CD4, baseline viral load, smoking status and Framingham 10 year coronary heart disease risk. The most commonly

experienced primary end-point events were cardiovascular disease, non-AIDS defining cancers and tuberculosis, with 62% of the tuberculosis events observed in Africa. Aside from the rate of bacterial infections, which was 48% lower in immediate treatment arm, no evidence of differences between the arms in the secondary outcome of symptomatic grade 4 events (potentially life-threatening symptomatic non-AIDS events requiring medical intervention) was found at the 5% level. As the majority of primary end-point events were observed at CD4 counts >500, and AIDS-related events were observed amongst individuals with full viral suppression, the authors postulate that damage to the immune system is done early in infection and is not adequately captured by measuring CD4 count.

The ANRS TEMPRANO trial also provided randomised evidence supporting immediate versus deferred ART initiation, though in this case using a 2x2 factorial trial design incorporating isoniazid preventive therapy and conducted in the Ivory Coast [259]. The study team reported a 44% lower risk of the primary endpoint (a composite of AIDS and non-AIDS related events, all-cause mortality at 30 months) in those starting immediate ART arm versus the deferring (HR 0.56; 95% CI 0.41-0.76). Unlike in START where a CD4 threshold was used to define early versus deferred therapy, deferred ART was initiated in TEMPRANO according to WHO guidelines and these changed twice over the course of the study period [260,261]. Nonetheless, when the study team restricted the analysis to individuals with CD4>500 at baseline to rule out any bias from the WHO guideline changes the effect of early ART on severe events remained unchanged.

Understanding of the clinical benefits of initiating ART specifically in PHI also improved over the study period, thanks to further observational analyses indicating improved immunological recovery to normal levels with earlier treatment [262], reduced the HIV RNA and DNA reservoir size [263], lower T-cell activation [263] and protection of T-cell memory cells [264] thus improving dedicated immune response [265,266]. However the three randomised trials designed to evaluate the benefits of short-course ART in PHI that were published over the study period; ACTG A5217, Primo SHM and SPARTAC, all found modest but transient beneficial effects of early therapy. The ACTG A5217 trial randomised individuals presenting within 6 months of seroconversion to receive 36weeks of short-course ART or deferred ART. A higher proportion of the deferred treatment arm met criteria for antiretroviral re-initiation at 72 weeks; 50% versus 10% in the early treatment arm, and median time to re-initiation was modestly higher in the early treatment arm [267]. PRIMO SHM also found that individuals with PHI randomised to receive transient ART (of 24 or 60 weeks duration) had a

lower viral set point (4.0 and 4.3 log_{10} copies/mL, respectively) at 36 weeks post treatment interruption versus 4.8 in the deferred treatment group, though this effect was transient [268]. They also found time to ART re-initiation was longer in the 24 and 60 week early treatment arms compared to the deferred treatment arms, with a hazard ratio risk of restarting 0.42 (95% CI 0.25-0.73) and 0.55 (0.32-0.95), respectively. The SPARTAC trial examined 12 and 48 week short-course ART in PHI, compared to no therapy [216]. Compared to the no-early treatment arm, the time to needing long-term treatment after treatment interruption was delayed in the 48 week treatment arm, but this was only by an average of 65 weeks, only 17 weeks more than the length of the short-course treatment itself. Importantly, timing of initiation was crucial, as higher CD4 and viral load benefits were seen the closer ART was initiated to HIV infection. In addition, further analyses of SPARTAC data have shown that those who spent longer on ART were more likely to control viral load after HIV infection [269]. It is notable that across all trials, the beneficial effects of early ART were transient in the majority of individuals.

Whilst the high proportion of men who believed in a health benefit of earlier ART was likely due to the wealth of observational data available in conjunction with the international guidelines recommending earlier ART, the in-depth interview study highlighted that MSM's definition of health was not always in concordance with the medical definition of health. The clinical benefit of early ART, most commonly operationalised as maintenance of a high CD4 count, an undetectable viral load and absence of HIV-related morbidity and mortality, is what drives ART recommendations for the majority of clinicians [270]. What was apparent from the in depth interviews, was that whilst men appreciated that these were important elements of good health as an HIV-positive man, they were also abstract concepts and were only as part of a wider concept of holistic health. Men talked about ART affording other health benefits by improving quality of life, giving more energy for socialising and exercising and improving mental health by reducing stress and anxiety of transmission and reducing HIV-related stigma. These perceived benefits can be as important in the decision to start ART as the clinical benefits, but are rarely considered in randomised controlled trials. So, whilst the START findings have resulted in a shift in the clinical recommendation of ART and in the attitudes of clinicians, it may not have had such a profound effect on patient attitudes, as many men believed in a health benefit of early ART prior to the START results.

7.1.3.4 Early ART was empowering and brought hope of a functional cure

The in-depth interview study highlighted the role early ART could play in empowering MSM who were coming to terms with their HIV infection, thus increasing self-efficacy and agency. Men reported feeling a loss of control over their lives and bodies at this time due to the virus. Early ART could be perceived as an empowering force by virtue of it facilitating regaining the control lost by HIV infection, both of one's body by fighting and controlling viral replication, and of one's sex life, by easing the anxiety over infectiousness as previously discussed. These findings were also notably similar to those reported by the recently diagnosed Australian MSM interviewed by Down et al, who reported a strong discourse of control amongst the men, with fighting the virus, taking charge of one's body and being proactive all cited as reasons to start early [226].

ART was also empowering for a different reason for the men interviewed in this thesis. During 2013 and 2014, much mainstream media attention was given to the idea of early ART facilitating a functional cure to HIV, after publication of findings from the VISCONTI (Virological and Immunological Studies in Controllers after Treatment Interruption) cohort in 2013 [214]. VISCONTI involved follow up of a cohort of 14 seroconverters who maintained virological control for at least 24 months after stopping treatment initiated in PHI. Contrary to the "short-course" approach to treatment in PHI, typically lasting between 12 and 60 weeks, the median time spent on ART amongst the VISCONTI cohort was 36.5 months, the range was 12-92 months. The authors noted the probability of post-treatment control at 12 months after treatment interruption, in the French Hospital Database on HIV (FHDH ANRS CO4), was 15.3% (95% CI 4.4-26.3) and this remained stable at 24months. Interestingly, the prevalence of post-treatment control in VISCONTI was notably higher than has been reported by the CASCADE collaboration, who found only 4% could maintain undetectable viral load for longer than 2 years following interruption of ART [271,272].

Nonetheless, the widespread publication of the VISCONTI results in the mainstream media led to two interview respondents, who were highly knowledgeable about HIV and ART, starting early ART in the hope they may be able to achieve a functional cure. To these men, early therapy presented the hope that they too could be post-treatment controllers and achieve a functional cure. Interestingly these men were confident that there would be a cure in their lifetime, and there was a hope that by controlling the viral reservoir so early on, they would be in a better position to benefit from any future cure. Whilst I did not estimate the prevalence of belief in a future HIV cure in the survey, a recent survey of

PLWH in the UK showed that overall support for HIV cure research was high (at 86%) and that the majority of respondents expected an HIV cure to be found within 10 years [273,274].

7.1.3.5 Healthcare providers attitudes to early ART were important in the decision to start

Healthcare providers' recommendation to start ART was highly associated with early initiation of ART in the survey. After adjusting for other associated factors, MSM were five-times more likely to have started early ART if they reported their clinician had recommended it. The importance of the healthcare providers', and in particular the HIV clinician's, opinions on early ART was highlighted in the in-depth interview study and was one of the reasons I chose to enquire about it in the survey.

As mentioned previously, the equipoise over clinical benefit of early ART over the study period, either in PHI or at high CD4 count, likely resulted in personal differences in the recommendation of early ART for clinical benefit. Certainly, the divergence of official recommendations between the US and UK around when to start ART was a source of consternation for some of the men interviewed who could not understand how this was possible given a shared evidence base on both sides of the Atlantic. Clinicians themselves may have held favourable views towards early ART prior to the START results, but be employed by an NHS CCG with strict commissioning rules in place preventing the prescribing of ART in the absence of RCT evidence demonstrating clinical benefit. Suspicions were raised amongst the men interviewed over whether the additional financial cost that would be incurred by recommending earlier treatment was a prohibitive factor for the NHS and the UK government to adopt a test and treat strategy, or higher CD4 threshold.

Even from a TasP perspective, whilst the results from HPTN-052 and the PARTNER interim results provided evidence of a very low risk of sexual transmission of HIV if undetectable on ART for vaginal sex over the study period [215,230], questions still surrounded the risk of transmission from anal sex. The PARTNER 2 study aims to boost the number of MSM recruited and followed up to provide to reduce the confidence interval around the estimated probability of transmission through anal sex whilst undetectable on ART [275]. Additionally, there is still no consensus on whether the presence of an STI increases the probability of transmission from PLWH with undetectable viral load though the absence of linked transmission events in PARTNER despite 18% of HIV-positive MSM reporting an STI

during follow-up is encouraging [231]. In addition, data from Australian ART prescribers showed that over half of the respondents agreed very strongly that clinical benefit should be the priority when considering TasP [270]. With the uncertainty surrounding clinical benefit and questions remaining over the application of TasP findings to MSM it was understandable that many UK clinicians held differing opinions over whether to recommend early ART to an individual or not.

The qualitative data in this thesis revealed that men's trust in the opinion of their HIV clinician was usually unequivocal as they were regarded as the "experts". These findings were mirrored in a qualitative study amongst 53 Australian MSM, who stressed how important their clinician's expertise and advice was in the matter of when to start ART [226]. Underlying the implicit trust was the assumption amongst the men that in any given situation, different clinicians will have the same opinions over early ART and will make the same recommendation. Frustrations arose for men when their opinions over early ART were not in alignment with their healthcare providers, and this could lead to a breakdown in trust and communication. In one example, a clinician was apparently dismissive of early ART when the patient requested it. In this case, the doctor allegedly told the patient the he regularly sees patients for whom "the last thing they want to do is be on treatment, they beg not to be on treatment". This scared the patient into delaying ART until after AHI, causing regret and stress. Since 2012, BHIVA guidelines have stated that all healthcare professionals should discuss the evidence for TasP, and it should be made available to those who wish to start [229], but an audit of UK HCP recently highlighted that subtle assumptions are made in the interpretation of these guidelines. Whilst 98% of clinicians would discuss TasP with individuals diagnosed in PHI who reported sexual partners since their diagnosis, fewer (81%) reported they would if no sexual partners were disclosed [276].

In the UK, HIV clinicians are the gatekeepers to early ART, and have a responsibility to present both its risks and benefits to PLWH. The results of this thesis highlight that this discussion should include the potential benefits to individual wellbeing in the form of reduced stigma, anxiety and stress, and improved self-efficacy, in addition to the clinical benefits and reduced infectiousness, which can all assist with coming to terms with HIV diagnosis. Furthermore, the survey results have shown that this discussion is acceptable to patients at the point of diagnosis. Qualitative work with HIV Specialist Nurses has highlighted the complexity involved in implementing TasP in the UK, however, reporting that decisions to start TasP are largely made on an individualised, patient by patient

basis [277]. Under these circumstances, assessing the complexity and diversity of patients' social scenarios, relationships and beliefs was perceived to be difficult and time-consuming, with the current lack of guidance and evidence available on which to base recommendations troubling.

7.1.3.6 Short-course treatment in PHI had mixed appeal to MSM with early HIV infection

Analysis of data from the UK Register of HIV Seroconverters in workstream 1 highlighted a notable decrease in the proportion of people opting for the short-course approach from 87% of those who started ART in PHI in 2006-7, to 11% in 2008-2010. From early in the in-depth interview study, a belief that initiation of short-course ART in PHI was not good for one's health was apparent amongst some respondents. Compared to the 61% of ART-naïve men in the survey who agreed with the statement "I am ready to start ART now", only 35% agreed with the statement "I would start ART now if I only had to take it for a year" and further 28% of men were unsure or undecided.

The observed pattern of decreased use of short-course ART since 2006-7 could be the effect of the Strategies for Management of Antiretroviral Therapy (SMART) trial findings [48]. This trial of CD4-guided treatment interruptions was stopped early in 2006 after interim analysis indicated increased risk of disease progression, AIDS and death was higher in the treatment interruption arm. Of note, death from cardiovascular, renal and hepatic diseases, which are typically attributed to ART toxicity, were hypothesised to be lower amongst those in the episodic treatment arm due to the lower exposure to ART, but were in fact 1.7 times higher (95% CI 1.1-2.5). Whilst the relevance of the SMART findings to a treatment naïve EHI population has been questioned (95% of participants enrolled in SMART were ART experienced) they may be off-putting for PLWH considering short-course therapy and their clinicians. Notably though, the SPARTAC trial found no evidence of increased risk of death or adverse events in the treatment interruption arm over the average follow-up of 4.2 years [216]. Men in the interview study certainly expressed confusion as to how the short-course strategy can still be used given the SMART findings. However, short-course treatment also held some appeal amongst the men interviewed. As the commitment to start was for a short period with a tangible end date, it could mediate the fears surrounding the permanence of treatment and reduce the barrier of commencing lifelong therapy.

The changes to international treatment guidelines following the START trial results have brought the feasibility of observational research into short-course ART into question. Any subsequent observational research into the clinical benefit of treating primary HIV infection will likely be problematic due to the loss of the temporal distinction between treatment in PHI and treatment in chronic infection. There is, however, still much research interest into the role of early ART in affording a functional cure. The RIVER (Research In Viral Eradication of HIV Reservoirs) trial is currently recruiting to investigate whether a "kick and kill" approach can reduce the size of the viral reservoir by using a combination of vorinostat to activate dormant reservoir cells, HIV-vaccines to boost the immune system, and early ART to kill the activated reservoir cells [278].

7.1.3.7 Fear of side effects, adherence, resistance, stigma and permanence of treatment are barriers to early ART

Concern over the side effects of ART was reported by 70% of ART-naïve men who agreed with the statement "I am concerned about the possible side effects of ART". Fear of side effects was repeatedly mentioned in the in-depth interviews and it was notable that they were regarded almost as inevitable. Interestingly, it was not entirely the side effects themselves that induced fear amongst the men, but the impact that they could have on life and work, as well as the associated increased visibility of being ill. These were at odds with the desire to maintain as normal a life as possible, and to hide one's HIV status as well as possible by avoiding looking ill. Interestingly, HIV resistance was rarely mentioned in the in-depth interviews, and almost half of MSM responded that they were unsure or undecided whether "Starting ART now could reduce my treatment options". Those who discussed drug resistance in the interviews presented it as a confusing concept, with men unsure as to whether early treatment would increase or decrease the risk of drug resistance. This finding was backed up in the survey data with, 47% of men unsure as to whether starting ART early would affect their future treatment options.

Horne et al [279] have suggested that patient's beliefs towards early ART can be grouped into two categories: perceptions of the personal needs for treatment, and concerns over adverse effects. Applying this "necessity-concerns" framework to a cohort of PLWH who had just been recommended treatment, the researchers found that those who expressed concerns about adverse events prior to starting ART were more likely to delay starting and once on ART had lower adherence at 12 months. Conversely, those scoring highly on perceived necessity were more likely to adhere to ART. What was interesting in this thesis

was the fact that despite 70% of ART-naïve men reporting concerns about drug side effects, 61% agreed with the statement "I am ready to start ART now", possibly indicating that the perceived benefits of treatment outweigh the concerns.

For 11% of survey respondents, initiating ART was perceived to not fit into their lifestyle. The in-depth interviews highlighted that adhering to ART was perceived to be logistically problematic amongst those who performed shift work or travelled long haul regularly, especially when drugs had to be taken at regular intervals and with food. Regular air travel with work was also a problem, with concerns that airport security may unintentionally disclose men's HIV status to colleagues.

The workstream 2 survey demonstrated that over half of respondents disagreed with the statement "I would not start ART now as I would have to be on it for the rest of my life", however, 1 in 5 men agreed. The lifelong permanence of treatment was deemed a sobering prospect for some men in the interviews, especially the younger ones who thought it a very abstract concept. Interestingly, the older men interviewed held a more pragmatic view of daily ART, which was seen as just another set of pills to take on top of their existing ones. What was clear was that although men were aware that ART was likely lifelong, there was also hope in the discovery of a cure for HIV in their lifetimes.

The barriers identified to early ART in this thesis, are similar to those reported from a qualitative study using focus group discussions to assess acceptability to ART amongst members of MSM and black African MSW communities living in Scotland by Young et al [242]. Additional barriers reported by the authors were the perception that taking daily ART was too much work and a lack of knowledge and awareness about TasP, which was likely to be more of an issue as half of the respondents were HIV-negative.

7.1.4 The utility of early ART in reducing onward transmission

In this section I use the biological parameters of the simple model of HIV transmission ($R_0=\beta cD$) [61,65] to describe the potential utility of early ART to reduce secondary transmission from MSM with EHI. The utility of ART to reduce secondary transmission is primarily dictated by the acceptability and uptake of ART, which was demonstrated to be high in this population, with 47% of respondents having started ART by the time of survey completion. Utility also depends on whether MSM present to clinic in time to reduce peak viraemia, which influences the per contact risk of transmission. Through the use of secondary

analysis of epidemiological data from the UK Register of HIV Seroconverters, in workstream 1, it was possible to characterise viral load at first clinic presentation amongst UK MSM, estimate peak viraemia and changes in viral load at first presentation over calendar time. The ability of ART to reduce secondary transmission also depends on sexual behaviour over the period of EHI, which forms the "c" parameter (defined by Boerma and Weir as the exposure of susceptible to infected individuals [65]). Data from the cross-sectional survey permitted estimation of transmission-risk behaviours following HIV diagnosis, along with identification of factors associated with them, with the in-depth interviews aiding understanding of these risk behaviours.

7.1.4.1 Peak viraemia is seen in men who present to clinic at around 30 days after date of seroconversion

Modelling of viral load at first presentation by time since seroconversion estimated peak viraemia to coincide with MSM presenting to clinic at around 30 days after estimated date of seroconversion, with a steady-state plateau reached at around 100 days. From a public health perspective, if investigating risk of HIV transmission for a single sexual act, these results indicate that the benefit of immediate TasP in UK MSM presenting in EHI wanes after 30 days post seroconversion and, by 100 days post-seroconversion, becomes no more than it would be for those presenting in chronic infection. Current HIV testing practices in the UK, as demonstrated by the MSM recruited to the UK Register, result in only 24% of those diagnosed in EHI presenting to clinic within 30 days of their seroconversion. Even if ART is initiated immediately amongst those who present within this time, the median time to achieving undetectable viral load is estimated at 12 weeks [219]. Hence, achievement of undetectable viral load by the advent of peak infection is unlikely in all but a few of the men presenting to clinic under current testing strategies. Notable however, were the large proportion of men (nearly 40%) who presented to clinic between 6 and 12 months after seroconversion with a viral load over 5.0 $\log_{10}$ copies/mL, indicating that some individuals present a heightened transmission risk after 100 days post-seroconversion. There is inevitably benefit in initiating TasP in EHI regardless of timing of peak viral load if the cumulative protective benefit is considered, as any reduction in the period of infectiousness will constrain the number of potential transmission events.

Under current UK testing guidelines compiled by BHIVA and BASHH, MSM are recommended to test "annually or more frequently if clinical symptoms are suggestive of seroconversion or ongoing high risk exposure" [280], though no further guidance as to the

frequency is given in the document. BASSH and PHE more recently published recommendations that MSM at high risk of HIV acquisition, (defined as having UAI with new or casual partners, or engaging in ChemSex) test for HIV and other STIs every three months [281]. HIV testing coverage amongst MSM attending sexual health clinics remains high, with 87% of MSM attending sexual health clinics tested in accordance with BASSH and PHE recommendations in 2015, and 80% of GUM clinics meeting testing targets in this risk group [282]. This accompanies reported increases in proportion of MSM in the community who report ever having an HIV test and testing in the last year, though the extent of this increase varies between sub-populations. NATSAL-3, a weighted probability survey conducted in the UK between 2010-2012, estimated 60% of MSM had ever HIV tested in the UK [283], an increase from 44% from NATSAL-2 conducted in 2000 [184], although the proportion of those ever testing who reported testing in the last year remained similar between surveys at one in three. This compares to the 91% of MSM recruited from gay commercial venues in London in 2013 who reported ever testing and 60% who reported testing in the last year, up from 63% and 26% respectively in 2000 [284]. Despite the observed increases over time in the proportion of men ever testing and those who test regularly, both amongst clinic attenders and in the wider community, HIV incidence remains high within the UK MSM population.

Recent mathematical modelling studies support the findings from the thesis literature review that undiagnosed EHI is disproportionately responsible for the ongoing increase in incidence observed amongst MSM in the UK [285–288], though estimates of the proportion of new infections vary by model from to 10% (95% CI 3-28%) [288] to 48% for undiagnosed PHI (90% CI 34-63%) [286]. These models suggest more frequent HIV testing, in combination with immediate ART initiation, could have a large impact on HIV incidence amongst MSM in the UK [285–288]. This may only be possible with a culture shift towards more regular HIV testing and immediate treatment in the UK, as to achieve an incidence of 1 per 1,000 person-years 90% of MSM would need to be diagnosed within 1 year of infection, and 90% of those diagnosed would need to be undetectable on ART [285]. The “test and treat” model was implemented in San Francisco in 2010, and since then a decrease in the population-level time to reaching undetectable viral load has been observed from 13 months in 2008 to 5 months in 2012 [289] with a decrease in the number of new infections diagnosed from 522 in 2008 to 302 in 2014 [290].

One suggested method of increasing repeat testing is through active recall, where STI clinics actively contact MSM who are at high risk of HIV acquisition, by phone, email or SMS (short message service). A recent meta-analysis of 17 studies which concluded that active recall improved re-attendance and retesting rates, though the increases differed notably across studies from 18-89% [291]. The national rollout of PHE's home-sampling initiative is designed to reach members of high-risk populations who may not attend an STI clinics [292]. Additionally, home-testing kits were licensed in the UK in 2014, and kits went on sale in 2015, though there are concerns over linkage to care, with fears that people who test positive may not present to clinic for treatment.

Nearly two thirds of the survey respondents in this thesis reported feeling unwell in the months preceding their HIV diagnosis but only one third of men reported testing for HIV because they felt unwell. Of these, over half reported their symptoms were severe enough to disrupt their daily routine. Improvement of the awareness of HIV symptoms amongst both MSM, and amongst primary and secondary care-givers to whom MSM may present with HIV seroconversion-like symptoms, should be a priority to improve HIV diagnosis in EHI. Awareness of seroconversion symptoms is of particular importance given that 1 in 5 men who reported seroconversion-like symptoms also reported UAI whilst unwell, and this was more likely to be with a regular partner. Outside of sexual health services in the UK, adherence to the BHIVA/BASHH testing guidelines has been demonstrated to be poor, with only 27% of individuals eligible for a test actually receiving one [293].

One potential method of increasing HIV testing outside of sexual health services is by the routine use of opt-out testing, whereby patients attending primary care centres and hospitals are automatically offered an HIV test, with the patient actively having to refuse the test. Indeed, current BHIVA testing guidelines recommend opt-out HIV testing upon registration with a GP surgery in areas of the UK where HIV prevalence is exceeds 2 per 1000 people [280]. Whilst no randomised evidence exists in the UK to endorse opt-out methods, recent evidence from a US RCT showed opt-out HIV testing, compared to opt-in and active choice testing, in an A&E department increases the acceptance rate (66%, versus 38% and 51%, respectively) [294]. In the UK, observational studies have estimated test uptake to range from 70-96.7% in acute general medicine (AGM) hospital settings [295–299] and between 44.5-75.4% in primary care settings [295,300–302], with qualitative studies also indicating positive attitudes to opt-out testing amongst STI clinic attendees in the South East of England [303,304]. The feasibility of implementation has also been reported to be

good [305], with evidence that coverage rates in primary care settings can be increased further with staff training and promotion of HIV testing in surgeries [300]. In addition, implementing opt-out testing in AGM scenarios in geographical areas where HIV prevalence exceeds two per 1000 people has been shown by all studies to date to exceed the cost-effectiveness threshold of one new diagnosis per 1,000 tests [297–299,305–307] and may be more cost effective than implementing universal testing in primary care settings [306].

7.1.4.2 Increase in viral load at first presentation seen over calendar time

Analysis of UK Register data highlighted a temporal increase in viral load at first presentation from 4.7 to 5.1 $\log_{10}$ copies/mL between 1997 and 2012, a difference of 75,774 copies/mL. Given the known positive correlation between infectiousness and viral load [66] this increased viraemia may translate to an increased risk of transmission in EHI over time.

Increasing initial viral loads have previously been identified amongst a European cohort of seroconverters, with those seroconverting in 2001-2 having a 0.626 (0.497-0.754) $\log_{10}$ copies/mL higher initial viral load than those seroconverting in 1985-90 [195]. Increases in viral set-point have also been reported over time, from 4.05 $\log_{10}$ copies/mL in 1980 to 4.5 $\log_{10}$ copies/mL in 2002 [308]. Upward trends in viral load in early infection, have been summarised in a meta-analysis which indicated an upward trend in viral load in early infection of 0.39 $\log_{10}$ copies/mL between 1985 to 2010 [309], though the authors note that the trend has decelerated between 2005 and 2010. Interestingly, this deceleration is reflected in my study findings, however no study published to date has included data collected after 2010, so it is not currently possible to corroborate the upward trend observed from 2010 onwards.

These observed increases in initial viral load and viral set point have led some researchers to propose an evolutionary hypothesis that HIV has evolved over time to maximise transmissibility, necessitating a trade-off between higher viraemia and disease duration [194]. Under this theory, plasma viral load is defined as a heritable trait, and maximum transmissibility is achieved by balancing the highest possible viral load achievable with the longest possible duration of infection. This theory has been challenged by recent research indicating that only 6% (95% CI 3-9%) of the variance in viral load can be explained by the viral genotype [310], and that the remaining variance is likely due to a combination of host and environmental factors.

7.1.4.3 Attenuation of transmission risk following diagnosis

Amongst the men surveyed, 57% of men attenuated their HIV transmission-risk between diagnosis and questionnaire completion, a median of 76 days (IQR 29-191). 36% of men reported total abstinence from AI since HIV diagnosis, and a further 21% reported exclusively using condoms for AI. This reduction in high-risk sex following diagnosis is in line with findings from a meta-analysis demonstrating HIV transmission risk in the US is highest amongst undiagnosed individuals compared to diagnosed with HIV [125]. It is also broadly in line with findings reported previously amongst MSM with PHI in London [128], though the proportion of MSM attenuating their risk of transmission in that study was higher at 76%. This may be due to differences in the definition of "risk elimination" which was defined by Fox et al as absence of all of the following at 3 months post-diagnosis: UAI with a regular partner of unknown or negative HIV status, UAI with casual male partners, and incident STI [128]. Time from diagnosis to questionnaire completion was also different due to the study design, with men surveyed up to 12 months post-diagnosis in my study compared to 3 months post-diagnosis.

Whilst attenuation of risk behaviour following diagnosis has been previously reported, there are concerns surrounding the duration of this reduction. Heijman et al, compared sexual behaviour in the 12 months prior to seroconversion to sexual behaviour reported every year up to 4 years following seroconversion amongst MSM participating in the Amsterdam Cohort Studies [311]. The authors reported that prevalence of UAI in the ART era was significantly lower at 1 year post-diagnosis at 53% compared to 72% at 12 months pre-diagnosis. However, by 4 years post-seroconversion this had increased to 61%, with the 95% confidence interval including the pre-diagnosis prevalence 48-74%. Furthermore, this finding did not appear to be driven by individuals who were on ART; the results were unchanged after restricting the analysis only to individuals who were ART naïve at the time of their study visit. It is therefore important to note that any risk attenuation seen amongst the men in this thesis is likely to be transient. Given the 12 week period often cited between initiating ART and achieving viral suppression, there is a potential public health argument to initiate ART as soon as possible after diagnosis in order for viral suppression to be achieved over the transient period of risk attenuation, meaning individuals will likely be undetectable by the time of resumption of UAI post-diagnosis. 1 in 3 MSM reported engaging in high-risk sex after HIV diagnosis

Whilst the majority of men attenuated high transmission risk behaviours after diagnosis, 1 in 10 men had reported engaging in serodiscordant UAI since being diagnosed with HIV. Sadly, the small number of survey respondents meant there was not sufficient power to identify risk factors for engagement in serodiscordant UAI alone. But also of concern, and reported by a far higher proportion of men, was the engagement in ChemSex (defined as the use of any of any the following drugs before or during sex: GHB/GBL, methedrone, methamphetamine, piperazines or ketamine). The use of drugs during sex, especially in group sex scenarios, was highlighted in the in-depth interviews a situation where consistent condom use, strategic positioning and serosorting were often challenging due to loss of inhibitions and control. The cross-sectional survey indicated that attending sex parties and engaging in ChemSex were very popular practices amongst UK MSM in the 6 months before HIV diagnosis, and remained so after diagnosis, with 1 in 3 MSM reporting ChemSex after diagnosis. As explained eloquently by one respondent in the in-depth-interviews, Chems are often a necessary part of group sex, especially when BDSM practices such as fisting are involved, due to the length of time it takes to prepare the body and the potential for boredom if not using drugs. The documented lack of awareness and control whilst on Chems, and it's often co-occurrence with UAI, group sex and BDSM practises [312,313], likely results in a high HIV transmission-risk from men with EHI who engage in these behaviours.

After controlling for differences in the time from diagnosis to questionnaire completion, men were more likely to have reported engagement in serodiscordant UAI or ChemSex, if they had previously received PEP, if they had engaged in ChemSex prior to diagnosis, and if they reported serodiscordant UAI, and higher partner numbers prior to diagnosis. These findings are similar to those of Fox et al, who reported MSM with continued transmission-risk behaviour were more likely to have another STI, use ketamine and have more sexual partners at baseline [128]. These findings would indicate that men at most risk of transmitting HIV after receiving their HIV diagnosis were those who were at highest risk of acquiring (and likely also transmitting) HIV prior to diagnosis. It also supports the proposed theory that a "core group" of MSM are at risk of acquiring and transmitting HIV have a prominent role in the sustained increase in incidence observed in the UK [314].

Of those who engaged in serodiscordant UAI or ChemSex since diagnosis, 59% were on ART though no clinical measures were available to determine undetectability amongst these men. This was higher than the proportion of men who did not engage in high-risk sex who were on ART (41%) though the difference was not found to be significant at the $p<0.05$

level. This could be because there is no true difference in the populations, or because the difference is too small to be detected within a study of this size (type II error). Even if these men had undetectable plasma viral load on ART, their engagement in UAI puts them at risk of contracting an STI. Increasing rates of gonorrhoea and syphilis have been observed amongst HIV-positive MSM in the UK [315], alongside outbreaks of novel STIs such as shighella and lymphogranuloma venereum (LGV) [316,317].

Both the Swiss Statement and the BHIVA position statement on TasP emphasise the importance of absence of STI as a condition for being uninfectious [5,217]. The BHIVA statement goes one step further by defining the conditions under which absence of STI can be assumed (both partners have had a comprehensive negative STI screen, and neither partner has had sex with anyone else since the screen, and the screen is repeated for each individual exposure with every new sexual partner and a negative result is obtained within the relevant 'window' period for each STI before the couple have sex again). A strong correlation has been demonstrated between HIV viral load in blood plasma, the genital tract and semen, and viral shedding has been shown even when plasma viraemia remains undetectable in the presence of STIs [318–320], though Kelley et al reported no increase in rectal viral load in the presence of STI when viral load was undetectable in the blood plasma [73]. With the very high rates of STI observed in this population of MSM (44% had an STI co-infection at the time of HIV diagnosis) it is unlikely that the assumption of absence of STI can be reliably implemented in the case of MSM who engage regularly in UAI, and/or ChemSex.

Interestingly, UAI with serosorting for positive partners was reported by a minority of men after diagnosis (8%). This is considerably lower than the proportion of HIV-positive MSM who report serosorting in the community (64%) [284]. This may be due to the emotional upheaval that follows diagnosis and the necessary self-efficacy and agency involved to be able to disclose HIV status to partners, in combination with felt stigma. For those men who did serosort for HIV-positive partners to eliminate risk of transmission, it was not without problems. Men in the interviews reported a social pressure to bareback when having sex with other known positive men or in group sex scenarios. Requesting to use condoms in these scenarios could be difficult as other positive MSM sometimes did not see the point, and could even result in sexual rejection.

One of the survey findings was that engagement in high risk sexual behaviour was associated with the two statements traditionally suggestive of HIV treatment optimism: "Better HIV treatment means that people are less worried about catching HIV" and "Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom". Greater HIV optimism has consistently been shown to be independently associated with engagement in high-risk sexual behaviour amongst MSM [3,321–323]. However, research from early to mid-2000 amongst MSM in England and Scotland reported under a third of MSM surveyed to be optimistic about HIV treatment [323–325]. This relatively low prevalence of treatment optimism resulted in a low (estimated at between 8-13%) population attributable risk of HIV treatment optimism on the increasing high-risk behaviour observed at this time [326], meaning that 92-87% of the observed increase in risk was likely due to other factors. It is important to acknowledge though that the construct of treatment optimism is essentially a measure of men's attitudes and beliefs towards ART and these are likely to change over time given the improvements in understanding and increased evidence of the efficacy and effectiveness of TasP. Given the RCT evidence of the efficacy of TasP afforded by HPTN-052 [215], and the encouraging real-world effectiveness reported by the PARTNER study [230], it is unsurprising that a large proportion of MSM (around 55%) agreed with the HIV optimism statements in my survey. It remains to be demonstrated, however, that an increase in treatment optimism will result in a further increase in high-risk behaviour, i.e. risk compensation. Longitudinal analysis of the risk behaviour component of the START trial will shed light on whether increases in high-risk sexual behaviours are seen amongst individuals on ART, with only the ART-naïve baseline data published to date [327].

7.2 Strengths and weakness of the research design

7.2.1 The mixed methods approach

This study is the first mixed methods design to address acceptability of early ART amongst MSM with EHI. The combination of quantitative and qualitative methods has permitted me to get closer to a multidimensional understanding of the acceptability and utility of early ART in preventing secondary transmission in the UK. Whilst the in-depth interviews revealed some of the social, cultural and psychological issues experienced during early infection in a small group of men from a central London HIV clinic, the survey permitted estimation the prevalence of attitudes, beliefs and acceptability towards early ART in a wider population more representative of MSM across the UK. Triangulation of the survey

and qualitative data has also facilitated understanding of the mechanisms and explanations for the findings. This has been particularly helpful in understanding mechanisms behind surprising results, such as the large proportion of men who started early ART primarily for health benefit, though it was not recommended for clinical benefit in UK treatment guidelines at the time due to the lack of randomised evidence.

A recent review article by Young and McDaid highlighted the lack of research into the acceptability of PrEP and TasP [221], noting there is no widely accepted method of measuring acceptability. A multitude of methods were identified in the literature to measure the construct of acceptability, ranging from ART/PrEP uptake and adherence, to attitudinal measures investigating: stigma, risk perception, concerns or barriers and scepticism of risk reduction. Of the three studies in the review investigating acceptability towards TasP, all were cross-sectional surveys and measured acceptability by assessing attitudinal measures only [222,223,225]. Another strength of this thesis is that it combines measures of attitudinal constructs assessing acceptability from both a qualitative and quantitative perspective, along with estimation of ART uptake amongst those with EHI through use of data from the UK Register and the cross-sectional survey. From this perspective it measures both acceptability and the intention to initiate ART, along with the actual uptake of ART.

A weakness of this thesis was the lack of investigation into healthcare providers' views on early ART, resulting in a one-sided perspective of early ART. Given the weight reportedly placed in healthcare providers' opinions towards early ART by the men interviewed and the survey respondents, conducting both qualitative and quantitative research into provider's attitudes and acceptability towards early ART would have been beneficial, though not possible in this programme of work given the time and funding constraints.

Adopting a sequential mixed methods design in workstream 2 allowed the cross-sectional survey to be guided by findings from the qualitative component, and resulted in themes of enquiry which I would not have considered myself, for example the belief that early ART makes it easier to disclose HIV. By piloting the resulting questionnaire using cognitive interviewing, it was possible to ensure men understood the questions and belief statements as was intended, and provided an opportunity for men to suggest solutions where problems existed. Nonetheless there were also disadvantages in using this study design. The sequential manner in which the qualitative and quantitative components of workstream 2 were planned proved to be problematic due to the length of time it took to

recruit MSM with EHI for in-depth interviews in the first phase. This resulted in only half of the interviews informing the design of the questionnaire for phase 2, the cross-sectional survey. The sequential design also increased the total duration of workstream 2, which in combination with a one-year maternity leave, and the fast-moving world of research of early ART, meant that pivotal study results and policy changes occurred over the course of the PhD. This likely resulted in shifts in attitudes amongst MSM with EHI over this time and rendered findings out of date relatively quickly.

7.2.2 The study population

Overall weaknesses were also apparent in the selection of the study population. The men recruited to the studies in this thesis were relatively well-educated, currently employed, predominantly white and of a fairly homogenous age range. The relationship between virological rebound on ART and low socioeconomic status has previously been noted to be higher amongst people who are unemployed, non-university educated, those who did not own their own home and did not have a support network [328]. These people are largely underrepresented in my study population, which brings to question representativeness of the findings of high acceptability of early ART to the wider UK MSM population. In addition, the ethics committee stipulated that only MSM without mental illness could participate in workstream 2 studies, which may have resulted in the exclusion of men who were depressed or who particularly struggled to come to terms with their HIV diagnosis. PLWH with depression are known to be less likely to adhere to ART [329], and it is also conceivable that they may be less likely to want to initiate early.

The MSM eligible for this study (recent HIV seroconverters) are likely to be more health conscious than those diagnosed in chronic infection [212]. This is due to the selection bias imposed by eligibility criteria for seroconverter cohorts, involving a negative antibody followed by a positive within 12 months (requiring more frequent than annual repeat testing) or awareness of HIV seroconversion symptoms leading to presentation during acute infection (which may be more likely amongst MSM more knowledgeable about HIV). The rollout of RITA assays by PHE, which has enabled detection of MSM who likely seroconverted in the last 6 months but may who not have presented for a previous HIV test, may reduce this bias somewhat. However, 70% of survey respondents were identified through repeat HIV tests, and only 15% through a RITA assay, so any effect would have been marginal. If current efforts to expand HIV testing to include irregular and first time testers are successful, the findings of this thesis may not be relevant to this new population

of MSM diagnosed in EHI. First time or irregular HIV testers, given their irregular, or total lack of, previous interaction with GUM services in the past, are likely to be less health conscious and have differing levels of HIV knowledge. As could be observed from the in-depth interview study, knowledge and beliefs about ART are likely to influence attitudes and beliefs towards early HIV treatment. Indeed, repeat cross-sectional national survey of a wider population of HIV-positive, negative and untested MSM in Australia, conducted in 2011 and repeated in 2013, found only around 3% of respondents believed that HIV treatment reduced risk of transmission [224].

Caution should also be used when triangulating results from the various workstreams and study phases, as respondents for the different phases of the studies were from different populations, though all men included in the PhD studies had confirmed laboratory evidence of recent seroconversion. The qualitative data was collected from men attending only one inner-London HIV clinic, whilst the survey recruited men from 16 HIV clinics across the UK, and the secondary analysis of UK Register data involved data from all of the UK Register HIV centres, including those who did not participate in the survey. The UK-wide representativeness of the survey cannot be guaranteed as no sampling procedure was put in place at either the clinic, or patient level to ensure a representative population. Instead a convenience approach had to be adopted for financial and logistical reasons, and this is noted as an important limitation to the study. In the qualitative study, whilst I intended to sample MSM for the interview using an age-quota, this was not possible due to recruitment problems and the low response rate. Recruitment of men from multiple HIV clinics, sampled across the UK and stratified on age, ethnicity and ART status would have resulted in a more representative sample of MSM in the qualitative study. In the case of this study, where there was no money and the limited resources of just myself to conduct the study, this approach would not have been possible so I can only acknowledge the limitations resulting from a sub-optimal sampling procedure.

7.3 Implications for practice and policy

The original reason for undertaking this PhD in 2008 was for the findings to inform the development of policy surrounding TasP in recent seroconverters, under the assumption of no clinical benefit to early ART. Whilst the release of the START trial results in 2015 resulted in the change of guidelines to recommend ART to all, irrespective of infection stage or CD4

count, there are still findings from this thesis which are applicable to clinical care under the new BHIVA guidelines.

7.3.1 Implications for HIV healthcare providers

The two key implications of these thesis findings for healthcare providers are:

1) that the perceived psychological and emotional benefits of early ART to PLWH are important in the decision to start ART early, and that initiating early ART may facilitate adjustment to an HIV diagnosis,
2) that men are able to come to terms with an offer of ART at the point of diagnosis, and that many expect it to be offered then.

My experience from both the in-depth interviews, and as backed up by the survey data, was that most men were open to discussion about early ART at the point of diagnosis. Furthermore, for some men early ART is an essential step in dealing with HIV diagnosis by reducing the stigma and anxiety caused by being "infectious", thus facilitating living a "normal" life. To quote one of the survey respondents, who notably had not resumed sexual activity, "Being on Atripla straight away has helped me feel better about my status. Emotionally I manage better knowing I am not infectious".

Current BHIVA guidelines recommend the evidence for TasP is discussed with all PLWH [330]. They also state that assessment of risk of transmission should also be performed at this time and ART is offered to all PLWH, though these recommendations are graded as "good practise points" based on the clinical experience of the writing team. There is however a notable absence in the guidelines pertaining to the timing of such a discussion after diagnosis. Healthcare providers occupy a position of trust and many men rely on their transparency and judgement, especially on very complex decisions such as when to start ART. The high acceptability of early ART and expectation of starting at diagnosis found amongst MSM in this thesis supports the need for presentation of the clinical and preventive evidence for early ART to all patients at diagnosis, regardless of reported sexual behaviour, only then can both parties make an informed decision on when to start.

The findings that a core group of MSM who report ChemSex, PEP and high partner numbers prior to diagnosis are more likely to engage in high-risk sex after diagnosis have important implications for prevention. The prevention benefits of early ART should be discussed and

TasP offered as a matter of priority amongst men who report these behaviours at HIV diagnosis, as they may be more likely to continue engaging in these behaviours. Extended risk-reduction counselling should also be discussed and recommended to assist them with assessing transmission risk.

7.3.2 The importance of earlier diagnosis

The findings from this thesis demonstrating attenuation of high-risk behaviour following diagnosis underline the influence of early diagnosis on reducing transmission risk. This in combination with the finding that only 24% of MSM seroconverters enrolled in the UK Register first present to clinic in the 30 days preceding peak viraemia, indicate the need for improving the rate of very early detection of HIV. The reduction the HIV window period afforded by the 4th generation ELISA, which detects antigen as well as antibody, in addition to rollout of RITA methods to identify likely recent infection, will likely have increased identification of EHI. But more will need to be done to increase detection within the 30 day window for ART to influence peak viraemia.

The post-diagnosis attenuation in risk behaviour reported by the men recruited to the study by Fox et al [128] used in a stochastic model by White et al [331] to predict the number of infections likely arising from the population in the event that: HIV infection remained undiagnosed, and pre-diagnosis sexual behaviour continued throughout PHI; or that the infection was diagnosed immediately so post-diagnosis sexual behaviour was assumed through the entirety of PHI. If HIV remained undiagnosed throughout PHI, the estimated number of infections arising from the 98 men was 33-45, with a 65% reduction in this number if diagnosis of HIV had been made immediately following infection. The authors also modelled varying proportions of post-diagnosis sexual behaviour in PHI according to different testing intervals, and found that monthly testing could reduce the number of onward transmission events over PHI by 49-52%.

The best approaches to facilitate diagnosis of HIV in early infection are currently unknown, but suggestions include active recall by GUM clinics of MSM known to be at high risk of HIV acquisition every three months, the use of home sampling and home testing. Perhaps the largest challenge will be in encouraging those who have never HIV tested to test. The national rollout of PHE's home-sampling initiative is designed to reach members of high-risk populations who may not attend STI clinics [292]. Additionally, home testing kits were licensed

in the UK in 2014, and kits went on sale in 2015, though there are concerns over linkage to care, with fears that people who test positive may not present to clinic for treatment.

7.4 Recommendations for future research

Given the high acceptability and early uptake of ART amongst UK MSM observed in this thesis, one crucial piece of work will be to monitor adherence in those who initiate early ART. Men who initiate early ART, in the absence of HIV symptoms may not be as motivated to take their medications and transmissions may occur when ART adherence is sub-optimal; a recent phylogenetic analysis demonstrated a high proportion of transmission events were attributable not just to PHI, but to chronic infection when ART interruption had occurred [332]. Amongst respondents to my cross-sectional survey, 5% (n=3) of the MSM who started ART had stopped by the time they completed the questionnaire, though no further information was provided by them as to the reason for terminating ART. Clearly, this has worrying implications for onward transmission, HIV resistance, and also potentially increases the risk for non-AIDS complications. Studies investigating the rate of treatment interruption and non-adherence are necessary amongst MSM who initiate ART in EHI, alongside qualitative investigation of the reasons behind poor adherence and ART discontinuation.

As expected, time from questionnaire completion to HIV diagnosis was highly associated with engagement in high-risk sex after diagnosis, with men more likely to engage the longer time since diagnosis. A temporary abstinence and reduction in risk-behaviour is unsurprising given the emotional and social upheaval that was described in the interviews following receipt of an HIV diagnosis. Men expressed the need to assimilate and adjust to their HIV status before resumption of sex, with the added barriers of HIV-related stigma and anxiety over transmission resulting in long-term sexual abstinence in some cases. The cross-sectional study design of this PhD did not permit identification of the typical time from diagnosis to resumption of sexual behaviour, and how this may differ amongst men who engage in high transmission-risk behaviours. A deeper understanding of factors surrounding resumption of sex after diagnosis during EHI, and the part early ART may play in facilitating it, may be achieved by incorporating repeat interviews and surveys into a cohort of recent seroconverters.

Whilst the majority of the men in the survey were amenable to early ART, 9% of men stated they would not have initiated ART at diagnosis if offered, and the same percentage agreed

with the statement “I would prefer to delay starting ART for as long as possible even if it meant a small increased risk of getting serious illness”. Given the START trial results, it is important to further understand the barriers to early ART amongst MSM who hold these views in order to maximise uptake of early ART, and reduce the morbidity and mortality associated with treatment delays. It would also be useful to estimate the transmission potential from men who are less likely to initiate early, given the longer period of infectiousness amongst them.

That 1 in 10 men surveyed reported serodiscordant UAI and 1 in 3 reported ChemSex following HIV diagnosis, indicates the presence of a core group at high risk of transmitting HIV over EHI. From a public health perspective, these men may hold the key to maximising the impact of TasP on secondary transmission during EHI, however, they may also present potential problems over the effectiveness of TasP. Recurrent UAI episodes put these men at high risk of contracting other STIs, which may increase viral load in the genital tract even when plasma viraemia is undetectable [333,334]. ChemSex is also known to influence risk perception, further undermining the ability to negotiate safer-sex. A deeper understanding of the reasons men engage in ChemSex and how it can be performed in as safer environment as possible is necessary to understand how TasP can be used effectively

Finally, treatment optimism is known to be associated with high-risk behaviours, and is likely to have increased over time given the randomised evidence of health benefits of early treatment and TasP, and subsequent changes to national and international guidelines. Questions remain however, as to whether this increase in optimism has resulted in an increase in high-risk sexual behaviour, i.e. risk compensation. Sexual behaviour studies have repeatedly shown increases in UAI, however the plethora of risk-reduction practices now adopted by MSM go beyond the basic use of condoms. Even the measure of serodiscordant UAI is subject to elements of risk-reduction if undetectable viral load, PrEP, strategic positioning and withdrawal before ejaculation are factored into the equation. Future work to assess the presence of risk-compensation is necessary, however such studies will be challenging given the many nuances of risk-reduction currently used by MSM in the UK.

7.5 Final conclusions

MSM in the UK continue to carry a disproportionate burden of HIV with a continued rise in the annual number of new diagnosis from 2,760 in 2009 to 3,360 in 2015, and accounted for over half of the new diagnoses in 2015 [335]. This has occurred despite a good cascade of

HIV care in the UK with increased frequency of HIV testing and high uptake of ART; PHE estimate that 91% of diagnosed PLWH in the UK who are retained in care are on ART, of whom 95% are virally suppressed [335].

The results presented in this thesis suggest that MSM diagnosed with EHI and attending UK clinics find early ART to be a largely acceptable prospect, with very few men stating they would not have taken ART at diagnosis if offered. Importantly, these findings pre-dated the results of the START trial, so acceptability is likely to have increased further with new evidence of clinical benefit at CD4>500 cells/mm^3 and the subsequent changes to BHIVA guidelines. The qualitative and quantitative components of this PhD highlighted that men believed in a health benefit from early ART, even in the absence of RCT evidence at the time. Interestingly, the men's definition of health transcended the traditional medical definition of health as the absence of disease, or the improvement of surrogate markers of HIV progression. In their opinion, reduced anxiety about transmission and lessening the stigma of being infectious were major health benefits of early ART, and could contribute to better mental health, though these benefits are often overlooked by the medical profession. Notably, very few men who reported initiating ART in EHI in the survey did so purely to reduce transmission and this tied in with findings from the qualitative work. Whilst evidence of an altruistic element of protecting one's sexual partners did exist, it was often accompanied by the responsibility to protect one's own self from the negative feelings of guilt from secondary transmission and, in a worst case scenario, the possibility of prosecution.

Ultimately though, whilst this study indicates that acceptability and uptake of early ART may be high in the study population, much still needs to be done to optimise the number of men who are diagnosed in EHI. Further expansion of HIV testing, especially targeted to those at risk of seroconversion is necessary to maximise any impact of TasP in EHI, with the most benefit from a public health perspective theoretically gleaned if ART is initiated by 30 days post-seroconversion as was identified in my statistical analysis. Presently, this factor limits the utility of early ART to prevent transmission from individuals in EHI, with only 1 in 4 MSM recruited to the UK Register presenting within this window period. Additionally, if the increase in viral load at first presentation over calendar time observed in this study is validated by other studies, earlier initiation may become increasingly effective in curbing the relatively higher transmission risk presented by those with EHI now, as compared to in previous years.

Also mediating the prevention effect of ART in EHI, is the reported attenuation of high transmission-risk sexual behaviour after diagnosis, with over a third of men reporting no sex since diagnosis in the survey. The in-depth interview study provided insight that sexual abstinence as a result of HIV diagnosis can be due to fear and anxiety over transmission, as well as felt and enacted stigma. Though the majority of men presented little to no transmission risk following diagnosis, a persistent population of around 1 in 3 MSM reported engagement in ChemSex and/or serodiscordant UAI following diagnosis. This core group of men, who typically report higher partner numbers, engagement in ChemSex and PEP use prior to diagnosis, likely have a key role to play in sustaining the epidemic. Increasing the proportion of this core group who start TasP in EHI may have a large impact on secondary transmission.

Being diagnosed with HIV was undeniably a stressful time for the men interviewed, with many issues to come to terms with, including poorer health, a new sexual identity and the potential breakdown of relationships. Whilst presenting work from this thesis at various conferences, I have had many discussions with HIV care providers over the appropriateness of discussing ART at diagnosis, and was surprised that a notable proportion found it an unsuitable time to discuss ART. I believe that the results of this thesis provide evidence that men are receptive to discussion about ART at diagnosis, and furthermore, that it can be discussed in the context of being an empowering force as well as a lifelong duty. By identifying the positive elements it can bring to people's lives, such as facilitating status disclosure, or removing the stigma of infectiousness,

In conclusion, I have demonstrated that early ART initiation is acceptable at diagnosis amongst MSM with EHI attending HIV clinics in the UK, not only to reduce risk of transmission to partners but for personal health reasons. It is perceived by men to provide holistic health benefits beyond the typically measured surrogate markers of HIV progression, morbidity and mortality. Men believed early ART increased quality or life, improved mental health by reducing or removing the stigma associated with infectiousness and facilitated the living of a "normal" life. The utility of ART in EHI to curb incidence in UK MSM is currently hampered by the small proportion of MSM who present to clinic, and are diagnosed, before peak viraemia. Given the sexual risk attenuation observed following diagnosis in this MSM population, expansion of HIV testing will not only increase the detection of individuals at peak viraemia, but earlier diagnosis will likely lead to further transmission-risk attenuation over the period of high infectiousness. That said, a core-

group, comprising 1 in 3 of the MSM surveyed, appear to present a significant transmission-risk following HIV diagnosis. Immediate initiation of early ART amongst these men is recommended to maximise the public health benefit of TasP, although engagement in ChemSex and UAI amongst this core-group may reduce the effectiveness of TasP through affecting ART adherence, interactions between ART and recreational drugs and the increasing risk of concurrent STI which is known to increase viraemia in the genital tract. Real-world evidence into transmission risk from MSM with EHI on sub-optimal ART, either due to the presence of STI, through recreational drug use, or poor adherence, is needed to further understand the role these men can play in the onward transmission of HIV.

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Appendix 1 – Poster presented at BHIVA Spring Conference (2009), Manchester

How high is viral load in HIV seroconverters once they present to a clinic?

MRC Clinical Trials Unit

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UCL

Background

Infection with HIV results in a rapid increase in HIV RNA within the host peaking around the time of HIV seroconversion, although the duration of high viraemia is highly variable between individuals.

Risk of HIV transmission has been shown to increase with increased HIV RNA titre.

Much attention has been given recently to medical intervention in early HIV infection, particularly with combination antiretroviral therapy (cART). The effectiveness of such an intervention is dependant on whether HIV seroconverters present to clinic early enough, when viral load is still sufficiently high to benefit from early intervention with cART.

Objectives

- To describe HIV RNA at first clinic presentation in a recently infected population.
- To assess factors associated with high HIV RNA (≥5.0 log_{10} copies/ml) at first presentation.
- To describe changes in HIV RNA over time following seroconversion.

Methods

Using data from the UK Register of HIV Seroconverters (see boxed text below) we included individuals first testing HIV antibody positive on or after 01/01/1997 (when HIV RNA testing became routine in clinics) and who were ART-naïve at first HIV RNA measurement.

Median (interquartile range [IQR]) time from estimated seroconversion to first HIV RNA test was determined, along with median (IQR) first HIV RNA measurement.

Risk factors for HIV RNA ≥5.0 log_{10} copies/ml at first presentation were assessed using logistic regression and restricted to individuals testing positive within 1 year of negative test and with HIV RNA test within 1 month of positive test. We adjusted for sex, risk group, age at seroconversion, presence of seroconversion illness, ethnicity, year of positive test, HIV test interval and time interval from first positive test to HIV RNA measurement.

Repeat blood plasma HIV RNA measurements were used to describe changes in median HIV RNA in the 3 years following seroconversion, with individuals censored to follow-up on commencement of ART. Where HIV RNA was undetectable, the midpoint of limit of detection for the assay was used.

Results

Of the 2527 seroconverters in the cohort, 1019 (40.3%) met eligibility criteria, these were mostly white men who have sex with men (MSM). The overall median (IQR) age was 32 (27-39) years.

Cohort characteristics by viral load at first presentation

	VL <5.0 log_{10} copies/ml (n=563)	VL ≥5.0 log_{10} copies/ml (n=456)
Median (IQR) age at seroconversion (years)	31.4 (26.3-37.3)	33.6 (28.0-40.9)
Sex (%)		
Male	90.1	95.4
Ethnicity (%)		
White	81.5	87.9
Black African	4.8	3.3
Black Caribbean	3.7	0.9
Other/unknown	10.0	7.9
Probable route of transmission (%)		
MSM	84.7	87.3
MSW	12.3	9.4
IDU	1.6	1.8
Other/unknown	1.4	1.5
HIV Subtype (%)		
A	1.4	1.1
B	38.7	41.2
C	2.3	3.3
Recombinant	1.4	2.0
Other	0.7	0.7
Unknown	55.4	51.8
Seroconversion illness reported (%)		
Yes	29.1	60.8
No	60.4	34.0
Unknown	10.5	5.3
Median (IQR) year of positive test	2002 (1999-2004)	2002 (2000-2005)
Median (IQR) CD4 count (cells/mm3)	545 (387-695)	456 (363-584)

HIV RNA at first presentation

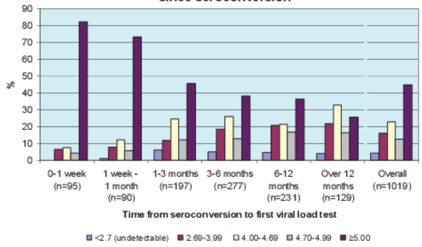
Median (IQR) HIV RNA at first presentation was 4.89 log_{10} copies/ml (4.18-5.46), at median 8 (2-19) days following first positive test, and median 129.5 (54.5-258.5) days following seroconversion.

Overall, 456 (44.8%) of the seroconverters had HIV RNA ≥5.0 log_{10} copies/ml at first presentation (the upper limit of detection of the assay for a considerable proportion) of whom 96 (21.1%) were known to have HIV RNA ≥6.0 log_{10} copies/ml.

Over a third of individuals whose first clinic attendance was as long as 6-12 months after estimated seroconversion date had HIV RNA ≥5.0 log10 copies/ml at first presentation.

Undetectable HIV RNA at first presentation was found in 43/1019 (4.2%) of seroconverters. Closer examination of this group showed those presenting with undetectable HIV RNA were less likely to be white and less likely to have reported seroconversion illness.

HIV RNA (log_{10} copies/ml) at first presentation by time since seroconversion



Factors associated with HIV RNA ≥5.0 log_{10} copies at first presentation

Of the 1019, 635 tested HIV antibody positive within 1 year of a negative result and had a HIV RNA test within 1 month.

Increasing age and presence of seroconversion illness were found to be significantly independently associated with a HIV RNA ≥5.0 log_{10} copies/ml at first presentation after adjusting for all other variables, $p=0.045$ and $p<0.001$ respectively.

Women were significantly less likely to present with high HIV RNA, $p=0.016$.

No other factors examined were found to be independently associated with high HIV RNA.

Factors associated with HIV RNA ≥5.0 log_{10} copies/ml at first clinic presentation

	AOR*	95% CI	p-value
Age - per 10 year increase	1.21	1.00-1.46	p=0.045
Sex			
Male	1.00	-	p=0.016
Female	0.29	0.11-0.81	
Ethnicity			
White	1.00	-	p=0.478
Black African	0.57	0.18-1.84	
Black Caribbean	0.41	0.08-2.03	
Other/unknown	0.77	0.40-1.50	
Probable route of transmission			
MSM	1.00	-	p=0.754
MSW	1.18	0.50-2.77	
IDU	2.43	0.35-16.80	
Other/unkown	1.54	0.44-5.44	
Seroconversion illness reported			
No	1.00	-	
Yes	3.05	2.09-4.52	p<0.001
Unknown	0.95	0.40-2.23	

* Odds ratio adjusted for other factors in table, HIV test interval and time from positive test to first HIV RNA test

Changes in HIV RNA following seroconversion

Analysis of repeat measure data from the 1019 individuals showed median HIV RNA decreasing over time as expected, but remaining over 4.7 log_{10} (50,000) copies/ml until 6 months after seroconversion. Of interest, 25% of the individuals with an HIV RNA at 12 months post seroconversion had ≥5.0 log_{10} copies/ml.

Conclusions

- Presentation with very high HIV RNA (≥5.0 log10 copies/ml) remained common in the first month after seroconversion and over 4.7 log_{10} copies/ml for 6 months thereafter.
- Given that heterosexual transmission rates have been estimated at 23 per 100 person years at ≥4.7 log_{10} copies/ml and 14 per 100 person years at between 4.0-4.6 log_{10} copies/ml, cART intervention within 6 months, and possibly 12 months, of seroconversion may be worthwhile from a public health perspective to reduce onward transmission.
- This is assuming that sexual behaviour remains consistent over this period and early cART intervention for public health benefit is deemed acceptable by recently infected individuals.
- Work to assess whether these assumptions are valid for recent seroconverters in the UK is ongoing.

UK Register of HIV Seroconverters

Is an observational study of HIV infected persons in the UK for whom the time of HIV seroconversion is well estimated. The original objectives of the study, to investigate the natural history of HIV infection and its determinants, have been modified with the advent of effective therapy for HIV, to monitoring temporal changes in the time to AIDS and death (i.e. the population effectiveness of therapy) and examining the effect of time since infection and transmitted drug resistant HIV on virological and immunological response to therapy. The study recruits and follows up, from over 100 clinical centres in the UK, individuals who are 16 years or more with documented evidence of a negative HIV antibody test performed within 3 years of the positive test, or with laboratory evidence of acute HIV infection or those testing incident at low level (optical density <1.0) using detuned assay (subtype B only).

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1015

Increase in HIV Plasma Viral Load Set-Point Among UK MSM

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UCL

Background

- High viral loads (VL) during Primary HIV Infection (PHI) may disproportionately contribute to the propagation of the epidemic.
- Whether there has been a temporal increase in viral load set point (VLSP) is debateable as findings are conflicting.
- We sought to describe temporal trends in VL at initial presentation and VLSP in MSM HIV seroconverters (SC) from the UK.

Methods

- Analysis restricted to MSM aged 16 years or over, diagnosed between 1st January 1997 & 31st December 2012 and with 1 or more ART-naïve VL measure available within 3-12 months of SC.
- All had SC interval (time between negative & positive HIV Ab tests) of 1 year or less, or laboratory evidence of acute infection, or an "incident" result using a RITA (recent incident testing algorithm) assay.
- **Initial VL** was defined as the first VL on or after the date of HIV diagnosis and within 12 months of SC.
- **VLSP** defined as the mean of ART-naïve VL measurements taken between 3 and 12 months after date of SC.
- Multiple regression used to examine whether initial VL & VLSP had changed by calendar year of SC (1997-99, 2000-01, 2002-03, 2004-05, 2006-07, 2008-09, 2010-12) after adjusting for potential confounders.
- Year of SC modelled as a 5 knot restricted cubic spline to allow for non-linear trends.
- The following sensitivity analyses were performed:
  - restricting the dataset to white ethnicity MSM
  - restricting to MSM with a SC interval ≤180 days
  - right truncating the data at 5.0 log_{10} copies/ml, in line with the upper limit of linear range in the earlier assay types

UK Register of HIV Seroconverters

Is an observational study of HIV positive persons in the UK for whom the time of HIV seroconversion is well estimated. The original objectives of the study, to investigate the natural history of HIV infection and its determinants, have been modified with the advent of effective therapy for HIV, to monitoring temporal changes in the time to AIDS and death (i.e. the population effectiveness of therapy) and examining the effect of time since infection and presence of transmitted drug resistant HIV on virological and immunological response to therapy

Results

- 1,194 of the 3,626 individuals enrolled in the UK Register met eligibility criteria.
- The majority were of white ethnicity (90.1%), the median age was 32.6 years, and large proportion had missing HIV subtype data (60.8%).
- As expected, VL assay type and upper range of detection were strongly associated with calendar time, with increasing use of PCR assays (49.6% in 1997-99 to 93.0% in 2010-12) and an increase in the upper linear range of assays.

Table 1: Demographic & clinical characteristics for MSM in the UK Register of HIV Seroconverters

		Overall
N		1194
Median (IQR) year of SC		2006 (2003, 2010)
Median (IQR) age at SC (years)		32.6 (26.8, 40.1)
Median (IQR) SC interval (months)		4.8 (1.6, 8.1)
Median (IQR) days from diagnosis to first VL measure		7 (1, 15)
Median (IQR) months from diagnosis to first VLSP measure		4.5 (3.7, 5.5)
Median (IQR) months from diagnosis to last VLSP measure		9.4 (6.7, 10.8)
Median (IQR) number VL measures included in VLSP		2 (2, 3)
Acute infection* (N)		166
Ethnicity (N)	White	1087
	Non-white	90
	Missing	17
HIV Subtype (N)	B	437
	Non-B	31
	Missing	726
VL assay upper range of detection copies/ml (N)	>100,000	137
	>500,000	139
	>750,000	289
	>6,000,000	45
	>10,000,000	513
	Missing	71

* Defined as SC interval ≤30 days or laboratory evidence of acute infection

Figure 1: Estimated (95% CI) temporal trends in initial viral load at first clinic presentation in UK MSM after adjusting for all variables in table 2

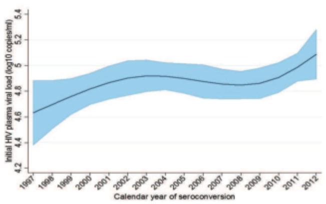
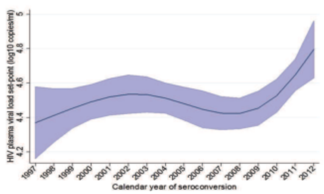


Figure 2: Estimated (95% CI) temporal trends in viral load set-point amongst UK MSM after adjusting for all variables in table 3



Initial Viral Load

- Median (IQR) initial VL overall was 4.99 log_{10} copies/ml (4.34, 5.62).
- Initial VL was lowest at 4.71 log_{10} copies/ml (4.05, 5.21) in 1997-99 and highest at 5.05 (4.46, 5.70) in 2010-12 (p=0.005), but there was some evidence of departure from linearity (p=0.050).
- Initial VL remained associated with calendar year of SC in adjusted models (see table 2) and all sensitivity analyses.

Viral Load Set-Point

- Median (IQR) VLSP overall was 4.64 log_{10} copies/ml (4.05, 5.08).
- VLSP increased from 4.51 log_{10} copies/ml (4.10, 4.89) in 1997-99 to 4.76 (4.15, 5.16) in 2010-12 (p=0.013), but there was evidence of departure from linearity (p=0.028).
- Table 3 shows the overall effect of SC year on VLSP remained significant in the adjusted model.
- Findings held in all sensitivity analyses apart from restricting to white ethnicity MSM (p=0.060).

Contact

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Study website: http://www.ctu.mrc.ac.uk/research_areas/study_details.aspx?s=42

Conclusions

- We found evidence of an overall increase in both VL at first presentation and VLSP between 1997 and 2012, with evidence of non-linearity in the trends.
- This overall increase remained after sensitivity analyses accounting for changes over time to assay type and upper range of detection.
- A bias towards earlier recruitment of the more symptomatic men to the UK Register may be responsible for particularly high measures observed in most recent years, although the calendar year effect remained significant, albeit weakened, when excluding MSM seroconverting in 2012 from the analysis.
- As VL is known to be correlated with risk of transmission, these findings may translate to increased virulence over time and, potentially, increased incidence.
- However, interpretation of the reasons for increased VLSP over time is not straightforward because analyses of the viral genotype do not suggest an effect of increased virulence (see poster 288, Hodcroft et al). Other factors, many of which have changed over time, could be responsible for the increase observed.

Table 2: Factors associated with initial viral load at first clinic presentation

		Unadjusted coefficient	95% CI	p-value	Adjusted coefficient*	95% CI	p-value
Year of seroconversion							
	1997-99	0.00	-	0.005	0.00	-	0.018
	2000-01	0.33	0.03, 0.62		0.24	-0.04, 0.53	
	2002-03	0.26	0.00, 0.53		0.23	-0.03, 0.49	
	2004-05	0.37	0.11, 0.62		0.21	-0.04, 0.46	
	2006-07	0.36	0.11, 0.62		0.29	0.04, 0.54	
	2008-09	0.16	-0.10, 0.42		0.05	-0.20, 0.30	
	2010-12	0.44	0.21, 0.66		0.35	0.12, 0.57	
Acute infection (acute vs. not acute)		0.73	0.56, 0.91	<0.001	0.60	0.40, 0.80	<0.001
Seroconversion interval (per month)		-0.05	-0.07, -0.04	<0.001	-0.02	-0.04, 0.00	0.026
Time diagnosis to initial VL (per day)		-0.10	-0.15, -0.05	<0.001	-0.09	-0.14, -0.04	<0.001
Age at seroconversion (per decade)		0.07	0.01, 0.14	0.025	0.05	-0.02, 0.11	0.153

*Adjusted for all other variables in table

Table 3: Factors associated with viral load set point

		Unadjusted coefficient	95% CI	p-value	Adjusted coefficient*	95% CI	p-value
Year of seroconversion							
	1997-99	0.00	-	0.013	0.00	-	0.010
	2000-01	0.14	-0.10, 0.37		0.16	-0.08, 0.39	
	2002-03	0.08	-0.14, 0.29		0.08	-0.13, 0.30	
	2004-05	0.07	-0.14, 0.28		0.10	-0.11, 0.31	
	2006-07	0.09	-0.12, 0.30		0.13	-0.08, 0.33	
	2008-09	-0.10	-0.30, 0.11		-0.04	-0.25, 0.17	
	2010-12	0.21	0.03, 0.40		0.26	0.07, 0.44	
Age at seroconversion (per 10 years)		0.06	0.00, 0.11	0.033	0.06	0.01, 0.11	0.021
Seroconversion interval (per month)		0.02	0.00, 0.03	0.010	0.03	0.01, 0.05	0.011
Time from diagnosis to first VLSP measure (per month)		-0.01	-0.03, 0.01	0.331	0.06	0.02, 0.10	0.008
Time from diagnosis to last VLSP measure (per month)		-0.02	-0.03, 0.00	0.055	-0.04	-0.07, -0.01	0.019
Number of VL measures contributing to VLSP calculation (continuous)		0.00	-0.04, 0.04	0.980	0.12	0.03, 0.20	0.007
Acute infection (acute vs. not acute)		-0.08	-0.22, 0.07	0.290	0.04	-0.13, 0.20	0.673

* Adjusted for all other variables in table

Appendix 3 – Presentation given at BHIVA (2014), Liverpool

Trends in cART Initiation Amongst HIV Seroconverters in the UK

Victoria Parsons
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Background

- ART guidelines changed nationally & internationally since advent of cART
- Movement towards starting at higher CD4 counts (BHIVA CD4 200 to 350 in 2008)
- Lack of consensus about optimal time to start for individual benefit (CD4 350 vs 500)
- Treatment as prevention
- cART in primary HIV (within 6 months of SC) - possible immunological and virological benefit

Aims & Objectives

Aim:

To characterise temporal trends in cART initiation amongst UK seroconverters, specifically:

Objectives:

1. CD4 count at cART initiation
2. Time from seroconversion to cART initiation
3. Trends in cART initiation and interruption in PHI (within 6 months of seroconversion)

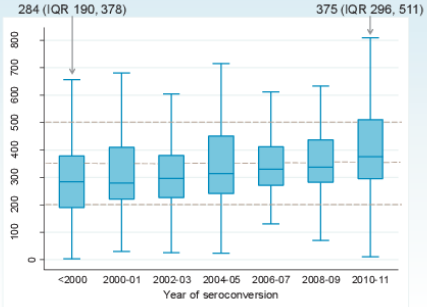
Methods

- UK Register of HIV Seroconverters
- Dataset restricted to:
  - ≥16 years of age at seroconversion
  - Seroconverted ≥01/01/1998 and ≤31/12/2011
- Time to event analyses – median time from seroconversion to cART initiation
  - Censor: date last assessed in clinic or date of death
  - Cox proportional hazards model – temporal trends
  - Adjusted for age at seroconversion, sex, HIV exposure category, and seroconversion interval
- Proportions and logistic regression – cART initiation & interruption in primary infection

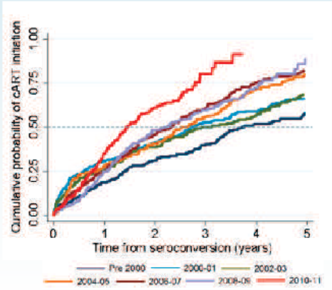
UK Register of HIV Seroconverters Characteristics

		Overall
N		1,734
Median (IQR) year of SC		2005 (2001, 2009)
Median (IQR) age at SC in years		33 (27, 40)
Sex (%)	Male	94
Exposure (%)	MSM	90
	MSW	9
	IDU	1
Lab evidence acute infection (%)		17
Median (IQR) SC interval in days		151 (39, 294)

Median CD4 at cART initiation in UK seroconverters



Kaplan Meier plot of time to cART initiation by calendar year of seroconversion



Year of SC	Median (95% CI) years to cART initiation
1998-99	3.7 (3.2, 4.9)
2000-01	2.8 (2.2, 3.5)
2002-03	2.9 (2.3, 4.0)
2004-05	2.6 (2.2, 3.0)
2006-07	2.3 (1.8, 2.7)
2008-09	2.2 (1.8, 2.7)
2010-11	1.4 (1.3, 1.7)

Factors associated with risk of cART initiation

N=1734, Events=1337, PY at risk=4633.5

	Adjusted* HR	95% CI	p
Calendar year of SC	1.04	(1.03, 1.06)	<0.001
Age at seroconversion (per 10 years)	1.14	(1.08, 1.21)	<0.001
Seroconversion interval (per month)	0.97	(0.97, 0.98)	<0.001
Sex			
Male	1	-	0.556
Female	1.11	(0.78, 1.58)	
Exposure group			
MSM	1	-	0.984
MSW	1.02	(0.77, 1.35)	
IDU	1.06	(0.49, 2.30)	

HR= Hazard ratio; *Adjusted for all other variables in the table

cART initiation in primary infection (<6 months following seroconversion)

	Calendar year of seroconversion						
	Pre 2000	2000-1	2002-3	2004-5	2006-7	2008-9	2010-11
N	61	98	114	175	148	139	232
% starting cART in PHI	27.9	50.0	35.1	29.1	20.3	13.0	19.8
Median (IQR) years spent on cART	1.1 (0.5, 3.0)	0.6 (0.2, 1.4)	0.5 (0.3, 1.1)	0.5 (0.2, 0.9)	0.5 (0.2, 0.9)	3.1 (2.4, 3.7)	1.6 (0.9, 2.1)
% of those starting cART in PHI who interrupted within 12 months	47.1	59.2	70.0	80.4	83.3	11.1	10.9

cART initiation in primary infection (<6 months following seroconversion)

	Calendar year of seroconversion						
	Pre 2000	2000-1	2002-3	2004-5	2006-7	2008-9	2010-11
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Median (IQR) years spent on cART	1.1 (0.5, 3.0)	0.6 (0.2, 1.4)	0.5 (0.3, 1.1)	0.5 (0.2, 0.9)	0.5 (0.2, 0.9)	3.1 (2.4, 3.7)	1.6 (0.9, 2.1)
% of those starting cART in PHI who interrupted within 12 months	47.1	59.2	70.0	80.4	83.3	11.1	10.9

Conclusions

- Trend towards earlier cART initiation amongst UK seroconverters
  - Median time to starting cART now 1.4 years after seroconversion
  - >25% initiated cART at CD4>500 cells/ml
  - 44% initiated with CD4<350 cells/ml
- Changing trends in cART initiation during primary infection
  - Longer median duration of cART & less interruption of cART within 12 months
  - Less short-course treatment since 2008

Discussion

- Time to initiation is decreasing, even when excluding those starting in primary infection
- Why are people starting earlier?
  - Recommendations of starting CD4>500
  - Greater acceptability of cART amongst patients
  - Use of treatment as prevention of transmission
- UK Register of HIV Seroconverters sub-study examining attitudes & acceptability towards early cART amongst MSM seroconverters
  - Open for enrolment at UK centres
  - **Contact me at v.jones@ucl.ac.uk for more information**

Acknowledgments

We would like to thank all the UK Register participants for allowing their routine clinical data to be included. We gratefully acknowledge the work of the members of the Steering Committee and colleagues at the clinical centres.

UK Register Steering Committee: Andrew Philips (Chair), University College London (UCL), London; Abdel Babiker, UCL , London; Simon Collins, iBASE, London; Valerie Delpech, Public Health England, London; Sarah Fidler, St. Mary's Hospital, London; Martin Fisher, Brighton & Sussex University Hospitals NHS Trust, Brighton; Julie Fox, Guys and St Thomas' NHS Trust/Kings College, London; Richard Gilson, UCL, London; David Goldberg, Health Protection Scotland, Glasgow; David Hawkins, Chelsea & Westminster NHS Trust, London; Anne Johnson, UCL, London; Margaret Johnson, UCL and Royal Free NHS Trust, London; Clifford Leen, University of Edinburgh, Edinburgh; Ken McLean, West London Centre for Sexual Health, London; Eleni Nastouli, UCL, London; Frank Post, King's College, London.

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Appendix 4 – Poster presented at HIV Therapy (2014), Glasgow

P200

Attitudes and beliefs towards early ART initiation in MSM with primary HIV infection

V Parsons, K Porter, R Gilson and G Hart
University College London, UK

Background

ART initiation in primary HIV infection (PHI) could reduce risk of transmission to sexual partners at a time of high viraemia, although health benefit for the individual remains unknown. We examined attitudes to early ART and associated beliefs in men who have sex with men (MSM) with PHI.

Methods

Semi-structured face-to-face in-depth interviews were conducted with 13 MSM aged ≥16 years. Men were recruited from a central London HIV clinic and interviewed within 12 months of date of estimated HIV seroconversion. Audio recordings of interviews were transcribed verbatim, imported into NVIVO and analysed thematically using the Framework approach developed by NatCen.

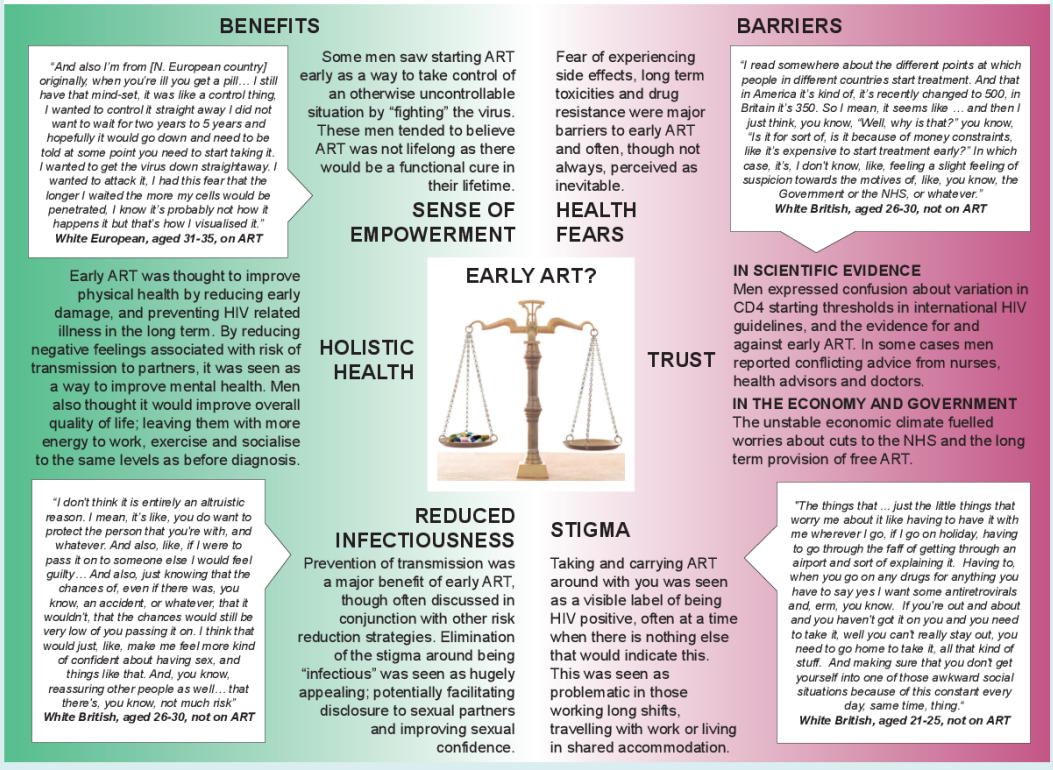
Results

Median age of participants was 33 years (range 22-47), majority were of white British ethnicity (n=8), educated to university level (n=11), and were not on ART at the time of interview (n=10).

Expectations around starting ART were diverse, with some men assuming they would be prescribed ART immediately upon diagnosis. Deferral until CD4<350 came as a surprise and seemed counterintuitive to these men when put into the context of treating other diseases. As expected, the role of the doctor in the decision making process was central, with many men stating they will start when told to by their clinician.

Key themes around early ART emerging from the interviews are presented in figure 1, with descriptions and quotes from the participants.

Figure 1. Perceived benefits and barriers to early initiation of ART in MSM with PHI attending a central London HIV clinic



Conclusions

Factors involved in the decision to start ART early are complex and involve balancing the perceived benefits and barriers. Uncertainty over evidence of individual health benefits and long term free provision of ART in the NHS, in conjunction with fear of side effects, toxicities and resistance were barriers to starting ART early. By contrast early ART was seen as a way of improving future health, reducing stigma, facilitating disclosure, and limit the consequences of infection until a cure is found.

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MRC Clinical Trials Unit

Appendix 5 – Poster presented at IWHOD (2015), Catania, Sicily

Attitudes towards early ART initiation in a UK cohort of MSM seroconverters

Victoria Parsons[1], Andrew Phillips[1], Richard Gilson[1], Sarah Fidler[2], Martin Fisher[3], Anne Johnson[1], David Hawkins[4], Ken McLean[5], Margaret Johnson[6], Graham Hart[1] and Kholoud Porter[1] for the UK Register of HIV Seroconverters

[1]University College London, London, UNITED KINGDOM, [2]Imperial College London, London, UNITED KINGDOM, [3]Brighton & Sussex Medical School, Brighton, UNITED KINGDOM, [4]Chelsea & Westminster NHS Foundation Trust, London, UNITED KINGDOM, [5]West London Centre for Sexual Health, London, UNITED KINGDOM, [6]Royal Free London NHS Foundation Trust, London, UNITED KINGDOM.

UCL

Background

The very high viraemia associated with recent HIV infection means that immediate initiation of ART can reduce the risk of transmission to sexual partners. Despite an absence of RCT data on individual survival benefits of early treatment many individuals presenting with early HIV infection consider starting ART. Of all new HIV diagnoses in the UK, the vast majority are amongst MSM (men who have sex with men) and approximately 25-30% are recent infections. We examined the expectations, attitudes & acceptability towards early ART amongst MSM recruited to the UK Register of HIV seroconverters (UKR) from UK HIV clinics, along with factors associated with uptake of early ART.

Methods

We conducted a cross-sectional survey sub-study of the UKR (July 2013-January 2015) in 16 HIV centres across the UK. Men recruited to the UKR were eligible for the survey sub-study if they were MSM, aged≥16 years and first diagnosed HIV positive in the last 12 months. A self-completion pen and paper questionnaire captured demographic factors, HIV testing history, seroconversion (SC) symptoms, sexual behaviour in the 6 months before and time since diagnosis, attitudes and acceptability towards ART and reasons for starting in those who started. The survey and clinical data from the UKR were merged for analysis. Logistic regression was used to assess factors associated with early ART adjusting for time from HIV diagnosis to survey completion.

Results

- Data from 116 MSM were available for this analysis, corresponding to a response rate of 46% of survey-eligible MSM recruited to the UKR during the study period.
- Median (IQR) age at SC was 33 (28, 39) years, HIV test interval 81 (0, 168) days and time from diagnosis to survey completion 75 (39, 190) days. Men were predominantly of white ethnicity (84%), currently employed (82%) and with higher level education (89%).
- Median (IQR) CD4 at diagnosis was 518 (403, 667) cells/mm^3, median viral load at diagnosis was 4.8 (4.3, 5.8) $\log_{10}$ copies/ml.
- 47% (55/116) of men had started ART by the time of questionnaire completion and 69% (38/55) of those on ART had started within 1 month of diagnosis.
- Starting ART at the point of diagnosis was acceptable to most men; 48% (55/115) expected to start within 1 month of their diagnosis and 67% (76/114) of men said they would have accepted ART at diagnosis if offered it (8% would not and 25% were unsure).
- Men were more likely to have started early ART if their doctor had advised them to start, if they agreed with the statement "Starting ART earlier rather than later is better for my health", if they stated they would have accepted ART at diagnosis if offered and if they had previous PEP experience (see table).
- Those with a sexually transmitted infection (STI) infection at HIV diagnosis were less likely to be on ART (see table) but no associations observed between sexual behaviour factors and uptake of early ART (data not shown).

Factors associated with starting early ART in UK MSM seroconverters

	ART naïve MSM		MSM on early ART				
Variable	n	% or median(IQR)	n	% or median(IQR)	OR*	95% CI	p-value
Time from HIV diagnosis to survey completion							
Per month increase	61	1.4 (0.7, 5.5)	55	3.7 (1.6, 8.0)	1.14**	1.02, 1.27	0.019
Seroconversion interval							
Per month increase	61	2.8 (0, 5.9)	55	2.5 (0, 5.5)	0.95	0.83, 1.07	0.396
Age at HIV seroconversion							
Per year increase	61	32.5 (27.3, 38.2)	55	33.4 (27.9, 41.3)	1.01	0.97, 1.06	0.55
CD4 count at diagnosis							
Per √cells/mm3 increase***	58	520 (411, 718)	53	491 (390, 629)	0.92	0.84, 1.02	0.103
HIV viral load at diagnosis							
Per log10 copies/ml increase	57	4.8 (4.3, 5.8)	54	4.8 (4.3, 5.8)	1.12	0.81, 1.53	0.495
Ethnicity							
White	49	80.3	48	87.3	1		
Non-white	12	19.7	7	12.7	0.6	0.21, 1.69	0.331
Years full time education after 16 years of age							
<3 years	7	11.5	10	18.2	1		
3 years or more	54	88.5	45	81.8	0.62	0.21, 1.81	0.383
Currently employed							
No	8	13.1	13	23.6	1		
Yes	53	86.9	42	76.4	0.5	0.19, 1.36	0.176
Current regular male partner (RMP)							
No RMP	31	51.7	32	58.2	1		
HIV+ RMP	14	23.3	8	14.5	0.48	0.17, 1.36	
HIV- or unknown status RMP	15	25.0	15	27.3	0.99	0.40, 2.41	0.364
STI co-infection at HIV diagnosis							
No	25	41.7	38	70.4	1		
Yes	35	58.3	16	29.6	0.28	0.13, 0.63	0.002
Ever taken PEP							
No	52	86.7	36	65.5	1		
Yes	8	13.3	19	34.5	3.15	1.22, 8.09	0.017
Expected to start ART within 1 month of HIV diagnosis							
No	33	55.0	26	48.1	1		
Yes	27	45.0	28	51.9	0.6	0.27, 1.33	0.209
Would have accepted ART at HIV diagnosis if offered							
No	7	11.7	3	5.7	1		
Yes	29	48.3	47	88.7	7.57	1.49, 38.40	
Maybe	24	40.0	3	5.7	0.31	0.05, 2.13	<0.001
Doctor advised starting ART							
No	32	58.2	12	23.1	1		
Yes	23	41.8	40	76.9	7.34	2.76, 19.50	<0.001
"It is better for my health to start ART earlier rather than later"							
Don't agree	22	39.3	5	9.3	1		
Agree	34	60.7	49	90.7	13.1	3.60, 47.27	<0.001
"Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom"							
Don't agree	17	39.5	21	38.9	1		
Agree	26	60.5	33	61.1	1.08	0.47, 2.51	0.849
"It is not necessary to disclose your HIV status to a sexual partner if you are on ART and have an undetectable viral load"							
Don't agree	36	83.7	43	81.1	1		
Agree	7	16.3	10	18.9	1.13	0.38, 3.38	0.821
"Better HIV treatment means that people are less worried about catching HIV"							
Don't agree	22	51.2	22	40.7	1		
Agree	21	48.8	32	59.3	1.93	0.82, 4.56	0.135

*Odds ratio adjusted for time from HIV diagnosis to survey completion. ** Unadjusted OR *** CD4 count at diagnosis modelled as square-root transformed CD4. IQR = interquartile range, OR=odds ratio, 95% CI=95% confidence interval

Reasons MSM seroconverters started early ART (n=55)

- **96%** Control the spread of HIV in body
- **96%** Decrease the damage HIV causes to body
- **89%** Reduce risk of transmission to partners
- **85%** Improve life expectancy
- **85%** Improve quality of life
- **85%** Reduce anxiety of transmission to partners
- **51%** Because they were advised to by their doctor

Acceptability & attitudes towards early ART amongst ART naïve MSM seroconverters (n=61)

- **81%** Would consider starting to reduce transmission even in the absence of proven health benefit
- **75%** Had considered starting ART since diagnosis
- **47%** Expected to start in the next month
- **62%** Would start when their doctor told them to

Perceived barriers to early ART

- **70%** Concerned about side effects
- **21%** Put off by lifelong commitment to ART
- **11%** Thought early ART wouldn't fit in with their lifestyle
- **7%** Thought it would reduce future treatment options

Conclusions

Most respondents would have accepted immediate ART at diagnosis if offered. Whilst treatment as prevention was a common reason for starting early, there were also strong beliefs in the health benefits of early ART, even in the absence of randomised evidence. Men with previous ART experience through PEP were more likely to start ART early, though worryingly those with STI infection at HIV diagnosis (a proxy for high-risk sexual behaviour) were less likely to. Importantly, acceptability of early ART was high amongst those not yet on ART, although fear of side effects was prevalent in this group.

Appendix 6 – Poster presented at BHIVA (2015), Brighton

Attitudes, beliefs and acceptability towards early ART amongst men who have sex with men (MSM) recruited to a UK cohort of HIV seroconverters

Victoria Parsons[1], Andrew Phillips[1], Richard Gilson[1], Sarah Fidler[2], Martin Fisher[3], Anne Johnson[1], David Hawkins[4], Ken McLean[5], Margaret Johnson[6], Julie Fox[7], Simon Collins[8], Graham Hart[1] and Kholoud Porter[1] for the UK Register of HIV Seroconverters

[1]University College London, London; [2]Imperial College London, London; [3]Brighton & Sussex Medical School, Brighton; [4]Chelsea & Westminster NHS Foundation Trust, London; [5]West London Centre for Sexual Health, London; [6]Royal Free London NHS Foundation Trust, London; [7]Guy's & St Thomas' Hospital, London; [8]HIV iBase, London.

UCL

BACKGROUND

- Immediate initiation of ART as prevention (TasP) amongst those with recent infection can reduce the risk of transmission to sexual partners at a time of high viraemia.
- 25-30% of HIV infections in the UK are recent infections.
- Many individuals presenting with early HIV infection consider starting early ART despite an absence of RCT data indicating an individual survival benefit.

AIM

To examine the expectations, attitudes & acceptability towards early ART (initiation within 1 year of diagnosis) amongst MSM seroconverters recruited to the UK Register of HIV seroconverters (UKR), along with factors associated with uptake of early ART.

METHODS

- Cross-sectional survey sub-study of the UKR (July 2013-January 2015) in 16 UK HIV centres.
- Men were eligible if they were MSM, aged≥16 years and first diagnosed HIV positive in the last 12 months with a SC interval (time between HIV Ab negative & positive test) ≤12 months.
- Self-completion pen and paper questionnaire captured demographic factors, HIV testing history, seroconversion (SC) symptoms, sexual behaviour in the 6 months before and time since diagnosis, attitudes and acceptability towards ART and reasons for starting in those who started.
- Survey and clinical data from the UKR were merged for analysis.
- Logistic regression was used to assess factors associated with starting early ART adjusting for time from HIV diagnosis to survey completion.

RESULTS

- N=116 MSM were recruited with a median (IQR) seroconversion interval of 81 (0, 168) days.
- Response rate was 46% of eligible MSM recruited to UKR.
- Median (IQR) age at SC was 33 (28, 39) years and time from diagnosis to survey completion 75 (39, 190) days.
- Men were predominantly of white ethnicity (84%), currently employed (82%) and with higher level education (89%).
- Median (IQR) CD4 at diagnosis was 518 (403, 667) cells/mm^3 and median viral load at diagnosis was 4.8 (4.3, 5.8) $\log_{10}$ copies/ml.
- 47% (55/116) of men had started ART by the time of questionnaire completion and 69% (38/55) of those on ART had started within 1 month of diagnosis.
- None of the demographic factors, sexual behaviour, or CD4 and HIV viral load at HIV diagnosis were associated with starting early ART.

MSM were LESS likely to have started ART early*...

- If they had an **STI co-infection** at HIV diagnosis (OR 0.28; 95% CI 0.13-0.63; p=0.002)

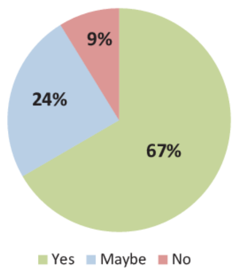
MSM were MORE likely to have started ART early*...

- If they stated they **would have accepted ART at diagnosis** if offered (OR 7.57; 95% CI 1.49-38.40; p<0.001)
- If their **doctor had advised starting ART** (OR 7.34; 95% CI 2.76-19.50; p<0.001)
- If they agreed with the statement **"It is better for my health to start ART earlier rather than later"** (OR 13.10; 95% CI 3.60-47.27; p<0.001)
- If they had **ever taken PEP** (OR 3.15; 95% CI 1.22-8.09; p=0.017)

* OR adjusted for time from HIV diagnosis to questionnaire completion

WOULD YOU HAVE ACCEPTED ART AT HIV DIAGNOSIS IF OFFERED?

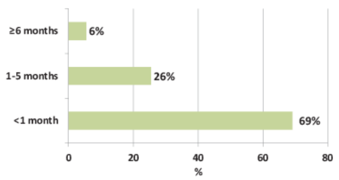
(n=114)



MSM WHO INITIATED EARLY ART

(n=55)

How long after diagnosis did they start?



Reasons for starting early ART

96% Control the spread of HIV in body

96% Decrease the damage HIV causes to body

89% Reduce risk of transmission to partners

85% Improve life expectancy & quality of life

85% Reduce anxiety of transmission to partners

51% Because they were advised to by their doctor

ART NAÏVE MSM

(n=61)

Acceptability and attitudes towards early ART

81% Would consider starting to reduce transmission even in the absence of proven health benefit

75% Had considered starting ART since diagnosis

62% Would start when their doctor told them to

47% Expected to start in the next month

Perceived barriers to early ART

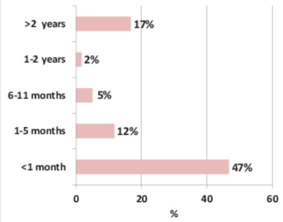
70% Concerned about side effects

21% Put off by lifelong commitment to ART

11% Thought early ART wouldn't fit in with their lifestyle

7% Thought it would reduce future treatment options

How long after questionnaire completion did ART naïve MSM expect to start ART?



CONCLUSIONS

Acceptability of early ART was high amongst this cohort of MSM seroconverters; 47% had started ART, and 47% of men not yet on ART expected to start within the next month. TasP was a commonly cited reason men started early ART, but many also believed in a health benefit, even in the absence of RCT evidence. Men whose doctor advised starting were more likely to start early, highlighting the important influence of clinicians' opinion on the decision to start early. Potentially of concern was that men with an STI at HIV diagnosis were less likely to start early ART, although we found no evidence to suggest that higher-risk sexual behaviour (such as reporting chem-sex or serodiscordant condomless anal sex) prior to, or since, HIV diagnosis was associated with early ART uptake.

CONTACT

Victoria Parsons

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+44 (0)20 7670 4864

We would like to thank all the UK Register participants for allowing their routine clinical data to be included. We gratefully acknowledge the work of the members of the Steering Committee and colleagues at the clinical centres.

Appendix 7 – Search strategy for scoping literature review "What is the rationale for initiation of ART in early HIV infection?"

The database searched listed below were conducted by me and the abstracts reviewed. In addition to the database searches listed below, abstracts for the following conferences were searched by hand from January 2008 to March 2010 to ensure the inclusion of recently collected data which may not have been published: International AIDS Society (IAS), AIDS, European AIDS Conference (EACS) and Conference on Retroviruses and Opportunistic Infections (CROI).

References cited in the articles included in the literature review chapter were also checked to ensure studies were not overlooked.

Clinical and prevention benefits of early ART

Total abstracts searched:	5193
Databases searched:	PubMed and Ovid (search formatted for PubMed listed below)
Dates:	Literature published up to March 2010
Language:	English

Boolean operator	Search terms
	hiv[tiab] OR human immunodeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR acquired immunodeficiency[tiab] OR acquired immuno-deficiency[tiab]
AND	Highly Active Antiretroviral Therapy [tiab] OR Anti-Retroviral Agents[tiab] OR ((anti) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti) AND (retroviral*[tiab])) OR HAART[tiab] OR ART[tiab] OR HIV treatment[tiab] OR TasP[tiab] OR (treatment as prevention[tiab])
AND	seroconver*[tiab] or early[tiab] or primary[tiab] or acute[tiab] or recent[tiab] or prevent*[tiab]
AND	initiat*[tiab] or start*[tiab] or begin*[tiab] or commenc*[tiab]
NOT	perinatal[tiab] or mother to child[tiab] or mother-to-child[tiab] or vertical[tiab] or infant[tiab] or child[tiab] or ped*[tiab] or paed[tiab]

Attitudes and acceptability towards early ART

Databases searched:	PubMed and Ovid (search formatted for PubMed listed below)
Dates:	Literature up to March 2010
Language:	English
Total abstracts searched:	1545

Boolean operator	Search terms
	HIV[tiab] OR human immunodeficiency virus[tiab] OR human immuno-deficiency virus[tiab] OR acquired immunodeficiency[tiab] OR acquired immuno-deficiency[tiab]
AND	Highly Active Antiretroviral Therapy [tiab] OR Anti-Retroviral Agents[tiab] OR ((anti) AND (hiv[tiab])) OR antiretroviral*[tiab] OR ((anti) AND (retroviral*[tiab])) OR HAART[tiab] OR ART[tiab] OR HIV treatment[tiab] OR TasP[tiab] OR (treatment as prevention[tiab])
AND	attitud*[tiab] OR belie*[tiab] OR accept*[tiab] OR barrier*[tiab] OR facilitat*[tiab] OR feasib*[tiab] OR adopt*[tiab]
AND	seroconver*[tw] or ((early[tw]) or (primary[tw]) or (acute[tw])) or prevent*[tiab]
AND	MSM[tiab] or (men who have sex with men[tiab]) or gay[tiab] or bisexual[tiab] or homosexual[tiab]
NOT	(perinatal[tiab] or mother to child[tiab] or mother-to-child[tiab] or vertical[tiab](perinatal[tiab] or mother to child[tiab] or mother-to-child[tiab] or vertical[tiab] or paed*[tiab] or child*[tiab])

Appendix 8 – UK Register of HIV Seroconverters case report proforma

UK REGISTER OF HIV SEROCONVERTERS
INITIAL REGISTRATION FORM

MRC Clinical Trials Unit

Clinic number	Sex	Initials	Soundex	Date of birth	Seroconverter Register number *Office use only*

1. **Is the patient alive?** Yes ☐ No ☐ Unknown ☐ *If yes or unknown* give date last known alive: ___/___/___

2. **Date first attended this clinic:** ___/___/___ **Date last assessed at this clinic**: ___/___/___

3. **Ethnic group**
(tick one only):
☐ White
☐ Black African
☐ Black Caribbean
☐ Indian/Pakistani/Bangladesh
☐ Other (Specify): _____

4. **Probable route of transmission**
(tick one or more):
☐ Sex between men
☐ Injecting Drug Use
☐ Sex between men & women
☐ Mother to Child
☐ Other (specify):_____

5. **What is the likely country of infection?**
_____

6. **Was an HIV seroconversion-type illness reported?** Yes ☐ No ☐ If yes, start date of symptoms: ___/___/___
Main symptoms _____

7. **Patient must have confirmed Primary HIV Infection by at least 1 of the following 5 criteria:**
Please tick all criteria below that apply and enter the relevant dates and where test done:

Yes

A. **HIV positive antibody test within 12 months of an HIV negative antibody test** ☐
Date of HIV **negative** antibody test: ___ / ___ / ___ **Where?** _____
Date of HIV **positive** antibody test: ___ / ___ / ___ **Where?** _____

B. **HIV antibody negative with positive PCR (or positive p24 Ag or viral load detectable)** ☐
Date of HIV **negative** antibody test with **positive** PCR/p24/viral load: ___ / ___ / ___ **Where?** _____

C. **RITA (recent incident test algorithm) assay result consistent with/indicative of recent infection** ☐
Date of RITA assay: ___ / ___ / ___ **Assay used:** _____

D. **Equivocal HIV antibody test supported by a repeat test within 2 weeks showing a rising optical density** ☐
Date of **equivocal** antibody HIV test: ___ / ___ / ___ **Where?** _____
Date of **first positive** antibody HIV test: ___ / ___ / ___ **Where?** _____

E. **Have clinical manifestations of symptomatic HIV seroconversion illness supported by antigen positivity and <4 bands positive on Western Blot** ☐
Date of positive antigen test and <4 bands positive on Western Blot: __ / __ / ___ **Where?** _____

F. **Reported to the CHIPS paediatric cohort /received paediatric HIV care in the UK** ☐
Date of first **Positive HIV test (approximate):** ___ / ___ / ___ **CHIPS Study number if known**: _____

8. **Give (absolute) CD4 cell count results:**

Date	CD4 count	Date	CD4 count	Date	CD4 count
___/___/___		___/___/___		___/___/___	
___/___/___		___/___/___		___/___/___	
___/___/___		___/___/___		___/___/___	
___/___/___		___/___/___		___/___/___	

9. **Give plasma HIV viral load results:**

Date	VL result	Assay used	Date	VL result	Assay used
___/___/___			___/___/___		
___/___/___			___/___/___		
___/___/___			___/___/___		
___/___/___			___/___/___		

10. Has antiretroviral therapy ever been prescribed? Yes ☐ No ☐

Anti-HIV drug	Date started	Date stopped
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___

Anti-HIV drug	Date started	Date stopped
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___
	___/___/___	___/___/___

11. Has an AIDS defining condition ever been diagnosed Yes ☐ No ☐

If Yes, please provide details including date and method of diagnosis (Definitive or Presumptive)

Disease	Date diagnosed	Method (D/P)
	___/___	
	___/___	

Disease	Date diagnosed	Method (D/P)
	___/___	
	___/___	

12. Have any of the following conditions ever been diagnosed?

Myocardial infarction	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Diabetes Mellitus	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Cerebrovascular accident	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Liver disease	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Renal disease	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Pancreatitis	Yes ☐	No ☐	If yes, date of diagnosis	____/____
Non-AIDS defining malignancy	Yes ☐	No ☐	If yes, date of diagnosis	____/____

13. Has patient been tested for Hepatitis B infection?
Yes ☐ No ☐ If yes provide results (+ or -) and all relevant dates

Date	surface antigen (HBS) +/-
_____/_____/_____	
_____/_____/_____	

14. Has patient been tested for Hepatitis C infection? Yes ☐ No ☐

If yes, provide results (+ or -) and all relevant dates

Date	Anti-HCV +/-	HCV RNA Measurement Value	HCV genotype (I, II, III, IV)	HCV RNA Assay Type
_____/_____/_____				
_____/_____/_____				
_____/_____/_____				

15. Has a 10 ml specimen been taken for storage for the Register as near as possible to first positive test*?

☐ No (*please arrange at next clinic visit*) ☐ Yes Date of sample ___/___/___

16. Has a one-off 10ml specimen been taken for genetics testing*?
☐ No (*please arrange at next clinic visit*) ☐ Yes Date of sample ___/___/___

17. Date of death: ___/___/___ **Cause(s) of death:** _____

_____

18. Additional information from Q1-17 above:

Centre name:	Signature:	Print name:	Date signed:

Please send this form in the pre-addressed envelope to:
Data Manager, UK Register of HIV Seroconverters, MRC Clinical Trials Unit, 4th Floor Aviation House, 125 Kingsway, London WC2B 3NH Tel 020 7670 4619. Fax 020 7670 4814

* **Following informed signed consent, arrange for a 10 ml EDTA sample to be taken annually. This should be sent directly to central storage: marked as UK Register Samples, to Tony Oliver, 3rd Floor Dept Virology, Pathology and Pharmacy Building, Royal London Hospital, 80 Newark Street, Whitechapel, London E1 2ES. For genetics samples this is a one-off sample; please send to the same place, highlighting it as the genetics sample.**

Appendix 9 – UK Register of HIV Seroconverters MREC approval letter

NHS

South Birmingham Research Ethics Committee

Chairman: Mr R K Vohra
Administrator: Mrs R M Downing

27 Highfield Road
Edgbaston
Birmingham
B15 3DP

Tel: 0121 245 2533/2534/2538
Fax: 0121 245 2535

Ref: RAS/rmd
Date: 12 November 2004

Dr. K Porter
Senior Epidemiologist
MRC Clinical Trials Unit
222 Euston Road
London
NW1 2DA

Dear Dr. Porter,

REC reference number: 04/Q2707/155
The UK Register of HIV Seroconverters: an observational study of HIV infected persons in the UK for whom the time of HIV seroconversion is well-estimated
Protocol number: 1.1

Thank you for your letter of 11th November 2004, responding to the Committee's request for further information on the above research.

The further information has been considered on behalf of the Committee by the Vice-Chairman.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation.

The favourable opinion applies to the research sites listed on the attached sheet. Confirmation of approval for other sites listed in the application will be issued as soon as local assessors have confirmed that they have no objection.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

- Application Version: 3.0 Dated: 23/07/2004
- Investigator CV Dated: 18/08/2004
- Protocol Version: 1.1 Dated: 04/11/2004
- Covering Letter Dated: 11/11/2004
- Participant Information Sheet Version: 1.1 Dated: 04/11/2004
- Participant Consent Form Version: 1.1 Dated: 04/11/2004

Management approval

If you are the Principal Investigator for the lead site: You should obtain final management approval from your host organisation before commencing this research.

The study should not commence at any other site until the local Principal Investigator has obtained final management approval from the relevant host organisation.

All researchers and research collaborators who will be participating in the research must obtain management approval from the relevant host organisation before commencing any research procedures. Where a substantive contract is not held with the host organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Notification of other bodies

We shall notify the research sponsor, University Hospital Birmingham NHS Trust that the study has a favourable ethical opinion.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

REC reference number: 04/Q2707/155	**Please quote this number on all correspondence**

Yours sincerely,

[redacted]

Vice Chairman

Enclosures List of names and professions of members who were present at the meeting and those who submitted written comments
Standard approval conditions SL-AC2
List of approved sites

CC Trusts

Enclosure 1

List of Names and Professions of Members who were Present at the Meeting or who Submitted Written Comments

Professor R Ashford
Lay Member

Rev'd Barry Clark [Vice Chair]
Hospital Chaplain

Dr C Chapman
Consultant in Clinical Genetics

Mrs Joy Grech
Research Sister

Dr John Isaac
Consultant Liver Transplant Anaesthetist

Dr Sue Kelly
Lecturer/Research Facilitator Physiotherapy

Mrs Frances Mant
Lay Person

Dr Elizabeth Rankin
Consultant Rheumatologist

Ms Ros Salter [Vice Chair]
Research Fellow

Dr Yvonne Searle
Consultant Clinical Psychologist

Ms Rosemarie Seadon
Pharmacist

Mr R K Vohra [Chair]
Consultant Vascular Surgeon

Appendix 10 – In-depth and cognitive interview study LREC approval letter

NHS
National Research Ethics Service

Camden & Islington Community Research Ethics Committee
REC Offices
South House, Royal Free Hospital
Pond Street, London
NW3 2QG

Telephone: 020 7794 0500 extn 36906
Facsimile: 020 7794 1004

10 February 2010

Professor Graham Hart
Head of Department
UCL Centre for Sexual Health & HIV Research
Research Dept of Infection & Population Health
3rd Floor, Mortimer Market Centre
Off Capper Street,
London, WC1E 6JB

Dear Prof Hart

Study Title: **Exploring the sexual behaviour, attitudes and beliefs of recent HIV seroconverters: a qualitative study**

REC reference number: **09/H0722/92**
Protocol number: **Version 1.0**

Thank you for your letter of 05 February 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk. *Where the only involvement of the NHS organisation is as a Participant Identification Centre, management permission for research is not required but the R&D office should be notified of the study. Guidance should be sought from the R&D office where necessary.*

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
REC application		20 November 2009
Protocol	Version 1.0	20 November 2009
Investigator CV	C.I.s CV - Graham Hart	
Participant Consent Form: Phase A_PI_Cogl	Version 1.0	16 November 2009
Participant Consent Form: Phase A_PI_IDI	Version 1.0	16 November 2009
Evidence of insurance or indemnity	Zurich Municipal for UCL	31 July 2010
Referees or other scientific critique report	NoCLoR Peer Reviewer; Prof. Paul Flowers	12 November 2009
Interview Schedules/Topic Guides	Version 1.0	16 November 2009
Letter from funder	Suzanne Wright, MRC Centre London	01 August 2008
Investigator CV	Student's CV - Victoria Jones	
Participant Information Sheet: Phase A_PI_IDI	Version 1.1	05 February 2010
Participant Information Sheet: Phase A_PI_Cogl	Version 1.1	05 February 2010
Response to Request for Further Information		05 February 2010

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

09/H0722/92	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Ms Stephanie Ellis
Chair

Email: katherine.ouseley@royalfree.nhs.uk

Enclosures: *"After ethical review – guidance for researchers"*

Copy to: *Student - Ms Victoria Jones, UCL Centre for Sexual Health & HIV Research*

R&D office for NHS care organisation at lead site – Angela Williams, Camden Primary Care Trust (NoCLoR)

Appendix 11 – In-depth interview study final topic guide

In-Depth Interview Topic Guide

Exploring the sexual behaviour, attitudes and beliefs of recent HIV seroconverters

Introduction
Introduce self & organisations
Information sheet
Explain study
Consent
Recording

Background
To start off, could you tell me little about yourself?

- Age
- Employment
- Education
- Ethnicity
- Living arrangements
- Current relationship status
- What you enjoy doing/hobbies

PHI pre-diagnosis (~6 months prior to diagnosis)
Could me how you came to know you had HIV?

- Any times where you felt you were at risk of acquiring HIV?
- Sexual behaviour in 6 months prior to diagnosis
  - Number/nature of partners
  - Type of sex/ location
  - Knowledge of HIV status of partners
  - Condom usage/reasons/accidents
  - Ejaculation
  - Typical of usual sex life
  - Clustering of contacts/peak sexual behaviour in this period
    - Reasons for behaviour
- Risk assessment of situations/ partners
- Attitudes regarding unprotected sex
- Any other sexual encounters
- Alcohol/drug use

At diagnosis
Why did you come to MMC for an HIV test?

- Health concerns/symptoms/seroconversion illness
  - Duration
  - Symptoms
  - Severity
  - Changes to lifestyle because of ill health
  - Changes in sexual activity because of ill health

    - STIs (over PHI)
        - Which?
        - When?
        - Symptoms
        - How diagnosed?
        - Reason behind STI testing
- Suspicions/ regular testing
    - Previous testing history

How did you feel when you received the diagnosis?

- Expectant/surprise
- Reasons
- Self esteem
- Have you disclosed to anyone, how did it go?

PHI after HIV diagnosis

What effect has the diagnosis had on your life?

- Priorities
- Changes in lifestyle/behaviour?
- Self esteem?
- Confidence?

What effect has the diagnosis had on your sex life?

- When?
    - Before/after diagnosis?
- Who?
    - Number/type of partners
    - Type of sex
    - Nature of situation
    - Knowledge of HIV status of partners
    - Condom usage/breakage/incidents
    - Reasons behind condom usage/non usage
- How?
    - Understanding of HIV transmission
    - Perceived risk of transmitting to partners
    - Knowledge of viral load
- Concerns
    - Concerns about transmission
    - Disclosure of status/sero-sorting
    - Feelings about UAI since diagnosis

HIV treatment

Could you tell me what you know about HIV treatment?

- When to start?
- What is involved?
- Knowledge/beliefs
- Impact on sexual behaviour
- Risk of transmission
- Sources of information

Have you ever heard of PEP? Have you taken it?

How do you feel about starting HIV treatment?

- What are your thoughts and feelings based on?

How would you have felt about starting HIV treatment when you were first diagnosed?

How do you think being on HIV treatment would change life/has it changed your life?

What do you understand about treatment, viral load and HIV transmission?

How much do you agree with the following statements and why?

A) An undetectable viral load means that HIV is unlikely to be passed to a sexual partner even if we have anal sex without a condom

B) Having an undetectable viral load makes it less important to disclose my HIV status to sexual partner(s)

Would starting treatment early be more acceptable if you only had to take it for a shorter period and not for life?

Debriefing

Thank
Re-iterate confidentiality
Offer list of useful counselling or support services
Participation in cognitive interview study?
Want summary sheet of the main study findings?

Appendix 12 – In-depth interview study participant information sheet

Participant Information Sheet

Exploring the sexual behaviour, attitudes and beliefs of recent HIV seroconverters

We would like to invite you to take part in our study. Before you decide you will need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and ask us if you are unclear about anything or would like more information. The contact details of the research co-ordinator can be found at the end of the information sheet.

What is the purpose of the study?
People who have been recently infected with HIV (recent HIV seroconverters) may play an important role in the UK epidemic, however little is known about their sexual behaviour, knowledge, beliefs and attitudes. We want to explore the sexual behaviour, knowledge and attitudes people recently infected with HIV have towards HIV treatment, particularly how they would feel about starting HIV treatment early.

Why have I been invited?
You have been invited to participate in this study as you presented to our clinic very early on in your HIV infection; in other words you are a recent seroconverter.

Do I have to take part?
You are under no obligation to take part in this study. It is up to you to decide whether you want to take part or not. If you decide you do want to take part and sign a consent form, you are still free to withdraw from the study at any point should you wish to, without giving a reason. Your healthcare will not be affected if you decide not to participate in the study.

What will happen to me if I take part?
Participating in this study involves you having a one-to-one face-to-face interview with the researcher. If you decide you wish to participate, we will first arrange a time that is convenient for you to come and take part in the study. This could be now or at some point in the future up to 3 months after your HIV diagnosis.

When you arrive at Mortimer Market Centre to take part in the study, you will be met by the research co-ordinator and shown to the private room. You will have the study explained to you and be asked to sign a study consent form saying that you are happy to be involved in this study. During the interview we will be asking you personal questions about your sexual behaviour, your feelings at the time you were diagnosed and your beliefs and attitudes to HIV treatment. You are not obliged to answer a question if you do not want to. The interview will last around 1 hour and will be audio-recorded.

Will my taking part in the study be kept confidential?
Yes, the interview recording will be kept secure in a locked cabinet and destroyed immediately after the interview has been transcribed. No identifiable information will be

kept with the recording or transcript. Excerpts from the interview transcripts will be used in reports and publications but you will be referred to as a number and personally identifiable information will not be revealed. The only time we may have to pass information on is if you make a disclosure of intent to seriously harm yourself or others. In the rare event of this happening, we will talk to you first before speaking to a senior member of your clinical care team here at the Bloomsbury Clinic.

Who is carrying out this study?
This study is being carried out in part fulfilment of the research co-ordinator's PhD at the UCL Centre for Sexual Health & HIV Research, in collaboration with Camden Primary Care Trust. The PhD is funded by the Medical Research Council. This study has received ethical approval by Camden & Islington Community Research Ethics Committee.

What will happen to the results of the research study?
The results of the study will be written up as part of the research co-ordinator's PhD thesis, and a paper will be submitted for publication in an academic journal. A poster of the results will be placed in the Bloomsbury Clinic for the benefit of patients. If you are interested in receiving a summary sheet of the results please give your contact details to the research co-ordinator and she will ensure you are sent one.

What are the disadvantages of taking part in this study?
There are no disadvantages of taking part in this study. This study involves questions that some people may find sensitive or personal in nature. You are not obliged to answer a question if you do not want to.

What are the benefits of taking part in this study?
There are no direct benefits of participating in this study, however the results will be useful in better understanding the needs of recent seroconverters and the role that early initiation of HIV treatment can play in UK in the future.

What do I go if I have a complaint about the study?
If you are unhappy about an aspect of this study, please discuss your concerns with a member of the research team in the first instance using the contact details below. If you are still unhappy and would like to make a formal complaint you can telephone patient support service at Camden PCT on 020 3317 3003, or email at pss@camdenpct.nhs.uk. More information is available at http://www.camden.nhs.uk/patientsupportservice.

If you have any queries regarding the study please contact the research team using the details below:

Research Co-ordinator: Vicky Jones
UCL Centre for Sexual Health & HIV Research
3rd Floor Mortimer Market Centre
London
WC1E 6JB
Email: vjones@gum.ucl.ac.uk
Tel: 0845 1555 000 ext. 5019

Chief Investigator: Graham Hart
UCL Centre for Sexual Health & HIV Research
3rd Floor Mortimer Market Centre
London
WC1E 6JB
Email: ghart@gum.ucl.ac.uk

Appendix 13 – In-depth interview study consent form

Participant Consent Form

Agreement to take part in an in-depth interview exploring the sexual behaviour, attitudes & beliefs of recent HIV seroconverters

I (Name of participant) _____

(Please indicate your consent to each of the following statements by writing your initials in the relevant boxes)

Have read the patient information sheet (ref: PhaseA_PI_IDI, version:1.1) and agree to take part in the above study.	☐
I confirm that the nature of the study has been explained to me and that I have fully understood the information I have received.	☐
I have had the opportunity to ask questions about all aspects of the study and am satisfied with the responses given to me.	☐
I understand that the interview will be audio recorded and give my consent for this to happen.	☐
I understand that I may withdraw from the study at any time and this will not affect my treatment at the clinic in any way.	☐

Participant

Signed: _____ Date: _____

Name (block letters): _____

Research co-ordinator

Signed: _____ Date: _____

Name (block letters): _____

Appendix 14 – Extract from framework analysis for the in-depth interview study

	A : Early treatment	B : Reasons for starting
1. M20 Age=31-35 Ethnicity=White British On ART=No Partnership status=Single Education=University Employment=Employed FT Diagnosis to interview=0-3 months SC ID Method=Ab- then + HCV Coinfection=No	Assumed would be starting treatment straight away after diagnosis. Subsequently realised after reading books that there was a "non-progressive phase" "I just assumed that the second you got diagnosed there would be this flurry of medical activity and you would end up on lots of tablets and I'd feel like shit for a few weeks and then things would go back to normal... I didn't really, it didn't register, it never occurred to me that you wouldn't be starting treatment instantly anyway" Happy to start treatment now "if any use" even if there was no evidence of a benefit. Did not have a problem with idea of taking tablets. "If there's no benefit I don't mind either because it's no skin off my nose whether I take a tablet or not." **Short course:** If there's no medical evidence against short course does not have a problem with it as long as could go back on treatment "When the graph is wrong and the CD4 count is dropping". As long as the drugs don't lower the CD4 count.	If it's not known when is the best time to start - now or later then would say later unless if it was a study where the data is useful & if "it's not going to bring me an early grave then why not" (importance of research - gives a reason to start) "Pragmatic" approach to starting - "if there is a benefit then there wouldn't really be a problem."
2 : D02 Age=31-35 Ethnicity=White British On ART=No Partnership status=Single Education=University Employment=Employed FT Diagnosis to interview=3-6 months SC ID Method=PCR+ Ab- HCV Coinfection=Yes	Would only consider cART now if "really good evidence" of a benefit to him. Short course: A friend was on SPARTAC trial. Unsure what the idea of it was though but knew you start then come off it "just to see whether that meant you didn't need to go on treatment again for 15 years or something like that." Not a decisive person so not sure what he would have done if offered short course. Would need a "fair bit" of information but would want to know "as much as possible" and without having looked at it it's a flip of the coin decision. Got to think of yourself in the end but knows that with a trial the whole point is that you don't know. So mind not made up on short-course treatment.	Not looked at treatment as does not need it yet. Expects to have to start when CD4 drops from around 400 now to 250 or 350. Aware it may move up to 500 but thinks that's treating the population not the individual. But thinks that is good to reduce tranmission. "I know there some talk of moving up to 500 which in my opinion then makes me wonder whether it's actually treating the population rather than necessarily treating the individual because obviously then that's good to stop infecting other people which I can understand" Would start if CD4 was "plummeting" & becoming ill. "I would, if ... when I know I need it because my CD4 is plummeting and I'm becoming ill or whatever, like that then yes I'll happily start, then prior to that I would have to be shown some very convincing argument to make me ... " Knows about people who have had HIV 20 years & still don't need treatment and would love to be one of those. Not "scared of taking" it but would be worried about being "bullied into it" at a sensitive time. Wants to see "really good evidence that "starting early was of benefit to me" Would "happily start" if CD4 was "plummeting" & "becoming ill" but earlier than that would need "some very convincing argument".
3 : L67 Age=31-35 Ethnicity=White British On ART=No Partnership status=Single Education=NK Employment=Self employed Diagnosis to interview=10-12 months SC ID Method=Ab- then + HCV Coinfection=No	Would follow doctor's advice on starting early. Not against it at all. Being on cART for life was a big thing to deal with. "If a doctor had recommended it I think I would have taken their advice, yeah. And I'm not anti starting treatment. I do realise that when I take that tablet tonight. That's going to be forever now." Would start short-course if doctor recommended it. Understands people choose to start earlier than they have to - a friend has done this. Will be time to start when told counts are too low so will start when the clinician tells him. "They could … they did start to creep up but now they've dropped back down. And quite a bit. Um, but yeah in the last year, they've all been within 300. The last one was 290. But they've all been within the 300 mark you know. Um, no perhaps because I've just got complete faith in the medical world that I would just the advice off … off whoever you know."	Falling CD4 count means starting is imminent - last one 290. *"I don't think ever really thought I … "I can't start this you know."*". Also friend's brother died recently as refused treatment *"so that's in the back of my head."* Friend who's been diagnosed 7 years *"doesn't need to start"* but has asked to start because he thinks it is better. Thinks counts are *"so low"* (around 300 mark) that might have to start soon. Also hopeful that low counts are *"because I'm newly infected"* as doctor said there was a chance. *"I've just got complete faith in the medical world"* so took advice from doctor as to when to start. Scared of the unknowns of putting off treatment - perhaps doctor doesn't know HIV is affecting liver, kidneys, lungs etc. "But maybe I will never know that." Understands people choose to start earlier than they have to - a friend has done this. Will be time to start when told counts are too low so will start when the clinician tells him. "They could … they did start to creep up but now they've dropped back down. And quite a bit. Um, but yeah in the last year, they've all been within 300. The last one was 290. But they've all been within the 300 mark you know. Um, no perhaps because I've just got complete faith in the medical world that I would just the advice off … off whoever you know."
4 : B21 Age=31-35 Ethnicity=White African On ART=Yes Partnership status=Single Education=University Employment=Employed FT Diagnosis to interview=3-6 months SC ID Method=Ab- then + HCV Coinfection=No	I thought I would probably get treatment straightaway but then when I was referred here they said it would be when my viral ... when my, erm CD4 count was lower than 350. Wanted to take part in a treatment study so asked straight away to be involved. Didn't know much about cART but recommended by other HIV positive men to start early so he did. Early treatment is a good thing "feeling healthier with more energy".	Got a phone call saying he could enrol on a study and was happy as "I wanted to start treatment." *"I didn't, I didn't see any point in waiting until I got more ill. And I was quite happy with that."* Main reason for starting was to avoid being ill all the time. Did not want HIV to interfere in busy life & "always be sickly". Well I think it's "because I was so ill at the time, I thought that if it can do that to me so easily, err, I don't really want to have ... you know, have to worry all the time about getting ill. It's like rather just take the medication, erm, it's basically I have a busy life and I didn't want that to interfere with ... you know, always be sickly and I just didn't want that." If ill tries to "clamp down" & "carry on as normal" .HIV making him really *"exhausted the whole time"* & hard to *"carry on as normal"* . Had *"no motivation"* to go to gym, doing light weights as no energy. *"I thought it must be the HIV doing that so I wanted to get rid of that to be honest."* Doesn't think *"long-term"* in terms of benefits of cART. *"I just think about now so I want a better life now. I'm not too bothered about living until I'm 70, so. You know, I don't even know if I want to but, erm I just don't ... I want to have a good life in the now, not ... you know. And I still want to be healthy, I want to be healthy. I always try to be healthy"*
5 : R78 Age=31-35 Ethnicity=White European On ART=Yes Partnership status=Single Education=University Employment=Employed FT Diagnosis to interview=4-6 months SC ID Method=Ab- then + HCV Coinfection=No	On cART Actually asked clinician to start - was not recommended it. Thought there'd be "battle" but doctor agreed. Knew he didn't have to start immediately but wanted to. Would have taken treatment at diagnosis if offered it. Wanted to "attack" the virus, to "take control". Not to be passive & wait for when his immune system was so damaged. Would have started cART even if didn't have a HIV- partner. Harder decision though & would have taken longer to decide. Concerns around resistance. Wanted clarity from clinician on whether current regimen would stop being effective, would it only last 10 years. Would early cART effect cART choice later on? Assured should be "fine for life so to speak". *"And I thought I was going to be up for a battle I thought they wouldn't let me but then the doctor was actually quite, well if that's what you wanted, you can do, but she didn't actively advise me to do it."* *"I knew it was very recent I knew there was a fair chance that I wouldn't have to start within six months but I wanted to do it straight away."* *"If I had been offered antiretroviral treatment when I was first diagnosed I would have taken it"* *"It was like a control thing, I wanted to control it straight away I did not want to wait for two years to 5 years and hopefully it would go down and need to be told at some point you need to start taking it. I wanted to get the virus down straightaway I wanted to attack it, I had this fear that the longer I waited the more my cells would be penetrated, I know it's probably not how it happens it but that's how I visualised it."* **Short course** Only would have started short-course if it led to undetectability & situation where transmission not theoretically possible. "I would only have done it for a short period if that would have led me to being undetectable or if that would have led me to a level where I couldn't theoretically pass it on as quickly" Not sure what it would entail & whether you would need to go back on again after 2 years.	Started because in country he's from *"when you're ill you get a pill, you take antibiotics for everything, I still have that mindset, it was like a control thing".* He visualised virus pentrating cells if he didn't act. *"I wanted to control it straight away I did not want to wait for two years to 5 years and hopefully it would go down and need to be told at some point you need to start taking it. I wanted to get the virus down straightaway I wanted to attack it, I had this fear that the longer I waited the more my cells would be penetrated, I know it's probably not how it happens it but that's how I visualised it."* Aware of reduced tranmsission too if undetectable & as partner was HIV- was the least that he could do to reduce risk. Having HIV- partner is a reason to start. *"also I knew that once you're undetectable it's very, well I don't know this, but I have been told that it's very unlikely that you'll pass it on, and still seeing P1 I thought that was the least I could do, to reduce the risk for him."* Biggest motivation was to protect partner as didn't consider there to be a major clinical benefit. *"I suppose there was no clinical benefit to me in any case of doing it, in the sense that you know … I wasn't going to die if I didn't, I mean I could well have done without it for 5 years, if anything there's probably a small risk there's a clinical ... deficit, yeah whatever. Whatever long term effect there might be…"* Asked for treatment himself thinking Dr wouldn't let me but doctor said if that's what you want to do. Knew infection was very recent so wouldn't have to start for 6 months but wantedt o do it straight away. *"I knew it was very recent I knew there was a fair chance that I wouldn't have to start within six months but I circled expect because I wanted to do it straight away."*

Appendix 15 – Cognitive interview study participant information sheet

Participant Information Sheet

Exploring the sexual behaviour, attitudes and beliefs of recent HIV seroconverters – questionnaire pilot study

We would like to invite you to take part in our study. Before you decide you will need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and ask us if you are unclear about anything or would like more information. The contact details of the research co-ordinator can be found overleaf.

What is the purpose of the study?
People who have been recently infected with HIV (recent HIV seroconverters) may play an important role in the UK epidemic, however little is known about their sexual behaviour, knowledge, beliefs and attitudes. We want to explore the knowledge and attitudes people recently infected with HIV have towards HIV treatment, particularly how they would feel about starting HIV treatment early. We have designed a questionnaire to do this but we need to test whether the questionnaire is easily understood by the people who will be completing it.

Why have I been invited?
You have been invited to participate in this study as you presented to our clinic very early on in your HIV infection, in other words you are a recent HIV seroconverter.

Do I have to take part?
You are under no obligation to take part in this study, it is up to you to decide. If you decide you do want to take part and sign a consent form, you are still free to withdraw from the study at any point should you wish to, without giving a reason. Your healthcare will not be affected if you decide not to participate in the study.

What will happen to me if I take part?
Participating in this study requires you to complete a study questionnaire on a computer and have a one-to-one face-to-face interview with the researcher. If you decide you wish to participate, we will first arrange a time that is convenient for you to come and take part in the study. This could be now or at some point in the future up to 3 months after your HIV diagnosis. When you arrive at Mortimer Market Centre to take part in the study, you will be met by the research co-ordinator and shown to the private room.

You will first be asked to sign a study consent form saying that you are happy to be involved in this study. You will then be given a palm PC to complete the questionnaire. Whilst you are answering each question, you will be asked to tell the interviewer what you understand each question to be asking and how you go about answering it. If you had trouble understanding the questions the researcher may ask you about how you might improve the questions. The interview will last around 1 hour and will be audio-recorded. During the questionnaire and interview we will be asking you personal questions about your

sexual behaviour, your feelings at the time you were diagnosed and your beliefs and attitudes to HIV treatment. You are not obliged to answer a question if you do not want to.

Will my taking part in the study be kept confidential?
Yes. The interview recording will be kept secure in a locked cabinet and destroyed after the interview has been transcribed. No identifiable information will be kept with the recording or transcript and the questionnaire data will be deleted at the end of the interview. Excerpts from the interview transcripts will be used in reports and publications but you will be referred to as a number and personally identifiable information will never be revealed. The only time we may have to pass information on is if you make a disclosure of intent to seriously harm yourself or others. In the rare event of this happening, we will talk to you first before speaking to a senior member of your clinical care team here at the Bloomsbury Clinic.

Who is carrying out this study?
This study is being carried out in part fulfilment of the research co-ordinator's PhD at the UCL Centre for Sexual Health & HIV Research, in collaboration with Camden Primary Care Trust. The PhD is funded by the Medical Research Council. This study has received ethical approval by Camden & Islington Community Research Ethics Committee.

What will happen to the results of the research study?
The results of this pilot study will be used to review the questionnaire and make changes so that it can be used in a larger multi-centre study amongst recent seroconverters. If you are interested in receiving a summary sheet of the results of the larger study please give your email address to the research co-ordinator and she will ensure you are sent one.

What are the disadvantages of taking part in this study?
There are no disadvantages of taking part in this study. This study involves questions that some people may find sensitive or personal in nature. You are not obliged to answer a question if you do not want to.

What are the benefits of taking part in this study?
There are no direct benefits of participating in this study, however the results will be useful in better understanding the needs of recent seroconverters and the role that early initiation of HIV treatment could play in the future.

What do I go if I have a complaint about the study?
If you are unhappy about an aspect of this study, please discuss your concerns with a member of the research team in the first instance using the contact details below. If you are still unhappy and would like to make a formal complaint you can telephone patient support service at Camden PCT on 020 3317 3003, or email them at pss@camdenpct.nhs.uk. More information is available at http://www.camden.nhs.uk/patientsupportservice.

If you have any queries regarding the study please contact the research team using the details below:

Research Co-ordinator: Vicky Jones
UCL Centre for Sexual Health & HIV Research
3rd Floor Mortimer Market Centre
London
WC1E 6JB
Email: vjones@gum.ucl.ac.uk
Tel: 0845 1555 000 ext. 5019

Chief Investigator: Graham Hart
UCL Centre for Sexual Health & HIV Research
3rd Floor Mortimer Market Centre
London
WC1E 6JB
Email: ghart@gum.ucl.ac.uk

Appendix 16 – Cognitive interview study consent form

Participant Consent Form

Agreement to take part in an interview to test a questionnaire exploring the sexual behaviour, attitudes & beliefs of recent HIV seroconverters

I (name of participant) _____

(Please indicate your consent to each of the following statements by writing your initials in the relevant boxes)

Have read the patient information sheet (ref: PhaseA_PI_CogI, version: 1.1) and agree to take part in the above study. ☐

I confirm that the nature of the study has been explained to me and that I have fully understood the information I have received. ☐

I have had the opportunity to ask questions about all aspects of the study and am satisfied with the responses given to me. ☐

I understand that the interview will be audio recorded and give my consent for this to happen. ☐

I understand that I may withdraw from the study at any time and this will not affect my treatment at the clinic in any way. ☐

Participant

Signed: _____ Date: _____

Name (block letters): _____

Research co-ordinator

Signed: _____ Date: _____

Name (block letters): _____

Appendix 17 – Questionnaire change log from piloted to final version for cross-sectional survey

UK Register of HIV Seroconverters Sub-study: Sexual Behaviour Attitudes to ART in MSM
Questionnaire change log: version 1.0 (dated 9th April 2011) to verison 2.0 (dated 12th February 2013)

v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
Overall questionnaire	-	-	-	Wording changed from "insertive or receptive" to "active or passive" when referring to anal intercourse.	The pilot study raised issues with using the terms "receptive & insertive" to define specific roles during anal intercourse. Men typically said they found the terms very "medicalised" and were keen for us to adopt the terminology "active or passive" or "top or bottom" which they felt were more widely used & understood amongst MSM.
Overall questionnaire	-	-	-	Wording changed from "anal sex" to "anal intercourse"	In the pilot study some men considered other sex acts such as fisting, rimming and using sex toys, to fall under the umbrella term "anal sex". It was suggested that the term "anal intercourse" was used as an alternative as this was regarded to specifically refer to penetrative anal intercourse than "anal sex".
Overall questionnaire	-	-	-	Wording changed from "I would start ART early..." to "I would start ART now..." in intention questions.	It became apparent in the piloting of this questionnaire that men had very different definitions as to what starting ART "early" actually meant. This was mainly due to the different expectations as to how long it would be before they would be starting ART given current circumstances. There was a need to be more specific and to use a definition that was easy to conceptualise for men. At first we tried defining early ART in the completion instructions at the top of the section as "ART within a year of being diagnosed" however we found that men were not reading the instructions carefully enough to process the definition or not reading them at all! In the end we opted for the term starting ART "now" as it was much easier to conceptualise and all men completing the questionnaire would be doing so within 1 year of their diagnosis so it coincides with the definition of "Early ART" as within 1 year of diagnosis.
Title page	-	Title page	-	Study title changed	Men felt more self conscious about completing a questionnaire which had "sexual behaviour" printed in large font on the front. We changed the title to lessen this experience.
2	-	2	-	Now blank	N/A
2	-	3	-	Instructions simplified & clarified	Many men in the pilot did not read the lengthy text in v1.0. The instructions in v2.0 have the important points highlighted to encourage people to read them.
-	-	4	-	Section heading inserted - "Section A: Background Information"	Clearer style of presentation
4	5	5	A5	Answer option added for living with parents of close family	No option existed in v1.0 and it came up several times during piloting

UK Register of HIV Seroconverters Sub-study: Sexual Behaviour Attitudes to ART in MSM
Questionnaire change log: version 1.0 (dated 9th April 2011) to verison 2.0 (dated 12th February 2013)

v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
4	7b	5	A7b	Question reworded from "What is their HIV status?" to "What is his HIV status?"	Grammatical correction
	-	6	-	Section heading inserted - "Section B: HIV testing & symptoms"	Clearer style of presentation
5	8	6	B1	Question reworded from "When was the last time you had a negative HIV test before your HIV diagnosis?" to "When was the last time you had a negative HIV test?"	Question lacked clarity in v1.0 & caused confusion in pilot study
5	8	6	B1	Answer option "I had never tested before my diagnosis" changed to "I had never tested before my positive HIV test"	Answer option lacked clarity in v1.0
5	9	6	B2	Question reworded from "What were your reasons for HIV testing when you first found out you were positive?" to "What were your reasons for your most recent HIV test?"	Question lacked clarity in v1.0 & caused confusion in pilot study
5	9	6	B2	Answer option "Experienced HIV seroconversion -like symptoms" changed to "Felt unwell".	Some participants in the pilot study were unsure what counted as a seroconversion-like symptom.
5	9	6	B2	Answer option "GP/ hospital recommended it" added	No option existed in v1.0 and it came up several times during piloting
6	10	7	B3a	Question reworded from "Did you experience HIV seroconversion-like symptoms?" to "Did you feel unwell in the months preceding your HIV diagnosis?"	In the pilot study it became apparent that many men were not familiar with what exactly "seroconversion like symptoms" were. Instead we introduced a more general question about feeling unwell and introduced question B3b enquiring about specific symptoms.
	-	7	B3b	New question - "If yes, what symptoms did you experience?" Answer options: Rash/headache/sore throat/fever/body aches/vomiting/diarrhoea/night sweats/other (please specify)"	This was originally introduced as an open ended question with space to write in symptoms however in piloting some men said they would be reluctant to write all the symptoms as it took longer than ticking boxes. It was decided to add options for some of the most common symptoms as well as an open ended option for any not mentioned.
6	11	7	B4	Question reworded from "If you had HIV seroconversion-like symptoms, how long did they last?" to "If you had symptoms, how long did they last?"	See comments above regarding interpretation of "seroconversion-like symptoms".
7	16	8	B9	New layout of answer options	Clearer style of presentation
-	-	9	Instructions	Instructions amended in line with the addition of questions on oral sex acts	Men in the pilot study commonly referred to oral sex as a "blow job" so we adopted their terminology in these instructions.

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
-	-	9-10	C1a-C6	Addition of questions about oral sex in the 6 months prior to diagnosis	During questionnaire piloting we discovered men who failed to report any acts of unprotected anal intercourse in the 6 months prior to their HIV diagnosis. On further probing there a subset of these men had engaged in prolific amounts of unprotected oral sex with multiple partners under the assumption this behaviour "safe". v1.0 of the questionnaire failed to capture any information at all about oral sex so we were keen to remedy this in v2.0.
8	Instructions	12	Instructions	Change of terminology in instructions from "insertive" and "receptive" to "active" and "passive"	See 1st table entry about questionnaire wide change in terminology
8-9	17a-20	12-13	C7a-C10	Introduction of "active" and "passive" to clarify questions about anal intercourse	See 1st table entry about questionnaire wide change in terminology
9	19a	13	C9a	Question reworded from "In the 6 months before receiving your HIV diagnosis, how many of the men you had anal sex without a condom with did you know were HIV negative?" to "In the 6 months before receiving your HIV diagnosis, how many of the men with whom you had anal intercourse (active or passive) without a condom did you know were HIV negative?	Clarification of the question
-	-	14	C11	Addition of questions about drug use & options to tick all that apply. Question taken from the 2013 Gay Men's Sexual Health Survey.	There was no provision in v1.0 to collect information on drug taking, a factor which is usually associated with HIV transmission. We decided to introduce questions on drug taking to assess the prevalence of drug use in the 6 months prior to HIV diagnosis, and whether there is an association with the acceptability and likelihood of starting ART early.
-	-	15	C12	Addition of question regarding injecting drugs.	To assess the prevalence of injecting drug use in the 6 months prior to HIV diagnosis.
10	21	15	C13	Rewording of question from "In the 6 months before receiving your HIV diagnosis, tick all the locations where have you met sexual partners?" to "In the 6 months before receiving your HIV diagnosis, tick all the locations where you have met new sexual partners?"	During piloting, several men were confused as to whether this question referred to where you met you existing partners for sex & suggested I put home on the list. We changed the question to clarify the focus of the question is on where you made contact with new sexual partners, not necessarily where you met your existing partners for sex.
10	21	15	C13	Addition of 2 answer options "Through friends" and "Sex party"	These options came up frequently in the piloting and were not present in v1.0
-	-	16	Instructions	Instructions amended in line with the addition of questions on oral sex acts	
-	-	16-18	D1a-D6	Addition of questions about oral sex in the time since HIV diagnosis	Oral sex questions were not included in v1.0. The answers to these questions will be used to compare with oral sex behaviour before diagnosis as measured in questions C1a-C6

v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
11	24a	20	D9a	Question reworded from "Since receiving your HIV diagnosis, how many of the men you had anal sex without a condom with did you know were HIV positive?" to "Since receiving your HIV diagnosis, how many of the men with whom you had anal intercourse (active or passive) without a condom did you know were HIV positive?"	Clarification of the question
-	-	14	D11	Addition of questions about drug use & options to tick all that apply. Question taken from the 2013 Gay Men's Sexual Health Survey.	Introduced to assess the prevalence of drug use in the time since HIV diagnosis for comparison with drug use prior to HIV diagnosis as measured in question C11.
-	-	15	D12	Addition of question regarding injecting drugs.	To assess the prevalence of injecting drug use in the time since HIV infection and permit comparison to drug use prior to HIV diagnosis as measured in question C12.
12	26	22	D13	Rewording of question from "Since receiving your HIV diagnosis, tick all the locations where have you met sexual partners?" to "Since receiving your HIV diagnosis, tick all the locations where you have met new sexual partners?"	Reworded to clarify the focus of the question is on where you made contact with new sexual partners, not necessarily where you met your existing partners for sex.
12	26	22	D13	Addition of 2 answer options "Through friends" and "Sex party"	These options came up frequently in the piloting and were not present in v1.0
13	27	23	D14	Question reworded from "Who out of the following have you told that you are HIV positive" to "Who have you told that you are HIV positive?"	Question was unnecessarily wordy and has been simplified
13	27	23	D14	Answer option changed from "Close family member" to "Family member". Option "Nobody" moved to top.	Men overlooked the option "Nobody" in the pilot so it was moved to the top. It was unnecessary to differentiate between whether disclosure was to close family members or just family members in general.
13	28	23	D15	Question reworded from "Since receiving your HIV diagnosis, how often do you disclose your HIV status to your sexual partners before having sex?" to "Since receiving your HIV diagnosis, how often have you disclosed your HIV status to sexual partners before you have sex?	Clarification of the question
14	29	24	D16	Question reworded from "Since receiving your HIV diagnosis, how have you disclosed your HIV status to your sexual partners before you have sex?" to "Since receiving your HIV diagnosis, which methods have you used to disclose your HIV status to sexual partners before you have sex?"	Clarification of the question

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
-	-	25	Section E	New section "Section E" created for HIV treatment questions relevant for all to answer	In v1.0 of the questionnaire there was no routing through the questionnaire according to whether or not the patient was ART naïve. This rendered some of the questions unsuitable for patients who had treatment experience. Section E was created for all men to complete some basic questions about ART experience.
16	33	25	E1	Question moved into section E	
16	33	25	E1	New answer option "Straight away or within 1 month of being diagnosed"	The earliest category in v1.0 "Within 6 months of being diagnosed" did not capture those expecting to start treatment straight away after diagnosis to those expecting to wait a few months.
17	35	25	E2	Question moved into section E & answer options redesigned to yes/no format from a likert scale in v1.0	There was no need for a likert scale answer to this question.
	30a/b	26	E3a/b	Question moved into section E	Allows for questionnaire routing
15	31	26	E4	Question moved into section E	Allows for questionnaire routing
15	32	26	E5	Question moved into section E	Allows for questionnaire routing
15	32	26	E5	Question used as the routing question with those who have not taken ART since receiving their HIV diagnosis completing section F and those who have taken ART since receiving their HIV diagnosis completing section G	Allows for questionnaire routing
-	-	27	Section F	New section "Section F" created for HIV treatment naïve individuals	This section contains the questions about ART that are applicable only to ART naïve men about acceptability, expectations, intentions to start ART and attitudes towards ART.
16	34	27	F1	Question moved into section F	Question only applicable to those who are currently ART naïve
16	34	27	F1	New answer option "Within 1 month of being diagnosed"	Introduces an option for those who expecting to start ART imminently which was not present in v1.0.
-	-	27	F2a/b	New questions added - "Have you considered starting ART since receiving your HIV diagnosis?" & "If yes, why did you choose not to start ART?"	Allows the estimation of the proportion of men who have thought about starting & chosen not to. In addition we will be able to look at the barriers to starting early treatment. Question F2b is open ended as it was felt that there were too many potential reasons to give tick boxes.
17	36	28	F3	Question moved to section F	Question only applicable to those who are currently ART naïve
19	51	28	F4	Question moved to section F	Question only applicable to those who are currently ART naïve
17	37	28	F5	Question moved to section F	Question only applicable to those who are currently ART naïve
19	50	-	-	Question removed	The SPARTAC trial reported earlier this year that there was no benefit in a 3 months short-course of ART in early infection. Therefore there was no reason for this question to remain.

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
18	44	28	F6	Question moved to section F & reworded from "I would take ART to reduce the chance of passing HIV to my sexual partners, even if there were no health benefits to me" to "I would start ART now if it reduced the chance of passing HIV to my sexual partners, even if there were no proven health benefits to me".	This question was reworded to match the question from the ASTRA study of longstanding HIV infection to facilitate comparisons of attitudes in those who are recently infected to those living with HIV for years.
-	-	28	F7	New question "I would prefer to delay starting ART for as long as possible, even if this meant a small increased risk of getting a serious illness"	This question was introduced from the ASTRA study of longstanding HIV infection to facilitate comparisons of attitudes in those who are recently infected to those living with HIV for years.
18	45	29	F8	Question moved to section F	Question only relevant to ART naïve men
18	39	29	F9	Question moved to section F Statement reworded from "I would not start ART earlier than I have to as I am concerned about the side effects" to "I am concerned about the possible side effects of ART"	Question only relevant to ART naïve men. Statement simplified.
18	43	29	F10	Question moved to section F Question reworded from "I do not see the point in starting ART when I feel well" to "There is no point in starting ART when I feel well"	Question only relevant to ART naïve men. Statement simplified.
-	-	29	F11	New question "Starting ART now would not fit in with my lifestyle"	This reason for not starting ART was given by a number of men in an in-depth interview study we conducted so we wanted to assess the prevalence of the belief.
19	49	29	F12	Question moved to section F Question reworded from "Starting ART in early infection will reduce my treatment options in the future" to "Starting ART now could reduce my future treatment options"	In the pilot men were confused about how to define "early infection" so we reworded the statement.
-	-	29	F13	New question "I will start ART when the doctor tells me I should start"	We encountered this attitude to starting ART in the pilot study and the in-depth interview study so it warranted inclusion in v2.0
18	41	29	F14	Question moved to section F	Question only relevant for ART naive men.
-	-	30	Section G	New section "Section G" created for questions relevant only to those who have taken ART since their HIV diagnosis	This section contains the questions about ART that are applicable only to men who have started ART after their HIV diagnosis & before completing the questionnaire. The questions look at reasons for starting ART as well as attitudes and beliefs towards ART.
-	-	30	G1	New question "How soon after your HIV diagnosis did you start ART?"	To assess how early in infection treatment was initiated.

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
-	-	30	G2a/c	New questions "Are you still taking ART now?", "If no, how long did you take it for", "Why did you stop taking ART?"	Measure proportion of men starting early ART who terminate early & the reasons for this.
-	-	31	G3	New question "When you think of your main reason for starting ART, would you say it was mainly for your own health or to reduce HIV transmission to your sexual partner(s)?	Allows us to assess proportion of men starting primarily for their own health and how many to protect sexual partners
-	-	31	G4	New question "What was your last CD4 count before you started ART?"	To assess whether ART commencement was clinically indicated
-	-	31	G5	New question "What was your last viral load measurement?"	Will be used to assess whether men with undetectable viral load hold different attitudes on HIV transmission (see section H)

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
-	-	32	G6	New statement "I started ART to reduce the risk of passing HIV to my sexual partner(s)"	Statements included to assess the reasons for starting HIV applied to men who started ART within the first year of infection.
-	-	32	G7	New statement "I started ART because my doctor told me I should start"	
-	-	32	G8	New statement "I started ART to increase my life expectancy"	
-	-	32	G9	New statement "I started ART as usually when I am ill I take medication straight away to fight the illness"	
-	-	32	G10	New statement "I started ART to improve my quality of life"	
-	-	33	G11	New statement "I started ART to reduce the damage HIV was causing to my body"	
-	-	33	G12	New statement "I started ART as I felt ill"	
-	-	33	G13	New statement "I started ART to control the spread of HIV in my body"	
-	-	33	G14	New statement "I started ART to reduce my anxiety about transmitting HIV to my sexual partner(s)"	
-	-	33	G15	New statement "I started ART as part of a clinical trial"	
-	-	33	G16	New statement "I started ART as my partner wanted me to"	
18	41	33	G17	Statement replicated from section F "It is better for my health to start ART earlier rather than later"	Replicated from section F for comparison of attitudes to early treatment initiation & health between treatment naïve MSM and those who have started.
-	-	33	G18	New statement "Being on ART makes it easier to disclose my HIV status to sexual partners"	This idea came up in the pilot study and in-depth interview study so we wanted to assess whether men think that being on ART makes it easier to disclose HIV status in a larger population of MSM.
-	-	33	G19	New statement "Stopping or having a break in ART will be bad for my health"	To assess how much men agree with the statement
-	-	34	Section H	New section "Section H"	For all responders to complete asking beliefs about HIV transmission on ART, disclosure of HIV status whilst taking ART and treatment optimism.
-	-	34	H1	New statement "Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom"	Statement to assess level of belief of the "Swiss Statement". Question taken from ASTRA questionnaire conducted amongst HIV positive men with longstanding infection and results will be compared between new infected MSM from this survey & men with chronic infection in the ASTRA study
-	-	34	H2	New statement "It is not necessary to disclose your HIV status to a sexual partners if you are ART and have an undetectable viral load"	To assess whether there are differences in attitudes to disclosure of HIV status whilst on ART amongst treatment naïve MSM and those on treatment

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v1.0 Page No.	v1.0 Q No.	v2.0 page No.	v2.0 Q No.	Change	Reason
-	-	34	H3	New statement "Better HIV treatment means that people are less worried about catching HIV"	Statement to assess level of treatment optimism belief. Question taken from ASTRA questionnaire conducted amongst HIV positive men with longstanding infection and results will be compared between new infected MSM from this survey & men with chronic infection in the ASTRA study
-	-	35	Comments	Provision of space for men to leave comments and feedback about the questionnaire	In piloting some men wished to make comments about the questionnaire and thought it would be nice to be invited to do so.

Appendix 18 – Final questionnaire used in cross-sectional survey

UKRHS

MRC Clinical Trials Unit

MEN'S HEALTH & BEHAVIOUR QUESTIONNAIRE

SECTION TO BE COMPLETED BY NURSE/DOCTOR

Centre name: _____

Date of completion (D/M/Y): __ __ / __ __/ 201__

Patient date of birth (D/M/Y): __ __ / __ __/ 19__ __

Date first HIV positive: __ __ / __ __/ 201__

Last 4 digits of patient clinic no: __ __ __ __

Questionnaire no:

Version 2.0

12th February 2013

2

INSTRUCTIONS

Thank you for agreeing to complete this questionnaire.

Over the next few pages we will be asking you about HIV testing, your relationships and sexual behaviour over the past few months and how you feel about antiretroviral (anti-HIV) treatment.

***This questionnaire is anonymous -** you will not be asked to give your name and it will not be kept with your clinic notes.*

***Guidance is given throughout the questionnaire in italics.** Please pay particular attention to the arrows next to the answers which indicate where you can skip questions and sections that are not applicable.*

If you find that you don't want to answer a particular question please skip it and continue with the next question.

This questionnaire should take you between 20 and 30 minutes to complete.

Once you have completed the questionnaire please put it in the envelope provided and hand it back to the person who gave it to you.

SECTION A: BACKGROUND INFORMATION

A1 Have you ever had sex with another man?

- ☐ No → *End of questionnaire*
- ☐ Yes

A2 How many years full time education have you had since the age of 16?

- ☐ None
- ☐ Up to 2 years
- ☐ 3 years or more
- ☐ Still in full time education

A3 Are you employed at present?

- ☐ No
- ☐ Yes, I'm employed full-time (30+ hours/week)
- ☐ Yes, I'm employed part-time (Less than 30 hours/week)
- ☐ Yes, I'm self-employed

A4 Do you own or rent the place where you currently live?

- ☐ Own – outright or with a mortgage/loan
- ☐ Rent – from council or housing association
- ☐ Rent – from private landlord
- ☐ Neither own nor rent - *please specify below*

_____

A5 How would you describe your current living arrangements?

4

- ☐ Live alone
- ☐ Live with partner(s)
- ☐ Live with friends/tenants/lodgers
- ☐ Live with parents/close family
- ☐ Live in temporary accommodation/homeless
- ☐ Other - *please specify below*

_____

A6 How would you describe your sexual orientation?

- ☐ Gay/homosexual
- ☐ Bisexual
- ☐ Heterosexual
- ☐ Other - *please specify below*

_____

A7a Do you currently have a regular male partner/boyfriend/lover?

- ☐ No ➔ *Go to section B on page 6*
- ☐ Yes
- ☐ Don't know

A7b If yes, what is his HIV status?

- ☐ Negative
- ☐ Positive
- ☐ Never tested
- ☐ Don't know

SECTION B: HIV TESTING & SYMPTOMS

B1 When was the last time you had a <u>negative</u> HIV test?

- ☐ Less than 6 months before my HIV diagnosis
- ☐ Between 6 months and 1 year before my HIV diagnosis
- ☐ Between 1 and 5 years before my HIV diagnosis
- ☐ Over 5 years before my HIV diagnosis
- ☐ I had never tested before my positive HIV test
- ☐ Don't know

B2 What were your reasons for your most recent HIV test?

*Please tick **all** that apply*

- ☐ Routine test
- ☐ Condom broke or came off during sex
- ☐ Had sex without a condom with someone I knew to be HIV positive
- ☐ Had sex without a condom with someone of unknown HIV status
- ☐ Had sex without a condom with someone who said they were HIV negative
- ☐ Felt unwell
- ☐ GP/hospital recommended it
- ☐ Other - *please specify below*

_____

6

B3a **Did you feel unwell in the months preceding your HIV diagnosis?**

- ☐ Yes
- ☐ No ➔ ***Go to question B8***
- ☐ Don't know

B3b **If yes, what symptoms did you experience?**

- ☐ Rash
- ☐ Headache
- ☐ Sore throat
- ☐ Fever
- ☐ Body aches
- ☐ Vomiting/ diarrhoea
- ☐ Night sweats
- ☐ Other *(please specify)*

_____

B4 **If you had symptoms, how long did they last?**

__ __ __ days

B5 **Did you change your daily routine because of these symptoms?**

- ☐ Yes
- ☐ No ➔ ***Go to question B7a***
- ☐ Don't know

B6 **For how many days did these symptoms prevent you from performing your daily routine?**

__ __ __ days

B7a **Did you have anal intercourse (active or passive) with a man without a condom whilst you were experiencing these symptoms?**

- ☐ No ➔ ***Go to question B8***
- ☐ Yes
- ☐ Don't know

B7b **If yes, with how many men?**

If none, please write 0

— — —

B7c **How many were once only partners?**

If none, please write 0

— — —

B8 **Were you surprised at the positive result of your HIV test?**

- ☐ No
- ☐ Yes
- ☐ Don't know

B9 **At the time you were diagnosed with HIV, were you diagnosed with any sexually transmitted infections?** *Tick all that apply*

- ☐ None
- ☐ Syphilis
- ☐ Gonorrhoea
- ☐ Chlamydia
- ☐ Genital herpes
- ☐ Genital warts
- ☐ Hepatitis C
- ☐ Other *(please specify)*

_____

8

SECTION C: SEXUAL BEHAVIOUR BEFORE YOUR HIV DIAGNOSIS

*We are now going to ask you some questions about your **sexual behaviour** in the **6 months before** you received your **positive HIV diagnosis.***

*These next questions are about **men** you have had **oral sex** with. By **oral sex** we mean **giving or receiving a blow job**.*

If the answer to questions C1-C3 is none, please write 0 in the space provided.

C1a **In the 6 months before receiving your HIV diagnosis, how many men did you have oral sex with?**

If none please write 0

__ __ __ ➔ ***If 0 go to page 12***

C1b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C2a **In the 6 months before receiving your HIV diagnosis, with how many men did you have oral sex without a condom?**

If none please write 0

__ __ __ ➔***If 0 go to page 12***

C2b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C3a **In the 6 months before receiving your HIV diagnosis, how many of**

the men with whom you had oral sex without a condom did you know were HIV negative?

If none please write 0

__ __ __ ➔ ***If 0 go to question C4***

C3b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C4 **In the 6 months before receiving your HIV diagnosis, when you had oral sex without a condom were you?**

- ☐ Always receiving
- ☐ Mostly receiving
- ☐ Equally both
- ☐ Mostly giving
- ☐ Always giving
- ☐ Don't know

C5 **In the 6 months before receiving your HIV diagnosis, when you had oral sex without a condom how often did you ejaculate/come in their mouth?**

- ☐ All of the time
- ☐ Most of the time
- ☐ About half of the time
- ☐ Not very often
- ☐ Never
- ☐ Don't know

C6 **In the 6 months before receiving your HIV diagnosis, when you had oral sex without a condom how often did they ejaculate/come in your mouth?**

- ☐ All of the time
- ☐ Most of the time
- ☐ About half of the time
- ☐ Not very often
- ☐ Never
- ☐ Don't know

*The following questions are about men who you have had **anal intercourse** with in the **6 months before receiving your HIV diagnosis.***

*By **anal intercourse** we mean **either active where you are the top partner or passive where you are the bottom partner.***

If the answer to questions C7-C9 is none, please write 0 in the space provided.

C7a **In the 6 months before receiving your HIV diagnosis, with how many men did you have anal intercourse (active or passive)?**

If none please write 0

__ __ __ ➔ ***If 0 go to question C11***

C7b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C8a **In the 6 months before receiving your HIV diagnosis, with how many men did you have anal intercourse (active or passive) without a condom?**

If none please write 0

__ __ __ ➔***If 0 go to question C11***

C8b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C9a **In the 6 months before receiving your HIV diagnosis, how many of the men with whom you had anal intercourse (active or passive) without a condom did you know were HIV negative?**

If none please write 0

__ __ __ ➔***If 0 go to question C10***

C9b **Of these, how many were once only partners?**

If none please write 0

__ __ __

C10 **In the 6 months before receiving your HIV diagnosis, when you had anal intercourse (active or passive) with a man without a condom were you?**

- ☐ Always the active (top) partner
- ☐ Mostly the active (top) partner
- ☐ Equally both (versatile)
- ☐ Mostly the passive (bottom) partner
- ☐ Always the passive (bottom) partner
- ☐ Don't know

C11 **In the <u>6 months before receiving your HIV diagnosis</u>, did you use any of the following drugs <u>just before or during sex</u>?**

*Tick **all** that apply*

- ☐ Alcohol
- ☐ Cannabis/marijuana
- ☐ Poppers (Amyl or other nitrite inhalants)
- ☐ Viagra/Cialis
- ☐ Liquid Ecstasy/Liquid X/Liquid G/Fantasy/GHB/GBL
- ☐ Mephedrone (Drone/MCAT/meow meow)
- ☐ Amphetamine (speed)
- ☐ Cocaine (coke)
- ☐ Ketamine (K/Special K)
- ☐ Meth Amphetamine (Crystal meth, ice/glass, Tina)
- ☐ Heroin (Smack)
- ☐ Crack
- ☐ Piperazines (BZP/TFMPP/DBZP/mCPP)
- ☐ Don't know
- ☐ Declined to answer
- ☐ Other - *please specify below*

_____

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C12 **In the 6 months before receiving your HIV diagnosis, did you inject any of these drugs?**

- ☐ No
- ☐ Yes
- ☐ Don't know

C13 **In the 6 months before receiving your HIV diagnosis, tick all the locations where you met new sexual partners?**

*Tick **all** that apply*

- ☐ Bar/club
- ☐ Internet dating/networking sites (e.g. Gaydar)
- ☐ Smartphone apps (e.g. Grindr)
- ☐ Cruising ground/cottage
- ☐ Sauna
- ☐ Gym
- ☐ Backroom/ sex club
- ☐ Sex party
- ☐ Through friends/social groups
- ☐ College/work
- ☐ Telephone chatline
- ☐ Other - *please specify below*

_____

SECTION D: SEXUAL BEHAVIOUR AFTER YOUR HIV DIAGNOSIS

*The following questions ask about your sexual behaviour **since you received your HIV diagnosis.***

*These next questions are about **men** you have had **oral sex** with. By **oral sex** we mean **giving or receiving a blow job**.*

If the answer to questions D1-D3 is none, please write 0 in the space provided.

D1a **How many men have you had oral sex with since receiving your HIV diagnosis?**

If none please write 0

__ __ __ ➔ *If 0 go to page 19*

D1b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D2a **Since receiving your HIV diagnosis, with how many men have you had oral sex without a condom?**

If none please write 0

__ __ __ ➔ *If 0 go to page 19*

D2b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D3a **Since receiving your HIV diagnosis, how many of the men with whom you had oral sex without a condom did you know were HIV positive?**

If none please write 0

__ __ __ ➔***If 0 go to question D4***

D3b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D4 **Since receiving your HIV diagnosis, when you had oral sex without a condom were you?**

- ☐ Always receiving
- ☐ Mostly receiving
- ☐ Equally both
- ☐ Mostly giving
- ☐ Always giving
- ☐ Don't know

D5 **Since receiving your HIV diagnosis, when you had oral sex without a condom how often did you ejaculate/come in their mouth?**

- ☐ All of the time
- ☐ Most of the time
- ☐ About half of the time
- ☐ Not very often
- ☐ Never
- ☐ Don't know

D6 **Since receiving your HIV diagnosis, when you had oral sex without a condom how often did they ejaculate/come in your mouth?**

- ☐ All of the time
- ☐ Most of the time
- ☐ About half of the time
- ☐ Not very often
- ☐ Never
- ☐ Don't know

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*These next questions are about **men** you have had **anal intercourse** with **since receiving your HIV diagnosis**. Once again, when we talk about **anal intercourse** we mean **either active where you are the top partner or passive where you are the bottom partner**.*

If the answer to questions D7-D9 is none, please write 0 in the space provided.

D7a **How many men have you had anal intercourse (active or passive) with since receiving your HIV diagnosis?**

If none please write 0

__ __ __ ➔ ***If 0 go to question D11***

D7b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D8a **Since receiving your HIV diagnosis, with how many men have you had anal intercourse (active or passive) without a condom?**

If none please write 0

__ __ __ ➔ ***If 0 go to question D11***

D8b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D9a **Since receiving your HIV diagnosis, how many of the men with whom you had anal intercourse (active or passive) without a condom did you know were HIV positive?**

If none please write 0

__ __ __ ➔ ***If 0 go to question D10***

D9b **Of these, how many were once only partners?**

If none please write 0

__ __ __

D10 **Since receiving your HIV diagnosis, when you have had anal intercourse (active or passive) with a man without a condom were you?**

- ☐ Always the active (top) partner
- ☐ Mostly the active (top) partner
- ☐ Equally both (versatile)
- ☐ Mostly the passive (bottom) partner
- ☐ Always the passive (bottom) partner

D11 **<u>Since receiving your HIV diagnosis</u>, have you used any of the following drugs <u>just before or during sex</u>?**

*Tick **all** that apply*

- ☐ Alcohol
- ☐ Cannabis/marijuana
- ☐ Poppers (Amyl or other nitrite inhalants)
- ☐ Viagra/Cialis
- ☐ Liquid Ecstasy/Liquid X/Liquid G/Fantasy/GHB/GBL
- ☐ Mephedrone (Drone/MCAT/meow meow)
- ☐ Amphetamine (speed)
- ☐ Cocaine (coke)
- ☐ Ketamine (K/Special K)
- ☐ Meth Amphetamine (Crystal meth, ice/glass, Tina)
- ☐ Heroin (Smack)
- ☐ Crack
- ☐ Piperazines (BZP/TFMPP/DBZP/mCPP)
- ☐ Don't know
- ☐ Declined to answer
- ☐ Other - *please specify below*

_____

D12 **<u>Since receiving your HIV diagnosis</u>, have you injected any of these drugs?**

- ☐ No
- ☐ Yes
- ☐ Don't know

D13 **<u>Since receiving your HIV diagnosis</u>, tick all the locations where you have met new sexual partners?**

*Tick **all** that apply*

- ☐ Bar/club
- ☐ Internet dating/networking sites (e.g. Gaydar)
- ☐ Smart-phone applications/apps (e.g. Grindr)
- ☐ Cruising ground/cottage
- ☐ Sauna
- ☐ Gym
- ☐ Backroom/ sex club
- ☐ Sex party
- ☐ Through friends/social groups
- ☐ College/work
- ☐ Telephone chatline
- ☐ Other - *please specify below*

_____

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D14 Who have you told that you are HIV positive?

*Tick **all** that apply*

- ☐ Nobody
- ☐ Regular partner/boyfriend/lover
- ☐ Family member(s)
- ☐ HIV positive friend(s)
- ☐ HIV negative friend(s)
- ☐ Work
- ☐ GP
- ☐ Other - *please specify below*

_____

D15 Since receiving your HIV diagnosis, how often have you disclosed your HIV status to sexual partners before you have sex?

- ☐ Every time
- ☐ More than half the time
- ☐ About half the time
- ☐ Less than half the time
- ☐ Never ➔ ***go to section E on page 25***
- ☐ I have not had sex since my diagnosis ➔ ***go to section E on page 25***
- ☐ Don't know

D16 **<u>Since receiving your diagnosis</u>, which methods have you used to disclose your HIV status to sexual partners <u>before</u> you have sex?**

*Tick **all** that apply*

- ☐ Face-to-face
- ☐ Profiles on dating websites
- ☐ Internet chatrooms/social networking sites
- ☐ Smart phone apps
- ☐ Email
- ☐ Text message (SMS)
- ☐ Phone
- ☐ Another way - *please specify below*

_____

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SECTION E: HIV TREATMENT

We're now going to ask you about your attitudes and beliefs towards anti-HIV treatment (antiretroviral treatment), which we refer to here as ART.

E1 If you think back to when you first received your HIV diagnosis, when did you expect to start ART?

- ☐ Straight away or within 1 month of being diagnosed
- ☐ Between 1 and 6 months of being diagnosed
- ☐ Between 6 months to 1 year after diagnosis
- ☐ Between 1 and 2 years after diagnosis
- ☐ Over 2 years after diagnosis
- ☐ Don't know

E2 If you had been offered antiretroviral treatment (ART) when you were first diagnosed HIV positive would you have taken it?

- ☐ No
- ☐ Yes
- ☐ Maybe
- ☐ Don't know

E3a **Have you ever taken post-exposure prophylaxis (PEP)?**

- ☐ No ➔*Go to question E4*
- ☐ Yes
- ☐ Don't know

E3b **If yes, on how many different occasions have you taken PEP in the past?**

___

E4 **Has your doctor advised you to start ART since your HIV diagnosis?**

- ☐ No
- ☐ Yes
- ☐ Don't know

E5 **Have you taken ART since receiving your HIV diagnosis?**

- ☐ No
- ☐ Yes ➔*Go to section G on page 30*
- ☐ Don't know

SECTION F: ONLY COMPLETE THIS SECTION IF YOU HAVE NOT TAKEN ART SINCE RECEIVING YOUR HIV DIAGNOSIS

IMPORTANT - If you have taken ART since receiving your HIV diagnosis please go straight to section G on page 30

F1 When do you expect to start ART?

- ☐ Within the next month
- ☐ Between 1 and 6 months from now
- ☐ Between 6 months to 1 year from now
- ☐ Between 1 and 2 years from now
- ☐ Over 2 years from now
- ☐ Don't know

F2a Have you considered starting ART since receiving your HIV diagnosis?

- ☐ No
- ☐ Yes
- ☐ Don't know

F2b If yes, why did you choose not to start ART?

_____

_____

_____

_____

*Please indicate the level to which you agree or disagree with each statement below by **circling** the appropriate **number**:*

1=Strongly agree, 2=Agree, 3=Neither agree or disagree, 4=Disagree, 5=Strongly disagree, 6=Don't know.

		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Don't know
F3	I feel ready to start ART now	1	2	3	4	5	6
F4	I would start ART now if I only had to take it for a year	1	2	3	4	5	6
F5	I would start ART now if there was a proven health benefit to me	1	2	3	4	5	6
F6	I would take ART now if it reduced the chance of passing HIV to my sexual partners, even if there were no proven health benefits to me	1	2	3	4	5	6
F7	I would prefer to delay starting ART for as long as possible, even if this meant a small increased risk of getting a serious illness	1	2	3	4	5	6

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		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Don't know
F8	I would not start ART now because I would have to be on it for the rest of my life	1	2	3	4	5	6
F9	I am concerned about the possible side effects of ART	1	2	3	4	5	6
F10	There is no point in starting ART when I feel well	1	2	3	4	5	6
F11	Starting ART now would not fit in with my lifestyle	1	2	3	4	5	6
F12	Starting ART now could reduce my future treatment options	1	2	3	4	5	6
F13	I will start ART when the doctor tells me I should start	1	2	3	4	5	6
F14	It is better for my health to start ART earlier rather than later	1	2	3	4	5	6

➔ *NOW PLEASE GO TO SECTION H ON PAGE 34*

SECTION G: ONLY COMPLETE THIS SECTION IF YOU HAVE TAKEN ART SINCE RECEIVING YOUR HIV DIAGNOSIS

IMPORTANT - If you have not taken ART since receiving your HIV diagnosis please complete section F on page 27

G1 How soon after your HIV diagnosis did you start ART?

- ☐ Within 1 month of receiving my HIV diagnosis
- ☐ More than 1 month and less than 6 months after
- ☐ More than 6 months after
- ☐ Don't know

G2a Are you still taking ART now?

- ☐ Yes, I am still taking it ➔ *Go to question G3*
- ☐ No, I stopped taking it
- ☐ Don't know

G2b If no, how long did you take ART for?

_____

G2c Why did you stop taking ART?

_____

_____

_____

_____

G3 When you think of your main reason for starting ART, would you say was it mainly for your own health or to reduce HIV transmission to your sexual partner(s)?

- ☐ Only for my own health
- ☐ Mostly for my own health, but a little to reduce transmission to my sexual partner(s)
- ☐ Equal mix of both
- ☐ Mostly to reduce transmission to my sexual partner(s), but a little for my own health
- ☐ Only to reduce transmission to my sexual partners(s)
- ☐ Don't know

G4 What was your last CD4 count before you started ART?

- ☐ Less than or equal to 200
- ☐ 201-350
- ☐ 351-500
- ☐ Over 500
- ☐ I can't remember/ don't know

G5 What was your last viral load measurement?

- ☐ 50 copies/mL or less ('undetectable' or 'suppressed')
- ☐ More than 50 copies/mL ('detectable' or 'raised')
- ☐ I can't remember/ don't know

*Please indicate the level to which you agree or disagree with each statement by **circling** the appropriate **number**:*

1=Strongly agree, 2=Agree, 3=Neither agree or disagree, 4=Disagree, 5=Strongly disagree, 6=Don't know.

		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Don't know
G6	I started ART to reduce the risk of passing HIV to my sexual partner(s)	1	2	3	4	5	6
G7	I started ART because my doctor told me I should start	1	2	3	4	5	6
G8	I started ART to increase my life expectancy	1	2	3	4	5	6
G9	I started ART as usually when I am ill I take medication straight away to fight the illness	1	2	3	4	5	6
G10	I started ART to improve my quality of life	1	2	3	4	5	6

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		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Don't know
G11	I started ART to reduce the damage HIV was causing to my body	1	2	3	4	5	6
G12	I started ART as I felt ill	1	2	3	4	5	6
G13	I started ART to control the spread of HIV in my body	1	2	3	4	5	6
G14	I started ART to reduce my anxiety about transmitting HIV to my sexual partner(s)	1	2	3	4	5	6
G15	I started ART as part of a clinical trial	1	2	3	4	5	6
G16	I started ART as my partner wanted me to	1	2	3	4	5	6
G17	It is better for my health to start ART earlier rather than later	1	2	3	4	5	6
G18	Being on ART makes it easier to disclose my HIV status to sexual partners	1	2	3	4	5	6
G19	Stopping or having a break in ART will be bad for my health	1	2	3	4	5	6

SECTION H: YOUR BELIEFS

*Please indicate the level to which you agree or disagree with each statement by **circling** the appropriate **number**:*

1=Strongly agree, 2=Agree, 3=Neither agree or disagree, 4=Disagree, 5=Strongly disagree, 6=Don't know.

		Strongly agree	Agree	Neither agree or disagree	Disagree	Strongly disagree	Don't know
H1	**Being on ART and having an undetectable viral load means that HIV is unlikely to be passed to a sexual partner even through anal intercourse without a condom**	1	2	3	4	5	6
H2	**It is not necessary to disclose your HIV status to a sexual partner if you are on ART and have an undetectable viral load**	1	2	3	4	5	6
H3	**Better HIV treatment means that people are less worried about catching HIV**	1	2	3	4	5	6

Thank you for taking the time to answer our questions!

Is there anything else you would like to share with us, or any comments you wish to add?

_____

_____

_____

_____

_____

PLEASE NOW PUT THIS QUESTIONNAIRE IN THE ENVELOPE PROVIDED AND RETURN IT TO THE PERSON WHO GAVE IT TO YOU!

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Appendix 19 – MREC approval letter for amendment of the UK Register of HIV Seroconverters protocol to include the cross-sectional survey

NHS
Health Research Authority

National Research Ethics Service

NRES Committee West Midlands - South Birmingham
HRA NRES Centre Manchester
3rd Floor
Barlow House
4 Minshull Street
Manchester
M1 3DZ

Tel: 0161 625 7815
Fax: 0161 625 7299

07 May 2013

Dr Kholoud Porter
MRC Clinical Trials Unit
Senior Epidemiologist
MRC Clinical Trials Unit
222 Euston Road
London
NW1 2DA

Dear D. Porter

Study title:	**The UK Register of HIV Seroconverters: an observational study of HIV infected persons in the UK for whom the time of HIV seroconversion is well-estimated**
REC reference:	**04/Q2707/155**
Amendment number:	**Protocol version 3.1**
Amendment date:	**05 March 2013**

- The amendment consists of a revised Questionnaire.
- It also includes some minor amendments to the Protocol.

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Questionnaire Change Log	1.0	12 February 2013
Questionnaire: Men's Health & Behaviour Questionnaire	2.0	12 February 2013
Participant Consent Form: Sexual Behaviour and Attitudes Survey Patient Consent Form F	2.0	12 February 2013

Participant Information Sheet: Sexual Behaviour and Attitudes Survey Patient Information Sheet F	2.0	12 February 2013
Protocol	3.1	05 March 2013
Notice of Substantial Amendment (non-CTIMPs)	Protocol Version 3.1	05 March 2013
Covering Letter		23 April 2013

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

R&D approval

All investigators and research collaborators in the NHS should notify the R&D office for the relevant NHS care organisation of this amendment and check whether it affects R&D approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

04/Q2707/155:	**Please quote this number on all correspondence**

Yours sincerely

[redacted]

Signed on behalf of:
Professor Simon Bowman
Chair

E-mail: nrescommittee.westmidlands-southbirmingham@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: Sarah Meredith – MRC Clinical Trials Unit

NRES Committee West Midlands - South Birmingham

Attendance at Sub-Committee of the REC meeting on 03 May 2013

Name	*Profession*	*Capacity*
Professor Simon Bowman (Chair)	Consultant Rheumatologist	Expert
Dr John David Cochrane (Vice-Chair)	Retired GP	Expert

Appendix 20 – Participant information sheet for the cross-sectional survey nested in the UK Register

(Form to be printed on local hospital headed paper)

Version 2.0 **12th February 2013**

APPENDIX F **The UK Register of HIV Seroconverters**

An observational study of HIV infected persons in the UK for whom the time of HIV seroconversion is well-estimated

SEXUAL BEHAVIOUR AND ATTITUDES SURVEY
PATIENT INFORMATION SHEET F

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

People who have been recently infected with HIV (recent HIV seroconverters) may play an important role in the UK epidemic, however little is known about their sexual behaviour, knowledge, beliefs and attitudes. We want to explore the sexual behaviour, knowledge and attitudes that people recently infected with HIV have towards HIV treatment, particularly how they would feel about starting HIV treatment early.

Why have I been invited?

You have been invited to participate in this study as you are a recent seroconverter; in other words you presented to our clinic very early on in your HIV infection.

Do I have to take part?

No you don't have to. Participation is entirely voluntary and you are free to say no without giving a reason. This will not affect the standard of care you receive or your participation in the main study.

What will happen to me if I take part?

If you agree to take part in this study you will be first be given a consent form to sign. Once this is done you will be given a pen and a short paper questionnaire to fill out. You will only complete this questionnaire once and it will take about 20-25 minutes of your time to fill out. Once you have completed the questionnaire please give it back to the nurse or doctor who gave it to you.

You can opt to agree to only participate in the main study and not to completing the questionnaire.

What are the disadvantages or risks of taking part?

There are no disadvantages of taking part in this study. The questionnaire asks questions about sexual behaviour that some people may find sensitive or personal in nature. You are not obliged to answer a question if you do not want to.

Will the study benefit me?

There will be no direct clinical benefit to you; however, the information we get from this study may help us to treat future patients with HIV better.

Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the study will be kept strictly confidential. In no circumstances will your name, address or telephone number be disclosed outside the clinic. The questionnaire will be stored coded, i.e. without any personal identifiers, only your centre name and date of birth.

Contacts for further information

If you would like to talk to someone about this study please contact:

(Clinics to insert their study contact's details and
Patient Advisory Liaison Service details here)

_____

_____

_____

You will be given a copy of this information sheet and a signed consent form to keep.

Thank you for considering joining this study.

Appendix 21 – Consent form for the cross-sectional survey nested in the UK Register

(Form to be printed on local hospital headed paper)

Version 2.0 **12th February 2013**

APPENDIX F **The UK Register of HIV Seroconverters**

An observational study of HIV infected persons in the UK for whom the time of HIV seroconversion is well-estimated

SEXUAL BEHAVIOUR AND ATTITUDES SURVEY

PATIENT CONSENT FORM F

(supplementary to Patient Consent Form A version 3.1 dated 05/03/2013)

Please initial box if you agree

I have read the UK Register Sexual Behaviour and Attitudes Survey Information Sheet (version 2.0) dated 12/02/2013 ☐

I have had an opportunity to discuss this study and ask questions ☐

Which doctor or nurse have you spoken to about this study?

PLEASE PRINT HIS/HER NAME _____

I agree to take part in this study by authorising this clinic to pass on the completed sexual behaviour and attitudes questionnaire to the MRC Clinical Trials Unit ☐

I understand that I am free to decline participation in this study without giving a reason, and without this affecting my medical care ☐

IMPORTANT:
One signed original to be given to patient (with a copy of the Patient Information Sheet)
One signed original to be kept by clinic in a study folder
One signed photocopy to be kept in the hospital notes

Signed _____ Date _____

PRINT NAME _____

Doctor or Nurse Taking Consent

Signature _____ Date _____

PRINT NAME _____

Appendix 22 – Sensitivity analysis: factors associated with cART initiation, excluding individuals diagnosed in primary HIV infection

		Unadjusted HR	95% CI	p	Adjusted[a] HR	95% CI	p
Year of SC (continuous per year increase)		1.09	1.07, 1.12	<0.001	1.09	1.07, 1.12	<0.001
Sex							
	Male	1	-	0.534	1	-	0.086
	Female	1.12	0.78, 1.61		2	0.91, 4.41	
Exposure group							
	MSM	1	-		1	-	
	MSW	0.97	0.70, 1.37	0.878	0.57	0.20, 3.24	0.196
	IDU	1.34	0.43, 4.18		0.81	0.28, 1.15	
Age at seroconversion (per 10 year increase)		1.11	1.01, 1.21	0.022	1.12	1.03, 1.22	0.011

Analyses based on 767 individuals, contributing 2621 person years at risk, of whom 590 initiated ART. HR= Hazard ratio; CI=confidence interval; MSM=sex between men; MSW=sex between men and women; IDU=injecting drug use. a=adjusted for all other variables in the table

Appendix 23 – Sensitivity analysis: factors associated with risk of cART initiation including CD4 at HIV diagnosis

		Unadjusted HR	95% CI	p	Adjusted[a] HR	95% CI	p
Year of seroconversion (per year increase)		1.04	1.02, 1.06	<0.001	1.04	1.02, 1.06	<0.001
Sex							
	Male	1.00	-	0.985	1	-	0.335
	Female	1.00	0.77, 1.31		1.21	0.82, 1.79	
Exposure group							
	MSM	1.00	-		1	-	
	IDU	1.05	0.85, 1.29	0.859	0.85	0.63, 1.15	0.441
	MSW	0.87	0.36, 2.11		1.29	0.52, 3.20	
Age at seroconversion (per 10 year increase)		1.14	1.08, 1.22	<0.001	1.13	1.06, 1.20	<0.001
HIV test interval[b]							
30 days or more		1.00	-		1	-	<0.001
<30 days		1.42	1.24, 1.63	<0.001	1.36	1.19, 1.56	
CD4 count at HIV diagnosis[c] (continuous)		0.91	0.89, 0.92	<0.001	0.91	0.89, 0.92	<0.001

Analyses based on 1353 individuals, contributing 3172 person years at risk, of whom 1026 initiated ART. HR= Hazard ratio; CI=confidence interval; MSM=sex between men; MSW=sex between men and women; IDU=injecting drug use. a=adjusted for all other variables in the table; b=interval between HIV antibody negative and positive tests; c=CD4 count modelled as square root transformed cells/mm3

Appendix 24 – Sensitivity analysis: Temporal trends in ART initiation, starting combinations and time to stopping ART in patients with primary HIV infection, excluding those enrolled in SPARTAC trial

	Calendar year of seroconversion[a]							
	1998-99	**2000-01**	**2002-03**	**2004-05**	**2006-07**	**2008-09**	**2010-11**	**p-value**
N	61	98	107	113	116	139	232	
% (95% CI) initiating ART in PHI	27.9	50	32.7	9.7	7.8	13	19.8	<0.001[b]
% (95% CI) of those starting ART in PHI who stop within 12 months[c]	47.1	59.2	68.6	63.6	88.9	11.1	10.9	<0.001[d]

ART=combination antiretroviral therapy; PHI=primary HIV infection; CI=confidence interval; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor. a=Calendar year of seroconversion modelled as categorical year groups; b=p-value for heterogeneity from logistic regression model of effect of year group of seroconversion (categorical) adjusting for sex, exposure group (MSM, MSW, IDU), age at seroconversion (continuous, per 10 years) and HIV test interval (30 days or more, < 30 days); c=time to event analysis assessing time from ART initiation in PHI to stopping ART; based on 251 individuals starting ART in PHI, contributing 478 person-years at risk, of whom 168 stopped therapy; d p-value for heterogeneity in Cox proportional hazards model, modelling year group of seroconversion (categorical) and adjusting for sex, exposure group (MSM, MSW, IDU), age at seroconversion (continuous, per 10 years) and HIV test interval (30 days or more, < 30 days)