The evolution and effectiveness of the South African antiretroviral therapy program

by

Morna Cornell

Thesis presented for the degree of

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This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work included in this thesis is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely my work, or, in the case of multi-authored published papers, constitute work for which I was the lead author. My contribution to multi-authored papers is outlined in the preface to the thesis and in the introduction to each included paper as appropriate.

Morna Cornell
September 2014

ABSTRACT

Although South Africa has the largest antiretroviral therapy (ART) program worldwide, data on key outcomes like mortality and loss to follow-up (LTF) are limited. A few cohorts have published patient outcomes but there is no national reporting on ART scale-up and its impact on the health of HIV-infected individuals. Yet such monitoring of outcomes is vital to inform and improve service delivery. The International epidemiologic Databases to Evaluate AIDS Southern Africa collaboration (IeDEA-SA) was established in 2005 to collect and analyze individual-level data from the larger cohorts of individuals on ART in Southern Africa. Using routine, anonymized data from the South African sites, this thesis aims to describe how the program has evolved over 10 years and to assess its effectiveness.

Five quantitative analyses were performed using descriptive statistics and survival analysis methods. The studies used patient-level data on adult patients starting ART to describe characteristics and to explore outcomes and temporal changes in outcomes over time. Patient numbers ranged from 19,481 (limited to cohorts with civil identification numbers) to 83,576 adults, followed for up to 214,400 person-years. The results are presented as four published papers and one submitted for publication.

The thesis describes a rapid, massive scale-up of services. Despite improvements in baseline immunologic status, late diagnosis and ART initiation especially in men are a challenge. Over five years, 12-month mortality drops and 12-month LTF increases, suggesting that LTF is a greater challenge to program effectiveness than mortality. Excluding early deaths after TFO/LTF, mortality risk compared with retained patients is similar among TFOs and higher among LTF. Censoring TFOs did not bias mortality estimates due to the lower incidence of TFO and subsequent death compared with LTF. Mortality increases with age at ART initiation, but the effect of age is modified by baseline immunologic status. The proportions of patients ≥50 years old enrolling and remaining in care each year increases. Men have higher

mortality on ART than women and this is only partly explained by more advanced HIV disease at ART initiation, differential LTF and subsequent mortality, and differences in responses to treatment. Observed gender differences in mortality on ART may be best explained by background differences in mortality between men and women unrelated to HIV/AIDS or ART.

The thesis concludes that the major challenges to program effectiveness are programmatic and not clinical. They include the earlier initiation of patients, especially men and patients ≥50 years old, and the need for good monitoring systems and strategies to retain patients in lifelong chronic care.

ACKNOWLEDGEMENTS

My interest in antiretroviral therapy (ART) arises from years of activism for the rights of people living with HIV/AIDS during the bleak time before treatment was available. In 2014, with the largest ART program worldwide it seems unbelievable that there was ever a time when the South African government denied that HIV caused AIDS and refused to offer ART.

This has been a challenging and fascinating journey and I am extremely grateful to everyone who has helped along the way. I would like to thank and acknowledge the following people:

- Landon Myer, my supervisor, for his deft and inspiring mentorship, luminous intelligence, inspiration, encouragement, humor and faith in my abilities.
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As always, the first come last. I am unbelievably fortunate to have a loving family who have been endlessly supportive despite the all-encompassing nature of this thesis. Thanks to Devlin, for living through these years of study and growth with me and to Zara, for her unflagging support, strength and humor. And great thanks to John Trafford: for caring about my work and helping me clarify my thinking, for his insights, love and support, for the music and dancing and for helping me take myself more lightly.

This thesis is in memory of all who suffered and died

without access to antiretroviral treatment

PREFACE

This thesis includes published papers as per the general provision 6.7 in the General Rules for the degree of Doctor of Philosophy (PhD) of the University of Cape Town, and as approved in 2010 by the University Doctoral Degrees Board. The following five papers are formally included as part of the thesis as chapters in the following order:

1 Cornell M, Technau K, Fairall L, Wood R, Moultrie H, van Cutsem G, Giddy J, Mohapi L, Eley B, Macphail P, Prozesky H, Rabie H, Davies M-A, Maxwell, N, Boulle A for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Monitoring the South African ART Program 2003-2007: the IeDEA-Southern Africa Collaboration. *South African Medical Journal* 2009, 99(9): 653-660.

2 Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J, Wood R, Prozesky H, Mohapi L, Graber C, Egger M', Boulle A, Myer L for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Temporal changes in program outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007. *AIDS* 2010, 24(14):2263-2270.

3 Cornell M, Lessells R, Fox MP, Garone DB, Giddy J, Fenner L, Myer L, Boulle A for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Mortality among adults transferred and lost to follow-up from antiretroviral therapy programs in South Africa: a multicenter cohort study. *Journal of Acquired Immune Deficiency Syndromes* 2014, 67(2):e67-75.

4 Cornell M, Wood R, Tanser F, Prozesky H, Giddy J, Stinson K, Maskew M, Johnson L, Schomaker M, Boulle A, Myer L for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Aging in the South African antiretroviral therapy program. Being prepared for submission to *PLoS Medicine*

5 Cornell M, Schomaker M, Garone DB, Giddy J, Hoffmann C, Lessells R, Maskew M, Prozesky H, Wood R, Johnson L, Egger M, Boulle A, Myer L for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicenter cohort study. *PLoS Medicine* 2012, 9(9):e1001304.doi:10.1371.

My contribution is described in the introduction to each paper. I was lead and corresponding author on all papers, prepared the datasets for analysis, conducted the analyses for all except Chapter 3 and drafted all versions of the articles. I circulated the manuscripts to co-authors, reviewed their suggestions and comments and made the final decisions regarding further revisions to the manuscripts. All co-authors reviewed and approved the submitted manuscripts. I was primarily responsible for responding to reviewer comments and circulating these to co-authors. My supervisor has confirmed to the University of Cape Town Doctoral Degrees Board that the included papers reflect overwhelmingly my own scientific work.

All analyses are based on data collected as part of the International epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration. I played a central role in developing this high-level collaboration and its scientific agenda. I have been Cohort Collaboration Manager since 2007, shortly after the inception of the IeDEA-SA Data Center at the School of Public Health and Family Medicine.

LIST OF ABBREVIATIONS

AIDS	acquired immune deficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AIDS	acquired immune deficiency syndrome
CI	confidence interval
DoH	Department of Health
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
HR	hazard ratio
IeDEA	International epidemiologic Databases to Evaluate AIDS
IeDEA-SA	IeDEA Southern Africa
IQR	interquartile range
LTF	loss to follow-up
MAR	missing at random
MCAR	missing completely at random
MI	multiple imputation
MNAR	missing not at random
MO	month/s
NAP	National AIDS Plan
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NR	not reported
NSP	National Strategic Plan
OECD	Organization for Economic Co-operation and Development
PhD	Doctor of Philosophy
PMTCT	Prevention of mother-to-child transmission
PYR	person-year
SA	South Africa
SACBC	Southern African Catholic Bishops' Conference

SANAC	South African National AIDS Council
SDSS	Health and Socio-demographic Surveillance System
SSA	Sub-Saharan Africa
STI	Sexually transmitted infection
TasP	Treatment as prevention
TFO	transfer out
UCT	University of Cape Town
VL	viral load
WHO	World Health Organization

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Chapter 1: Introduction

1.1 Introduction and background

1.1.1 Epidemiology of HIV/AIDS

In 2013, an estimated 35 million people were living with HIV worldwide. According to the 2013 UNAIDS Global Report, 70% of new infections occurred in Sub-Saharan Africa (SSA), home to nearly 25 million individuals infected with human immunodeficiency virus (HIV), 58% of whom are female(1). South Africa remains the epicenter of the epidemic with 12.2% adult prevalence and 6.4 million people living with HIV in 2012(2). The overall prevalence masks large differences between and within provinces as well as differences by age, gender, race and urban vs. rural location. The scale of the HIV epidemic in South Africa has had a huge impact on both individual and population health. The burden of opportunistic infections has grown and HIV has been responsible for increased morbidity and mortality and decreased life expectancy(3).

1.1.2 Antiretroviral therapy (ART)

Antiretroviral drugs were available in Europe and North America in mono- or dual-therapy regimens from the late 1980s. In 1996, at the 11th International Conference on Acquired Immunodeficiency Syndrome (AIDS) in Vancouver, researchers announced that a combination of three antiretroviral (ARV) drugs ('triple therapy') delayed the onset of AIDS(4). Triple therapy was introduced into clinical practice in developed countries and resulted in declining morbidity and mortality(5), but only for those who could afford the prohibitive expense. At an estimated cost of US$10,000-15,000 per person per year in the late 1990s(6), it seemed unlikely that public sector ART would ever be affordable in resource-constrained settings.

1.1.2 Individualized ART

In developed countries, patients are prescribed highly individualized care. In Switzerland, for example, patients are prescribed ART selected from 36 different regimens(7). The choice of treatment regimens may impact on patient outcomes and on the effectiveness of an ART program. High levels of adherence to ART are required to ensure virologic suppression, some studies suggesting up to 90% for protease-inhibitor-based drugs and at least 95% for non-nucleoside-based treatment(8).

First-line regimens need to be simple and manageable for patients to stay on lifelong therapy and to avoid unnecessary and costly switching or substitution of drugs. In the early years, treatment regimens were complex with heavy pill burdens. For example, in an early study on adherence patients with a low pill burden took <10 pills/day while those with a high burden took more than 15 pills/day(9). Short- and long-term adverse drug reactions were frequent, serious and sometimes life-threatening. Such complex regimens and serious side effects increase the likelihood that patients will be non-adherent, fail therapy and require either drug switches (swapping one or two drugs due to intolerance) or drug substitution (swapping the entire regimen as virologic replication was not suppressed). In addition to the implications for patients, increased drug switching and substitution have major cost implications. Second- and third-line ART are far more expensive than first-line and it is important to prolong the durability of first-line ART as far as possible(8).

1.1.3 The public-health approach to ART

In contrast with the highly individualized approach to ART in most developed countries, South Africa and many other resource-constrained countries have adopted a public-health approach following recommendations from the World Health Organization. South African activists and health care workers were centrally involved in helping to drive down the exorbitant cost of treatment. In 2013, the average cost of first-line ART for low- and middle-income countries was US$115 per

patient per year, and $330 for second-line treatment(6), and the cost continues to drop.

Such huge reductions in cost paved the way for the provision of public sector ART in developing countries. However there was recognition that highly individualized ART was not feasible in resource-constrained settings. In September 2002, the World Health Organization (WHO) published guidelines for a public-health approach to offering ART in resource-constrained settings with standardized drug regimens, clinical decision-making and patient monitoring(10). Regimens are chosen on the basis of cost and ease of administration and may include antiretroviral drugs which are no longer used in developed countries. This thesis highlights some successes and challenges in applying the public-health approach in the South African national program.

1.2 ART in South Africa

1.2.1 Background: a history of inequality

In addition to HIV, South Africa faces numerous other major public-health challenges. It has one of the most serious TB epidemics in the world, with over 50% of new TB cases being in patients co-infected with HIV and growing epidemics of multidrug-resistant and extensively drug-resistant TB(3). These overlapping epidemics are compounded by a high burden of non-communicable disease, injury and violence-related deaths and mental health disorders, placing enormous strain on a beleaguered health system. Indeed, South Africa's health burden per capita is reportedly the highest of any middle-income country worldwide(11).

To some degree, the roots of the public-health challenges facing the country – including the scope of the HIV epidemic – may lie in the violent and divisive history of South Africa(12). Health inequities are evident in racial and gender differences in rates of mortality and disease, reflecting differential access to services and health. In addition, huge inequities persist in health outcomes between and within provinces. Historically, funding for health services was extremely uneven and

focused primarily on tertiary care. Primary-level services were underdeveloped and there was little funding for the former Bantustans, poorly-resourced areas of land to which black South Africans were assigned according to their ethnic identity(13). At the time of the first democratic elections in 1994, there were 14 separate health departments. Since then, the health system has restructured with the focus on delivery through primary health care. Despite good policies and the existence of many excellent facilities, it is argued that implementation of the system has been poor, largely due to failures in leadership and weak management(14). Levels of socio-economic inequality have continued to increase despite government's commitment to reducing poverty. Indeed in 2013 the Organization for Economic Co-operation and Development (OECD) stated that 'no progress toward income equality has been made since the end of apartheid'(15).

1.2.2 South Africa's response to the HIV epidemic

The first documented cases of HIV in South Africa were two white homosexual flight stewards(16). Over the next few years, HIV remained concentrated largely within the gay community, paralleling the epidemic in developed countries. During this time, the apartheid government failed to address HIV prevention beyond a number of unsuccessful advertising campaigns. From the early 1990s, the country has faced a more generalized epidemic with heterosexual transmission the dominant route of transmission(17). In 1993, the National AIDS Convention of South Africa (NACOSA) was established. NACOSA was an extremely inclusive body with representatives from government as well as a wide range of HIV/AIDS activists, unions, business groupings, health workers, religious groups and others. The explicit intention of NACOSA was to formulate a National AIDS Plan (NAP) for urgent implementation following the election of a democratic government. Despite the NAP being adopted and prioritized as a lead project, high-level political support was not forthcoming. The newly-formed HIV/AIDS and STD directorate was located within the Department of Health (DoH) and not within the President's Office, as intended. The DoH was dogged by a series of widely-publicized debacles including government support for a controversial anti-AIDS play and a supposed cure for AIDS as well as

government's refusal to fund treatment to prevent mother-to-child transmission of HIV(3).

1.2.3 Delays & denialism

In 1998, the struggle for public sector ART in South Africa began in earnest, strongly opposed by the Minister of Health (MoH) at the time, Nkosazana Dlamini-Zuma. She argued that ART was toxic and that drug companies were trying to persuade Africans into buying expensive medication unnecessarily. Following the election of President Mbeki and his appointment of Manto Tshabalala-Msimang as MoH in 1999, the situation worsened. In conflict with the country's stated HIV/AIDS policy, President Mbeki openly stated that HIV did not cause AIDS and the new MoH did not contradict him. Mbeki established an 'advisory panel' of dissident scientists who supported this controversial position in the face of the overwhelming body of expertise within and outside the country. While Mandela could be criticized for delaying implementation and not prioritizing HIV/AIDS during his presidency, it is estimated that Mbeki's era was responsible for the unnecessary loss of over 330,000 lives(18).

In addition to Mbeki's opposition to ART, others raised high-level concerns about the capacity of health systems in developing countries to provide ART. In 2001, for instance, the USAID Administrator Andrew Natsios said that 'Africans don't know what Western time is. You have to take these [AIDS] drugs a certain number of hours each day, or they don't work. Many people in Africa have never seen a clock or a watch their entire lives … They know morning, they know noon, they know evening, they know the darkness at night'(19). Indeed Natsios later argued that the newly-established Global Fund to fight AIDS, TB & Malaria should focus on prevention and include little if any funding for treatment. Even among individuals committed to the provision of ART in developing countries, there were concerns about possible 'antiretroviral anarchy' including the development of resistance and transmission of resistant virus(20).

Fortunately a group of committed health care practitioners supported by Médecins sans Frontières and the Treatment Action Campaign found creative ways of circumventing official channels to offer lifesaving ART. A number of pilot projects tested the feasibility and logistics of offering public sector ART(21) while activists brought court actions to force government to provide widespread access to ART. In 2002 the Constitutional Court ruled in favor of the Treatment Action Campaign, forcing government to provide treatment to prevent mother-to-child transmission (MTCT) of HIV(22). In 2003, the South African cabinet eventually ordered Minister Tshabalala-Msimang to initiate a national ART program(23). In April 2004, government officially launched the national ART program, one of the largest, most intensely-funded health care programs in South Africa and the largest ART program worldwide.

By the end of 2012, an estimated 2.1 million individuals had initiated therapy in South Africa, saving more than 2.7 million life-years and preventing hundreds of thousands of new HIV infections(24). HIV-positive individuals starting ART with CD4+ cell counts over 200 cells/µL had near-normal life expectancy(25). By any standard this is an extraordinary achievement, but even more so when it has been implemented against a backdrop of high-level political opposition to ART.

1.2.4 Monitoring

Unfortunately the expansion of ART services has not been matched by the ability to monitor and report on service delivery and data on key program outcomes such as mortality, LTF and retention are limited. The cascade or continuum of HIV care includes linkage from HIV testing to enrollment into pre-ART care, enrollment onto ART when eligible, adherence to ART and retention in long term treatment(26). Monitoring of these stages provides insight into where patients are being lost to care and/or non-adherent to treatment. A few cohorts have published patient outcomes(21,27-29). These analyses provide insights into the performance of specific programs but the generalizability of findings may be limited. There is still no national reporting of key indicators of ART scale-up and its impact on the health

of HIV-infected individuals. Yet monitoring of program outcomes is vital to inform and improve service delivery. Planning for current and future ART services is dependent on accurate data on enrollment and retention. Information is also needed on those groups of eligible patients who are not currently in care. Mortality is a crude indicator of how patient management and understanding how mortality risk differs between groups facilitates targeted prevention and testing campaigns. Differentiating between patients truly lost to care vs. those lost to monitoring informs strategies to trace these patients and ensure that they are re-engaged in care. The ability to do so ensures a more accurate estimate of program retention, increasingly regarded as the most important measure of effectiveness.

Given these key indicators, this thesis makes two significant contributions towards our understandings of the response to the epidemic. Firstly, it uses routinely collected data from the IeDEA-SA collaboration to provide the first – if partial – picture of the evolution and effectiveness of the national program. Secondly, it identifies key gaps in the existing program which could be addressed to improve its performance. The 2007-2011 National Strategic Plan on HIV/AIDS identified the lack of a monitoring and evaluation (M&E) operational plan as a major concern(30). This thesis aims to address part of the existing gap in monitoring and evaluating the national ART program.

1.2.5 South African ART guidelines

Since 2004, South Africa has issued three sets of ART guidelines, each time expanding the criteria for eligibility(31-33). In 2004, patients were eligible for ART if they had a CD4+ cell count ≤200 cells/µL or were classified WHO stage IV(31). From 2004-2008, first-line ART in South Africa consisted of two nucleoside reverse transcriptase inhibitors (NRTI) and one non-NRTI (NNRTI). Tolerability was poor, with frequent side effects including peripheral neuropathy, lipodystrophy, lactic acidosis, hepatotoxicity, neutropenia and anemia(34). In 2009, after four years providing ART in a busy clinic in Johannesburg, Sanne et al commented that “High

rates of single drug substitution suggest that the public-health approach to HAART could be further improved by the use of a more durable first-line regimen"(35).

In 2010, in response to concerns about d4T, WHO issued revised guidelines which recommended replacing d4T with tenofovir (TDF), a drug with a better safety profile. From April 2010, despite concerns about the six-fold higher cost, South Africa started initiating new patients on TDF(32). Eligibility was extended to include pregnant women and people co-infected with TB with CD4+ cell counts ≤350 cells/µL, and all individuals in WHO stage IV or with drug-resistant TB, regardless of immunologic status. Since then a study comparing public-health and individual approaches to ART has reported similar virologic responses but a far lower rate of drug switching for TDF than for AZT or d4T, both of which had far higher rates of total substitution(7). Simplifying first-line regimen is an important step in improving adherence and retaining patients on ART. In 2012 the Minister of Health announced the tender for a triple fixed-dose combination (FDC) tablet of TDF, FTC and EFV which is cheaper and simpler than the previous regimen and will be used in the initiation of an estimated 90% of new patients(36).

In the most recent change to ART guidelines, Minister of Health Aaron Motsoaledi has announced that from January 2015, eligibility will be extended to patients with a CD4+ cell count <500 cells/µL(37). Raising the threshold of eligibility has major implications for service delivery, increasing the number of individuals eligible for ART. For example, raising the CD4+ cell count from 200 to 350 cells/µL was estimated to create a backlog of 1 million patients(38). This thesis highlights existing challenges in the ART program that will be compounded by such increases in patient load unless they are addressed.

1.3 Problem statement and rationale

South Africa has the largest antiretroviral treatment program worldwide, which has enrolled over 2 million individuals on ART since 2004. While there have been

reports from individual cohorts and two provinces, there has been little consolidated monitoring or reporting of ART outcomes at a national level. After ten years of ART, there is a need to evaluate the program in order to plan and deliver future services efficiently and equitably.

1.4 Aim and objectives

The aim of this thesis is to review the evolution and effectiveness of the South African national antiretroviral therapy (ART) program using data from the IeDEA-Southern Africa collaboration. The thesis uses individual patient-level data to describe the baseline characteristics of a large sub-set of adults who have started ART nationally, and to explore patient outcomes over time in the context of a rapid and massive scale-up of services.

Specific objectives include:

1. To characterize adults accessing public sector ART in South Africa over five years of enrollment;
2. To investigate temporal changes in mortality, loss-to-follow-up (LTF) and overall program retention over five years;
3. To explore mortality among patients transferred and lost from these ART services compared with mortality among patients retained;
4. To explore the impact on ART outcomes of age at enrollment;
5. To explore gender differences in adult survival on ART.

1.5 The IeDEA-Southern Africa Collaboration

1.5.1 Background to IeDEA

The International Epidemiologic Databases to Evaluate AIDS collaboration (www.iedea.org) is an international research network that was established by the National Institute of Allergy and Infectious Diseases (NIAID) of the US National Institutes for Health (NIH) in 2005. IeDEA evolved from the work of previous historic collaborations such as the Antiretroviral Therapy in Low Income Countries (ART-LINC), the Antiretroviral Therapy Cohort Collaboration (ART-CC) and others.

Participating sites within the collaboration collect and provide patient-level data. These data are analyzed by researchers in the data centers, site investigators and others to address research questions that cannot be answered in single cohorts or with small patient numbers.

1.5.2 IeDEA-Southern Africa

IeDEA-SA (www.iedeasa.org), the Southern African Collaboration, is one of seven regional centers, with administrative and scientific oversight at data centers at the Universities of Cape Town and Bern. The University of Cape Town has primary responsibility for managing data and relationships with South African sites, while the University of Bern liaises with sites in other Southern African countries. The broad aims of the collaboration are to conduct epidemiologic, clinical and health services research to inform and improve the delivery of ART in the region. IeDEA-SA successfully re-competed for funding in 2011 and is funded until 2016. The African networks of IeDEA-SA have been previously described(39).

During the course of this thesis, the regional collaboration has evolved. New cohorts have joined and where possible, their data has been included in subsequent analyses. By December 2013, the IeDEA-SA database included data on 476,067 adults on ART and 72,474 HIV-positive patients not on ART in Zimbabwe, Malawi, Mozambique, South Africa, Zambia and Lesotho. In its second cycle of funding, IeDEA-SA focuses on long-term issues including the effectiveness and outcomes of ART over time, long-term and temporal trends in regimen durability and important co-morbidities of HIV infection.

The collaboration has relied on data routinely collected in ART services, which entails a balance between quantity and quality. On the one hand, routine data are likely to be more generalizable than data from closely monitored research sites. On the other hand, the sheer volume of patients and the caseload result in missing laboratory and other values for key variables. For instance, although some cohorts were included in earlier analyses, missing data and data quality issues sometimes

precluded them from later analyses. However IeDEA-SA has successfully enhanced routine data through, for example, linking HIV cohort data with the National Population Register to improve mortality ascertainment and using appropriate statistical methods to minimize the impact of missing data and LTF and mortality estimates.

1.5.3 Data center management

I have managed the South African data center since 2007. In this capacity I have had primary responsibility for independently managing the organizational aspects of the data center including relationships with sites and management of the complex scientific process that has been developed to govern analyses of shared datasets, collaborative writing committees and authorship processes. I participate in the IeDEA-SA Executive Committee which has scientific oversight over the collaboration.

Patient data are transferred anonymously from participating sites to the data centers using the IeDEA-SA data transfer protocol (DTP) which was developed within the UCT data center in consultation with other staff and investigators. Based on the HIV Cohorts Data Exchange Protocol (HICDEP) used by the large European network EuroCoord, the DTP provides the structure and format for the collaborative IeDEA-SA and for data imports from sites to the database. After transfer, data from different sites are merged into a single IeDEA-SA Microsoft SQL Server database stored securely at each data center, with access restricted to data managers. I was involved in revising the HICDEP format for resource-constrained settings. The DTP has now been accepted as the South African Data Exchange Standard for all data transfers between HIV monitoring programs nationally.

All analyses included in this thesis used data from the South African cohorts of the IeDEA-SA combined dataset. Figure 1.1 shows the location of current and historical cohorts. Tables were extracted via open database connectivity download to STATA (versions 12-13, College Station, Texas). I undertook all data management including merging data from different tables, checking quality and data cleaning in discussion

with participating sites. Data management and analysis in Chapter 4 were done by a co-author, Ms A Grimsrud.

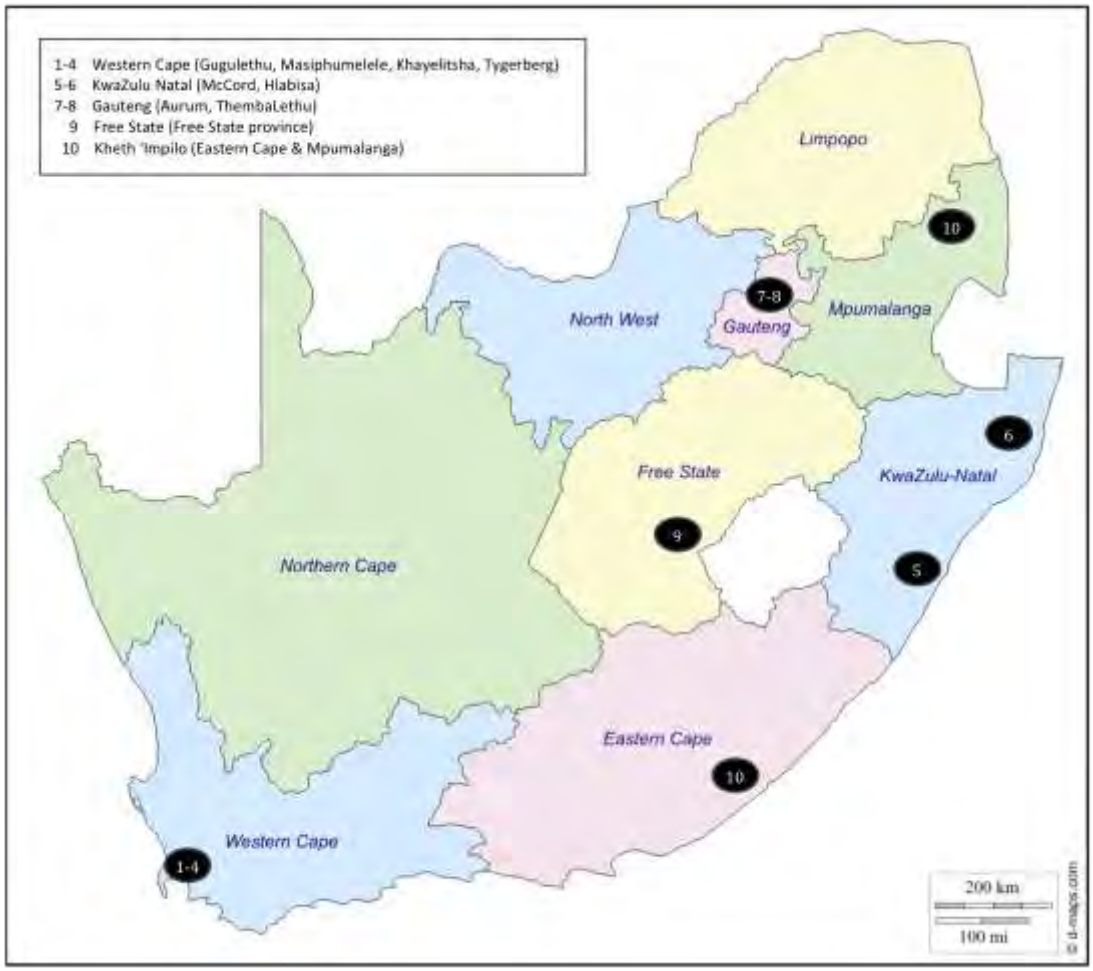


Figure 1.1. Location of adult IeDEA-SA cohorts in South Africa

1.5.4 Publication process

I was responsible for formulating and managing an explicit process to access and analyze the data (Appendix A). Briefly this process consists of the proposal of a regional or multiregional concept sheet which describes the analysis and specifies the required variables. The concept sheet is circulated to the data centers and to all site investigators, who decide whether to participate in the analysis. Once the analysis results are available, sites may not withdraw their data. In the event where any data are shared between the data centers and any third party, a data sharing agreement is completed. For each of the analyses in this thesis, I developed,

circulated and finalized the concept sheet and confirmed which sites would participate.

1.5.6 Ethics

The IeDEA-SA (first known as the Observational Antiretroviral Studies in Southern Africa [OASIS] study has ethical approval from the UCT Health Sciences Faculty Research Ethics Committee (HREC REF: 084/2006, Appendix B), renewed annually. In addition, each cohort has ethical approval from their respective institutional body to contribute data to the collaboration.

1.6 Meta-analysis of individual patient-level data

The approach used in these analyses can be thought of as individual patient-level meta-analysis. The use of individual-level data differentiates this approach from study-level meta-analysis which combines aggregate-level data from a range of studies to provide a summary estimate(40). A body of literature addresses the comparative benefits and disadvantages of individual patient-level meta-analysis. Compared with meta-analysis of observational studies in the literature, Stewart et al(41) argue that a meta-analysis of individual patient data provides the least biased way of addressing questions that have not been answered by clinical trials. As the length of survival is of great importance in most chronic diseases, using individual survival times to estimate the overall relative benefit of a treatment is a particular advantage. Meta-analysis of individual level observational studies can also detect small effects which may not be evident in smaller sample sizes, notably in genetic epidemiology(42), or with limited follow-up.

The results from meta-analysis of individual-level observational studies may also be more directly relevant and applicable than results from trials(43). Clinical trials often exclude whole groups such as women or older individuals, or apply such strict eligibility criteria that their subjects differ from patients accessing public sector health services. On the other hand, the absence of randomization in observational studies may increase confounding, bias or both. Even when analyses have adjusted

for potential confounding, there may be residual confounding and increasing the sample size of an analysis may produce very precise but invalid estimates.

1.7 Conceptual framework of thesis

The provision of ART is not a single intervention. Individuals with HIV must pass through a care continuum to ensure optimal health outcomes. McNairy and El-Sadr(26) have identified four key steps in the HIV continuum (or cascade) of care: 1) HIV testing and linkage to HIV care, 2) engagement in pre-ART care with counseling, support and monitoring, 3) initiation of treatment as soon as ART-eligible and being retained in care, and 4) ensuring continued adherence and virologic suppression, with patients lost to care at each point(44,45). Pre-ART care plays an important role in ensuring good outcomes on ART, maintaining patient wellness and ensuring that patients start ART as soon as it is indicated. However most national HIV programs do not report retention during pre-ART care and services that collect data during the pre-ART phase report high levels of disruption of care(46). As the participating cohorts in IeDEA-SA do not generally collect pre-ART data, the first two steps are beyond the scope of this thesis, which focuses on outcomes after enrollment on ART.

1.8 Overview and structure of thesis

This Chapter introduces the topic of HIV/AIDS and antiretroviral therapy programs in resource-constrained settings. It includes the thesis problem statement, rationale aims and objectives. As the analyses were based on data from the IeDEA-Southern Africa Collaboration, the chapter also includes a description of the regional network and its processes for data center management and publication of papers.

Chapter 2 provides the background to the thesis in a comprehensive review of the literature on adult enrollment and outcomes on ART in South Africa published from 2000-2013. The review includes patient numbers and characteristics at ART initiation and gives a sense of the pace and magnitude of the national ART program scale-up. It identifies gaps in the literature which are subsequently addressed in the

empirical parts of the thesis. These include men's access to and outcomes on ART, mortality among patients transferred and LTF from ART, and the impact of age on ART enrollment and outcomes.

Chapters 3-7 present the empirical studies included in the dissertation. These map to the objectives, exploring and discussing the key research questions and findings. Broadly, the studies reflect the temporal nature of the ART program and of the thesis. Chapters 3 and 4 set the scene, describing the baseline characteristics and outcomes of adults starting ART and how these change over five years of enrollment. Chapter 3 relates to the first objective of the thesis and characterizes patients accessing public sector ART. It describes the characteristics at ART initiation of 20% of children and 10% of adults who started public sector ART nationally. It finds some improvement in these characteristics over five years of ART initiation, although many patients still start treatment with advanced HIV disease. The chapter highlights areas for further research including the impact of gender and age at enrollment on ART outcomes and is the motivation for much of the empirical section of the thesis. Chapter 3 highlights the challenge of missing data and finds that with scale-up, data on key variables including laboratory measurements are less complete. The chapter concludes by arguing for the establishment of sentinel surveillance sites to facilitate the collection of good quality data without unduly burdening staff at ART sites.

Chapter 4 addresses the second objective of the thesis, documenting strong temporal trends in mortality and LTF. With each successive year of enrollment and with duration on ART, mortality decreases but LTF increases and poses the major challenge to program effectiveness. The impact of baseline immunologic status, gender and age on outcomes are reported, for detailed exploration in later chapters. The chapter highlights the difficulty of long-term chronic care and the need to better understand the context-specific meaning of LTF. At the time of publication, this was the first report on outcomes from multiple cohorts in the world's largest ART program. To our knowledge it was the largest analysis of individuals starting ART at the time of writing.

Chapter 5 explores mortality after TFO and LTF in an attempt to minimize possible bias in mortality ascertainment, addressing objective 3. As the ART program continues to expand, it is increasingly important to transfer patients between facilities without resulting in poorer outcomes. However, due to inadequate monitoring systems little is known about the outcomes of patients after TFO or LTF in South Africa. Restricted to patients with ID numbers, this analysis traces the vital status of patients after TFO/LTF and finds that compared with patients retained, the mortality risk is similar among TFOs and three times higher in patients LTF. Thus censoring TFOs at the date of transfer may not bias mortality estimates but cohort analyses should correct mortality estimates for LTF to avoid bias, particularly where LTF rates are high.

Chapters 6 and 7 provide evidence on how age at ART initiation and gender impact on enrollment and ART outcomes. Chapter 6 explores the impact of aging in ART programs (Objective 4). Age is frequently reported as an explanatory variable but its specific impact is little understood. In a context of high HIV prevalence and good ART coverage, the proportion of older individuals living with HIV is set to increase dramatically yet there are few empirical data from South African sites to inform planning. Chapter 6 finds that increasing proportions of patients over 50 years of age are starting treatment and being retained in care each successive year, and that their outcomes are generally poorer than younger patients. There is a need to provide services tailored to older individuals with HIV and to extend epidemiologic measures beyond 50 years of age.

Chapter 7 addresses the explanations that are frequently cited in the literature for men's poorer survival than women on ART (Objective 5). During the analysis and writing of Chapters 2 & 3, it became clear that disproportionately more women than men were accessing ART. Concurrently, African cohorts had started reporting poorer outcomes among men than women on ART. Differential outcomes on ART were frequently attributed to men's poorer 'health-seeking behavior' resulting in later HIV diagnosis and initiation of ART. In addition it was suggested that men might be less adherent to ART and more likely lost to care. This paper assessed

whether the evidence supported these explanations and found that only delays in ART initiation explained any of the gender difference in mortality. Indeed, the gender difference in mortality among HIV-negative individuals was less than among HIV-positive people on ART. This was a new and important finding, highlighting the fact that people with HIV do not die of HIV-related causes only. Further, the paper focused attention on a broader issue of major public-health relevance - the invisibility of men's health(47-51).

Chapter 8 summarizes the empirical findings of the thesis and considers the public-health implications of the thesis. It concludes that the major challenges to the success of the ART problem are not related to clinical management or treatment adherence, but relate to the way in which the health system is structured and the ART program was implemented. The chapter makes recommendations for targeted, evidence-based prevention and intervention efforts to increase equitable enrollment and improve ART outcomes in the transition to a chronic care program.

1.8.1 Context of thesis

This thesis began in 2009 as an evaluation of the adult ART services in South Africa, explicitly focusing on program outcomes (Chapters 3-5). As it became clear that age and gender, two key socio-demographic variables, also impacted on ART outcomes, these became the subject of further detailed analyses (Chapters 6 and 7). My research thus forms part of, and contributes to the evolution of, the literature which is reviewed in the following section and is referred to as the IeDEA-SA analyses.

Chapter 2: Literature Review

2.1 Background

At the time when this thesis was initiated, there was a paucity of evidence on ART in developing countries. Given the fairly recent introduction of public sector ART, this was not surprising. As yet there is still no reporting at a national level on mortality, LTF or retention on ART in South Africa. Using empirical evidence, the thesis aims to describe and evaluate the effectiveness of South African ART program. The literature review contextualizes the thesis.

The review provides a clear picture of how the priorities of the program have changed over time as the epidemic response matured. The initial priority was to prove that it was feasible to enroll and retain patients on ART in a resource-constrained setting. Papers from two pilot projects describe intensive patient preparedness and follow-up and short-term outcomes comparable with those from developed countries. Later studies describe massive, rapid increases in enrollment in urban and rural settings nationwide from 2004 onwards. Following these are reports of longer-term outcomes including later mortality, immunologic and virologic response in the context of differential mortality ascertainment in large ART programs in developing countries. Important gaps in the literature include the outcomes of patients transferred out (TFO) and LTF compared with patients retained in care, and the impact of gender and age on ART outcomes, each the subject of a chapter in the thesis.

2.2 Aim and objectives

The objectives of this literature review are to review and discuss the published literature on adult characteristics at ART initiation and outcomes on treatment in South Africa from 2000-2013. Given that gender/sex and age are two of the basic determinants of population health, the review also explores published literature on their effect on outcomes on antiretroviral therapy in South Africa. The review

focuses on public sector programs but includes other studies reporting outcomes for example in the private sector. Specifically the review explores:

- The number and characteristics of adults initiating ART and temporal changes in these characteristics.
- Mortality and LTF among adults starting ART.
- Mortality among patients TFO and LTF compared with those retained at the ART enrollment site.
- Gender differences in enrollment and outcomes on ART.
- The impact of age on ART outcomes.

2.3 Search strategy

The Medline bibliographic database was searched using the PubMed interface (National Library of Medicine, Bethesda, MD). The following search strategy was used: "((antiretroviral therapy OR antiretroviral treatment) AND (South Africa) AND (mortality OR survival))". In additional searches the following terms were added: (loss to follow-up OR loss OR retention) AND (transfers) AND (sex OR gender) AND (aging OR ageing).

The inclusion criteria for the literature review were:

- The review included studies published in English between 2000 and 2013 that reported patient characteristics at ART initiation and/or outcomes (mortality, loss to follow-up and/or retention) of adults 16 years or older in South Africa.

The exclusion criteria for the review were:

- The review excluded articles from countries outside South Africa unless they were methodological.
- Studies undertaken prior to 2000 were excluded.
- Studies which included individuals who were HIV-positive but not on ART were not included.

- Clinical trials were excluded, as were studies that focused exclusively on the choice of treatment regimens and/or cost effectiveness.

Studies which included individuals not on ART were not included. In cases where there was more than one report from a cohort, the study containing the most detailed data and longest follow-up period was generally selected for inclusion in the tables. Short- and long-term outcomes were included for the two pilot projects and two other large cohorts, Free State Province and Themba Lethu clinic.

2.4 Results

2.4.1 Overview of included studies

2.4.1.1 Number of studies included

The search strategy generated over 600 studies, twenty-six of which fulfilled the eligibility criteria and are reviewed in detail below (Tables 1.1-1.3). These include short- and long-term reports from two pilot sites (Gugulethu and Khayelitsha, Cape Town) as well as individual cohorts, the IeDEA-SA and other multi-cohort collaborations (with some cohorts contributing data to different analyses), two provinces (Free State and Western Cape) and two health and socio-demographic surveillance system (SDSS) sites in Limpopo and KwaZulu Natal.

2.4.1.2 Characteristics of included studies

The characteristics of the eligible studies published between 2000 and 2013 are summarized in Table 1.1. Early reports from the pilot projects in Khayelitsha and Gugulethu, Cape Town include small numbers of patients and are clearly intended to support advocacy for a national ART program(28,52). They include minute details of patient selection, preparedness training, staffing, regimens, cost-effectiveness etc. The first paper from the IeDEA-SA collaboration describes changes in baseline

Table 2.1. Characteristics of studies included in the literature review and characteristics of patients at enrollment onto ART in South Africa.

Study	Cohort name	Cohort location & description	Enrollment dates	Adults on ART (n)	Female (%)	Median (IQR) CD4+ count (cells/µL)	Median (IQR) age (years)
Bekker et al, 2003(52)	Gugulethu	Urban township, Cape Town Pilot project in a primary care clinic	2002	62	NR	NR	NR
Lawn et al, 2006(53)		Death and non-death losses	2002-2005	927	76	100 (IQR 47-160)	33 (28-38)
Nglazi et al, 2011(54)		Seven-year experience of scale-up	2002-2008	3,162	67	87: 2002-04 121: 2007-09	2002-04: 34 2007-08: 35
Coetzee et al, 2004(28)	Khayelitsha	Urban township, Cape Town First pilot project in 3 primary care clinics	2001-2002	287	70	43	33 (29-38)
Boulle et al, 2010(55)		Project scaled-up to an ART service in three clinics		7,323	68	102 (44-164)	31 (26-36)
Nachega et al, 2006(56)	Aid for AIDS	Countrywide Private sector disease management program (DMP)	1999-2004	6,288	61	149	37
Johnson & McLeod, 2007(57)	N/A	DMPs, workplace (administered by DMPs) and community treatment programs countrywide	2001-2006	67,600	NR	NR	NR
Barth et al, 2008(58)	Elandsdoorn Medical Center	Rural Mpumalanga ART administered by general practitioners in a primary care clinic	2003-2006	609	71	67 (1-466)	35
Fairall et al, 2008(29)	Free State	Free State province 13 clinics, 4 treatment sites and 3 combined sites located in all districts	2004-2005	3,619	65	NR	35
Uebel et al, 2010(59)		Free State Four year experience	2006-2008	18,310	NR	2004: 89 2007: 124	NR
Boulle et al, 2008(21)	Western Cape	Western Cape Province 43 sites, mainly in primary care settings (includes Gugulethu, Khayelitsha)	2001-2006	14,123	70	NR	NR
Cornell et al, 2009(60-64)	IeDEA-SA	Multi-cohort collaboration, sites in Western Cape, Gauteng, Free State & KwaZulu Natal	2002-2007	45,383	68	102 (44-164)	35 (30-41)

Study	Cohort name	Cohort location & description	Enrollment dates	Adults on ART (n)	Female (%)	Median (IQR) CD4+ count (cells/µL)	Median (IQR) age (years)
MacPherson, 2009(65)	Rixile clinic	Tintswalo Hospital, Acornhoek, rural Limpopo	2005-2007	1,353	67	93 (37-148)	37 (31-45)
Sanne, 2010(35)	Themba Lethu	Helen Joseph Hospital, Johannesburg Public sector ART program based at Themba Lethu clinic	2004-2007	7,583	67	87 (31-158)	35: women 39: men
Fox et al, 2012(66)		Seven year experience	2004-2010	13,227	69	2004-05: 82 2008-09: 114	2004-05: 35 2008-09: 37
Bassett et al, 2010(67)	McCord & St Mary's Hospital	Durban & Mariannhill, KwaZulu Natal outpatient departments, two partly government-subsidized hospitals	2006-2008	538 ART-eligible	49	159 (65-299)	NR
Charalambous, 2010(68)	Aurum workplace program	Countrywide Anglo American-funded ART program providing free treatment and care for employees in 70 rural and urban sites	2002-2005	3,270	5	158	41 (36-47)
Russell, 2010(69)	Aurum community	Countrywide Multi-clinic community and GP program	2005-2006	1,350	60	83 (27-147)	36
Barth et al, 2011(58)	Ndlovu Medical Center	Rural Limpopo	NR	735	66	NR	NR
Boyles, 2011(70)	Madwaleni	Rural Eastern Cape	2005-2009	1,803	68	123 (55-184)	32 (27-39)
Klausner et al, 2011(71)	PEPFAR-supported ART sites	Countrywide ART programs supported by PEPFAR funding	2005-2009	631,985	65	NR	NR
Fatti, 2012(72)	Kheth 'Impilo	Multicenter cohort, 57 public sector clinics	2004-2010	66,953	70	127	35
Lim, 2012(73)	Platinum miners	Rustenburg, Northwest Workplace program	2003-2010	2,078	0	162 (89-240)	32
Fox, 2012(66)	Themba Lethu, Johannesburg	Helen Joseph Hospital, Johannesburg Seven year experience	2004-2010	13,277	69	2004-05: 82 2009-10: 114	2004-05: 35 2009-10: 27
Ahonkhai et al, 2012(74)	Southern African Catholic Bishops Conference (SACBC) network	Eight provinces Faith-based NGO providing community HIV care in 71 sites in rural, urban, peri-urban, squatter and mining communities.	2004-2008	11,397	67	101 (43-160)	35
Mutevedzi, 2013(75)	Africa Center Demographic Information System (Hlabisa)	Imkhanyakude rural district, Northern KwaZulu Natal Longitudinal demographic surveillance system monitoring patients initiating ART	2004-2011	4,674	71	129 (67-182)	34 (28-42)

characteristics and patient numbers over five years in eight large adult cohorts(64). Three subsequent studies report on early mortality as well as long-term outcomes up to seven years on ART in a context of rapid scale-up(53-55). Other studies reporting longer-term outcomes include the IeDEA-SA collaboration of sites in Western Cape, Gauteng, Free State and KwaZulu Natal(61), some of which also report on outcomes as individual cohorts. In addition, the review includes two studies from Themba Lethu, a public sector ART program based at a tertiary hospital in Johannesburg reporting shorter and long-term outcomes(35,66).

Four studies reported the outcomes of private sector ART. One was a report from Aid for AIDS, a private sector disease management program (DMP)(56). A more comprehensive study reported on private sector ART including 13 DMPs and 10 community treatment programs(57). One study describes two workplace programs, one in mines with numerous sites(76) and the other among male platinum miners in the Northwest province(73). Two large community programs are included: the Southern African Catholic Bishops' Conference ART program(74), a network of community-based treatment sites in a wide range of settings, and the Aurum community program, which offers care and treatment delivered largely by general practitioners(69). Bridging the gap between public and private sector ART, one study reports on patients at two partly government-subsidized hospitals in KwaZulu Natal(67).

Six papers provide insight into ART delivery in under-resourced and often extremely poor rural areas. Two studies are from demographic and health surveillance sites in Mpumalanga(77) and KwaZulu Natal(75). Others are reports from rural cohorts in Limpopo(58,65), Mpumalanga(78) and the Eastern Cape(70).

The review identified two provinces which have been able to report at a provincial level on enrollment and outcomes on ART. The Free State provided an early report on the effectiveness of public sector ART(29) and a subsequent report after four years of scale-up and a large increase in enrollment(59). Free State data were also included in the first IeDEA-SA collaborative paper. The Western Cape reported on

43 sites, mainly in primary care settings, including data from Khayelitsha and Gugulethu. Other large studies were from ART sites receiving PEPFAR funding(71) and the Kheth 'Impilo multicenter cohort including 57 public sector clinics(79).

2.4.1.3 Enrollment dates and number of adults initiated on ART

Before 2004, access to ART was largely through private sector programs. Aid for AIDS, the single largest DMP, started enrolling patients in 1999(56). By mid-2005, nearly 70,000 individuals had started ART through disease management programs, workplace and community treatment programs. Expansion was rapid in these programs, on average 32% growth in a single year and twice as fast in community programs(57).

Initiation onto public sector ART started slowly with small numbers of patients in Khayelitsha and Gugulethu in Cape Town. The Khayelitsha program was established in 2001 by MSF and the provincial government, and Gugulethu began providing ART in September 2002 with donor funding for 150 patients. In a context of high-level opposition to ART, these cohorts were trying to prove that it was feasible to offer ART in resource-constrained settings. Both sites reported small numbers initially and a huge increase in enrollment from 2004 onwards.

After the public ART program was formally launched in 2004, numerous sites reported a trend of rapid and sustained increase in enrollment. For example enrollment at Themba Lethu, Johannesburg, increased annually and by 2010 nearly 14,000 patients had initiated treatment(66). Similarly in eight South African sites of the IeDEA-Southern Africa collaboration, ART initiation increased 11-fold between 2003-2007, mostly in 2006-2007(61). The Western Cape enrolled around 1,000 patients/month, with over 16,000 patients having started ART in 43 mainly primary care sites(21). Reports from the PEPFAR-funded sites in South Africa provide additional insight into the scale of ART initiation and expansion(71). From 2005-2009, the rate of ART initiation in these sites increased nearly four-fold. By

September 2009, an estimated 631,985 patients were still on ART in these facilities, an 18-fold increase from 2005.

2.4.1.4 Gender and baseline immunologic status

Two notable features of the literature are the consistent gender distribution and improving immunologic status at enrollment over time. Almost all of the cohorts were predominantly female. The exceptions were workplace programs in mines with male employees(68,73) and a study in hospitals which charged a user fee for services, which might have restricted women's access to ART(67). All studies reported a similar temporal pattern in baseline CD4+ cell count: extremely low in the first year of ART enrollment and increasing with calendar year of enrollment. Predictably the lowest median CD4 count was in Khayelitsha, the oldest cohort, with a range from 43-131 cells/µL over different calendar years(55). Similar temporal patterns were also reported by the Free State Province, IeDEA-SA and two public sector clinics(29,54,61,66). Generally patients in private sector programs(56) started treatment at higher median CD4+ cell counts than those entering public sector ART.

2.4.1.5 Age at ART initiation

There was little variability in age among patients starting ART, the majority being 34-35 years of age in urban and rural sites. Patients were slightly younger in a rural site in the Eastern Cape(70) and a platinum mine in Northwest and slightly older in a workplace program, median age 41 years(73). There was no clear temporal pattern of increasing or decreasing baseline age. Themba Lethu cohort reported that patients were enrolling at younger ages over time, with a median age of 27 years in those enrolling 2009-2010. In contrast, in the IeDEA-SA analysis (which included Themba Lethu data), there was a trend towards increasing age at enrollment(61).

2.4.1.6 Pace of ART scale-up

Despite increasing enrollment, there were concerns about delays in initiating ART among patients who were eligible. Two years after eligibility in the Free State, 68% of patients had started ART and 26% had died prior to initiation(80). Similar

concerns were highlighted in a study in Durban hospitals, where only 39% of ART-eligible patients started treatment within 12 months(67).

2.4.1.7 Estimation of ART need and coverage

Estimation of ART need and coverage presents many challenges, particularly in the light of changing guidelines on ART. In the first place, estimates (including those of UNAIDS) regularly refer to the number of people *on ART* instead of the number who *have started ART*. In reality we are unable to report at a national level the number of individuals who are still on treatment, having not died or been LTF. The issue is further complicated as coverage is a cross-sectional measure, defined as the number of people receiving ART at a particular time divided by the number of people eligible to receive ART at the same point, including patients already receiving treatment(81). This measure may be too sensitive to ART eligibility criteria and annual enrollment. For example, in 2012 South Africa was one of ten African countries that reported reaching over 80% of adults eligible for ART, based on 2010 WHO guidelines. However new guidelines issued in 2013 once again increased the number of people in need(82). In an alternative longitudinal measure of program performance proposed, the denominator is the number of people becoming eligible for treatment in the same year based on the current ART guidelines(81).

2.4.1.8 Conclusion

In summary, this review found evidence of a sustained increase in enrollment in many single and multi-site urban and rural cohorts across the country since 2004. The improving baseline immunologic status suggests improved coverage. Men's disproportionately lower access to ART is a clear gap that needs urgent attention. Waiting times remain a challenge.

2.4.2 Mortality in ART programs

This literature points to three distinct phases in mortality in ART programs in South Africa: undocumented pre-treatment deaths, early (within the first three to four months on ART) and late mortality (after four months). Although outside the scope

of this literature review, mortality prior to ART initiation is extremely high, reflecting the high burden of untreated HIV in the community. For example, in Gugulethu mortality pre-treatment was 36/100 person-years(83). Despite increased access to ART, many patients still start ART with advanced HIV infection resulting in elevated mortality in the first three or four months on treatment. After a few months on ART, patients stabilize and mortality drops steeply. Both calendar year of enrollment and duration on ART impact on mortality. Mortality is high among LTF patients, and correction via linkage to the National Population Register (detailed below, section 2.5.3) almost doubles mortality estimates. A body of literature addresses the underlying issue of mortality ascertainment in large cohorts of patients, particularly in developing countries.

2.4.2.1 Mortality during early ART

Mortality rates were extremely high during the first few months on ART (Table 1.2). Reporting on the first two years on ART, 71% of deaths in the Khayelitsha pilot site took place in the first three months on treatment(28) and in the Gugulethu pilot site, the rate for early mortality was 19/100 person-years (pyrs)(53). Even higher rates were reported by the Aurum community program delivered by community-based general practitioners(69), the large urban Themba Lethu clinic(66) and a rural program(65). There was some evidence to suggest that as the program matured, rates of early mortality dropped. For example in the Western Cape, mortality at six months on ART dropped from 13% in 2001 to 7% in 2006(21).

2.4.2.2 Mortality during later ART

Once patients were stable on ART, mortality dropped dramatically. After the initial peak in the first few months on ART, mortality rates were far lower and ranged from 3/100 pyrs in Gugulethu(53) to 9/100 pyrs in a workplace program(76). With successive years of enrollment too, mortality dropped(61). Evidence that ART was impacting on overall mortality was reported from Agincourt, Limpopo, where an all-cause mortality rate of 8/1,000 pyrs resulted from a higher rate of 13/1,000 pyrs before ART followed by a sharp decrease in mortality after 2004(77). Duration on

Table 2.2. Studies reporting mortality on ART in South Africa, 2000-2013.

Study	Cohort name	Enrollment dates	Mortality incidence rate/proportion
Coetzee, 2004(28)	Khayelitsha	2001-2002	71% of mortality (0-3 months) 86% survival at 24 months
Boulle, 2010(55)		2001-2007	21%: corrected mortality, 5 years on ART
Lawn, 2006(53)	Gugulethu	2002-2005	19/100 pyrs: early deaths (0-4 months) 3/100 pyrs: later deaths (>4 months)
Nglazi, 2011(54)		2002-2008	11% after seven years
Nachega, 2006(56)	Aid for AIDS	1999-2004	4% crude
Fairall, 2008(29)	Free State	2004-2005	aHR 0.14, 95% CI 0.11-0.18: ART vs. no ART
Boulle, 2008(21)	Western Cape	2001-2006	13%: 0-6 months, 2001 7%: 0-6 months, 2005
Barth, 2008(78)	Elandsdoorn medical center	2003-2006	19%, especially in first few months
MacPherson, 2009(65)	Acornhoek	2005-2007	20/100 pyrs: 0-6 months 8/100 pyrs: 6-12 months 3/100 pyrs: 12-24 months
Cornell, 2010(61)	IeDEA-SA	2002-2007	9%: 12-months, 2002-03 cohort 6%: 12-months, 2007 cohort
Russell, 2010(69)	Aurum community	2005-2006	24/100 pyrs: 0-3 months 13/100 pyrs: 3-9 months 6/100 pyrs: >9 months
Charalambous, 2010(68)	Aurum workplace	2004-2007	9/100 pyrs: overall 4 vs. 11/100 pyrs: unadjusted, IPT vs. no IPT
Barth, 2011(58)	Ndlovu Medical Center	NR	23%, mostly 0-3 months
Boyles, 2011(70)	Madwaleni	2005-2009	11%
Fatti, 2012(72)	Kheth 'Impilo	2004-2010	aHR: 0.65, 95% CI 0.59-0.72: adherence support vs. none
Fox, 2012(66)	Themba Lethu	2004-2010	24/100 pyrs: month 1 5/100 pyrs: month 12 4/100 pyrs: overall
Ahonkhai, 2012(74)	SACBC	2004-2008	10%: 12 months on ART 11%-7%: early deaths, 2004-08

ART influenced mortality in the Aurum community program, where the mortality rate dropped from 13/100 pyrs for patients three to nine months on ART to 6/100 pyrs for patients who had been on treatment for over nine months(69). Mortality corrected via linkage to the National Population Register was generally about twice observed mortality recorded by sites. For example, Gugulethu and the SACBC network reported approximately 10% uncorrected mortality(54,74) while Khayelitsha reported corrected mortality of 21% after five years of ART(55).

Interestingly, estimates from two rural sites(58,78) were close to corrected mortality, suggesting that in rural areas mortality ascertainment may be better than in large, highly mobile urban sites. The lowest mortality was reported by Aid for AIDS (56), one of the first private sector programs to enroll patients.

2.4.2.3 Mortality estimation

Numerous studies over the past ten years have addressed the complex issue of mortality estimation, particularly in developing countries(84-88). Many countries with rapidly expanding ART programs lack functioning vital registration systems. Reliable ascertainment of death is difficult under these circumstances, particularly as LTF is often high in these programs. In contrast, South Africa's National Population Register reportedly captured 94% of deaths in the period 2007-2011(89). Through linkage of their databases to this Register, some of the IeDEA-SA sites are able to report mortality corrected for deaths previously misclassified as LTF, TFO or alive.

High mortality among patients LTF has been well documented, particularly in programs with high levels of LTF(84). In the past few years, a number of studies from outside South Africa and within have attempted to correct for mortality among LTF patients using different approaches. Using a sampling-based approach in Uganda, the cumulative mortality incidence at one year increased from 2% to 8%(88). Studies in South Africa used patients' civil identification (ID) numbers to link to the National Population Register and ascertain the vital status of LTF

patients(55,63,75,90,91). After linkage, for example, mortality on ART in Themba Lethu cohort more than doubled from 4% to 11%(90). In Khayelitsha, correction for mortality reversed the direction of LTF, which was then found to have increased over time(91). In five ART programs in sub-Saharan Africa, crude estimates of mortality at one year increased from 6-11%, while estimates adjusted for excess mortality in patients LTF ranged from 10-17%(84). On the basis of this multi-cohort study, Egger et al developed a nomogram to correct mortality estimates in sub-Saharan Africa for LTF(92). The nomogram provides a correction factor based on the proportion of patients LTF and the estimated ratio of mortality between patients LTF and retained and is a simple method to correct potential bias in mortality estimates.

2.4.2.4 Conclusion

The literature describes an evolution in mortality outcomes in ART programs. The first few months of extremely early mortality are followed by a decrease and stabilizing of mortality rates. There was some suggestion that mortality rates decrease with each successive year of enrollment. Overall, uncorrected mortality is about 10% and correction for mortality in LTF patients generally doubles this estimate, with uncorrected estimates from rural areas approximating corrected mortality.

2.4.3 Loss to follow-up and program retention

This review found that LTF increases with each successive year of enrollment and with duration on ART. LTF poses a challenge to ART program effectiveness. Once patients leave care they are at increased risk of morbidity and mortality, generally within the first few months after being LTF(84,93). Even if they re-engage in care at a later stage, their outcomes are generally worse than those who are retained(94). Given the magnitude of LTF, there is a growing body of research on different methodological approaches to ascertaining mortality among LTF with a view to standardizing a definition to improve evaluation within and between

Table 2.3. Studies reporting loss to follow-up and retained on ART in South Africa, 2000-2013.

Study	Cohort name	Definition of LTF	LTF rate/percentage	Percentage retained
Boulle, 2008(21)	Western Cape	90 days without a clinical visit	0.4%: 6-month, 2002 5%: 6- month, 2005	76%: 4 years on ART
Boulle, 2010(55)	Khayelitsha	6 months without a clinic visit	23% (95% CI 20-27)	65% uncorrected, 65% uncorrected, 80%: 5 years corrected
Cornell, 2010(61)	IeDEA-SA	No contact with clinic >6 months before database closure	1%: 12- month, 2003 13%: 12- month, 2006 29%: 36 month cumulative	80%: 2 years 64%: 3 years
Boyles, 2011(70)	Madwaleni	No patient contact >6 months before study end	11%: 48 month	82%: 4 years
Nglazi, 2011(54)	Gugulethu	No clinic visit for ≥12 weeks & not died or transferred	19% overall	60%: 7 years
Fatti, 2012(72)	Kheth 'Impilo	No clinic visit for ≥180 days	13 vs. 17%, adherence support vs. none, 5 years on ART	79 vs. 74%: adherence support vs. none
Ahonkai, 2012(74)	Southern African Catholic Bishops Conference	No follow-up visits 30-400 days after ART initiation	20%: enrolled 2004 14%: enrolled 2008	60%: 1 year
Fox, 2012(66)	Themba Lethu	≥3 months late for a scheduled visit Mortality among LTF corrected	4%: 2004/05, lost in 1 year 12%: 2009/10, lost in 1 year	76%: 1 year 38%: 7 years
Mutevedzi, 2013(75)	Africa Center Demographic Information System (Hlabisa)	180 days since last visit. Disengagement defined as LTF adjusted for mortality.	12% LTF 10% disengaged	61%: 5 years

programs(84,87,88,90-92,95,96). Some later studies correct for mortality among LTF while others report crude LTF estimates, generally inflated due to misclassified deaths. In contrast with LTF, retention on ART has not received much attention to date. Although retention in ART programs in SSA was the subject of two systematic reviews, most South African studies include retention as a secondary outcome only. This review found estimates of long-term retention in large urban and rural ART programs ranging from 60-80% up to seven years of ART. Retention was higher in a rural cohort and in a study which compared retention with adherence support versus none.

2.4.3.1 Definitions of loss to follow-up

Although cohorts routinely report on LTF, the variability in definition is notable. A number of studies have attempted to identify the most efficient definition of LTF. Chi and colleagues used an empirical approach and found the best-performing LTF definition was ≥60 days after a missed visit(97). Within the South African cohorts, a variation in the definition of LTF impacted on the estimated proportions of LTF. The LTF definition currently used by IeDEA-SA analyses was found to be the most conservative definition(98), minimizing misclassification. In general retention was defined as the total number of patients who initiated ART minus the total number of patients lost to the program (Figure 2.1). Some studies treated TFO patients as retained, others excluded TFO patients as their outcomes were unknown.

Figure 2.1. Definition of retention.

2.4.3.2 Estimates of loss to follow-up and retention

Most studies reported on the proportion of patients LTF and/or retained on ART, often at different time points and by calendar year of enrollment. The lowest reported LTF was in rural cohorts(70,75). In the Eastern Cape, for example, only 11% of their cohort was LTF after four years on ART and a similar proportion in Hlabisa. The Hlabisa cohort corrected for mortality among LTF, differentiating between LTF and disengagement (LTF corrected for death). In contrast the highest proportions LTF were reported in the IeDEA-SA collaboration(61), possibly as the study used the most conservative definition of LTF(98) and did not correct mortality for LTF. While it is possible that the challenges of retaining patients may be less in rural than urban areas, it is also plausible that rural sites are better able to ascertain deaths, and hence may not overestimate LTF. Two studies which reported mid-range estimates were both from sites offering some form of adherence support, which may have increased the probability of remaining in care(72,75). Estimates from these studies are in line with the weighted average from a systematic review in SSA(99).

There were strong temporal trends in LTF which increased with successive year of enrollment and with duration on ART. The first study to identify this trend was from the Western Cape, which reported that six-month LTF increased from 0.4-5% in patients enrolled in 2002 and 2005(21). Temporal trends in LTF were explored in detail in the IeDEA-SA analysis, which documented 12-month LTF increasing annually from 1-13% between patients enrolled in 2003 and 2006(61). Subsequently Themba Lethu reported a similar trend, with LTF three times higher among patients enrolled in 2009-2010 compared with those enrolled in 2004-2005(66). These results suggest that as a program increases in size, LTF may become an increasing challenge to effectiveness.

Not all cohorts demonstrated this phenomenon, however. The SACBC study reported the opposite trend, with lower LTF among patients enrolled in 2008 compared with 2004. This study explored one year outcomes in a large community program differentiating between LTF (liberally defined as 30-400 days without a

visit) and interrupted laboratory monitoring (ILM), where a patient may have been missing laboratory measures for an extended period but returned to care within the window period. If they had excluded patients with ILM, the LTF proportion would have increased from 17 to 28%, highlighting the difficulty of comparing outcomes across programs without standardizing a definition of LTF. The program also used the existing care network between the church and communities to identify treatment defaulters and support return to care, suggesting a different dynamic from that operating in public sector programs.

While measures of LTF provide insight into programmatic challenges, some suggest that retention is the best metric for evaluating long-term effectiveness as it includes all losses to program(21,99). Two systematic reviews highlight the challenge of retaining patients in large, rapidly expanding African programs(99,100). The first review included studies from 2000-2007 with limited follow-up and caused widespread concern when it reported the weighted average retention after 24 months in African ART programs was 62%(100), with individual estimates reporting 24-month follow-up ranging from 46-85%. A subsequent update reported 72% retention after 36 months, declining to 65% after adjusting for variable follow-up time(99). In this literature review a number of sites reported similar proportions retained for durations of ART up to five years(54,61,75). Estimates from the IeDEA-SA and Gugulethu cohorts may have been higher if they had been able to correct for misclassified mortality. Such correction increased retention estimates in the Khayelitsha cohort from 65-80% at five years(55). It is notable that this corrected estimate was similar to the retention reported by the rural Madwaleni cohort, which had the highest proportion of patients retained(70), suggesting that rural cohorts may be better than urban cohorts at ascertainment of vital status and retention of patients.

2.4.3.3 Conclusion

Generally there was strong evidence that LTF increases with each successive year of enrollment and with duration on ART. Over time LTF has emerged as a greater

challenge to program effectiveness than mortality but lack of a standardized measure makes it difficult to compare between programs. Community-based and rural programs utilizing existing networks may be better equipped to retain patients in care than public sector programs.

2.4.4 Virologic responses and adherence to ART

In order for ART to be effective HIV must be suppressed below detectable levels, referred to as viral suppression. The level at which viral load can be detected has decreased with improvements in laboratory assays from 400 cells/μL to 50 cells/μL. Viral suppression is generally regarded as a proxy for individual adherence to treatment in the absence of accurate adherence measures. Where adherence is reported, it is based on pill counts, pharmacy records and/or patient recall.
In those patients retained and alive with viral loads, virologic outcomes were excellent up to seven years on ART. This could be interpreted as a reflection of good adherence to ART among patients retained in a program. However this finding should be tempered by a) the proportion of missing viral load measures, and b) the possibility that patients who had viral loads measured may be different from patients who did not.

2.4.4.1 Estimates of adherence and viral suppression

In a context of high-level concern about whether Africans could successfully take ART(101), two studies from pilot sites addressed the issue of adherence at an early stage. Gugulethu reported 94% median adherence among some of the earliest patients on ART(102). Adherence was better among patients who spoke the same language as site staff, and with simplified dosing. In Khayelitsha, 70% of patients achieved undetectable viral loads after 24 months on ART(103).

With duration on ART, good virologic outcomes were sustained in a range of settings. For example, 80-90% of patients were virologically suppressed up to seven years in large cohorts in Themba Lethu, Khayelitsha and Gugulethu(35,54,55). A large private sector program also provided evidence of good virologic suppression,

with 80% suppressed over five years of ART(56) while 84% of rural patients with more than three months follow-up were virologically suppressed after two to four years on ART(58).

Any interruption in care resulted in poorer outcomes. The SACBC network of treatment clinics reported a 30% increase in detectable viremia among patients who had interrupted care compared with those retained(74), confirming that virologic outcomes are poorer among patients who interrupt or are lost to care(94).

2.4.4.2 Conclusion

The literature describes good virologic responses to ART among patients with viral load measures, sustained up to seven years of treatment.

2.4.5 Immunologic responses to ART

Immunologic responses are an important measure of the effectiveness of ART(104). Previous studies have established that immunologic response is strongly predicted by CD4+ cell count at ART initiation and that there are gender differences in baseline and subsequent CD4+ cell counts. In general despite low baseline CD4+ cell count this review found a consistent increase in immunologic response up to five years on ART, with women responding better to ART than men.

2.4.5.1 CD4+ cell count increases from baseline

Although reported baseline CD4+ cell counts are low, immunologic response was generally good among patients with available laboratory measures. In Khayelitsha, for example, where patients started with the lowest median CD4+ cell counts, median increases at 12, 24 and 36 months of ART were 192, 282 and 341 cells/µL respectively(55). Similar immunologic responses up to three years are reported by Themba Lethu(66) while in Gugulethu after 48 weeks on ART, the proportion of patients with a CD4+ cell count <200 cells/ µL proportion dropped to 21%-31%, depending on the year of enrollment(54). Even patients in a rural ART program responded well to ART, with a median increase of 236 cells/µL after 24 months(78).

These responses are better than those in a large collaborative analysis of patients in SSA, Latin America and Asia with a median baseline CD4+ cell count of 114 cells/µL, which reports median increases from baseline of 147, 189 and 258 cells/ µL in the same time periods(104).

Several investigators found gender differences in baseline CD4+ cell count and in immunologic responses. In the IeDEA-SA cohort, women started ART at higher CD4+ cell counts (110 vs. 85 cells/µL) and had better immunologic responses than men(63). These findings are in line with results from four ART programs in SSA These gender differences may partly explain why the poorest immunologic responses are from a predominantly male workplace program, which reports median increases from baseline of 90, 113 and 164 cells/µL at 6, 12 and 24 months(68).

Two rural cohorts also reported good immunologic responses despite patients having started ART at low CD4+ cell counts. Patients who initiated ART in Mpumalanga at a median CD4+ cell count of 67 cells/µL had a median gain of 297 cells/µL after 12 months on treatment(78). Reporting longer term outcomes in Ndlovu cohort, 87% of patients had good immunologic responses over two to four years(58). These studies provide evidence that ART is effective even when patients start treatment with severely compromised immune systems.

2.4.5.2 Conclusion

In general, despite poor baseline immunologic status, patients in these cohorts appear to have had good immunologic responses on ART, sustained over three years. Women had higher baseline CD4+ cell counts and slightly better immunologic responses.

2.4.6 Mortality among patients transferred and lost from ART

As ART programs continue to scale-up, it is essential that sites transfer patients efficiently to ensure uninterrupted linkage to care for optimal outcomes. Patients

have been transferred between ART facilities in South Africa for some years yet almost nothing is known about their outcomes after TFO. Indeed only one paper specifically explored TFO as an outcome (105) while most papers simply reported the proportion TFO. In Gugulethu cohort, 13% were TFO over seven years and the probability of TFO increased with each successive year of enrollment. The IeDEA-SA study reported a range in the proportions TFO and increased mortality directly after TFO and LTF compared with patients retained(62). Excluding this elevated mortality, the risk of death was similar in patients TFO and retained, but LTF patients had three times the mortality of those retained in care.

2.4.6.1 Definition of transfer out

Studies reported TFO as recorded by sites(63). Generally TFO was regarded as different from referral, which could include up-referral to a higher level of care for patients who require more specialized management and down-referral of patients who are stable on ART and whose treatment could be managed with less expertise. As these groups of patients are very different, outcomes of such patients could be expected to differ. In the IeDEA-SA cohorts patients were TFO for convenience, relocation to another geographic area or at the patient's request, reason unknown. Patients were regarded as TFO from Hlabisa rural cohort if they had formally transferred care to another facility(75).

2.4.6.2 Estimates of transfer out

On average about 10% of patients had TFO over four years(70) or longer periods of follow-up(63,66). The lowest proportion was reported by Hlabisa rural cohort (6%)(75) while in Gugulethu cohort 13% had TFO over seven years(105). In addition the probability of being transferred by one year on ART increased substantially from 1% to 9% among patients enrolled in 2002-2004 compared with 2009, with an overall rate of 5/100 pyrs (95% CI 4-5).

2.4.6.3 Analytic approach to transfer out

Most studies censor patients' observation time at the date of TFO(55,63,66) or at the date of last clinic visit(75). This analytic approach assumes implicitly that mortality after TFO is similar to mortality among patients who are retained in care. If this is not the case, differential outcomes after TFO may bias mortality estimates on ART(62). The IeDEA-SA study was undertaken in response to the lack of literature on TFO and outcomes thereafter(62). In this study, the mortality hazard was three times higher among TFOs than among patients retained (aHR 3.11, 95% CI 2.42-3.99). Excluding deaths within three months after TFO, the mortality hazard was comparable in TFOs and patients retained (aHR 0.75, 95% CI 0.54-1.03). In these cohorts, the low incidence of TFO and subsequent death meant that censoring TFOs did not bias mortality estimates. However in cohorts which TFO a large proportion of patients, it is important to understand their mortality after TFO in order to avoid biased estimates.

2.4.6.4 Conclusion

This literature review has identified one of the major gaps in our understanding of ART services. With poor monitoring systems, little is known about mortality after TFO compared with patients retained at the site of ART initiation. Future cohort analyses should explicitly consider the proportions TFO and mortality event rates when exploring whether their estimates are biased.

2.4.7 Age in ART programs

This review found that although most studies report age as a baseline covariate, little is known about its specific effect in ART programs in South Africa. Both HIV and ART impact on the body's aging process, appearing to mimic the effects of natural aging(106-110), possibly through acceleration (hastening premature aging) or accentuation (increasing the incidence of morbid co-infections)(106). This accelerated or accentuated aging is compounded by long-term toxicity of ART and interactions with co-medications for other age-related conditions. In recent years it has been suggested that aging may occur faster with AIDS in Africa(111) and that

ART may change the age composition of the HIV epidemic in sub-Saharan Africa(112). Despite the importance of age in ART programs, this review identified only two papers explicitly assessing its effect(113,114). Further research is needed to understand and plan for the impact of age on ART outcomes.

2.4.7.1 Definition of age

A striking feature of the literature reviewed on age and ART is that most epidemiologic measures related to ART use end at 49 years of age. Surprisingly, there is also no universal definition of 'old', 'older' or 'elderly'. The United Nations defines older as being older than 60 years, based on retirement ages in most developed countries. However, as most old persons in sub-Saharan Africa live in rural areas and do not work in formal sector employment, the World Health Organization (WHO) has accepted ≥50 years as a working definition for the Minimum Data Set Project on Ageing(115).

2.4.7.2 HIV prevalence and ART initiation among older individuals

HIV prevalence in older ages is generally underestimated. HIV prevalence estimates are derived from antenatal clinic surveillance (limited to women of child-bearing age), nationally representative household surveys limited to individuals <50 years with a few unrepresentative samples of men up to 60 years and targeted surveys within specific groups. In the absence of data on older individuals, Negin et al reported the most conservative estimates of approximately 7% in patients aged 55-59 years and 3% in those aged 60-64 years(116). The 2012 South African Household Survey reported higher levels, notably 10% among females aged 55-59 years(117). The highest estimates were from two rural demographic surveillance sites. In Hlabisa, older prevalence peaked at ages 50-54 years (30% vs. 17%, men vs. women)(118). In the Agincourt rural site, peak prevalence occurred later and was higher than in Hlabisa: in patients 55-59 years, prevalence peaked at 27% for females and 35% for males(119). The study also documented prevalence above 10% through to 70 years of age and even reported prevalence among individuals over 80 years old. These results suggest that there may be a high burden of undiagnosed

HIV in older individuals. Information on ART initiation among older adults is similarly scarce. The 2012 National HIV Survey estimated that 1.6 million adults 15-49 years old had ever initiated ART, but did not report any statistics for individuals ≥50 older(120). Given the aging of the world, and in particular the aging of the HIV epidemic, it is essential that epidemiologic and ART data are collected on older individuals.

2.4.7.3 Outcomes of older individuals on ART

Prior to ART, the two major determinants of survival in Europe, North America and Australia were age at, and time since, seroconversion(121). In recent years numerous papers have focused on ART outcomes among older individuals in developed countries. Although this review will not cover these papers, it may be useful to have a sense of their scope. Broadly these articles explore the long-term impact of both HIV and ART on the body's natural aging process, the additional burden of co-morbidities common with increasing age as well as opportunistic infections common with HIV, long-term toxicities of ART and potential interactions with medications for co-morbidities(106) (Figure 2.2). Current debates center on

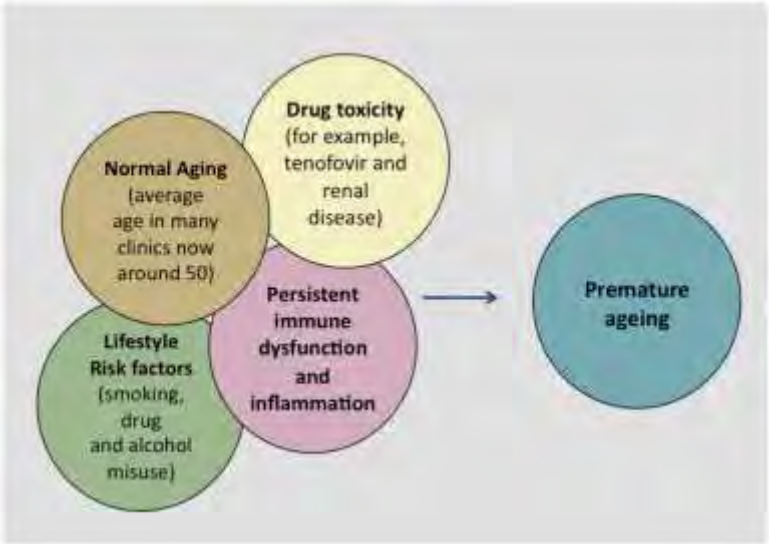


Figure 2.2. Among patients who successfully suppress HIV, a range of factors may be causally associated with premature development of aging-related complications

Adapted with permission from: HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity, Steven G Deeks & Andrew N Phillips, BMJ 2009; 338:a3172

whether HIV and ART accelerate or accentuate the aging process i.e. whether the aging process occurs faster or co-morbidities are more frequent(122). (See also Supplementary Figures S2.1 and S2.2, acceleration and accentuation.)

Within South Africa, age is routinely reported as an explanatory variable. Two published studies and one in press have explored the issue in more depth(60,113,114). In Hlabisa rural cohort, 10% of patients on ART were older than 50 years of age with an overall mortality rate of 9/100 pyrs compared with 6/100 pyrs among 16-24 year old patients(114). After one year on treatment, there was no significant difference in mortality rates by age. Immunologic response was poorer among older patients. Despite higher baseline immunologic status in older patients, the proportion who failed to increase ≥50 cells/μL in the first six months was highest in those aged ≥50 years (20 vs. 11% in 16-24 year olds). Conversely virologic response was better in older than young patients (90 vs. 82%). Themba Lethu also reported poorer ART outcomes with increasing age(113). There was a dose response in the impact of age on mortality and after twenty four months on ART. Patients aged 60 years and older had nearly twice the adjusted hazard of patients 18-29 years old (aHR 1.74, 95% CI 1.00-3.03). In contrast the risk of LTF decreased with age. As was reported in Hlabisa, immunologic responses were poorer and virologic responses better in older than younger patients.

Chapter 6 is an attempt to address the current gap in the literature on age in ART programs in South Africa(60). In a study of over 80,000 patients, increasing proportions of older patients started ART and were retained in care each successive year of enrollment. Mortality increased with age at enrollment up to two years of ART, after which only patients 50 years or older at enrollment had an increased risk compared with patients 16-29 years. Baseline immunologic status was similar across all ages, and modified the effect of age on mortality. Over time, immunologic responses were diminished in older individuals.

2.4.7.4 Conclusion

There is a surprising dearth of studies on the effect of age in ART programs in South Africa. Estimates of prevalence on older individuals are variable and epidemiologic measures generally stop at 50 years of age. Mortality increases with age on ART up to two years.

2.4.8 Gender in ART programs

Gender differences in access to and outcomes on ART appear to be context-specific. Studies from developed countries document poorer access and outcomes for women, while those from Southern Africa report the same for men. Differences in patterns of health may be attributed to sex or gender, i.e. biological influences or social factors which may be different for men and women. Given the numerous ways in which biologic and social factors overlap, this review uses the term gender to encompass both. As there are few publications on gender and ART in South Africa, key studies and reviews from elsewhere have been included.

2.4.8.1 Gender and access to ART

Women have had better access to ART than men in Southern Africa. In 2007, Muula et al reported that disproportionately more women than men were accessing ART in Southern Africa, even after taking into account the slightly higher prevalence in women(123). In this review, 60-70% of patients were female. This is in line with results from a meta-analysis of twenty-three African cohort studies which reported a pooled proportion of 35% of men receiving ART(124). It has been suggested that men might be the 'losers of the antiretroviral treatment scale-up'(125) while others have argued that there is a blindness towards men's health, particularly in ART programs(47,50,63).

Three studies enrolled more male than female patients. Two studies with predominantly male enrollment were undertaken in workplace programs for male miners. The third study took place in two KwaZulu hospitals and reported almost equal proportions male and female on ART(67). Patients in this study were charged

a subsidized fee for services. As unemployment is higher among women than men in South Africa(126), having to pay for services may have restricted women's access in this study. Notably, despite almost equal gender balance in enrollment, men were still less likely than women to start ART.

In a range of studies from resource-constrained settings, women started ART at younger ages and with less advanced HIV infection than men. The IeDEA-SA collaboration confirmed these findings(63). Women had a median age of 33 vs. 38 years, higher baseline CD4+ cell counts (110 vs. 85 cells/µL) and a smaller proportion in WHO stages III/IV (77% vs. 86%) than men. These results conflict with review findings that men in the USA and Europe initiated ART at an earlier stage of infection than women(127), suggesting that gender differences in access to ART may be context-specific.

2.4.8.2 Gender and mortality on ART

In South Africa, men had higher mortality on ART than women. Two studies specifically explored the impact of gender on ART outcomes(63,128). In the IeDEA-SA analysis, men were 31% more likely to die than women over 36 months on ART(63). Although the hazard ratios for the site of ART initiation ranged from aHR 1.15 to 1.68, male mortality was consistently higher in all eight cohorts. After adjusting for men's later initiation on ART, the observed gender difference in mortality persisted and appeared likely due to gender differences in mortality in the South African population unrelated to HIV/AIDS or ART. Even within a virally suppressed group of patients, men had higher mortality and poorer immune responses than women(128).

2.4.8.3 Conclusion

There is a dearth of studies on gender and ART in South Africa. This review found that disproportionately fewer men than women access ART in South Africa. Men start ART at older ages and with more advanced HIV disease than women and their immunologic responses are poorer. Gender differences at enrollment account for

some of the increased mortality among men. However men's increased mortality on ART may also reflect men's elevated mortality risk regardless of HIV and ART. There is a need for a greater focus on men's access to, and outcomes on, ART.

2.5 Discussion

The literature reflects the evolution of our knowledge of ART cohorts and cohort analysis. Studies track the remarkable expansion of antiretroviral services in South Africa over ten years from a series of small, closely-managed pilot sites to the largest ART program worldwide. Early outcomes are comparable with those of patients initiating ART at low CD4+ cell counts in the developed world. From 2004 onwards, there are massive increases in enrollment, with good outcomes up to seven years after ART initiation. High early mortality in the first few months on ART reflects the burden of untreated HIV in the community. After this peak, mortality drops steeply to approximately 10%, with corrected mortality about twice this. Immunologic and virologic responses are good. One of the main challenges to program effectiveness is LTF, which increases with each calendar year and with duration on ART. In general women have better access to, and outcomes on, ART than men. Only one study explicitly addresses the outcomes of patients TFO and LTF, highlighting a clear gap in the literature. Aging and male gender are associated with poorer outcomes on ART and are also under-researched in South Africa.

This review also highlights a number of cross-cutting themes in the literature which impact on enrollment and outcomes on ART. These include the variability in definition and measurement of outcomes, the challenge of missing data, the location of ART services (rural vs. urban), public compared with private ART services, and the study period (both calendar year of enrollment and duration on ART).

2.5.1 Definition and measurement

Variability in the definition and measurement of outcomes impacts on estimates and renders comparisons within and between programs difficult. For example, mortality was either observed (site-recorded) or corrected, which was about twice observed mortality. Thus a comparison between programs that estimate or report mortality in different ways might be meaningless. In another example, LTF was defined as anything from 30 to 400 days late for a visit. In the study, redefining as LTF those patients who had interrupted laboratory monitoring but subsequently returned to care would have increased the LTF proportion from 17-28%, a considerable difference. The lack of standardized measures hampers the evaluation of program effectiveness.

2.5.2 Missing data

Missing data pose a challenge in the analysis and interpretation of HIV observational data. Data which are not missing at random may bias estimates. In the light of this, it was surprising that most of the studies under review did not report the proportion of missing values on important covariates as well as missing outcomes. In particular, accurate ascertainment of deaths is a major challenge in the analysis of routine data, particularly in programs with high rates of LTF.

2.5.3 Location of ART services

This review found that the location of ART services impacted on patients outcomes. The lowest LTF and highest retention of patients on ART was reported from rural programs. There are several possible explanations for this finding. Both mortality ascertainment and retention may be better in rural areas due to the existence of strong community networks. If mortality ascertainment is better, there would be less misclassified mortality and consequently lower levels of LTF. Indeed some rural cohorts reported site-observed mortality on a par with corrected mortality. Finally, data collection may be better in rural sites, particularly the DHSS sites with annual community surveys. For example rural cohorts reported far higher HIV prevalence in older age groups than any other study and these estimates may be more accurate

than those from population-level surveys. Improved patient outcomes in some rural compared with urban areas may be due to improved community support as well as improved ascertainment of vital status.

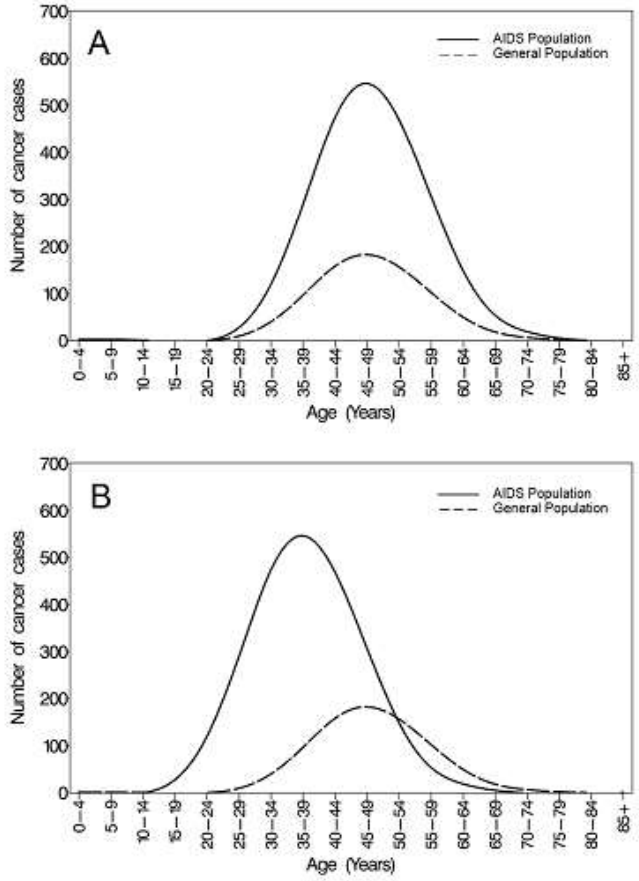
2.5.4 Public vs. private

Although a large number of individuals have started ART through the private sector, few studies report on outcomes. The outcomes of private patients might plausibly be better than outcomes of patients accessing public sector ART as private patients access treatment with less advanced HIV disease and may receive more individualized care. Studies reporting outcomes of private sector ART patients are needed.

2.5.5 Conclusion

In conclusion, this review has found evidence of a successful, rapidly expanding ART program in South Africa with good outcomes sustained over seven years. Studies in the early years focused on proving feasibility and demonstrating similar outcomes among patients in care compared with developed countries. Later studies assessed short- and long-term outcomes of large numbers of patients on ART.

This review identified a number of gaps in the literature including the impact of gender and aging on outcomes and mortality among patients TFO and LTF from ART. Both gender and age impact on access to treatment as well as outcomes on ART. The thesis attempts to address these gaps in the form of chapters focusing specifically on these issues. However ongoing research is needed to understand how gender and age impact on long-term outcomes of ART. Mortality after TFO and LTF is also poorly understood and requires further study. Missing data remains a challenge.



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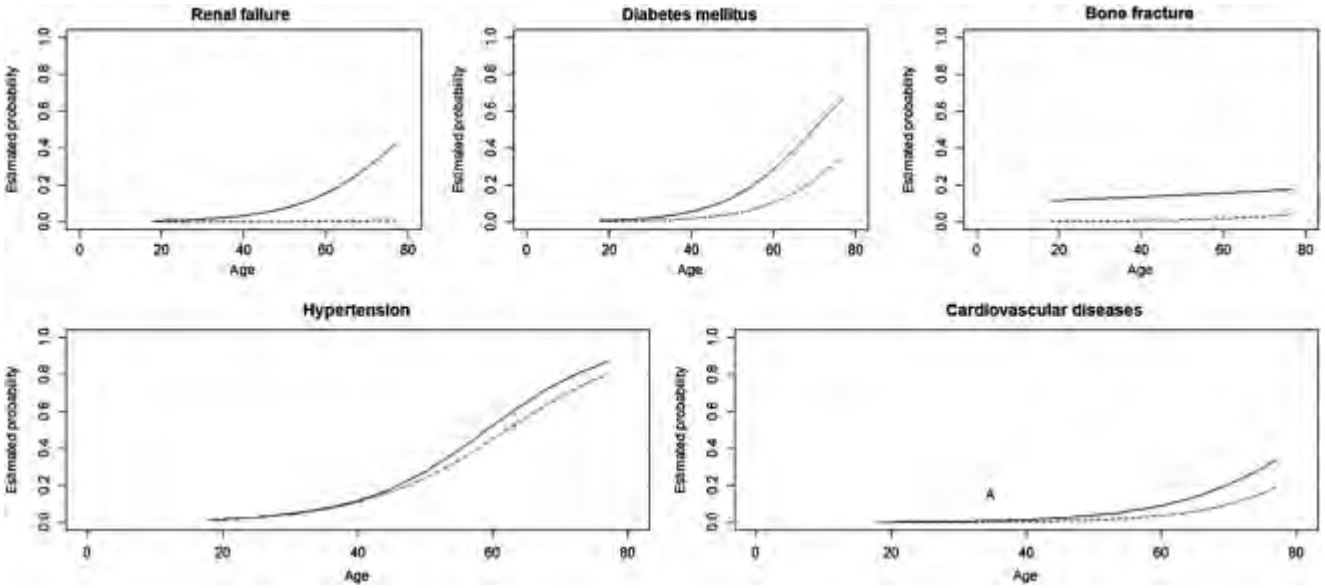
Supplementary Figure S2.1. Hypothetical examples of age distributions of cancers in the AIDS and general populations. (A) Accentuated; cancer occurs at the same ages but more often among HIV-infected participants than among HIV-uninfected comparators. (B) Accelerated and accentuated: cancer occurs younger among HIV-infected participants compared with HIV-uninfected comparators and there are more cancer events.



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Supplementary Figure S2.2. Comparative risk of hypertension, diabetes mellitus, renal failure, cardiovascular disease, and fracture, by age, among patients versus controls. Solid line: HIV-positive individuals, dotted line: age-matched HIV-negative controls

Chapter 3:
Monitoring the South African National Antiretroviral Treatment Program, 2003-2007

Cornell M, Technau K, Fairall L, Wood R, Moultrie H, Van Cutsem G, Giddy J, Mohapi L, Eley B, Macphail P, Prozesky H, Rabie H, Davies M-A, Maxwell N, Boulle A, for the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration

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Author contributions

MC conceptualized the study, wrote the study concept, managed the data collaboration which received the data and analyzed the data. MC wrote all versions of the manuscript and submitted it to the journal. KT, LF, RW, HM, GvC, JG, LM, BE, PM, HP & HR managed the cohorts, provided data and gave input in the writing process. NM did the data management. MAD & AB reviewed the paper critically. All authors approved the final version before submission.

Abstract

Objectives

To introduce the combined South African cohorts of the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration as reflecting the South African national antiretroviral treatment (ART) program; to characterize patients accessing these services; and to describe changes in services and patients from 2003 to 2007.

Design and setting

Multi-cohort study of eleven ART programs in Gauteng, Western Cape, Free State and KwaZulu-Natal.

Subjects

Adults and children (<16 years old) who initiated ART with three or more antiretroviral drugs before 2008.

Results

Most sites were offering free treatment to adults and children in the public sector, ranging from 264 to 17,835 patients per site. Among 45,383 adults and 6,198 children combined, median age (interquartile range) was 35 years and 43 months (15-83), respectively. Of adults, 68% were female. The median CD4+ cell count (IQR) was 102 cells/µl (44-164) and was lower among males than females, 86 cells/µl (34-150) vs. 110 cells/µl (50-169), $p<0.001$. Median CD4% among children was 12% (7-18). Between 2003 and 2007, enrollment increased 11-fold in adults and 3-fold in children. Median CD4+ count at enrollment increased for all adults (67-111 cells/µl, $p<0.001$) and for those in WHO stage IV (39-89 cells/µl, $p<0.001$). Among children younger than five years, baseline CD4% increased over time (12-16%, $p<0.001$).

Conclusions

IeDEA-SA provides a unique opportunity to report on the national ART program. The study describes dramatically increased enrollment over time. Late diagnosis and ART initiation, especially of men and children, need attention. Investment in sentinel sites will ensure good individual-level data while freeing most sites to continue with simplified reporting.

3.1 Introduction

The World Health Organization (WHO) estimated that in 2007, 9.7 million people in low- and middle-income countries needed antiretroviral treatment (ART)(129), 9% of whom were living in South Africa(130). By the end of 2007, the South African DoH reported that 371,731 people had initiated highly active antiretroviral therapy (HAART)(130), making it the largest ART program in the world(129). As the public health system has only provided ART since 2004, this has involved a massive scale-up of services within a comparatively short space of time.

In the context of such an ambitious undertaking, trends in enrollment and key outcomes must be understood in order to plan for the changing needs of health services and patients. Monitoring is a major challenge to effective delivery of ART at a national level(130), and it becomes increasingly important as the continued scale-up of ART creates a tension between service provision and collecting good data.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) Southern Africa collaboration (IeDEA-SA) has assembled a collaborative individualized dataset of children and adults starting ART at sites in South Africa. Numerically the collaboration represents 20% of all children and 10% of all adults entering the public sector roll-out program. This provides a unique opportunity to report in detail, based on individual patient data, on a subset of the national ART program.

This paper aims to introduce the South African cohorts participating in IeDEA as a collaboration that reflects the South African national ART program, to characterize the children and adults accessing these services, and to describe changes in services and patients over the past five years.

3.2 Background and setting

3.2.1 The IeDEA collaboration

IeDEA is an international collaboration of seven regional data centers funded by the National Institutes of Health (NIH). It was established to pool data across numerous cohorts of patients on ART, creating large datasets to address research questions that cannot be answered within single cohorts.

3.2.2 IeDEA Southern Africa

IeDEA-SA is the regional cohort collaboration of southern Africa. Since its establishment in 2006, 22 sites have joined the collaboration. The current database includes cohorts from South Africa, Zimbabwe, Mozambique, Zambia, Malawi and Botswana. Some countries have more than one cohort participating, providing an opportunity to describe characteristics and outcomes at a national level, in the absence of good routine national monitoring systems. In South Africa, eleven large sites from four provinces have joined the collaboration.

3.2.3 The South African ART program

Since the start of the national ART roll-out program in 2004, the South African guidelines for initiation of ART(31) have recommended treatment for adults with CD4+ cell counts <200 cells/µl or WHO stage IV illness except for extrapulmonary tuberculosis, who are assessed to be willing and ready to take and adhere to ART. Before this, most sites offering ART followed similar criteria, based on the 2002 WHO guidelines(10). First-line therapy in ART-naïve adults, unless contraindicated, is stavudine (d4T), lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP). Women of child-bearing age who are unable to guarantee reliable contraception should receive NVP instead of EFV. Patients receive monthly medication and are seen by a doctor at four, eight and twelve weeks and three-monthly thereafter if well. CD4+ count and viral load are measured six-monthly. Patients with a detectable viral load (>400 copies/µl) receive a stepped-up adherence package. If their viral load persistently exceeds 5,000 copies/µl despite adherence support, they may be switched to second-line therapy. Second-line therapy comprises

zidovudine (AZT), didanosine (ddI) and lopinavir/ritonavir (LPV/r). Drug substitutions are also made if patients experience toxicity on first-line therapy.

The 2004 South African pediatric guidelines(31) recommend ART initiation based on a confirmed HIV diagnosis (HIV DNA polymerase chain reaction (PCR) testing if the child is <18 months of age) and one of the following criteria: (*i*) recurrent hospitalizations (more than two admissions/year) or prolonged hospitalization (exceeding four weeks) for HIV-related illness; (*ii*) WHO stage III/IV disease; or (*iii*) CD4 <20% if under 18 months or <15% for older children. Based on the new WHO staging(131), most pediatric sites changed from the three- to the four-stage system towards the end of 2004, which may have impacted to some extent on the pediatric staging data in this dataset. Pediatric first-line ART for children from six months to three years is d4T, 3TC and LPV/r. For children older than three years who weigh above 10 kg, EFV replaces LPV/r.

3.3 Methods

3.3.1 Study population

Most participating 'sites' comprise single clinics in urban or peri-urban areas. The definition of site is broad: one site encompasses three clinics, and another includes all the facilities within an entire province, from primary to tertiary level. The study included data on all adults and children (<16 years old) with documented age, gender and ART start date who initiated ART with at least three antiretrovirals before 2008.

3.3.2 Data collection and management

The study utilized data that are routinely collected by sites. All sites have current ethics committee approval for contribution of their data to IeDEA analyses. The data were all anonymized before transfer to the data center. Sites submitted data during the course of 2007 and early 2008. Data on program-level characteristics were collected through site assessment questionnaires.

3.3.3 Data analysis

Cleaning, coding and analysis of data were done in Intercooled STATA 10.0 for Windows (STATA Corporation, College Station, TX). Continuous variables were described by medians and interquartile ranges and categorical variables as proportions. Temporal trends were tested using the Kruskal-Wallis test (continuous variables) and the chi-square test (categorical variables).

3.4 Results

3.4.1 Program-level characteristics

Seven of the sites offer services to children and adults, either in separate or combined clinics (Table 3.1); one site treats children and pregnant women and the other sites treat children or adults exclusively. Nine sites are public programs funded largely by the DoH with strong research partnerships. One site is funded entirely by donor funding and another is a not-for-profit hospital that receives a DoH subsidy and external funding for research projects. The study utilized data on adult patients from eight sites, contributing between 642 and 17,835 patients. Seven sites contributed data on pediatric patients, contributing between 264 and 2,226 patients.

Treatment was free to all patients except those attending the state-subsidized hospital, who were charged a small inclusive monthly co-payment. Although most sites reported active follow-up of patients, follow-up of defaulting patients was generally limited owing to resource constraints. Patients were referred for treatment primarily from clinics, hospital wards and other medical facilities. Treatment readiness and patient preparation was fairly consistent across sites, involving a baseline psychosocial assessment and three individual or group education sessions over three consecutive weeks. This process could be fast-tracked if the patient was pregnant or required immediate treatment for medical reasons. Patients were encouraged to disclose their HIV status and to have ‘treatment buddies’, and were referred to support groups where available.

Table 3.1. Characteristics of IeDEA-SA sites providing pediatric and adult ART in South Africa.

Cohort	Level of Care	No. of patients	Type of site	Patients	Date of enrollment	Cost to patient	Tracing of patients LTF	Main sources of referral to site
Empilweni Clinic, Johannesburg	All levels	1,088 children	Public & research	Children & pregnant women	2002	Free	No	Hospital wards
Free State provincial roll-out program	All levels	17,835 adults	Public	Adults & children, mostly combined	2003	Free	Some active tracing*	Clinics, TB, antenatal
Gugulethu, Cape Town	Primary	2,924 adults 264 children	Public & research	Adults & children, separate clinics	2002	Free	Active tracing	Other facilities; clinics: PMTCT, TB
Harriet Shezi clinic, Johannesburg	All levels	2,226 children	Public & research	Children only	2002	Free	Active tracing	Hospital wards
Khayelitsha, Cape Town	Primary	8,119 adults 662 children	Public & research	Adults & children, combined clinic	2001	Free	Phone call only	Clinics: PMTCT, TB; other facilities
Masiphumelele, Cape Town	Primary	642 adults	Public & research	Adults & children	2003	Free	Active tracing	Clinics: PMTCT, STIs, TB; other facilities
McCord Hospital, Durban	Secondary	3,575 adults 415 children	Government-subsidized, not-for-profit hospital	Adults & children, combined clinic	1999 (drug trial); 2000 (fee-paying); 2004 onwards (PEPFAR funding)	Small co-payment	Active tracing	Clinics: PMTCT, TB; other medical facilities
Perinatal HIV Research Unit, Johannesburg	Tertiary	948 adults	Research	Adults & children, combined clinics	2004 with some trials <2004	Free	Active tracing	Wellness program for people with HIV
Red Cross Children's Hospital, Cape Town	Tertiary	859 children	Public & research	Children only	2001	Free	Active tracing	Hospital wards
Themba Lethu, Johannesburg	Tertiary	9,250 adults	Public & research	Adults	2004	Free	Active tracing	Other medical facilities
Tygerberg Hospital, Cape Town	Tertiary	1,504 adults 684 children	Public & research	Adults & children, separate clinics	2004, with some trials <2004	Free	Active tracing	Other medical facilities; clinics: PMTCT, TB

* Active tracing implies dedicated resources to undertake one or more of the following: telephone call, home follow-up, physician's report and/or data linkage.

LTF = lost to follow-up; PMTCT = prevention of mother-to-child-transmission program; TB = tuberculosis; STIs: sexually transmitted infections.

3.4.2 Characteristics of patients

The analysis included 45,383 adults and 6,198 children. The median age among adults was 35 years (interquartile range (IQR) 30-41) and among children 43 months (IQR 15-83) (Table 3.2). Of children, 21% (*N*=1,315) were younger than one year old and 39% (*N*=2,411) were aged five years and older. Adult patients were predominantly female (68%, *N*=30,684). In contrast, the gender balance of children was even.

Among adults, the median CD4+ cell count was 102 cells/µl (IQR 44-164). The median CD4+ cell count was lower among adult males than females (86 vs. 110 cells/µl, $p<0.001$). Among patients with baseline CD4+ cell counts, the majority (89%, *N*=30,105) commenced therapy with CD4+ cell counts below 200/µl. A total of 9,363 adult patients (28%) initiated ART with CD4+ cell counts <50 cells/µl.

Among children, the median CD4% was 12% (IQR 7-18), and 65% of pediatric patients (*N*=3,004) initiated therapy with CD4% <15%. In cohorts reporting WHO staging (28% of adults, *N*=12,763 and 67% of children, *N*=4,120) most patients had advanced HIV disease (WHO stage III or IV).

In line with the national protocol, the majority of adult patients (88%, *N*=31,852) started on a regimen containing d4T and 3TC as the two nucleoside reverse transcriptase inhibitors (NRTIs); 68% (*N*=24,734) of adults and 53% (*N*=2,846) of children started on a regimen containing EFV. Data on previous ART and prevention of mother-to-child (PMTCT) exposure were limited. Where previous ART exposure was recorded, most adults (93%, *N*=22,062) and children (96%, *N*=4,100) were reportedly ART-naïve. In cohorts that reported PMTCT exposure, 13% (*N*=696) of women and 25% of children (*N*=617) were known to have been exposed. Reliable data on tuberculosis (TB) at ART initiation were available from two adult and two pediatric cohorts. Among these adult patients, 3,722 (21%) had TB, while the proportion among children was slightly higher (32%, *N*=1,052). Of the three adult cohorts that provided pregnancy data (*N*=8,828 female patients), 7% of female patients (*N*=633) were pregnant at ART initiation. In these cohorts, median CD4+

Table 3.2. Patient characteristics at ART initiation: 45,383 adults and 6,198 children followed up in 11 IeDEA-SA sites in South Africa, 2003-2007.

Characteristic	Adults (≥16 years) *N*=45,383	Children *N*=6,198
Age		
Adults (years), median (IQR)	35 (30-41)	43 (15 - 83)
Children (months), median (IQR)		
Age categories, *N* (%)		
<12 months		1,315 (21)
12-23 months		891 (14)
24-59 months		1,581 (26)
≥60 months		2,411 (39)
Gender		
Female, *N* (%)	30,684 (68)	3,051 (49)
Absolute CD4+ cell count (cells/µl)	*N*=33,672 (75%)*	*N*=4,900 (79%)
All adults, median (IQR)	102 (44-164)	
Men	86 (34-150)	
Women	110 (50-169)	
CD4+ cell count categories, *N* (%)		
<50	9,363 (28)	
50 - 199	20,742 (62)	
≥200	3,567 (11)	
All children, median (IQR)		391 (172-730)
CD4%	N/A	*N*=4,648 (75)†
Median (IQR)		12 (7-18)
CD4% categories, *N*(%)		
<15%		3,004 (65)
15 - 19%		760 (16)
≥20%		884 (19)
WHO stage, *N* (%)	*N*=12,763 (28)‡	*N*=4,120 (67)§
I	1,134 (9)	270 (6.5)
II	1,512 (12)	752 (18.3)
III	6,118 (48)	
IV	3,999 (31)	3,098 (75) ¶
HIV RNA level (log_{10} copies/ml)	*N*=14,955 (33)‖	*N*=4,116 (66)
Median (IQR)	4.9 (4.3-5.4)	5.3 (4.7-5.9)
1st-line ART regimen used, *N* (%)	*N*=36,319 (81)**	*N*=5,331 (86)
d4T+3TC+EFV	23,568 (65)	2,692 (51)
d4T+3TC+NVP	8,284 (23)	93 (2)
AZT+3TC+NVP	1,350 (4)	74 (1)
AZT+3TC+EFV	1,166 (3)	154 (3)
d4T+3TC+KLT††		1,343 (25)
d4T+3TC+RTV		268 (5)
Other	1,951 (5)	707 (13)
Previous ART exposure, *N* (%)	*N*=23,735 (53) ‡‡	*N*=4,262 (69)
ART exposure	1,673 (7)	162 (4)
PMTCT exposure, *N* (%)	*N*=5,526 (12) §§	*N*=2,430 (39) ¶¶
Known exposed women/children	696 (13)	617 (25)
TB at ART initiation, *N* (%)	*N*=17,369 (39) ‖‖	*N*=3,305 (53)
Yes	3,722 (21)	1,052 (32)
Pregnant at ART initiation, *N* (%)	*N*=8,828***	N/A†††
Yes	633 (7)	

* Data from all cohorts; CD4+ cell counts not always provided.
† Data from six pediatric cohorts.
‡ Includes data from four cohorts.
§ Data from all cohorts; WHO stage not always provided in dataset.
¶ Stages III & IV combined for children.
‖ Data from all cohorts; viral load not always provided in dataset.
** Only listed those regimens prescribed to >4% of adult patients.
†† Includes 209 children on ritonavir and Kaletra.
‡‡ Data from three cohorts.
§§ Data from two cohorts.
¶¶ Data from four cohorts.
‖‖ Data from two cohorts.
*** Data on female patients from three cohorts.
††† Data not provided in pediatric datasets.

IQR = interquartile range; TB = tuberculosis.

cell count was higher among pregnant women than those who were not pregnant (150 vs. 104, p<0.001) and higher among non-pregnant women than men (104 vs. 80, p<0.001).

3.4.3 Temporal trends

Table 3.3 shows temporal trends in enrollment, absolute CD4+ cell counts and CD4 percentages and WHO stage. Over five years, patient numbers increased nearly 11-fold among adults (from 1,462 to 15,628), and three-fold among children (from 376 to 1,139). The majority of adults in this analysis (63%, N=28,643) started treatment in 2006-2007. Although pediatric enrollment appeared to drop substantially in 2007, this is probably because data from one of the largest pediatric cohorts were not available for the second half of 2007.

There was an increase in overall adult baseline CD4+ cell count, from a median of 67 cells/µl (IQR 23-134) in 2003 to 111 cells/µl (IQR 49-171; p<0.001) in 2007, although the rate of increase declined over the years. Of all the pediatric patients, 3,787 (61%) were under five years of age. Among these patients, baseline CD4% was available for 76% (N=2,884) and median CD4% increased from 12% (IQR 7-18) in 2004 to 16% (11-23; p<0.001) in 2007. In cohorts that provided data on staging, the proportion of adult patients in stage IV at enrollment fell from 50% (N=494) in 2003 to 27% (N=800) in 2007 (p<0.001). This was mirrored by an increase in median CD4+ cell count in this group from 39 cells/µl (IQR 13-93) in 2003 to 89 cells/µl (IQR 40-162; p<0.001) in 2007. Over time, the availability of baseline CD4+ cell counts decreased from 72% to 65%.

3.4.4 Variation between sites

Tables 3.4 and 3.5 demonstrate some degree of heterogeneity in patient characteristics between sites. Median adult age at enrollment ranged from 32 to 36 years. Baseline median CD4+ cell count ranged from 85 to 121 cells/µl. Within the pediatric sites, patients at two exclusively tertiary pediatric hospitals were younger, with a greater proportion under one year of age, than those from other sites.

Table 3.3. Temporal changes in enrollment, baseline immunologic status and availability of baseline laboratory tests.

Year of ART initiation		≤2003	2004	2005	2006	2007	*p*-value for trend	Combined
Patients enrolled, *N* (%)								
Adults		1,462 (3)	5,340 (12)	9,938 (22)	13,015 (29)	15,628 (34)		45,383 (100)
Children		376 (6)	1,094 (18)	1,849 (30)	1,740 (28)	1,139 (18)		6,198 (100)
Baseline CD4+ (cells/µl)								
All adults	*N*	1,055	4,597	8,476	9,417	10,127		33,672
	Med. (IQR)	67 (23-134)	86 (38-147)	101 (43-159)	105 (45-168)	111 (49-171)	<0.001	102 (44-164)
Men	*N*	341	1,433	2,726	3,177	3,397		11,074
	Med. (IQR)	54 (18-123)	74 (33-138)	87 (33-149)	88 (34-154)	93 (36-154)	<0.001	86 (34-150)
Women	*N*	714	3,164	5,750	6,240	6,730		22,598
	Med. (IQR)	74 (26-138)	91 (41-150)	107 (48-164)	115 (52-174)	120 (56-179)	<0.001	110 (50-169)
Children <5 years	*N*		638*	1,160	1,091	684		3,787
CD4%	Med. (IQR)		12 (7-18)	12 (8-18)	14 (9-20)	16 (11-23)	<0.001	13 (9-19)
Adults in stage IV	*N* (%)	494 (50)	708 (39)	998 (31)	999 (27)	800 (27)		3,999 (33)
	Med. CD4+ count, cells/µl (IQR)	39 (13-93)	54 (20-115)	68 (24-138)	74 (29-147)	89 (40-162)	<0.001	66 (25-236)
Availability of laboratory tests at baseline, %	CD4+ cell count	72	86	85	72	65		74
	CD4% <5 years	NR	75	77	79	72		76

*In this table, all children younger than five years old before 2004 were combined owing to low numbers and erratic enrollment in different sites.
Med. = median; IQR = interquartile range.

Table 3.4. Adult patient characteristics by cohort.

Cohort	Free State Province	Gugulethu	Khayelitsha	Masi-phumelele	McCord	PHRU	Themba Lethu	Tygerberg
Adults enrolled, *N* (%)	17,835 (39)	2,924 (6)	8,119 (18)	642 (1)	3,575 (8)	948 (2)	9,836 (22)	1,504 (3)
Age (years), med. (IQR)	36 (31-43)	33 (29-39)	33 (28-39)	32 (27-37)	35 (30-41)	34 (30-40)	35 (30-41)	34 (29-41)
CD4+ cell count (cells/μl), med. (IQR)	114 (55-167)	101 (48-158)	101 (45-165)	121 (46-193)	85 (31-152)	108 (43-171)	88 (32-158)	116 (52-174)
Patients with CD4+ cell count <50 cells/μl, *N* (%)	2,175 (22)	631 (25)	1,932 (27)	152 (26)	1,025 (35)	197 (26)	2,966 (34)	284 (24)

med. = median; IQR = interquartile range.

Table 3.5. Pediatric patient characteristics by cohort.

Cohort	Empilweni	Gugulethu	Harriet Shezi	Khayelitsha	McCord	Red Cross	Tygerberg
Children enrolled, *N* (%)	1,088 (18)	264 (4)	2,226 (36)	662 (11)	415 (7)	859 (14)	684 (11)
Age (months), med. (IQR)	44 (16-85)	47 (19-82)	56 (22-90)	42 (20-74)	72 (33-109)	16 (6-50)	22 (9-57)
Children <1 year, *N* (%)	216 (20)	42 (16)	331 (15)	97 (15)	31 (7)	361 (42)	237 (35)
Children <5 years, CD4%, med. (IQR)	14 (9-19)	-	12 (7-17)	14 (10-20)	13 (9-17)	14 (9-21)	16 (11-23)
Children <5 years with CD4 <15%, *N* (%)	243 (54)	-	707 (66)	145 (52)	30 (58)	367 (56)	168 (44)

med. = median; IQR = interquartile range.

3.5 Discussion

3.5.1 IeDEA-SA: the South African collaborative cohort

This paper introduces the South African sites of IeDEA-SA, a dynamic collaboration that offers an excellent opportunity to provide information on the South African ART program. It describes the baseline characteristics and temporal trends of the largest national cohort yet assembled of adults and children starting ART. The collaborative cohort is representative of patients accessing ART through the national program in large urban centers, which constitute the largest part of this program. It is constrained by the absence of cohorts from some provinces and by limited participation from rural sites. Many of the sites linked to research programs may also have more capacity for monitoring than other sites in the national program. The cohorts included in this collaboration have dramatically increased enrollment in line with the national roll-out of treatment, and demonstrate the same uniformity of clinical practice and patient preparation recommended in national guidelines.

3.5.2 Evidence of national scale-up

The massive increase in enrollment over time, especially over the last two years, provides strong evidence of the successful scale-up of ART in South Africa. Patients are enrolling with less advanced disease in urban sites: among patients with a baseline measure, there has been a trend towards higher CD4+ cell counts at initiation, and the proportion of patients in WHO stage IV has decreased.

3.5.3 Late diagnosis and initiation of treatment

Patients in this combined cohort were still being diagnosed later than recommended in national and international guidelines, increasing their risk of early mortality on treatment(132). In our collaborative cohort, more than 25% of patients started with a CD4+ cell count <50 cells/µl, and similarly with stage IV disease. Earlier diagnosis and initiation of ART would reduce the risk of morbidity and mortality among these patients, especially for men, who present with more

advanced HIV disease and appear to be disadvantaged in their access to treatment(123,127).

3.5.4 Children

The pediatric component of this collaboration is to our knowledge the largest national cohort of children on ART in the world. While the successful enrollment of so many children on ART is encouraging, limited success in preventing vertical transmission of HIV remains a major concern.

In addition, children also started ART later than is now internationally recommended(129). South African data have demonstrated the high risk of disease progression and mortality in the first year of life(93,133). The low proportion enrolled in the first year of life in this cohort, and high numbers of children with advanced disease, suggest massive under-diagnosis and missed treatment opportunities, and an enormous hidden burden of morbidity and mortality among children.

3.5.5 First-line regimen

Unlike many countries in southern Africa, in which the first-line regimen is a fixed-dose combination of d4T, 3TC and NVP, EFV use predominates in adults on treatment in South Africa in spite of the higher cost of EFV-based regimens. Analyses in South Africa have, however, reported inferior virological outcomes in patients on NVP-containing compared with EFV-containing regimens(134,135). For many adults starting ART, concomitant TB at the time of starting ART precludes the use of NVP. In addition, the greater toxicity profile of NVP compared with EFV has discouraged many clinicians from using it as first-line treatment. The use of protease inhibitors (PIs) versus non-nucleoside reverse transcriptase inhibitors (NNRTIs) in children in this analysis is in line with the proportions of children starting ART above and below three years of age.

3.5.6 Data challenges and the need for sentinel surveillance

Although South Africa has implemented the largest number of individuals on treatment in the world, the ability to monitor the program closely has not kept pace with this expansion(130). The lack of complete data on baseline characteristics in these cohorts - among the best-monitored ART programs nationally - provides insight into the pressures facing the public health system.

Numerous challenges face cohort analysis of ART programs in developing countries, chiefly the need to balance service provision and the collection of good-quality data in the face of rapidly increasing patient numbers. An 11-fold increase in patients over five years is bound to result in a corresponding decrease in data quality unless substantial resources are provided to support monitoring systems. For health care workers, providing access to clinical care is - and should be - the priority. It is therefore essential to find ways to avoid overwhelming health care providers and prioritizing monitoring over service provision(136). Establishing selected, representative sentinel surveillance sites may facilitate the collection of good-quality individual data on a subset of patients in the national program, thus freeing most government sites to continue with simplified aggregate reporting(134).

3.6. Conclusion

The South African cohorts participating in IeDEA-SA provide a unique opportunity to undertake analyses of the national ART program based on individual patient data, to complement routine monitoring. This analysis demonstrates the massive scale-up in recent years and the improvement in the level of disease severity at ART initiation. Earlier diagnosis and enrollment of patients, particularly children and men, need to be prioritized. A solid investment in representative sentinel surveillance could support a context-appropriate national ART monitoring system.

3.7. Acknowledgements

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Chapter 4:
Temporal changes in program outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002-2007

Cornell M, Grimsrud A, Fairall L, Fox MP, van Cutsem G, Giddy J, Wood R, Prozesky H, Mohapi L, Graber C, Egger M, Boulle A and Myer L for the International epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration

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Author contributions

MC, Landon M and AB conceptualized the study and interpreted the data. MC wrote the study concept, managed the data collaboration which received the data, wrote all versions of the manuscript, finalized and submitted it to the journal. AG undertook statistical analyses. LF, MPF, GvC, JG, RW, HP and Lerato M managed the cohorts, provided data and gave input in the writing process. CG did data management. ME, L Myer & AB critically reviewed the paper and provided input. All authors approved the final version before submission.

Abstract

Objective

Little is known about the temporal impact of the rapid scale-up of large ART services on program outcomes. We describe patient outcomes (mortality, loss to follow-up [LTF] and retention) over time in a network of South African ART cohorts.

Design

Cohort analysis utilizing routinely collected patient data.

Methods

Analysis included adults initiating ART in eight public sector programs across South Africa, 2002-2007. Follow-up was censored at the end of 2008. Kaplan-Meier methods were used to estimate time to outcomes, and proportional hazards models to examine independent predictors of outcomes.

Results

Enrollment (n=44,177, mean age 35 years; 68% female) increased 12-fold over five years, with 63% of patients enrolled in the last two years. 12-month mortality decreased from 9-6% over five years. 12-month LTF increased annually from 1% (2002/03) to 13% (2006). Cumulative LTF increased with follow-up from 14% at 12 months to 29% at 36 months. With each additional year on ART, failure to retain participants was increasingly attributable to LTF compared to recorded mortality. At 12 and 36 months respectively, 80% and 64% of patients were retained.

Conclusion

Numbers on ART have increased rapidly in South Africa, but the program has experienced deteriorating patient retention over time, particularly due to apparent LTF. This may represent true loss to care, but may also reflect administrative error and lack of capacity to monitor movements in and out of care. New strategies are needed for South Africa and other low- and middle-income countries to improve monitoring of outcomes and maximize retention in care with increasing program size.

4.1 Background

South Africa has the largest antiretroviral therapy (ART) program in the world(129). Between 2004 (the start of the national ART program) and 2007, an estimated 370,000 people initiated treatment in the public sector(137). But despite the scope and rapid growth of this program there are no data on outcomes at a national level. The International epidemiologic Databases to Evaluate AIDS collaboration of Southern Africa (IeDEA-SA) has assembled a series of HIV treatment cohorts from across the country that includes approximately 10% of all adults who initiated public sector ART in South Africa by the end of 2007. The aim of this paper is to describe trends in mortality, loss to follow-up (LTF) and program retention of these adult patients over the first five years of the country's national ART program.

4.2 Methods

4.2.1 Study design, population & eligibility criteria

The South African cohorts of IeDEA-SA have been described in detail elsewhere(64). Briefly, the collaboration includes eight adult cohorts providing ambulatory ART services located in the four largest provinces in the country (Western Cape, Free State, Gauteng and KwaZulu-Natal). This analysis included all HIV-positive adults (≥16 years) who initiated ART in these cohorts between 2002 and 2007.

4.2.2 Variables and definitions

Baseline characteristics included demographics (age, sex), available measures of disease severity (CD4+ cell count, WHO stage and viral load) and calendar year of ART initiation. Outcome measures were mortality, LTF and program retention. Deaths and transfers were defined by active or passive follow-up at site level. Patients were defined as LTF if their last patient contact was more than six months before the date of closure of the cohort database and were censored at their last contact date. Patients who were transferred out were censored at the transfer date. For patients who started ART but had no further contact with the clinic, one day of follow-up was added to allow their inclusion in survival analyses. Program

retention was defined as those who were enrolled and alive (including transfers out) at analysis closure. Person-time in the database included patients commencing ART from January 2002 until December 2007. Database closure was on or before 31 December 2008 (with minor variation across cohorts).

4.2.3 Analysis

Baseline characteristics were described with summary statistics (medians, interquartile ranges and proportions). Due to variability in the completeness of baseline data, patient numbers are reported for each analysis. Mean age, median CD4+ cell count and proportion in WHO Stage IV were calculated by year of enrollment. Temporal trends were tested with the nonparametric test for trend across continuous variables (age and CD4+ cell count). Differences between proportions were tested with the chi-square test. Time to death, LTF and overall program retention were analyzed using Kaplan-Meier methods and presented by year of enrollment with use of the log rank test for trend of the survivor function.

Separate proportional hazards regression models, stratified by cohort, were used to assess crude and adjusted associations between patient characteristics and different outcomes. We modeled the proportional hazards of death separately for different time periods as the risk factors for death vary, particularly during the first year on ART(132,138). The proportional hazards assumption was confirmed using Schoenfeld and scaled Schoenfeld residuals. Models were built by adding relevant variables with progressively less complete data, to preserve as many observations as possible. Data on WHO staging, an important predictive variable, were missing for 74% of patients. Consequently, we present two final models (including and excluding WHO stage) for each time period. We report findings from the models excluding WHO stage, and where WHO staging impacted appreciably on results, we report this.

Although the national ART roll-out program started on 1 April 2004, we included a small proportion of adults who had received ART through donor-funded programs

prior to this date. There were no differences in baseline characteristics between patients started in 2002/2003 and those started in 2004, and in a sensitivity analysis (not shown) no aspect of the study findings was substantively different when patients starting ART in 2002/2003 were excluded. Data were analyzed using STATA 11.0 (STATA Corporation, College Station, Texas, USA). Two-sided statistical tests were used at alpha=0.05.

4.3 Results

4.3.1 Patient characteristics

This analysis included 44,177 adults who started ART between 2002 and 2007 (median age 35 years; 68% female, Table 4.1), contributing a total of 66,434 person-years of follow-up (median 1.3 years, interquartile range (IQR) 0.6-2.2). Among those with CD4+ cell counts at baseline (83%, n=36,549), median CD4+ cell count was 103 cells/µL (IQR 45-164), and 27% had a measure <50 cells/µL. The median baseline log viral load measure (available on 18,684 participants, 42%), was 4.9 copies/ml (IQR 4.4-5.4). A total of 11,393 (26%) patients had baseline staging, and 80% of these (n=9,079) were classified WHO stage III/IV.

4.3.2 Temporal changes in patient characteristics and outcomes

Enrollment increased each calendar year, from 1,173 in 2002/03 to 14,728 in 2007 (Table 4.2). The majority of patients were enrolled in the last two years of the period under analysis (63%, n=27,833). With each successive year of the program, patients were enrolled at older ages and with less advanced HIV disease. Mean age increased from 34 years in 2002/03 to 37 years in 2007 (p<0.001). Median CD4+ cell count increased from 68 cells/µL in 2002/03 to 113 in 2007 (p<0.001). Over the same period, among patients with baseline WHO staging, the proportion of patients with Stage IV disease decreased from 50% to 28% (p<0.001). Between 2002/3 and 2006, 12-month reported mortality declined from 9% to 6% (p<0.001) (Table 4.2). Meanwhile 12-month LTF increased with each calendar year of enrollment, from 1% in 2002/03 to 13% in 2006 (p<0.001), and 12-month program retention declined

from 90% to 82% over the same period (p<0.001). The crude effect of calendar year persisted over five years of follow-up (Figures 4.1a-c).

Table 4.1. Patient characteristics at ART initiation.

Characteristic	Adults (≥16 years) n=44,177
Gender, *n(%)*	44,177 (100)
Female	29,904 (68)
Age, *n(%)*	44,177 (100)
Adults (years), *median (IQR)*	35 (30-42)
Age categories, *n(%)*	
16-24	2,306 (5)
25-34	17,654 (40)
35-44	16,177 (37)
45+	8,040 (18)
Year of initiation, *n(%)*	44,177 (100)
2002 & 2003	1,173 (3)
2004	5,262 (12)
2005	9,909 (22)
2006	13,105 (30)
2007	14,728 (33)
Absolute CD4+ cell count (cell/µL), *n(%)*	36,549 (83)
All adults, *median (IQR)*	103 (45-164)
CD4+ cell count, categorical, *n(%)*	
<50	9,947 (27)
50-199	22,703 (62)
>=200	3,899 (11)
HIV RNA level, $\log_{10}$ copies/ml, *n(%)*	18,684 (42)
Median (IQR)	4.9 (4.4-5.4)
RNA level, categorical, *n(%)*	
<=5 Log	10,405 (56)
>5 Log	8,279 (44)
WHO stage, *n(%)*	11,393 (26)
I	979 (9)
II	1,335 (12)
III	5,463 (48)
IV	3,616 (32)

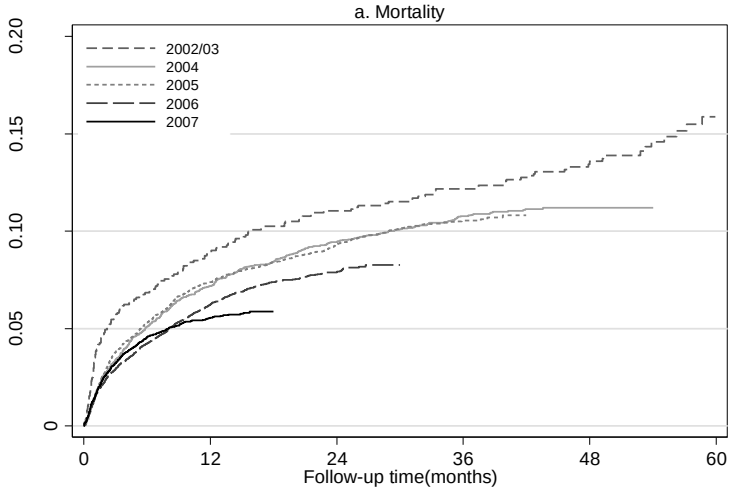
Table 4.2. Baseline characteristics and 12-month outcomes by calendar year of ART initiation.

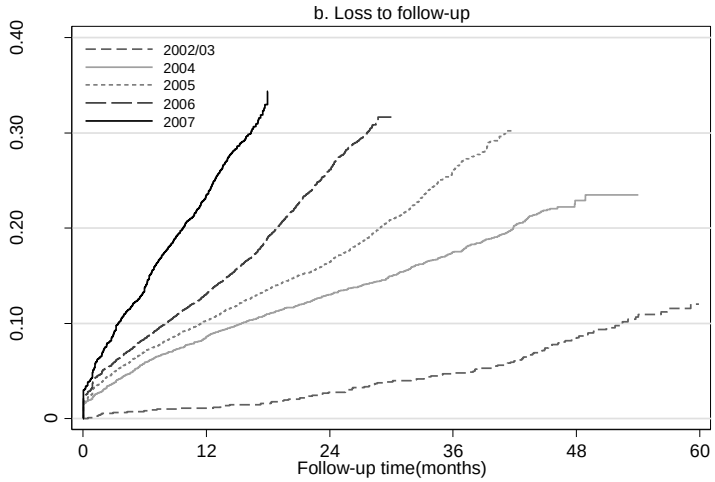
	YEAR OF ART INITIATION				
	2002/03	**2004**	**2005**	**2006**	**2007**
Age, *mean (95%CI)*	34 (34-35)	36 (35-36)	36 (36-36)	36 (36-36)	37 (37-37)
CD4+ cell count, *med (IQR* (n=36,549)	68 (23-130)	87 (38-147)	102 (44-160)	106 (46-168)	113 (51-170)
Patients in Stage IV, *n(%)* (n=11,393)	434 (50)	708 (39)	998 (31)	998 (27)	478 (28)
12-month mortality *% (95% CI)*	9 (7-11)	7 (7-8)	7 (7-8)	6 (6-7)	6 (5-6)
12-month LTF *% (95% CI)*	1 (1-2)	9 (8-9)	10 (10-11)	13 (13-14)	24 (23-24)
12-month retention *% (95% CI)*	90 (88-92)	85 (84-86)	83 (82-84)	82 (81-82)	72 (71-73)

LTF increased with duration on treatment (Table 4.3, Figure 4.1b) and made an increasing contribution to overall patient attrition. At six months on ART, one-third of the losses to program were due to mortality: 5% of patients had died while 9% were LTF. By 36 months, mortality accounted for one-quarter of patient losses: 10% were dead and 30% were LTF. Overall program retention dropped from 86% at six months to 71% at 24 months and 64% at 36 months.

4.3.3 Associations with baseline characteristics

In all time periods, there was a slight increase in the crude and adjusted risk of death for older patients (adjusted hazard ratio (aHR) 1.03, 95% CI, 1.02-1.04, Table 4.4, 12-36 months). There was a strong association between year of enrollment and the risk of death on ART. With each successive year of enrollment the risk of mortality decreased. The risk of death in the first four months on ART among those enrolled in 2007 was 31% lower than in those enrolled in 2002/2003 (aHR 0.69, 95% CI 0.52-0.91). Similar results were found in the later durations on treatment.





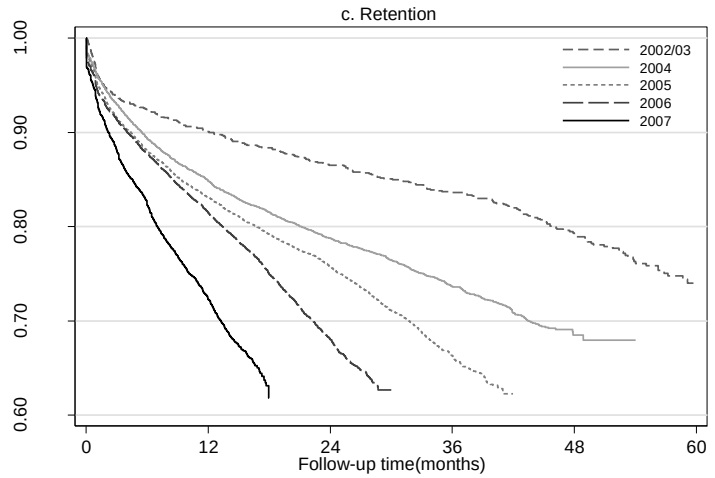


Figure 4.1. Kaplan-Meier plots showing by year of ART initiation, 60-month: (a) mortality, (b) loss to follow-up, (c) retention.

Table 4.3. Kaplan-Meier estimates of mortality, loss to follow-up and retention by duration of follow-up (n=44,177 at baseline)

Duration of follow-up	n (%)	Mortality	Loss-to-follow-up	Retention
		% (95% CI)	*% (95% CI)*	*% (95% CI)*
6 months	35,627 (81)	5 (5-5)	9 (9-10)	86 (86-87)
12 months	26,315 (60)	7 (6-7)	14 (14-15)	80 (80-80)
18 months	18,788 (43)	8 (7-8)	19 (18-19)	75 (75-75)
24 months	13,115 (30)	9 (8-9)	22 (22-23)	71 (71-72)
36 months	5,486 (12)	10 (9-10)	29 (28-29)	64 (64-65)
48 months	803 (2)	11 (10-11)	33 (32-34)	60 (59-61)
60 months	185 (0)	13 (11-15)	36 (34-37)	56 (54-58)

CD4+ cell count was strongly associated with early mortality on ART in both crude and adjusted analyses: in the first four months on ART, patients with CD4+ cell counts <50 cells/µL had a six-fold higher risk of mortality than those with ≥200 cells/µL (aHR 5.85, 95% CI 4.47-7.65, Table 4.4). With longer duration on ART, patients with baseline CD4+ cell count <50 cells/µL continued to be at an elevated risk of death compared with those above 200 cells/µL: the risk was nearly three-fold higher for patients 4-12 months on treatment (aHR 2.83, 95% CI 2.08-3.85) and two-fold higher for patients 12-36 months on ART (aHR 1.84, 95% CI 1.24-2.71). The addition of WHO staging attenuated the association between CD4+ cell count and death over all durations on ART, particularly in the group of patients with CD4+ cell counts 50-199 cells/µL at baseline.

In crude and multivariable analysis, younger patients were more likely to be LTF than older (aHR, 0.99, 95% CI 0.98-0.99, Table 4.5). Year of enrollment strongly predicted the risk of LTF in the early and later time periods on ART: the risk of LTF increased substantially with each successive year of enrollment and the strength of the association persisted after controlling for baseline age and CD4+ cell count. After adjustment for these factors, patients enrolled on ART in 2007 had a 12-fold

Table 4.4. Cox's proportional hazards models of 0-4, 4-12 and 12-36 month mortality by baseline characteristics and year of ART initiation*.

	0-4 months			4-12 months			12-36 months		
	Univariate	Multivariable models		Univariate	Multivariable models		Univariate	Multivariable models	
		Model 1** (n=36,549)	Model 2*** (n=9,951)		Model 1* (n=31,038)	Model 2** (n=8,343)		Model 1* (n=21,992)	Model 2** (n=6,055)
Variables	***HR (95% CI)***	***aHR (95% CI)***	***aHR (95% CI)***	***HR (95% CI)***	***aHR (95% CI)***	***aHR (95% CI)***	***HR (95% CI)***	***aHR (95% CI)***	***aHR (95% CI)***
Age (years)	1.01 (1.00 -1.02)	1.01 (1.00-1.01)	1.01 (1.00-1.02)	1.02 (1.01-1.02)	1.02 (1.01-1.03)	1.03 (1.01-1.04)	1.03 (1.02-1.04)	1.03 (1.02-1.04)	1.05 (1.03-1.07)
Year of enrollment									
2002/2003	1	1	1	1	1	1	1	1	1
2004	0.65 (0.50-0.86)	0.62 (0.46-0.82)	0.82 (0.60-1.13)	1.03 (0.70-1.53)	0.89 (0.59-1.35)	0.98 (0.61-1.57)	1.13 (0.78-1.65)	1.03 (0.68-1.57)	1.01 (0.67-1.59)
2005	0.71 (0.55-0.91)	0.73 (0.56-0.96)	0.70 (0.620-0.96)	0.95 (0.65-1.39)	0.87 (0.58-1.30)	0.85 (0.54-1.33)	0.86 (0.60-1.27)	0.82 (0.54-1.25)	0.73 (0.45-1.20)
2006	0.56 (0.43-0.72)	0.62 (0.47-0.81)	0.62 (0.45-0.85)	0.83 (0.57-1.22)	0.73 (0.49-1.10)	0.64 (0.40-1.02)	0.69 (0.45-1.05)	0.66 (0.42-1.06)	0.84 (0.23-1.22)
2007	0.63 (0.49-0.82)	0.69 (0.52-0.91)	0.56 (0.37-0.86)	0.49 (0.32-0.73)	0.47 (0.30-0.72)	1.10 (0.37-3.22)	0.24 (0.11-0.51)	0.25 (0.11-0.57)	-
CD4+ cell count (cells/μL)									
≥200	1	1	1	1	1	1	1	1	1
50-199	1.67 (1.27-2.19)	1.64 (1.25-2.16)	0.93 (0.60-1.44)	1.50 (1.11-2.03)	1.41 (1.04-1.91)	0.78 (0.46-1.32)	1.24 (0.85-1.81)	1.16 (0.79-1.69)	1.07 (0.51-2.22)
<50	5.95 (4.55-7.78)	5.85 (4.47-7.65)	2.80 (1.83-4.28)	3.00 (2.21-4.07)	2.83 (2.08-3.85)	1.53 (0.90-2.59)	1.94 (1.31-2.87)	1.84 (1.24-2.71)	1.39 (0.66-2.95)
WHO Stage									
I & II	1	-	1	1	-	1	1	-	1
III	3.27 (2.03-5.28)	-	2.35 (1.41-3.91)	2.01 (1.21-3.34)	-	1.49 (0.87-2.53)	1.48 (0.83-2.66)	-	1.32 (0.72-2.54)
IV	10.21 (6.41-16.26)	-	5.82 (3.51-9.62)	4.12 (2.50-6.79)	-	2.78 (1.62-4.74)	2.54 (1.43-4.52)	-	1.98 (1.04-3.75)
HIV RNA level, log_{10} copies/ml									
<=5 Log	1	-	-	1	-	-	1	-	-
>5 Log	1.90 (1.63-2.22)	-	-	1.32 (1.09-1.59)	-	-	1.42 (1.12-1.82)	-	-

*Also adjusted for cohort. **Model 1 excludes WHO staging. ***Model 2 includes WHO staging.

Table 4.5. Cox's proportional hazards models of loss to follow-up at 0-12 and 12-36 months by baseline characteristics and year of ART initiation*.

	0-12 months			12-36 months		
	Univariate	Multivariable Models		Univariate	Multivariable Models	
		Model 1** (n=36,549)	Model 2*** (n=9,951)		Model 1* (n=21,992)	Model 2** (n=6,055)
Variables	***HR (95% CI)***	***aHR (95% CI)***	***aHR(95% CI)***	***HR (95% CI)***	***aHR (95% CI)***	***aHR (95% CI)***
Age (years)	0.99 (0.99-0.99)	0.99 (0.99-0.99)	0.98 (0.97-0.99)	0.99 (0.98-0.99)	0.99 (0.98-0.99)	0.97 (0.96-0.99)
Year of enrollment						
2002 & 2003	1	1	1	1	1	1
2004	6.69 (3.77-11.89)	5.74 (3.06-10.79)	2.63 (1.29-5.39)	2.76 (1.96-3.89)	3.37 (2.20-5.15)	3.54 (2.17-5.77)
2005	7.68 (4.34-13.59)	6.29 (3.36-11.76)	4.99 (2.54-9.80)	4.13 (2.92-5.84)	4.98 (3.25-7.65)	3.57 (3.94-10.93)
2006	9.40 (5.32-16.61)	7.67 (4.10-14.34)	9.27 (4.76-18.05)	7.27 (5.11-10.35)	8.01 (5.17-12.40)	10.62 (5.73-19.68)
2007	15.34 (8.68-27.13)	11.89 (6.36-22.25)	10.89 (5.47-22.10)	12.77 (8.78-18.59)	12.58 (7.91-20.00)	-
CD4+ cell count (cells/μL)						
≥200	1	1	1	1	1	1
50-199	0.77 (0.71-0.85)	0.83 (0.76-0.91)	1.03 (0.77-1.38)	0.92 (0.80-1.07)	0.98 (0.85-1.14)	0.55 (0.39-0.78)
<50	0.97 (0.88-1.07)	1.05 (0.95-1.15)	1.30 (0.95-1.79)	0.85 (0.72-1.00)	0.91 (0.77-1.08)	0.56 (0.38-0.83)
WHO stage						
I & II	1	-	1	1	-	1
III	0.98 (0.79-1.21)	-	1.16 (0.92-1.46)	0.86 (0.65-1.13)	-	1.07 (0.78-1.45)
IV	1.12 (0.90-1.39)	-	1.35 (1.04-1.74)	0.67 (0.49-0.91)	-	0.95 (0.68-1.35)
HIV RNA level (log_{10} copies/ml)						
<=5 Log	1	-	-	1	-	-
>5 Log	0.98 (0.89-1.08)	-	-	0.92 (0.81-1.03)	-	-

*Also adjusted for cohort. **Model 1 excludes WHO staging. ***Model 2 includes WHO staging.

increase in the risk of being LTF during the first year on ART compared with those starting treatment in 2002/03 (aHR 11.89, 95% CI 6.36-22.25). Those with a baseline CD4+ cell count 50-199 cells/μL were less likely to be LTF in the first year on treatment than those with a CD4+ cell count ≥200 (aHR 0.83, 95% CI 0.76-0.91). This association did not persist when WHO staging was added to the model (aHR 1.03, 95% CI 0.77-1.38).

4.4 Discussion

This analysis demonstrates the increasing role played by LTF over time in the program outcomes of the South African national ART program. The rapid pace of ART scale-up in South Africa is evident from the 12-fold increase in this analysis in the number of patients starting ART since 2002, with 63% of all patients initiating ART during 2006 and 2007 alone. While recorded mortality has declined during this period, observed LTF has increased substantially and presents a major threat to evaluating the effectiveness of the national program.

Patient retention is a vital measure of the effectiveness of ART services(139,140). Retention in long-term care is complex, especially in low- and middle-income countries(141-143), but not a new issue: primary health care services have long faced the problem of patient attrition in providing care for chronic diseases(139,144). A systematic review of ART programs in Sub-Saharan Africa found large variation in patient retention across programs, ranging from 46-85% after two years on ART(100). At the start of the South African national program, based on experience with other chronic diseases, it was suggested that the ART service may retain 60-80% of patients annually(144). Retention in the earlier years of the program exceeded this expectation: at two years, 71% of all patients were still known to be in care, but the steady increase in attrition during the first 12 months on ART in successive years of enrollment is cause for concern.
Mortality is one reason for patient attrition: in this cohort, observed mortality at 12

months was 6.6%, which is comparable with results from other developing countries(127). With successive years of enrollment, 12-month mortality decreased. This may be a true decline due to improved coverage of services and patients enrolling with less advanced HIV disease(21). It is also plausible that as a program expands, its ability to accurately ascertain patient deaths deteriorates, and high observed LTF may be associated with poor mortality ascertainment(145). It is likely that our study, based on routine surveillance, underestimates true mortality in these cohorts. Recent corrected mortality estimates for single South African ART cohorts (based on linkage to the national death register) found that at three years on ART, corrected cumulative mortality was 12-15%(55,90) compared with our uncorrected estimate of 10%. There is an urgent need to improve ascertainment of deaths in low- and middle-income countries(146-148).

Yet even with such underestimation, mortality is not the major reason for patient attrition in large ART programs in developing countries. The greater threat to the success of the South African ART program may be the observation of high levels of LTF, insofar as this outcome reflects patients who have truly left care. The size and pace of ART scale-up may have contributed to observed LTF. The program has grown in size dramatically, with our combined cohort increasing enrollment 12-fold over five years. Such rapid increases have placed considerable strain on health services that were already overburdened(12,55,141) and may have undermined the program's ability to monitor and retain patients in care. During 2007 alone, 33% of patients in this study were enrolled onto ART: compared with the 2002/2003 cohort of patients, they had a 12-fold higher risk of appearing LTF. In addition, with longer duration on ART, observed LTF accounted for an increasing proportion of overall program attrition: from 9% at six months to 29% at 36 months on ART.

If the rapid expansion of ART services does increase observed LTF, the situation may worsen as countries continue to expand access to HIV treatment. Based on 2002

WHO treatment guidelines, adult ART coverage in South Africa was an estimated 40% in 2008(149). In addition, the South African government recently revised its treatment guidelines to include all infected infants below one year of age, pregnant women with CD4+ cell counts ≤350 cells/µL, patients co-infected with TB(150). South Africa and many other countries in sub-Saharan Africa will need to continue to expand services while retaining large numbers of patients in care. This will require strengthening systems for chronic disease care in these countries(139), where most health programs are oriented towards episodic illnesses and acute care.

Successfully re-orienting health systems towards long-term chronic care will require a better understanding of the phenomenon of LTF. Often viewed as a single construct, observed LTF in an ART cohort more likely represents a range of patient outcomes including patients truly LTF (i.e. lost to care) as well as those classified LTF through administrative error or inadequate patient monitoring systems(145,151). In a situation of rapid scale-up of ART in resource-limited health systems, the ability to capture and report patient data may become increasingly inadequate(151). Indeed, our results suggest that larger cohorts may have become more subject to these challenges in recent years. For example, the apparently sharp increase in observed LTF among patients enrolled in 2007 is likely to reflect the cumulative burden of increasing patient numbers on both ART services and health informatics systems. This phenomenon may be particularly acute at larger and rapidly expanding ART sites, some of which enrolled up to 50% of their cumulative number of patients in 2007 alone.

Despite the scope of the problem of observed LTF in ART services in southern Africa, relatively little is known about this phenomenon. These cohorts, which are largely funded by the national Department of Health, report active tracing (i.e. dedicated resources to undertake one or more of the following: telephone call, home follow-

up, physician's report and/or data linkage(64). However, largely due to resource constraints, funding for patient follow-up, particularly at this scale, is limited. There is a small literature on factors associated with patient retention highlighting the possible role of patient preparation(103), treatment supporters(152), patient costs (143,153), improved databases(151), community support(154) and simplified services(139). However, research is needed to better understand observed LTF and the relative contributions of true LTF (patients dropping out of ART services) versus administrative LTF (patients who are retained in care but appear LTF due to problems with data capturing and reporting). In contrast to these individuals, patients who are truly LTF are likely to be non-adherent to treatment and at higher risk of death(55,155). In addition, they face increased risk of drug resistance to ART, undermining the long-term effectiveness of treatment programs(55,100). Additional research is needed into the program-level determinants of LTF, better characterization of patients classified LTF and insights into patients' movements in and out of care.

This is the first report on outcomes from multiple cohorts in the world's largest antiretroviral therapy program, and to our knowledge, the largest analysis of individuals starting ART in sub-Saharan Africa. It is strengthened by up to five years of patient follow-up on more than 40,000 patients. The results are likely generalizable to the patient population accessing public sector ART in most of South Africa(64) where 80% of the population rely on the public sector for services(156). However, this analysis has several important limitations. As is the case with other large-scale ART programs based on routine M&E, it is constrained by issues of outcome ascertainment and missing data(151). Outcome ascertainment should improve as more cohorts in South Africa link to the death register, presumably increasing observed mortality and decreasing observed LTF. Data completeness may continue to present a challenge, particularly as programs continue to expand. WHO staging was the least complete data point in this analysis, yet their inclusion in

multivariable analysis impacted on the association between baseline CD4+ cell count and outcomes, highlighting the importance of complete baseline data. Finally, this paper reports on averages across cohorts which may differ in data quality, completeness and outcome ascertainment. Despite these constraints, this analysis utilizes routinely collected data to provide valuable insight into the effectiveness of a huge national program, and has important implications for South Africa and for other programs in similar contexts.

In summary, this analysis demonstrates that the South African national ART program has undergone rapid scale-up over the past five years. While recorded mortality has decreased, program retention has deteriorated, as decreasing patient mortality has been greatly offset by high and increasing levels of LTF. This increased LTF may represent true loss to care, but also may be due to increasing difficulty in monitoring patients enrolling into care as well as patient movements in and out of care. These possibilities require further investigation. Innovative, effective strategies are needed to follow and retain patients in large HIV treatment programs while rapidly expanding access to ART services.

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Chapter 5:
Mortality among adults transferred and lost to follow-up from antiretroviral therapy programs in South Africa: a multicenter cohort study

Cornell M, Lessells R, Fox MP, Garone DB, Giddy J, Fenner L, Myer L, Boulle A, for the IeDEA-Southern Africa collaboration

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Author contributions:

MC and AB conceived and designed the study. MC wrote the study concept and analyzed the data. AB provided statistical support. MC wrote all versions of the manuscript and submitted it to the journal. RL, MPF, DBG and JG maintained the cohorts, provided data and gave input in the writing process. LM, LF & AB reviewed the paper critically. All authors approved the final version before submission.

Abstract

Background & objectives

Little is known about outcomes after transfer out (TFO) and loss to follow-up (LTF) and how differential outcomes might bias mortality estimates, as analyses generally censor or exclude TFOs/LTF. Using data linked to the National Population Register (NPR), we explored mortality among patients TFO and LTF compared with patients retained and investigated how linkage impacted on mortality estimates.

Methods

A cohort analysis of routine data on adults with civil-identification numbers starting ART 2004-2009 in four large South African ART cohorts. The number, proportion, timing and mortality of TFOs and LTF were reported. Mortality was compared using Kaplan-Meier curves, Cox's proportional hazards and competing risks regression.

Results

Before linkage, 1,207 patients (6%) had died, 2,624 (13%) were LTF, 1,067 (5%) were TFO and 14,583 (75%) were retained. Compared with retained, mortality risk was three times higher among TFOs (aHR 3.11, 95% CI 2.42-3.99) and 20 times higher among LTF patients (aHR 22.03, 95% CI 20.05-24.21). Excluding early deaths after TFO or LTF, the risk was comparable among TFOs and retained (aHR 0.75, 95% CI 0.54-1.03) and higher among LTF (aHR 2.85, 95% CI 2.43-3.33). After linkage, corrected mortality was higher than site-reported mortality. Censoring did not however lead to substantial underestimation of mortality among TFOs.

Conclusions

While TFO and LTF predicted mortality, the lower incidence of TFO and subsequent death compared with LTF meant that censoring TFOs did not bias mortality estimates. Future cohort analyses should explicitly consider proportions TFO/LTF and mortality event rates.

5.1 Introduction

Over the past ten years, antiretroviral therapy (ART) programs have undergone rapid expansion. There are now numerous large ART programs in developing countries. As patient numbers increase, particularly in countries like South Africa with highly mobile populations, health systems will need to transfer patients efficiently to ensure uninterrupted linkage to care for optimal outcomes.

Although many programs report the proportion of patients who are transferred out (TFO) to other services, little is known about how patients transition between services and their outcomes after TFO. Sites have limited capacity to keep track of large numbers of patients enrolled for on-going care, while also continuing to increase enrollment onto ART(64), and accurate estimation of mortality within and outside ART programs presents major challenges(63).

In recent years there has been a major focus on improving outcome ascertainment for patients who are lost to follow-up (LTF). Studies have documented increased mortality in LTF patients, especially within three months of being lost(91,155,157). There have been attempts to standardize a definition of LTF in order to improve comparability across sites(158), and studies have used different methods in order to correct for unascertained deaths among patients LTF(88,91,92,159). In contrast with the growing body of literature on patients who are LTF, the group of patients who are TFO to another facility has received less attention. This is a significant group: in South Africa about 10% of patients who started ART over five years were TFO(61). In addition, the probability of being TFO increased with each successive year of ART initiation(75,105). Despite the scale of these losses, there is a dearth of information regarding patient outcomes after TFO and the extent to which differential outcomes after TFO may bias mortality estimates on ART. Most analyses censor TFO patients' observations at the date of TFO(160-163), implicitly assuming that mortality after transfer is similar to mortality among patients retained, or

exclude them from analysis(100).

Large and rapidly expanding ART programs are unable to follow patients and confirm their vital status(164), and tracing studies are expensive and time-consuming. The International epidemiologic Databases to Evaluate AIDS Southern African (IeDEA-SA) collaboration is uniquely placed to assess mortality after TFO/LTF. South Africa's vital registration system was estimated to capture 94% of deaths in the period 2007-2011. Many IeDEA-SA cohorts collect civil identification (ID) numbers, and using linkage to the National Population Register (NPR), we can ascertain the vital status of patients with ID numbers after TFO/LTF.

In this study, we used data linked to the NPR to explore mortality among patients TFO and LTF compared with patients who were retained at the site of ART initiation. In addition, we investigated the extent to which the inclusion of deaths ascertained through linkage to the NPR for TFO and LTF patients impacted on mortality estimates compared to censoring at the time of TFO or LTF.

5.2 Methods

This was a cohort analysis of routine data from four large South African adult IeDEA-SA sites which collect ID numbers: Hlabisa, a large rural program encompassing seventeen primary health care clinics; Khayelitsha, a primary care public sector clinic; McCord, a private/public urban hospital; and Themba Lethu, an urban public hospital. Treatment was free except in the McCord cohort, where patients paid a small co-payment. All ART-naïve HIV-positive adults (≥16 and ≤80 years) with ID numbers who started ART 2004-2009 were eligible for inclusion. The analysis was restricted to patients with ID numbers (65% overall) in order to ensure near-complete mortality ascertainment. Patients with and without ID numbers were compared to assess for potential selection bias.

Mortality was reported uncorrected (as recorded at site) and corrected (after linkage to the National Population Register). Once the data had been linked we checked whether patients had a date of death recorded. Patients whose date of death from the NPR preceded the date recorded for their outcome were recoded as dead, with the date from the NPR. TFO was defined by sites and was considered different from up-referral for treatment or down-referral for programmatic reasons. Generally patients were TFO at their own request for reasons of relocation, convenience or cost. A transfer letter and clinical summary were given to the patient along with sufficient ART to last until re-engaging in care. Patients were recorded as TFO and their status was updated in the database. There was no further follow-up. In Hlabisa, patients transferring between clinics within the sub-district were not regarded as TFOs. LTF was defined as no contact with the health facility for six months prior to analysis closure(63,91) and not documented to be dead or TFO. Analysis was closed six months prior to database closure to allow time for this definition to be met for all individuals. The last contact date was taken as the date of LTF for those who met this definition.

Summary baseline characteristics (median, interquartile range (IQR) and proportions) were described by status (TFO, LTF and retained) for each cohort and overall. Differences between groups were tested with the chi-squared test (categorical variables) and the Wilcoxon rank-sum test (continuous). A sensitivity analysis was undertaken to compare baseline characteristics of patients with and without IDs. The number, proportion, timing and mortality of patients TFO and LTF up to analysis closure were reported.

TFO and LTF were treated as time-varying covariates to avoid potential survivor bias in that these patients could not have died before TFO/LTF. All patients started in the retained group, with the date of ART initiation as the origin. Patients who were TFO/ LTF contributed survival time to the retained group until the point at which

they were transferred or lost, after which they contributed time to the relevant exposure category. Mortality was compared using Kaplan-Meier curves and Cox's proportional hazards regression. As there was high mortality directly after TFO/LTF, we undertook sensitivity analyses limited to, and then excluding, the first three months after TFO/LTF to ascertain whether there was a persistent difference in the risk of death. Three crude and multivariable models of associations between baseline characteristics, status (retained/lost to follow-up/transferred) and mortality are presented: Model 1 - overall period; Model 2 restricted to three months following the date of TFO/LTF; and Model 3 restricted to deaths beyond this period. Kaplan-Meier methods were used to estimate i) cumulative loss to program; ii) mortality after TFO and LTF compared to retained patients, and iii) mortality after ART initiation in which patients previously classified as TFO or LTF were reclassified as having survived to analysis closure or having died based on NPR linkage. In addition, competing risks regression was used to estimate the cumulative incidence functions of death, LTF and TFO at 12 and 24 months after ART initiation. We assessed whether the effect of TFO on mortality risk was modified by the site of ART initiation ("cohort") by including interaction terms in the models and testing with the F-test.

5.3 Results

Overall 19,507 eligible ART-naïve adults with ID numbers started ART during the study period (Figure 5.1). Of these, 26 (0.1%) were excluded due to: invalid dates (n=25) or unknown sex (n=1). The analysis included 19,481 patients followed for 350,463 person-months. The median duration of follow-up on ART was 16 person-months (IQR 6-28). At analysis closure, 1,067 (5%) patients had been transferred out, 1,207 (6%) had died, 2,624 (13%) were LTF and 14,583 (75%) were retained. Patients who were retained were more likely to be female than those LTF (68 vs. 61%, p<0.001, Table 5.1). Compared with those retained, the median CD4+ cell count was lower in those TFO and LTF (90 and 85 vs. 109 cells/µL respectively,

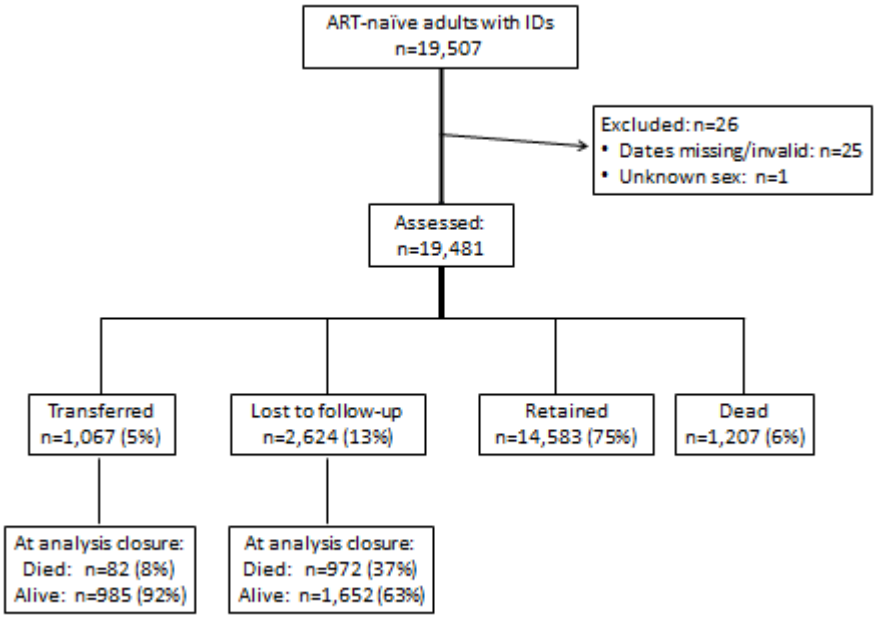

Figure 5.1. Flowchart of 19,507 ART-naïve adults with civil identification numbers initiating ART 2004-2009

p<0.001), both overall (Table 5.1) and within each cohort (Table S5.1). At two years after ART initiation, the unadjusted cumulative incidence proportions were: 7% death, 15% LTF and 6% TFO (Figure 5.2). Overall 82 (8%) patients died after transfer date (Table 5.2). McCord transferred a far higher proportion of patients than the other sites (21% vs. <6%) and had a higher proportion of deaths among TFOs (9% vs. 6-8%). The majority of deaths after transfer took place during later ART (>3 months on ART), ranging from 77% in Khayelitsha to 100% in Themba Lethu. Among TFOs who died, the median time from ART to TFO was 4 months (IQR 1-11 months), and was shorter in Khayelitsha and McCord hospital (<3 months) than in the other cohorts (7-8 months). The median baseline CD4+ cell count in patients who died was nearly half the median count in patients who survived (53 vs. 94 cells/µL, p=0.005).

Table 5.1. Baseline characteristics of patients by outcome status (transferred/lost to follow-up/retained) in four South African cohorts of IeDEA-SA.

Baseline characteristic	TFO n=1,067 (5%)	LTF n=2,624 (13%)	Retained n=14,583 (75%)	TOTAL n=19,481* (100)	p-value TFO vs. retained	p-value LTF vs. retained
Gender, female, n(%)	744 (70)	1,613 (61)	9,939 (68)	12,992 (67)	0.286	<0.001
Age, years, median (IQR)	34 (29-41)	34 (29-41)	34 (29-41)	35 (30-42)	<0.001	<0.001
CD4+ cell count, cells/µL						
Median (IQR)	90 (39-152)	85 (35-155)	109 (51-168)	103 (44-164)	<0.001	<0.001
0-24 n(%)	160 (15)	453 (17)	1,791 (12)	2,718 (14)		
25-49	127 (12)	316 (12)	1,433 (10)	2,071 (11)		
50-99	223 (21)	511 (19)	2,803 (19)	3,771 (19)		
100-199	362 (34)	818 (31)	5,782 (40)	7,236 (37)		
>=200	67 (6)	223 (9)	1,378 (9)	1,743 (9)		
missing, n(%)	128 (12)	303 (12)	1,396 (10)	1,948 (10)		
Hemoglobin, g/dL						
Median (IQR)	11 (9.6-12.1)	11 (9.2-12.1)	11.1 (10-12.6)	11 (9.8-12.4)	<0.001	<0.001
Weight, kg						
Median (IQR)	58 (51-66)	58 (50-66)	60 (53-68)	59 (52-68)	<0.001	<0.001
Calendar year ART initiation, n(%)						
2004	205 (19)	342 (13)	1,303 (9)	1,990 (10)	<0.001	<0.001
2005	312 (29)	639 (24)	2,381 (16)	3,613 (19)		
2006	261 (25)	607 (23)	3,283 (23)	4,447 (23)		
2007	145 (14)	489 (19)	3,199 (22)	4,128 (21)		
2008	120 (11)	389 (15)	2,804 (19)	3,461 (18)		
2009	24 (2)	158 (6)	1,613 (11)	1,848 (9)		

* including 1,207 patients dead at analysis closure

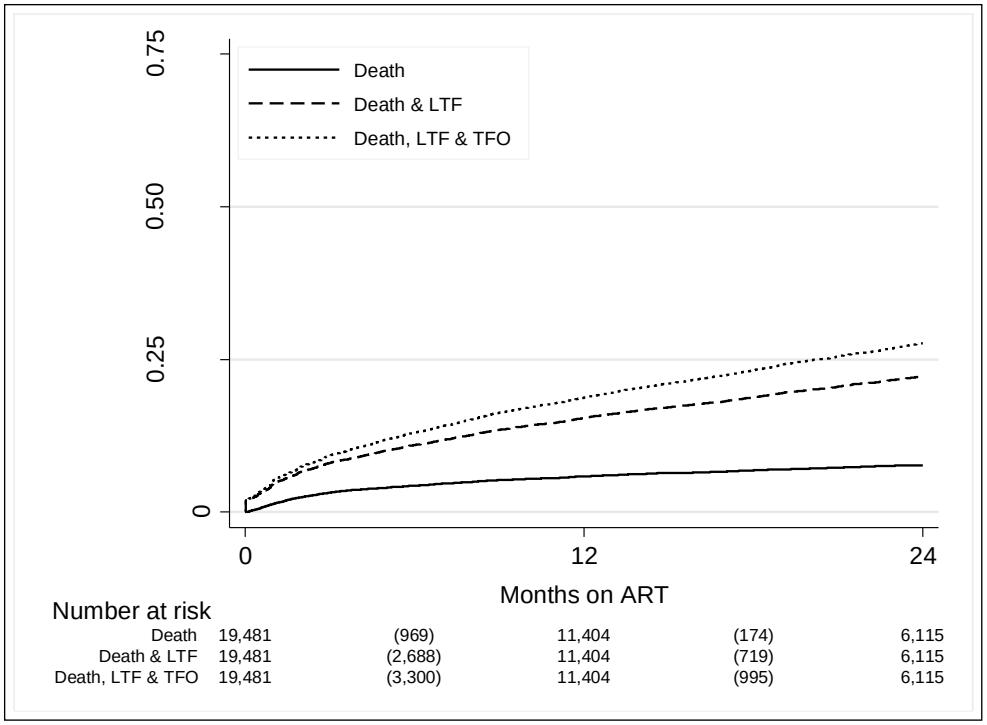

Figure 5.2. Cumulative proportion of patients lost to program by method of loss

Table 5.2. Number (%), timing and mortality of patients transferred and lost to follow-up.

	Total n=19,481	Hlabisa n=8,208	Khayelitsha n=3,397	McCord n=1,641	Themba Lethu n=6,235	p-value*
Patients transferred out (TFO), n(%)	1,067 (5)	287 (3)	161 (5)	349 (21)	270 (4)	<0.001
Deaths after transfer date, n(%)	82 (8)	21 (7)	13 (8)	31 (9)	17 (6)	<0.001
Deaths during early ART (0-3 months)	7 (9)	2 (10)	3 (23)	2 (6)	0 (0)	0.026
Deaths during later ART (> 3 months)	75 (91)	19 (90)	10 (77)	29 (94)	17 (100)	0.721
Among deaths during later ART, deaths <3 months after TFO	27 (36)	8 (42)	6 (60)	5 (17)	8 (47)	0.151
Median months from ART start to transfer	9 (4-19)	9 (4-19)	8 (3-16)	9 (4-19)	11 (4-20)	
Median months from ART start to TFO in patients who died	4 (1-11)	7 (3-12)	2 (0-6)	3 (2-7)	8 (3-15)	
Median months from TFO to death	4 (1-12)	3 (1-7)	1 (1-3)	8 (3-15)	5 (1-18)	
Median months from ART to death	12 (5-20)	13 (6-17)	5 (4-10)	13 (9-21)	20 (7-25)	
Median baseline CD4+ cell count in patients who died, cells/µL (IQR)	53 (14-121)	90 (11-162)	40 (17-99)	41 (12-90)	77 (14-121)	0.005**
Median baseline CD4+ cell count in patients who survived, cells/µL (IQR)	94 (41-153)	116 (53-167)	88 (38-134)	92 (42-158)	79 (30-137)	
Patients lost to follow-up (LTF), n(%)	2,624 (13)	921 (11)	281 (8)	265 (16)	1,157 (19)	<0.001
Deaths after LTF, n(%)	972 (37)	380 (41)	94 (33)	114 (43)	384 (33)	<0.001
Deaths during early ART (0-3 months)	379 (39)	170 (45)	46 (49)	52 (46)	111 (29)	<0.001
Deaths during later ART (> 3 months)	593 (61)	210 (55)	48 (51)	62 (54)	273 (71)	0.105
Among deaths during later ART, deaths <3 months after LTF	379 (64)	147 (70)	38 (79)	37 (60)	157 (58)	<0.001
Median months from ART start to LTF	7 (1-17)	6 (1-16)	8 (2-17)	5 (1-12)	7 (1-18)	
Median months from ART to LTF in patients who died	2 (0-8)	2 (0-9)	2 (1-6)	2 (1-7)	3 (1-9)	
Median months from LTF to death	1 (0-2)	1 (0-2)	0 (0-1)	1 (0.-2)	1 (1-4)	
Median months from ART to death	5 (2-13)	4 (1-12)	3 (1-10)	3 (1-11)	7 (3-16)	
Median baseline CD4+ cell count in LTF who died, cells/µL (IQR)	59 (19-121)	69 (24-136)	65 (34-122)	40 (11-88)	52 (15-110)	<0.001**
Median baseline CD4+ cell count in LTF who survived, cells/µL (IQR)	104 (48-168)	117 (60-177)	113 (57-169)	79 (36-114)	98 (42-163)	

* proportions across cohorts

**p-value for difference between median CD4+ cell counts (died/survived)

The proportions LTF varied by site from 8% in Khayelitsha to 19% in Themba Lethu (Table 5.2). Mortality among LTF patients was 37% (n=972) (Table 5.2), ranging from 33-43% (Khayelitsha and McCord respectively). Mortality was high during later ART, ranging from 51-71% across cohorts. Among those who died during later ART, the majority of deaths occurred within three months of the LTF date, ranging from 58% in Themba Lethu to 79% in Khayelitsha, p<0.001. The median time from ART enrollment to LTF in patients who died was two months. The median baseline CD4+ cell count in LTF patients who died was about half that of patients who survived (59 vs. 104 cells/μL), p<0.001.

Transfer was predicted by CD4+ cell count and site of ART initiation (Table S5.2). In multivariable analysis, patients with a CD4+ cell count ≥200 cells/μL were less likely to be TFO than patients with a baseline count <25 cells/μL (aHR 0.74, 95% CI 0.60-0.91). McCord was five times as likely as Khayelitsha to transfer patients (aHR 5.24, 95% CI 4.27-6.42) and Hlabisa and Themba Lethu less likely (respectively aHR 0.74, 95% CI 0.60-0.91 and aHR 0.70, 95% CI 0.57-0.87) (Table S5.2). The effect of baseline CD4+ cell count on the likelihood of transfer was different in McCord from the other cohorts (p=0.04). Patients with higher baseline CD4 counts were less likely to be transferred except at McCord where CD4 count was not associated with risk of transfer. TFOs increased cumulative program loss by 24 months from 22% to 28% compared to accounting only for mortality and LTF (Figure 5.2).

Figure 5.3 shows mortality with LTF and TFO treated as time-varying to remove potential survivor bias (presented separately by cohort in Figure S5.1). Patients TFO had higher mortality than patients retained. At 24 months on ART, 21% of the TFO patients compared with 8% of those retained had died. Patients who were LTF had extremely high early mortality. Twenty four months after starting ART, cumulatively 81% of LTF patients had died.

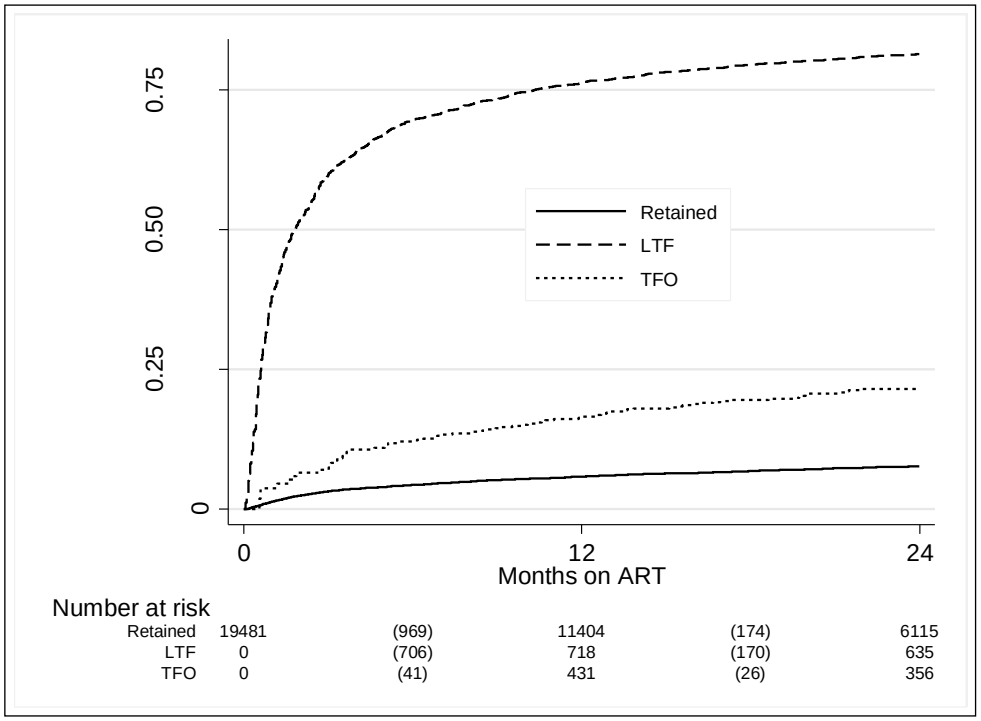

Figure 5.3. Mortality among patients transferred and lost to follow-up compared with patients retained. LTF and TFO are included as time-varying and not baseline covariates.

In crude analysis, mortality was associated with male gender, age, baseline CD4+ cell count, cohort and having been TFO or LTF (Table 5.3, Model 1). Men were more likely than women to die (HR 1.65, 95% CI 1.52-1.79). The risk of death increased with age and adults aged 45+ years compared with those 16-24 years had the highest mortality risk (HR 1.58, 95% CI 1.30-1.93). Mortality was inversely associated with baseline CD4+ cell count (HR 0.32, 95% CI 0.26-0.39, CD4+ cell count ≥200 vs. 0-24 cells/μL). Compared with Khayelitsha, patients in McCord and Hlabisa had higher crude mortality risk (HR 2.26 and HR 1.48 respectively) and Themba Lethu patients had comparable risk (HR 1.06, 95% CI 0.94-1.22). In comparison with patients retained, the risk of death was higher for LTF patients (HR 20.2, 05% CI 18.5-22.05) and those TFO (HR 3.71, 95% CI 2.96-4.65).

In multivariable analysis of the total time period, adjustment for baseline characteristics, site of ART initiation and TFO/LTF status attenuated the association

between mortality and male gender (aHR 1.19, 95% CI 1.09-1.31) and strengthened the association with age (Table 3, Model 1). The impact of ART initiation site on mortality varied: the effect at Hlabisa and McCord was attenuated after controlling for the effect of LTF on mortality (Table 5.3, model 2), with little additional impact of controlling for the effect of TFO on mortality (Table 5.3, model 3). In Themba Lethu, adjustment for baseline characteristics reduced mortality estimates relative to other cohorts (aHR 0.59, 95% CI 0.51-0.69), with or without the inclusion of deaths amongst patients TFO or LTF. In sensitivity analyses, mortality was extremely high in the three-month period directly following LTF/TFO: aHR 32.21 (95% CI 29.18-35.56) and aHR 3.54 (95% CI 2.52-4.98) for LTF and TFO respectively compared with retained (Table 5.3 Model 2). Excluding deaths in the three months after TFO and LTF substantially changed mortality estimates for the effect of ART initiation site and TFO/LTF status (Table 5.3, Model 3). Compared with Khayelitsha, the effect of Hlabisa and McCord were strengthened and the effect of Themba Lethu was attenuated. Compared with patients retained, the risk among LTF was reduced from aHR 22.03 to aHR 2.85 (95% CI 2.43-3.33) and patients who were TFO had comparable mortality risk (aHR 0.75, 95% CI 0.54-1.03). In testing for interaction, Khayelitsha had higher mortality after TFO than the other cohorts, consistent with Supplementary Figure S5.1. However, the impact of these additional deaths on mortality in the cohort was negligible (Supplementary Figure S5.2).

Table 5.3. Associations with mortality, with time-varying status (retained/lost to follow-up/transferred).

Variable	Model 1*		Model 2**		Model 3***	
	Total time period		3 months after TFO/LTF		Excluding 3 months after TFO/LTF	
	Crude HR	aHR	Crude HR	aHR	Crude HR	aHR
Male gender	1.65 (1.52-1.79)	1.19 (1.09-1.31)	1.67 (1.53-1.83)	1.21 (1.10-1.33)	1.56 (1.41-1.73)	1.27 (1.14-1.42)
Age (years)						
16-24 (reference)	1	1	1	1	1	1
25-34	1.13 (0.94-1.36)	1.29 (1.05-1.57)	1.11 (0.92-1.35)	1.23 (0.99-1.52)	1.11 (0.88-1.39)	1.14 (0.89-1.46)
35-44	1.28 (1.06-1.54)	1.48 (1.20-1.82)	1.24 (1.02-1.52)	1.35 (1.09-1.68)	1.22 (0.97-1.54)	1.22 (0.95-1.57)
45+	1.58 (1.30-1.93)	1.99 (1.61-2.47)	1.60 (1.30-1.96)	1.85 (1.48-2.32)	1.52 (1.19-1.93)	1.58 (1.22-2.05)
CD4+ cell count (cells/µl)						
0-24 (reference)	1	1	1	1	1	1
25-49	0.77 (0.68-0.88)	0.72 (0.63-0.82)	0.76 (0.66-0.87)	0.70 (0.61-0.81)	0.82 (0.69-0.96)	0.78 (0.66-0.92)
50-99	0.52 (0.46-0.58)	0.50 (0.44-0.57)	0.50 (0.44-0.57)	0.48 (0.42-0.55)	0.53 (0.46-0.62)	0.51 (0.44-0.60)
100-199	0.32 (0.29-0.36)	0.33 (0.29-0.37)	0.30 (0.27-0.34)	0.32 (0.28-0.36)	0.33 (0.29-0.38)	0.31 (0.27-0.36)
>=200	0.32 (0.26-0.39)	0.29 (0.24-0.36)	0.30 (0.25-0.38)	0.29 (0.24-0.36)	0.36 (0.29-0.46)	0.33 (0.26-0.42)
Cohort						
Khayelitsha (reference)	1	1	1	1	1	1
Hlabisa	1.48 (1.30-1.69)	1.27 (1.10-1.46)	1.46 (1.28-1.68)	1.27 (1.09-1.47)	1.54 (1.31-1.80)	1.48 (1.25-1.75)
McCord	2.26 (1.92-2.66)	1.21 (1.01-1.46)	2.13 (1.79-2.53)	1.25 (1.03-1.51)	2.8 (2.20-3.27)	1.92 (1.54-2.39)
Themba Lethu	1.06 (0.94-1.22)	0.59 (0.51-0.69)	0.96 (0.83-1.11)	0.61 (0.52-0.71)	0.96 (0.81-1.15)	0.74 (0.61-0.89)
Status (time-varying)						
Retained (reference)	1	1	1	1	1	1
Lost to follow-up	20.20 (18.50-22.05)	22.03 (20.05-24.21)	31.59 (28.83-34.63)	32.21 (29.18-35.56)	2.38 (2.06-2.76)	2.85 (2.43-3.33)
Transferred	3.71 (2.96-4.65)	3.11 (2.42-3.99)	3.54 (2.52-4.98)	3.03 (2.09-4.40)	0.93 (0.69-1.24)	0.75 (0.54-1.03)

* Overall model; ** sensitivity analysis only including first three months after TFO/LTF; *** sensitivity analysis excluding deaths within three months of LTF/TFO

Figure 5.4 shows the impact of correcting mortality estimates via NPR linkage. In all cohorts, crude (site-reported) mortality substantially underestimated mortality. Correction for deaths among patients LTF substantially increased mortality estimates, while additionally accounting for unascertained deaths in the smaller proportion of patients TFO had a limited effect on overall cumulative mortality estimates.

5.4 Discussion

In this analysis of 19,481 ART-naïve adults with civil identification numbers starting ART between 2004 and 2009, patients who were transferred had higher mortality than patients retained at the ART initiation site. Mortality among TFOs was low, with one third occurring in the three-month period directly after TFO. Mortality after LTF was far higher, particularly during early ART and in the period directly after LTF. Excluding the mortality directly after TFO/LTF, the mortality risk among

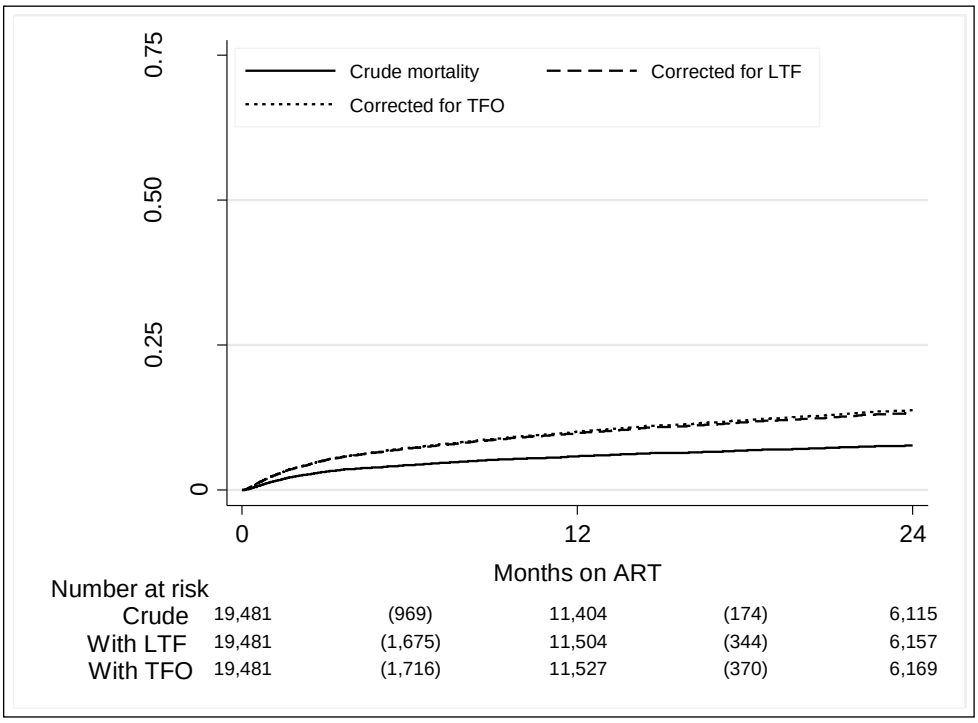

Figure 5.4. The impact on mortality estimates of correction via the National Population Register

patients TFO and retained was similar, but patients LTF had three times the mortality risk of those retained. After linkage to the NPR, correction for deaths among patients TFO had limited impact on mortality but correction for LTF substantially increased mortality estimates. The inclusion of deaths after LTF, but not those after TFO, changed the association between treatment cohort and mortality.

The South African ART program has undergone rapid expansion since its inception in 2004. In 2009/10, a total of 550 accredited facilities were established to offer ART(165). By 2012, 3,686 facilities (80% of the total) offered ART(166). This expansion in facilities offering ART has provided more opportunity for TFOs within the health system. Indeed the probability of TFO at one year increased from 1% in patients enrolled 2002-2004 to 9% in patients enrolled in 2009(105). Lowering the threshold of ART eligibility is likely to increase patient numbers further(75) and may mean that more mobile individuals are enrolled on ART. In addition, evidence suggests that even in low-income countries, patients actively seek better quality health care despite higher costs if they believe that this may improve their outcomes(167). There is thus a need for a robust system in order to ensure that patients who are TFO successfully re-engage in care in another facility without increased risk of mortality. Our study highlighted a number of issues related to patient transfers which have programmatic implications.

Firstly, over a third of deaths in those TFO during later ART occurred in the three month period directly after TFO. It is plausible that patients may have been requesting transfer at a time of severe illness in order to be cared for at home or in the expectation of death(168), or may have been actively transferred to better equipped services due to illness. South Africa has a long history of circular labor migration. Individuals leave home to find work in urban areas and return home to receive care and to die in rural areas where their families remain(169). Our findings

suggest the need for close monitoring after TFO to ensure that TFO patients have successfully linked to care, and for the rapid recall of lost patients.

Second, patients who were transferred had comparable or lower mortality than those retained beyond the three months following transfer (aHR 0.75, 95% CI 0.54-1.03, Table 5.3, Model 2). This is important new information on a group of patients whose outcomes have been largely unknown. Our finding differs from a Malawi study which reported improved survival among TFOs compared with patients retained over 24 months (5% vs. 12%)(170). Our results suggest that once patients have stabilized on treatment, TFO may not impact on mortality, or that beyond the early months on ART stable patients are more likely than others to be transferred. Indeed, in Malawi, patients who were transferred had less advanced clinical stage of disease and better survival than those retained.

Third, some transfers may have been due to resource constraints among patients battling to access health care. For example, McCord Hospital transferred a far larger proportion of patients, and experienced far higher mortality after TFO. In this cohort, patients were required to make a small co-payment towards their treatment. The co-payment covered all HIV-related out-patient care for the month, with no additional costs for any investigation or treatment, but did not cover in-patient admission care. Previous research has found free provision of ART associated with lower mortality in low-income countries(127). It is plausible that patients requesting transfer in this cohort were unable to afford even the small co-payment, which increased from R120 per consultation in 2005 to R140 in 2008.

Fourth, our study confirms the major threat that LTF poses to program effectiveness(61,91,99,171-173). Almost half of the LTF patients had died, mostly within three months of being LTF. The timing of deaths was similar to deaths after TFO, but mortality was far higher. Even excluding the three month period directly

after LTF, LTF patients still had nearly three times the risk of death compared with retained patients (AHR 2.85, 95% CI 2.43-3.33). Retention in chronic HIV care has long been recognized as a major challenge(61,70,145,160,172), with LTF increasing by calendar year as ART programs scale-up enrollment(61,145,166). Numerous strategies have been proposed to retain patients in care including decentralizing ART provision and task shifting(174), reducing clinic caseloads(175) and managing ART at community(176) and home-level(177). Urgent attention is needed to prevent LTF particularly in the first few months on ART.

Finally, although in all cohorts the median CD4+ cell count at ART initiation was lower among TFOs and LTF than those retained, there was substantial heterogeneity across sites including in the proportions TFO/LTF, the incidence of mortality, the median time from ART initiation to TFO/LTF in patients who died, and the median baseline CD4+ cell count in patients who died compared with those who survived. Such variability suggests that although TFO is reported as a single outcome, it may have different meanings in different sites which may impact on mortality. Sites need to understand what TFO means in their own context.

In addition to the implications for patient care, our analysis has implications in terms of program evaluation. Accurate ascertainment of mortality poses major challenges, particularly in large programs in developing countries with limited capacity to actively follow patients. In the absence of additional outcome ascertainment, many studies censor the follow-up time of patients who are TFO, assuming that mortality is the same as among patients retained. Using linkage, our study provides evidence that in a context of low TFO rates and mortality rates after TFO, censoring follow-up time at TFO date did not lead to a substantial underestimation of mortality. In contrast, including deaths among LTF compared with censoring at the time of LTF impacted on mortality estimates and the effect of baseline characteristics as well as cohort on mortality. Thus if the proportion

transferred and the event rates were higher, it might be necessary analytically to treat TFO in a similar way to LTF. In situations where additional outcome information is available from, for example, tracing studies or linkage to a population register, statistical methods such as inverse probability weighting and/or multiple imputation (MI) can be used(96). In the absence of such information, options include the use of a nomogram to correct mortality estimates(92) and use of selection and pattern-mixture models(178).

So what are the implications of our findings, particularly in the context of policy initiatives to test and treat all people with HIV? The study highlights the need for improved follow-up especially in the months after TFO and LTF. South Africa has a number of factors which should support good patient follow-up. ART is widely available; by 2013, approximately 80% of all primary health care facilities were offering ART services and this number appears set to increase(150). In addition, there are standardized ART guidelines which are widely disseminated, ensuring a fairly unified approach to treatment across facilities and providers. These guidelines could be substantially strengthened by a standardized approach to transferring and following patients, with a particular focus on the timing of patients transferred. We recommend: 1) extreme caution in transferring patients until they are clinically stable on ART; 2) prompt and comprehensive reassessment at the receiving facility to ensure continuity of care, not only in terms of ART but also for co-morbid conditions, particularly in the three-month period directly after TFO/LTF; 3) prompt follow-up of patients who are LTF; and 4) a single patient identifier for all health facilities and much improved national health information systems to support monitoring and evaluation.

To our knowledge, this is the first study to report mortality among patients TFO, using data from linkage to the NPR. Most analyses from large ART programs underestimate mortality due to high LTF and poor vital registration. This study was

strengthened by our ability to explore the vital status of patients after leaving a program, which would generally only be possible by undertaking expensive tracing studies with limited success. The analysis only included patients with ID numbers, ensuring good mortality ascertainment. A limitation is that patients with ID numbers may have been different from those without ID numbers which may have led to some underestimation of the true mortality after TFO. However, in sensitivity analysis there was no evidence of any substantial differences between those with and those without IDs. A further limitation is the possible misclassification of outcomes. Patients classified as LTF may be silent TFOs, while some patients LTF may be incorrectly classified as TFO. In addition, different reasons for patient transfer may independently impact on mortality risk but cohorts did not capture patients' reasons for TFO. Finally, due to the observational nature of the study, we were unable to determine whether the increased risk of mortality in those transferred was causally related to the transfer itself or was related to unmeasured characteristics of the individuals transferred, or information bias due to misclassification.

In summary, improved administrative and clinical procedures to ensure continuity and quality of care for patients TFO and LTF are needed. As the proportion of patients TFO grows, it will become increasingly important in cohort analyses to consider the potential for differential outcomes in TFO patients.

Table S5.1 Baseline characteristics of patients transferred and lost to follow-up compared with patients retained, by cohort

Baseline characteristic	Hlabisa			Khayelitsha			McCord			Themba Lethu		
	TFO n=287 (4%)	LTF n=921 (11%)	Retained n=6378 (78%)	TFO n=161 (5%)	LTF n=281 (8%)	Retained n=2782 (82)	TFO n=349 (21%)	LTF n=265 (16%)	Retained n=870 (53%)	TFO n=270 (4)	LTF n=1157 (19)	Retained n=4553 (73)
Gender												
Females, n(%)	744 (70)	1613 (61)	9939 (68)	117 (73)	183 (65)	1948 (70)	241 (69)	157 (59)	549 (63)	198 (73)	745 (64)	3056 (67)
Age, years, median (IQR)	34 (29-41)	34 (29-41)	35 (30-42)	34 (30-40)	32 (28-37)	33 (29-39)	34 (30-41)	34 (29-40)	35 (30-40)	36 (30-43)	35 (30-41)	35 (31-41)
CD4+ cell count, cells/µL												
Median (IQR)	90 (39-152)	85 (35-155)	109 (51-168)	84 (34-136)	96 (46-159)	112 (55-168)	85 (41-157)	66 (17-132)	92 (32-151)	79 (30-135)	81 (32-149)	91 (36-156)
Haemoglobin, g/dL												
Median (IQR)	11 (9.6-12.1)	11 (9.2-12.1)	11.1 (10-12.6)	10.4 (9.5-11.5)	10.6 (9.1-11.8)	11.1 (9.7-12.2)	10.8 (9.4-12.1)	10.7 (9.3-12)	11 (9.7-12.4)	11 (10-13)	11 (10-13)	12 (10-13)
Weight, kg												
Median (IQR)	58 (51-66)	58 (50-66)	60 (53-68)	56 (50-65)	57 (50-65)	60 (53-69)	61 (51-70)	56 (49-68)	61 (54-68)	59 (50-66)	58 (50-66)	60 (52-68)

Table S5.2. Associations between baseline characteristics, cohort and the probability of being transferred out

Variable	Crude	AHR
Male gender	0.96 (0.84-1.09)	0.89 (0.77-1.03)
Age		
16-24	1	1
25-34	0.95 (0.75-1.20)	0.91 (0.71-1.16)
35-44	0.81 (0.63-1.03)	0.81 (0.63-1.05)
45+	0.73 (0.56-0.96)	0.83 (0.62-1.10)
CD4+ cell count, cells/μL		
<25	1	1.00
25-49	1.02 (0.81-1.29)	1.07 (0.85-1.35)
50-99	0.95 (0.77-1.16)	1.06 (0.86-1.30)
100-199	0.81 (0.67-0.97)	0.90 (0.74-1.08)
>=200	0.63 (0.47-0.83)	0.73 (0.55-0.97)
Cohort		
Khayelitsha (ref)	1	1
Hlabisa	0.67 (0.55-0.82)	0.74 (0.60-0.91)
McCord	5.09 (4.22-6.13)	5.24 (4.27-6.42)
Themba Lethu	0.68 (0.56-0.82)	0.70 (0.57-0.87)

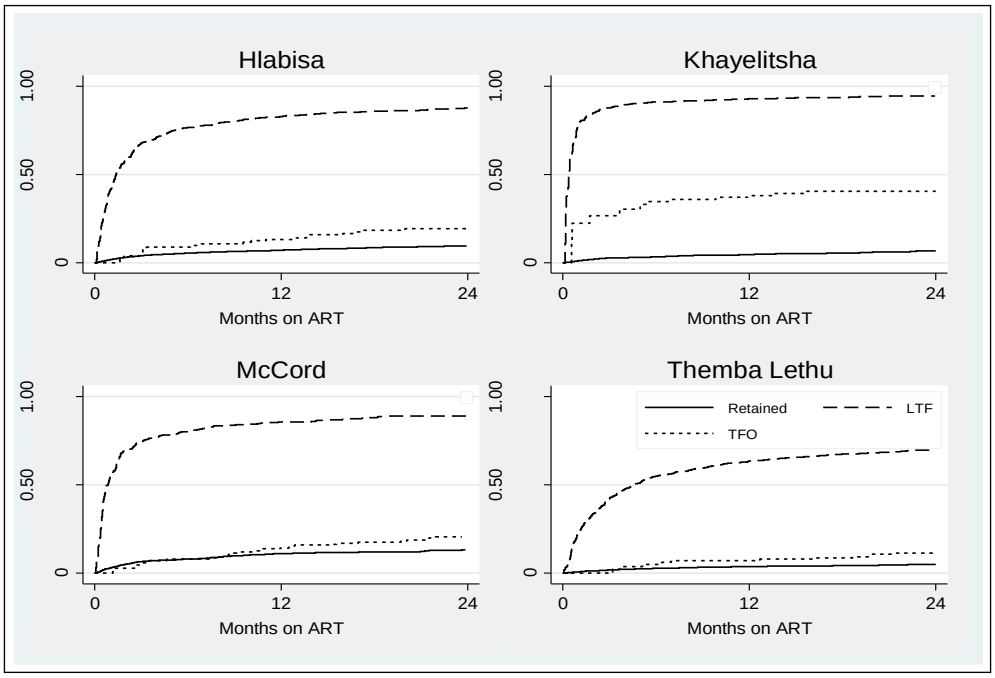

Figure S5.1. Mortality among patients transferred and lost to follow-up compared with patients retained, by cohort

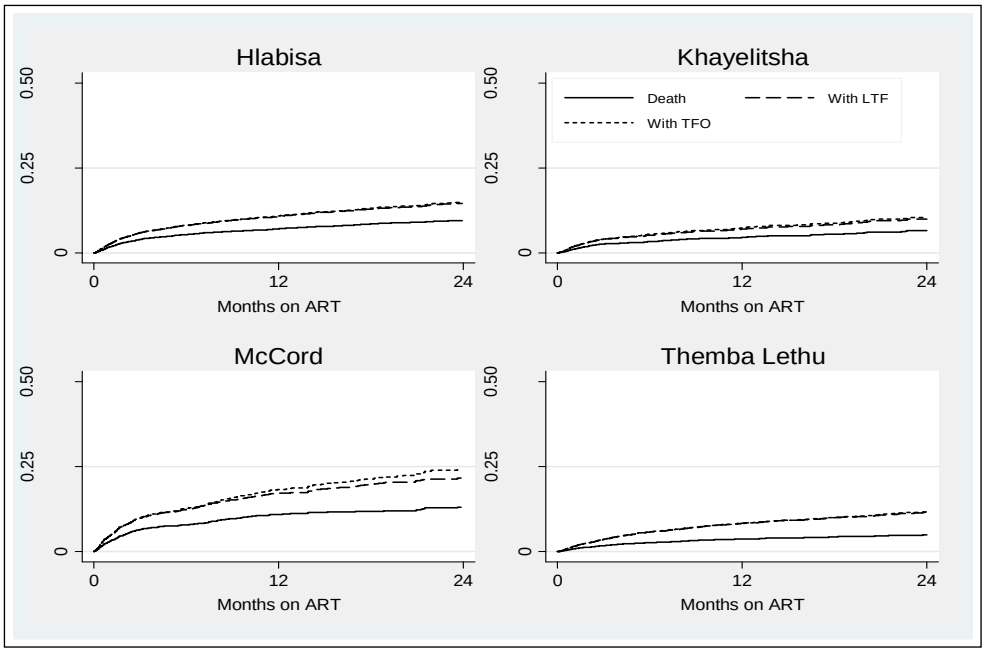

Figure S5.2: The impact of correcting mortality via linkage to the National Population Register, by cohort.

Chapter 6:

Aging in antiretroviral therapy programs in South Africa: a multi-cohort analysis

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MC conceived and designed the study, analyzed the data and wrote the manuscript. FT, MM, RW, HP, JG, KS, LFJ, MS, AB and LM approved the paper outline. MS and LFJ gave statistical support.

Abstract

Introduction

Age is routinely reported in epidemiologic studies but little is known about its specific effect in South African ART programs. We explored the effect of age on the hazard of mortality and whether this effect was mediated by baseline immunologic status.

Methods

A cohort analysis of routine data on adults with civil-identification numbers starting ART 2004-2013 in six large South African public sector ART cohorts. Mortality was estimated using Cox's proportional hazards and competing risks regression. HIV-positive and non-HIV mortality were compared. Interaction between baseline CD4+ cell count and age was tested. Immunologic responses were graphed by age and duration on ART.

Results

83,756 patients were followed for 214,400 patient-years. The median age was 35 (IQR 29-42) years and 10% were classified as older (≥50 years). Patients <35 years were predominantly female, notably 81% of the youngest age group. The proportion of older patients enrolling increased with calendar year from 6 to 10% while the number retained in care increased from 2% to 20%. The hazard of mortality increased with age in a dose response. Patients with HIV had an 11% higher five-year cumulative mortality hazard than HIV-negative individuals and this was consistent across all ages. Despite similar baseline CD4+ cell counts across age groups, immunologic response deteriorated with increasing age. The effect of age on mortality was mediated by baseline immunologic status and was most pronounced in patients enrolling with CD4+ cell counts <50 cells/μL.

Conclusions

There is a need to test and treat young men. Health services need re-orientation towards diagnosing and starting ART in older individuals. Policies are needed for long-term care of older people with HIV.

6.1 Introduction

The world's population is aging rapidly. By 2025, it is estimated that there will be two billion elderly people worldwide, 80% in developing countries(109). South Africa has the largest population of people above 50 years in SSA(179) and one of the highest population prevalences of HIV in the world. These numbers are expected to increase and by 2025, nearly 5.23 million people will be above 60 years(180). In addition to this rapid aging in the general population, the HIV epidemic in sub-Saharan Africa (SSA) is aging. Recent estimates suggest that the total number of HIV-positive individuals older than 50 years in SSA may triple from one in seven in 2011 to more than one in four in 2040(112). South Africa also has the largest ART program worldwide, having enrolled an estimated 2 million individuals on treatment. The country is now facing the challenges of a successful ART program in the middle of a major demographic transition(181). As access to treatment expands, we are likely to see increasing numbers of older patients starting ART and remaining in care for longer periods.

Initiating and retaining older individuals on ART has major implications for the South African public health system. Health care workers are less likely to ask older patients about sexual practices and to consider HIV as a possibility when older individuals present for care. There are no campaigns that target older people for HIV prevention and testing(130). As a result older people may be diagnosed and enter ART services with more advanced HIV disease than younger people. In addition, older people are more likely to have co-morbidities and will require more specialized care than younger patients(109,182,183). Poorer outcomes on ART have been reported in older than younger adults(107,184). In South Africa, for example, mortality rates appear higher among older than younger adults in cohorts from both rural and urban settings (113,114,185).

While HIV increases the risk of mortality as people age, there is debate about the mechanisms through which this occurs. Specifically, it has been suggested that the

combination of HIV and/or ART use *accelerate* biological aging through the same pathways as the natural aging processes; alternately HIV and/or ART may *accentuate* aging by acting as additional risk factors for specific chronic disease processes (186,187). In many ways, HIV appears to mimic the effects of aging in the immune system, compounded by long-term ART toxicity and interactions with co-medications for other age-related conditions(106-110). Whether HIV accelerates or accentuates aging may be specific to the co-morbidity and/or affected organ(186).

To date there has been limited research on aging and ART programs in resource-constrained settings. The International epidemiologic Databases to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration provides a unique opportunity to explore the long-term outcomes of a large number of older individuals starting ART in since 2002. We investigated the association between age and mortality risk and whether this effect was modified by pre-ART immunologic status.

6.2 Methods

The study was a cohort analysis of routine data from six large South African cohorts of IeDEA-SA. Four of these cohorts have been described previously(64): Gugulethu and Khayelitsha, two primary care public sector clinics, McCord, a public/private urban hospital, and Tygerberg, a tertiary level public sector hospital. Two additional cohorts are Hlabisa, a large rural cohort in KwaZulu Natal, and Themba Lethu, a large urban cohort based in Gauteng. All ART-naïve HIV-positive adults (≥16 and ≤80 years) who started ART 2004-2013 were eligible for inclusion.

Patients were followed from the time of ART initiation to one of the following: death, loss to follow-up (LTF), transferred out (TFO) or alive at analysis closure. The primary outcome was death and LTF was the secondary outcome. TFOs were censored at the date of TFO. Mortality was reported by sites and estimates were corrected for patients with ID numbers. Given that a high proportion of patients are likely to have died(157),

we used inverse probability weighting to correct mortality and LTF for deaths misclassified as LTF(96). LTF patients with ID numbers were linked to the National Population Register to confirm their vital status (and date of death if deceased) and weighted to represent all LTF patients. TFO was defined by sites and was considered different from up-referral for treatment or down-referral for programmatic reasons. LTF was defined as no contact with the health facility for six months and not documented to be dead or TFO. The analysis excluded patients enrolled up to six months prior to database closure to allow time for the LTF definition to be met for all individuals, and with the last contact providing the LTF date.

Patients were analyzed by age group (16-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-65, 65+). Summary baseline characteristics (median, interquartile range (IQR) and proportions) were described by age group and overall. The number and proportion of patients dead, the median follow-up times to death and the incidence of mortality were reported by age. The proportions of patients ≥50 years old at baseline and by calendar year of enrollment were reported.

Cox's proportional hazards models were used to assess crude and adjusted associations between patient characteristics and outcomes. Mortality was estimated using Kaplan-Meier and competing risks methods. Models were adjusted for baseline patient characteristics (gender, CD4+ cell count, WHO stage, hemoglobin, TB, weight and site of ART initiation), by duration on ART. As hemoglobin levels vary by gender, the variable anemia was generated from the hemoglobin value (measured in g/dl), which was defined as: none: females >11.9, males >13.1; mild: females 10-11.9, males 11-13.1; moderate: females 8.1 to <10, males 8.1 to <11; severe: <8.1(188). Assuming that data were likely missing at random, we used MI(189) by chained equation methods(190) to impute missing baseline covariates. We multiply imputed ten times CD4+ cell count (baseline, 12-month and 24-month), baseline WHO stage, weight, hemoglobin and tuberculosis (yes/no). We assessed whether the effect of age on

mortality risk was modified by baseline CD4+ cell count by including interaction terms in the models and testing with the F-test. We also recategorized age (16-39, 40-49 and ≥50 years) and baseline CD4+ cell count (<50, 50-199, ≥200 cells/μL) and generated a combined variable with age 16-39 and CD4+ cell count <50 as the reference category. We plotted the effect of this variable. The five-year cumulative hazards of HIV and non-HIV mortality were graphed by age group. To compare age-related differences in mortality in our cohorts with expected age-related differences in the HIV-negative population, we calculated HIV-negative mortality in the South African population age-standardized to our patients. Age-specific HIV-negative mortality rates in males and females were obtained from the Actuarial Society of Society Africa (ASSA) estimates of non-HIV mortality in the year 2005, which are derived from vital registration statistics as well as census and survey data(31). The five-year cumulative hazard of HIV and non-HIV mortality was graphed by age. The median CD4+ cell count responses were graphed by age group and duration on ART.

6.3 Results

Overall 84,078 eligible ART-naïve adults started ART in these cohorts from 2004-2013. Of these, 502 were excluded due to: missing/invalid dates (n=494) and unknown sex (n=8). The analysis included 83,576 patients followed for 214,400 person-years (pyrs).

Patient characteristics and outcomes by age

Patients were predominantly young, with a median age of 35 (IQR 29-42) years. The proportion of patients enrolled in each age group decreased from 28% (16-29 year olds) to 1% (≥65 years) (Table 6.1). Patients in the younger age groups were predominantly female, comprising 80% of patients aged 16-29 and 66% of those aged 30-34. Above 40 years of age, the gender proportions were nearly equal. There was no difference in median CD4+ cell count between the youngest and the oldest patients (137 vs. 135 cells/μL, p=0.129). From 40 to 60 years of age, the proportions enrolled each calendar year increased. At analysis closure, 8,039 (10%) had died, 8,961 (11%)

Table 6.1. Baseline characteristics, mortality estimates and patient outcomes by age at enrollment.

	Age categories (years)									
	16-29	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65+**	**Overall**
Patients enrolled, n (%)	23,261 (28)	19,372 (23)	16,233 (19)	10,619 (13)	6,795 (8)	4,007 (5)	1,991 (2)	806 (1)	492 (1)	83,576 (100)
Females, n(%)	81	66	58	56	56	54	52	50	50	65
CD4+ cell count, median cells/µL (IQR)	137 (62-210)	120 (152-188)	117 (51-186)	120 (53-186)	124 (59-190)	128 (64-195)	125 (60-190)	130 (66-195)	135 (75-208)	125 (56-192)
CD4+ cell count, categorical										
0-49	3,693 (16)	3,696 (19)	3,184 (20)	2,002 (19)	1,189 (17)	615 (15)	326 (16)	111 (14)	51 (10)	14,865 (18)
50-99	3,003 (13)	2,863 (15)	2,514 (15)	1,635 (15)	1,003 (15)	653 (16)	300 (15)	117 (14)	91 (19)	12,179 (15)
100-199	6,678 (29)	5,613 (29)	4,646 (29)	3,178 (30)	2,114 (31)	1,210 (30)	637 (32)	269 (33)	143 (29)	24,467 (29)
200-349	4,030 (17)	2,826 (15)	2,267 (14)	1,471 (14)	979 (14)	649 (16)	278 (14)	136 (17)	83 (17)	12,719 (15)
350-499	377 (2)	246 (1)	232 (1)	156 (1)	118 (2)	66 (2)	32 (2)	11 (1)	10 (2)	1,248 (2)
≥500	196 (1)	120 (1)	118 (1)	78 (1)	62 (1)	40 (1)	28 (1)	4 (1)	9 (2)	655 (1)
Missing	5,305 (23)	4,008 (21)	3,272 (20)	2,099 (20)	1,330 (20)	774 (19)	390 (20)	158 (20)	105 (21)	17,441 (21)
TB at ART start	1,726 (17)	1,730 (20)	1,467 (19)	982 (18)	633 (17)	321 (15)	155 (13)	64 (14)	35 (12)	7,112 (18)
Missing	55%	54%	51%	49%	46%	45%	42%	42%	24%	52%
Year of ART initiation										
2004	1,419 (28)	1,335 (27)	1,030 (21)	583 (12)	342 (7)	178 (4)	69 (1)	27 (1)	16 (0)	4,999 (100)
2005	1,976 (29)	1,745 (26)	1,340 (20)	799 (12)	527 (8)	242 (4)	108 (1)	39 (1)	18 (0)	6,794 (100)
2006	2,292 (26)	2,181 (26)	1,629 (19)	1,162 (14)	623 (7)	375 (4)	167 (2)	59 (1)	34 (0)	8,522 (100)
2007	2,265 (26)	2,129 (25)	1,737 (20)	1,166 (13)	714 (8)	379 (4)	202 (2)	67 (1)	38 (0)	8,697 (100)
2008	2,751 (27)	2,347 (23)	1,990 (20)	1,294 (13)	841 (8)	506 (5)	244 (2)	94 (1)	63 (1)	10,130 (100)
2009	2,893 (26)	2,615 (23)	2,169 (19)	1,475 (13)	997 (9)	588 (5)	289 (3)	121 (1)	57 (1)	11,204 (100)
2010	3,606 (30)	2,664 (22)	2,322 (19)	1,440 (12)	938 (8)	589 (5)	319 (3)	127 (1)	84 (1)	12,088 (100)
2011	3,304 (29)	2,346 (20)	2,149 (19)	1,492 (13)	956 (8)	639 (6)	347 (3)	150 (1)	100 (1)	11,483 (100)
2012 & 2013	2,756 (29)	2,010 (21)	1,867 (19)	1,208 (13)	857 (9)	511 (5)	246 (3)	122 (1)	82 (1)	9,659 (100)
Outcome at analysis closure, n(%)										
Deaths	1,820 (8)	1,746 (9)	1,558 (10)	1,127 (11)	768 (11)	516 (13)	275 (14)	136 (17)	93 (19)	8,039 (10)
Lost to follow-up	6,828 (29)	5,229 (27)	4,068 (25)	2,536 (24)	1,500 (22)	815 (20)	417 (21)	186 (23)	88 (18)	21,667 (26)
Transferred out	2,749 (12)	2,128 (11)	1,672 (10)	1,060 (10)	667 (10)	385 (10)	187 (9)	73 (9)	40 (8)	8,961 (11)
Alive	11,864 (51)	10,269 (53)	8,935 (55)	5,896 (56)	3,860 (57)	2,291 (57)	1,112 (56)	411 (51)	271 (55)	44,909 (54)
Mortality rate per 100 pyrs	2.1	2.2	2.4	2.6	3.1	3.6	3.9	6.0	7.7	2.4
Median follow-up, person-days	774	903	833	841	783	743	639	503	438	811

had TFO, 21,667 (26%) were LTF and 44,909 (54%) were alive. The median duration of follow-up to death was 811 person-days (IQR 311-1539) and decreased with age. The proportion of patients ≥50 years old alive and in care increased from 2% in 2004 to 20% in 2012/2013 (Supplementary Table S6.1).

6.3.1 The effect of age on mortality

The cumulative incidence of death, having not experienced the competing risks of LTF or TFO, at 12 and 36 months was 4% and 6% respectively (Supplementary Table S6.2). Mortality increased with age from 2 to 8/100 pyrs in the youngest and oldest groups (Table 6.1). In keeping with this the median time to death halved between individuals aged 40-44 and 65+ years (841 vs. 438 days). In univariate analysis, there was a dose response in the effect of age on the hazard of mortality (Table 6.2). Compared with patients 16-29 years, the crude hazard was slightly higher in those 30-34 (HR 1.08, 95% CI 1.01-1.15) and three-fold higher in patients aged ≥65 years old (HR 2.94, 95% CI 2.35-4.67). These associations were attenuated but persisted in multivariable analysis adjusted for baseline characteristics (aHR 2.14, 95% CI 1.63-2.79, 65+ vs. 16-29 years old). Other baseline characteristics which increased the risk of mortality were male gender, decreasing CD4+ cell count and WHO stages III/IV vs. I & II.

HIV increased mortality risk across all ages. On average, the five-year cumulative hazard of death was consistently approximately 10% higher among patients with HIV than in the HIV-negative population with the same age profile (Figure 6.1). For example an HIV-positive patient aged 16-29 starting ART had a similar five-year cumulative hazard of mortality compared to an HIV-negative 60 year old patient. At older ages HIV mortality increased compared with non-HIV mortality and the difference was greatest in the 60-64 year age group.

Table 6.2. Crude and adjusted mortality after multiple imputation, overall and by duration on ART.

	Overall		0-12 months	12-24 months	24-36 months
	HR	aHR	aHR	aHR	aHR
Age (years)					
16-29	1	1	1	1	1
30-34	1.08 (0.99-1.17)	1.05 (0.97-1.15)	1.05 (0.90-1.22)	0.99 (0.73-1.35)	0.83 (0.56-1.23)
35-39	1.17 (1.07-1.27)	1.12 (1.03-1.23)	1.14 (0.99-1.32)	1.11 (0.82-1.50)	0.83 (0.57-1.22)
40-44	1.25 (1.14-1.38)	1.21 (2.20-1.34)	1.26 (1.09-1.46)	1.14 (0.84-1.55)	0.78 (0.53-1.17)
45-49	1.48 (1.33-1.64)	1.41 (1.26-1.58)	1.37 (1.17-1.60)	1.39 (1.01-1.91)	0.87 (0.57-1.32)
50-54	1.71 (1.51-1.94)	1.62 (1.42-1.85)	1.52 (1.28-1.80)	1.63 (1.16-2.27)	1.26 (0.82-1.93)
55-59	1.77 (1.50-2.09)	1.65 (1.38-1.97)	1.89 (1.57-2.27)	1.85 (1.30-2.66)	1.87 (1.20-2.92)
60-64	2.57 (2.04-3.24)	2.28 (1.78-2.93)	2.04 (1.63-2.54)	1.77 (1.11-2.82)	2.44 (1.45-4.10)
65+	3.11 (2.39-4.05)	2.53 (1.90-3.38)	2.79 (2.21-3.53)	3.21 (2.04-5.06)	2.06 (1.07-3.98)
Male gender	1.63 (1.54-1.73)	1.43 (1.35-1.53)	1.28 (1.19-1.37)	1.38 (1.20-1.59)	1.74 (1.45-2.10)
CD4+ cell count (cells/µL)					
<50	1	1	1	1	1
50-99	0.64 (0.60-0.71)	0.71 (0.65-0.78)	0.60 (0.55-0.65)	0.82 (0.69-0.97)	0.91 (0.72-1.17)
100-199	0.41 (0.38-0.44)	0.54 (0.80-0.59)	0.40 (0.37-0.44)	0.61 (0.52-0.72)	0.85 (0.68-1.06)
200-349	0.24 (0.21-0.27)	0.38 (0.33-0.43)	0.30 (0.26-0.35)	0.53 (0.41-0.68)	0.60 (0.42-0.86)
350-499	0.33 (0.25-0.44)	0.47 (0.35-0.63)	0.43 (0.31-0.59)	0.64 (0.34-1.22)	1.25 (0.58-2.70)
≥500	0.22 (0.13-0.36)	0.33 (0.20-0.56)	0.39 (0.25-0.62)	0.40 (0.13-1.26)	1.60 (0.59-4.31)
WHO stage					
I & II	1	1	1	1	1
III	2.28 (2.04-2.54)	1.62 (1.44-1.82)	1.61 (1.34-1.93)	1.70 (1.34-2.16)	1.53 (1.12-2.08)
IV	3.39 (3.00-3.83)	2.26 (1.94-2.62)	2.42 (1.98-2.97)	2.15 (1.69-2.75)	2.14 (1.52-3.02)
Anemia					
none	1	1	1	1	1
mild	1.76 (1.64-1.89)	1.37 (1.23-1.53)	1.51 (1.31-1.75)	1.37 (1.10-1.71)	1.33 (1.00-1.76)
moderate	3.10 (2.87-3.35)	1.99 (1.80-2.20)	2.40 (2.05-2.81)	1.77 (1.41-2.22)	1.57 (1.14-2.15)
severe	4.72 (4.00-5.56)	2.89 (2.49-3.35)	3.89 (3.35-4.52)	2.03 (1.46-2.84)	1.66 (1.04-2.64)
TB at enrollment	1.53 (1.40-1.65)	0.82 (0.75-0.90)	0.81 (0.73-0.91)	0.83 (0.66-1.04)	0.92 (0.72-1.18)
Weight (kg)	0.96 (0.96-0.96)	0.98 (0.97-0.98)	0.97 (0.97-0.98)	0.98 (0.98-0.99)	0.99 (0.99-0.99)

The effect of age on mortality modified by duration on ART

The effect of age on mortality changed with duration on ART (Table 6.2). In the first year on ART, there was an increase in the risk of mortality at all ages ≥40 years compared with the youngest age group. With longer duration on ART, the age threshold for elevated mortality increased: in the second year on treatment, mortality was higher among patients ≥45 years at baseline. In the third year on ART, only patients who had started ART ≥55 years of age had a higher risk of death than those 16-29 years. The effects of other baseline characteristics were attenuated but persisted over time on ART.

6.3.3 Age, immunologic status and mortality

Although there was no age difference in the baseline median CD4+ cell count between the youngest and oldest groups, immunologic responses on ART were clearly age-related, with smaller gains in CD4+ cell counts on ART with increasing age (Table 6.3, Figure 6.2). The pattern of response by age was sustained over three years. After 36 months on ART, the median CD4+ cell count increase from baseline was 290 cells/μL, ranging from 310 cells/μL in the youngest to 193 cells/μL in the oldest group. The differences observed over time appeared to be driven by changes in the first year on treatment (Figure 6.2). In subsequent years, immunologic response followed the same age pattern as in the first year. The effect of age on mortality was modified by baseline immunologic status and was more pronounced at lower baseline CD4+ cell counts (Figure 6.3). Comparing patients 50+ years old with those 16-39, there was a 1.5-fold higher hazard of death if they started ART at ≥200 cells/μL and a 2.5-fold higher hazard if they started at <50 cells/μL (aHR 1.54, 95% CI 1.33-1.78 vs. aHR 2.52, 95% CI 2.04-3.11, p-value for interaction=0.004) (Supplementary Table S6.3).

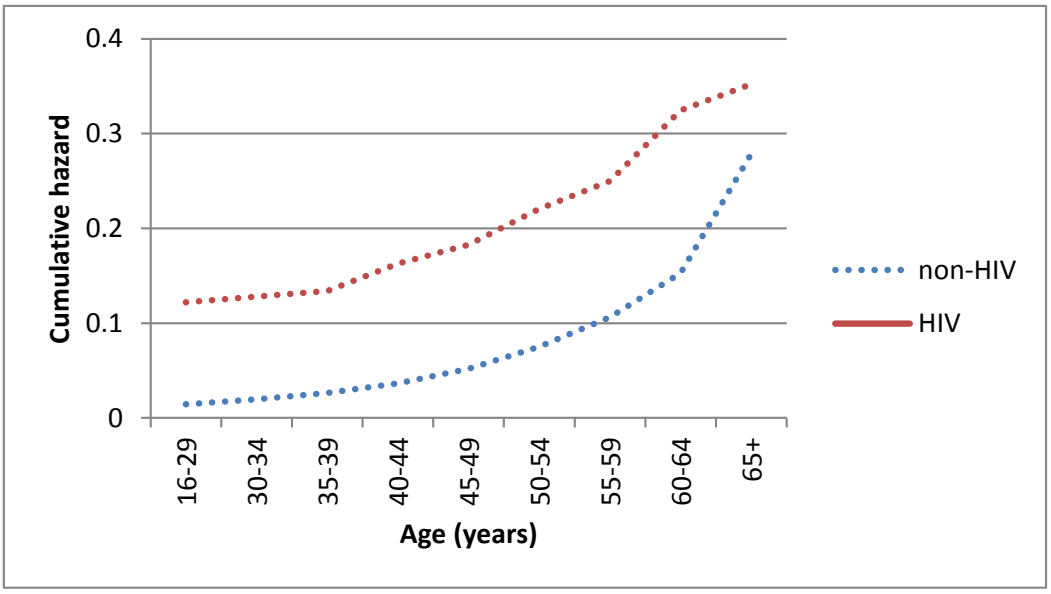

Figure 6.1. Five-year cumulative hazard of HIV* and non-HIV mortality by age.**

* HIV mortality was corrected via linkage to the National Population Register.
** Non-HIV mortality estimates were derived from the ASSA 2005 model.

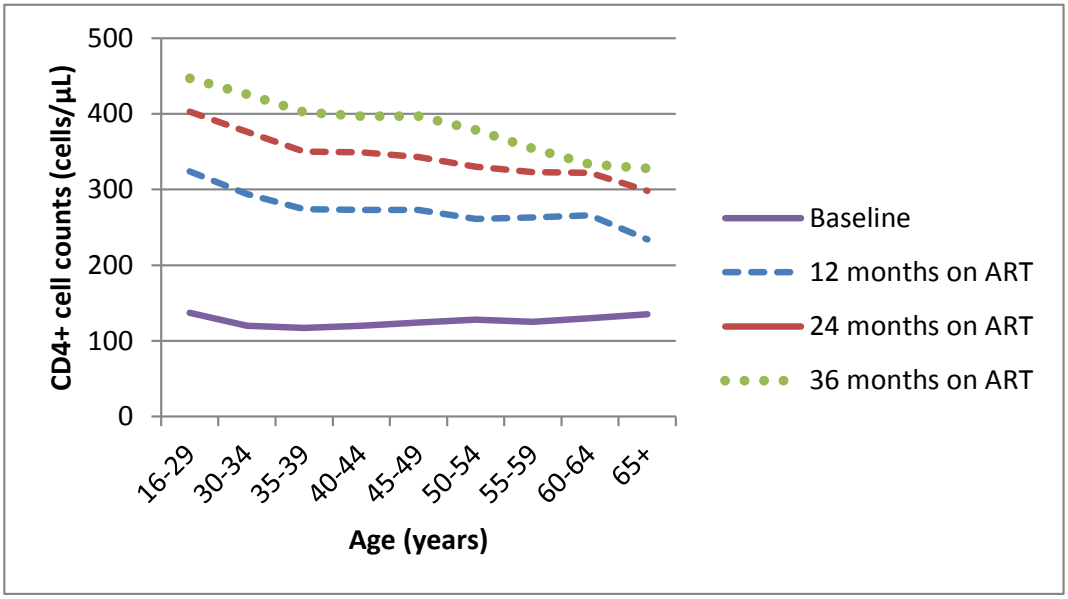

Figure 6.2. Median CD4+ cell count by age and duration on ART.

Table 6.3. Immunologic responses by age and duration on ART.

	Age categories (years)									
CD4+ cell count (cells/µL)	**16-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65+**	**TOTAL**
Baseline										
Median	137	120	117	120	124	128	125	130	135	125
12 months on ART										
Median	324	294	274	273	273	261	263	266	234	291
Median increase from baseline	194	173	156	155	147	138	127	120	102	167
24 months on ART										
Median	403	376	350	349	343	330	323	322	298	367
Median increase from 12 months	79	82	76	76	70	69	60	56	64	76
Median increase from baseline	266	256	233	229	219	202	198	192	163	242
36 months on ART										
Median	447	426	402	397	397	379	354	333	328	415
Median increase from 24 months	44	50	52	48	54	49	31	11	30	48
Median increase from baseline	310	306	285	277	273	251	229	203	193	290

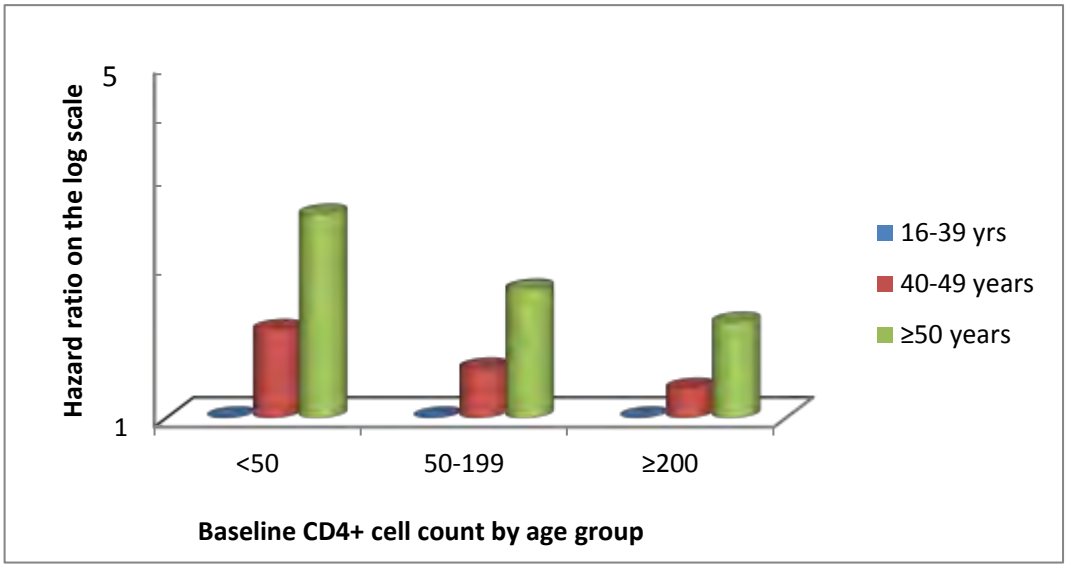

Figure 6.3. Hazard ratios of the interaction between the effects of age and baseline CD4+ cell count on mortality

6.3.4 The effect of age on LTF

The cumulative incidence of LTF, having not experienced the competing risks of TFO or death, at 12 and 36 months was 12% and 23% respectively (Supplementary Table S6.2). In contrast to mortality, the proportion of patients LTF decreased with increasing age (Table 6.1). In crude and multivariable analysis after correction via the NPR, patients aged 16-29 had the highest hazard of LTF (Supplementary Table S6.3). All patients >50 years had a 20-30% lower hazard of being LTF than those aged 16-29 years (aHR 0.69, 95% CI 0.65-0.74).

6.4 Discussion

In this study of 83,576 ART-naive individuals starting treatment from 2002-2013, we observed increasing proportions of older patients initiating ART and remaining in care in successive calendar years. The majority of patients were aged <35 years and 9% were ≥50 years old. Eighty percent of the youngest age group were female. Mortality increased with baseline age up to two years on ART but by the third year, only patients who started treatment at ≥50 years had a higher risk than those 16-29 years. Baseline CD4+ cell counts were similar across all age groups. The effect of age on mortality was modified by baseline immunologic status and was more pronounced at lower CD4+ cell counts. Immunologic responses were diminished over time in older patients.

In recent years there has been growing concern about the lack of data on HIV and ART in older adults in Africa(106-108,116,182,183,191). Our study provides important new evidence that a substantial proportion of older individuals are initiating ART across South Africa, and that this proportion has increased each successive year. We found that despite the absence of a program targeting older individuals for HIV testing and treatment, nearly ten percent of all new patients were ≥50 years, paralleling recent findings from Malawi(192), Uganda(184) and nine countries in sub-Saharan Africa(193).

Baseline immunologic status modified the effect of age on mortality. The effect of age was stronger at lower baseline CD4+ cell counts. This new finding has important clinical implications, suggesting that both age and baseline CD4+ cell count need to be considered when enrolling patients on ART. The development of a mortality risk index for Africa such as the Veterans Aging Cohort Study (VACS) Index has previously been mooted(107) and a prognostic model for patients starting ART in SSA has been reported (188). Both approaches include age and CD4+ cell count, and would be strengthened by adding the interaction between baseline age and immunologic status.

The effect of age on mortality was also modified by duration of ART use. During the first year on ART there was an apparent increase in mortality risk for every additional five years of age at enrollment. However with increasing duration of therapy, the association between age and mortality diminished in the younger age groups: by the second year on ART, risk was elevated in patients aged ≥45 years and by the third year, only among adults ≥55 years compared with 16-29 years. In sensitivity analysis with age as a binary (<50 vs. ≥50 years), individuals 50 years and older had nearly twice the hazard of death compared with individuals younger than 50 years (aHR 1.72, 95% CI 1.59-1.85). These data have programmatic implications, suggesting that individuals >50 years starting ART should be considered a high risk category with specific clinical and policy considerations up to three years on ART.

While we have found evidence that HIV and/or ART increase mortality as patients age, it remains unclear whether this is due to acceleration or accentuation of the natural aging processes. However our results suggest that mortality may be higher among older people because of acceleration. We observed a higher five-year cumulative hazard of death in all age groups of HIV-infected adults compared with an HIV-negative population with the same age-profile. In an African context, accelerated aging has major social and financial implications. Older people, particularly older women, are often the primary caregivers(194). In 90% of the poorest households in South Africa, old age pensions are the only form of income. Benefits extend to the broader household and include improved child health status, especially for girls living with grandmothers who receive pensions. Given their social roles, the removal of older adults will have broad impact.

If HIV accentuated the natural aging process, we would expect HIV to increase mortality disproportionately with increasing age. Instead we found a fairly constant difference in the mortality hazard across all HIV-positive age groups. This is in keeping with results of the 2007-2008 nationally representative World Health Organization

Study of Global Aging and Adult Health (SAGE) which found no association with HIV despite a higher incidence of chronic conditions among South African adults ≥50 years compared with those 18-49 years(191). In contrast, the Dutch AGEhIV Cohort Study reported more co-morbidity among HIV-positive individuals than controls (195). The establishment of a prospective cohort study of older individuals starting ART could provide important evidence on whether HIV accentuates aging in a South African context.

Several commentators have noted that older individuals have been neglected in understandings of the HIV epidemic, particularly in SSA. This analysis makes a novel contribution to understanding one aspect of the HIV epidemic in older adults. However there remains an urgent need for more epidemiologic data on HIV in older African adults. For example, HIV prevalence is not generally measured in older individuals. Prevalence estimates are largely based on data from antenatal surveys limited to women of reproductive age and Demographic & Health Surveys (DHS) restricted to adults ≤50 years. Estimates of prevalence among older adults in South Africa are highly variable and are twice as high in two rural health and socio-demographic surveillance system (DHSS) sites as in other ART roll-out sites (114,119,196). There is an urgent need to extend epidemiologic measures beyond 50 years of age and to include older individuals in studies to ensure their successful engagement in ART services.

Finally, it is well established that women in Africa have better access to ART than men(63,123,197). However we found that the gender difference in enrollment is largely concentrated in the ages 16-34. One interpretation of this novel finding is that there may be undiagnosed HIV in younger men. In 2012 HIV prevalence in South Africa was reportedly highest in 30-34 year old women and 35-39 year old men (36% vs 29%), suggesting that men are infected at older ages than women(2). While this may be true, our results suggest that prevalence in young males may be underestimated given the disproportionately high enrollment by young females. There is a need to target young

men for HIV prevention, testing and linkage to HIV care. In addition, analyses should disaggregate data by gender and age in order to identify and address pronounced differences that may be masked by overall estimates.

To our knowledge this is the first study to report that baseline immunologic status modifies the effect of age on mortality in ART programs. The study is strengthened by large patient numbers including a substantial number of patients ≥50 years and lengthy patient follow-up time. A further strength is consistency of findings across cohorts, increasing confidence in the overall estimates (Supplementary Table S6.4). However, interpretation of these results is subject to several limitations. These data come from numerous ART programs and there is a substantial amount of missing data. For example, national identity (IDs) numbers were only available on 50% of patients and it is possible that there are systematic differences between patients with and without IDs which has not been accounted for. Data were missing for baseline CD4+ cell count, which we addressed by using MI and sensitivity analyses to confirm our main findings. Data on time since infection could have informed interpretation of the findings, but these were not available. Lastly, we have not observed mortality in HIV-negative populations where our study populations are located, but used a national-level actuarial model to estimate HIV-negative mortality. We were also unable to differentiate between mortality from HIV and from other causes as these data are not routinely available. All-cause mortality is differentially higher in older persons than in younger individuals, which might explain some of the age differential in mortality. It is likely that our findings are generalizable to the national ART program and to other settings in SSA, but further research is needed in different contexts.

Age is routinely reported as a demographic variable but its specific effect on HIV-related mortality has received surprisingly little attention in African ART programs. With increasing numbers of older individuals on ART, the emphasis in developed countries has shifted from managing drug resistance and toxicities to retaining patients

in care and managing premature complications associated with age(106). Ten years into the national ART program, a similar shift is required in South Africa. Prevention and testing campaigns need to target older adults. Health care workers need training in initiating and managing older individuals on ART, to ensure good outcomes on treatment. The risk of co-morbidities and polypharmacy in older patients needs to be quantified, whether through longitudinal studies or the linkage of data platforms. Policies for long-term care of older individuals with HIV are urgently needed.

Supplementary Table S6.1. Patient enrollment, median age, proportions of patients ≥50 years enrolled and in care, by calendar year of enrollment.

	2004	2005	2006	2007	2008	2009	2010	2011	2012 /13	OVERALL
Patients enrolled (n)	4,999	6,794	8,522	8,697	10,130	11,204	12,088	11,483	9,659	83,592
Median age (years)	34	34	35	35	35	35	35	35	35	35
Percentage enrolled ≥50 years old	6	6	8	8	9	9	9	11	10	9
Percentage >=50 years old in care	2	3	5	7	11	13	16	23	20	100

Supplementary Table S6.2. Estimates of mortality and loss to follow-up using competing risks and Kaplan-Meier methods.

Duration on ART	Cumulative Incidence Function	Failure function (%)	Cumulative Incidence Function	Failure function (%)
12 months	4.1 (4.0-4.2)	4.4	12.0 (11.8-12.2)	9.6
24 months	5.4 (5.2-5.6)	6	17.6 (17.4-17.9)	16.2
36 months	6.3 (6.1-6.5)	7.2	22.5 (22.2-22.8)	22.6

Supplementary Table S6.3. Crude and adjusted estimates of the hazard of loss to follow-up.

	Crude HR	Adjusted HR
Age groups (years)		
16-29	1	1
30-34	0.87 (0.84-0.90)	0.81 (0.78-0.84)
35-39	0.87 (0.84-0.90)	0.76 (0.73-0.79)
40-44	0.84 (0.80-0.87)	0.73 (0.70-0.77)
45-49	0.81 (0.76-0.85)	0.69 (0.66-0.74)
50-54	0.80 (0.74-0.85)	0.66 (0.62-0.72)
55-59	0.93 (0.85-1.01)	0.74 (0.67-0.82)
60-64	1.17 (1.02-1.33)	0.90 (0.78-1.04)
65+	0.93 (0.76-1.13)	0.82 (0.67-1.02)
Male gender	1.25 (1.21-1.28)	1.26 (1.22-1.29)
CD4+ cell count, median (cells/μL)		
<50	1	1
50-99	0.94 (0.90-0.98)	1.01 (0.96-1.05)
100-199	0.93 (0.89-0.96)	1.02 (0.98-1.06)
200-349	0.98 (0.94-1.03)	1.01 (0.95-1.06)
350-499	1.01 (0.90-1.14)	1.15 (1.00-1.31)
≥500	1.03 (0.88-1.20)	1.23 (1.04-1.45)
WHO stage		
I & II	1	1
III	0.97 (0.94-1.00)	1.00 (0.96-1.04)
IV	0.95 (0.91-1.00)	0.96 (0.90-1.01)
Anemia		
none	1	1
mild	1.08 (1.04-1.12)	1.09 (1.05-1.14)
moderate	1.20 (1.15-1.26)	1.20 (1.15-1.27)
severe	1.27 (1.19-1.35)	1.34 (1.26-1.43)
TB at ART start	1.06 (1.01-1.11)	1.10 (1.04-1.16)
Cohort		
Gugulethu	1	1
Hlabisa	0.26 (0.24-0.27)	0.14 (0.14-0.15)
Khayelitsha	0.33 (0.32-0.35)	0.19 (0.19-0.20)
McCord	1.45 (1.39-1.51)	0.71 (0.67-0.75)
Themba Lethu	0.50 (0.48-0.52)	0.37 (0.35-0.39)
Tygerberg	0.25 (0.23-0.27)	0.17 (0.16-0.19)
Year		
2004	1	1
2005	1.38 (1.30-1.47)	1.61 (1.50-1.72)
2006	1.80 (1.69-1.91)	2.45 (2.29-2.62)
2007	2.27 (2.13-2.42)	3.23 (3.01-3.47)
2008	2.58 (2.41-2.75)	4.06 (3.78-4.37)
2009	3.68 (3.45-3.93)	5.76 (5.34-6.20)
2010	4.43 (4.15-4.73)	8.29 (7.68-8.95)
2011	4.57 (4.26-4.91)	11.76 (10.84-12.77)
2012 & 2013	6.30 (5.81-6.92)	16.98 (15.49-18.62)

Supplementary Table S6.4. Hazard ratios of the interaction between the effects of baseline CD4+ cell count and age on mortality.

	Median baseline CD4+ cell count (cells/μL)		
Age (years)	**<50**	**50-199**	**≥200**
16-39	1	1	1
40-49	1.49 (1.24-1.80)	1.25 (1.15-1.36)	1.14 (1.03-1.27)
≥50	2.52 (2.04-3.11)	1.79 (1.62-1.98)	1.54 (1.33-1.78)

Supplementary Table S6.5. Exploring heterogeneity between cohorts: median age and proportion of patients ≥50 years old and estimates of the effect of age on mortality adjusted for baseline characteristics, by cohort.

	Cohort					
	Gugulethu	**Hlabisa**	**Khayelitsha**	**McCord**	**Themba Lethu**	**Tygerberg**
Age, median (years)	34 (29-40)	35 (29-42)	34 (29-40)	35 (30-42)	36 (31-43)	34 (29-41)
Proportion of patients ≥50 years old	407 (7)	2,167 (11)	1,473 (6)	612 (9)	2,294 (10)	346 (8)
Age categories (years)	**Adjusted Hazard Ratios (aHR), effect of age on mortality adjusted for baseline characteristics, by cohort**					
16-29	1	1	1	1	1	1
30-34	0.92(0.69-1.23)	1.07 (0.94-1.22)	1.06 (0.93-1.21)	1.02 (0.71-1.47)	1.03 (0.90-1.19)	1.01 (0.73-1.41)
35-39	1.18 (0.87-1.61)	1.11 (0.97-1.27)	1.07 (0.93-1.24)	1.28 (0.91-1.80)	1.21 (1.04-1.40)	1.17 (0.84-1.63)
40-44	1.41 (1.03-1.94)	1.11 (0.96-1.30)	1.26 (1.07-1.49)	1.68 (1.16-2.45)	1.38 (1.18-1.61)(	1.34 (0.95-1.88)
45-49	1.42 (0.99-2.03)	1.40 (1.19-1.65)	1.37 (1.09-1.73)	1.89 (1.20-2.97)	1.44 (1.20-1.73)	1.00 (0.66-1.51)
50-54	1.40 (0.89-2.18)	1.53 (1.24-1.91)	1.58 (1.23-2.03)	3.57 (2.21-5.76)	1.77 (1.44-2.17)	1.97 (1.26-3.06)
55-59	2.41 (1.30-4.48)	1.35 (1.04-1.74)	2.42 (1.82-3.23)	2.13 (0.97-4.69)	2.42 (1.90-3.08)	1.42 (0.69-2.92)
60-64	3.50 (1.88-6.51)	2.35 (1.73-3.20)	3.29 (2.02-5.36)	2.35 (1.02-5.36)	2.55 (1.76-3.70)	2.71 (1.31-5.59)
65+	1.09 (0.32-3.65)	1.98 (1.37-2.87)	5.67 (3.24-9.93)	1.44 (0.33-6.27)	3.55 (2.00-6.30)	2.20 (0.85-5.65)

Chapter 7:

Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicenter cohort study

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Author contributions

MC, LM and AB conceived and designed the study. MC and LFJ analyzed the data. MC wrote the first draft of the manuscript. MC, LM, AB, MS, ME, DBG, JG, CJH, RL and LFJ contributed to the writing of the manuscript. MC, MS, DBG, JG, CJH, RL, MM, HP, RW, LFJ, ME, AB and LM read and met ICMJE criteria for authorship. MC, MS, DBG, JG, CJH, RL, MM, HP, RW, LFJ, ME, AB and LM agree with manuscript results and conclusions. DBG, JG, CJH, RL, MM, HP, RW enrolled patients. MS & LFJ gave statistical support.

Abstract

Introduction

Increased mortality among men on antiretroviral therapy (ART) has been documented but remains poorly understood. We examined the magnitude of, and risk factors for, gender differences in mortality on ART.

Methods and findings

Analyses included 46,201 ART-naïve adults starting ART between January 2002 and December 2009 in eight ART programs across South Africa (SA). Patients were followed from initiation of ART to outcome or analysis closure. The primary outcome was mortality; secondary outcomes were loss to follow-up (LTF), virologic suppression and CD4+ cell count responses. Survival analyses were used to examine the hazard of death on ART by gender. Sensitivity analyses were limited to patients who were virologically suppressed and patients whose CD4+ cell count reached >200 cells/μL. We compared gender differences in mortality among HIV+ patients on ART with mortality in an age-standardized HIV-negative population.

Among 46,201 adults (65% female, median age 35 years), during 77,578 person-years of follow-up, men had lower median CD4+ cell counts (85 vs. 110 cells/μL, $p<0.001$), were more likely to be classified WHO stage III/IV (86 vs. 77%, $p<0.001$), and had higher mortality in crude (9 vs. 6 deaths/100 person-years, $p<0.001$) and adjusted analyses (aHR 1.31, 95% CI 1.22-1.41). After 36 months on ART, men were more likely than women to be truly LTF (aHR 1.20, 95% CI 1.12-1.28) but not to die after LTF (aHR 1.04, 95% CI 0.86-1.25). Findings were consistent across all eight programs. Virologic suppression was similar by gender; women had slightly better immunologic responses than men. Notably, the observed gender differences in mortality on ART were smaller than gender differences in age-standardized death rates in the HIV-negative South African population. Over time, non-HIV mortality appeared to account for an increasing proportion of observed mortality. The analysis was limited by missing data on baseline HIV disease characteristics, and we did not observe directly mortality in HIV-negative populations where the participating cohorts were located.

Conclusion

HIV-infected men have higher mortality on ART than women in SA programs, but these differences are only partly explained by more advanced HIV disease at the time of ART initiation, differential LTF and subsequent mortality, and differences in responses to treatment. The observed differences in mortality on ART may be best explained by background differences in mortality between men and women in the South African population unrelated to the HIV/AIDS epidemic.

7.1 Introduction

South Africa has the largest antiretroviral therapy (ART) program worldwide. The program has undergone rapid expansion with nearly 1.8 million individuals initiating ART since 2004(198). Given the unprecedented scale of this initiative there is an urgent need to evaluate the outcomes of the program in order to improve delivery of services. There is particular interest in gender differences in ART program access and survival. Disproportionately more women than men have accessed antiretroviral therapy (ART) in sub-Saharan Africa(123,197). Studies from Europe and North America suggest a higher risk of death on ART for women than men(199); in contrast, across sub-Saharan Africa men appear to experience greater mortality than women on treatment(71,200-202).

A range of possible explanations for gender differentials in mortality on ART have been suggested but there has been no comprehensive evaluation of the putative mechanisms. Baseline characteristics strongly predict mortality on ART(5,132,171) and men initiating ART in many African programs have more advanced HIV disease than women(61,197,201). In addition, loss to follow-up (LTF) is associated with mortality(145) and men are more likely to become LTF than women in many settings(54,203). Evidence regarding gender differences in immunologic and virologic responses is mixed(199). It is vital to understand such differentials in order to improve health outcomes in this large and rapidly expanding health service.

We examined the magnitude of, and risk factors for, gender differences in mortality. We included data from eligible adults starting ART in the South African sites of the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) collaboration between 2002 and 2009, representing about 10% of all patients enrolled nationally during this period(198). We hypothesized that increased mortality in men on ART, if present, would be explained by differences in: 1) baseline characteristics; 2) differential risk of LTF and subsequent mortality; and/or 3) gender differences in virologic and immunologic responses.

7.2 Methods

7.2.1 Study design, population & eligibility criteria

The South African cohorts of IeDEA-SA have been described in detail elsewhere(39,64). Briefly, the collaboration includes eight adult cohorts providing ART services in 3 of the most populous provinces (Gauteng, KwaZulu-Natal and Western Cape). Cohorts range in size and are predominantly government-funded and follow national HIV treatment guidelines. The multicenter cohort is broadly representative of patients accessing public sector ART in rural and urban centers. This retrospective cohort analysis included all ART-naïve HIV-positive adults (≥16 and <=80 years) who initiated ART between 2002 and 2009.

7.2.2 Variables and definitions

Baseline characteristics measured immediately before ART initiation included demographics (age, gender), available measures of HIV disease severity (CD4+ cell count, WHO stage, HIV viral load), clinical and laboratory characteristics (hemoglobin, weight) and calendar year of ART initiation. CD4+ cell count and viral load measures were taken after 12, 24 and 36 months on ART. When measurements were not available at these time points, we included the closest laboratory measurement within a three-month period on either side of the date as available. All laboratory tests were performed by the South African National Health Laboratory Services.

We treated the following variables as categorical: age (16-24, 25-34, 35-44, 45+ years), CD4+ cell count (0-24, 25-49, 50-99, 100-199, 200+ cells/µL), WHO stage (I & II, III, IV) and hemoglobin; we treated weight and log viral load as continuous variables. Due to gender variability in hemoglobin levels, we generated a categorical variable (anemia) from the hemoglobin level (measured in g/dL), which was defined as: none: females >11.9, males >13.1; mild: females 10-11.9, males 11-13.1; moderate: females 8.1-<10, males 8.1-<11; severe: <8.1(188). We defined virologic failure as a viral load measurement >400 copies/milliliter.

The primary outcome was mortality. Secondary outcomes were LTF, virologic suppression and CD4+ cell count responses. Deaths were identified by the sites or by linkage to the National Population Register (NPR) of the Department of Home Affairs. Transfers were recorded by programs and observation time was right-censored at the date of transfer. Patients were defined as LTF if there was no patient contact between analysis closure and database closure. Analysis closure preceded database closure by six months to allow patients to meet the LTF definition. LTF date was defined as the last patient contact date. In order to differentiate between patients who were truly LTF and patients who had died within three months of being LTF (misclassified deaths), we used linkage information to trace patients LTF with South African civil identification (ID) numbers (Supplementary Figure S7.1). Patients who had a date of death within three months after LTF were defined as misclassified deaths. Those with ID numbers who were not found in the population register in this period were defined 'true LTF'(91) For patients who started ART but had no further contact, we added one day of follow-up to allow their inclusion in survival analyses.

7.2.3 Missing data

Based on the assumption that data were likely missing at random, we used MI(189) by chained equation methods(190) to impute missing baseline data. We multiply imputed (20 times) baseline CD4+ cell count, WHO stage, viral load, weight and hemoglobin. The MI models included all measured variables.

Given that a high proportion of patients LTF are likely to have died(145), we used inverse probability weighting(55) to correct mortality and LTF for missing deaths among those defined as LTF. Briefly, LTF patients with ID numbers (approximately 50%) were linked to the South African National Population Register registry to determine their true vital status (and date of death if deceased) and weighted to represent all patients LTF, enabling more accurate estimates of vital status.

7.2.4 Analysis

Data were analyzed using STATA 11.0 (STATA Corporation, College Station, Texas, USA). Baseline characteristics were described with summary statistics (median, interquartile range (IQR) and proportions) by gender. Differences between proportions and medians were tested with Pearson's chi-squared test for proportions or the two-sample Wilcoxon rank-sum test. Two-sided statistical tests were used at alpha=0.05. Time to death and time to 'true' LTF were analyzed from date of ART initiation using Kaplan-Meier curves.

Cox's proportional hazards regression models were used to assess crude and adjusted associations between patient characteristics and outcomes. All available plausible demographic and clinical variables were considered potential confounders and were included in multivariable models if they altered the association between gender and mortality or were significantly associated with the outcome under study. Results are presented as hazard ratios (HRs) with a 95% confidence interval (CI) by duration on ART. The proportional hazards assumption was confirmed by testing gender/time and gender/log time interaction terms. We undertook sensitivity analyses limited to patients who were virologically suppressed and patients whose CD4+ cell count reached >200 cells/μL. We explored heterogeneity in analyses stratified by cohort. The gender mortality ratio was defined as the male divided by the female mortality rate.

To compare gender differences in our cohort with expected gender differences in the HIV-negative population, we calculated HIV-negative mortality in the South African male population and female population, age-standardized to our patients. Age-specific HIV-negative mortality rates in males and females were obtained from the Actuarial Society of South Africa (ASSA) estimates of non-HIV mortality in the year 2005(204) which are derived from vital registration statistics as well as census and survey data (further explanation of the derivation of these rates is provided in Supplementary Text S7.1).

7.3 Results

Among 58,124 patients assessed for eligibility, 11,923 were ineligible for the following reasons: age <16 or >80 years (n=4,344), missing or invalid dates (birth, ART initiation, last visit, outcomes) (n=4,770), non-naïve (n=2,806), unknown sex (n=3) (Figure 7.1). This analysis included 46,201 adults who started ART between 1 January 2002 and 31 December 2009 (median age 35 years; 65% female, Table 7.1), contributing a total of 77,578 person-years of follow-up. Men had a shorter median time to death (483 vs. 532 person-days) and 'true' LTF (434 vs. 495 person-days) than women. By the end of the study period, 29,901 patients were still on ART, 67% (n=20,151) of these female.

At initiation of ART, men were older than women (38 vs. 33 years) and had lower median CD4+ cell counts (85 vs. 110 cells/μL) (Table 7.1). Men were more likely than women to have a CD4+ cell count <50 cells/μL (34 vs. 26%) and to be classified WHO stage III/IV (86 vs. 77%). The median hemoglobin level was similar for men and women (12 vs. 11 g/dL). Among females initiating ART, 7% were pregnant. Gender differences in baseline characteristics were consistent across all the eight cohorts (Figure 7.2).

7.3.1 Gender and mortality

In total, after correction via linkage to the National Population Register, there were 3,946 deaths, 57% among women. Men had a higher risk of mortality (Figure 7.3). The crude mortality on ART was higher for men than women: 8.5 vs. 5.7/100 person-years, unadjusted hazard ratio 1.46 (1.37-1.56), p<0.001. In multivariable analysis, after adjusting for baseline age, cohort, CD4+ cell count, WHO stage, log viral load, anemia and weight, men had a 31% higher risk of death than women (aHR 1.31, 95% CI 1.22-1.41) (Table 7.2). Other baseline factors associated with mortality were age >35 years, CD4+ cell count, WHO stage, anemia, weight and viral load (Supplementary Table S7.1). The association between gender and death persisted with increasing duration on ART. In a stratified analysis, the elevated risk of death for men compared with women was consistent across cohorts (Figure 7.2).

Excluding WHO stage from the adjusted model did not change our main finding (aHR 1.34, 95% CI 1.25-1.44). There was no evidence of interaction between gender and age.

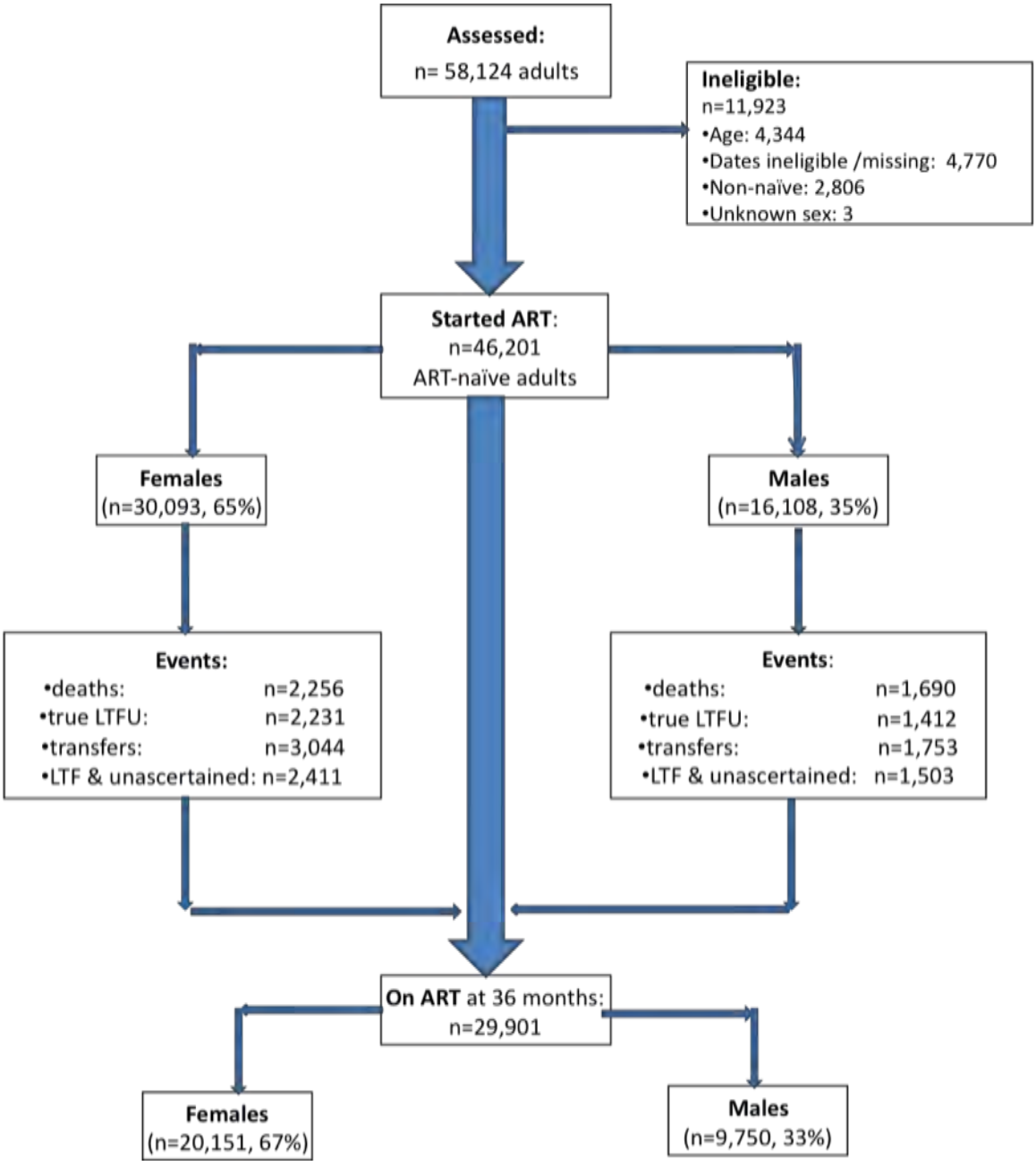


Figure 7.1: Patient flowchart of a combined cohort of adult patients initiating public sector antiretroviral therapy in South Africa, 2002-2009.

Table 7.1. Patient characteristics among 46,201 adults initiating public-sector ART in South Africa, 2002-2009.

Baseline characteristic*	Males	Females	Total
	(n=16,108, 35%)	(n=30,093, 65%)	(n=46,201)
Age, median (IQR), years	38 (33-44)	33 (29-40)	35 (30-42)
16-24 n(%)**	442 (3)	3,124 (11)	3,566 (8)
25-34	5,639 (35)	14,214 (47)	19,853 (43)
35-44	6,486 (40)	8,810 (29)	15,296 (33)
>=45	3,541 (22)	3945 (13)	7,486 (16)
CD4+ cell count, median (IQR), cells/μL	85 (33-153)	110 (48-171)	101 (42-166)
0-24 n(%)	2,785 (20)	3,770 (15)	6,555 (16)
25-49	1,965 (14)	2,832 (11)	4,797 (12)
50-99	3,002 (22)	5,267 (20)	8,269 (21)
100-199	4,798 (35)	10,772 (41)	15,570 (39)
>=200	1,321 (10)	3,353 (13)	4,674 (12)
Missing data	14%	14%	14%
WHO stage, n(%)	5,538 (34)	11,290 (38)	16,828 (36)
I & II	790 (14)	2,704 (24)	3,494 (21)
III	3,221 (58)	5,933 (53)	9,154 (54)
IV	1,527 (28)	2,653 (24)	4,180 (25)
Missing data	66%	62%	64%
Viral load, n(%)	8,092 (50)	14,876 (49)	22,968 (50)
Log_{10} copies/ml, median (IQR)	4.9 (4.4-5.3)	4.8 (4.2-5.3)	4.8 (4.3-5.3)
Missing data	50%	51%	50%
Hemoglobin, n(%)	11,714 (73)	20,237 (67)	33,239 (72)
Median (IQR), g/dL	12 (10-14)	11 (10-12)	11 (10-13)
Missing data	27%	33%	28%
Anemia, n(%)	11,714 (73)	20,237 (67)	33,239 (72)
None	3,813 (33)	4,968 (23)	8,781 (26)
Mild	5,638 (48)	12,997 (60)	18,635 (56)
Moderate/severe	2,263 (19)	3,560 (17)	15,823 (18)
Weight, n(%)	12,740 (79)	23,788 (79)	36,528 (79)
Median (IQR), kg	60 (53-67)	59 (51-68)	59 (52-68)
Pregnant, n(%)***		1,494 (7%)	
Calendar year of ART initiation			
2002 & 2003	439 (3)	856 (3)	1,310 (3)
2004	1,338 (8)	2,847 (9)	4,271 (9)
2005	2,743 (17)	5,568 (19)	8,640 (18)
2006	4,345 (27)	7,851 (26)	12,992 (26)
2007	3,629 (23)	6,506 (22)	10,944 (22)
2008	2,323 (14)	4,398 (15)	7,479 (15)
2009	1,291 (8)	2,067 (7)	3,836 (8)
Follow-up, median (IQR), person-days			
time to death	483 (172-877)	532 (216-918)	515 (200-905)
time to 'true' LTF	434 (142-827)	495 (185-879)	476 (170-864)

* All differences between men and women were statistically significant (p<0.001)

** n(%) reflects the number (proportion) of patients with values for this variable

*** Data from five cohorts

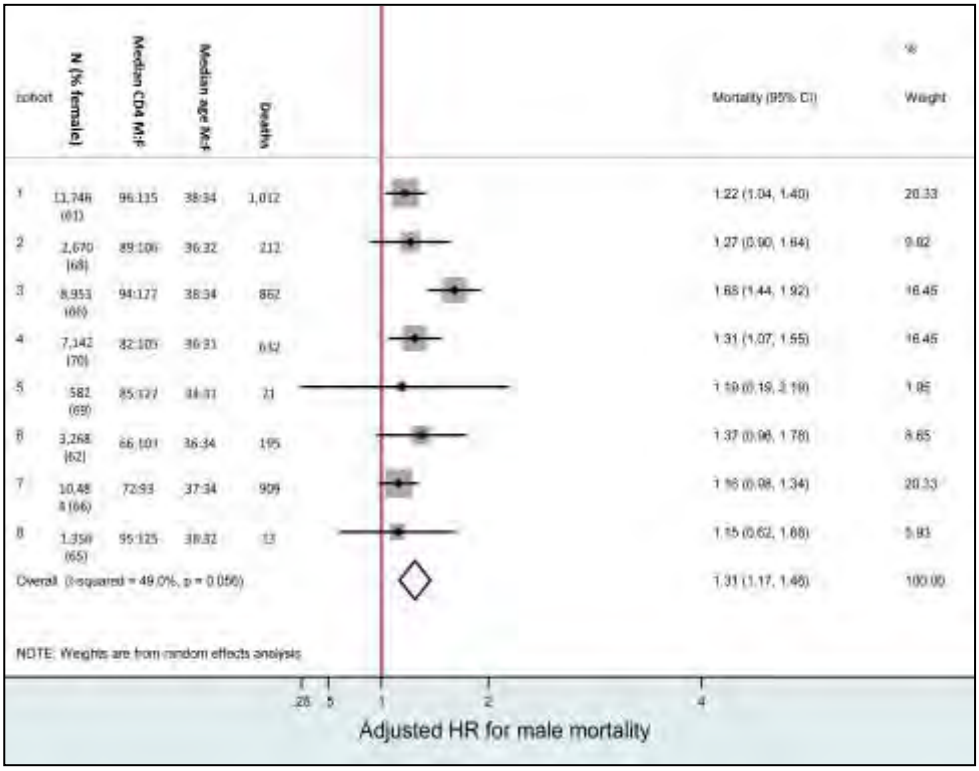


Figure 7.2. Baseline characteristics and hazard ratios for male vs. female (M:F) mortality by cohort, adjusted for baseline characteristics.

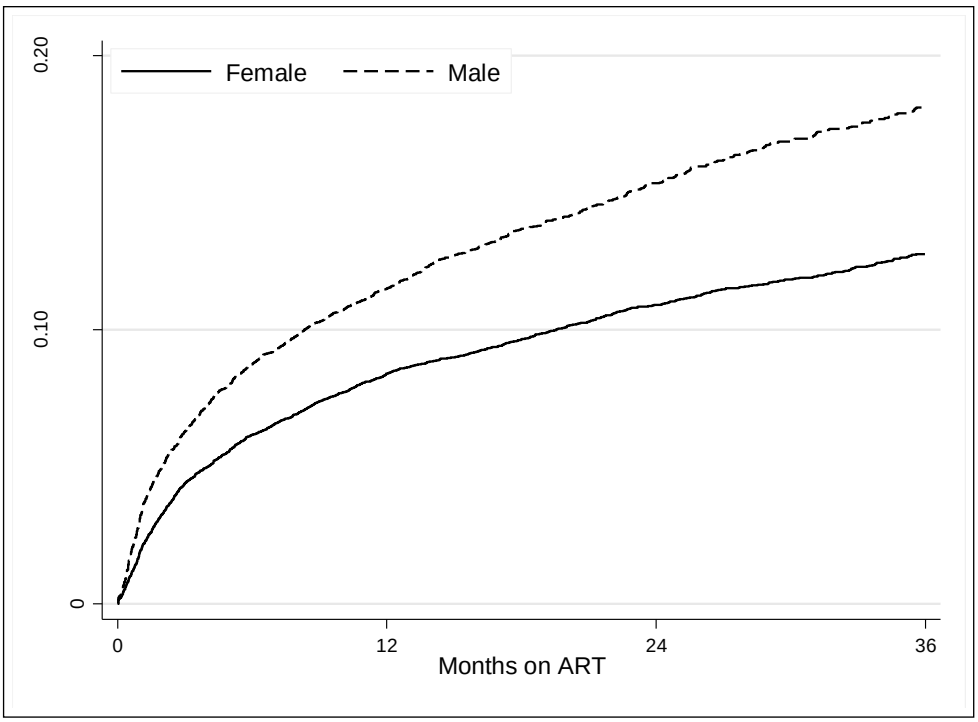


Figure 7.3. Corrected mortality by gender and ART duration.

Table 7.2. Crude and adjusted associations between male gender and mortality by duration on ART.

Duration	HR	aHR
0–12 months	1.28 (1.09–1.51)	1.10 (0.93–1.31)
12–24 months	1.63 (1.37–1.94)	1.36 (1.05–1.78)
24–36 months	1.62 (1.22–2.14)	1.39 (0.94–2.06)
>36 months	1.71 (1.08–2.70)	1.35 (0.76–2.38)
Total time	1.46 (1.37–1.56)	1.31 (1.22–1.41)

Multivariable models adjusted for cohort, age, CD4+ cell count, WHO stage, anemia, weight, and log viral load at ART initiation. 95% CI in brackets after HR and aHR.

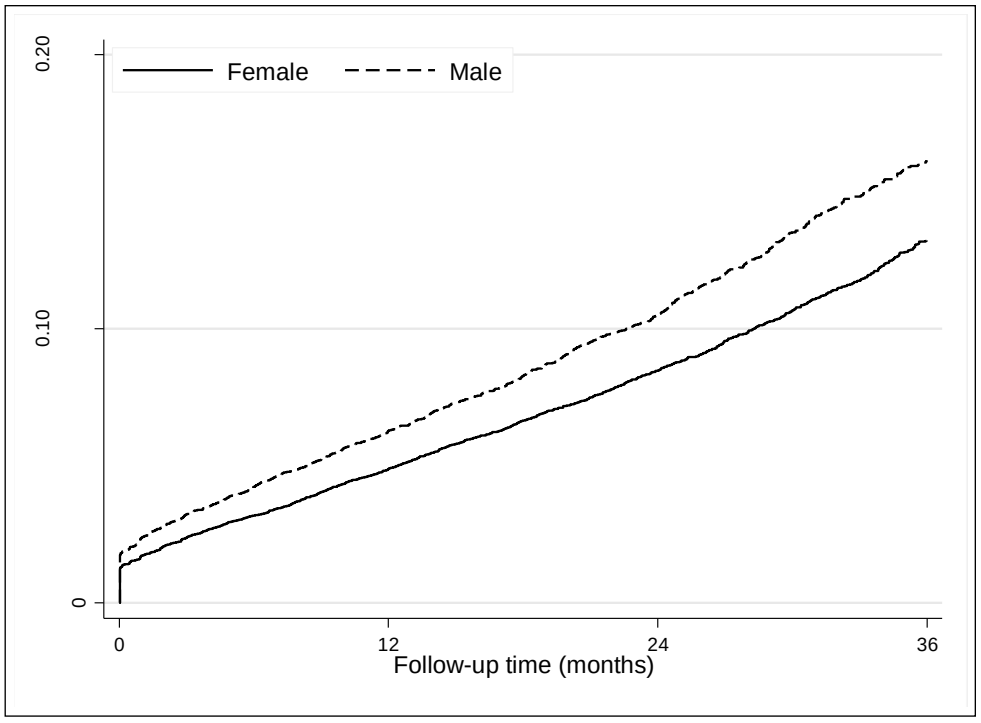


Figure 7.4. 'True' loss to follow-up by gender and ART duration.

7.3.2 Gender and loss to follow-up

Using our initial definition, 8,303 adults were suspected LTF, 61% female (Supplementary Figure S7.1). We were able to ascertain the vital status of 4,389 patients who had ID numbers (61% female). Among those patients who were LTF without ID numbers and whose outcomes could not be ascertained (n=3,914), 62% were female. After linkage to the NPR, we identified 746 patients who had died within three months of being suspected LTF. We regarded these as misclassified deaths (57% female). After correction for these deaths, a total of 3,643 patients were defined as 'true' LTF, 61% female.

Men were more likely than women to experience 'true' LTF (Figure 7.4). The crude 'true' LTF rate was 10/100 person-years, lower among women than men (9 vs. 12/100 person-years respectively). In multivariable analysis, after adjusting for baseline age, cohort, CD4+ cell count, WHO stage, anemia, weight, viral load and calendar year of initiation, men were more likely to be 'truly' LTF than women (aHR1.20, 95% CI 1.12-1.28). Within each cohort, the trend towards increased risk of 'true' LTF was consistent but estimates were less precise. Using linkage to the NPR, we then explored mortality among those who were truly LTF with ID numbers (i.e. still alive three months after being suspected LTF). We found no gender difference in the hazard of death among those patients who were 'truly' LTF (aHR 1.04, 95% CI 0.86-1.25).

7.3.3 Gender and virologic and immunologic responses to ART

There was a high proportion of virologically suppressed patients at 12, 24 and 36 months on ART, with no evident gender difference in proportions (Table 7.3). When analysis of mortality was restricted to individuals who were virologically suppressed at 12 months, men still had a higher risk of death than women (aHR 1.38, 95% CI 1.07-1.79). Women initiating ART had a higher baseline CD4+ cell count and better CD4+ cell count responses to men over 36 months (Supplementary Figure S7.2). The median incremental CD4+ cell gains for women and men at 12, 24 and 36 months were 184 vs. 154, 87 vs. 76 and 56 vs. 44 cells/µL respectively (Table 7.3, p<0.001

for all comparisons). In a sensitivity analysis limited to patients who had reached a CD4+ cell count >=200 after a year on ART, the gender difference in mortality persisted (aHR 1.37, 95% CI 1.03-1.83) (analysis not shown).

7.3.4 Gender and non-HIV mortality

Given the persistence of the gender differential in mortality among patients on ART, we compared this to the background gender differential in mortality in the South African population. Figure 7.5 shows that the gender mortality ratio among patients on ART appears to be smaller than the age-standardized HIV-negative mortality ratio for men versus women in South Africa. HIV-negative men with the same age distribution as that in the ART cohort would be expected to die at twice the rate in HIV-negative women of the same age, compared with our adjusted hazard ratio of 1.31 on ART.

With increasing duration of ART, the contribution of expected non-HIV mortality to observed mortality increased from an estimated 5% in the first six months to 36% after 36 months among men, and from 3-25% among women during the same period (Table 7.3). In further analysis stratified by age (16-34 and 35+ years), expected non-HIV mortality accounted for a larger proportion of deaths in the older men than in the younger men (Supplementary Table S7.2). One exception was the proportion of observed male mortality attributable to non-HIV mortality at >36 months, likely to be random error due to the small number of deaths at the longest duration. In both age groups, non-HIV mortality contributed more substantially to male mortality than to female mortality. In addition, over all periods on ART, although the expected ratio of male to female non-HIV deaths differed at younger and older ages, all ratios were greater than the male to female ratio of observed mortality on ART.

Table 7.3. Virologic and immunologic responses by gender and duration on ART.

Measurement	12 months		24 months		36 months	
	Female (n=21,032)	Male (n=10,702)	Female (n=13,232)	Male (n=6,826)	Female (n=7,440)	Male (n=3,950)
Viral load tests						
Total tested, n	13,529	6,600	8,280	3,798	4,225	1,958
Proportion suppressed[a]	0.87	0.86	0.86	0.86	0.93	0.95
Proportion missing data	0.36	0.38	0.37	0.44	0.43	0.50
CD4+ cell counts						
Total tested, n	15,882	7,752	9,510	4,438	4,728	2,168
Median, cells/µl (IQR)	294 (204-403)	239 (164-337)	381 (268-512)	315 (217-431)	437 (313-582)	359 (243-493)
Median CD4+ cell count increase,[b] (IQR)	179 (100-273)	145 (78-223)	89 (13-175)	70 (9-141)	63 (-22-147)	39 (-21-114)
Proportion missing data	0.24	0.28	0.28	0.35	0.36	0.45

[a] Proportion suppressed is the proportion of patients with available data who achieved a viral load ≤400 copies/ml.

[b] Median CD4+ cell count increase is the difference in CD4+ cell count at each time point between this measure and the measure taken at the previous time point; all differences between men and women were statistically significant, p<0.001.

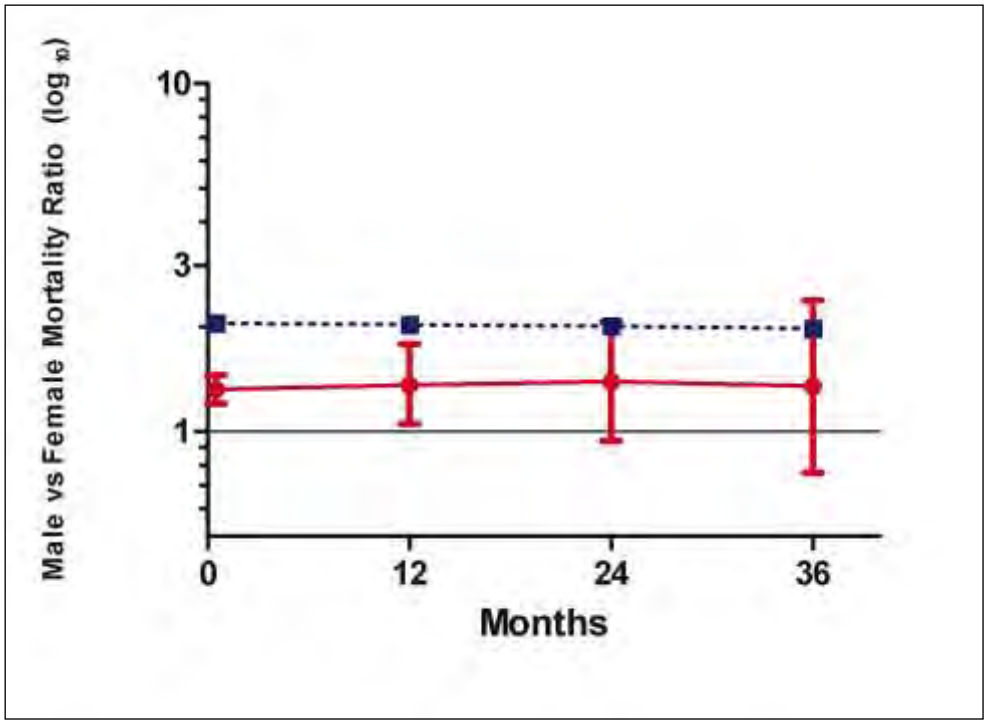


Figure 7.5. Age-standardized male versus female mortality ratios.

Table 7.4. Observed crude mortality,* age-standardized HIV-negative mortality and expected non-HIV mortality as a proportion of observed mortality among men and women, by duration on ART.

Gender	Mortality	Duration on ART				
		0-6 mo**	6-12 mo	12-24 mo	24-36 mo	>36 mo
Male	Observed mortality (crude)	19	6	4	3	3
	HIV-negative mortality (age-standardized)	0.90	0.92	0.95	0.98	1.03
	Expected non-HIV mortality as a percentage of observed mortality	5%	15%	21%	29%	36%
Female	Observed mortality (crude)	13	5	3	2	2
	HIV-negative mortality (age-standardized)	0.36	0.37	0.38	0.39	0.42
	Expected non-HIV mortality as a percentage of observed mortality	3%	8%	14%	19%	25%

* per 100 person-years
** mo=months

7.4 Discussion

These analyses demonstrate that among patients initiating ART between 2002 and 2009 at sites across South Africa, men had higher mortality than women. We hypothesized that gender differences in mortality would be explained by differences in baseline characteristics, LTF and subsequent mortality, and/or virologic and immunologic responses. However we found that the increased mortality risk among men persisted throughout each analysis, including after adjustment for measures of HIV disease at the time of ART initiation; in the subset of patients who achieved virologic suppression; and among patients with good immune responses to treatment.

There is a large and growing body of work on gender and ART in developing countries, much of which documents the same association repeatedly(205): disproportionately fewer men than women access ART(123,125,197), and there is higher mortality among men than women on ART(54,64,200,202,206,207). Such studies typically speculate as to the possible mechanisms underlying the observed associations. Putative mechanisms include: poor health-seeking behaviors among men leading to more advanced disease at the time of ART initiation, differential rates of LTF leading to higher mortality, behavioral factors such as poor adherence, and/or biologic factors such as gender differences in immunologic responses to ART. However, there have been few systematic attempts to evaluate each of these possible mechanisms.

In this study, women comprised the majority of adults starting ART across the country. In the early years of ART programs there were understandable concerns that due to gender imbalances, women may have reduced access to ART services(208). Contrary to this, however, there is mounting evidence that men appear disadvantaged in their access to ART programs. Numerous papers and a systematic review have suggested gender inequalities in ART access, particularly in Sub-Saharan Africa(123,197,202), and ART initiation in South Africa, relative to ART need, is substantially higher in women than in men(198).

Among patients who do start ART, late presentation has been cited as one of the main reasons for increased male mortality in ART programs(199-202). In sub-Saharan Africa, men appear to initiate ART at older ages and with more advanced HIV disease than women(64,123,197,201) and markers of advanced HIV disease at the time of ART initiation strongly predict early mortality on ART(61,69,138,171,209). However in our multivariable models we found that adjustment for baseline characteristics accounted for only part of the gender difference in mortality, and that the gender differentials in mortality continued to appear for several years after ART initiation. The reasons for men's later entry into ART programs are poorly understood but frequently are attributed to gender differences in health-seeking behavior or in routes of referral(48). An alternate and more compelling explanation may be that while prioritizing maternal and child health services in many public health systems, men's primary health care needs may have been neglected(48,210-212), a possibility that warrants further research attention.

We then assessed the role of LTF in explaining mortality differentials. Increased mortality among patients LTF, especially within the first three months after LTF, has been well documented(91,155,157,173,213,214). In turn, it is plausible that if males are more likely to be LTF, this could explain their elevated mortality risk. Through linkage to the South African Population Register we were able to identify a group of patients who were truly LTF, and to trace their vital status after being LTF. Although men were more likely to be LTF compared with women, we found no gender difference in mortality after LTF, and deaths after LTF contributed only a small proportion of all deaths. Thus in these data, LTF alone did not appear to explain men's increased mortality.

Behavioral factors such as treatment adherence could also help to explain the observed increased male mortality on ART. Poor adherence to ART, measured by virologic non-suppression, significantly increases the risk of mortality on treatment.

We found no apparent gender difference in virologic suppression, although previous studies have suggested that adherence may vary by gender(56). Of note, this finding was consistent across all cohorts, and in a sensitivity analysis restricted to patients who were virologically suppressed at twelve months, men still had a higher risk of subsequent death than women. As a result, gender differences in adherence to treatment do not appear to explain differences in mortality.

Biologic differences between men and women have been suggested as shaping immunologic responses to ART and mortality risk. We found that women had higher CD4+ cell counts at ART initiation than men, and slightly better absolute CD4+ cell increases on treatment. This is in line with results from two collaborative studies in sub-Saharan Africa which documented greater immune recovery in women than in men, with gender-based differences increasing with time on ART(104,215). However even among patients with similar immunologic responses by one year on treatment, the gender difference in mortality persisted.

In these data, the finding for persistently increased male mortality for up to three years on ART does not appear to be explained entirely by baseline differences in HIV disease status, variation in LTF, differences in virologic suppression, or sex-linked differences in immune responses to treatment. Having thus refuted our a priori hypotheses, we explored alternate explanations for the observed association. We examined evidence for gender differences in non-HIV adult mortality in South Africa, and found pronounced differences that appear independent of the HIV/AIDS epidemic. Specifically, evidence from actuarial modeling suggests that HIV-negative South African men in the same age groups as our study population have twice the mortality risk of women, although the male-female differences tend to be more pronounced in young adults than in older adults. This pattern is not unique to South Africa: similar trends are seen elsewhere in Africa and worldwide(216-220). This evidence places these data, and previous studies showing increased mortality among men in ART services across Africa, into perspective: among patients on ART, men have an increased risk of death on ART compared to women, but this same

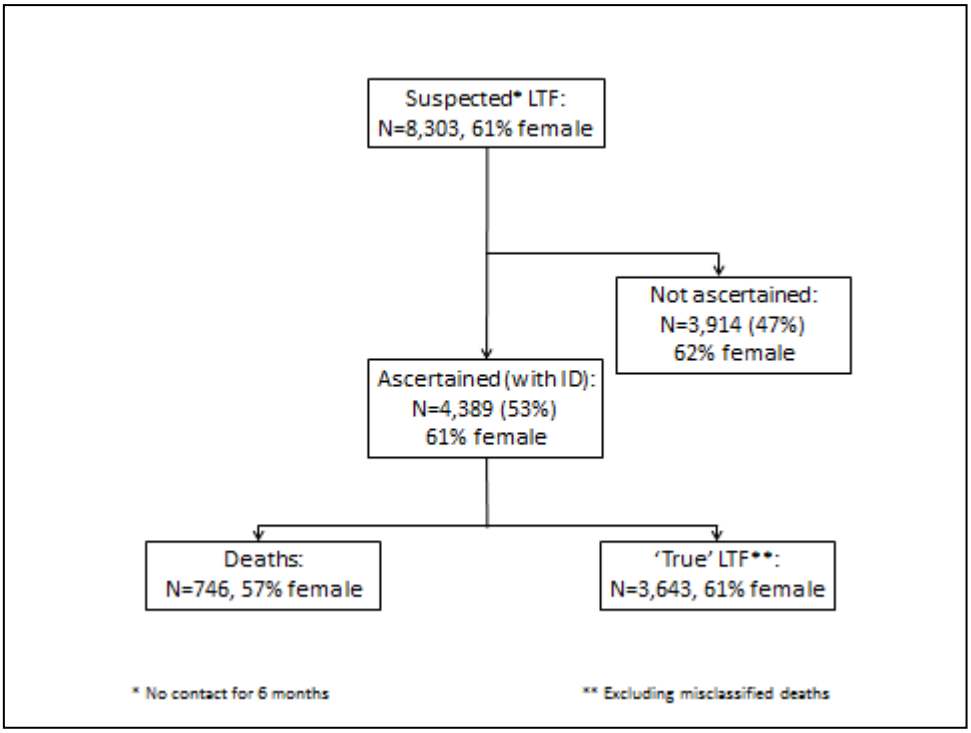
phenomenon operates in HIV-negative individuals. In fact, in South Africa the mortality ratio for men versus women on ART appears to be somewhat smaller than the age-standardized ratio for men versus women estimated for the HIV-negative population. Gender differentials in the mortality of HIV-negative individuals are well-documented in South Africa and include an increased burden of mortality among younger men due to traumatic causes and non-HIV TB(221). It is possible that through accessing ART services, men and women may access other preventive and curative services which reduce non-HIV mortality. While these findings are intriguing, it is important to recognize that our original hypotheses did not include gender differences in non-HIV mortality, and this phenomenon clearly requires further investigation.

Observational studies of patients on ART face major constraints in terms of mortality ascertainment, LTF and missing measurements. Most cohort analyses from sub-Saharan Africa – and especially large collaborative analyses – have limited ability to ascertain true outcomes as they have little capacity to follow patients actively(201). In addition, few African countries have high quality vital statistics(219,222,223). In turn, most large ART programs have difficulty confirming patients' true vital status(224) and in the absence of reliable death registration, researchers have undertaken targeted tracing studies(155). In South Africa, the National Population Register captures nearly 90% of adult deaths(89). Through our linkage with this register, we are able to distinguish between 'true' LTF and unrecognized mortality in many patients. Moreover, consistency of findings across different cohorts strengthens the generalizability of our results.

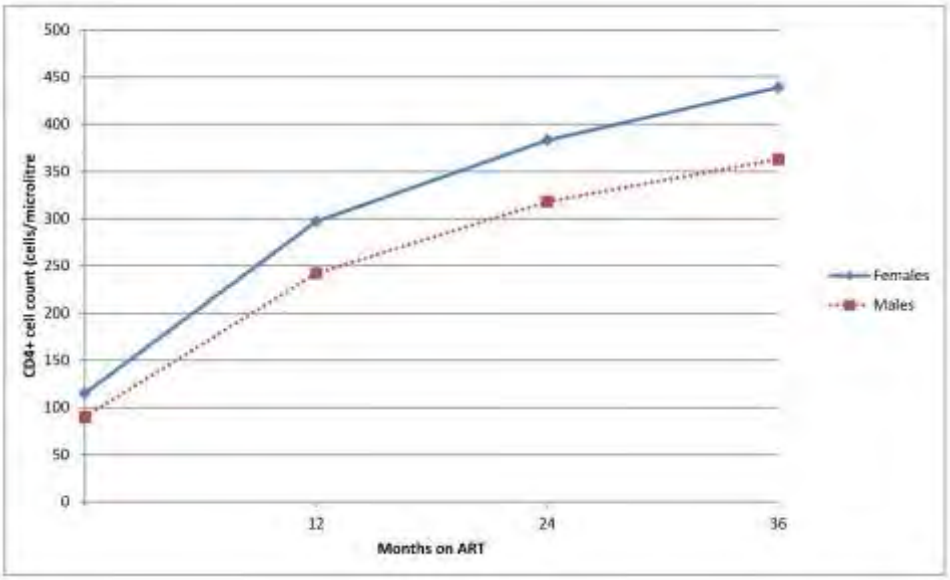
Interpretation of these results is subject to several important limitations. These data come from multiple service delivery programs from across South Africa, and there is a substantial amount of missing data in this analysis. For example, SA national identity numbers were only available for 53% of those who were suspected to be LTF, and it is possible that there are systematic differences between patients with and without ID numbers for which we have not accounted. There was also a high

proportion of missing values for WHO stage and viral load; we tried to address this with MI and sensitivity analyses confirming our main findings. Missing data on specific risk factors for mortality, particularly prevalent tuberculosis at ART initiation(225), further limited this analysis. Finally, we did not observe mortality in HIV-negative populations where the participating cohorts are located, and instead used a national-level actuarial model to estimate mortality in men and women who are HIV-negative. These findings are likely to be generalizable to the South African national ART program, and potentially to other parts of the region, but further investigation in other settings is warranted.

In summary, there have been concerns raised about the presence of gender differences in mortality on ART in South Africa and many other parts of the continent. In this study we systematically explored this phenomenon and found that none of the explanations posited for this association adequately explains the increased mortality observed among men on ART. Instead, the observed differences in mortality on ART appear may be best explained by background differences in death rates between men and women in the South African population, unrelated to the HIV/AIDS epidemic.



Supplementary Figure S7.1. Determining 'true' loss to follow-up.



Supplementary Figure S7.2. Crude CD4+ cell count responses by gender

Supplementary Table S7.1: Crude and adjusted associations between male gender and mortality.

	Overall Mortality	
	Crude HR	**Adjusted* HR**
Male gender	1.46 (1.37-1.56)	1.31 (1.22-1.41)
Age (years)		
16-24	ref	ref
25-34	1.03 (0.90-1.18)	1.02 (0.89-1.17)
35-44	1.21 (1.06-1.39)	1.21 (1.05-1.39)
>=45	1.45 (1.25-1.68)	1.49 (1.28-1.73)
WHO Stage		
I & II	ref	ref
III	1.72 (1.36-2.16)	1.21 (0.94-1.55)
IV	2.80 (2.04-3.85)	1.58 (1.10-2.26)
CD4+ cell count (cells/µl)		
0-24	ref	ref
25-49	0.79 (0.72-0.88)	0.81 (0.73-0.90)
50-99	0.52 (0.48-0.58)	0.61 (0.55-0.67)
100-199	0.33 (0.30-0.36)	0.46 (0.41-0.51)
>=200	0.31 (0.27-0.36)	0.49 (0.41-0.57)
Weight (kg)	0.96 (0.96-0.97)	0.98 (0.97-0.98)
Viral load (log_{10} copies/ml)	1.42 (1.33-1.53)	1.15 (1.06-1.26)
Anemia		
none	ref	ref
mild	1.64 (1.48-1.82)	1.31 (1.19-1.46)
moderate	2.73 (2.46-3.04)	1.85 (1.66-2.07)
severe	3.81 (3.38-4.30)	2.43 (2.14-2.77)

Supplementary Table S7.2. Mortality by duration on ART, stratified by age.

		Duration since ART initiation				
		0-6 months	**6-12 months**	**12-24 months**	**24-36 months**	**>36 months**
Ages 16-34						
Male	Observed mortality (crude)	18.3	5.9	3.2	3.6	1.5
	HIV-negative mortality (age-standardized)	0.56	0.57	0.57	0.57	0.58
	Expected non-HIV mortality as % of observed	3%	10%	18%	16%	38%
	Standardized mortality rate (SMR)	32.3	10.2	5.5	6.2	2.7
Female	Observed mortality (crude)	12.7	4.5	2.2	2	1.5
	HIV-negative mortality (age-standardized)	0.23	0.23	0.23	0.23	0.24
	Expected non-HIV mortality as % of observed	2%	5%	10%	12%	16%
	SMR	55.8	19.8	9.7	8.5	6.2
Ages 35+						
Male	Observed mortality (crude)	19.6	6.4	5.1	3.4	3.2
	HIV-negative mortality (age-standardized)	1.09	1.09	1.11	1.12	1.16
	Expected non-HIV mortality as % of observed	6%	17%	22%	33%	36%
	SMR	18	5.8	4.6	3.0	2.8
Female	Observed mortality (crude)	13.8	5.2	3.3	2.2	1.8
	HIV-negative mortality (age-standardized)	0.53	0.53	0.53	0.53	0.54
	Expected non-HIV mortality as % of observed	4%	10%	16%	24%	30%
	SMR	26.2	9.8	6.3	4.2	3.4

Supplementary Text S7.1. Method for estimating non-HIV mortality.

Due to the lack of vital registration systems in many developing countries(226), direct estimates of mortality by age and sex are often not available. To address this problem, life tables are often estimated for developing countries by taking 'standard' life tables (which define mortality rates by individual age and sex) and adjusting these to be consistent with aggregate measures of mortality (such as the under-5 mortality rate or probability of death between ages 15 and 60), as estimated in local surveys(227). For example, in the Brass logit life table system(228), the proportion of individuals who survive to age *x* (l_x) is modelled using the equation

$$\frac{1}{2}\ln\left(\frac{1-l_x}{l_x}\right) = \alpha + \frac{1}{2}\beta\ln\left(\frac{1-l_x^S}{l_x^S}\right),$$

where l_x^S is the proportion of individuals who survive to age *x* in the standard life table. In this model there are only two parameters that need to be estimated in adjusting the standard life table to the local population: α and β (the former determines the adjustment to the overall level of mortality, the latter determines the adjustment to the age gradient in mortality rates).

In South Africa and other countries facing generalized HIV/AIDS epidemics, the use of these simple adjustments to standard life tables has become problematic because of the dramatic change in the patterns of mortality (by age and sex) caused by AIDS. One possible solution to this problem is to split all-cause mortality into HIV mortality and non-HIV mortality, the former being estimated by mathematical models that are fitted to local HIV prevalence data, and the latter being estimated through the adjustment of standard life tables (on the assumption that AIDS would not substantially change the age pattern of non-HIV mortality). This is the process that has been followed in the estimation of mortality rates in the ASSA2008 AIDS and Demographic model, published by the Actuarial Society of South Africa (ASSA)(204). The procedure followed is to

a) use estimates of mortality in 1985 (when HIV prevalence in the South African population was negligible(229,230)) as the standard in the estimation of non-HIV mortality;
b) use the time-dependent Brass logit life table approach to define non-HIV mortality in each subsequent year;
c) use ASSA2008 estimates of HIV-related mortality in each year (based on calibration to South African HIV prevalence data from antenatal clinic surveys and household surveys); and
d) vary the α and β parameters and model HIV parameters until the combined model estimates of all-cause mortality (by age and sex) are consistent with the numbers of deaths in each year, as recorded in the National Population Register(89), after correcting for under-reporting of deaths.

An obvious limitation of this method is that it involves the estimation of non-HIV mortality without any direct data on the cause of death. However, it is important to note that because of the very distinct change in the pattern of deaths by age and sex, brought about by AIDS, the age- and sex-specific death data over time are actually very informative regarding the extent of AIDS mortality, even without cause-of-death data. It is also worth noting that an independent assessment, based on cause-of-death data, has validated the estimates of AIDS mortality produced by a previous version of the ASSA model(231).

Although the non-AIDS mortality estimates cannot be quantified with pinpoint accuracy, they are likely to be roughly of the right order of magnitude.

In the present analysis, we have used the ASSA2008 lite model estimates of non-HIV mortality in 2005. Although other years could have been chosen, 2005 was selected because it was close to the median date of ART enrolment in the IeDEA-SA collaboration(64), and because ART coverage in South Africa in 2005 was still relatively low(149) (so that potential bias due to mis-specification of mortality on ART would not have been substantial). The ASSA2008 estimates of non-HIV mortality do not change substantially by year; for example, annual non-HIV mortality probabilities in 40-year old men drop steadily from 0.0079 in 2000 to 0.0074 in 2007, and corresponding probabilities in 40-year old women drop from 0.0041 in 2000 to 0.0037 in 2007. Estimates of non-HIV mortality would therefore not change substantially if alternative years were selected.

Chapter 8:
DISCUSSION

8.1 Summary

This thesis provides novel evidence of a massive, rapid scale-up of ART services in South Africa between 2002 and 2013, despite a delayed start due to initial political opposition to ART. With each successive year the number of patients enrolled has grown and their baseline immunologic status has improved, suggesting increased coverage at a population level. Among patients who are initiated and retained on ART, mortality after 12 months on ART decreases with each successive year of ART initiation and patients have good immunologic and virologic responses to ART.

However ART programs in South Africa have been less successful in ensuring early and equitable access to ART and in retaining patients on treatment. Late diagnosis and initiation of treatment remain a challenge. LTF poses a threat to effectiveness and increases each year of enrollment and with duration on ART. The proportion of patients TFO between ART services is increasing, but the risk of death in these patients is similar to those retained in care.

This thesis highlights how age and gender, both major determinants of health regardless of HIV status, also impact on enrollment and outcomes on ART. Increasing proportions of patients over 50 years of age are starting and remaining on treatment over time. While mortality increases with age at ART initiation, the effect is modified by baseline immunologic status. Men are older and have more advanced HIV disease than women at the start of ART. Men have higher mortality than women after ART initiation, but this difference is only partially explained by HIV disease stage at ART initiation, differential LTF and differences in responses to treatment. Indeed, the gender difference in mortality is greater in HIV-negative

individuals than among people on ART, pointing to the need to understand context-specific factors which may influence mortality in ART programs.

In light of historical opposition to ART and the restrictive environment within which treatment was first rolled out in South Africa, the expansion of services to over two million individuals in ten years is remarkable. However, these patients constitute less than one-third of the six million HIV-positive individuals who will eventually require ART or die without treatment in the next few years(232). These challenges are compounded by the growing epidemic of non-communicable diseases particularly among older people. In turn the number of people needing care may continue to increase if prevention efforts are not successful. This chapter discusses the findings of this thesis and concludes with recommendations to increase enrollment on ART and to support a successful transition into chronic care for the millions of individuals who will require care in the near future.

8.2 Discussion

Given the results of these analyses, this discussion addresses two broad underlying themes which impact on the effectiveness of ART programs, namely *what* we research (and by implication what is overlooked, for instance the effects of gender and age on mortality) and *how* we research these factors and outcomes. In the first place, if we do not measure a construct adequately, we cannot address its potential impact on ART outcomes. Chapters 3-5 reported on *what* has been measured including the frequency and determinants of key measures of effectiveness such as patient enrollment, mortality, LTF and retention. The thesis found strong temporal trends in enrollment, baseline characteristics and outcomes related to scale-up, discussed in section 8.1.1 below. These chapters also highlighted what had *not* been studied adequately and Chapters 6 and 7 used the lenses of age and gender to explore patient outcomes more fully, discussed in section 8.1.2 below.

Secondly, *how* we undertake research is equally important in interpreting our findings. It is argued, for instance, that meta-analysis of routinely gathered

individual patient-level data can result in “tight confidence intervals around a spurious estimate”(43). Factors which could impact on the validity of inferences from this thesis include missing data, heterogeneity of findings, differential measurement and the need for simpler patient monitoring, discussed in section 8.2 below.

8.2.1 *What* we found in researching the ART program

8.2.1.1 Temporal trends in baseline characteristics and outcomes

Chapters 3-7 provide evidence of strong temporal trends in enrollment, baseline characteristics and patient outcomes in the South African cohorts of IeDEA-SA. Chapter 3 described patient numbers increasing with each successive year of enrollment, from 1,462 patients enrolled in 2002/2003 to 15,628 patients enrolled in 2007. These findings were extended in Chapter 6, which found that the year-on-year increase in enrollment persisted through to 2013. Despite such rapid increases in enrollment the need for ART continues to grow with each new revision of the guidelines for ART initiation. Each lowering of the threshold for ART initiation increases the numbers of eligible individuals.

Another temporal theme was the impact of calendar year of ART initiation on baseline characteristics. With each successive year of enrollment, the program enrolled patients with less advanced HIV disease, evident in the increasing baseline CD4+ cell count and decreasing proportion of patients with WHO stage IV disease. While the increase in baseline immunologic status suggests some improvement in coverage at a population level(21), patients still started ART later than was recommended in national guidelines, increasing their mortality risk. In Chapter 4 nearly 30% of patients started ART with a CD4+ cell count <50 cells/μL between 2002 and 2007. Such severely immune-compromised patients have extremely high early mortality(132). Earlier initiation of treatment, especially among young men, could prevent much early mortality and improve patient outcomes on ART. Integrating ART into TB as well as maternal and child health services can improve ART coverage(233). Combining an ART clinic with treatment for other prevalent

chronic conditions such as diabetes mellitus and hypertension can support retention in lifelong chronic care(172).

Over five years, the availability of baseline CD4+ cell count decreased from 72% to 65% of patients enrolling on ART(Chapter 3). In light of the rapid increases in enrollment, it is understandable that patients may not have all laboratory tests performed at baseline. Even if the tests are done, it is likely that many results are not recorded due to administrative overload. This thesis suggests that data collection should be limited to the most important variables at particular time points. For example, given the role of baseline CD4+ cell counts in determining the level of immunologic responses over three years (Chapter 6), efforts should be made to collect more complete baseline CD4+ cell counts. However after baseline, it may not be necessary to continue to monitor immunologic response. Our findings are in line with a recent study among 14,792 adults which found that up to ten years on ART, >90% of virologically suppressed patients sustained good immunologic responses(234). Follow-up CD4+ cell counts may be adding unnecessary clinical and administrative complexity and cost and consideration should be given to dropping these tests.

The evidence for strong temporal trends in enrollment, baseline patient characteristics and laboratory measures informed the decision to explore whether similar trends existed in mortality, LTF and retention. It was encouraging to find in Chapter 4 that the rapid pace of scale-up does not increase mortality risk. Indeed as the program grows in size, mortality after 12 months on ART declines. This may reflect improved coverage as programs enroll patients with less advanced HIV disease. In contrast, increasing LTF suggests that rapid scale-up reduces the program's ability to retain and trace patients, a particular concern in light of initiatives to offer treatment as prevention (TasP)(235). For TasP to be effective in improving health outcomes for people with HIV/AIDS, patients need to complete the entire HIV care continuum(26). Enrolling large numbers of healthy individuals on

ART and being unable to retain them in care may result in increased resistance and transmission of resistant virus, reviving fears about 'antiretroviral anarchy'(20). Given the need to improve retention, successfully re-orienting health systems towards chronic care will require a better understanding of the phenomenon of LTF. Often viewed as a single construct, LTF in an ART cohort more likely represents a range of patient outcomes including patients truly LTF (i.e. lost to care), interrupting care(94) and receiving care at other facilities ('silent transfers') as well as those classified LTF through administrative error or inadequate patient monitoring systems(151,236). For example, the apparently sharp increase in observed LTF among patients enrolled in more recent years is likely to reflect the cumulative burden of increasing patient numbers on both ART services and health informatics systems. In addition, risk factors for LTF may differ according to context. For instance, LTF may be associated with higher or lower nadir CD4+ cell counts(91,237). Understanding what LTF means in a specific context is the first step towards finding effective strategies to retain patients in care.

Such strategies should include models to simplify ART delivery as LTF increases with patient caseload(175,237). Two recent systematic reviews used GRADE[1] methodology to assess the quality of evidence on decentralization and taskshifting. LTF was lower when ART was initiated and continued at the health center level(238), although confounding could not be excluded due to the observational nature of most of the studies. In terms of taskshifting, nurse-initiated care may decrease LTF(239). However conflicting results in the literature suggest the need for different models in different settings. For example, one study in South Africa found higher LTF in patients down-referred to nurse-managed services(240), particularly among males, while another reported far lower LTF among patients down-referred than retained at the site of treatment initiation(241). Retention in care may be improved by separating ART delivery for stable patients from clinical assessments. Other initiatives that have shown promising results include the use of mobile health

[1] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group was set up in 2000 to provide a common approach to grading the quality of evidence and informing the strength of recommendations in guidelines.

electronic technology(242,243), workplace programs to increase access and retention among men(244) and the use of courier services for home ART delivery(245). Reducing the frequency of clinical and pharmacy visits, ART adherence clubs, community ART distribution and patient-led community ART groups removed patient barriers to treatment including travel and lost income and reduced the burden on the health system(246). For all approaches, costs were also lower. Additional evidence that adherence support reduces LTF was reported in an ecologic study in ten SSA countries(247).

Harries et al propose ten key interventions to improve retention in care in SSA(172). South Africa has made progress on a number of these interventions including improving outcome ascertainment, reducing death rates and providing fixed-dose combination ART. However other key interventions which could improve retention include a simple, standardized system for monitoring and reporting the numbers enrolling and key standardized outcomes, ensuring uninterrupted drug supplies (an ongoing challenge) as well as full decentralization and integration of ART services with other chronic care conditions.

8.2.1.2 Impact of age and gender on ART enrollment and outcomes

Two of the primary factors that impact on population health are age and gender, which strongly determine access to services and health outcomes(248). Easier to measure than most other determinants of health, age and gender are routinely reported in studies on ART outcomes but their specific impact is little understood in the South African setting.

Despite a growing body of evidence that older people and men are disadvantaged in access to ART and have poorer outcomes on treatment than younger individuals and women, these large groups of the population remain under-researched. National programs and international funders continue to prioritize access for women in particular(47,48,249). This disjuncture between public health evidence

and planning for ART programs informed the decision to undertake the detailed analyses on age and gender in Chapters 6 and 7.

In recent years concerns have been raised about the absence of older patients in HIV and ART programs in Africa(107,116,182). This thesis provided novel empirical evidence that increasing proportions of patients older than 50 are starting and being retained on ART despite the lack of HIV prevention and treatment programs targeting older individuals. Chapter 4 reported a 1% increase in the hazard of mortality for every additional year at enrollment. More detailed investigation found that mortality, mediated by baseline immunologic status, increases with baseline age up to two years on ART. Thereafter patients over 50 years old at ART initiation have a higher mortality risk than patients 16-29 years at baseline. Health care workers need training to diagnose HIV and start ART in older HIV-positive individuals. Nationally representative surveys need to extend data collection to include older individuals in order to estimate the true HIV prevalence of older people and address their future health needs.

The health needs of men have also been neglected in the responses to the epidemic. Chapter 3 provided early evidence that men are disadvantaged in access to treatment in South Africa despite widespread concerns that the opposite would be true. Sixty eight percent of patients were female while HIV prevalence in 2012 was estimated to be 60% female(196). These findings were in line with those from a systematic review of ART access in Southern Africa(123). Further investigation of the gender distribution by age in Chapter 6 uncovered a new finding, that females dominated enrollment only in the younger age groups. From the age of 50 onwards, the gender proportions were almost equal. HIV testing campaigns need to target boys and young men urgently.

The investigation of a gender difference in mortality on ART drew attention to the fact that many deaths in ART programs are unrelated to HIV and ART. Concerns have been raised about ‘circular epidemiology’, in which studies repeat what has

been previously reported without any attempt to acquire new knowledge(205,250). This phenomenon was evident in studies of gender and ART in developing countries, many documenting the same association repeatedly and concluding that men's elevated risk of mortality is due to their poorer 'health-seeking behavior'. Chapter 7 tried to avoid this circular approach by systematically assessing the putative mechanisms which might explain this finding. Finding a far greater gender difference in HIV-negative mortality than among patients on ART prompted a consideration of the broader context within which ART programs exist. In the Western Cape, for example, the leading cause of death for men in 2010 was interpersonal violence while HIV/AIDS was the leading cause for women(251). Chapter 7 also raises important questions about assumptions that are made about men's health, regardless of evidence, and the need to prioritize men in prevention and treatment programs.

Disaggregating data by age and gender provides important new insights into study findings. Prioritizing the earlier initiation of ART, particularly among men and older individuals, could impact at a population level to improve the health of people living with HIV.

8.2.2 *How* we research ART programs

Individual patient level meta-analysis has been described as the least biased way of addressing questions that remain unanswered by clinical trials(41). In addition it is argued that the findings may be more generalizable than results of trials with strict eligibility criteria(43). On the other hand, in the absence of randomization, observational studies may be more subject to bias than clinical trials. The following sections discuss potential sources of bias in our studies.

8.2.2.1 Selection bias

Selection bias in these ART cohort data can include biases due to ascertainment, attrition (LTF) and survivorship. Chapters 6 and 7 addressed possible bias due to differential mortality ascertainment by correcting estimates through linkage to the

NPR, see section 8.2.2 below. This thesis used a conservative, standardized approach to estimating LTF which increased the comparability of outcomes between cohorts and strengthened confidence in the finding of increased LTF with each successive year of enrollment. However recent research by Johnson et al(252) suggests that much of the apparent increase in LTF in more recent years of ART initiation may be due to a bias caused by brief interruptions in care which differentially affect patients enrolled in different time periods. Patients who enroll in care more recently and subsequently interrupt care have less time to re-engage in care than patients enrolled in earlier years, which may result in an overestimation of LTF. If LTF is overestimated, retention could be higher than estimates suggest. Finally, Chapter 5 addressed the issue of potential survivor bias in mortality after TFO/LTF. In this analysis, patients had to survive long enough to be TFO/LTF. This may lead to survivor bias in that sicker patients may have died before this point. To limit this bias, TFO and LTF were treated as time-varying covariates in the analysis. Collaborative analyses of individual-level data must attempt to address and discuss potential sources of bias and the implications thereof.

8.2.2.2 Missing data

One of the most common challenges facing the analysis of routine observational data from ART cohorts is the proportion of missing data on key variables and outcomes. Incomplete data on important covariates may result in biased or incorrect estimates of associations or failure to identify associations which exist(253). For instance, Chapters 4-7 highlighted the importance of baseline CD4+ cell count in understanding ART outcomes and in measuring improvements in ART coverage. In the South African context where ART eligibility depends largely on baseline immunologic status, most patients must have undergone testing before starting treatment. Despite this, a quarter of baseline CD4+ cell counts were missing. If patients with and without recorded baseline measures had different outcomes, our findings may be biased. Similarly in Chapter 4 a large proportion of data on WHO staging was missing yet the inclusion of staging in multivariable analysis impacted on the association between baseline CD4+ cell count and

outcomes. In another example, studies reporting proportions virally suppressed generally restrict the denominator to patients with available viral loads at that time point. However patients with viral load measures may differ from patients lacking such measures as they have already returned to care to undergo testing(254). They may be more adherent than patients who do not return for testing and this may artificially inflate estimates of virologic suppression. In the context of a further three-fold increase in patient numbers, further deterioration in the collection of data is likely(61). With such huge patient loads, it is likely that less complete measures are taken at baseline and follow-up visits, and if they are taken, that they are recorded.

Missing data on patient outcomes can bias estimates of mortality and retention. Mortality ascertainment is a challenge in developed as well as developing countries, particularly with high levels of LTF. One of the major contributions of the IeDEA-SA collaboration is the development of new methods for ascertaining mortality among those LTF. Linkage to the NPR has allowed correction of mortality for LTF. Using this method, we found that corrected mortality is about twice the mortality observed by sites and that mortality on ART declines over time. Our finding is in line with a recent study which found that after two years on ART, mortality in South Africa declines to levels below those reported from cohorts from North America, and approaches those reported from European cohorts(255).

Surprisingly few studies report the proportion of missing data(200,206), despite its importance in interpreting the results of a study(256). Indeed, in Chapter 4 our first outcomes analysis did not explicitly report on the proportions of missing baseline data as the importance of this issue was not apparent at the time. Subsequent analyses in Chapters 6 and 7 attempted to address this concern through transparent reporting of missing data and the use of statistical methods such as MI and inverse probability weighting (IPW).

MI is recommended over complete case analysis where data are missing for covariates in a regression model(253). It allows the inclusion of observations with missing values, increasing the power of the study, and provides more accurate results for associations of interest(257). However it is also more complex and time-consuming and may not always be the appropriate analytic approach, depending on the outcome of interest. Decisions on using MI depend on the nature of the missing data. If the data are 'missing completely at random' (MCAR) the probability of being missing is independent of both observed and missing data. In this case, estimates from both complete cases and MI will be unbiased and there would be no benefit in using MI. However missing data are 'missing at random' (MAR) if the probability of being missing depends only on observed data(257). In this instance, MI produces unbiased results in contrast to complete cases. The third possibility is 'missing not at random' (MNAR) where the probability of data being missing depends on the missing data itself. On the assumption that our data were MAR, Chapters 6 and 7 used MI to avoid potential bias.

Further investigation found that where mortality was the outcome, the data might have been MCAR (Supplementary Table S8.1) as estimates were similar between complete cases and MI, but with tighter confidence intervals in MI. In this analysis, regardless of the fact that there were only 4,670 complete cases out of 83,576 observations, using complete cases would have been simpler and quicker and provided similar results. In contrast, a comparison of methods with LTF as an outcome showed fairly large differences in associations: the adjusted effect of being male decreased by 50% from aHR 1.76 (95% CI 1.46-2.13) to aHR 1.26 (95% CI 1.22-1.29), CD4+ cell count ≥500 cells/μL significantly increased the risk of LTF (aHR 1.23, 95% CI 1.04-1.45) and the effect of calendar year of enrollment was attenuated particularly in the most recent years (aHR 11.76 vs. aHR 37.40 for patients enrolled in 2011 vs. 2004) (Supplementary Table S8.2). These findings suggest that where LTF is the outcome, the data might be MAR and analysis of complete cases may produce biased results. It is also possible that the missing data are MNAR but testing this assumption requires sensitivity analyses to assess how inferences vary under

different models. Depending on the nature of the analysis, MI may reduce bias and provide more valid estimates than complete cases.

An alternative approach to missing data used to address missing outcome data for LTF patients is IPW, used in Chapters 6 and 7. Patients who had ID numbers and were LTF were linked to the NPR to confirm their vital status. Mortality was then corrected with these patients weighted to represent all patients LTF, improving our mortality estimates. This form of correction was dependent on whether the cohort collected ID numbers and if so, on the completeness of ID numbers. With scale-up, the collection of ID numbers has been less complete and the most recent analysis only included 50% of patients with IDs, raising questions about whether these patients truly represent all LTF patients. If not, these findings are once again subject to bias.

The level of attention paid to the missingness of data in these analyses is unusual in HIV cohort literature. Future research should report the proportion of missing data to allow qualitative assessment of possible bias. In the absence of a well-maintained population register, researchers should use appropriate methods to correct mortality estimates(96). This would allow more valid comparisons of mortality within and between ART services and better planning for services.

8.2.2.3 Heterogeneity in collaborating cohorts

Heterogeneity between cohorts can influence the external validity of study findings from collaborative analyses of observational data, limiting their generalizability(41,258,259). A single overall estimate could conceal marked differences in estimates from different settings, with programmatic implications. For instance, among patients who died after TFO, 9% died within the first three months of ART but cohort-specific estimates ranged from 0 to 23%. Similarly among deaths in patients during later ART, 36% of patients died within three months of TFO, with cohort estimates ranging from 17 to 60%. These instances illustrate how an average estimate might lead to misdirected site-level interventions to reduce

mortality after TFO. Collaborative analyses should undertake sensitivity analyses to confirm that their main study findings hold across different sites as in Tables 5.2, S5.1, S6.5 and Figures 7.2, S5.1 and S5.2.

Chapter 3 described heterogeneity in patient numbers and in characteristics at enrollment. The proportion of patients enrolled by cohort ranged from <2% to 39% cohorts. There was variability in age and in baseline immunologic status across cohorts. As differences in baseline age and immunologic status might explain differences in outcomes, later chapters also explored and reported the consistency of the main findings within cohorts.

In these Chapters, heterogeneity in outcomes was specific to the outcome under analysis. When mortality was the study outcome, there was little variability between cohorts. This is an important finding, suggesting that mortality risk does not depend on site-level factors. In contrast, when TFO and LTF were the outcomes, there was substantial heterogeneity in the characteristics and proportions of patients TFO/LTF and in the incidence and timing of mortality after TFO/LTF. Although TFO and LTF are reported and compared as if they have a single meaning, such variability suggests that they may have different meanings in different contexts. As such differences may impact on mortality, there is a need to understand the specific meaning of TFO/LTF to inform the development of appropriate interventions and policies.

8.2.2.4 Monitoring

This thesis highlights the need for simple, effective monitoring of the South African ART program. At the time of writing, ten years after the program was officially launched in South Africa, there is still no national reporting on key program indicators. This gap may be partly due to the complexity of existing systems, which include over 40 different patient management systems with numerous non-standard and non-networked systems in the public sector(260). Even within the same facility, multiple systems for monitoring have been used(261). In 2011 the

DoH adopted a three-tier monitoring and evaluation (M&E) system for ART, a major step towards a more standardized system for the entire program. In place of 144 different unstandardized indicators, six monthly data elements and 27 quarterly indicators are required. Despite the attempt to simplify reporting, four years later only the comparatively well-resourced Western Cape, which developed this system, has produced regular quarterly cohort reports.

In 2012 the South African National AIDS Council (SANAC) produced a lengthy M&E framework based on findings from previous reviews(262). However the complexity of this framework raises concerns about perpetuating these problems. SANAC has produced a national core set of 34 key indicators with additional indicators to track 'strategic enablers' of the NSP. Further complexity is added with the need to align provincial and district level indicators to national outputs and outcomes. Such complexity in M&E is unlikely to increase the program's ability to enroll more individuals or to retain them in care. In the context of six million individuals requiring treatment and a health system facing multiple challenges, complex monitoring may result in poor data collection and meaningless results. Yet reliable data are required to inform planning and the provision of adequate services for those who need treatment(263).

Notably it is essential to have accurate data on how many patients remain in care, in order to plan for their chronic health care services. Although mortality is an important metric for monitoring and evaluating program performance, this thesis suggests that it may not be the most useful or important measure in the long term. ART is effective provided patients are enrolled at an early enough stage of disease and are adherent to medication. Retention in care at the site of ART initiation and keeping patients in care as they transition between services pose greater challenges to sustainability. The ART program should use retention in care as a more meaningful and comparable measure of performance than mortality. National government should engage with international donors to simplify reporting systems in line with national priorities and to avoid duplication of reporting systems.

In addition to a simplification of existing monitoring systems, this thesis suggests the need to separate detailed clinical monitoring from ART delivery services. Where more detailed monitoring is required, for example of older patients starting ART and long-term toxicity of ART as well as interaction with co-medications, this could be done in sentinel sites. IeDEA-SA has adopted an approach which combines the collection of a limited number of standardized indicators on large numbers of patients with smaller, more intensive studies which require additional data collection on specific issues.

8.3 Strengths and limitations

These analyses were strengthened by large sample sizes, the inclusion of individual survival times to estimate key indicators of effectiveness and the use of new methods to address various sources of potential bias. In addition, disaggregating data on the basis of gender and age provided important new insights into gaps in service delivery.

However, the interpretation of these data is subject to a number of cross-cutting limitations. These studies are constrained by generalizability. IeDEA-SA does not claim that its cohorts are representative of the country's national ART program and no formal sampling has taken place to confirm the generalizability of findings. Chapters 3 and 4 assumed that the inclusion of 10% of all public sector patients from different settings meant that the findings would be generalizable to patients accessing public sector ART in South Africa. However, IeDEA-SA cohorts all have strong academic links and it is likely that their data are better and more complete than data from ART roll-out sites across the country. Indeed, analyses in Chapters 5-7 excluded data from the Free State province due to intractable data problems, yet this provincial cohort may more accurately represent the situation in roll-out sites for which we do not have data. Interpretation of these results should be tempered by an understanding of these differences in context. In addition, cohorts differed from each on many key factors including geographic location, patient numbers,

dates of patient enrollment, duration of follow-up, data quality and completeness, level of care, provision of services and sources of referrals. Despite these differences, findings that were consistent across cohorts are likely generalizable to the national ART program while those which were not consistent may require additional research within a specific context. Missing data on baseline covariates and outcomes was a further constraint which was partially addressed through the use of MI. In analyses comparing complete cases and multiply imputed data sets, mortality estimates were similar between complete cases and imputed data, but with tighter confidence intervals in the latter, while a similar comparison with LTF as an outcome showed fairly large differences in associations.

The analyses were also constrained by our inability to distinguish between HIV- and non-HIV-related mortality. Including information about whether the deaths were HIV-related would have provided more insight into the specific effects of gender and age on mortality in ART programs. In addition it was only possible to correct mortality estimates in cohorts that collected identification numbers (IDs), and within these cohorts the proportion of patients with ID numbers dropped as patient numbers increased. However we found little evidence that patients with ID numbers differ from patients who lacked these. Finally, despite attempts to minimize confounding, residual and unmeasured confounding are ongoing challenges in observational studies. The aging analysis in Chapter 5, for instance, does not include data on co-morbidities or co-medication which may partly explain some of the mortality differential across ages.

8.4 Future research needs

This thesis suggests three main areas for research to strengthen and expand service delivery in the ART program: improving patient tracing, increasing earlier enrollment and improving patient retention in care. Arguably the most important challenge is to find an innovative, affordable and easy way of tracing patients so that we know who is in care and who has been lost. Possible solutions include the use of biometrics in all health facilities(264), so that if a patient interacts with the

health care system at any point in the HIV treatment cascade, this information is recorded and the program knows the patient is still alive and accessing some form of care. Programs could then differentiate between patients who are in care elsewhere and those who are truly LTF. Reducing the proportion of patients LTF would facilitate active tracing to bring these patients back into care. A range of alternative models of care to improve enrollment and retention have been tested including decentralization, taskshifting, ART initiation by nurses, integration and adherence clubs(238,239). Future operational research should focus on ways of implementing and scaling up models that improve enrollment and retention(265).

Other future research should include a properly sampled, representative study to assess the generalizability of these findings across the national ART program. Such a study would entail random proportional sampling of the South African cohorts in the IeDEA-SA database stratified on the basis of gender, age, calendar year of enrollment and cohort of ART initiation, factors which influence outcomes on ART(266). IeDEA-SA should also undertake a study to try to quantify the proportion of mortality on ART that is HIV-related. Such a study could benefit from the use of verbal autopsies, for instance, which identified HIV/AIDS-related deaths in five African countries with a specificity of 90% (95% CI 89-91%)(267). Further work is needed to understand and address the obstacles boys and men face in accessing ART and to increase enrollment by older individuals.

The IeDEA-SA collaboration is well-placed to address some of these future research needs. The collaboration collects a limited, standardized set of indicators on a large number of patients starting ART nationally. In this capacity, IeDEA-SA can continue to provide data on key indicators to reflect the national program and to highlight areas which require context-specific analyses. IeDEA-SA also undertakes surveys and sub-studies to collect additional data for in-depth analysis. Historically such surveys have included, for example, the incidence and management of Kaposi's sarcoma in different cohorts. Such surveys may identify questions for further investigation elsewhere. Separately funded sub-studies have included, for instance, a study to quantify the waiting time for patients with TB to start ART. Chapter 3

mooted the idea of sentinel surveillance sites, an idea which was gaining currency in HIV cohort analysis at the time. While sentinel surveillance could provide a level of detail way beyond the scope of IeDEA-SA, such findings may not be generalizable to a routine setting.

8.5 Conclusion

This thesis suggests that the major challenges to the success of the South Africa ART program are not related to clinical management of patients or patient adherence to treatment. Instead, the major challenges relate to the health system and the way in which the ART program is implemented. ART services were initially provided as a desperate humanitarian effort which then grew with the increasing demand. At the same time, there was close monitoring to ensure that outcomes were comparable with developed countries. Although South Africa has subsequently adopted a public-health approach to delivering ART, it seems that we still aspire to aspects of the individualized approach to ART. Had the country today faced starting six million people in a new public health care initiative, implementation might have been very different. After ten years of ART, it is time to use what we know about the program to plan for the next period of time.

In terms of *what* is implemented, interventions addressing the existing blindspots about gender and age could prevent further new infections, increase equitable enrollment and improve outcomes on ART. Health services require a major re-orientation towards the health of boys and men and individuals over 50 years of age. Engaging with health services increases the probability of being offered HIV testing and treatment and may be protective against other risk factors for mortality. Such campaigns should link to wellness services given the dearth of primary care services for boys and men.

Additional interventions are also required in terms of *how* the ART program is implemented and measured. A national campaign is needed to encourage earlier testing and starting ART with less advanced HIV disease, in order to improve long-

term outcomes on treatment. Integrating point-of-care CD4+ cell count testing and initiating ART in as many different health care facilities as possible would increase enrollment. A range of alternative models of care need to be tried and evaluated quickly and the program needs the flexibility to adopt and scale-up innovative and effective models for enrolling and retaining more individuals in care.

Simpler, more efficient monitoring systems are needed to enable increased enrolment and improved retention. The program should differentiate between clinical monitoring, reporting to funders and monitoring to inform planning of services. Clinical monitoring could be made more efficient by ensuring better collection of baseline CD4+ cell counts and dropping follow-up measures. Program monitoring should be limited to four key outcomes: dead, transfers, LTF and alive, which should also form the basis of simpler reporting to funders. A single standardized measure of LTF should be used to enable comparison within and across programs. Finally, the program urgently needs to find a simple, inexpensive way of uniquely identifying patients across all health services to differentiate between patients who are alive and in some form of care and patients who are truly lost to care and require tracing. Planning for the existing program is inefficient in the absence of such vital information. Expanding the program three-fold may be catastrophic unless solutions are found.

In conclusion, this thesis set out to provide a picture of ART scale-up in South Africa. It finds that the ART program is a remarkable example of what can be achieved with high levels of commitment. Over the past ten years South Africa has improved and extended the lives of millions of individuals who would have died without treatment. Addressing the gaps identified in this thesis would strengthen the program and help to ensure that these benefits are extended to those individuals who have not yet accessed treatment.

Supplementary Table S8.1. Crude and adjusted mortality in complete cases and after multiple imputation.

	OVERALL COMPLETE CASES**		OVERALL AFTER IMPUTATION	
	HR (n=83,576)	aHR (n=4,670)	HR (n=83,576)	aHR*** (N=83,576)
Age (years)				
16-29	1		1	1
30-34	1.11 (1.03-1.21)	1.10 (0.82-1.47)	1.08 (0.99-1.17)	1.05 (0.97-1.15)
35-39	1.21 (1.11-1.31)	1.28 (0.96-1.71)	1.17 (1.07-1.27)	1.12 (1.03-1.23)
40-44	1.29 (1.17-1.41)	1.25 (0.90-1.72)	1.25 (1.14-1.38)	1.21 (1.10-1.34)
45-49	1.47 (1.33-1.63)	1.44 (1.01-2.06)	1.48 (1.33-1.64)	1.41 (1.26-1.58)
50-54	1.68 (1.49-1.90)	1.78 (1.21-2.64)	1.71 (1.51-1.94)	1.62 (1.42-1.85)
55-59	1.76 (1.50-2.08)	1.45 (0.79-2.65)	1.77 (1.50-2.09)	1.65 (1.38-1.97)
60-64	2.52 (2.01-3.14)	2.62 (1.22-5.67)	2.57 (2.04-3.24)	2.28 (1.78-2.93)
65+	3.03 (2.34-3.94)	2.62 (1.21-5.69)	3.11 (2.39-4.05)	2.53 (1.90-3.38)
Male gender	1.62 (1.53-1.71)	1.38 (1.13-1.68)	1.63 (1.54-1.73)	1.43 (1.35-1.53)
CD4+ cell count (cells/μL)				
<50	1	1	1	1
50-99	0.61 (0.57-0.66)	0.56 (0.43-0.72)	0.64 (0.60-0.71)	0.71 (0.65-0.78)
100-199	0.39 (0.37-0.42)	0.47 (0.37-0.59)	0.41 (0.38-0.44)	0.54 (0.80-0.59)
200-349	0.23 (0.20-0.26)	0.32 (0.22-0.45)	0.24 (0.21-0.27)	0.38 (0.33-0.43)
350-499	0.36 (0.26-0.48)	0.06 (0.01-0.42)	0.33 (0.25-0.44)	0.47 (0.35-0.63)
≥500	0.24 (0.14-0.40)	0.11 (0.02-0.82)	0.22 (0.13-0.36)	0.33 (0.20-0.56)
WHO stage				
I & II	1	1	1	1
III	2.62 (2.35-2.93)	1.74 (1.34-2.26)	2.28 (2.04-2.54)	1.62 (1.44-1.82)
IV	3.25 (2.87-3.67)	2.80 (1.99-3.95)	3.39 (3.00-3.83)	2.26 (1.94-2.62)
Anemia				
none	1		1	1
mild	1.53 (1.38-1.71)	1.27 (0.94-1.74)	1.76 (1.64-1.89)	1.37 (1.23-1.53)
moderate	2.69 (2.42-2.99)	1.67 (1.22-2.29)	3.10 (2.87-3.35)	1.99 (1.80-2.20)
severe	4.52 (3.98-5.12)	2.81 (1.97-4.02)	4.72 (4.00-5.56)	2.89 (2.49-3.35)
TB at enrolment	1.58 (1.46-1.71)	0.82 (0.66-1.01)	1.53 (1.40-1.65)	0.82 (0.75-0.90)
Weight (kg)	0.96 (0.96-0.97)	0.98 (0.97-0.99)	0.96 (0.96-0.96)	0.98 (0.97-0.98)

Supplementary Table S8.2. Crude and adjusted loss to follow-up in complete cases* and after multiple imputation.

	Complete cases		Multiple imputation	
	Crude HR	aHR without MI (n=4,670)	Crude HR	Adjusted HR (n=83,576)
Age groups (years)				
16-29	1	1	1	1
30-34	0.85 (0.82-0.88)	0.69 (0.54-0.87)	0.87 (0.84-0.90)	0.81 (0.78-0.84)
35-39	0.82 (0.79-0.85)	0.64 (0.50-0.82)	0.87 (0.84-0.90)	0.76 (0.73-0.79)
40-44	0.80 (0.76-0.84)	0.39 (0.28-0.55)	0.84 (0.80-0.87)	0.73 (0.70-0.77)
45-49	0.76 (0.72-0.80)	0.41 (0.28-0.60)	0.81 (0.76-0.85)	0.69 (0.66-0.74)
50-54	0.75 (0.69-0.80)	0.40 (0.25-0.64)	0.80 (0.74-0.85)	0.66 (0.62-0.72)
55-59	0.86 (0.78-0.95)	0.42 (0.23-0.78)	0.93 (0.85-1.01)	0.74 (0.67-0.82)
60-64	1.06 (0.92-1.23)	0.69 (0.28-1.67)	1.17 (1.02-1.33)	0.90 (0.78-1.04)
65+	0.90 (0.73-1.11)	0.49 (0.18-1.31)	0.93 (0.76-1.13)	0.82 (0.67-1.02)
Male gender	1.23 (1.20-1.27)	1.76 (1.46-2.13)	1.25 (1.21-1.28)	1.26 (1.22-1.29)
CD4+ cell count, median (cells/μL)				
<50	1		1	1
50-99	0.95 (0.91-0.99)	0.66 (0.48-0.89)	0.94 (0.90-0.98)	1.01 (0.96-1.05)
100-199	0.92 (0.88-0.95)	1.01 (0.79-1.29)	0.93 (0.89-0.96)	1.02 (0.98-1.06)
200-349	1.06 (1.01-1.11)	1.04 (0.78-1.39)	0.98 (0.94-1.03)	1.01 (0.95-1.06)
350-499	1.10 (0.97-1.25)	1.01 (0.57-1.78)	1.01 (0.90-1.14)	1.15 (1.00-1.31)
≥500	1.12 (0.94-1.32)	0.93 (0.40-2.14)	1.03 (0.88-1.20)	1.23 (1.04-1.45)
WHO stage				
I & II			1	1
III	0.92 (0.88-0.96)	0.93 (0.74-1.16)	0.97 (0.94-1.00)	1.00 (0.96-1.04)
IV	0.92 (0.88-0.97)	1.31 (0.92-1.87)	0.95 (0.91-1.00)	0.96 (0.90-1.01)
Anemia				
none	1		1	1
mild	1.05 (1.00-1.09)	1.20 (0.94-1.52)	1.08 (1.04-1.12)	1.09 (1.05-1.14)
moderate	1.19 (1.13-1.25)	1.23 (0.95-1.59)	1.20 (1.15-1.26)	1.20 (1.15-1.27)
severe	1.36 (1.27-1.46)	1.47 (1.04-2.07)	1.27 (1.19-1.35)	1.34 (1.26-1.43)
TB at ART start	1.12 (1.07-1.18)	1.21 (0.97-1.51)	1.06 (1.01-1.11)	1.10 (1.04-1.16)
Cohort				
Gugulethu	1	1	1	1
Hlabisa	0.25 (0.23-0.26)	omitted	0.26 (0.24-0.27)	0.14 (0.14-0.15)
Khayelitsha	0.32 (0.31-0.34)	omitted	0.33 (0.32-0.35)	0.19 (0.19-0.20)
McCord	0.60 (0.57-0.63)	omitted	1.45 (1.39-1.51)	0.71 (0.67-0.75)
Themba Lethu	0.49 (0.47-0.51)	omitted	0.50 (0.48-0.52)	0.37 (0.35-0.39)
Tygerberg	0.25 (0.23-0.27)	omitted	0.25 (0.23-0.27)	0.17 (0.16-0.19)
Year				
2004		1	1	1
2005	1.40 (1.31-1.49)	1.22 (0.15-9.89)	1.38 (1.30-1.47)	1.61 (1.50-1.72)
2006	1.84 (1.73-1.96)	3.33 (0.38-29.00)	1.80 (1.69-1.91)	2.45 (2.29-2.62)
2007	2.18 (2.04-2.33)	4.90 (0.57-42.50)	2.27 (2.13-2.42)	3.23 (3.01-3.47)
2008	2.35 (2.19-2.52)	11.58 (1.34-100.12)	2.58 (2.41-2.75)	4.06 (3.78-4.37)
2009	3.18 (2.96-3.40)	16.82 (1.94-145.70)	3.68 (3.45-3.93)	5.76 (5.34-6.20)
2010	4.02 (3.75-4.32)	24.59 (2.82-214.31)	4.43 (4.15-4.73)	8.29 (7.68-8.95)
2011	4.73 (4.39-5.09)	37.40 (4.28-326.51)	4.57 (4.26-4.91)	11.76 (10.84-12.77)
2012 & 2013	6.24 (5.75-6.78)	71.98 (8.01-647.09)	6.30 (5.81-6.92)	16.98 (15.49-18.62)

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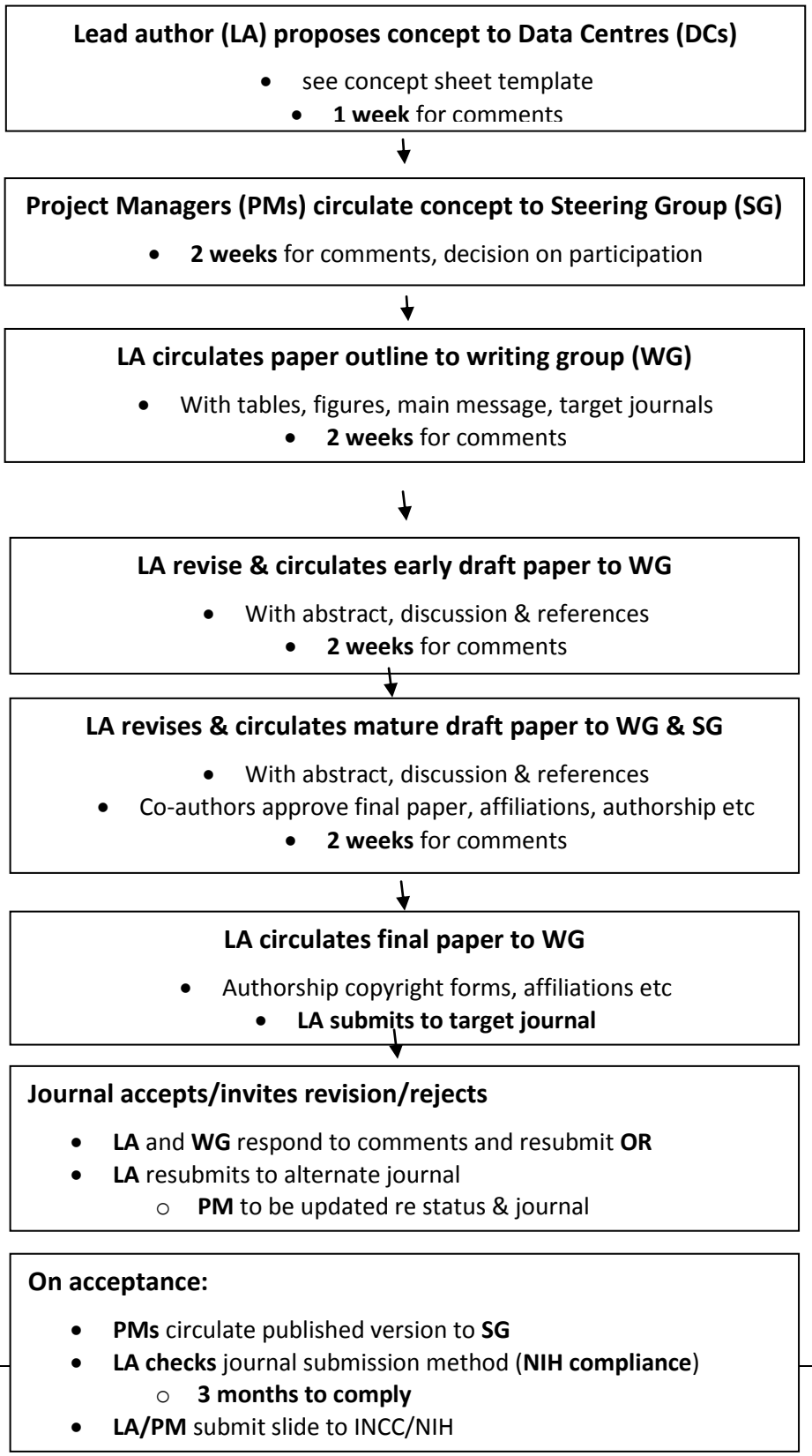
Appendix A

IeDEA-SA publication process

A1. Papers: from concept sheet to publication



A2. Conference abstracts:

Ideally conference abstracts will be based on concepts that have gone through the formal concept proposal and approval process as above. For such abstracts:

LA circulates abstract to concept writing group

- **2 days** for comments

PM circulates submitted version to **participating sites & Project Managers**

If the abstract is not based on an approved concept sheet, the following simpler process may be followed in order to allow submission before the conference deadline.

Lead author (LA) submits abstract to Data Centres (DCs)

- **2 days** for comments

↓

Project Managers circulate abstract to Steering Group

- **5 days** for comments, decision on inclusion of data

↓

LA submits abstract

LA circulates submitted version to participating sites & Project Managers

↓

After the conference:

- if LA plans to develop into a paper, the full process outlined above must then be followed

A3. Fast-tracking requests:

In the event of a request for data that may be used to inform assumptions in models, or for summary information for the purpose of reports on the state of the epidemic etc, a fast-track process may be followed. The following criteria apply:

- The request is for aggregated information, not individual-level data.
- The requested information can be supplied easily by a member of the data centre and does not require substantial time spent on data cleaning or substantial new analytical work.
- The IeDEA data are not the primary focus of the study, i.e. the proposed study could be published even without the IeDEA data (the IeDEA data are a 'nice to have' rather than a necessity).

If these criteria are met we will ask for the following:

- The title of the project
- The names of the investigators involved in the project and their affiliations
- A very brief description of the aims of the project and the motivation for the project (1 paragraph)
- A description of the summary data that are requested
- An explanation of how these data will be used in the project
- Expected outputs (journal publication/policy document/report)

This will first be sent to the data centres, who will judge whether the fast track criteria have been met before circulating to the steering group, who will be given **one week** in which to raise any concerns. If the members of the data centre feel that the fast track criteria are not met, they will recommend that the applicants rather go through the full concept sheet process.

We will ask that IeDEA-SA is acknowledged for any information provided through this fast track process. While we will not require that IeDEA-SA members be included as co-authors, co-authorship can be explored where this is appropriate. We will require that the data centres review any potential publications before these are published.

APPENDIX B

Ethics approval for IeDEA-SA data center, UCT

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
HUMAN RESEARCH ETHICS COMMITTEE
08 MAY 2013
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	15 5 2014
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	8/5/13

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	6 May 2013		
HREC REF Number	084/2006	Current Ethics Approval was granted until	15 May 2013
Protocol title	International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) – formerly known as the Observational Antiretroviral Studies in Southern Africa – Collaboration		
Principal Investigator	Dr Mary-Ann Davies		
Department / Office Internal Mail Address	CIDER, School of Public Health & Family Medicine, 5th Floor, Falmouth Building, Anzio Rd, Observatory		
1.1 Does this protocol receive US Federal funding?		√ Yes	☐ No

2. Protocol status (tick ✓)

√	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		N/A
Total number of records or specimens collected, reviewed or stored since last progress report		N/A
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report	☑ Yes	☐ No

4. Signature

Signature of PI		Date	3 May 2013
Signature of Supervisor (if PI is a student)		Date	

Appendix C

The evolution of IeDEA-SA and the selection of cohorts for inclusion in analyses

The inclusion of cohorts in the analyses in this dissertation reflects the evolution of the IeDEA-SA collaboration over the past few years. With the intention of being as inclusive as possible, new cohorts were included as they joined. However each analysis had different data requirements and raised different challenges. As a result, it was not possible to work with the same cohorts for all the analyses.

At the start of this thesis, there were eleven South African cohorts participating in IeDEA-SA: eight sites offering services to adults exclusively or to adults and children combined and three pediatric sites. The adult cohorts were: Gugulethu, Masiphumelele, Khayelitsha, McCord, Themba Lethu, Tygerberg, Perinatal HIV Research (PHRU) and the Free State Province. The pediatric cohorts were: Harriet Shezi, Red Cross and Rahima Moosa. Chapters 3 and 4 were based on data from all adult sites. Data from the pediatric sites were included in Chapter 3 as the children in these cohorts had not yet been characterized. Since then there has been extensive research published on the pediatric patients, which is outside the scope of the thesis.

Community-based and rural cohorts from Aurum and Hlabisa subsequently joined the IeDEA-SA collaboration and their data were included in the gender analysis (Chapter 7), from which the Free State province and PHRU were excluded due to data problems. The aging analysis in Chapter 6 included the same patients except for the Aurum cohort, which was excluded as outcomes were poorly recorded. Chapter 5 aimed to ascertain mortality after TFO/LTF and thus only included cohorts which collect South African civil identification numbers (Hlabisa, Themba Lethu, Khayelitsha and McCord).