Loss to follow-up from South Africa's antiretroviral treatment programme: Trends, risk factors, and models of care to improve retention

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Thesis presented for the degree of Doctor of Philosophy in the School of Public Health and Family Medicine, University of Cape Town

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By

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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 the work of the candidate, or, in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. The contribution of the candidate to multi-authored papers is outlined in the preface to the thesis.

Anna Grimsrud

February 2015

ABSTRACT

Over the past decade, antiretroviral therapy (ART) programmes have rapidly expanded in resource-limited settings. Access to ART has been accelerated through a public health approach to reduce morbidity and mortality, thereby transforming HIV from a humanitarian crisis to a chronic disease. However, the benefits of ART to patients and communities are dependent on patients being retained in care. This thesis investigates loss to follow-up (LTFU) after ART initiation, in the context of scale-up and limited resources and evaluates models of ART delivery to improve retention.

After a brief introduction that offers orientation to the key issues and concepts in the field, Chapter 2 provides a comprehensive literature review discussing the public health concerns related to LTFU in ART programmes, as well as the methodological concerns encountered in studying LTFU. Six results chapters (Chapters 3-8) are presented using complementary cohort data from two collaborative datasets (one from programmes in resource-limited settings and one including only South African cohorts) and from a single ART programme at a community health centre. How to define LTFU is the focus of Chapter 3, demonstrating that definitions can have an appreciable impact on estimates of LTFU. In Chapter 4, temporal factors related to the expansion of ART programmes are investigated, with evidence that the risk of patient LTFU increases with each successive calendar year of ART initiation, and that the rate of programme expansion has a stronger association with the risk of LTFU than absolute programme size. Analyses in Chapter 5 suggest that patients initiating ART at higher CD4 cell counts, above 300 cells/μl, may have an increased risk of LTFU compared to patients initiating ART with lower CD4 cell counts. Taken together, these findings underscore the notion that LTFU is a burgeoning threat to the long-term successes of ART programmes in South Africa and other resource-limited settings. Chapters 6-8 report on the implementation and outcomes from innovative models of ART delivery for stable ART patients. Patient outcomes from (i) a nurse-managed ART service and then (ii) community-based 'Adherence Clubs' highlight that comparable and, in some cases, favourable patient outcomes may be achieved when ART delivery is decentralised.

This thesis concludes that LTFU is a significant challenge faced by ART programmes. In the context of ambitious targets and evidence of the potential benefits of ART for individuals and communities, concurrent changes to the health system are necessary to support retention in care. The successes of ART programmes in treating a chronic condition in resource-limited settings can be built upon by expanding community-based ART provision and potentially integrating management of other adulthood illnesses.

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My mother kept exceptional records of our childhood. This is exemplified by my "School Days" scrapbook; where every year's photos, report cards and projects were stored alongside notes of future career ambitions. Year after year, I would check the boxes beside "teacher" and "doctor" and in the "other" box I would write down "mountain climber". I am finally on the summit of this mountain!

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PREFACE

This thesis includes published papers, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town, and with the approval of the University Doctoral Degrees Board in 2012. The following six papers are included as part of the thesis and are presented as self-contained chapters in the following order:

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Grimsrud AT, Cornell M, Schomaker M, Fox MP, Orrell C, Prozesky H, Stinson K, Tanser F, Egger M, Myer L. CD4 count at antiretroviral therapy initiation and the risk of loss to follow-up: Results from a multicentre cohort study. *Submitted February 2015 to PLOS ONE.*

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The contribution of the candidate to each paper is outlined in the acknowledgements section of each paper (pages 87, 109, 128, 145, 164 and 183). The candidate was the lead and corresponding author for each paper, prepared all the data for the analyses, conceptualised and conducted all analyses and drafted all versions of the manuscripts during the period of doctoral degree registration. All co-authors critically reviewed and approved the submitted manuscripts, and the candidate reviewed co-author comments and suggestions and integrated them into the manuscript as appropriate. The supervisor of the candidate has separately confirmed to the University of Cape Town Doctoral Degrees Board that the included papers overwhelmingly reflect the independent and original thinking of the candidate and her own scientific work.

LIST OF ABBREVIATIONS

3TC	Lamivudine
ACs	Adherence Clubs
aHR	Adjusted hazard ratio
AIDS	Acquired Immune Deficiency Syndrome
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
ART	Antiretroviral therapy
ARV	Antiretroviral
BMI	Body mass index
CACs	Community-based adherence clubs
CAGs	Community adherence groups
CBART	Community-based antiretroviral therapy
CBO	Community-based organization
CD4	Cluster of differentiation 4
CHC	Community health centre
CHW	Community health worker
CI	Confidence interval
CIPRA-SA	Comprehensive International Program for Research in AIDS in South Africa
d4T	Stavudine
DOH	Department of Health
DRC	Democratic Republic of the Congo
EFV	Efavirenz
FDC	Fixed-dose combination
FTC	Emtricitabine
HBC	Home-based care
HCTC	Hannan Crusaid Treatment Centre
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ID	Identification number

IeDEA	International epidemiological Databases to Evaluate AIDS
IQR	Interquartile range
IMAI	Integrated Management of Adult Illnesses
IMCI	Integrated Management of Childhood Illnesses
IPW	Inverse probability weighting
KM	Kaplan Meier
LTFU	Loss to follow-up
M&E	Monitoring and evaluation
MOC	Model of care
MSF	Médecins sans Frontierès
MTCT	Mother to child transmission
NIAID	National Institutes of Allergy and Infectious Diseases
NPC	Non-physician clinicians
NPR	National Population Register
OR	Odds ratio
PGWC	Provincial government of the Western Cape
PLWHIV	People living with HIV
POC	Point of care
RCT	Randomised control trial
RD	Risk difference
RR	Risk ratio
SSA	sub-Saharan Africa
STRETCH	Streamlining Tasks and Roles to Expand Treatment and Care for HIV
TDF	Tenofovir
UNAIDS	Joint United Nations Programme on HIV and AIDS
VL	Viral load
WHO	World Health Organization

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Chapter 1. Introduction

1.1 INTRODUCTION & BACKGROUND

Background

The first case of Acquired Immune Deficiency Syndrome (AIDS) was reported more than 30 years ago in 1981 [1]. Soon after, the human immunodeficiency virus (HIV), the virus that causes of AIDS, was identified and named [2]. Today, HIV is a global epidemic with an estimated 35 million people living with HIV (PLWHIV) worldwide and 2.1 million new infections annually [3].

HIV has disproportionately affected Africa. The continent is home to 69% of PLWHIV, but only makes up 12% of the overall global population [3]. South Africa has the largest HIV epidemic, with an estimated 6.4 million cases [4]. The adult prevalence in South Africa is 18% and the majority of transmission is through heterosexual sex [4, 5].

Substantial progress has been made in the development of antiretroviral drugs (ARVs) to treat HIV and slow the progression to AIDS. In 1996, the first triple therapy combination antiretroviral treatment was available in developed countries [2, 6]. Adherence to a highly active combination ARV regimen, commonly referred to as antiretroviral therapy or ART, has transformed HIV from an infectious to a chronic disease [7, 8]. ART has dramatically increased the life expectancy of PLWHIV [9] and recent data from South Africa highlights that if patients access ART early, they can have a near normal life expectancy [10, 11].

Scaling up ART in resource-limited settings

Initially there was a slow response to providing ART in resource-limited settings [12]. The reluctance for scaling up ART was argued on the basis that ART was too expensive and the regimens too complicated to expand access [13]. Concerns were raised around the potential transmission of drug-resistant HIV and the case made to prioritize

prevention efforts instead of scaling up ART [6]. However, as a result of considerable advocacy by patients, activists, scientists and academics, ART became increasingly available in resource-limited countries from the early 2000s [14, 15]. Data from early cohorts highlighted that patients in resource-limited settings could have comparable outcomes, including rates of retention and loss to follow-up (LTFU), to patients in developed countries [12, 16-19].

In South Africa, treatment access lagged behind other low- and middle-income countries [15, 20]. The government denied that HIV caused AIDS and only after litigation in court and uprising by civil society was ART finally made available in the public sector [21]. After a slow start of public sector ART roll-out beginning in April 2004, there has been exceptional scale-up over the past decade [15, 22]. By mid-2013, South Africa had the largest ART programme in the world with more than 2 million patients on ART [4], and was acclaimed for its progressive HIV policies [23].

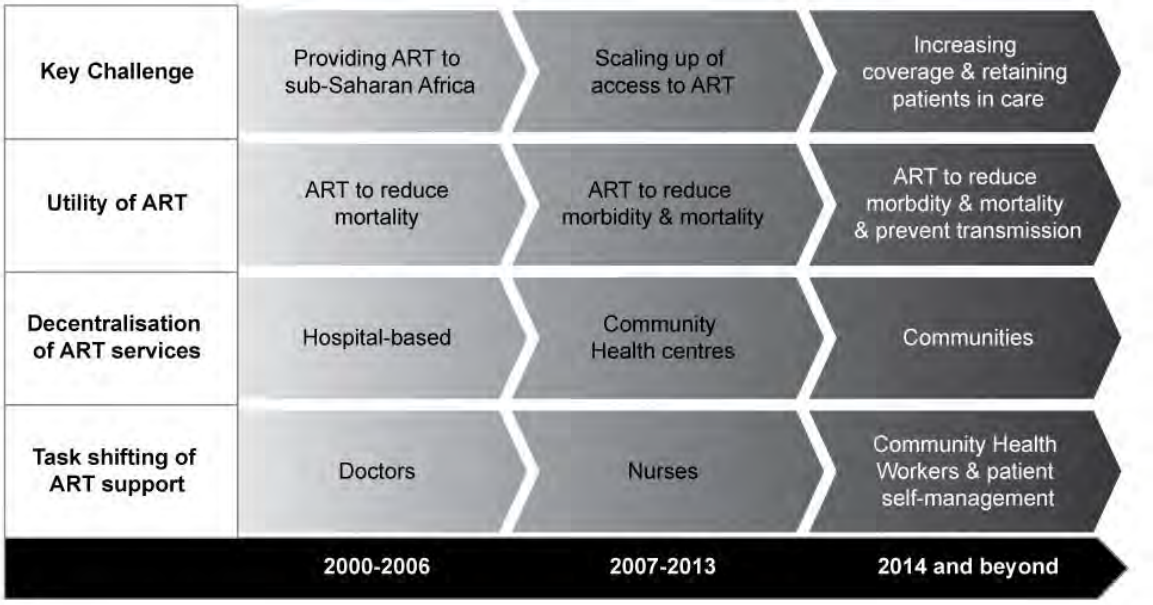
The unprecedented scale-up of ART has increased the size of the ART cohort in low- and middle-income countries from just 300,000 patients in 2002 to 9.7 million patients by the end of 2012 [24, 25]. The number of people in low- and middle-income countries on ART has tripled over 5 years, including 1.6 million new ART patients in 2012 alone [24]. The most rapid scale-up has been in Africa. In 2012, 4 out of every 5 new ART patients in 2012 were in the region [24]. This trend is most evident in South Africa, making up a third of all new ART patients globally between 2010 and 2013 [26, 27].

The evolution of ART programmes in resource-limited settings

The scale-up of ART has resulted in an estimated 4.2 million deaths averted [24] and been heralded as the fastest implementation of a life-saving public health intervention [28]. Over time and with improvements to the ARVs and regimens, ART was shown not only to extend life, but also to reduce morbidity. Most recently, with the results of the HIV Prevention Trials Network 052 trial, ART has also been shown to reduce new infections by lowering viral loads [29]. Modelling studies have shown the potential for ART to act as prevention, through test and treat strategies where

community viral load is decreased thus reducing transmission [30, 31]. Emerging data from pilot projects suggest very low rates of new infections can be achieved with universal testing and treatment and community viral load suppression [32]. ART is therefore no longer recommended only to reduce the risk of mortality and morbidity in HIV-positive individuals, but also to prevent transmission (Figure 1.1). However, the benefits of ART are dependent on patients being both retained and adherent to ART [33].

Figure 1.1 Evolution over the first decade of ART in sub-Saharan Africa



With improvements in ARVs and increasing evidence of the potential benefits of ART, guidelines around the provision of ART have been updated [28, 34]. The World Health Organization (WHO) recommendations on use of ARVs have recently been revised in favour of earlier initiation of ART both to benefit patients, but also to reduce transmission to uninfected partners. As guidelines have expanded eligibility, patients are accessing treatment earlier in their HIV disease progression. In all regions of the world, median CD4 cell count at ART initiation is increasing [24]. In light of the potential benefits to individuals and communities, there is renewed pressure for ART programmes to expand and accelerate access [3].

Changes have also been made to recommended first-line regimens. These recommendations have been adapted as new drugs and combinations have been developed and as generic versions of more expensive drugs have become available. Early regimens were complicated with multiple pills at multiple times of day and serious side effects and toxicities. The 2013 WHO guidelines recommend a single-pill once a day fixed-dose combination [28]. For the first time since WHO began providing recommendations for ART, the first-line therapy recommended in resource-limited settings is the same as that utilised in resource-rich settings.

The challenge of loss to follow-up

The initial focus of ART programmes in resource-limited settings was on accelerating scale-up and expanding ART coverage to save lives. The achievement of providing ART to such a high volume of patients in resource-limited settings cannot be understated. However, the benefits of ART are dependent on patients being retained in care and adherent to treatment. Reducing LTFU and improving the proportion of patients retained in care is thus crucial, given that ART is a life-long therapy. Increasingly, retention, and in turn LTFU, are acknowledged as key measures of ART programme effectiveness [35, 36].

Loss to follow-up represents a growing and pervasive problem to ART programmes. A patient who is LTFU is at risk of HIV-related morbidity and mortality, as well as developing drug-resistant HIV. Systematic reviews suggest that approximately a third of patients are lost to the ART programme within the first two years on treatment [37-39]. A 2007 systematic review from sub-Saharan Africa estimated retention to be 79%, 75% and 62% at 6, 12, and 24 months, respectively [37]. In a 2010 updated review of more than 200,000 patients, programme retention was 86%, 80, 77% and 72% at 6, 12, 24, and 36 months, respectively [38]. Therefore, the key challenge in the provision of ART in resource-limited settings is no longer merely scaling up access to ART, but simultaneously ensuring patients are not LTFU (Figure 1.1). Further research is warranted to understand how temporal effects of scale-up are related to the challenge of LTFU and retention in care.

The public-health approach to ART provision

When ART was first made available, its provision was an emergency response to a humanitarian crisis. The health systems that initially provided ART were for an acute condition and have since evolved to support life-long chronic management of HIV [40]. Today, HIV is considered a manageable chronic condition. ART programmes in resource-limited settings have adapted to the huge demand for services, despite considerable health systems and human resource challenges. Expansion of ART in resource-limited settings has been through a public health approach, based on the principles of simplification, standardisation, decentralisation, equity and patient and community participation [41].

Models of ART delivery were originally based on the model from resource-intensive settings with doctor-led provision in hospitals providing highly specialised and individualised care [42]. In high-prevalence resource-limited settings, including South Africa, the response to the sheer volume of HIV patients and limited capacity of the health care system led to model adaptation. ART delivery has become increasingly decentralised with programmes moving out of hospitals and into primary health care clinics, or community health centres. Along with decentralisation, tasks have been shifted from doctors to nurses and community health workers (CHWs), often PLWHIV, have been engaged to provide counselling and support to ART patients. Decentralised models of ART delivery with elements of task shifting were implemented not simply out of necessity but also because they can increase programme efficiency and effectiveness [43]. Figure 1.1 highlights the evolution to ART over the first decade of ART provision in sub-Saharan Africa, including the key challenges, utility of ART and adaptations to ART models of care delivery.

The early responses to HIV aimed to initiate as many people onto ART as quickly as possible to avert mortality and perinatal transmission; decisions were often made without data or as data was being collected. The most ethical and sensible approach for the context of the period was not to wait for results before implementing adapted delivery models. Operational research of the effectiveness of adaptations was often

conducted in parallel to providing care [42]. For example, in South Africa, the practice of nurses prescribing ART was implemented while randomised control trials were being conducted on the effectiveness of this task shifting [6, 44, 45]. Given the ambitious treatment targets and the high rates of LTFU, further adaptation of models of care delivery is needed to support patients and health systems.

Extending ART programmes in resource-limited settings

In many resource-limited settings, ART programmes were the first large-scale chronic disease programmes [46]. There is growing recognition of interfaces between HIV and other chronic conditions [46-48]. Given the successes of the ART programmes and the acknowledgment of the burden of other chronic conditions in resource-limited settings, there are calls for integration of previously fragmented, disease-specific programmes [40, 46, 47, 49].

While the implementation of effective ART programmes can be built upon and leveraged for other chronic conditions, the issue of LTFU remains. This thesis provides insight into the pervasive challenge of LTFU from ART programmes in resource-limited settings over the past decade with the view to offering insight into how further programme adaptation can support long-term retention in care.

1.2 PROBLEM STATEMENT AND RATIONALE

LTFU from ART programmes in resource-limited settings such as South Africa presents a significant challenge to programme effectiveness. Without being retained in care, ART patients are susceptible to HIV-related morbidity and mortality as well as at risk of transmitting drug-resistant strains of the virus. Given the high rates of LTFU, more data on risk factors for LTFU in the context of scale-up are needed. Temporal factors relating to programme expansion, higher CD4 cell counts at ART initiation and year of ART initiation require further investigation as they may relate to LTFU. In addition, the

role of innovative models of ART delivery to support the expanding ART cohort and improve patient LTFU needs to be explored.

1.3 AIM AND OBJECTIVES

The aim of this thesis is to address the challenge of defining LTFU and describe temporal factors contributing to loss to follow-up during scale-up of ART in resource-limited settings to inform strategies for improving the retention of South Africa's ART program.

Specific objectives are:

1. To examine the impact of the analytic approach to defining loss to follow-up on estimates of programme outcomes.

2. To elucidate temporal factors contributing to loss to follow-up during scale-up of ART programmes in resource-limited settings, specifically:

    a. To determine if the temporal trend of increasing loss to follow-up is observed across resource-limited settings,
    b. To determine if the temporal trend of increasing loss to follow-up can be attributed to programme expansion,
    c. To determine if ART initiation at higher CD4 cell counts is associated with an increase risk of loss to follow-up.

3. To evaluate the effectiveness of decentralised models of care with task shifting for stable ART patients, specifically:

    a. To examine and compare outcomes of stable ART patients down-referred to innovative models of care with patients in a community health centre,
    b. To investigate if innovative models of care are more appropriate for different sub-groups of patients.

1.4 OVERVIEW, CONTEXT AND STRUCTURE OF THIS THESIS

When this thesis was conceptualised in 2009, the public sector ART programme in South Africa was only five years old. Data were emerging to suggest that patients initiating ART in more recent years were at an increased risk of LTFU. Models of care to support ART delivery were evolving with decentralisation to community health centres and task shifting to nurses and CHWs. The relationship of temporal factors with LTFU and how models of ART delivery could adapt to face the challenge of expanding access while improving retention became evident. It is within this context that this thesis was conceived. This thesis includes a literature review, six results chapters and a discussion chapter summarizing the contributions of this thesis.

The literature review introduces the treatment cascade, highlighting how HIV patients may be lost at each step from HIV testing and diagnosis, through to ART initiation and viral suppression. The challenges in defining LTFU are presented and the relationship between LTFU, retention and adherence are clarified. Temporal factors for LTFU are described and classified at the levels of the health system, the disease and its treatment (HIV and ART) and the individual, in order to inform discussions on how to improve ART delivery. Models of care for ART delivery, which incorporate decentralisation and task shifting interventions to improve LTFU, are reviewed.

Six results chapters, in the form of published papers or those submitted or prepared for publication, are presented. Chapters 3-5 focus on challenges in LTFU from ART programmes in resource-limited settings over the past decade of expansion. Chapter 3 addresses Objective 1 of the thesis and concludes that analytic definitions in LTFU can appreciably impact on estimates of LTFU. In all of the analyses presented in this thesis, the most conservative definition of LTFU is used, per the recommendation resulting from Chapter 3.

Objective 2a, determining the temporal relationship between year of ART initiation and risk of LTFU, is explored in Chapter 4. To investigate if the observed association between year of ART initiation and increasing risk of LTFU that was observed in South

Africa extended to other countries, data from a multicentre cohort in other resource-limited settings was used. An increased risk of LTFU was observed for each successive calendar year of ART initiation in both early (0-12 months) and late (12-72 months) LTFU. Given the association between LTFU and year of ART initiation, year of ART initiation was adjusted for in all subsequent thesis chapters reporting on programme outcomes. Risk of LTFU in Chapter 4 was also adjusted for two measures of programme expansion, programme size and rate of scale-up. Adjusting for programme expansion relates to Objective 2b, and assessing the role of expansion on outcomes. In the findings from Chapter 4, the association between rate of expansion and LTFU was more important that programme size. Measures of programme expansion were therefore included in the multicentre analysis in Chapter 5.

Chapter 5 addresses Objective 2c and describes the association with higher CD4 cell counts at ART initiation and risk of LTFU. The temporal trend of higher CD4 cell counts at ART initiation, combined with the continued increase in CD4 threshold recommended for ART initiation, was the rationale for this analysis. Final models adjusted for year of ART initiation and programme expansion as well as correcting for unascertained deaths through linkage with the National Population Register. Results conclude that patients initiating ART at higher CD4 cell counts may have an increased risk of LTFU in the first year on ART.

Chapters 6-8 present two models of care delivery for stable ART patients implemented at the Gugulethu Community Health Centre (CHC) and address Objective 3. Implementation and outcomes from the Green Clinic, a nurse-managed down-referral programme (Chapter 6), and community-based Adherence Clubs (CACs) (Chapters 7 and 8) address Objective 3a, comparing outcomes with the CHC. The risk of mortality and viral rebound were comparable in the Green Clinic and the CHC, with a slight increase in the risk of LTFU in patients down-referred. CACs offered improved LTFU compared to the CHC. Details of the outcomes of different sub-groups of patients (Objective 3b) are included in Chapter 6 for the Green Clinic and Chapter 8 for the CACs. In the Green Clinic, the increased risk of LTFU was the result of higher LTFU among men, patients 25-34 years of age, and those who accessed ART with advanced HIV disease or in early years of the programme. Rates of LTFU were preferable in the

Green Clinic for patients with CD4 cell counts ≥200 cells/μl and those who recently initiated ART. Chapter 8 highlights the outcomes of CACs and suggests that all patients in CACs had a significant reduction in the risk of LTFU. The exception was youth, patients 16-24 years of age, who had a not significant difference in LTFU between the two models of care. Of note, men and women in CACs had comparable LTFU. This suggests that community-based models of care may offer significant benefits for men for whom outcomes on ART are generally worse than for women.

The results chapters 3-8 are directly from manuscripts published, submitted or prepared for publication. Minor revisions to the published versions of results chapters have been made to ensure consistency and continuity of terms throughout the thesis.

The discussion in Chapter 9 synthesises key findings from the thesis as a combined body of work. Recommendations are made for future research, policy and programmes and services. The conclusion summarises the novel contributions of this thesis.

1.5 DATA SOURCES

Data for this thesis came from three complementary cohort data sources: two data collaborations and an ART programme within a community health centre (Table 1.1). Details of each data source are described in detail below drawing attention to why they were drawn upon and their unique contributions.

Table 1.1 Summary of thesis results chapters by data source

Data Source	Chapter	Objective	Publication title	Data Source
1	3	1	Impact of definitions of loss to follow-up in antiretroviral therapy program evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU	IeDEA-SA
2	4	2a & 2b	Outcomes of antiretroviral therapy over a 10-year period of expansion: a multicohort analysis of African and Asian HIV programmes	MSF
1	5	2c	CD4 cell count at antiretroviral therapy initiation and the risk of loss to follow-up: results from a multicentre study	IeDEA-SA
3	6	3a & 3b	Outcomes of a nurse-managed service for stable HIV-positive patients in a large South African public sector antiretroviral therapy program	Gugulethu CHC
3	7	3a	Implementation of community-based Adherence Clubs for stable antiretroviral therapy patients	Gugulethu CHC
3	8	3a & 3b	Community-based Adherence Clubs for stable antiretroviral therapy patients: Outcomes from Gugulethu, South Africa	Gugulethu CHC

1.5.1 International Epidemiological Databases to Evaluate AIDS- Southern Africa (IeDEA-SA) collaboration

Background

The International Epidemiological Databases to Evaluate AIDS (IeDEA) is a collaboration of seven global regions initiated by the National Institutes of Allergy and Infectious Diseases (NIAID) in 2005. The purpose is to combine regional ART databases to answer questions that are unable to be assessed within single cohorts [50]. To date, the global cohorts contribute data on 750,000 patients on ART [51].

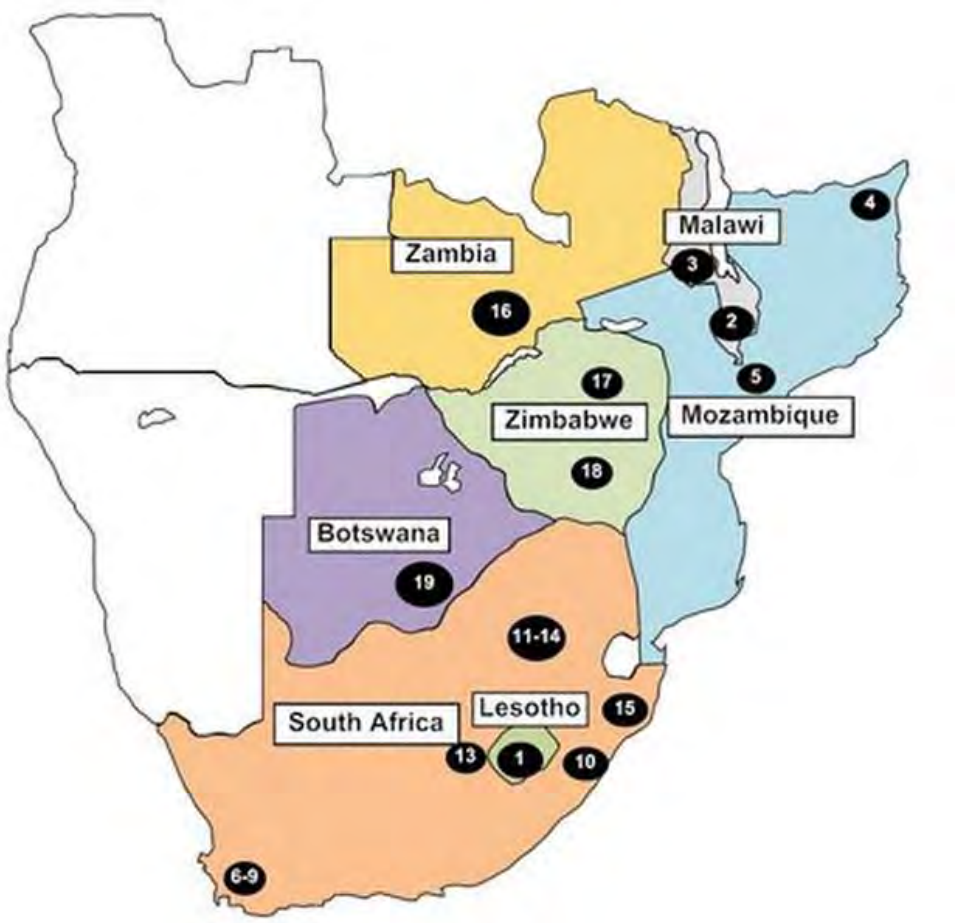
The Centre for Infectious Disease Epidemiology and Research at the University of Cape Town, in conjunction with the University of Bern in Switzerland, is the data centre for the IeDEA-Southern African regional collaboration (IeDEA-SA). Data are contributed from cohorts in Botswana, Lesotho, Malawi, Mozambique, South Africa, Zambia and Zimbabwe (Figure 1.2). Within South Africa, 10 ART sites have contributed data to the

collaboration, including eight adult sites. In 2010, the IeDEA-SA database included approximately 10% of all adults on treatment in South Africa [52]. The sites are in urban and peri-urban areas and located within four provinces: the Western Cape, Gauteng, Kwa-Zulu Natal and the Free State. Recently, efforts have been made to link the IeDEA-SA data with the National Population Register to ascertain the mortality status of patients in the collaboration [53, 54].

1.5.2 Contribution of IeDEA-SA data to the thesis

The IeDEA-SA data was included as it represents the largest cohort data set available in South Africa to evaluate the impact of definitions of LTFU and the relationship between CD4 cell count at ART initiation and LTFU. Two of the chapters (Chapters 3 and 5) utilised data from the South African adult cohorts in the IeDEA-SA collaboration. In Chapter 5, the primary results were further restricted to include only patients with recorded South African National Identification numbers. This further restriction was done so that estimates of LTFU could be corrected for unascertained mortality through linkage, based on National Identification numbers with the National Population Registry. The contribution of the IeDEA-SA data are unique in that it represents such a large proportion of the South African adult ART cohort, with data from multiple cohorts in multiple provinces. In relation to Chapter 5, the IeDEA-SA dataset had outcome data on a significant number of patients initiating ART at higher CD4 cell counts, thus allowing for sufficient sample size to investigate the association with higher CD4 cell counts and LTFU. The linkage with the National Population Registry further strengthens the IeDEA-SA contribution, allowing for analysis to correct for unascertained deaths and thus draw out associations between corrected LTFU and risk factors.

Figure 1.2 Map of IeDEA-SA contributing cohorts*



*Data from the IeDEA-SA collaboration utilised in this thesis was restricted to data from South African adult cohorts

Ethics

Ethical approval for the collaboration is obtained from the Human Research Ethics Committee at the Faculty of Health Sciences at the University of Cape Town and renewed annually (Ethics documents 1.1 and 1.2). Institutional ethical approval is obtained from each contributing cohort for participation in the collaboration.

1.5.3 Médecins Sans Frontières (MSF) supported HIV programmes

Background

Médecins Sans Frontières (MSF) is involved in HIV programmes in 32 resource-limited countries primarily in sub-Saharan Africa and Asia, as well as Latin America and Eastern Europe. At the end of 2013, MSF-supported programmes were supporting over 340,000 HIV patients [55]. Programmatic data are collected, anonymised and stored centrally at Epicentre in Paris, France. Chapter 4 of this thesis is based on MSF data from projects in eight resource-limited countries (Figure 1.3).

Contribution of MSF data to the thesis

The MSF dataset was utilised to investigate if the association between increasing LTFU and each successive calendar year of ART initiation, that was observed within an IeDEA-SA analysis of South African cohorts, extended to other resource-limited settings [56]. It offered a large cohort of patients from a number of resource-limited settings outside of South Africa and had sufficient data quality to assess multiple temporal risk factors. The cohorts within the dataset were also sufficiently heterogeneous, allowing for investigation into how measures of scale-up, including programme size and rate of scale-up, were associated with the outcomes of mortality and LTFU.

Ethics

Ethical approval for the analysis of data in Chapter 4 was obtained from the Human Research Ethics Committee at the Faculty of Health Sciences at the University of Cape Town (Ethics document 1.3). The analysis plan was submitted to the Ethical Review Board of MSF and satisfied the criteria for analysis of routinely collected programme data (Ethics document 1.4). A data transfer agreement for the analysis was signed between the University of Cape Town, the four operational centres of MSF contributing

data and Epicentre. The data transfer agreement specified that results of the analysis would be included within this thesis.

Figure 1.3 Map of MSF contributing cohorts to data in Chapter 4

1.5.4 Hannan Crusaid Treatment Centre at the Gugulethu Community Health Centre

Background

The Hannan Crusaid Treatment Centre (HCTC) is a public sector antiretroviral clinic located within the Gugulethu Community Health Centre (CHC) in the Cape Town suburb of Gugulethu. Gugulethu, in the Nyanga district of Cape Town, is a peri-urban area with a high prevalence of HIV and the majority of residents are of low socioeconomic status. In September 2002, the Desmond Tutu HIV Foundation (DTHF) began providing ART free of charge at the HCTC [16]. ART patients received counselling and support from the Sizophila programme, a group of HIV-positive patients educated in ART side effects and adherence [16, 57]. Collaboration with the Desmond Tutu HIV Foundation has continued since handover of the ART programme to

the Provincial Government of the Western Cape in the mid-2000s. Details of the site have been described previously [16, 58-65]. Routine patient data are collected at the site and merged with data from laboratory services and the pharmacy.

In Chapter 6, outcomes from the Green Clinic programme at the Gugulethu CHC are described. The Green Clinic was a nurse-managed programme where stable ART patients were down-referred for ART maintenance. It was started in 2006 in response to the growing patient numbers at the CHC and continued until the end of 2012. From June 2012, Adherence Clubs were started at the facility. The implementation and outcomes of the community-based Adherence Clubs at the Gugulethu CHC are presented in Chapters 7 and 8.

Contribution of the Gugulethu CHC data to the thesis

The Gugulethu cohort was uniquely positioned to compare ART delivery models with experience delivering ART within a facility-based CHC, a down-referral programme managed by nurses and a community-based model of care facilitated by community health workers. The Gugulethu cohort is a well-established research cohort with a large number of patients and follow-up from more than a decade of ART provision. The resources support good quality outcome ascertainment and the site also has access to the laboratory results of patients through the National Health Laboratory Service. This allowed for adjustment of time-updated measures of CD4 cell count and viral load within the models.

The Gugulethu CHC also contributes data to the IeDEA-SA collaboration. Data from the Gugulethu CHC was thus also part of Chapter 3 and in some of the sensitivity analyses in Chapter 5.

Ethics

Ethical approval was received from the Human Research Ethics Committee at the Faculty of Health Sciences at the University of Cape Town for the ongoing collection of

routine patient data and for the collection of data of the Green Clinic and Adherence Clubs (Ethics document 1.5).

1.5.5 Role of the candidate

The candidate conceptualised all of the primary research presented in the six results chapters and her original thinking compelled their development. Further, the candidate was the lead and corresponding author for each results chapter, prepared all the data for the analyses, conceptualised, conducted all analyses and drafted all versions of the manuscripts.

IeDEA-SA

For the two IeDEA-SA analyses in this thesis (Chapters 3 and 5), the candidate submitted concept sheets to the site investigators and data centres for approval. The concept sheets outlined the analyses and outputs and gave each cohort the opportunity for their data to be included or excluded. Both analyses were approved by the collaboration. Final papers were reviewed by co-authors, including representatives from sites contributing data, and the collaboration steering committee.

MSF

A concept sheet outlining the data required and analysis plan for Chapter 4 of the thesis was submitted to the HIV reference groups within MSF's five operational centers and Epicentre. The concept sheet was developed and drafted by the PhD candidate. Four of the five MSF operation centers approved involvement with the analysis and agreed to contribute data.

Gugulethu CHC

The candidate was responsible for designing and conducting the evaluation of the Green Clinic and the community-based Adherence Clubs. The Green Clinic programme started in 2006, in advance of the candidate's involvement at the site. The dataset for

analysis was merged by the candidate and incorporated data from the clinical database, laboratory database and review of Green Clinic source data.

The candidate supported implementation of the community-based Adherence Club model at the Gugulethu CHC. The candidate oversaw data collection from the CACs model and managed the CAC database. The dataset for analysis was created by the candidate, merging data from the CACs, the CHC and the laboratory.

Chapter 2. Literature Review

Overview

This literature review establishes the conceptual background for the thesis. It provides orientation to the topic of LTFU and retention from ART programmes and summarises key features of existing knowledge that are most relevant to the focus of the thesis. LTFU is presented as a key programme outcome with significant methodological challenges. The review is organised around the thesis objectives and addresses themes relevant to the following results chapters.

This review is not intended to be systematic but rather to represent key points in the literature on LTFU, in the context of rapid scale-up of ART in resource-limited settings. This is in accordance with the scope of the thesis, which addresses LTFU after ART initiation and how to support retention in care in the context of rapid expansion and limited resources. The review focuses on drawing specific attention to where there are gaps or ambiguity in our understanding and is divided into five sections.

Section 2.1 presents LTFU within the paradigm of the HIV "treatment cascade". While significant losses occur throughout the stages of the HIV treatment cascade, the scope of the thesis is on losses after ART initiation. Sections 2.2 to 2.4 review the literature to give context to the objectives of the thesis. The complexity of, and challenges in, defining the outcome LTFU is discussed at length in Section 2.2 and provides the background for Objective 1 and the content of Chapter 3. Given that the focus of thesis is on LTFU and retention, how these outcomes relate to each other is defined.

To address Objective 2 and provide background for Chapters 4 and 5, factors associated with LTFU are reviewed using a three-tiered multilevel framework in Section 2.3. The focus is on temporal factors related to the expansion of ART programmes: health systems level factors, given the demands of growing and maturing ART programmes; HIV and ART-related factors that have changed over the past decade; and individual level factors that should be considered when adapting ART delivery systems. Reviewing risk factors for LTFU (Section 2.3) is critical to informing

discussions on interventions to improve retention (Section 2.4). Frequently, the focus is on individual level risk factors and identifying specific at-risk groups for LTFU. However, given the size of the HIV epidemic and the challenge of retaining patients in ART programmes, there has been a burgeoning interest in operational research to assess the effectiveness of models of ART delivery.

The focus of Section 2.4 is on health systems interventions reviewing models of care for ART provision with elements of decentralisation and task shifting to address Objective 3. This section presents the background for Chapters 6-8. Findings from recent systematic reviews on decentralisation and task shifting are summarised. Models of care delivery that contributed to the systematic reviews are discussed, summarising the quality of the evidence and agenda for future research.

The concluding Section 2.5 summarises the key gaps identified from the literature review and outlines how the results chapters of this thesis contribute to these gaps.

Methodology of the literature review

The literature reviews aims to provide an overview on LTFU and retention in care in the context of rapid expansion of ART programmes in resource-limited settings and sub-Saharan Africa in particular. To assess temporal factors in this context and models of care to support retention, published work from 2004 to June 2014 was reviewed. PUBMED was searched limiting results to studies on adults (≥15 years of age) that described LTFU or programme retention after ART initiation. The search terms included "HIV" or "AIDS" AND "sub-Saharan Africa" or "Africa" or Southern Africa" AND "antiretroviral therapy" or "ART" or "HAART" AND "risk factors" or "task shifting" or "decentralisation" or "ART delivery" or "model of care" or "intervention". We also identified included literature from the WHO and UNAIDS that addressed LTFU, retention and support for scale-up. Reference lists in sources were also checked for publications to include. The intention of the review is to represent key points in the literature review and is not systematic or exhaustive.

2.1 LTFU AND THE TREATMENT CASCADE

The stages of an HIV programme – from testing, to care, treatment and suppression – are commonly referred to as the HIV "treatment cascade". In sub-Saharan Africa [66], it is estimated that less than half of adults with HIV know their status (45%) and a third (31%) of people living with HIV are on ART [4]. Overall, 29% of people living with HIV have a supressed viral load [67, 68].

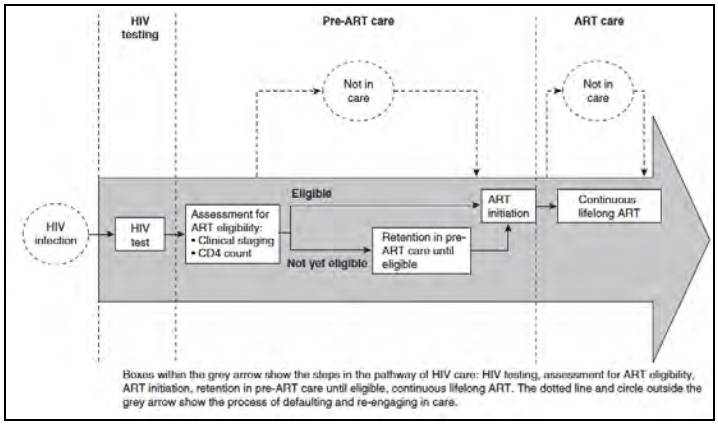
The reality of losing patients at each stage of the treatment cascade is not unique to sub-Saharan Africa ART programmes or to the management of HIV infection. In the United States, an estimated 82% of PLWHIV are diagnosed, 66% are linked to care, 37% are retained in care, with 33% prescribed ART and 25% with a supressed viral load [69]. The magnitude of these losses along the cascade is similar to those described in sub-Saharan Africa.

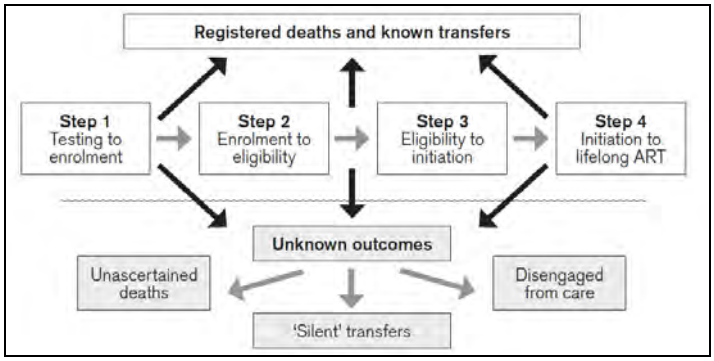
The notion of a cascade or continuum to describe patients being lost has been described previously for other chronic conditions. In 1972, the "rule of halves" was termed in regards to the management of hypertension where only half of hypertensive patients were diagnosed, of those diagnosed only half were treated and of those treated, only half were well controlled [70]. This cascade has since been applied to a number of additional chronic diseases including diabetes, asthma and osteoarthritis [71, 72] and more recently, to HIV.

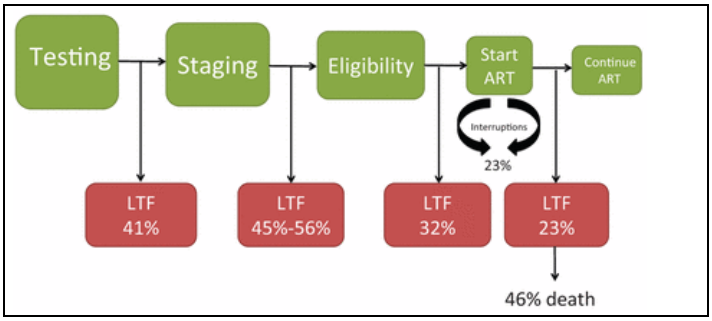
The notion of a "treatment cascade" within HIV was first depicted in reference to mother-to-child transmission (MTCT), describing the steps in preventing vertical transmission [73-75]. Recently, the treatment cascade concept has been expanded to describe the challenge of LTFU across the HIV epidemic, not only in relation to MTCT [76-84]. Stages of the cascade vary in different representations: some represent the proportion of patients eligible for ART after a positive HIV test, while others highlight the cyclical nature of LTFU and how patients can re-engage with care at a later stage. Four depictions of HIV treatment cascade from the literature are reprinted in Figure 2.1 to highlight the proliferation of the concept and the differences in what constitutes a stage in the cascade.

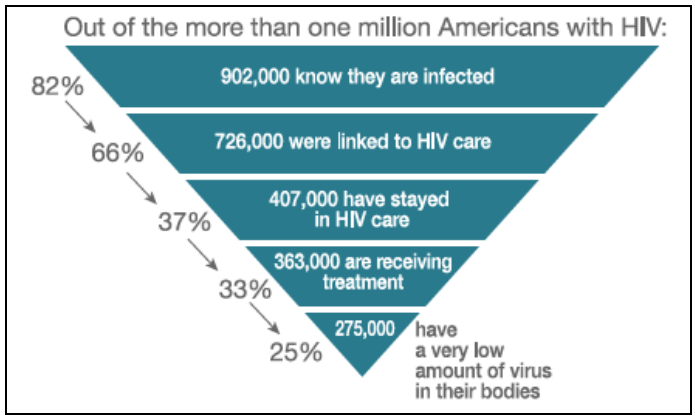
Figure 2.1 Different representations of the HIV treatment cascade

Four depictions of the HIV treatment cascade are reprinted to highlight the proliferation of the concept and differences in presentation.
From top to bottom: Kranzer et al. [76], WHO [77], Mills et al. [79], and the Centres for Disease Control [80]







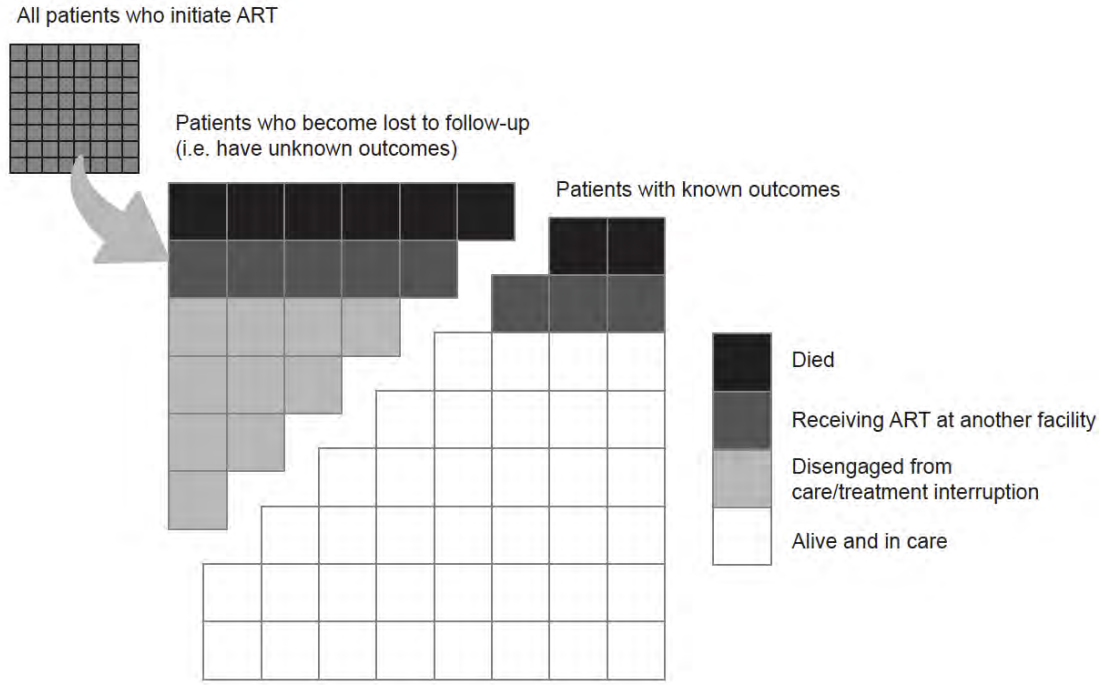


There are significant losses within the HIV treatment cascade prior to ART initiation (pre-ART). Two systematic reviews focussing on pre-ART retention in sub-Saharan Africa have been published [85, 86]. The 2011 review included 20 articles and eight conference abstracts and reported that 59% of patients who tested positive for HIV received information on their CD4 cell count or clinical staging, 46% received information on their eligibility to initiate ART, and 68% initiated ART [85]. The 2012 review included 29 studies of which data from 25 contributed to the meta-analysis. It found that 72% of patients with a positive HIV test result received a CD4 cell count, with 40% eligible for ART and 25% starting ART [86]. Ten articles were included in both reviews. In addition, both reviews conceded that there was substantial heterogeneity between cohorts and in definitions of the stages in the cascade. While acknowledging the substantial contribution of LTFU in pre-ART care, the focus of this thesis is limited to loss to follow-up after initiation onto ART. Furthermore, this literature review and thesis is focussed on LTFU among adults in ART programmes in resource-limited settings.

2.2 THE CHALLENGES IN DEFINING LTFU

Loss to follow-up (LTFU) from ART programmes describes all patients who are no longer in care and have an unknown outcome. It has been explained as a generic or "catch-all" term that refers to all patients who have not returned to the clinic following ART initiation [39, 87]. Therefore, the most accurate definition of LTFU is *patients with an unknown outcome* [77]. Figure 2.2 depicts patient outcomes dividing patients into those with known and unknown (LTFU) outcomes.

Figure 2.2 Patients with known and unknown (LTFU) outcomes*



*Adapted from Figure 2 in WHO, 2012. [77]

Patients who are defined as LTFU are heterogeneous and comprise of patients with three distinct outcomes: unascertained deaths, unascertained transfers and patients who are currently disengaged from care (boxes on the left, Figure 2.2) [87, 88]. The terminology used to describe these three patient groups is further confused due to the many different terms used to describe these three outcomes (Table 2.1). Those who are unascertained deaths (dark grey boxes on the right of Figure 2.2) are also called *patients who have died*, *unreported deaths* [87], and *unknown death*. Patients who are unascertained transfers are also referred to as *unknown transfers* [87], *'silent' transfers* [89], *undocumented transfers* [90], *receiving ART at another facility*, and *self-transferred care* [91] (grey boxes with horizontal lines on the left, Figure 2.2). There is also a third group of patients with unknown outcomes referred to as *disengaged from care* [87], meaning they are not presently on treatment. They are also defined as patients in an *unstructured treatment interruption* [92] if they return to care in the future.

Table 2.1 Summary of terms used to describe the three categories of patients who are LTFU

Patients who are LTFU		
Outcome 1: Unascertained transfer	Outcome 2: Unascertained death	Outcome 3: Currently disengaged from care
• Patients receiving ART at another facility • Self-transferred • Unknown transfers • Silent transfers • Undocumented transfers	• Patients who have died • Unknown death • Unreported death	• Patients who are currently not on ART • Discontinued treatment • "True" LTFU • Unstructured treatment interruption (if they return to care) • Not currently accessing treatment • Permanently LTFU

2.2.1 Loss to follow-up as a programme outcome

Traditionally within cohort analyses, the outcome of interest is the proportion of patients who survive. Patients who are LTFU are accordingly censored and this censoring is presumed to be uninformative and random [93, 94]. However, within the context of ART programmes and other chronic disease programmes, the proportion of patients LTFU is an outcome of interest independent of the survival proportion [95]. Given that LTFU reflects patients who are not retained in the programme, it is increasingly recognised as a key measure of programme effectiveness within chronic disease programmes [35, 36, 39, 96-98].

2.2.2 Differences in how LTFU is operationalised

As outlined above and depicted in Figure 2.2, LTFU is the absence of a known outcome, including patients who are dead, in care at another facility, and not currently on ART. LTFU is operationalised as the proportion of patients who are not in care and how this is defined varies. At the level of the individual, LTFU is commonly defined as a period of no visit, a missed appointment, or a number of days late for an appointment. Systematic reviews of retention in ART programmes in sub-Saharan Africa report

differences in definitions of LTFU in contributing cohorts [37, 38]. Among the cohorts in the Fox and Rosen 2010 review of patient retention, eight different LTFU definitions were reported including being late for appointments, not having contact for periods of time, and being untraceable [38]. Also of concern is that 14 of the 33 sources included did not report on how LTFU was defined. It is clear that there is no standardised definition of LTFU. Given both the uncertainty and heterogeneity in how LTFU was defined in the contributing cohorts, the appropriateness of deriving a summary estimate and then comparing retention after two years on ART between the 2007 and 2010 review has been questioned [99].

Additional concerns have been raised about the validity of the two systematic reviews [37, 38] that combined outcome data from multiple cohorts [99-101]. Access to ART varies by site with different criteria for starting ART, relating to disease status or social support networks. For example, some contributing cohorts required patients to nominate an adherence supporter and disclose to a family member [100, 101]. Differences in eligibility criteria could also impact the risk of mortality and unascertained mortality if ART was restricted to, or excluded, the sickest patients. Moreover, LTFU occurs at a different rate over time with higher rates immediately following treatment initiation and thus presuming a constant rate would be problematic. Some cohorts also had tracing programmes, which would lead to differential reporting of the outcome LTFU. Resources vary by cohorts as well, and those with additional resources for adherence support programmes may have greater retention in care [102].

2.2.3 Definitions of and the analytic approach to LTFU may also impact on outcomes

When this thesis was conceptualised, no work on definitions of LTFU had been published. Since then, Chi et al. has assessed what window period of no visit should be used to generate the outcome LTFU [103, 104] and Shepherd et al. has considered other components of how the analytic approach impacts the outcome LTFU [95]. Chi's work concluded that a period of 180 days since contact with the clinic has been recommended to minimise the number of misclassifications [103, 104]. Shepherd et

al. assessed the window period, as well as whether the last contact was from a laboratory or clinic visit, if patient loss was retrospective or prospective and if time was premeasured from last or missed visit. Estimates of LTFU varied depending on the components used to define LTFU and the authors concluded that how LTFU was operationalised could affect estimates of programme outcomes [95]. While Chi and Shepherd investigated the LTFU window period and some components of LTFU definitions, additional aspects of defining LTFU and how to approach LTFU as an outcome within analysis require attention. Potentially, the improvement cited by Fox and Rosen in 24-month retention between the 2007 and 2010 reviews was a spurious difference resulting from differences in LTFU definitions by the contributing cohorts [105].

There are three components of how LTFU is approached in an analysis that will determine who is defined as being LTFU: 1) the date assigned to the outcome LTFU (e.g. the last date of contact or the date the patient was expected to return); 2) the interval without contact (e.g. 60, 90 or 180 days); and 3) who is eligible for analysis (e.g. restricting to patients with 180 days of potential follow-up, adding a day of survival time to patients who initiate ART but never return). Given that all of these components will change estimates of LTFU, further assessment of the impact of different analytic definitions of LTFU on estimates of programme outcomes is needed.

2.2.4 LTFU, retention and adherence

The concepts of LTFU, retention and adherence are related and it is important to clarify the associations and differences between them. It is also fundamental to defining the scope of this thesis, which is limited to LTFU and retention after ART initiation.

Programme retention refers to all patients retained in the programme, depicted by the white boxes on the right of Figure 2.2. Patients who are no longer retained in care with unknown outcomes will be classified as LTFU, and therefore how LTFU is defined will impact on estimates of programme retention. The objective of improving or reducing LTFU is thus closely related to improving programme retention.

A patient who is adherent to treatment is a patient who is taking their prescribed dose of ART at the correct times and frequencies [106]. In order to be adherent, a patient needs an uninterrupted supply of ART and must consequently be retained within an ART programme. However, being retained in care does not equate to being adherent to treatment [107]. A patient can be attending their clinic visits and collecting their ART (retained) but not taking their ART as prescribed (not adherent). A measure of programme retention or LTFU does not, therefore, define adherence or the extent of viral suppression. It is incorrect to presume that patients retained in care are by default adhering to treatment.

Adherence is beyond the scope of this thesis, which focuses on LTFU and retention in care. While it is recognised that adherence is necessary for ART to be beneficial, this thesis does not specifically address the challenges of adherence.

2.2.5 Loss to follow-up threatens the effectiveness of ART

Systematic reviews of retention in ART programmes in sub-Saharan Africa

Three systematic reviews by Fox and Rosen have assessed ART retention, two in sub-Saharan Africa and one globally. The first, published in 2007, summarised retention in the first two years on ART from 33 cohorts. At 6, 12 and 24 months, the weighted mean retention rates were 79%, 75% and 62%, respectively [37]. In 2010, an updated version was published, with retention rates through to three years on treatment from 39 cohorts in the region. Estimates of retention were 86%, 80%, 77%, and 72% at 6, 12, 24, and 36, respectively [38]. Data from the 2013 review on patients in Africa estimated LTFU to be 82%, 76%, 68% and 65% at months 6, 12, 24, and 36, respectively [39]. While there is some variation in the estimates of programme retention, it is clear that retention is a substantial threat to ART programme effectiveness.

Increases in programme attrition are due to increases in LTFU

The contribution of LTFU within programme attrition is substantial and increasing [38]. A growing body of literature highlights that as programmes expand

and retention increases, that it is LTFU and not mortality that is increasingly responsible for losses to the programme [38, 53, 56]. A systematic review of tracing studies found an inverse relationship between mortality and LTFU; as LTFU increased the contribution of unascertained mortality decreased [88]. In other words, as the proportion of patients LTFU increases, it is not due to increases in unascertained mortality but rather from an increase in the number of patients who are receiving care at another facility (unascertained transfers) and/or patients who are not currently engaged in care. The systematic review also found that with each additional year on ART, the proportion of programme attrition due to LTFU increases [56].

With estimates of programme attrition at 20-40% after three years, LTFU is a considerable challenge to the long-term success of ART programmes. Improving retention by decreasing LTFU is essential to the effective provision of ART. Therefore temporal factors associated to LTFU during scale-up of ART in resource-limited settings are reviewed below.

2.2.6 Summary

Considerable methodological challenges exist in the measurement of LTFU. This thesis focuses on LTFU after ART initiation, defining LTFU as patients without a clinic visit in the period between analysis and database closure. Challenges exist in how to define LTFU and additional research is warranted to determine how analytic approaches to defining LTFU impact outcomes. Estimates of LTFU highlight that a significant portion of ART patients are not being retained in care. The growing contribution of LTFU to programme attrition warrants further research into factors associated with LTFU. Determining temporal factors for LTFU is also necessary to inform models of care delivery that support the large and maturing ART programmes in resource-limited settings.

2.3 TEMPORAL FACTORS CONTRIBUTING TO LTFU DURING SCALE-UP

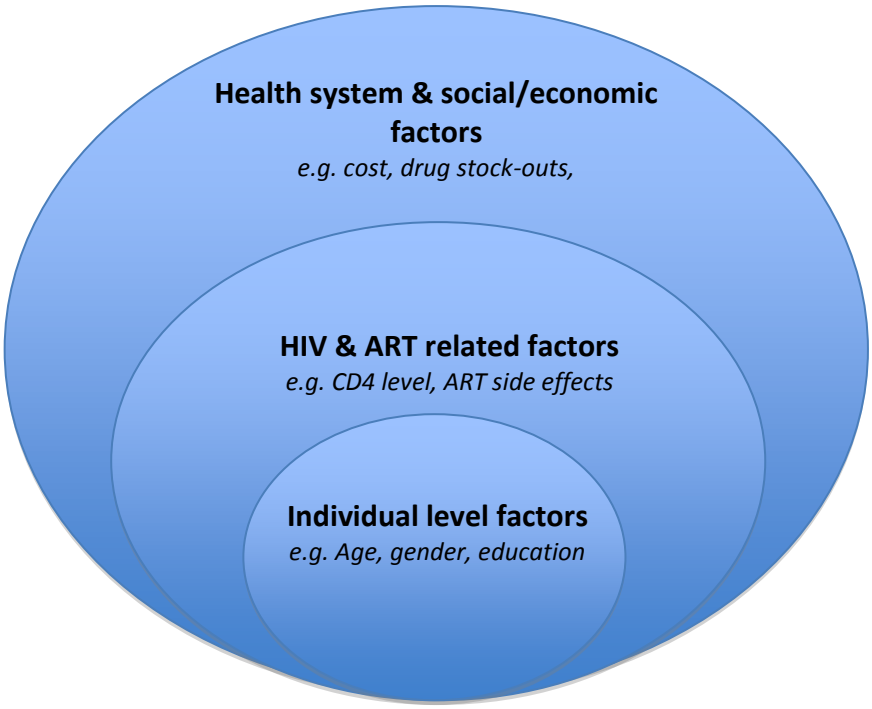
2.3.1 Challenges in determining risk factors for LTFU

Given that LTFU refers to patients with three distinct outcomes (Figure 2.2 and Table 2.1), it is difficult disentangle which of the observed associations with LTFU are driven by associations with unascertained morality, unascertained transfers and/or disengagement from care. Evidence of associations with LTFU is primarily from observational cohorts. Data from studies that utilise linkage to death registries is adjusted for unascertained deaths and thus presents risk factors for unascertained transfers and currently disengaged from care (Table 2.1). Tracing studies divide LTFU into its three components and therefore report on risk factors for patients currently disengaged from care. In this section, factors from observational cohorts, studies with linkage and tracing students are presented.

2.3.2 A framework for assessing risk factors for LTFU

Risk factors for LTFU may be defined at the level of health system, HIV and ART (the disease and its treatment) and the individual [108]. This review of the literature provides an overview of commonly cited and recurring factors highlighted in the literature, focussing on temporal factors that have changed with the rapid expansion of ART. For the purposes of this review, risk factors for LTFU will be placed within a three-tiered, multilevel framework (Figure 2.3). The distal components are comprised of health system and social/economic factors and reviewed given the interest in modifying ART delivery systems to improve programme retention. HIV and ART factors are presented as they have evolved during ART expansion. Individual level factors are summarised to inform targeted strategies and to understand how the composition of ART cohorts may affect programme outcomes.

Figure 2.3 Multilevel framework of risk factors for LTFU from ART programmes



2.3.3 Health systems & social/economic factors

The Commission on Social Determinants of Health define the socioeconomic and political context as the overarching structural determinant of health inequities [109]. Their framework further recognises the role of the health system and conceptualises the health system as a social determinant in its own right. These structural determinants are fundamental determinants of health outcomes. Eight reasons for decreased retention related to the health system and social/economic factors are listed in the 2013 WHO guidelines: i) High direct and indirect costs of receiving care, ii) Stock-outs of ARV drugs, iii) Lack of a system for monitoring retention in care, iv) Lack of a system for transferring people across different points of care, v) Lack of accurate information for patients and their families and peer support, vi) Adherence support, vii) Poor relationship between patient and care provider, and viii) Lack of time for educating people in HIV care [28].

Cost can be either direct, such as having to pay for ART, or indirect, such as the time away from childcare responsibilities in order to receive ART. Many studies have shown that paying for ART or ART services is directly related to an increased risk of

LTFU [110-112]. Brinkhof et al. investigated data from the first 12 months after treatment initiation in resource limited settings and found follow-up to be associated with advanced disease at baseline and services that charged a fee, as opposed to those that were freely offered [97]. Treatment costs were also reported as reasons responsible for treatment interruptions [92]. Drug shortages and stock-outs have been reported to increase LTFU and treatment interruptions [92, 110, 113, 114]. Issues with transportation and distance to the facility [115-117] and long queues and waiting times [118-120] are also commonly cited reasons for LTFU.

Data from tracing studies, where patients who are LTFU are found and interviewed, found similar health systems factors associated with LTFU, as did observational studies [121-125]. In the 2009 systematic review of tracing studies, the most commonly cited reasons were the cost of transport, followed by either an improvement or decline in health and then stigma [126]. In addition, competing commitments (work and childcare responsibilities) [122], social problems, use of traditional medication and side effects were also reported as reasons for disengaging from care [123]. Of patients traced in a Malawian cohort, men were more likely to report travelling away, while women were more likely to report transport costs as reasons for discontinuing ART [124]. A programme that has a tracing programme is also more likely to have improved retention compared to cohorts without tracing [87]. In summary, the structure of the health system as well as social and economic factors impact patient retention on ART.

Temporal trends in LTFU and year of ART initiation

When this thesis was conceived, there was conflicting evidence of how LTFU was changing as ART programmes expanded. Reporting an improvement in programme retention at 2 years between the 2007 and 2010 systematic reviews of retention in sub-Saharan Africa, authors Fox and Rosen concluded that retention in care was improving in the region [37, 38]. They suggested the improvement was due to programmes growing in experience, being better able to track patients and investing in interventions to trace patients and have them return to care.

While Fox and Rosen have suggested LTFU may be improving based on their estimates from meta-analyses, other cohorts have shown evidence of increasing LTFU with recent ART initiation [53, 56, 63, 90, 97, 127, 128]. There is also significant heterogeneity around estimates of LTFU from different cohorts. Differences may be due to variations in definitions and analytic approaches to LTFU, heterogeneity in the profile of patients accessing ART and disparities in how patients are initiated and supported on treatment. Alternatively, differences in LTFU could be related to the composition of the ART cohort. Early treatment cohorts may be more likely to have a significant proportion of acutely ill patients at risk of early mortality. Conversely, more mature cohorts may be more likely to have large numbers of unascertained transfers to programmes as the number of sites providing ART has expanded. It has also been suggested that publication bias may be leading to overestimates of retention in care, especially among the first ART cohorts that were established in the region [39]. Further research is necessary to determine the association between LTFU and year of initiation.

Contribution of programme expansion to LTFU

Health systems factors related to the high patient volume in HIV services are also related to LTFU. For example, high patient volume and the considerable numbers of patients per staff member has also been investigated as a risk factor for LTFU. In Mozambique, Lambdin et al. found high levels of attrition to be associated with medium and high burdens among pharmacy staff [129]. However, no association between clinical staff burden and patient attrition was found after adjusting for patient characteristics.

With the rapid expansion of ART, some postulate that the scale-up and sheer volume of patients may be leading to a decrease in the quality of care. In 2008 Boulle et al. highlighted that LTFU at 6-months was higher in 2005 than in previous years [96]. This was significant; especially given that mortality in the first 6-months was decreasing with year of enrolment. The authors attributed the increasing LTFU to the high volume of ART patients.

The relationship between LTFU and the size of ART programmes and rate of expansion has not received much attention in the literature. Programmes have focussed on scaling up access and expanding the number of patients initiating ART, but not necessarily measuring how this expansion is related to quality of care and patient outcomes. In previous analyses of ART cohorts, measures of size and scale-up have not been included, despite suggestions of their contributions to LTFU [56] and for limiting patient numbers to a manageable size [96]. Analyses adjusting for scale-up and expansion are required to ascertain how programme size and the rate of scale-up are related to LTFU.

2.3.4 HIV and ART-related factors

Factors related to HIV, and its treatment, ART, also affect LTFU. Over the past decade as access to ART has increased and thresholds for ART initiation have expanded, median CD4 cell count at ART initiation has increased in all regions of the world [24]. Concurrently, recommendations for first line ART have changed. The literature on the relationship between CD4 cell count at ART initiation and how ART affects LTFU is reviewed below.

Increasing CD4 cell count at ART initiation

With the median CD4 cell count increasing at ART initiation [24] and ART guidelines expanding to recommend initiation at higher CD4 cell counts [28], a growing body of literature describes the relationship between CD4 cell count at ART initiation and risk of LTFU. Some studies highlight a reduced risk of LTFU among patients initiating ART at higher CD4 cell counts. In a cohort from Lesotho and a South African cohort with linkage to the death registry [130], there was less LTFU among patients with CD4 cell counts >200 cells/μl [131]. Conversely, higher CD4 cells counts of >200 cells/μl [132, 133], >250 cells/μl [134] and ≥350 cells/μl [135] at ART initiation have been associated with an increased risk of LTFU in other observational studies. After adjusting for unascertained deaths through linkage to the death registry, a CD4>150 cells/μl had an increased risk of LTFU compared to patients with a lower CD4 cell

count at ART initiation [136]. Other cohorts have found no association between CD4 cell count at ART initiation and LTFU [137-139].

There are also conflicting in the association between CD4 cell count at ART initiation and the risk of being disengaged from care. In a systematic review of unstructured treatment interruptions, five studies reported an increased risk of LTFU and three reported a decreased risk of LTFU among those with higher CD4 cell counts at ART initiation [92]. In a recent study of interruptions in a large hospital cohort, patients with a CD4 cell count of ≥250 cells/μl were more likely to be LTFU, versus patients initiating ART < 250 cells/μl [140].

Differences in findings on the association between CD4 cell count at ART initiation and LTFU may be the result of a number of methodological differences between the studies. The reference groups and CD4 categories (including what is defined as low and high CD4 cell count) varies between studies. Given that low CD4 cell count is highly related to early risk of mortality, programmes with poor outcome ascertainment may see a higher proportion of unascertained mortality within their estimates of LTFU. In addition, some of the evidence was provided for studies where unascertained deaths were excluded from estimates of LTFU via linkage or tracing and therefore may be more accurately highlighting the association between CD4 cell count and LTFU. Conversely, patients with higher CD4 cell counts may be at increased risk of LTFU and early disengagement from care, as they may not have directly experienced the benefits of ART on their personal health.

In summary, conflicting evidence is available on the association between CD4 cell count at ART initiation and risk of LTFU. With ART eligibility expanding and supporting initiation at higher CD4 cell counts, additional analyses are needed to clarify the relationship between higher CD4 cell counts and risk of LTFU.

Changes to ART and the impact on LTFU

Considerable progress has been made in the development of antiretroviral drugs over the past decade. From monotherapy regimens to triple therapy and now fixed-dose

combinations, ART has become considerably easier to take and with less side effects. In addition, the price of ART has decreased dramatically. Data supports that drugs that are cheaper, with less side effects, and taken less frequently, support improved patient adherence [92, 110, 141]. A review by Kranzer et al. on the risk factors for treatment interruptions reported drug toxicity, adverse events and side effects as the most commonly reporting reasons for treatment interruptions [92]. ART regimens containing stavudine (d4T) have been increasingly phased out of preferred regimens and replaced with tenofovir (TDF) or zidovudine (AZT) due to the high rates of side effects and associated patient non-adherence. Data from observational cohorts highlights an increased risk of LTFU among patients on d4T regimens [135].

Fixed-dose combination (FDC) therapy is increasingly available in low- and middle-income countries. The 2013 WHO guidelines recommend a FDC option of TDF + lamivudine (3TC) (or emtricitabine [FTC]) + efavirenz [EFV] regimen to initiate ART [28]. A recent systematic review and meta-analysis on the patient and programme impacts of FDCs, concluded they were the preference in all of the 21 studies which were included [142]. Given the reduced volume of FDCs versus other regimens, they also offer benefits to decentralised models of care, by reducing the pre-packing burden and having simpler transportation [143].

2.3.5 Individual level factors

LTFU is generally higher in men [132, 135, 138, 144-146], younger patients [131, 132, 135, 147], patients with less education [132, 135, 146], and patients who are taking more complicated and toxic ART regimens. Recent data also highlight time-updated laboratory values of lower CD4 cell count and detectable viral load as being associated with higher risk of LTFU [132]. While not all of these risk factors are observed in all studies, there are the common patient-level associations observed across sub-Saharan Africa.

Tracing studies have found similar associations between individual level factors and LTFU. An increased risk of LTFU has been found in patients who are younger, male or have less income [148]. Patients who were younger and had initiated treatment in

more recent years were less likely to be re-engaged in care (unascertained transfers and treatment interrupters), compared to patients not on treatment [124].

A limited number of cohorts have reported on risk factors when LTFU is corrected with linkage to death registries. In data from the Khayelitsha ART cohort in peri-urban South Africa, being male, a more recent year of initiation, young age, and lower weight were all associated with an increased risk of LTFU in multivariate analysis before correction for unascertained deaths [136]. After linkage, the associations with younger age and calendar year of ART initiation were strengthened. In addition, women initiating ART while pregnant were at increased risk of being LTFU. The association with low weight did not persist after correction and hence is a risk factor for unascertained mortality. Males were also at an increased risk of LTFU after linkage in a study by Cornell et al. [149].

2.3.6 Summary

Data from cohorts, tracing studies and analyses with linkage to death registries to correct for unascertained deaths highlight multiple factors can affect retention in care. Temporal factors related to LTFU are present at the level of the health system, the disease and its treatment, and the individual.

Risk factors for LTFU are often described at the level of the individual. However, given the size of the ART programme and the scale of the challenge of retention in care, interventions at the level of the health system are needed. These system level changes in how ART is delivered are necessary to support the public health approach to ART. The public health approach is based on equity and ensuring ART access to all those in need. The key tenant is that it is based at the population and not individual level [41]. In line with this, interventions to decrease LTFU must also be at the population level.

The multilevel framework of risk factors (Figure 2.3) is useful when considering interventions. Health system interventions can address risk factors at all levels and thus hold the greatest potential for impact. Understanding of risk factors is thus crucial to discussions of health systems interventions, such as novel model of care.

This review of the challenges of LTFU and factors for LTFU in the context of rapid scale-up of ART provides the background for why additional models of care to support retention in care are needed. Over the first decade of ART delivery in resource-limited settings, substantial adaptations have been made to the models of care to provide ART. The adaptations have not been only out of necessity, but also because increased evidence supports different models of care, including models of decentralisation, with elements of task shifting. Insights into the types of patients at risk for LTFU was provided to highlight that future modifications of the model need to acknowledge that the risk of LTFU is not constant or uniform across sub-groups.

2.4 MODELS OF CARE TO SUPPORT PROGRAMME EXPANSION AND IMPROVE LTFU AND RETENTION

Overview

While many interventions have been suggested to improve LTFU and retention, it is increasingly acknowledged that health systems changes that are scalable and can increase the effectiveness of ART provision in the context of scale-up and regard HIV as a chronic condition, are essential to supporting long-term retention [150]. Recognising that health systems would need to adapt to implement the 2013 WHO guidelines, suggestions were also made for operations and service delivery [28]. These included specific recommendations for decentralisation and task shifting based on low- and moderate-quality evidence. The burgeoning interest in and support for adaptations to models of care delivery is evidenced by the 2014 WHO supplement on community-based models of care [151], a systematic review on improving ART effectiveness through decentralisation [152], and the recent Cochrane reviews on decentralisation [153] and task shifting [154]. The focus of this section is on models of care delivery with decentralisation and task shifting, given the potential impact on multiple factors for LTFU, as an intervention to improve retention and to inform Chapters 6-8 of this thesis.

Relationship between decentralisation, task shifting and models of care

In this section, models of care delivery with components of decentralisation and task shifting are reviewed. Decentralisation of HIV care is defined as moving services from centralised sites (usually hospitals) to health centres or other venues closer to the patients' home. This is done to increase the effectiveness of ART provision by decreasing costs and improving access for patients. With regards to the provision of ART, decentralisation can happen for ART initiation and/or maintenance. The type of health care worker who conducts the tasks related to ART provision is the task shifting component, where task shifting refers to the redistribution of tasks from more clinically trained health staff to other cadres of employees. Models of care are defined as the way in which ART services are provided including both *where* the services take place (decentralisation) and *who* conducts the tasks (task shifting).

Structure of this section

Models of care interventions are comprised of elements of both decentralisation and task shifting. It is consequently difficult to discuss decentralisation or task shifting in isolation, since that they are often implemented concurrently. Therefore, this review of the literature presents evidence on decentralisation and task shifting from systematic reviews. Subsequently, data from published models of care delivery are synthesised by the level of task shifting and type of decentralisation. The impact of the intervention on LTFU and retention in care are presented alongside data on mortality and virological suppression when available.

2.4.1 Recent systematic reviews on decentralisation and task shifting

The recent publication of a number of systematic reviews on decentralisation and task shifting evidences the current interest in how models of care can support improving LTFU and programme retention. Details of the systematic reviews reviewed here can be found in Supplementary Table 2.1. Below, the recent reviews are summarized.

Decentralisation

ART programmes in resource-limited settings were originally based on the traditional facility-based model in resource-rich settings where services were hospital-based and doctor-led and focussed on specialised and individualised care [6, 14, 42]. Given the prevalence of HIV and the capacity of health care systems in resource-limited settings, the scalability of this model was untenable. Programmes adapted implementing components of both decentralisation and task shifting to cope with the patient volume. The evidence regarding task shifting is discussed later in the chapter. First, the literature on decentralisation and patient outcomes is reviewed.

Types of decentralisation

There are four levels of decentralisation relating to when services are decentralised within the ART treatment cascade. A framework for defining the types of decentralisation is provided in Table 2.2, adapted from the Cochrane systematic review of decentralisation [153]. Throughout this thesis, the primary care clinic or community health centre (CHC) is referred to as the CHC for the sake of consistency.

Table 2.2 Levels of decentralisation for the provision of ART*

Name	Initiation	Maintenance	Description
Standard hospital model	Hospital	Hospital	Traditional model of ART care
Partial decentralisation	Hospital	Community Health Centre (CHC)	Starting ART in a hospital and being down-referred to a CHC
Full decentralisation	CHC	CHC	Both ART initiation and maintenance in a CHC
Community-based ART (CBART)±	Hospital/ CHC	CHC & Community	Facility-based ART initiation followed by down-referral for ART maintenance into the community

* Adapted from Kredo et al. [153]
± Within CBART, one must consider where within the community the ART is provided (community spaces, patient homes, etc.) and by whom (nurses, CHWs, PLWHIV, etc.).

The standard model of ART provision involves initiation and maintenance of ART within a hospital. "Partial decentralisation" describes the model whereby patients are initiated onto treatment at a hospital, but referred to a CHC for maintenance.

Increasingly, "full decentralisation" is occurring whereby patients are able to both initiate and be maintained on ART within their CHC. There is a growing interest for the provision of ART to happen within communities and such models of care are defined as "community-based ART" (CBART). Patients are initiated onto ART at a formal health facility, either hospital or CHC, and then down-referred for ART maintenance within the community. Commonly within CBART models, regular clinical consultations occur back within formal health facilities. The furthest level of decentralisation occurs when patients receive ART within their homes.

In all of these models, "down-referral" is the process whereby patients are decentralised to a level of care closer to home. Conversely, "up-referral" is when patients are recommended to access care either at the CHC or hospital due to clinical complications or non-compliance with the model of ART. In some models of care, patients are eligible to access decentralised models of care only once they are defined as stable. The definition of "stable patient" varies, but generally includes an indicator or virologic suppression and a period of good adherence.

Systematic reviews on decentralisation for the provision of ART

Three recent systematic reviews have addressed decentralisation of ART provision (Supplementary Table 2.1) [152, 153, 155]. A 2013 Cochrane review by Kredo et al. assessed decentralised models of care and combined data on the impact of partial decentralisation, full decentralisation and CBART on the outcomes loss to follow-up, programme retention, and mortality. A total of 16 studies were included; two cluster randomised control trials (RCTs) and 14 cohort studies (2 prospective, 12 retrospective). The review also included paediatric cohorts. Where possible, the results presented here are restricted to data on adults. Partial decentralisation led to a decreased risk of programme loss, loss to follow-up, and mortality at 12 months compared to traditional hospital-based models. In models with full decentralisation, the risk of 12-month programme loss and loss to follow-up were reduced with a statistically insignificant increased risk of mortality compared to traditional hospital-based, doctor-led models. Data from CBARTs was limited to three models that

provided home-based ART delivery. CBART models reported no difference in outcomes compared to facility care.

Suthar et al. published a rapid systematic review in 2014, which was conducted to inform the WHO 2013 ART guidelines [28, 152]. A total of ten articles on decentralisation were included; 4 on partial decentralisation, 4 on full decentralisation and 2 on CBART. All of the articles in the Suthar review were also included in the Cochrane review [153] (Supplementary Table 2.2). Accordingly, findings were the same as the Cochrane review, with partial decentralisation having preferable retention and mortality, full decentralisation improving retention, and data from CBART models (all of which were in models with home-based ART provision) were limited, with no significant difference in retention compared to facility-based models.

Decroo et al. conducted a review restricted to community-based models of ART [155]. Six different programmes were included in the review. Five of the programmes were CBART models with home-based ART delivery by CHWs, volunteers, or peer CHWs in Uganda or Kenya. The sixth model reviewed was Community Adherence Groups (CAGs), a model of care designed and piloted by MSF, in rural Mozambique. No meta-analysis was done, but the authors reported that all CBART models reported comparable attrition and virological outcomes to facility-based models.

In summary, reviews of decentralisation suggest that outcomes from full and partial decentralisation can provide similar or favourable outcomes compared to hospital-based models. All of the reviews have considerable overlap in the studies included (Supplementary Table 2.2). Limited data from CBART models exists and are almost exclusively limited to models with home-based ART delivery. With the data available, CBART outcomes are not significantly different from those in facility-based care. Details of the models included within these reviews are discussed later in this chapter as part of the review on models of care.

Task shifting

Task shifting involves the allocation of tasks to lower cadres of staff; from doctors to nurses, and nurses to CHWs [156]. The WHO has described four types of task shifting (Table 2.3). Task shifting I refers to tasks shifted from doctors to non-physician clinicians (NPCs)[1], task shifting II from NPCs to nurses, task shifting III from clinicians to CHWs and task shifting IV is for patient self-management. For continuity, other types of NPCs such as Clinical Officers have been referred to as NPCs, and all types of lay workers (counsellors, peer counsellors, etc.) are referred to as CHWs throughout this thesis.

Table 2.3 Four types of task shifting*

Name	Summary	Detailed definition
Task shifting I	Doctor to non-physician clinician	"The extension of the scope of practice of non-physician clinicians in order to enable them to assume some tasks previously undertaken by more senior cadres (e.g. medical doctors)." [156]
Task shifting II	Non-physician clinician to nurse	"The extension of the scope of practice of nurses and midwives in order to enable them to assume some tasks previously undertaken by senior cadres (e.g. non-physician clinicians and medical doctors)." [156]
Task shifting III	Clinicians to CHWs	"The extension of the scope of practice of community health workers (often called non-professional health workers or lay providers), including people living with HIV/AIDS, in order to enable them to assume some tasks previously undertaken by senior cadres (e.g. nurses and midwives, non-physician clinicians and medical doctors)." [156]
Task shifting IV	Patient self-management	"People living with HIV/AIDS, trained in self-management, assume some tasks related to their own care that would previously have been undertaken by health workers." [156]

*From *WHO's Task shifting: rational redistribution of tasks among health workforce teams: global recommendations and guidelines*. [156]

[1] Non-physician clinicians refer to a cadre of staff with less training than medical doctors who perform some functions of a medical doctor. Specific types of NPCs include health officers, physician assistants and nurse clinicians. A 2007 study reported that NPCs were involved in health care delivery in 25 of the 47 countries in sub-Saharan Africa [157. Mullan F, Frehywot S. Non-physician clinicians in 47 sub-Saharan African countries. Lancet. 2007 Dec 22;370(9605):2158-63.

In many resource-limited settings, task shifting in ART provision was done out of necessity in parallel to generating evidence of its effectiveness [42]. For example, the WHO recommended task shifting three years before the first randomised control trial on doctor- versus nurse-managed ART patients [44, 158]. In recent years, the published literature on the impact of task shifting on patient outcomes has grown.

Systematic review on task shifting

Five reviews of task shifting have been published since 2010 and are summarised in Supplementary Table 2.1 [154, 159-162]. The objectives and inclusion criteria of each review differed in the level of task shifting (Table 2.3), geographical location, study design, and where in the treatment cascade the task shifting was located.

Callaghan et al. assessed task shifting in Africa across the treatment cascade, reviewing qualitative and quantitative data and including grey literature [159]. Emdin et al. conducted a meta-analysis comparing outcomes in physician versus NPC models of care, excluding CHW models [160]. ART maintenance by physicians, nurses or CHWs was compared by Mdege, but no meta-analysis was presented due to the high degree of heterogeneity between models of care [161]. Both qualitative and quantitate data was reviewed by Mwai et al. in their review on the outcomes of models of care utilising CHWs [162]. A 2014 Cochrane review and meta-analysis compared doctor versus nurse models for ART initiation and maintenance and outcomes of community maintenance models [154].

Task shifting from doctors to nurses for ART initiation

In models comparing nurses and doctors for ART initiation, there was no difference in estimates of mortality from trial data [154]. Emdin et al. also reported no difference in mortality among almost 60,000 patients [160], while Kredo found a slight increased risk of mortality summarising cohort data [154]. LTFU was reduced for patients initiated in the nurse-led versus doctor-led models in the trial data in the Cochrane review and in the review by Emdin [154, 160].

Task shifting from doctors to nurses for ART maintenance

Mortality and LTFU when doctors initiated therapy and nurses provided follow-up also appeared to be comparable to doctor-led models. Trial data in the Cochrane review found non-significant differences in the risk of death and LTFU comparing nurse-led versus doctor-led models for ART maintenance [154]. Cohort data suggested models with nurse-maintenance may provide better patient outcomes, with reduced mortality and LTFU compared to doctor-led models [154]. In Chapter 6, outcomes from a nurse-managed programme for stable patients are presented contributing to the evidence on down referral to nurses for ART maintenance.

Task shifting to CHWs for ART maintenance

Less evidence is available on outcomes of patients who are maintained by CHWs. No difference in mortality or LTFU was reported in the Cochrane review on community models [154] or in the systematic review by Mdege et al. [161]. The review by Mwai et al. on the role of CHWs found evidence of contributions by this cadre of workers throughout the treatment cascade and reported comparable outcomes and quality of care to other models [162]. While non-inferior patient outcomes do suggest CHWs can provide comparable support during ART maintenance, patient numbers are limited and authors recommend additional research for more conclusive evidence.

Evidence from systematic reviews suggests patient outcomes of mortality and LTFU can be comparable or even slightly improved when ART initiation and maintenance is shifted from doctors to nurses. None of the models reviewed have CHWs initiating ART and there is limited data on patients for who are maintained on ART by CHWs. None of the reviews included data on Task shifting IV, models with patient self-management. To that end, more data are necessary to increase the quality of evidence for task shifting to NPCs and nurses and to determine the effectiveness of task shifting to CHWs and patients. In Chapters 7 and 8, the implementation and outcomes of a community-based model of care facilitated by CHWs, with considerable patient, self-managed are presented.

2.4.2 Models of Care

The level of decentralisation and task shifting involved defines each model of care. As discussed in the overview of this section, to review the literature on decentralisation or task shifting independently is difficult as models of care often in practice incorporate components of both. This section therefore looks to summarise the literature on models of care, programmes or interventions with components of both decentralisation and task shifting (Table 2.4). The models presented here were included in the Cochrane reviews on decentralisation and task shifting [153, 154]. Also reviewed are two additional models of care with published outcomes.

The level of decentralisation (Table 2.2) and type of task shifting (Table 2.3) are classified for each of the models included in this review (Table 2.4). The systematic reviews of decentralisation and task shifting had differences and similarities in the publications that were reviewed, and this is denoted in Supplementary Table 2.2. Details of models of care are presented below, summarised by study design, type of decentralisation and level of task shifting, to highlight gaps in the literature.

Trial data on nurses and decentralisation

The role of nurses in the provision of ART has greatly expanded. Two large RCTs were designed to provide evidence that nurses could provide non-inferior care to ART patients compared to doctors. The Comprehensive International Program for Research in AIDS in South Africa (CIPRA-SA) trial compared the *management* of ART patients by nurses and doctors within primary care clinics [44]. The trial concluded there to be non-inferiority nurse- and doctor-monitored ART. Following on from CIPRA-SA, the STRETCH (Streamlining Tasks and Roles to Expand Treatment and Care for HIV) trial evaluated nurse versus doctor care for ART *initiation and maintenance* within primary care clinics [45]. No difference was found in the proportion of deaths or time to death in the nurse-initiated versus doctor-initiated trial arms.

Observational data on nurses and decentralisation

Increasingly, patients who are defined as stable are down-referred to models of care with further decentralisation and task shifting than the model where they initiated ART. While definitions of stable varied from being adherent on first-line regimen for three to at least 11 months on treatment and virally supressed, outcomes were similar. This definition of stable may be difficult to apply outside of South Africa where access to viral load monitoring is limited. Models down-referred stable patients for ART maintenance at nurse-managed sites and found comparable or lower mortality and LTFU compared to patients in hospital-based, doctor-led sites [163-165].

Community-based models of ART delivery

Community-based models of care offer a further level of decentralisation and often a further shifting of tasks to CHWs and the patient themselves. CBART models in the Cochrane review of decentralisation included two studies in Uganda and one in Kenya [153]. All three of these models of care provide home-based ART delivery and reported comparable or favourable outcomes to facility-based models [166-175].

An RCT in Jinja, Uganda evaluated the impact of a home-based ART delivery and support model with ART maintenance in the CHC where the primary outcome was virologic failure over 3 years of follow-up [168]. ART initiation was done in the CHC by NPCs. In the intervention group, CHWs visited the homes of their patients every month delivery ART, screening for symptoms of toxicity and disease progression and providing adherence support. After 12 months on ART, no difference in mortality, LTFU or virological failure was observed between the two models of care. In rural Uganda, Kipp et al. compared a community-based model linked to a CHC with a hospital-based cohort [171]. Volunteer CHWs made weekly visits to the homes of patients providing support and monthly ART delivery. After two years, virological suppression was more than twice as likely in the CBART model patients versus those in the hospital-based model [172]. In the CBART model in Western Kenya, stable patients were randomised to receive either the standard of care within the clinic or a model where a CHW (who

was a PLWHIV) provided home-based ART delivery [175]. There were no differences in outcomes in the intervention and control arm after 12 months on ART [174].

Table 2.4 Publications on models of care with task shifting and/or decentralisation

Publication	Location	Study design	Objective	Observation time	No. of patients	Task shifting*	Decentralisation±	Main findings
Assefa 2012	Ethiopia	Retrospective cohort	Compare ART by doctors in hospitals to health officers/nurses in community health centers	2006-2009	184,978	Type I & II	Full vs. standard	After 24-months, higher retention in care at CHCs (76% vs. 67%) due to less LTFU (13% vs. 25%)
Balcha 2010	Ethiopia	Retrospective cohort	Compare ART outcomes between hospitals and CHCs	2007-2009	1,709	Type II	Full vs. standard	After 24-months, higher retention in care at CHCs (83% vs. 57%) and lower LTFU (10% vs. 23%)
Bedelu 2007	South Africa	Prospective cohort	Compare ART outcome from nurse-led CHC to doctor-led hospital	2004-2006	1,025	Type I & II	Full vs. standard	After 12 months, lower LTFU at CHC (2% vs. 19%)
Brennan 2011	South Africa	Matched cohort analysis	Compare outcomes of stable patients down-referred to a nurse-managed programme vs. doctor-managed site	2008-2009	2,772	Type I & II	Partial (stable) vs. standard	After 12-months, down-referred patients had reduced LTFU (HR 0.3) and viral rebound (RR 0.6)
Chan 2010	Malawi	Cohort study	Compare outcomes of central hospital clinic to decentralised sites	2004-2008	8,093	Type II	Partial (stable) vs. standard	Patients at CHC less likely to be LTFU (aOR 0.48)
Decroo 2014	Mozambique	Cohort	Describe outcomes of Community Adherence Group patients	2008-2012	5,729	Type II & IV	Full	Retention was 98% at 12 months and 96% at 24 months. Attrition associated with immunosuppression when joining a CAG and being male.
Fairall 2012	South Africa	Cluster RCT	Compare nurse initiated and maintained patients vs. doctors	2008-2010	15,483	Type II	Full	No difference in 12-month mortality between patients initiated by nurses or doctors (HR 0.94), no difference in12-month viral suppression between patients maintained by nurses vs. doctors (RD 1.1%)
Fatti 2010	South Africa	Retrospective cohort	Compare outcomes between CHC and hospitals	2004-2008	29,203	-	Full vs. standard	After 24 months, CHC had higher retention (80% vs. 72% & 69% at district and regional hospitals), lower LTFU in adjusted analysis
Humphreys 2010	Swaziland	Prospective cohort	Compare outcomes of stable patients referred to CHC vs. hospital care	2007	318	Type I & II	Partial (stable) vs. standard	No difference in LTFU, CHC patients less likely to miss an appointment (RR0.37)

Publication	Location	Study design	Objective	Observation time	No. of patients	Task shifting*	Decentralisation±	Main findings
Jaffar 2009	Uganda	Cluster RCT	Compare home-based ART to facility-based care	2005-2009	859	Type III	CBART vs. standard	After 12-months, no difference in mortality (11% vs. 11%), LTFU (1% vs. 2%), or virological failure (16% vs. 17%) between home-based and facility-based patients
Kipp 2012	Uganda	Prospective cohort	Compare outcomes of home-based ART to hospital-based program	2006-2009	385	Type I & III	CBART vs. standard	After 6-months, no difference in virological suppression (90% vs. 89%) or mortality (12% vs. 9%) in the home-based vs. hospital-based cohort
Luque-Fernandez 2013	South Africa	Cohort	Compare outcomes of stable patients in an Adherence Club to CHC	2007-2011	2,829	Type II & III	Full (stable)	At 18-months, Adherence Club patients had higher retention in care (97% vs. 85%) and reduced LTFU (aHR 0.43) compared to CHC
Massaquoi 2009	Malawi	Retrospective cohort	Compare outcomes of a decentralised programme to a centralised program	2006-2007	4,074	-	Full vs. standard	CHCs had lower retention in care (aHR 1.18), similar attrition (aHR 1.17) with lower LTFU (aHR 0.24) but more deaths (aHR 2.2) vs. the hospital
McGuire 2012	Malawi	Retrospective cohort	Compare outcomes of a decentralised programme to a centralised program	2001-2008	15,412	Type III	Full vs. standard	After 24-months, lower attrition at the decentralised site (10/100 person years vs. 21/100 person years) vs. the decentralised facility. No difference in immunological success or suppression after 12-months.
Sanne 2010	South Africa	RCT	Compare outcomes of nurse vs. doctor management models	2005-2009	812	Type II	Full	There were no differences in treatment failure, deaths, virologic failure, or programme losses between models
Selke 2010	Kenya	Cluster RCT	Compare outcomes of stable patients managed by CHWs in HBC vs. clinic based care	2006-2008	208	Type III	CBART (stable) vs. full (stable)	No differences in clinical outcomes, intervention patients made 1/2 as many clinic visits ($p<0.001$)
Sherr 2010	Mozambique	Retrospective cohort	Compare outcomes of patients in NPC vs. physician models	2004-2007	5,892	Type I	Full decentralisation	NPC patients had more clinical visits (RR1.02), higher adherence in the first 6 months (RR 1.05) and were less likely to be LTFU (RR 0.86, 95% CI 0.73-1.02)

Abbreviations: aHR – adjusted Hazard Ratio, aOR – Adjusted Odds Ratio, ART – antiretroviral therapy, CBART – community-based ART, CHC – community health centre, HBC – home-based care, HR – hazard ratio, LTFU – loss to follow-up, NPC – non-physician clinician, RCT – Randomised control trial, RD – risk difference, RR – risk ratio

*Types of task shifting denoted in Table 2.3, ± Levels of decentralisation denoted in Table 2

Other models of care

Médecins Sans Frontières (MSF) was one of the first non-governmental organisations to be involved with ART programmes in resource-limited settings. In recent years, their HIV programmes in sub-Saharan Africa have piloted different models of ART delivery with increased decentralisation. Published details of the Community Adherence Groups (CAGs) in Mozambique and Adherence Clubs, also referred to as peer educator-led ART refill groups, in South Africa are reviewed here.

Community Adherence Groups

CAGs were piloted in the Tete province in northern Mozambique starting in 2008 (CBART, Task shifting III & IV) [176]. A CAG is a self-forming group of up to 6 stable ART patients. Stable was defined as being clinically stable on ART for at least 6 months with a CD4 cell count of ≥200 cells/μl. CAGs members would rotate visiting the CHC and collect ART for all members. Pilot data found very low rates of LTFU and the programme expanded [176]. Retention among CAG members is 98%, 96% and 93% after 12, 24 and 36 months on ART [177]. Among CAG members, an increased risk of attrition was observed for men, patients with a CD4 cell count <200 cells/μl or missing at CAG initiation and in patients from a district or rural clinic compared to a peri-urban clinic. The model has been implemented nationally in collaboration with the Ministry of Health in Mozambique and at the end of 2013, more than 17,000 patients were receiving ART in a CAG [43].

Adherence Clubs

Adherence Clubs were piloted in Khayelitsha South Africa starting in 2007 [143]. Stable patients, defined as being in ART for 18 months or more, two consecutive suppressed viral loads, no opportunistic infections and good adherence, were recruited to join an Adherence Clubs. Adherence Clubs were comprised of approximately 30 patients and met every 8 weeks with a CHW or nurse for group counselling, a brief symptom screen, and collection of pre-packed ART. Data from the pilot found 97% of patients were retained in care, with club participation reducing the risk of LTFU by 57% [178]. Subsequently, in collaboration with the Provincial Government of the

Western Cape (PGWC) and the City of Cape Town, the Adherence Clubs model has been implemented across the Cape Metro. By June 2013, 19% of all ART patients in the Cape Metro were receiving ART in one of 776 Adherence Clubs [43].

2.4.3 Summary

Data from randomised control trials, observational cohorts and pilot programmes suggest that models of care with elements of decentralisation and task shifting can provide comparable and sometimes improved LTFU and retention compared to traditional hospital-based, doctor-led models of care. Data from two RCTs provides high-quality evidence that nurses can offer comparable ART initiation and maintenance to doctors [44, 45]. Observational cohorts confirm these findings and provide evidence for the decentralisation from hospitals to CHCs for both initiation and maintenance of ART. Decentralisation of stable patients provided comparable or beneficial outcomes compared to the model of care where the patients was initiated on ART. Comparative data from community-based models of care are limited to models with home-based ART delivery. In these models, patient outcomes were comparable or favourable to facility-based models. Innovative pilot projects highlight that approaches to ART delivery can be further decentralised and task shifting further delineated towards patient self-management. The effectiveness of community-based models of care requires additional research and further evaluation outside of the traditional research settings.

2.5 SUMMARY AND GAPS IN THE LITERATURE

Loss to follow-up from ART programmes in resource-limited settings represents a key challenge in the effective provision of ART. Challenges exist in defining LTFU, in understanding how LTFU is changing as ART programmes expand and in what adaptations can be made to the delivery of ART to support retention in care. Given the context of rapid scale-up and limited resources, potential interventions also need to consider the public health approach to ART delivery and the multilevel framework of

health system and social/economic factors, HIV- and ART-related factors, and patient level factors that are associated with LTFU. Key gaps identified in the literature review are summarised justifying the research focus of the subsequent chapters.

2.5.1 Temporal changes over the first decade of ART provision in resource-limited settings

Over the first decade of ART provision in resource-limited settings, a series of evolutions have occurred. As summarised in Figure 1.1, the key challenge of ART provision has shifted while the utility of ART has evolved from being a life-saving intervention to also a form of prevention. Concurrently, decentralisation and task shifting of models of care have reshaped the systems in which ART is delivered. These temporal changes underscore that the context is continually changing. Further research into the factors affecting LTFU and interventions to support retention is needed given the highly context-specific nature of the evidence.

2.5.2 Challenges in defining LTFU

LTFU is a key outcome to measure the effectiveness of ART programmes. However, it has not previously received significant attention, traditionally considered a censoring event within time-to-event analyses. LTFU, and in turn retention, are key to successful chronic care delivery. As an outcome, LTFU is complex and includes patients with three distinct outcomes: unascertained mortality, unascertained transfers and patients currently disengaged from care. This complexity leads to challenges in how to define LTFU and in assessment of factors related to LTFU.

As discussed in section 2.1, substantial variation exists in how LTFU is defined. Before investigating risk factors for LTFU, determining the impact of definitions of LTFU on outcomes is necessary. Differences in definitions and analytic approaches pose a challenge when combining data and comparing outcomes between programmes. How these differences in approaches to LTFU impact estimates of LTFU is not well understood. This thesis was conceived before any attention had been given to definitions of LTFU. In recent years, a small body of research has appeared focusing on

the optimal window period for defining no contact and sources of data to generate the outcome LTFU [95, 103, 104]. However, critical public health questions remain on the impact of methodologies to define LTFU, and further research is required to inform recommendations on a standardised definition. Specific attention to the impact of definitions of LTFU on outcomes is examined in Chapter 3.

2.5.3 Factors contributing to LTFU during scale-up of ART in resource-limited settings

LTFU and successive calendar year of ART initiation

As ART programmes have expanded and matured, there is conflicting evidence on how year of ART initiation is related to LTFU and programme retention. It has been hypothesised that as programmes have developed and matured, the quality and outcomes have improved with experience [38]. Alternatively, it has been suggested that programme expansion has outpaced sufficient resources to adequately support patients resulting in poorer outcomes [53]. The question on how year of ART initiation is related to LTFU in resource-limited settings was postulated following an analysis of temporal trends in South Africa [56]. While data from South Africa highlighted a significant increase in LTFU among patients who had recently initiated ART, it is unclear if this association will be found in other resource-limited settings. Therefore, data from MSF cohorts in other low- and middle-income countries and the association between year of ART initiation and LTFU is the focus of Chapter 4.

LTFU and programme expansion

Following from the ambiguity of the relationship between year of ART initiation and LTFU, limited data are available on how programme expansion relates to LTFU and retention in care. As summarised in Section 2.2, observational studies and studies that trace patients who are LTFU identified health systems factors associated with LTFU. Factors relating to scale-up of ART including waiting times, long queues and patient volume have been found to increase the risk of LTFU. However, it is less clear what

component of programme expansion relates to LTFU and if this association is independent of year of association. Consequently, the analysis in Chapter 4 includes two measures of expansion in addition to year of ART association. Both programme size and the rate of expansion are included in multivariate analyses to assess if temporal factors of scale-up are related to LTFU.

LTFU and increasing CD4 cell count at ART initiation

In all regions of the world, patients are accessing ART at progressively higher CD4 cell counts [24]. However, conflicting evidence exists on how initiation of ART at higher CD4 cell counts impacts patient outcomes. Given the push towards earlier initiation, it is crucial for additional analyses to investigate the impact of higher CD4 cell counts at ART initiation on risk of LTFU and retention in care. Previous findings on the relationship between CD4 cell count and LTFU has been inconsistent with few patients accessing ART above a CD4 cell count <200 cells/μl. Chapter 5 assesses the association between CD4 cell count and LTFU in the first two years on ART. The multivariate analyses in Chapter 5 adjust for health systems factors (year of ART initiation and programme expansion) and individual level factors (age and gender) given that LTFU is related to factors at multiple levels. Linkage with the National Population Register in this chapter corrects for unascertained deaths. This linkage is critical given that lower CD4 cell counts are related to mortality.

Individual risk factors for LTFU

Patient groups have disparate outcomes on ART. Consistently higher LTFU was observed in men, young adults and other underserved groups. As we expand ART eligibility criteria, the needs of these groups should be taken into consideration to ensure that all patients are supported as they endeavour to adhere to lifelong ART. Chapters 6-8 assess two novel models of care. To understand how these models of ART delivery impact on outcomes for specific patient groups, both Chapter 6 and Chapter 8 conduct sub-group analyses to address Objective 3b.

2.5.4 Models of care with decentralisation and task shifting

There is considerable interest in the role of models of care with decentralisation and task shifting to support continued ART expansion and improve LTFU and retention. Adapting how ART is delivered can address multiple risk factors and provide scalable interventions to support retention in care. To date, the literature on decentralisation has focussed on partial and full decentralisation, whereby patients are initiated and or maintained at health facilities peripheral to hospitals. WHO recommends decentralisation for ART initiation and maintenance to peripheral facilities on the basis of low quality evidence. Further data are needed, given the low quality of evidence available and the importance of the context in implementing novel models of care. To this end, Chapter 6 presents outcomes of the Green Clinic, a model of care with ART maintenance at a CHC.

More data on community-models of care are needed

Recently, community-based models of care have received increased attention. However, data from out-of-facility models are limited. The CBART models included in both the Cochrane review on decentralisation and the review by Suthar et al. were limited to models with home-based ART delivery [28, 153]. Nevertheless, WHO recommends ART provision at the community level [28].

To date, the data from community-based models of care for ART delivery are limited to home-based models. Home-based delivery is highly resource intensive and unlikely to be scalable in the contexts of generalised epidemics. Moreover, home-based delivery models do not encourage patient self-management. Chapters 7 and 8 describe the implementation and outcomes of a community-based model of care to support ART retention of stable patients.

Increased task shifting towards patient self-management

The transition towards decentralisation of ART is happening in parallel with the progression towards further task shifting. Overall, the WHO rates the quality of the evidence for task shifting as moderate [28]. The literature on task shifting is focused on

levels I-II, with tasks reallocated from doctors to NPCs and nurses. Limited data on task shifting to CHWs and patient self-managed is available despite the shift to patient self-management being regarded as the most important task shifting transition [41]. Chapter 6 contributes data on how nurse-managed and CHW-supported models can support ART maintenance. Chapters 7 and 8 present the community-based Adherence Club model, which are CHW-managed and include substantial shifting of tasks to individual patients.

Who do innovative models of care work for

The other gap in the models of care literature is which patient sub-groups do innovative models of care provide comparable, favourable or poorer outcomes compared to the standard of care. We do not know what profile of patients is best suited to these decentralised models. To address this question, Chapters 6 and 8 assess outcomes by sub-groups and investigate how outcomes vary within the novel model of care compared to the standard of care.

2.5.5 Conclusion

Questions remain in our understanding of LTFU from ART programmes in the context of scale-up in resource-limited settings. This thesis looks to contribute to some of the key areas where there is a paucity of evidence or conflicting findings. Specifically, how definitions of LTFU affect estimates of retention will be elucidated. Temporal factors related to LTFU in the context of scale-up including year of ART initiation, programme expansion and the role of higher CD4 cell counts at ART initiation will be investigated. Finally, models of care providing decentralised ART and utilising task shifting will be described and evaluated to inform how the health system can be reoriented to support expanding ART cohorts in resource-limited settings.

Chapter 3. Impact of definitions of loss to follow-up (LTFU) in antiretroviral therapy programme evaluation: variation in the definition can have an appreciable impact on estimated proportions of LTFU

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3.1 ABSTRACT

Background

To examine the impact of different definitions of loss to follow-up (LTFU) on estimates of programme outcomes in cohort studies of patients on antiretroviral therapy (ART).

Methods

We examined the impact of different definitions of LTFU using data from the International Epidemiological Databases to Evaluate AIDS-Southern Africa. The reference approach, Definition A, was compared with five alternative scenarios that differed in eligibility for analysis and the date assigned to the LTFU outcome. Kaplan-Meier estimates of LTFU were calculated up to two years after starting ART.

Results

Estimated cumulative LTFU were 14% and 22% at 12 and 24 months, respectively, using the reference approach. Differences in the proportion LTFU were reported in the alternative scenarios with 12-month estimates of LTFU varying by up to 39% compared with Definition A. Differences were largest when the date assigned to the LTFU outcome was 6 months after the date of last contact and when the site-specific definition of LTFU was used.

Conclusion

Variation in the definitions of LTFU within cohort analyses can have an appreciable impact on estimated proportions of LTFU over two years of follow-up. Use of a standardised definition of LTFU is needed to accurately measure programme effectiveness and comparability between programs.

3.2 INTRODUCTION

In 2011, 30 years since the first cases of AIDS were reported, 34 million people worldwide were living with human immunodeficiency virus (HIV) [179]. More than two thirds of the global cases are located in sub-Saharan Africa. Nearly six million people in the region were receiving antiretroviral therapy (ART) in 2011, up from only 100,000 people in 2003 [179]. Across sub-Saharan Africa, the expansion of ART services represents one of the largest pharmacologic interventions to promote population health to date, and there is considerable interest in monitoring the impact of these programs [180]. Given the high mortality rate of untreated HIV infection, mortality and disease progression have been the major clinical outcomes of interest in ART programs. However more recently, loss to follow-up (LTFU) has emerged as a key indicator of ART programme effectiveness [97] and there is a growing emphasis on monitoring programs to improve long-term retention in care [98].

Conventionally within most cohort analyses, LTFU is considered an uninformative censoring event [181, 182] and in practice relatively little attention may be paid to the definition of LTFU compared to clinic outcomes of interest (such as mortality in the case of ART programs). However when LTFU becomes an outcome of interest, greater attention to the definition of this phenomenon may be warranted. Within ART programs, consideration of LTFU is of particular importance and is generally higher in settings where mortality ascertainment may be weak [183].

Understanding the impact of varying definitions of LTFU on programme outcomes is a central consideration for other chronic disease programs that seek to retain patients in care over the long-term. However there has been relatively little attention to how LTFU should be defined in cohort analyses in ART and other chronic disease services. Within the evaluation of ART programs, the treatment of LTFU in analysis varies widely. The lack of a standard definition hampers systematic reviews of pooled data [37, 38, 99]. Previous work has focused on the optimal duration of loss to minimise LTFU misclassification [103, 104] but there is little consensus on other aspects of defining LTFU within analyses.

Definitions of LTFU used in the analysis of ART programs vary in their application of eligibility for inclusion in analysis, the date assigned to the LTFU outcome, and whether or not to utilise the outcome LTFU as defined by the site. In light of this heterogeneity, it is important to investigate whether and how definitions of LTFU impact on observed programme outcomes. It is plausible that varying analytic definitions give rise to spurious observed differences in estimates of LTFU as a programme outcome. We used data from the International Epidemiological Databases to Evaluate AIDS (IeDEA) – Southern Africa collaboration to explore the impact of varying LTFU definitions on programme estimates of LTFU.

3.3 METHODS

IeDEA is an international collaboration comprised of seven data centres that pool large HIV datasets [184-186]. The source dataset for this analysis included all adults who initiated therapy between 2002 and 2007 at eight public-sector antiretroviral programs in South Africa; details of the sites and sample have been reported previously [52]. The IeDEA-SA collaboration was approved by the ethics committees of the University of Cape Town, South Africa, and University of Bern, Switzerland and the ethics committees of each participating site.

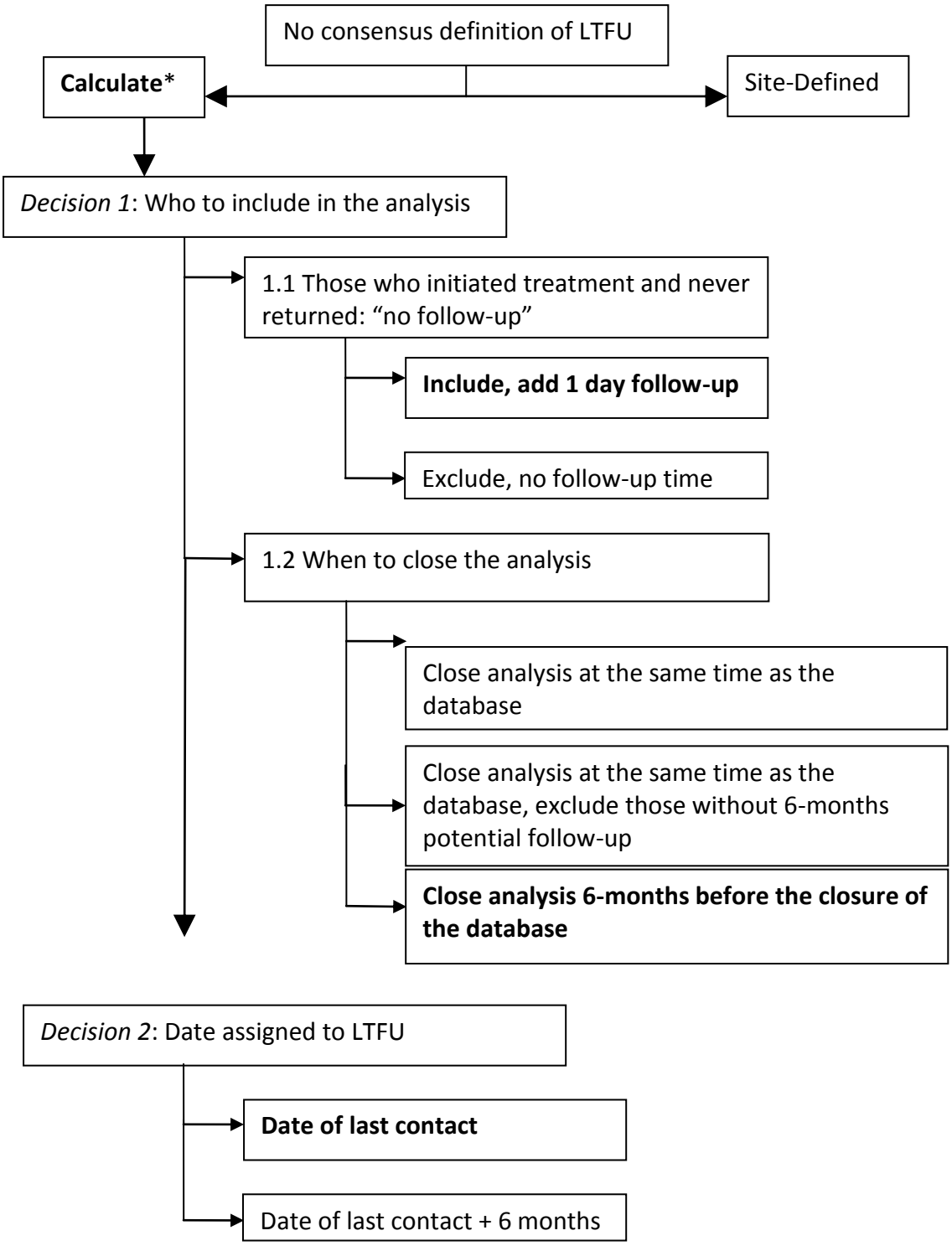
Within these data, six different scenarios with varying definitions of LTFU were tested to determine how variation in the definition of LTFU may influence programme retention outcomes over the first 24 months after ART initiation. Five definitions generated LTFU under varying assumptions, and the sixth used the site-defined variable of LTFU. Consistent within the five generated definitions were that individuals were defined as LTFU if they had no visit or contact in the previous 6-months. A 6-month period was used to accommodate the largest interval between visits within contributing cohorts. In addition, this time period has been shown to have the least misclassification when defining LTFU [103, 104]. Definitions of LTFU differed in: the timing of analysis and database closure, the approach to those who initiated treatment and never returned, and the date assigned to the LTFU outcome (Figure 3.1 and Table

3.1). Variations in these key factors gave rise to five generated definitions of LTFU analysed here.

3.3.1 Reference approach – Definition A

In Definition A, the analysis was closed 6 months before database closure. This ensured both sufficient follow-up time among those included as well as a window of observation to observe retention in care. For patients who initiated ART and never returned, one day of follow-up was added so that they were included in the time-to-event analysis. The last contact date was assigned to the outcome LTFU [56]. Definition A is the most conservative and likely to result in the highest estimates of LTFU. It is used as the reference to compare with all other scenarios (see bolded options in Figure 3.1).

Figure 3.1 Decision in defining LTFU in an ART programme cohort analysis



*Bolded option denotes decision illustrated in Definition A.

Table 3.1 Analytic approaches to defining ART programme loss to follow-up

	Inclusion of patients who started ART but never returned to clinic	Analysis closure 6-months before database closure	Date assigned to loss to follow-up
Definition A [56]	Yes*	Yes	Last visit
Variation A1 [139, 187]	Yes*	No†	Last visit
Variation A2 [188]	No	Yes	Last visit
Variation A3 [189]	Yes*	Yes	Last visit plus 6 months
Variation A4	No	No†	Last visit plus 6 months

* Patients were included by adding one day of follow-up
† All patients included, independent of window of observation and duration of follow-up
Variation A1: the analysis and database closure dates were the same and thus all those who initiated treatment in the 6 months preceding the database closure were included in the analysis
Variation A2: participants who did not return after ART initiation were excluded from analysis
Variation A3: assigned the date of LTFU as 6-months after the last contact date, allowing patients defined as LTFU to contribute additional person-time to the analysis
Variation A4: combined Variations A1-A3

3.3.2 Variations on the definition of loss to follow-up

Four variations to generating a definition of LTFU were applied. In Variation A1, the analysis and database closure dates were the same and thus all those who initiated treatment in the 6 months preceding the database closure were included in the analysis [139, 187]. In Variation A2, participants who did not return after ART initiation were excluded from analysis [188]. A third scenario, Variation A3, assigned the date of LTFU as 6-months after the last contact date, allowing patients defined as LTFU to contribute additional person-time to the analysis [189]. Variation A4 combined Variations A1-A3: the analysis and database closure dates were the same, those who initiated ART and never returned were excluded and the date assigned to the outcome LTFU was 6 months after the last contact date. The differences between these generated definitions are summarised in Table 3.1. A sixth definition of LTFU was based on the determination of LTFU by each site. In all of these scenarios above, those who were transferred out were censored at the date of transfer; deaths were censored on the date of death.

3.3.3 Statistical Analysis

For each of the scenarios, patient characteristics at baseline [age, sex, Cluster of Differentiation 4 (CD4) count and year of enrolment] were described with appropriate summary statistics. Kaplan-Meier estimates of LTFU under the six different definitions were calculated over 24-months and reported at 6-month intervals. Differences in the proportions LTFU were estimated using Definition A as the reference scenario throughout. Data were analysed using STATA 11.0 (STATA Corporation, College Station, Texas).

3.4 RESULTS

The scenarios included between 43,173 and 45,849 adults with slight variations in baseline characteristics based on eligibility for the different analyses. Definition A included 44,177 adults with a median age of 35 years and over 60% of participants initiating therapy in the last 2 years of enrolment (2006 and 2007) (Table 3.2). In Variation A1 with no window between the analysis and database closure, an additional 1,655 participants were included. Patient characteristics (gender, age, baseline CD4 and year of enrolment) of those LTFU were consistent across all scenarios (Table 3.3).

Changes in LTFU by definition

Under the reference approach (Definition A), estimated LTFU was 9.3%, 14.4%, 18.8% and 22.4% at 6-, 12, 18- and 24-months post ART initiation, respectively (Table 3.4). Compared to this definition, all other scenarios underestimated LTFU in the first year on treatment (Figure 3.2). When the analysis and database closure dates were the same (Variation A1), the LTFU underestimation increased from 4.3% at 6-months to 12.1% at 24-months compared to Definition A (Table 3.4). Excluding those who initiate ART and never return (Variation A2) resulted in lower estimates of the LTFU proportion compared to Definition A. At 6-months the difference was 21.5% decreasing to 7.6% at 24-months.

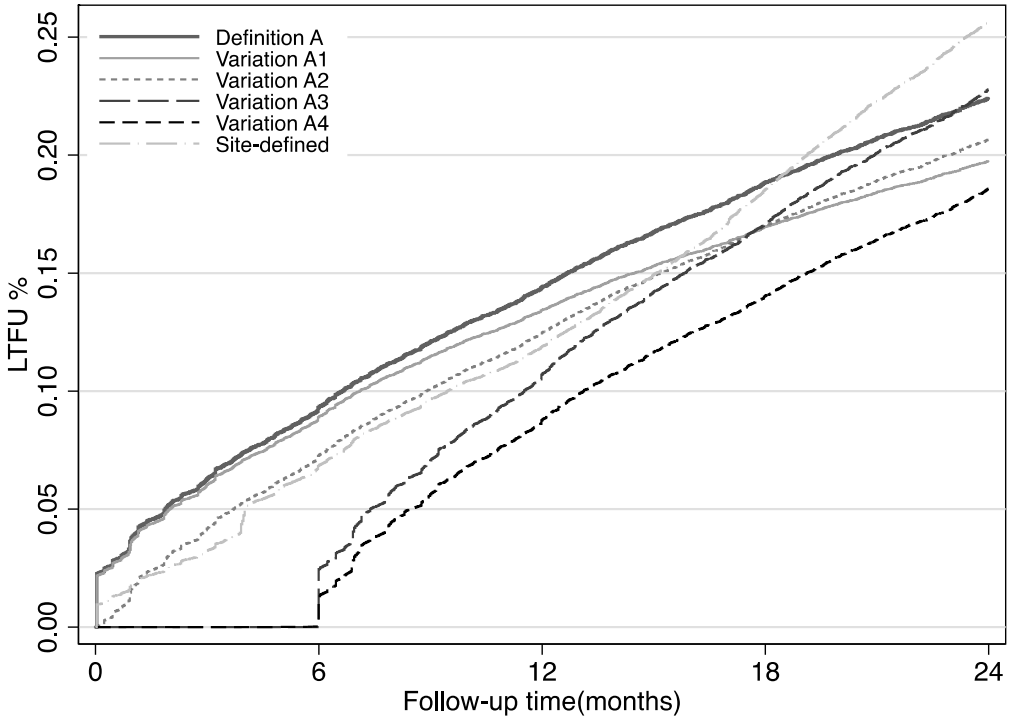
Table 3.2 Patient characteristics at ART initiation in Definition A

Characteristics	***N* (%)**
Adults (≥16 years)	44,177
Gender	
Female	29,904 (67.7)
Age,	
Age (years), median (IQR)	35.0 (29.9-41.6)
Age categories (year)	
16-24	2,306 (5.2)
25-34	17,654 (40.0)
35-44	16,177(36.6)
≥45	8,040 (18.2)
Baseline CD4 (cells/μl), categorical	
<50	9,947 (27.2)
50-199	22,703 (62.1)
≥200	3,899 (10.7)
Year of initiation *n(%)*	44,177 (100)
2002 and 2003	1,173 (2.7)
2004	5,262 (11.9)
2005	9,909 (22.4)
2006	13,105 (29.7)
2007	14,728 (33.3)

Table 3.3 Kaplan-Meier estimates of 12-month ART programme LTFU by covariates reported by LTFU definition

Characteristics	Definition A	Variation A1	Variation A2	Variation A3	Variation A4	Site defined
Gender						
Male	17.0	15.8	14.6	13.0	10.6	13.7
Female	14.8	13.8	12.7	10.5	8.5	12.2
Age (years)						
16-24	22.1	20.2	19.0	15.1	12.2	17.3
25-34	15.6	14.4	13.6	11.3	9.3	12.4
35-44	14.6	13.6	12.5	10.9	8.8	12.2
45+	15.4	14.3	13.0	11.1	8.6	13.0
Baseline CD4 (cells/μl), categorical						
<50	16.4	15.4	13.2	13.7	11.4	13.7
50-199	13.8	12.8	12.0	9.7	8.0	11.3
≥200	17.7	16.0	15.4	12.4	10.2	12.9
Year of initiation						
2002 & 2003	1.1	1.1	1.1	0.8	0.1	1.0
2004	9.0	9.0	7.5	6.4	6.0	7.8
2005	10.8	10.8	9.1	7.8	7.3	8.3
2006	14.0	13.7	11.8	9.6	8.5	9.9
2007	26.7	20.7	23.8	21.4	13.3	21.6

Figure 3.2 ART programme LTFU by LTFU definition 0-24 months follow-up



Variation A3 highlighted the effect of assigning the LTFU date 6-months after the date of last contact. The underestimation of LTFU was 73% at 6-months decreasing with time on treatment and at 24-months the LTFU proportion was 1.8% higher than Definition A (Table 3.4). Combining variants A1-A3 into Variation A4 produced the largest deviations from the reference definition with an 86% underestimation of LTFU (1.3% vs. 9.3%) at 6-months decreasing to a 17% underestimation at 24-months (Table 3.4).

Estimates of LTFU from site-defined LTFU varied appreciably, both in magnitude and direction of LTFU, compared to Definition A. The proportion LTFU at 6-, 12-, and 18-months was less than in Definition A (26.9%, 17.4% and 1.6%, respectively) and 14.3% higher at 24-months (Table 3.4).

Table 3.4 Kaplan-Meier estimates of cumulative mortality and LTFU reported 6 monthly and relative differences of LTFU* compared with Definition A

	6-months			12-months			18-months			24-months		
	% Mortality	% LTFU	Difference	% Mortality	% LTFU	Difference	% Mortality	% LTFU	Difference	% Mortality	% LTFU	Difference
Definition A	4.8	9.3	Ref	6.6	14.4	Ref	7.6	18.8	Ref	8.5	22.4	Ref
Variation A1	4.7	8.9	4.3	6.4	13.5	6.3	7.3	17.0	9.6	8.0	19.7	12.1
Variation A2	4.7	7.3	21.5	6.5	12.5	13.2	7.6	17.0	9.6	8.4	20.7	7.6
Variation A3	4.5	2.5	73.1	6.2	10.7	25.7	7.2	17.2	8.5	8.0	22.8	-1.8
Variation A4	4.5	1.3	86.0	6.0	8.8	38.9	6.9	14.1	25.0	7.6	18.6	17.0
Site-Defined	4.6	6.8	26.9	6.3	11.9	17.4	7.2	18.5	1.6	7.9	25.6	-14.3

* Differences reported are percentage differences compared to Definition A

3.5 DISCUSSION

This analysis demonstrates that different definitions of LTFU within an ART cohort analysis have an appreciable impact on estimated LTFU over time. Estimates of LTFU, particularly at 12-months, varied in each scenario when compared to the reference approach Definition A. If the nature of the analytic approach taken to LTFU varies, comparing programs and combining results is not possible.

There is a growing interest in LTFU and programme retention in ART programs [98]. Two systematic reviews of ART programme retention have combined the results from multiple cohorts despite differences in LTFU definitions [37, 38]. There is strong evidence that over time, LTFU is contributing an increasing proportion to those lost to care, and may be a more important indicator of programme performance than patient mortality [56]. However, it is difficult to assess trends and differences in LTFU between and within programs as variations in the definitions of LTFU obstruct comparability.

There are many variations as to how LTFU is defined within the literature. This analysis demonstrates empirically the impact of these variations on estimates of LTFU. One approach is to have the analysis and database close at the same time utilizing all of the available data [139, 187]. Although it is appealing in its use of all available data, this approach, Variation A1, leads to a consistent underestimate of LTFU, as those who had recently initiated treatment did not have sufficient potential to be LTFU.

An alternative approach is to exclude patients who have recently initiated therapy, those without sufficient potential to be LTFU, and keep the analysis and database closure dates the same [190-192]. The common closure of the analysis and database results in an artificial cessation of LTFU in the last 6 calendar months of observation because LTFU is impossible among those with a visit in the final 6-months. Excluding those who initiated treatment in the previously 6-months is either non-informative, or in context of temporal trends of increasing LTFU, contributes to under ascertainment of recent LTFU. This variation is not utilised here, as it is not recommend given that LTFU

is a meaningful event often more likely to occur in the final months of observed patient-time when the phenomenon is increasing due to service expansion.

Another approach utilises different dates for database and analysis closure [53, 97, 139, 193]. As was done in Definition A, restricting the analysis to person time observed at least 6-months before the database closure gives a window of observation to observe retention in care and ensures sufficient potential observation among those who recently initiated therapy.

Patients who initiate treatment and never return are a group that is often excluded from time-to-event analyses. Excluding this group, as in Variation A2, potentially underestimates true LTFU and inflates estimates of programme retention. Alternative approaches are to report them as a specific "no follow-up" group [97], or presume a small amount of follow-up time (e.g. one day) so that they are included in the analysis (Definition A) [56]. The LTFU in Variation A2 was consistently lower than in Definition A with the relative difference decreasing over duration of follow-up. Initiation without being confirmed on treatment is debatable, but where data systems are weak, the first visit is often preferentially recorded and those individuals with only the initiation visit recorded may well have been established on treatment.

Approaches to the assignment of a date to the outcome LTFU vary as well. Most analyses use the last visit or contact date [139, 194-199] while others choose a date somewhere between the date of last contact and the first missed visit date [189, 200]. Adding 6-months to the follow-up time as in Variation A3, lead to a LTFU estimate of 1.3% and 8.8% LTFU at 6- and 12-months compared to 9.3% and 14.4% in Definition A, respectively. Presuming follow-up time is working with the unknown whereas the differential closure approach (where the analysis closes before the database) has no need to make any assumptions. Given these potential variations in how LTFU is defined in analysis, it is unsurprising that few analyses of ART programme outcomes employ the same definition of LTFU.

The LTFU estimates from each of scenarios A1-A3 appeared only modestly different from Definition A but when combined in Variation A4, estimates of LTFU were

substantially different. This shows that the cumulative impact of small differences in defining LTFU can have an appreciable influence on LTFU estimates.

We found that the Site-Defined estimates of LTFU varied greatly when compared to Definition A. This variability around a calculated estimate highlights that sites are likely defining outcomes differently and it may be inappropriate to compare or combine site-defined outcomes across a number of sites [99]. The variability of site definitions suggests that the most efficient approach to standardizing LTFU in combined analyses is to generate LTFU from the data at the time of analysis.

To our knowledge, this analysis is the first to examine how defining LTFU in ART cohort analyses may produce different estimates of programme outcomes. This work builds on previous methodological research that proposed using 180 days without contact since the last clinic encounter as a an optimal period for defining LTFU in order to minimise misclassifications [103, 104]. Other research has focussed on determining risk factors for being loss to follow-up [183], early and late in the program. Here we focus on the analytic definition of LTFU in cohort analyses and the impact that this may have on estimates of LTFU.

The objective of the analysis is to demonstrate the impact of LTFU definitions of ART programme outcomes and we have focussed on a relatively short duration of 24 months follow-up. LTFU is defined in terms of the absence of death and transfers out and only at the analysis closure in terms of 6-months of non-attendance. We did not focus on treatment interruptions [92, 145] or distinguishing observed versus actual LTFU [103, 104] but acknowledge these are important related issues that require additional consideration. Of note, we have used standard Kaplan-Meier methods, which are common in the ART programme literature. Competing risks methods have been proposed as an alternative, but given the relatively low mortality observed in these data, the outcomes from the two methodologies are unlikely to differ substantively [130, 201].

Concerns around the definition of LTFU are not restricted to ART programme analyses, but are likely to emerge in any setting when LTFU may be an outcome of interest. For

chronic care programs to be successful, patients need to be adherent and retained in treatment services [202]. In order for a patient to be adherent, they must be retained within the programme and therefore all patients who are LTFU are by definition not adherent. Defining LTFU is therefore relevant in the operational research of all chronic care programs where patient retention is an outcome of interest.

In South Africa, the rate of ART programme expansion was so rapid that systems were not in place to track and monitor the outcomes of patients after initiation. There are now renewed efforts to determine the outcomes of patients on ART. To determine the number of patients retained in the national programs, accurate estimates of patients lost to care are needed. Linkage with the National Population Register (NPR) has improved the accuracy of mortality data [53, 203]. A standardised definition of loss to follow-up to improve the accuracy of LTFU estimates is analogous to the linkage with the NPR to improve mortality estimates necessary to appropriately assess ART programme loss.

These results point to the need for a standardised definition of LTFU for ART service evaluation if we are to understand changes within and differences between ART programs. They also highlight the need to consider how LTFU is defined and assessed within health systems research involving other long-term therapies. Based on this work, we propose a standardised definition to LTFU may facilitate comparisons of outcomes within and between ART programs. Our recommendation is the most conservative Definition A, in which the analysis closes 6-months before the database, one day of follow-up is added for those who initiate treatment and never return, and those who do not have contact in last 180 days be defined as LTFU on the date of last contact.

3.6 ACKNOWLEDGEMENTS

3.6.1 Author Contributions

AG, MC, AB, and LM conceived and designed the experiments. AG analysed the data. AG wrote the first draft of the manuscript. AG, MC, ME, AB, and LM contributed to the writing of the manuscript. AG, MC, ME, AB, and LM agreed with manuscript results and conclusions.

Chapter 4. Outcomes of Antiretroviral Therapy Over a 10-Year Period of Expansion: A Multicohort Analysis of African and Asian HIV Programmes

Grimsrud A, Balkan S, Casas EC, Lujan J, Van Cutsem G, Poulet E, Myer L, Pujades-Rodriguez M. Outcomes of antiretroviral therapy over a 10-year period of expansion: a multicohort analysis of African and Asian HIV programmes. *Journal of Acquired Immune Deficiency Syndrome*. 2014 Oct 1;67(2):e55-66.

4.1 ABSTRACT

Background

Little is known about the evolution of programme outcomes associated with rapid expansion of ART in resource-limited settings. We describe temporal trends and assess associations with mortality and loss to follow-up (LTFU) in HIV cohorts from 8 countries.

Methods

Analysis included adults in twenty-five Médecins Sans Frontières supported programs initiating ART between 2001 and 2011. Kaplan-Meier methods were used to describe time to death or LTFU, and proportional hazards models to assess associations with individual and programme factors.

Results

ART programs (n=132,334; median age 35 years; 61% female) expanded rapidly. While 36-month mortality decreased from 22% to 9% over 5 years (≤2003-2008), LTFU increased from 11% to 21%. Hazard ratios (HR) of early (0-12 months) and late (12-72 months) LTFU increased over time, from 1.09 (95% CI 0.83-1.43) and 1.04 (95% CI 0.84-1.28) in 2004, to 3.29 (95% CI 2.42-4.46) and 6.86 (95%CI 4.94-9.53) in 2011, compared to 2001-2003. Rate of programme expansion was strongly associated with increased early and late LTFU, adjusted HR (aHR)=2.31 (95%CI 1.78-3.01) and HR=2.29 (95%CI 1.76-2.99), respectively, for ≥125 vs. 0-24 patients/month. Larger programme size was associated with decreased early mortality (aHR=0.49, 95% CI 0.31-0.77 for ≥20,000 vs. <500 patients), and increased early LTFU (aHR=1.77, 95% CI 1.04-3.04 for ≥20,000 vs. <500 patients).

Conclusion

As ART expands in resource-limited settings, challenges remain in improving access to ART and preventing programme attrition. There is an urgent need for novel and sustainable models of care to increase long-term retention of patients.

4.2 INTRODUCTION

Over the past decade, there has been rapid expansion of antiretroviral therapy (ART) in resource-limited settings. By 2011, an estimated 9.7 million people in low- and middle-income countries were receiving ART [24]. During this growth, HIV programs have adapted services to cope with the increasing numbers of patients requiring ART. As programs mature and increase in size, the need to ensure long-term retention in care of patients receiving ART while continuing timely initiation of new patients onto treatment presents an ongoing challenge to policy makers and health care providers alike.

Over the past decade, the conditions in which ART programs operate in low and middle-income countries have changed considerably. The numbers of patients has increased rapidly and often disproportionately to the number of health care workers providing care [204]. Guidelines for initiation of ART have been simplified and context specific recommendations have been adapted to facilitate improving and expanding access to treatment. Furthermore, eligibility criteria for ART initiation have evolved and recommended CD4 cell count thresholds for treatment start have recently been increased to improve patient outcomes [28].

The effectiveness of ART in reducing morbidity and mortality depends on patient adherence to therapy and on the ability of HIV programs to retain patients in care. Previous analyses examining temporal trends in long-term programme outcomes in resource-limited settings have reported conflicting results. While data from South Africa showed increasing loss to follow-up (LTFU) by calendar year of enrolment [56, 63, 76]; systematic reviews of sub-Saharan African cohorts and findings from a large Kenyan cohort reported improvements in patient retention in recent years [38, 85, 117]. Evaluating programme outcomes, assessing temporal trends in programme retention and investigating the factors associated with poor outcomes are essential to improve the long-term effectiveness of ART services in low and middle-income countries. Understanding associations between programme expansion and treatment outcomes are particularly relevant in the context of the Treatment 2.0 initiative to

scale-up HIV treatment through promoting innovation and efficiency gains, and of the ambitious goal of expanding ART to fifteen million people by 2015 [24, 205].

The objective of this study was to describe temporal trends in patient characteristics at ART initiation and in ART outcomes using data from resource-limited countries where Médecins Sans Frontières (MSF) supports the provision of HIV treatment. We also examined associations between individual level risk factors, absolute programme size, and rate of ART programme expansion, and mortality and LTFU.

4.3 METHODS

4.3.1 Study population

We analysed patient electronic health records from 25 sites in eight countries where MSF supports the provision of ART care. Cohorts were located in Democratic Republic of Congo (DRC), India, Kenya, Malawi, Mozambique, Myanmar, Uganda and Zimbabwe. Details of these programs have been described previously [206]. All programs provided care and treatment free of charge. Criteria for ART initiation followed WHO guidelines. The analysis included all adults aged 16 years or older who initiated ART between March 2001 and September 2011 in one of the programs.

4.3.2 Data collection and definitions

Characteristics at ART initiation including sex, age, CD4 cell counts, WHO clinical stage, body mass index (BMI), and date of ART initiation, were prospectively collected with the FUCHIA software (Epicentre, Paris). Throughout, reference to baseline is a reference to time of ART initiation.

Patient follow-up began at the date of ART initiation and was censored at the earliest of: death, transfer out, last clinic visit, or analysis closure. Sites began initiating patients onto ART between 2001 and 2007. Only patients with a minimum of 6-months of follow-up were included with analysis closure preceding the database closure date by 6-months. The database closure ranged from 30 September 2011 to 20 March 2012. Deaths were events recorded before the analysis closure date. Loss to follow-up was defined as having no visit in the 6-months before analysis closure. Patients who initiated treatment but did not return were given 1-day of follow-up time so that they would contribute to survival analysis [207]. Programme retention was defined as being in care (i.e., not dead or LTFU) at the time of analysis closure.

To quantify the size of the ART programs two variables, programme size and the rate of programme expansion, were defined. For each patient, programme size was calculated as the total number of both pre-ART and ART patients receiving care in the programme at the end of the calendar year of patient ART initiation. To define the rate of programme expansion, the rank of each patient enrolled by site was divided by the duration of ART provision in the site up to the date of enrolment, in months. For example, if the one hundredth patient at the site was enrolled 4 months after the programme started, the rate of programme expansion for that patient would be 25 (100/4).

4.3.3 Statistical methods

Baseline characteristics were described by year of ART initiation using medians and interquartile ranges for continuous variables, and proportions for categorical variables. Kaplan-Meier methods were used to describe cumulative probabilities of death, LTFU and programme retention after ART initiation and were analysed overall, by calendar year of ART start, programme size, and rate of expansion.

Cox's proportional hazards models were used to assess associations between baseline patient characteristics and outcomes. Heterogeneity across sites was accounted for using random effects. To examine differences in risk factors over time, models were

stratified by early (0-12 months) and late (12-72 months) follow-up time periods. Adjusted models were built first by including all baseline characteristics (model 1), and then adding the programme size variable (model 2), or the rate of expansion variable (model 3), or both (model 4). The primary analysis only included patients with complete data on baseline characteristics (complete case analysis).
In sensitivity analyses, models including patients with missing baseline CD4 cell counts, clinical stage, and/or BMI as separate categories were used. We also assessed different measures of programme size including the number of patients who had previously initiated ART by site and the number of ART patients in care at each site at the end of the calendar year. Kaplan-Meier survival proportions and hazard ratios (HRs) stratified by site were assessed and compared with the primary results. Finally, to account for non-differential censoring (e.g. higher risk of death among patients LFTU early after ART start), models of time to death and LTFU were calculated using competing risks methods [208].

Data was analysed with STATA 12.0 (STATA Corporation, College Station, Texas, USA). All FUCHIA sites obtained agreement from health ministries for the prospective collection of data. No patient identifiers were included in datasets. The International Ethics Review Board of MSF reviewed the study and determined it did not require formal approval. The Human Subjects Research Ethics Committee of the Faculty of Health Sciences from the University of Cape Town reviewed and approved the data usage and analysis plan.

4.4 RESULTS

4.4.1 Characteristics at ART initiation

Between 2001 and 2011, 132,334 individuals contributed 299,658 person-years of follow-up (median per patient, 1.75 years, interquartile range (IQR), 0.57-3.56). At ART initiation, the median age was 35 years, 61% of patients were female, 69% had CD4 cell counts <200 cells/µl and less than 5% had CD4 cell counts >350 cells/µl

(Table 4.1). Twenty-five percent of patients had clinical stage IV disease and a third had a BMI below 18.5 kg/m^2. More than half of patients received treatment in Malawi (n=37,657) or Zimbabwe (n=30,783); Asian cohorts contributed 14% of patients.

4.4.2 Temporal changes in patient baseline characteristics and outcomes

The number of patients initiating ART increased substantially each calendar year (Table 4.2), from 4,427 in 2001-2003 to 22,863 in 2010. Median age was 35 years and remained constant over time. Median CD4 cell count increased over time from 97 in 2003 or earlier to 184 cells/µl in 2011 (Supplementary Figure 4.1). However, every year approximately 30% of patients initiated ART with a CD4 cell count <100 cells/µl (Supplementary Figure 4.2); the range across countries being 22-48%. The proportion of patients with clinical stage IV disease at the time of ART initiation decreased from 44% to 14%.

Mortality decreased over the study period (Figure 4.1A), from 17% to 5% at 12 months; and from 22% to 9% at 36 months (Table 4.3). Larger programs (Figure 4.1C) and those with greater rate of expansion (Figure 4.1D) had lower rates of mortality (Supplementary Table 1). In contrast, LTFU increased substantially over time, from 6% to 15% at 12 months; and from 11% to 21% at 36 months (Figure 4.1B). LTFU increased with programme size up to a number of 7 500 patients (Figure 4.1D). Programme retention was highest between 2006 and 2009. Trends in outcomes were homogeneous across sites (Supplementary Figure 4.3 and 4.4).

The contribution of LTFU to overall programme attrition increased with duration of ART (Supplementary Figure 4.4). During the first year of treatment, approximately half of the programme losses were LTFU (6% of patients had died compared to 8% who were LTFU). However, after five years, two thirds of the losses were LTFU patients (24% compared to 13% of deaths). Programme retention decreased from 82% at 12 months, to 73% at 36 months and 66% at 60 months. The smallest programs had the largest estimates of 12-month mortality: 12%, 11% and 9% in sites with less than 500,

500-999 and 1 000-2,499 people, respectively. However, 12 month LTFU was largest in medium size programs. Similarly, programs with a slow rate of expansion had double the risk of 12-month mortality compared to those with the fastest expansion (10.0% vs. 5.3%). LTFU was lowest in programs with a slow rate of expansion compared to those with medium or fast expansion (Figure 4.1F).

4.4.3 Risk factors for mortality

The risk of death decreased with each successive calendar year of enrolment (Table 4.3). After adjusting for programme size and rate of expansion this association was only seen for the 0-12 month period and up to 2007 (aHR=0.76, 95%CI 0.61-0.95 for 2007; and aHR=1.00, 95% CI 0.76-1.33, for 0-12 months, and aHR=1.21, 95% CI 0.73-2.00, for 12-72 months, vs. ≤2003).

Larger programme size was associated with decreased early mortality (aHR=0.49, 95% CI 0.31-0.77, for ≥20,000 vs. <500 patients). This association was not significant for late mortality (aHR=0.34, 95% CI 0.09-1.27). Fully adjusted models did not show evidence of association between rate of expansion and early or late mortality (aHR=1.13, 95%CI 0.87-1.48, and aHR=0.85, 95%CI 0.55-1.31, respectively, for ≥125 vs. <25 patients/month).

Increased early and late mortalities were associated with male gender (aHR=1.30, and 1.57, respectively, for male vs. female), older age (aHR=1.46, and 1.48, respectively, for ≥45 vs. 16-25 years), and low BMI (aHR=2.59, and 1.56, respectively, for ≤18.5 vs. 18.6-25.0 kg/m^2). Death was also strongly associated with advanced clinical stage and lower CD4 cell count level, with the strongest associations observed with early mortality (aHR=2.65 for stage IV vs. stages II or II; and aHR=0.29, 0.26-0.32 for 200-349 CD4 cells/µl vs. <25 CD4 cells/µl).

Table 4.1 Patient characteristics at ART initiation

Characteristics	No. of patients N=132,334
Sex, n (%)	
Females	80,456 (60.8)
Age (years), median [IQR]	35.0 [29.4-42.0]
Age group, n (%)	
16-25	11,840 (9.0)
25-34	53,332 (40.3)
35-44	42,894 (32.4)
45+	24,268 (18.3)
CD4 cell count (cell/μL)	n=103,197 (78.0)
Median (IQR)	142 [63-220]
CD4 categorical, n (%)	
<25	10,890 (10.6)
25-49	10,054 (9.7)
50-99	16,826 (16.3)
100-149	16,220 (15.7)
150-199	17,253 (16.7)
200-349	27,484 (26.6)
≥350	4,470 (4.3)
WHO stage, n(%)	n=129,859 (98.1)
I and II	41,105 (31.7)
III	56,619 (43.6)
IV	32,135 (24.8)
BMI group (kg/m^2), n (%)	n=121,809 (92.0)
Underweight (≤18.5)	40,122 (32.9)
Normal (18.6-25.0)	72,217 (59.3)
Overweight (25.1-30.0)	7,727 (6.4)
Obese (>30.0)	1,733 (1.4)
Country, n (%)	
DRC	4,140 (3.1)
India	1,526 (1.2)
Kenya	19,353 (14.6)
Malawi	37,657 (28.5)
Mozambique	12,492 (9.4)
Myanmar	16,784 (12.7)
Uganda	9,599 (7.3)
Zimbabwe	30,783 (23.3)

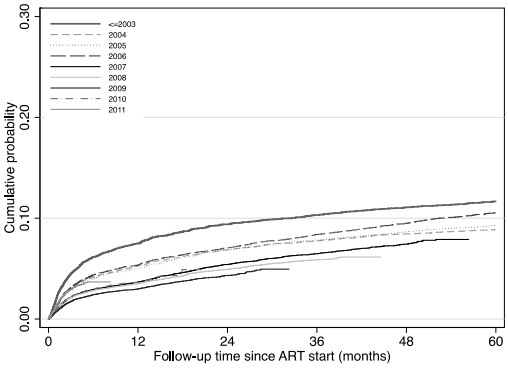
Table 4.2 Baseline characteristics and 6-, 12- and 36-month Kaplan-Meier cumulative mortality, loss to follow-up and overall programme retention stratified by calendar year of ART initiation

	Year of ART initiation				
	≤2003 n=4,427	**2004** n=8,410	**2005** n=10,974	**2006** n=15,383	**2007** n=19,826
Age (years), median [IQR]	34.7 [29.4-41.1]	35.1 [29.4-42.1]	35.0 [29.5-41.9]	34.9 [29.4-41.8]	35.0 [29.8-42.1]
CD4 cell count (cell/µl), median [IQR]	97 [42-162]	114 [51-178]	116 [50-182]	112 [48-189]	132 [58-205]
WHO stage IV, n(%)	1 914 (44.4)	3 659 (44.3)	4 276 (40.3)	5 254 (35.0)	5 266 (27.0)
Underweight, n(%)	1 567 (38.9)	2 672 (27.9)	3 744 (38.5)	5 470 (38 2)	6 254 (33.3)
Cumulative mortality, (95% CI)					
6-month	14.1 (13.1-15.2)	9.3 (8.7-9.9)	8.1 (7.6-8.6)	8.0 (7.6-8.5)	5.4 (5.1-5.7)
12-month	17.3 (16.2-18.5)	11.8 (11.1-12.6)	10.2 (0.6-10.8)	9.9 (9.4-10.4)	6.8 (6.4-7.2)
36-month	21.5 (20.3-22.8)	15.4 (14.6-16.3)	13.7 (13.0-14.4)	12.8 (12.2-13.3)	9.5 (9.1-10.0)
Cumulative LTFU, (95% CI)					
6-month	4.0 (3.4-4.6)	6.9 (6.4-7.5)	6.2 (5.8-6.7)	5.9 (5.5-6.3)	7.6 (7.2-8.0)
12-month	5.9 (5.2-6.7)	9.3 (8.7-9.9)	8.9 (8.4-9.5)	8.1 (7.7-8.5)	10.3 (9.8-10.7)
36-month	11.4 (10.4-12.5)	16.3 (15.5-17.2)	14.6 (13.9-15.3)	14.6 (14.0-15.2)	17.1 (16.6-17.7)
Cumulative programme retention in care, (95% CI)					
6-month	82.4 (81.3-83.5)	84.5 (83.7-85.2)	86.2 (85.6-86.9)	86.6 (86.0-87.1)	87.4 (87.0-87.9)
12-month	77.8 (76.6-79.0)	80.0 (79.1-80.8)	81.8 (81.1-82.5)	82.8 (82.2-83.4)	83.6 (83.1-84.2)
36-month	69.6 (68.2-70.9)	70.8 (69.8-71.7)	73.8 (72.9-74.6)	74.5 (73.8-75.2)	75.0 (74.4-75.6)

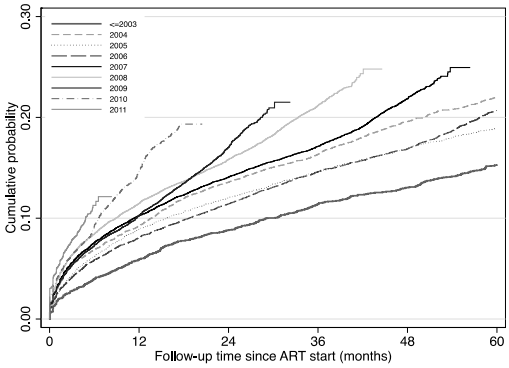
	Year of ART initiation			
	2008 n=18,991	**2009** n=19,410	**2010** n=22,863	**2011** n= 12,050
Age (years), median [IQR]	35.1 [29.4-42.1]	35.1 [29.3-42.0]	35.0 [29.3-42.0]	35.0 [29.4-42.0]
CD4 cell count (cell/µl), median [IQR]	150 [72-221]	155 [74-224]	171 [80-248]	184 [77-276]
WHO stage IV, n(%)	3 814 (20.7)	3 253 (17.0)	3 030 (13.4)	1 669 (14.0)
Underweight, n(%)	5 594 (31.5)	5 703 (31.3)	5 785 (27.7)	3 333 (30.1)
,Cumulative mortality, (95% CI)				
6-month	5.2 (4.9-5.5)	4.5 (4.2-4.8)	4.1 (3.8-4.3)	3.7 (3.3-4.2)
12-month	6.5 (6.1-6.9)	5.6 (5.2-5.9)	5.1 (4.8-5.4)	-
36-month	8.8 (8.4-9.2)	-	-	-
Cumulative LTFU, (95% CI)				
6-month	8.4 (8.0-8.8)	7.3 (7.0-7.7)	9.2 (8.8-9.6)	11.3 (10.4-12.2)
12-month	11.5 (11.0-11.9)	10.3 (9.9-10.7)	14.6 (14.1-15.2)	-
36-month	21.2 (20.5-21.8)	-	-	-
Cumulative programme retention in care, (95% CI)				
6-month	86.8 (86.3-87.3)	88.5 (88.1-89.0)	87.1 (87.7-87.6)	85.5 (84.5-86.4)
12-month	82.8 (82.2-83.3)	84.7 (84.2-85.2)	81.0 (80.5-81.6)	-
36-month	71.9 (71.2-72.6)	-	-	

Figure 4.1 Cumulative probability of death and LTFU stratified by year of ART initiation, programme size, or rate of expansion

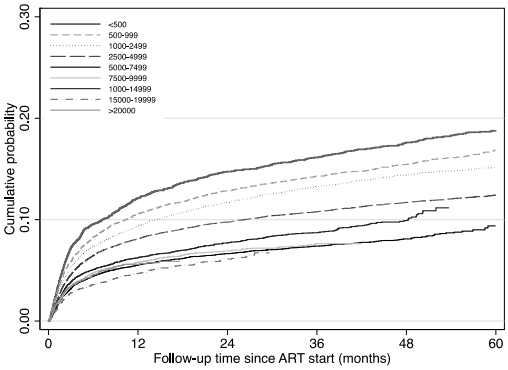
1A) Mortality by year of ART initiation



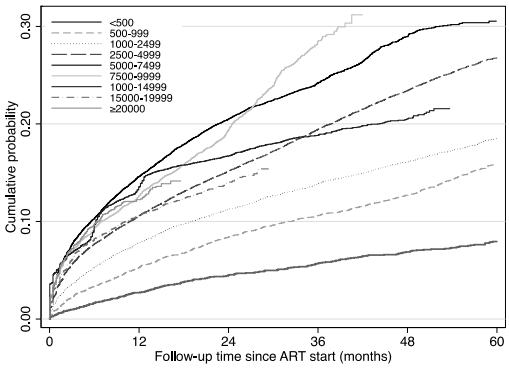
1B) LTFU by year of ART initiation



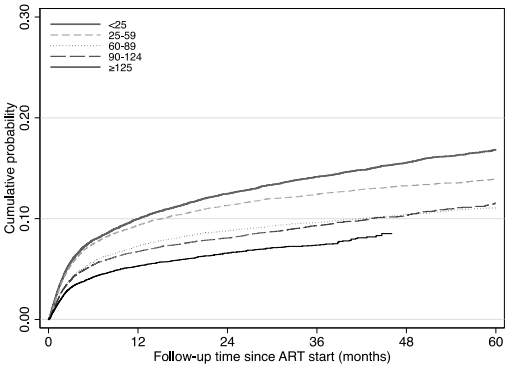
1C) Mortality by programme size



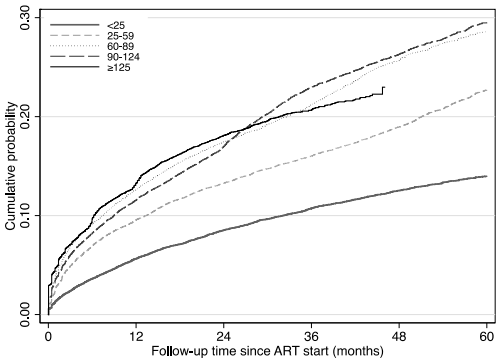
1D) LTFU by programme size



1E) Mortality by rate of expansion



1F) LTFU by rate of expansion



4.4.4 Risk factors for lost to follow-up

Increased risk of early and late LTFU was observed with each successive calendar year of ART initiation (Table 4.4). Adjusted hazard ratios for early LFTU increased from 1.09 (95%CI 0.83-1.43) in 2004 to 3.29 (95%CI 2.42-4.46) in 2011, compared to the 2001-2003 period; and adjusted hazard ratio for late LTFU from 1.04 (95%CI 0.84-1.28) to 6.86 (95%CI 4.94-9.53), respectively. Larger programme size was associated with a 7-fold increase in the risk of early (HR 7.35, 95% CI 5.55-9.73) and late LTFU (HR 7.03, 95% CI 4.30-11.48) but the association in final models attenuated for early LTFU (aHR 1.77, 95% CI 1.04-3.04) and was not observed for late LTFU (aHR 0.53, 95% CI 0.27-1.04). Rate of programme expansion was strongly associated with an increased risk of early and late LTFU (early aHR increased from 1.26 in programs with rates of 25-59 patients/month to 2.31 in those with ≥125 patients/month; and late aHR from 1.22 to 2.29 compared to programs with rates of 0-24 patients/month respectively). Late LTFU was only higher among patients who received treatment in programs with 500-4,999 HIV patients in care (aHR=1.34, 95%CI 1.00-1.80 for 2,500-4,999 vs. <500 programme size).

Male gender (aHR=1.25 and 1.21, for early and late periods), younger age (aHR=0.58 and 0.48, respectively, for ≥45 vs. 16-25 years) and advanced clinical stage (aHR=1.56 and 1.28, respectively, for stage 4 vs. stages 1 or 2) were also associated with an increased risk of LTFU. Patients with a CD4 cell count of less than 25 cells/µl had a higher risk of early LTFU (adjusted hazard ratio decreased from 0.89 among patients with 25-49 cells/µl to 0.60 among those with 200-349 cells/µl). No association between CD4 cell count and late LTFU was observed.

Sensitivity analyses including patients with missing data (Supplementary Tables 4.2 and 4.3) and stratification by site provided similar results. Estimates from competing risks models were slightly reduced but did not change results appreciably (Supplementary Tables 4.4 and 4.5).

Table 4.3 Cox proportional hazards estimates of mortality by baseline characteristics and year of ART initiation, adjusted by cohort*

	0-12 months				
	Univariate	Model 1 (n=94,571)	Model 2 (n=94,571)	Model 3 (n=94,571)	Model 4 (n=94,571)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.67 (0.61-0.74)	0.67 (0.58-0.78)	0.74 (0.62-0.88)	0.75 (0.64-0.87)	0.78 (0.65-0.94)
2005	0.53 (0.48-0.58)	0.62 (0.54-0.71)	0.77 (0.64-0.94)	0.75 (0.64-0.88)	0.82 (0.65-0.94)
2006	0.51 (0.47-0.56)	0.61 (0.54-0.69)	0.77 (0.64-0.93)	0.76 (0.65-0.89)	0.80 (0.66-0.97)
2007	0.36 (0.33-0.40)	0.47 (0.42-0.53)	0.71 (0.57-0.88)	0.60 (0.51-0.71)	0.76 (0.61-0.95)
2008	0.34 (0.31-0.38)	0.55 (0.48-0.62)	0.85 (0.68-1.07)	0.72 (0.60-0.86)	0.91 (0.72-1.14)
2009	0.29 (0.26-0.32)	0.54 (0.48-0.61)	0.94 (0.74-1.19)	0.71 (0.59-0.85)	0.98 (0.77-1.26)
2010	0.27 (0.24-0.29)	0.58 (0.51-0.65)	0.95 (0.74-1.21)	0.76 (0.63-0.91)	1.00 (0.78-1.29)
2011	0.28 (0.24-0.32)	0.60 (0.50-0.71)	0.95 (0.72-1.25)	0.78 (0.63-0.97)	1.00 (0.76-1.33)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.90 (0.79-1.03)		1.19 (0.98-1.45)		1.15 (0.94-1.40)
1,000-2,499	0.64 (0.57-0.72)		1.17 (0.95-1.42)		1.14 (0.94-1.40)
2,500-4,999	0.51 (0.45-0.57)		0.99 (0.78-1.24)		0.97 (0.77-1.24)
5,000-7,499	0.31 (0.27-0.35)		0.65 (0.49-0.86)		0.61 (0.45-0.82)
7,500 – 9,999	0.26 (0.23-0.30)		0.57 (0.42-0.76)		0.48 (0.34-0.68)
10,000-14,999	0.22 (0.19-0.25)		0.75 (0.54-1.03)		0.61 (0.41-0.90)
15,000-19,999	0.15 (0.12-0.18)		0.50 (0.34-0.73)		0.41 (0.26-0.63)
≥20,000	0.18 (0.15-0.22)		0.61 (0.41-0.89)		0.49 (0.31-0.77)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.64 (0.59-0.69)			0.93 (0.83-1.04)	0.93 (0.83-1.05)
60-89	0.43 (0.40-0.47)			0.75 (0.64-0.87)	0.88 (0.74-1.04)
90-124	0.37 (0.34-0.41)			0.75 (0.63-0.89)	1.06 (0.86-1.30)
≥125	0.21 (0.20-0.24)			0.70 (0.58-0.85)	1.13 (0.87-1.48)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.61 (1.54-1.68)	1.29 (1.22-1.36)	1.30 (1.23-1.37)	1.29 (1.22-1.37)	1.30 (1.22-1.37)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	1.07 (0.99-1.17)	1.11 (0.99-1.25)	1.10 (0.99-1.23)	1.11 (0.99-1.24)	1.10 (0.99-1.23)
35-44	1.16 (1.07-1.26)	1.18 (1.05-1.32)	1.16 (1.04-1.31)	1.17 (1.05-1.32)	1.17 (1.04-1.31)
45+	1.33 (1.22-1.46)	1.48 (1.31-1.67)	1.46 (1.29-1.65)	1.47 (1.31-1.66)	1.46 (1.29-1.65)
Body Mass Index					
Underweight	3.65 (3.47-3.83)	2.58 (2.43-2.74)	2.60 (2.45-2.76)	2.58 (2.43-2.74)	2.59 (2.44-2.75)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.59 (0.50-0.69)	0.75 (0.62-0.90)	0.74 (0.61-0.90)	0.75 (0.62-0.90)	0.74 (0.61-0.90)
Obese	0.88 (0.67-1.17)	1.23 (0.90-1.69)	1.22 (0.88-1.67)	1.24 (0.90-1.71)	1.22 (0.89-1.68)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.61 (0.57-0.66)	0.71 (0.65-0.78)	0.71 (0.65-0.78)	0.71 (0.65-0.78)	0.71 (0.65-0.78)
50-99	0.39 (0.36-0.42)	0.52 (0.48-0.56)	0.52 (0.48-0.56)	0.52 (0.48-0.560	0.52 (0.48-0.56)
100-149	0.26 (0.24-0.28)	0.41 (0.37-0.45)	0.41 (0.37-0.45)	0.41 (0.37-0.45)	0.41 (0.37-0.45)
150-199	0.19 (0.18-0.21)	0.35 (0.31-0.39)	0.35 (0.31-0.39)	0.35 (0.31-0.39)	0.35 (0.31-0.39)
200-349	0.15 (0.13-0.16)	0.29 (0.26-0.32)	0.29 (0.26-0.32)	0.29 (0.26-0.32)	0.29 (0.26-0.32)
≥350	0.24 (0.21-0.28)	0.42 (0.36-0.49)	0.43 (0.36-0.50)	0.42 (0.36-0.49)	0.42 (0.36-0.49)
Clinical stage					
1 and 2	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
3	2.60 (2.42-2.79	1.65 (1.51-1.80)	1.61 (1.47-1.76)	1.54 (1.50-1.79)	1.61 (1.47-1.76)
4	5.70 (5.31-6.11)	2.73 (0.48-2.99)	2.65 (2.41-2.91)	2.69 (2.45-2.96)	2.65 (2.41-2.92)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Table 4.3 (continued) Cox proportional hazards estimates of mortality by baseline characteristics and year of ART initiation, adjusted by cohort. *

		12-72 months			
	Univariate	Model 1 (n=62,080)	Model 2 (n=62,080)	Model 3 (n=62,080)	Model 4 (n=62,080)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.77 (0.66-0.91)	0.78 (0.63-0.97)	0.85 (0.66-1.09)	0.88 (0.70-1.10)	0.87 (0.68-1.13)
2005	0.69 (0.59-0.81)	0.72 (0.58-0.88)	0.84 (0.64-1.11)	0.82 (0.65-1.04)	0.85 (0.64-1.11)
2006	0.58 (0.50-0.68)	0.63 (0.52-0.77)	0.75 (0.57-0.98)	0.74 (0.58-0.94)	0.75 (0.57-0.99)
2007	0.53 (0.46-0.62)	0.64 (0.53-0.78	0.75 (0.55-1.03)	0.76 (0.59-0.98)	0.76 (0.55-1.04)
2008	0.46 (0.38-0.54)	0.58 (0.47-0.72)	0.69 (0.49-0.97)	0.71 (0.53-0.99)	0.72 (0.51-1.01)
2009	0.43 (0.35-0.52)	0.60 (0.47-0.76)	0.73 (0.50-1.06)	0.72 (0.53-0.99)	0.74 (0.51-1.08)
2010	0.50 (0.35-0.72)	0.83 (0.56-1.23)	1.19 (0.72-1.96)	1.01 (0.65-1.56)	1.21 (0.73-2.00)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.83 (0.69-1.00)		0.99 (0.77-1.27)		0.99 (0.77-1.27)
1,000-2,499	0.77 (0.65-0.91)		1.07 (0.83-1.39)		1.08 (0.83-1.40)
2,500-4,999	0.59 (0.49-0.71)		0.84 (0.62-1.14)		0.87 (0.63-1.21)
5,000-7,499	0.42 (0.34-0.52)		0.75 (0.51-1.11)		0.76 (0.50-1.16)
7,500 – 9,999	0.38 (0.29-0.51)		0.70 (0.44-1.10)		0.72 (0.42-1.22)
10,000-14,999	0.42 (0.33-0.54)		0.95 (0.59-1.53)		1.02 (0.59-1.77)
15,000-19,999	0.35 (0.25-0.50)		0.88 (0.49-1.57)		1.00 (0.51-1.96)
≥20,000	0.18 (0.06-0.55)		0.29 (0.08-1.06)		0.34 (0.09-1.27)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.74 (0.65-0.84)			0.89 (0.75-1.05)	0.93 (0.78-1.10)
60-89	0.56 (0.49-0.65)			0.75 (0.61-0.93)	0.87 (0.68-1.12)
90-124	0.52 (0.45-0.61)			0.84 (0.65-1.08)	1.02 (0.74-1.40)
≥125	0.39 (0.32-0.47)			0.74 (0.54-1.02)	0.85 (0.55-1.31)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.77 (1.64-1.91)	1.57 (1.42-1.73)	1.57 (1.42-1.73)	1.57 (1.42-1.73)	1.57 (1.42-1.73)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.94 (0.81-1.09)	0.85 (0.70-1.03)	0.85 (0.70-1.02)	0.85 (0.70-1.03)	0.85 (0.70-1.02)
35-44	1.10 (0.92-1.27)	0.99 (0.82-1.20)	0.99 (0.81-1.20)	0.99 (0.81-1.20)	0.99 (0.81-1.20)
45+	1.66 (1.42-1.95)	1.49 (1.22-1.82)	1.48 (1.21-1.81)	1.49 (1.22-1.82)	1.48 (1.21-1.82)
Body Mass Index					
Underweight	1.67 (1.54-1.82)	1.57 (1.42-1.73)	1.57 (1.42-1.74)	1.56 (1.31-1.73)	1.56 (1.41-1.73)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.85 (0.69-1.03)	1.01 (0.80-1.27)	1.01 (0.80-1.27)	1.01 (0.80-1.28)	1.01 (0.80-1.28)
Obese	0.93 (0.62-1.39)	0.76 (0.43-1.34)	0.76 (0.43-1.34)	0.77 (0.43-1.36)	0.76 (0.43-1.35)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.93 (0.78-1.10)	0.98 (0.82-1.18)	0.98 (0.81-1.18)	0.98 (0.82-1.18)	0.98 (0.81-1.18)
50-99	0.86 (0.72-1.00)	1.00 (0.85-1.18)	1.00 (0.85-1.18)	1.00 (0.85-1.18)	1.00 (0.84-1.18)
100-149	0.63 (0.54-0.75)	0.79 (0.66-0.95)	0.79 (0.66-0.95)	0.80 (0.67-0.95)	0.79 (0.66-0.95)
150-199	0.65 (0.55-0.76)	0.89 (0.74-1.07)	0.89 (0.74-1.06)	0.90 (0.75-1.07)	0.89 (0.74-1.06)
200-349	0.52 (0.44-0.61)	0.74 (0.62-0.89)	0.74 (0.62-0.88)	0.75 (0.62-0.89)	0.74 (0.62-0.89)
≥350	0.78 (0.60-1.03)	0.98 (0.72-1.33)	0.98 (0.72-1.34)	0.98 (0.72-1.33)	0.98 (0.72-1.33)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.54 (1.38-1.73)	1.20 (1.05-1.38)	1.19 (1.04-1.37)	1.19 (1.04-1.37)	1.19 (1.03-1.36)
IV	2.26 (2.01-2.53)	1.54 (1.32-1.79)	1.51 (1.30-1.76)	1.52 (1.31-1.76)	1.51 (1.30-1.75)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Table 4.4 Cox proportional hazards estimates of LTFU by baseline characteristics and year of ART initiation, adjusted by cohort*

	0-12 months				
	Univariate	Model 1 (n=94,571)	Model 2 (n=94,571)	Model 3 (n=94,571)	Model 4 (n=94,571)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.62 (1.40-1.88)	1.52 (1.22-1.90)	1.06 (0.81-1.39)	1.36 (1.08-1.72)	1.09 (0.83-1.43)
2005	1.69 (1.46-1.95)	1.99 (1.61-2.45)	1.34 (1.03-1.76)	1.74 (1.39-2.18)	1.37 (1.04-1.80)
2006	1.62 (1.41-1.86)	2.18 (1.79-2.66)	1.54 (1.19-1.98)	1.80 (1.43-2.26)	1.43 (1.09-1.88)
2007	2.04 (1.78-2.34)	3.25 (2.68-3.93)	2.25 (1.71-2.96)	2.60 (2.07-3.26)	2.19 (1.64-2.93)
2008	2.26 (1.98-2.59)	3.58 (2.95-4.33)	2.43 (1.83-3.21)	2.66 (2.10-3.35)	2.31 (1.72-3.09)
2009	2.14 (1.87-2.45)	3.58 (2.95-4.34)	2.37 (1.77-3.16)	2.52 (2.00-3.19)	2.14 (1.58-2.89)
2010	2.99 (2.62-3.42)	5.46 (4.51-6.61)	3.52 (2.62-4.72)	3.74 (2.96-4.73)	3.29 (2.42-4.46)
2011	3.64 (3.15-4.21)	6.17 (5.03-7.56)	3.61 (2.65-4.92)	4.06 (3.17-5.19)	3.51 (2.55-4.83)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.71 (1.29-2.26)		2.01 (1.32-3.06)		1.86 (1.23-2.82)
1,000-2,499	3.02 (2.33-3.92)		2.66 (1.75-4.05)		2.36 (1.55-3.58)
2,500-4,999	3.29 (2.54-4.27)		2.80 (1.81-4.32)		2.29 (1.48-3.55)
5,000-7,499	4.36 (3.36-5.67)		2.54 (1.61-4.00)		1.97 (1.24-3.10)
7,500 – 9,999	4.60 (3.53-5.99)		2.72 (1.72-4.32)		1.67 (1.04-2.69)
10,000-14,999	6.17 (4.73-8.04)		4.07 (2.53-6.53)		2.02 (1.22-3.34)
15,000-19,999	5.97 (4.49-7.93)		4.52 (2.73-7.47)		2.27 (1.34-3.87)
≥20,000	7.35 (5.55-9.73)		3.66 (2.20-6.10)		1.77 (1.04-3.04)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.57 (1.41-1.75)			1.36 (1.16-1.60)	1.26 (1.07-1.49)
60-89	1.94 (1.73-2.18)			1.39 (1.14-1.69)	1.36 (1.10-1.67)
90-124	2.16 (1.92-2.4)			1.61 (1.31-1.98)	1.70 (1.35-2.14)
≥125	3.09 (2.74-3.48)			2.21 (1.78-2.75)	2.31 (1.78-3.01)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.31 (1.27-1.36)	1.26 (1.20-1.32)	1.26 (1.20-1.32)	1.25 (1.19-1.31)	1.25 (1.2-1.31)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.72 (0.69-0.76)	0.72 (0.67-0.77)	0.72 (0.67-0.77)	0.72 (0.67-0.77)	0.72 (0.67-0.77)
35-44	0.60 (0.57-0.64)	0.60 (0.55-0.64)	0.59 (0.55-0.64)	0.60 (0.55-0.64)	0.59 (0.55-0.64)
45+	0.60 (0.56-0.64)	0.58 (0.53-0.63)	0.58 (0.53-0.63)	0.58 (0.53-0.63)	0.58 (0.53-0.63)
Body Mass Index					
Underweight	1.70 (1.63-1.77)	1.53 (1.45-1.60)	1.52 (1.45-1.59)	1.52 (1.45-1.60)	1.52 (1.45-1.60)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.91 (0.83-0.99)	0.93 (0.84-1.03)	0.93 (0.84-1.03)	0.93 (0.84-1.03)	0.93 (0.83-1.03)
Obese	1.21 (0.96-1.31)	1.14 (0.94-1.39)	1.14 (0.94-1.39)	1.14 (0.94-1.39)	1.14 (0.93-1.38)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.81 (0.74-0.87)	0.89 (0.82-0.97)	0.88 (0.81-0.97)	0.89 (0.81-0.97)	0.89 (0.81-0.97)
50-99	0.61 (0.57-0.66)	0.73 (0.67-0.79)	0.72 (0.66-0.78)	0.72 (0.67-0.78)	0.72 (0.66-0.78)
100-149	0.56 (0.52-0.60)	0.70 (0.64-0.76)	0.69 (0.66-0.78)	0.69 (0.64-0.75)	0.69 (0.64-0.75)
150-199	0.47 (0.44-0.51)	0.60 (0.55-0.66)	0.60 (0.64-0.75)	0.60 (0.55-0.65)	0.59 (0.55-0.65)
200-349	0.51 (0.48-0.55)	0.60 (0.56-0.66)	0.60 (0.55-0.65)	0.60 (0.56-0.65)	0.60 (0.55-0.65)
≥350	0.78 (0.71-0.87)	0.76 (0.68-086)	0.77 (0.68-0.86)	0.77 (0.68-0.86)	0.77 (0.68-0.86)
Clinical stage					
1 and 2	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
3	1.10 (1.05-1.14)	1.15 (1.09-1.22)	1.17 (1.11-1.24)	1.17 (1.11-1.24)	1.17 (1.10-1.23)
4	1.51 (1.44-1.59)	1.52 (1.42-1.62)	1.55 (1.45-1.65)	1.56 (1.46-1.67)	1.56 (1.46-1.66)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Table 4.4 (continued) Cox proportional hazards estimates of LTFU by baseline characteristics and year of ART initiation, adjusted by cohort*

		12-72 months			
	Univariate	Model 1 (n=62 ,080)	Model 2 (n=62,080)	Model 3 (n=62,080)	Model 4 (n=62,080)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.31 (1.16-1.49)	1.19 (1.02-1.40)	1.03 (0.84-1.27)	1.09 (0.92-1.29)	1.04 (0.84-1.28)
2005	1.19 (1.05-1.35)	1.20 (1.03-1.40)	1.03 (0.83-1.28)	1.00 (0.85-1.19)	0.94 (0.76-1.17)
2006	1.47 (1.31-1.66)	1.67 (1.44-1.93)	1.45 (1.18-1.80)	1.27 (1.07-1.51)	1.17 (0.94-1.46)
2007	1.82 (1.62-2.05)	2.37 (2.05-2.74)	2.19 (1.72-2.80)	1.76 (1.47-2.11)	1.83 (0.94-1.46)
2008	2.44 (2.15-2.75)	3.30 (2.83-3.84)	3.02 (2.34-3.89)	2.33 (1.92-2.83)	2.48 (1.91-3.23)
2009	3.60 (3.16-4.10)	4.71 (4.01-5.53)	4.54 (3.46-5.95)	3.26 (2.65-4.01)	3.58 (2.70-4.75)
2010	6.50 (5.45-7.76)	8.47 (6.92-10.53)	8.50 (6.18-11.68)	5.94 (4.62-7.46)	6.86 (4.94-9.53)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.64 (1.34-2.00)		1.45 (1.13-1.85)		1.40 (1.09-1.79)
1,000-2,499	2.35 (1.94-2.86)		1.55 (1.19-2.02)		1.44 (1.10-1.88)
2,500-4,999	2.66 (2.19-3.22)		1.64 (1.23-2.18)		1.34 (1.00-1.80)
5,000-7,499	3.80 (3.11-4.65)		1.39 (1.00-1.92)		1.03 (0.74-1.43)
7,500 – 9,999	5.47 (4.42-6.77)		1.44 (1.02-2.03)		0.83 (0.57-1.20)
10,000-14,999	4.06 (3.22-5.12)		1.34 (0.90-1.99)		0.83 (0.54-1.27)
15,000-19,999	4.89 (3.69-6.48)		1.11 (0.71-1.74)		0.74 (0.46-1.19)
≥20,000	7.03 (4.30-11.48)		0.81 (0.42-1.57)		0.53 (0.27-1.04)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.48 (1.33-1.64)			1.24 (1.08-1.41)	1.22 (1.06-1.39)
60-89	1.96 (1.75-2.18)			1.43 (1.21-1.68)	1.56 (1.31-1.85)
90-124	2.79 (2.48-3.14)			1.86 (1.55-2.23)	2.22 (1.81-2.72)
≥125	3.72 (3.25-4.27)			1.65 (1.33-2.05)	2.29 (1.76-2.99)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.16 (1.11-1.21)	1.21 (1.14-1.28)	1.21 (1.15-1.28)	1.21 (1.14-1.28)	1.21 (1.15-1.29)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.63 (0.59-0.67)	0.66 (0.60-0.72)	0.66 (0.60-0.72)	0.66 (0.60-0.72)	0.66 (0.60-0.72)
35-44	0.50 (0.47-0.54)	0.51 (0.46-0.56)	0.51 (0.46-0.56)	0.51 (0.46-0.56)	0.51 (0.46-0.56)
45+	0.51 (0.47-0.56)	0.49 (0.44-0.54)	0.49 (0.44-0.54)	0.49 (0.44-0.54)	0.48 (0.44-0.54)
Body Mass Index					
Underweight	1.12 (1.07-1.18)	1.06 (1.00-1.13)	1.07 (1.00-1.13)	1.06 (1.00-1.13)	1.07 (1.00-1.13)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.99 (0.90-1.109)	1.08 (0.96-1.20)	1.08 (0.96-1.20)	1.08 (0.97-1.21)	1.08 (0.97-1.21)
Obese	0.86 (0.70-1.07)	0.98 (0.77-1.25)	0.98 (0.76-1.25)	0.98 (0.76-1.25)	0.97 (0.76-1.25)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.93 (0.84-1.04)	0.98 (0.8-1.10)	0.99 (0.88-1.11)	0.98 (0.88-1.10)	0.99 (0.88-1.11)
50-99	0.87 (0.79-0.95)	0.95 (0.85-1.05)	0.95 (0.86-1.05)	0.94 (0.85-1.04)	0.95 (0.85-1.05)
100-149	0.85 (0.77-0.94)	0.97 (0.88-1.08)	0.98 (0.88-1.08)	0.97 (0.87-1.07)	0.97 (0.88-1.08)
150-199	0.88 (0.80-0.97)	0.98 (0.88-1.09)	0.98 (0.89-1.09)	0.97 (0.88-1.08)	0.98 (0.88-1.09)
200-349	0.92 (0.84-1.01)	0.91 (0.82-1.01)	0.92 (0.83-1.02)	0.91 (0.82-1.01)	0.92 (0.83-1.02)
≥350	1.13 (0.96-1.32)	1.07 (0.91-1.27)	1.09 (0.92-1.29)	1.05 (0.89-1.25)	1.05 (0.89-1.25)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.05 (0.99-1.11)	1.21 (1.13-1.30)	1.21 (1.13-1.29)	1.20 (1.12-1.28)	1.18 (1.10-1.27)
IV	1.11 (1.04-1.18)	1.29 (1.19-1.40)	1.29 (1.19-1.40)	1.29 (1.19-1.40)	1.28 (1.18-1.39)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

4.5 DISCUSSION

This multicentre cohort study included over 130,000 HIV-infected patients initiated on ART in 8 low and middle-income countries where the provision of ART has rapidly expanded over the last 10-years. In this challenging context where programs needed to adapt to the growing numbers of patients in need for care, we observed a gradual improvement in measures of disease severity at ART initiation and a decrease in mortality over time. Despite these findings, every year 30% of the total number of patients who initiated ART had CD4 cell counts less than 100 cells/µl. Furthermore, twelve, 24 and 36-month LTFU rates among patients initiating ART in successive calendar years doubled between the periods 2001-2003 and 2008.

Over the 10-year study period, ART provision was rapidly implemented and programs expanded to reach a growing number of people infected with HIV. Expansion rates ranged from 0-25 to 125-192 new patients/month, and programme size from <500 to 20,000-23,995 patients. Mortality gradually improved with 6-month estimates decreasing from 14% in the years before 2004 to less than 4% in 2011, which is consistent with reports from South Africa [56]. The observed decreased estimates of mortality may result from improved access to ART, as suggested by the increased number of patients initiating ART with less severe disease. The rapid growth of programs might have also led to poorer outcome ascertainment, with greater number of deaths occurring in recent years misclassified as LTFU [53]. Linkage to national population or death registries is not available in these cohorts highlighting the need to improve outcome ascertainment for programme evaluation in resource-limited countries.

The rapid growth of ART programs is related to a combination of several factors including the long-term availability of antiretroviral drugs, the implementation of new simplified guidelines for ART, and the widespread availability of CD4 enumeration to identify ART-eligible individuals. A third of patients initiated ART with a CD4 cell count below 100, placing a substantial strain on the health-care system requiring intensive support from clinically trained staff [209, 210]. Our findings do not suggest that

increases in treatment guideline thresholds prevent patients with more advanced HIV disease from accessing care, but rather that all programs still face challenges in timeously seeking, testing, and linking patients to ART care.

Even with continued challenges to improving access to ART, LTFU appears to present a ubiquitous challenge to the long-term effectiveness of ART programs. After 2-years of ART, 15% of the cohort was LTFU and retention was 77% and after 5-years of treatment two-thirds of patients remained in care. This is slightly less than the estimate from 23 countries with cohorts of more than 2,000 people which reported 72% retention after 5-years [24]. A temporal trend of increasing LTFU was observed with LTFU contributing an increasing proportion of overall programme attrition [37, 56]. These findings confirm the urgent need to refocus efforts to improve long-term retention and contradict systematic reviews from sub-Saharan Africa suggesting that programme outcomes are improving [37, 38]. A novel finding of our study is that the rate of programme expansion, more than the size of the HIV program, was associated with the high levels of LTFU. This is likely to relate to the need for timely adjustments in programs to cope with the increase in activity, independently of financial and human resource allocation. Associations observed between LTFU and male gender, younger age, and advanced clinical stage are consistent with previous reports [56, 136, 145, 147].

This analysis of long-term outcomes was based on substantial follow-up of a large number of patients treated in several resource-limited ART programs. All sites offered care and treatment free of charge, followed WHO recommendations for ART initiation, and site heterogeneity was accounted for using random effects in the Cox's models. These data are not likely to be representative of all ART programs since MSF provides additional resources and technical support. For example, quality and completeness of routine electronic data are challenging but MSF provides considerable means to address these concerns [204]. Without linkage to death registries, estimates of programme attrition may misclassify some proportion of deaths as losses to follow-up [53, 76, 88, 136, 203]. LTFU may be overestimated further due to administrative errors, incomplete records of patient decentralisation and unrecorded transfers and the contribution of treatment interrupters [92, 145, 204, 211, 212]. Furthermore, we

were unable to minimise this bias as we did not have data on tracing for all or a sample of those who were LTFU [213]. Our focus was limited to programme outcomes after ART initiating acknowledging that a substantial proportion of patients were lost during pre-ART care [214-217]. While programme size and the rate of expansion were adjusted for, residual confounding may be present if important internal organisational aspects were not sufficiently captured and from unmeasured factors. Sensitivity analyses confirmed our results investigating differences by program, including patients with missing covariate data, and adjusting for site heterogeneity. A competing risks approach led to very similar findings corroborating that the traditional Cox's proportional hazards models are appropriate [130, 201].

Our findings explore the tension and challenges involved in pursuing the ambitious goals of expanding ART to 15 million people by 2015 and implementing "Treatment 2.0" strategies in high prevalence, resource-limited settings [24, 205]. Recent Treatment as Prevention models assumed a long-term drop-out rate of 1.5% annually, which appears optimistic considering our estimates of long-term retention [218]. With a high burden of acutely ill patients, ART programs will struggle to expand access to patients in earlier stages of HIV disease without additional resources and a change to the models of ART delivery. With new 2013 WHO guidelines to expand ART access to an additional 9.2 million people in low- and middle-income countries, we need to fully understand the individual and programmatic implications of earlier initiation [24].

Over a decade, ART programs have expanded in high prevalence resource-limited settings with a focus to increase access to care and thus patient numbers. Today, many sites hold high numbers of HIV-infected patients, above 20,000 at some sites. The quality of ART services and psychosocial counselling at these large sites may be taking a back seat as the drive for expansion continues. The conscious trade-off between numbers and quality deserves more discussion and close monitoring as the targets for expansion of treatment continue to increase. The findings of our study suggest that, potentially, ART sites should be capped at a maximum number of patients and the rate of enrolment restricted in favour of balancing growth with quality care. Site human resource capacity and programme organisation characteristics are likely to be important determinants to consider in achieving this balance and deserve further

investigation to provide effective recommendations regarding maximum patient volume and expansion rate at programme level.

For the first time, the WHO guidelines acknowledge the challenge of long-term retention in ART programs with explicit guidance on operations and service delivery, including adherence, retention, decentralisation and task shifting [28]. Additional resources are needed to strengthen monitoring systems to ascertain true outcomes of children and adults lost to care pre- and post-ART initiation [53, 219]. Identification of ART patients disengaged from care is critical as they are at an increased risk of developing and transmitting drug resistant strains of HIV [37]. There is an urgent need to determine sustainable and optimal models of care for stable patients on lifelong ART, especially in large programs in high-prevalence resource-limited settings. Decreasing visit frequency by expanding intervals between prescription refills, decentralising ART delivery into community-based patient led groups, and introducing flexible systems to support mobile populations are all interventions that could be considered and assessed on a large-scale [42, 143, 176, 178].

In summary, ART programs in resource-limited settings have grown rapidly over the last decade. However, significant work remains to continue expanding access while addressing the growing challenge of programme attrition. Sustainable models of care for long-term retention of patients in large, high-prevalence resource-limited settings are urgently needed.

4.6 ACKNOWLEDGEMENTS

4.6.1 Author contributions

SB, EC, and JL established/maintained the cohorts and provided data. AG was responsible for writing the article and undertook the statistical analyses. AG, GvC, LM, and MPR contributed to prepare the plan of analysis and to write the report and interpreted the data. All authors comment on the draft manuscripts and approved the final version.

Chapter 5. CD4 cell count at antiretroviral therapy initiation and the risk of loss to follow-up: Results from a multicentre cohort study

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5.1 ABSTRACT

Background

To assess the association between higher CD4 cell counts at ART initiation and loss to follow-up (LTFU) in public sector antiretroviral therapy (ART) cohorts in South Africa.

Methods

We conducted a cohort analysis including all adults initiating ART between 2008-2012 at 3 public sector sites in South Africa. LTFU was defined as no visit in the 6-months before database closure. The Kaplan-Meier estimator and Cox's proportional hazards models examined the relationship between CD4 cell count at ART initiation and 24-month LTFU. Final models were adjusted for demographics, year of ART initiation, programme expansion and corrected for unascertained mortality.

Results

Among 17,038 patients, the median CD4 at initiation increased from 119 (IQR: 54-180) in 2008 to 257 (IQR: 175-318) in 2012. In unadjusted models, observed LTFU was associated with both CD4 cell counts <100 cells/μl and CD4 cell counts ≥300 cells/μl. After adjustment, patients with CD4 cell counts ≥300 cells/μl were 1.35 (95% CI: 1.12-1.63) times as likely to be LTFU after 24 months compared to those with a CD4 150-199 cells/μl. This increased risk for patients with CD4 cell counts ≥300 cells/μl was largest in the first 3 months on treatment. Correction for unascertained deaths attenuated the association between CD4 cell counts <100 cells/μl and LTFU while the association between CD4 cell counts ≥300 cells/μl and LTFU persisted.

Conclusion

Patients initiating ART at higher CD4 cell counts may be at increased risk for LTFU. With programs initiating patients at progressively higher CD4 cell counts, models of ART delivery need to be reoriented to support long-term retention.

5.2 INTRODUCTION

Access to antiretroviral therapy (ART) has improved considerably in the past decade. By the end of 2013, 12.9 million people globally were receiving ART [26]. Programs have increased in size and expanded access with patients initiating ART at higher CD4 cell counts. In all regions, median CD4 cell counts at ART initiation are increasing [24].

Increases in CD4 cell counts at ART initiation reflect progressive changes in WHO guidelines. Prior to 2010, ART was recommended for adults with CD4 cell counts below 200 cells/μl irrespective of World Health Organization (WHO) clinical stage [220]. The CD4 threshold was changed to 350 cells/μl in 2010 [221] and raised further in 2013 to include all patients with a CD4 cell count of less than 500 cells/μl[28]. In some countries, ART initiation is recommended irrespective of CD4 cell count [222-224]. The global trend towards earlier initiation of ART is the result of advances in science, improvements in ART drugs and developments in the delivery of HIV care [225].

Despite the potential benefits of earlier ART initiation, its impact on patient behaviour and resulting loss to follow-up (LTFU) is not well understood. LTFU in ART programs already represents a considerable challenge and increasing the CD4 threshold at ART initiation further increases the number of eligible patients who require treatment in resource-constrained health systems [56, 90, 226]. A critical obstacle to assessing associations with LTFU is determining whether a patient considered LTFU is truly lost or is an unascertained death. Having a valid measure of LTFU is particularly important when assessing the association between CD4 and LTFU because lower CD4 cell counts are related to mortality [96, 126]. The limited data available on the relationship between CD4 cell counts at ART initiation and LTFU is conflicting. In previous research higher CD4 cell counts have been associated with both an increased [134, 136] and decreased risk of LTFU [130, 227]. Given this conflicting evidence and the trend towards initiation at higher CD4 cell counts, the 2013 WHO guidelines highlight the need to assess adherence and retention in people initiating ART at these earlier stages of infection [28].

We investigated the relationship between CD4 cell counts at ART initiation and the risk of LTFU in the first 24 months on treatment among adults initiating ART between 2008-2012 in the South African cohorts of the International epidemiologic Databases to Evaluate AIDS – Southern Africa (IeDEA-SA) collaboration. We hypothesised that after adjustment for individual (age, sex, year of ART initiation) and programme (cohort size, rate of expansion) factors, patients initiating ART at higher CD4 cell counts would have an increased risk of LTFU.

5.3 METHODS

Study design, population and eligibility criteria

We conducted a multicentre, retrospective cohort analysis using data from the IeDEA-SA collaboration. The collaboration has been described in detail previously [52, 228]. Briefly, patients were included in the analysis if they were ART naïve, were 16 years of age or older, were not pregnant at ART initiation, initiated ART in 2008 or later, and had a CD4 cell count result available at ART initiation. Analysis was restricted to patients who had a minimum of 6-months follow-up and outcomes were restricted to the first 24-months of treatment. For the main analysis, only patients with a recorded South African civil identification (ID) number were included and thus the main analysis included data from three public sector sites [Hlabisa (Cohort 1), Khayelitsha (Cohort 2), Themba Lethu (Cohort 3)] providing ART free of charge to adults in three South African provinces (Kwa-Zulu Natal, the Western Cape and Gauteng). Data from an additional two cohorts (Gugulethu and Tygerberg) that did not collect IDs were included in sensitivity analyses.

Variables and definitions

At ART initiation, individual demographics (sex and age) and measures of disease severity (CD4 cell count and WHO stage) were assessed. Two variables were generated to quantify programme expansion: programme size and the rate of programme scale-up. For each cohort, the number of ART patients receiving care at the end of the

calendar year of ART initiation was defined as a measure of programme size [226]. The rate of programme scale-up was estimated as the rank of the patient divided by the number of months that the programme had been providing ART. For example, the 200th patient enrolling in the tenth month of the programme would have a rate of scale-up of 20 (200/10) [226].

Patients were defined as LTFU if they were not known to be dead or transferred out and had no visit in the 6 months before the database closure. The date of LTFU was defined as the date of last contact. For patients who had initiated ART and did not return, one day of follow-up was added so that they would be included in the survival analysis [207]. Patients who were dead or transferred out were censored at the date of death or transfer.

Corrected estimates of LTFU were made accounting for unascertained deaths through linkage by ID within the National Population Register (NPR) of the South African Department of Home Affairs. Patients previously defined as LTFU were reclassified as dead if they had a date of death in the NPR within 3 months of their date of LTFU [149]. Corrected estimates therefore reflect incorporating data from the NPR, "corrected LTFU", whereas uncorrected estimates are based on participant attendance, "observed LTFU".

Data Analysis

Patient characteristics at ART initiation were compared by CD4 cell count categories at ART initiation and reported with appropriate summary statistics (including proportions, medians and interquartile ranges [IQR]). The Kaplan-Meier (KM) estimator was used to obtain estimates of the proportion of those LTFU (observed or corrected) over the first 24-months of treatment and were reported every 6-months. KM curves were plotted and presented by CD4 levels at ART initiation.

To assess the association between CD4 cell count at ART initiation and the risk of LTFU, a series of Cox's proportional hazards regression models were fitted. CD4 cell count at ART initiation was modelled as a categorical variable in 50 cells/μl increments up to

≥300 cells/μl. The reference category used was a CD4 cell count between 150-199 cells/μl to facilitate examination of possible trends at lower and higher CD4 cell counts. All models were stratified by cohort. Separate models were used to assess observed and corrected LTFU. The proportional hazards of LTFU were modelled overall (0-24 months) and separately for 0-3 months, 3-12 months and 12-24 months after ART initiation. Adjusted models included other variables at ART initiation: year of ART initiation, sex, age, cohort size and rate of scale-up. In the main analysis, WHO status was excluded because of the large amount of missing data (36% missing).

A series of sensitivity analyses were conducted to explore the impact of missing data and non-differential censoring. To address missing IDs, inverse probability weighting was done whereby patients with IDs who were not alive and in care were weighted to represent all patients who were not alive and in care [97, 229-231]. Weighting of patients with IDs was determined as the probability of being in a cohort with IDs multiplied by the modelled probability of having a recorded ID (based on cohort, year of ART initiation, final outcome and CD4 cell count at ART initiation). Multiple imputation using chained equation methods [232] was used to impute missing CD4 cell counts at ART initiation. We multiply imputed CD4 cell counts (5 times) and the imputation models included the same variables as the Cox models. Competing risk regression was employed to model time to LTFU by taking the competing event of death into account [226].

Data were analysed using STATA 13.0 (STATA Corporation, College Station, Texas, USA). Ethical approval was received from the relevant institutions at each of the sites and the University of Cape Town Human Research Ethics Committee provided ethical approval of the collaboration.

5.4 RESULTS

The main analysis included 17,038 adults who initiated ART between January 2008 and June 2012 in one of three cohorts (Table 5.1). Median CD4 at ART initiation increased

with each successive calendar year from 119 cells/μl in 2008 (IQR: 54-180) to 257 cells/μl in 2012 (IQR: 175-318). The proportion of patients in WHO stage IV at ART initiation was 25%, 17%, 9%, 8% and 17% for patients in CD4 groups <50, 50-99, 100-199, 200-299 and ≥300 cells/μl, respectively. The median programme size was almost 10,000 patients (median: 9,846, IQR: 7,588-11,074) with an average of 160 new patients initiating treatment every month (median: 167, IQR: 132-192).

Proportion of LTFU

A cumulative total of 6%, 10%, 14% and 17% of patients were observed to be LTFU at 6, 12, 18 and 24 months, respectively. Observed proportions of LTFU differed by CD4 cell count at ART initiation (Figure 5.1A). The highest proportion of observed LTFU was seen in patients with CD4 cell counts at ART initiation <100 cells/μl or ≥300 cells/μl and the lowest proportions in patients initiating ART between 100-200 cells/μl. Rates of observed LTFU also varied by cohort with 12-month observed LTFU ranging from 7-13% and 24-month observed LTFU from 12-21%. Consistent across all cohorts were high proportions of observed LTFU in patients with CD4 cell counts below 50 cells/μl. Proportions of observed LTFU were highest in patients with <50 cells/μl and ≥300 cells/μl CD4 cell counts at ART initiation when stratified by year of ART initiation (results not shown).

After accounting for unascertained deaths, LTFU decreased over time with corrected cumulative LTFU estimated at 5%, 8%, 11% and 14% at 6, 12, 18 and 24 months, respectively (Figure 5.2). Correcting for deaths accounted for a relative reduction in LTFU of between 16% (24 month) to 30% (6 month) (results not shown). Corrected LTFU differed by CD4 cell count at ART initiation (Figure 5.1B, Figure 5.2). Proportions of corrected LTFU appeared similar among all patients initiating ART with CD4 cell counts <200 cells/μl and were highest in patients initiating ART at a CD4 cell count ≥300 cells/μl (Figure 5.1B). This was observed in all cohorts. As with observed LTFU, corrected LTFU varied by cohort. 12-month LTFU ranged from 7-10% and 24-month LTFU from 12-18% (results not shown).

Risk of LTFU

An increased risk of observed LTFU was seen in patients initiating ART with <100 cells/μl and CD4 cell counts ≥300 cells/μl (Figure 3, Supplementary Table 5.1). After adjusting for demographics, year of ART initiation, programme size and rate of scale-up, the increased risk of observed LTFU persisted for those with a CD4 cell count <100 cells/μl and ≥300 cells/μl at ART initiation (Table 5.2, Supplementary Table 5.1).

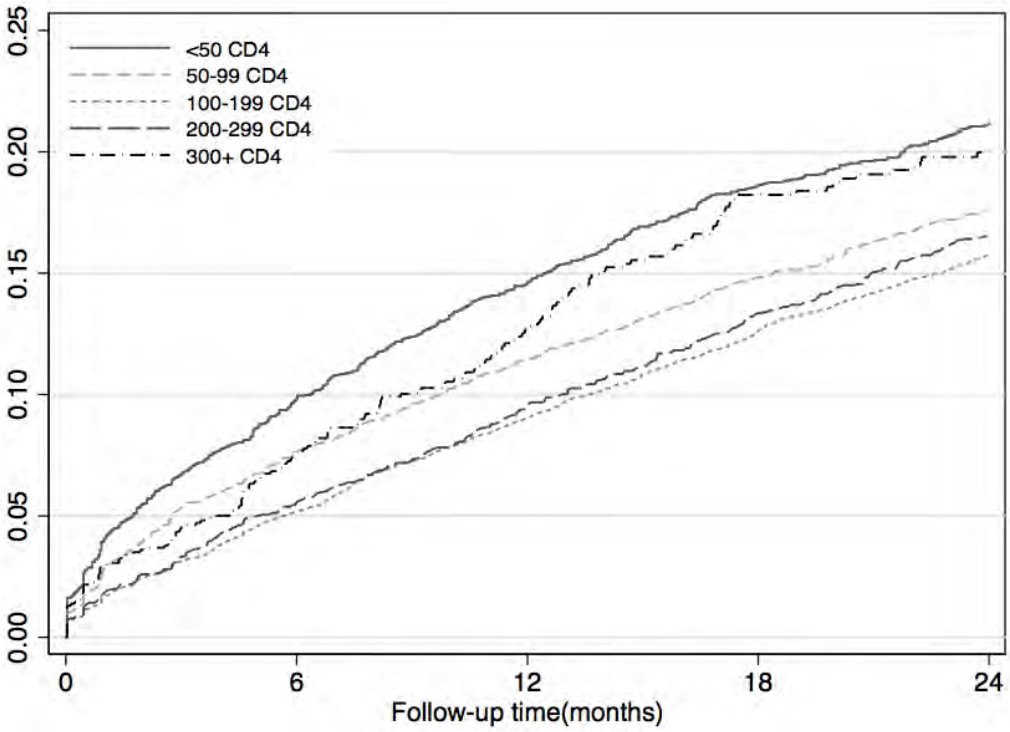
Patients initiating ART with CD4 cell counts ≥300 cells/μl were at an increased risk of being LTFU after 24-months of ART (Table 5.2, Supplementary Table 5.1). Specifically, these patients l were 35% more likely to be LTFU after 24 months of ART compared to patients with a CD4 cell count between 150-199 cells/μl at ART initiation [adjusted Hazard Ratio (aHR): 1.35, 95% CI: 1.12-1.63]. The risk of LTFU was largest in the first year on ART (Figure 5.3). After 12-months on treatment, no significant association was observed between CD4 cell count at ART initiation and corrected LTFU. The increased risk of LTFU among patients with lower CD4 cell counts at ART initiation was attenuated by correcting for unascertained deaths and did not persist in crude or adjusted models of corrected LTFU (Figure 5.3, Supplementary Table 5.1, Table 5.2).

Table 5.1 Patient characteristics among 17,038 adults initiating public-sector ART by CD4 cell count at ART initiation

Baseline characteristic	**CD4 <50 cells/µl** (n=3,145)	**CD4 50-99 cells/µl** (n=2,934)	**CD4 100-199 cells/µl** (n=6,850)	**CD4 200-299 cells/µl** (n=2,954)	**CD4≥300 cells/µl** (n=1,155)	**TOTAL** (n=17,038)
Cohort						
Hlabisa (1)	1,440 (45.8)	1,437 (49.0)	3,364 (49.1)	1,190 (40.3)	859 (74.4)	8,290 (48.7)
Khayelitsha (2)	841 (26.7)	925 (31.5)	2,406 (35.1)	1,398 (47.3)	194 (16.8)	5,764 (33.8)
Themba Lethu (3)	864 (27.5)	572 (19.5)	1,080 (15.8)	366 (12.4)	102 (8.8)	2,984 (17.5)
Gender						
Female	1,700 (54.1)	1,767 (60.2)	4,696 (68.6)	2 172 (73.5)	908 (78.6)	11,243 (66.0)
Age						
Median (IQR)	35.2 (30.0-41.7)	35.6 (29.9-42.4)	35.3 (29.8-42.7)	34.5 (28.9-41.3)	35.3 (29.0-43.2)	35.2 (29.6-42.2)
16-24	197 (6.3)	202 (6.9)	527 (7.7)	263 (8.9)	131 (11.3)	1,320 (7.8)
25-34	1,351 (43.0)	1,185 (40.4)	2,801 (40.9)	1,282 (43.4)	440 (38.1)	7,059 (41.4)
35-44	1,072 (34.1)	1,000 (34.1)	2,166 (31.6)	949 (32.1)	344 (29.8)	5,531 (32.5)
≥45	535 (16.7)	547 (18.6)	1,356 (19.8)	460 915.6)	240 (20.8)	3,128 (18.4)
Year of ART initiation						
2008	1,089 (34.6)	918 (31.3)	1,977 (28.9)	601 (20.4)	132 (11.4)	4,717 (27.7)
2009	1,061 (33.7)	938 (32.0)	2,165 (31.6)	781 (26.4)	199 (17.2)	5,144 (30.2)
2010	615 (19.6)	663 (22.6)	1,632 (23.8)	808 (27.4)	309 (26.8)	4,027 (23.6)
2011	358 (11.4)	386 (13.2)	980 (14.3)	615 (20.8)	366 (31.7)	2,705 (15.9)
2012	22 (0.7)	29 (1.0)	96 (1.4)	149 (5.0)	149 (12.9)	445 (2.6)
WHO stage						
I and II	342 (18.9)	595 (32.1)	2,260 (50.1)	1,209 (55.6)	321 (49.8)	4,727 (43.0)
III	1,011 (55.9)	938 (50.6)	1,838 (40.7)	793 (36.5)	217 (33.7)	4,797 (43.6)
IV	456 (25.2)	321 (17.3)	414 (9.2)	173 (8.0)	106 (16.5)	1,470 (13.4)
Missing	*1 336 (42.3)*	*1,080 (36.8)*	*2,338 (34.1)*	*779 (26.4)*	*511 (44.2)*	*6,044 (35.5)*
Cohort size at initiation (patients)						
<7 500	441 (14.0)	467 (15.9)	968 (14.1)	339 (11.5)	233 (20.2)	2,448 (14.4)
7 500-7 999	595 (19.0)	571 (19.5)	1,453 (21.2)	460 (15.6)	146 (12.6)	3,226 (18.9)
8 000– 9 899	812 (25.8)	629 (21.4)	1,387 (30.2)	430 (14.6)	218 (18.9)	3,476 (20.4)
9 900-11 499	781 (24.8)	730 (24.9)	1,639 (23.9)	843 (28.5)	137 (11.9)	4,130 (24.2)
≥11 550	515 (16.4)	537 (18.3)	1,403 (20.5)	882 (29.9)	421 (36.5)	3,758 (22.1)
Rate of scale-up (patients/month)						
<130	735 (23.4)	727 (24.8)	1,573 (23.0)	334 (11.3)	172 (15.0)	3,542 (20.8)
130-159	557 (17.7)	581 (19.8)	1,395 (20.4)	487 (16.5)	276 (23.9)	3,296 (19.3)
160-179	525 (16.7)	524 (17.9)	1,438 (21.0)	745 (25.2)	284 (24.6)	3,516 (20.6)
180-199	464 (14.8)	530 (18.1)	1,364 (19.9)	1,022 (34.6)	320 (27.7)	3,700 (21.7)
≥200	864 (27.5)	572 (19.5)	1,080 (15.8)	366 (12.4)	102 (8.8)	2,984 (17.5)

Figure 5.1 Kaplan-Meier plots showing observed and corrected 24 month LTFU by CD4 cell count at ART initiation

a. **Observed** LTFU by CD4 cell count at ART initiation 0-24 months follow-up



b. **Corrected** LTFU by CD4 cell count at ART initiation 0-24 months follow-up

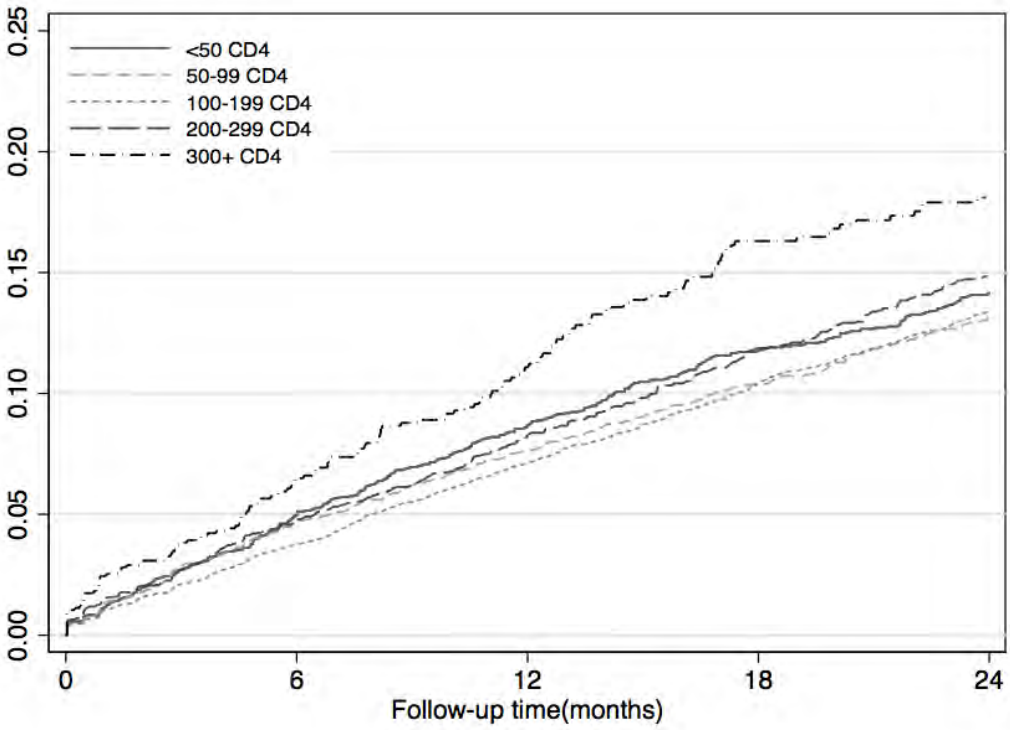
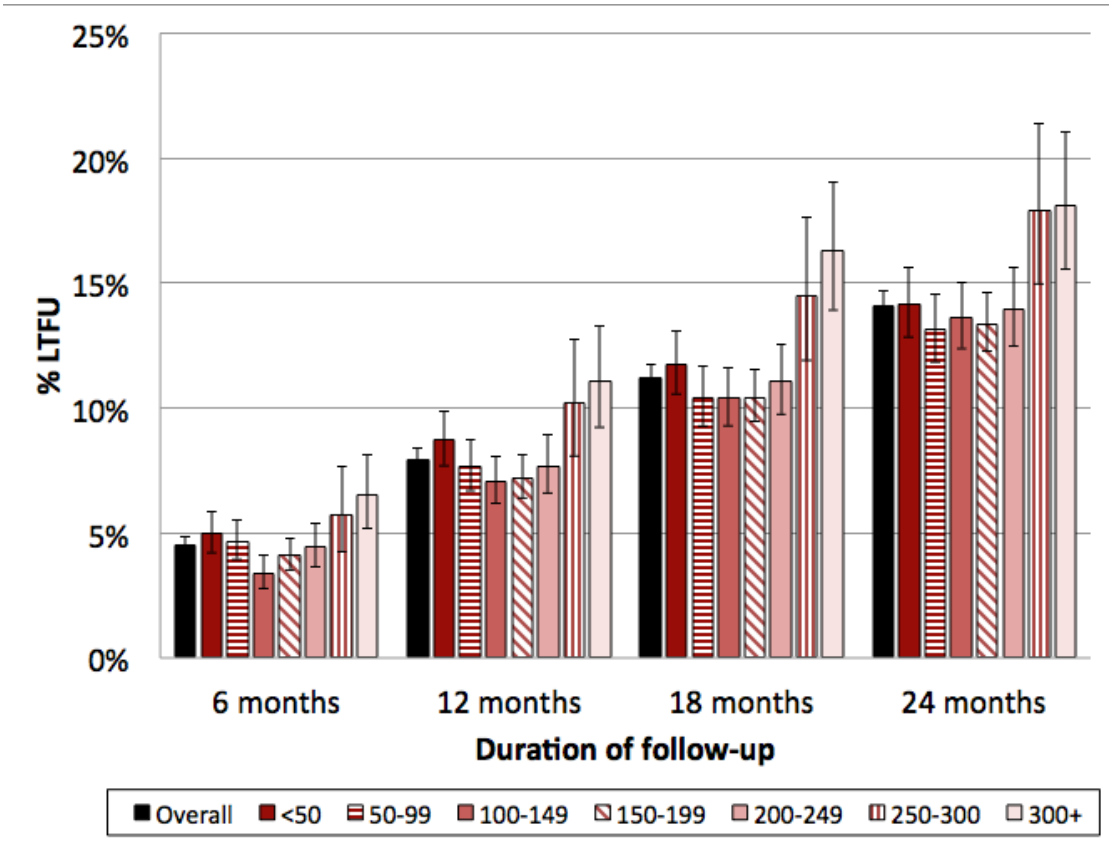


Figure 5.2 *Corrected loss to follow-up from Kaplan-Meier estimates by CD4 cell count at ART initiation**



Corrected loss to follow-up refers to estimates that have been adjusted for unascertained mortality as derived through the National Population Register.

The association between CD4 cell count at ART initiation and LTFU was assessed separately for each of the three cohorts (Supplementary Table 5.2). The results in Cohorts 1 and 2 were very similar to the overall associations observed between CD4 cell count and LTFU. For Cohort 3, patients with CD4 cell counts <100 cells/μl and between 200-249 cells/μl had a decreased risk of LTFU compared to patients initiating ART between 150-199 cells/μl. In this cohort, a limited number of patients initiated treatment at CD4 cell counts above 200 cells/μl (n<500) and later than 2009 (n<50). Median CD4 cell count in Cohort 3 was 105 compared to 142 and 151 in the other two cohorts, respectively (Supplementary Table 5.2).

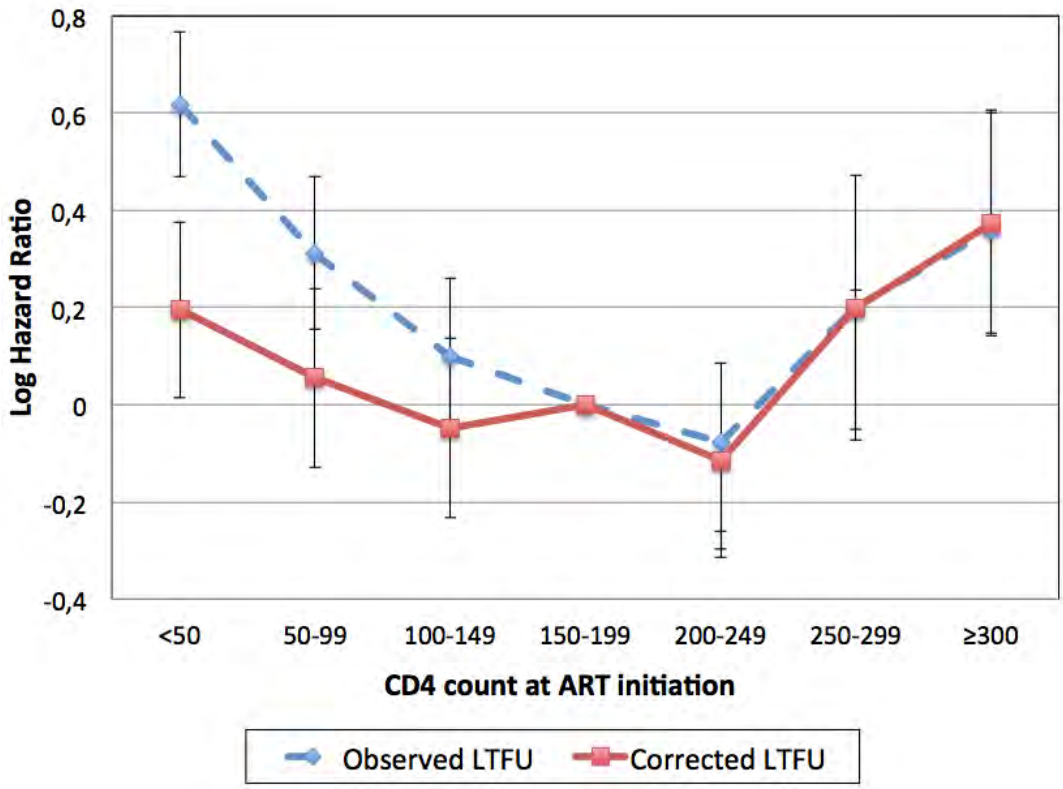
Table 5.2 Hazard ratios of overall, 0-3 month, 3-12 month and 12-24 month corrected LTFU by CD4 cell count at ART initiation±

	OVERALL (0-24 months)	**0-3 months**	**3-12 months**	**12-24 months**
	n=17 038	n=17 038	n=15 470	n=12 728
Crude HR				
<50 cells/µl	1.13 (0.98-1.30)	1.10 (0.81-1.49)	1.34 (1.07-1.68)	0.95 (0.75-1.20)
50-99 cells/µl	1.01 (0.88-1.17)	1.14 (0.85-1.54)	1.05 (0.83-1.33)	0.92 (0.73-1.15)
100-149 cells/µl	1.01 (0.88-1.17)	0.66 (0.47-0.94)	1.14 (0.92-1.43)	1.08 (0.87-1.33)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.95 (0.82-1.11)	0.84 (0.60-1.18)	1.03 (0.81-1.32)	0.94 (0.74-1.19)
250-299 cells/µl	1.38 (1.11-1.70)	1.56 (1.01-2.39)	1.39 (0.98-1.96)	1.27 (0.89-1.81)
≥300 cells/µl	1.62 (1.25-1.95)	1.95 (1.35-2.81)	1.70 (1.27-2.27)	1.34 (0.97-1.87)
Adjusted* - aHR				
<50 cells/µl	1.08 (0.94-1.24)	1.07 (0.79-1.45)	1.30 (1.04-1.63)	0.89 (0.70-1.12)
50-99 cells/µl	0.98 (0.85-1.13)	1.12 (0.83-1.52)	1.02 (0.81-1.29)	0.88 (0.70-1.11)
100-149 cells/µl	1.00 (0.87-1.14)	0.66 (0.47-0.93)	1.12 (0.90-1.40)	1.06 (0.85-1.30)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.89 (0.77-1.04)	0.80 (0.57-1.12)	0.95 (74-1.22)	0.90 (0.71-1.15)
250-299 cells/µl	1.18 (0.95-1.46)	1.40 (0.90-2.16)	1.14 (0.80-1.62)	1.12 (0.89-1.60)
≥300 cells/µl	1.35 (1.12-1.63)	1.68 (1.15-2.45)	1.35 (1.00-1.81)	1.17 (0.84-1.64)

±All estimates are stratified by cohort

*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Figure 5.3 Adjusted 12-month log hazard ratios of observed and corrected LTFU from Cox's proportional hazards models by CD4 cell count at ART initiation*



*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Sub-group analyses were done to assess the association between CD4 cell count at ART initiation and LTFU by year of ART initiation, sex, and age (Supplementary Table 5.3). In each year of ART initiation, an increased hazard of LTFU was observed among patients initiating ART with a CD4 cell count of ≥300 cells/µl compared to patients initiating ART between 150-199 cells/µl. In final models, women were 35% more likely (aHR: 1.35, 95% CI: 1.09-1.68) and men were 24% more likely (aHR: 1.24, 95% CI: 0.84-1.82) to be LTFU if they initiated ART with a CD4 cell count ≥300 cells/µl compared to patients initiating ART between 150-199 cells/µl (Supplementary Table 5.3). In patients 25-34 years of age, those initiating ART with a CD4 cell count ≥300 cells/µl were 1.58 times more likely to be LTFU (95% CI: 1.21-2.08) compared to patients initiating ART between 150-199 cells/µl. In patients ≥35 years, those with a CD4 cell count ≥300 cells/µl at ART initiation were also more likely to be LTFU compared to patients initiating ART between 150-199 cells/µl (35-44 HR: 1.23, 95% CI

0.84-1.80, ≥45 HR: 1.24, 95% CI 0.69-2.22). No association between a CD4 cell count ≥300 cells/μl and LTFU was observed in patients less than 25 years of age (HR: 0.99, 95% CI-0.61-1.58).

Of the 5 cohorts assessed for eligibility, 2 cohorts did not collect IDs. There were 26,466 patients with missing data (CD4 cell counts were missing in 5,457 patients at ART initiation, 4,828 did not have a recorded ID, and 16,161 did not have a CD4 cell count or recorded ID). In sensitivity analyses accounting for missing data, the association between higher CD4 cell count at ART initiation and increased risk of early LTFU persisted. Characteristics of patients with and without IDs are summarised in Supplementary Table 5.4. When inverse probability weighting was used to account for missing IDs, patients with a CD4 cell count ≥300 cells/μl at ART initiation were 55% more likely to be LTFU in the first 3 months of ART (aHR: 1.55, 95% CI 0.94-2.55) (Supplementary Table 5.5). This association was slightly reduced compared to the results of the main analysis (aHR:1.68, 95% CI 1.15-2.45) (Table 5.2). Similarly, in multiple imputation models including patients with missing CD4 cell counts, a CD4 cell count ≥300 cells/μl was associated with a 50% increase in LTFU in the first 3 months of ART (95% CI 1.04-2.18) (Supplementary Table 5.6). The competing risk analysis yielded similar conclusions to the main results (Supplementary Table 5.7).

5.5 DISCUSSION

Our analyses demonstrate that patients initiating ART at CD4 cell counts ≥300 cells/μl are at an increased risk of LTFU in the first 24-months on ART. The increased risk of LTFU among patients with higher CD4 cell counts at ART initiation was observed both with and without correction for unascertained deaths and persisted after adjustment for individual factors and measures of programme expansion. The greatest increase in risk of LTFU for patients initiating with higher CD4 cell counts was in the first year on treatment. While low CD4 cell count at ART initiation was associated with increased risk LTFU, correction for unascertained deaths removed this association.

Our finding that CD4 cell counts ≥300 cells/μl are associated with higher risk of LTFU is aligned with previous findings [134, 136] from smaller, individual studies. In Uganda, a tracing study of patients LTFU found higher rates of LTFU among those with CD4 cell counts ≥250 cells/μl. CD4 cell counts ≥250 cells/μl were also associated with treatment interruptions [233]. Conversely, other studies have found higher CD4 cell counts were associated with reduced LTFU [130, 131]. However, limited data were available on patients with CD4 cell counts ≥300 cells/μl and LTFU did not correct for unascertained deaths.

We can speculate as to why patients who initiate ART at higher CD4 cell counts may be at an increased risk of being lost to care. ART services have been designed to support acutely ill HIV patients with lower CD4 cell counts. Patients who initiate ART at higher CD4 cell counts without an illness experience are not catered for in the services and they may not experience any immediate benefits of ART and thus disengage from care early [136]. The association between CD4 cell counts of ≥300 cells/μl and risk of LTFU was highest in the first year on treatment, especially in the first 3-months. This suggests interventions are needed to change how patients with higher CD4 cell counts are initiated onto ART. Given the range of CD4 cell counts at which patients are now initiating ART, models of ART provision that triage patients at initiation based on CD4 cell count should be considered to provide more tailored support. In addition, pre-therapy counselling should be updated to address the distinct challenges faced by patients initiating treatment at higher CD4 cell counts [234]. Beyond ART initiation, patients with higher CD4 cell counts at ART initiation may benefit from receiving ART outside of traditional facility-based models by accessing ART in community-based models of care.

Our finding that patients initiating ART with higher CD4 cell counts are at greater risk of being LTFU is relevant as countries align national ART guidelines with the 2013 WHO guidelines [28]. With the CD4 threshold in South Africa changing to 500 cells/μl in 2015 [235], an additional 1.5 million people will be eligible for ART [236]. Given the advances in ART drugs and the evidence that earlier ART can benefit both the individual and the population, the question is less about when patients should initiate ART but how. It is paramount that the change in ART eligibility criteria is accompanied

by health system adaptations. We need to adapt where and how patients with higher CD4 cell counts are initiated onto ART given the increased risk of LTFU in the first year on treatment in this group. We are reliant on a limited number of service delivery models that may not provide the most appropriate care for our evolving ART programs. Furthermore, innovative models of care are needed to improve long-term retention of patients. It is also apparent that we are going to need a variety of models; models that can co-exist and have strong referral mechanisms to meet the different needs of increasingly heterogeneous populations accessing ART [237]. Options for populations who currently have inequitable access to ART including men, older populations, and underserved populations are also needed.

We are uniquely positioned to assess the association between a range of CD4 cell counts and LTFU. With data from multiple cohorts we could look at more patients at higher CD4 thresholds than previous research. The challenge faced by many ART cohort analyses of differentiating the risk factors for corrected LTFU from the risk factors for unascertained deaths is overcome in our case through linkage with the NPR. The quality of the NPR data are very high with nearly 90% of adult deaths captured [238]. A valuable finding provided through linkage was that no significant association between lower CD4 cell counts and corrected LTFU was observed. This suggests that the association in uncorrected models was an artefact of unascertained mortality. That fact the association between CD4 cell counts ≥300 cells/μl and LTFU remained after linkage gives weight to our findings. Novel to our findings is that the association persisted after adjusting for measures of programme expansion. Therefore, increases in LTFU are not necessarily the result of deteriorating quality of care as ART programs have expanded [239]. Changes to the profile of patients at ART initiation, including a greater number of patients at higher CD4 cell counts without an illness experience, are related to increased LTFU, a result of the model of ART delivery not being appropriate for all patients accessing ART.

Our study should be considered in light of a number of limitations. Data were missing on a number of key variables including CD4 cell counts at ART initiation and South African civil ID numbers. We chose to exclude patients with missing CD4 levels postulating that missing data was likely related to administrative and clerical errors

and is therefore likely to be missing completely at random (i.e. not related to particular covariates). In sensitivity analyses, models with imputed missing CD4 cell counts and weighted for missing IDs yielded findings consistent with the main results. Previous analyses also found patients with and without IDs were comparable [230]. Data on patients with CD4 cell counts ≥300 cells/μl were limited as the change in South African guidelines to initiation of patients with a CD4 cell count <350 cells/μl was only announced in August 2011 [240]. Therefore, patients with higher CD4 cell counts in our analysis may have been initiated for other clinic reasons and not be representative of patients initiating ART at higher CD4 cell counts. In this analysis, 17% of patients initiating with a CD4 cell count ≥300 cells/μl were in WHO stage IV. From a programmatic perspective, our analysis is limited to reporting on LTFU after ART initiation and ignores that a considerable proportion of the patients determined to be LTFU may be treatment interrupters who will re-engage with ART services at a later date [239].

Our study found that patients who initiate ART with a CD4 cell count ≥300 cells/μl are at an increased risk of being LTFU after 24-months on treatment compared to patients initiating with a CD4 cell count between 150-199 cells/μl. Acknowledging the potential benefits of early ART initiation, further research is needed on how to successfully support patients who initiate treatment at higher CD4 cell counts. This is especially relevant as ART guidelines expand who is eligible for ART initiation to increasingly healthy populations, such as those following Options B+ for the prevention of mother to child transmission. It is widely acknowledged that the greatest threat to the long-term success of the rapidly expanding ART programs is ensuring adherence and retention in care [77]. Given these challenges, now is the time to innovate our health systems to more effectively and efficiently deliver ART.

5.6 ACKNOWLEDGEMENTS

5.6.1 Author Contributions

MF, CO, HP, KS, FS established/maintained the cohorts and provided data. AG analysed the data and wrote the first draft of the manuscript. AG, MS, LM contributed to the plan of analysis and to writing the report, and interpreted the data. All authors commented on draft manuscripts and approved the final version.

Chapter 6. Outcomes of a nurse-managed service for stable HIV-positive patients in a large South African public-sector antiretroviral therapy programme

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6.1 ABSTRACT

Background

Models of care utilizing task shifting and decentralisation are needed to support growing ART programmes. We compared patient outcomes between a doctor-managed clinic and a nurse-managed down-referral site in Cape Town, South Africa.

Methods

Analysis included all adults who initiated ART between 2002 and 2011 within a large public sector ART service. Stable patients were eligible for down-referral to the Green Clinic. Outcomes (mortality, loss to follow-up [LTFU], viral rebound) were compared under different models of care using proportional hazards models with time-dependent covariates.

Results

5,746 patients initiated ART and over 5 years 41% (n=2341) were down-referred; the median time on ART before down-referral was 1.6 years (interquartile range, 0.9-2.6). The Green Clinic (or nurse-managed down-referral site) reported lower crude rates of mortality, LTFU and viral rebound compared to the doctor-managed clinic. After adjustment, there was no difference in the risk of mortality or viral rebound by model of care. However patients who were down-referred were more likely to be LTFU compared to those retained at the doctor-managed site (adjusted hazard ratio, 1.36; 95% CI, 1.09-1.69). Increased levels of LTFU in the Green Clinic versus doctor-managed service were observed in subgroups of male patients, those with advanced disease at initiation and those who started ART in the early years of the programme.

Conclusion

Reorganisation of ART maintenance by down-referral to nurse-managed services is associated with programme outcomes similar to those achieved using doctor-driven primary care services. Further research is necessary to identify optimal models of care to support long-term retention of patients on ART in resource-limited settings.

6.2 INTRODUCTION

The expansion of antiretroviral therapy in resource-limited settings has been rapid over the past decade. Almost ten million people in low and middle-income countries were receiving ART at the end of 2012; approximately 1.6 million of these initiating in 2011 alone [24]. In many settings the demand for ART services has often outpaced the ability of health care services and providers to care for increasing patient numbers [204]. As a result of the size and speed of ART expansion, elements of task shifting and decentralised provision of ART have been developed and implemented out of necessity in parallel to generating evidence of their effectiveness [42].

Task shifting has been increasingly promoted to address the human resource crisis in the health sector exacerbated in many countries by the HIV epidemic [241-243]. Early ART programmes in resource-limited settings followed a doctor-driven approach to highly individualised care with intensive clinical monitoring. In response to the limited capacity of primary health care systems and human resource constraints, increasing levels of responsibility within ART programmes were shifted to other cadres of staff [243]. Nurses now initiate and manage ART patients in South Africa and many other countries [44] and the expanding responsibilities of counsellors in these programmes is increasingly acknowledged [244]. Meanwhile, as treatment programmes have expanded, decentralisation of ART services from hospitals to primary care sites has been recommended to help facilitate access to care [183, 245, 246]. With more sites providing ART, the number of patients starting treatment and being down-referred to community-based facilities has increased, with favourable reports of retention rates [97, 128, 247].

Continued expansion of ART programmes is needed to reach the target of universal coverage by 2015 [248]. In addition, new treatment guidelines recommend earlier ART initiation thus increasing the number of patients eligible to start treatment [28]. As ART programmes mature, the long-term retention of patients in care is essential to the effectiveness of the programme. Models of care that are sustainable and can support life-long adherence to ART are needed. These models of care will combine elements of task shifting, decentralised care and hopefully innovative approaches to address the

growing challenge of loss to follow-up (LTFU). Despite the importance of and interest in non-physician led models of ART for ART care and maintenance, there are few data on long-term patient outcomes in these programmes Our objective was to evaluate the Green Clinic, a nurse-managed, decentralised model of care for stable ART patients, compared to a doctor-managed ART clinic, for patients receiving ART in primary care in Cape Town, South Africa.

6.3 METHODS

6.3.1 Study design

This was a cohort analysis of prospectively collected clinic data. Ethical approval for the use of patient information and the evaluation of models of care were obtained from the Faculty of Health Sciences Human Research Ethics Committee at the University of Cape Town. All patients gave written informed consent for their routine care records to be included.

6.3.2 Study setting

The study took place at a well-characterised, peri-urban community health centre (CHC) in Gugulethu, Cape Town [16, 249]. The community surrounding the clinic is of low socioeconomic status and the local antenatal HIV seroprevalence was 26% in 2013. The general ART service has been described in detail previously [16, 249]. Briefly, ambulatory patients who were eligible for ART based on South African national guidelines received clinical care, psychosocial counselling, and related services. All patients initiated ART at the CHC in the doctor-managed ART clinic (referred to hereafter as the treatment-initiation site). The service was supported by a network of peer counsellors [57]. Routine monitoring of CD4 cell count and viral load were done every 16 weeks during ART.

6.3.3 The down-referral process

In February 2006 in response to the growing congestion of the treatment-initiation site, a down-referral site was opened in a separate building on the grounds of the CHC (referred to hereafter as the Green Clinic). Patients were eligible for down-referral if: they had been on ART for at least 16 weeks, their most recent viral load was less than 50 copies/mL, they had no active opportunistic infections or poorly controlled chronic conditions, they were on a first-line ART regimen (comprised of two nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor) and they demonstrated good adherence by pill count.

For the first two years of the programme, the Green Clinic was staffed with a doctor and professional nurse thereafter, transitioning to a nurse-managed, counsellor and doctor-supported programme. Green Clinic patients were scheduled to return every four4 months to see a nurse for clinical care and a counsellor for adherence support and every two months to the pharmacy for ART collection. Green Clinic patients were all dispensed two months of ART compared to one to two months of ART for treatment-initiation site patients. CD4 cell count and viral loads were monitored every 16 weeks at both sites. Patients could also be up-referred to the treatment-initiation site if they developed opportunistic infections requiring more regular clinical care (e.g. active tuberculosis), or needed to switch drug regimens.

6.3.4 Data analysis

All ART-naïve patients were eligible for analysis and entered on the date of ART initiation. Database closure was June 2012 when referral to a new model of care was started and analysis closure was the end of December 2011 [207]. Patients known to be down-referred without a referral date were described but excluded from rate and time to event analyses. Deaths referred to all-cause mortality from any source. Transfers out were censored at the date of transfer.

The primary outcomes were death, LTFU, and viral rebound. Patients were censored at the earliest of date of outcome: death, LTFU, transfer out, or analysis closure. LTFU

was defined as no contact between analysis and database closure and the last date of contact was assigned as the outcome date [207]. Viral rebound was defined as a single viral load >1,000 copies/mL among patients who had a viral load below 1,000 copies/mL after four months on ART. Time-updated laboratory values for CD4 cell count and viral load were available for every four months on treatment, defined as the closest laboratory value plus or minus two months.

Pre-ART characteristics of all patients were summarised as proportions for categorical variables and medians with inter-quartile ranges (IQRs) for continuous variables, stratified by model of care (treatment-initiation site vs. treatment-initiation and Green Clinic). Because of variability in completeness of baseline data, numbers of observations are reported for each analysis. Changes in CD4 cell count and viral load as well as the proportion of patients with a CD4 cell count ever above 200 cells/μl and a viral load below 1,000 copies/mL at 4-months after ART initiation were presented by model of care. Pearson's chi-squared and Wilcoxon rank-sum tests were used to assess differences by model of care. Median time to down-referral was calculated by baseline characteristics with IQRs and Wilcoxon rank-sum tests used to determine associations with baseline characteristics.

We compared unadjusted rates of mortality, LTFU and viral rebound by patient characteristics and model of care. Rates of mortality, LTFU and overall attrition were calculated overall and by model of care and reported at 6-monthly intervals. Patients who were down-referred contributed analysis time to the treatment-initiation site until referral.

Separate Cox's proportional hazards models with time-varying covariates for model of care, CD4 cell count and viral load were used to calculate unadjusted and adjusted associations between model of care and outcomes. Analysis of viral rebound was restricted to patients with a viral load below 1,000 copies/mL after four months on ART. Multivariate models were generated adjusting for demographics (age and gender), baseline disease characteristics (CD4 cell count, WHO clinical stage, haemoglobin), year of initiation, and time-updated laboratory values [178]. Time-updated CD4 cell count was modelled as a continuous variable per 50-cell change and

time-updated viral load as a binary (<1,000 copies/mL vs. ≥1,000 copies/mL). We modelled the proportional hazards of virologic suppression from four months after ART initiation and 12 months after ART initiation. The proportional hazards of death and LTFU were modelled separately for different time periods (from ART initiation, from 4 months after ART initiation and from 12 months after ART initiation). Subsidiary analyses used proportional hazards models restricted to levels of baseline covariates. Post-estimation survival plots stratified by model of care were generated for LTFU following unadjusted and adjusted proportional hazards models.

All statistical tests were two-sided at an alpha of 0.05. Data were analysed using STATA version 12.0 (STATA Corporation, College Station, Texas, USA).

6.4 RESULTS

6.4.1 Pre-ART characteristics and changes in viral load and CD4 in the first year on ART

This analysis included 5,746 patients who initiated ART between 2002 and 2011 (67% female; median age 34, IQR 29-40) (Table 6.1). A total of 5,154 patients contributed 13 744 person-years of observation. Since 2006, 41% of patients were down-referred to the Green Clinic (n=2 341). There were no differences in gender (p=0.054), age (p=0.936), viral load (p= 0.691) and WHO clinical stage (p-value 0.093) at ART initiation between Green Clinic versus those retained in the doctor-managed service. After 4 months on ART, a higher proportion of Green Clinic patients had a viral load of <1,000 copies/mL (89.8% vs. 62.7%, p<0.001) and had a greater than 100-unit change in CD4 cell count from their pre-ART value (56.3% vs. 50.9%, p<0.001) compared to patients receiving care at the treatment initiation site only.

The median time to down-referral was 1.6 years (IQR 0.9-2.6) (Supplementary Table 6.1). Patients initiating ART with a CD4 cell count above 200 cells/µl were down-referred after 1.2 years on ART (IQR 0.7-2.1) compared to 2.1 years (IQR 1.3-3.1) for

patients initiating ART with a CD4 cell count less than 50 200 cells/µl. Green Clinic patients had better improvements in CD4 cell counts and were more likely to have viral loads <1,000 copies/mL compared to patients in the treatment-initiation site in the first year on ART (p-values all <0.001) (Table 6.1).

6.4.2 Mortality

The unadjusted mortality rate on ART was lower in the Green Clinic than in the treatment-initiation site (1.2 vs. 4.3/100 person-years, respectively) (Table 6.2). While mortality rates were consistently higher for the treatment-initiation site, similar trends by baseline characteristics were observed at both sites (Table 6.3).

The unadjusted risk of mortality was 29% lower in the Green Clinic compared to patients in the treatment-initiation site (HR 0.71, 95% 0.50-1.00, p=0.047) (Table 6.4). However after adjusting for variation in gender, age, pre-ART CD4, WHO stage and haemoglobin at baseline, year of ART initiation and time updated CD4 and viral load, there was no difference in the risk of mortality between the Green Clinic and treatment-initiation site patients (aHR 1.51, 95% CI 0.90-2.55). Mortality was associated with male gender, a CD4 cell count below 50 cells/µl at baseline, WHO IV at baseline, earlier year of ART initiation, lower time-updated CD4 cell count and not being virally suppressed (results not shown).

6.4.3 Loss to follow-up

The overall LTFU rate was 7.9 per 100 person-years and lower in the Green Clinic than in the treatment-initiation site (5.9 vs. 8.9/100 person-years, respectively; Table 6.2). Rates of LTFU were highest in the first 6 months after ART initiation and constant over 24-60 months. Over 24-48 months LTFU rates were between 6.0 and 6.6 per 100 person-years in both models of care. The highest rates of LTFU were observed in patients initiating ART with a CD4 cell count above 200 cells/µl in the treatment-initiation site (12.9/100 person-years) and those initiating ART in 2010-2011 both in the treatment-initiation site (20.7/100 person-years) and in the Green Clinic (9.9/100 person-years) (Table 6.3).

Table 6.1 Pre-ART characteristics and changes in viral load and CD4 in the first year on ART compared by model of care

	Treatment-initiation site only (n=3,405)	Treatment-initiation + Green Clinic (n=2,341)	Total (n=5 ,746)	p-value
Pre-ART characteristic				
Gender				
Females, n(%)	2,234 (65.6)	1,593 (68.1)	3,827 (66.6)	0.054
Age, years				
Median (IQR)	33.9 (28.6-40.6)	33.7 (29.2-39.8)	33.8 (28.9-40.2)	0.936
CD4 cell count (cells/µl), n(%)				
<50	651 (21.6)	426 (19.3)	1,077 (20.6)	<0.001
50-99	582 (19.3)	494 (22.3)	1,076 (20.6)	
100-199	1,086 (36.1)	950 (43.0)	2,036 (39.0)	
≥200	690 (22.9)	342 (15.5)	1,032 (19.8)	
Median (IQR)	123 (58-193)	118 (62-174)	121 (60-184)	0.005
Missing, n(%)	*396 (11.6)*	*129 (5.5)*	*525 (9.1)*	
Viral load, log_{10} copies/mL				
Median (IQR)	4.8 (4.4-5.3)	4.8 (4.4-5.3)	4.8 (4.4-5.3)	0.691
Missing, n(%)	*548 (16.1)*	*212 (9.1)*	*760 (13.2)*	
Haemoglobin, g/dL				
Median (IQR)	11.0 (9.7-12.4)	11.3 (9.9-12.5)	11.1 (9.8-12.4)	0.002
Missing, n(%)	*638 (18.7)*	*285 (12.2)*	*923 (16.6)*	
WHO stage, n(%)				
Stage I and II	1,138 (34.4)	739 (31.7)	1,877 (33.3)	0.093
Stage III	1,557 (47.1)	1131 (48.5)	2,688 (47.7)	
Stage IV	611 (18.5)	460 (19.7)	1,071 (19.0)	
Missing, n(%)	*99 (2.9)*	*11 (0.5)*	*110 (1.9)*	
Year of initiation, n(%)				
2002 - 2003	76 (2.2)	101 (4.3)	177 (3.1)	<0.001
2004 - 2005	364 (10.7)	675 (28.8)	1,039 (18.1)	
2006 – 2007	599 (17.6)	851 (36.4)	1,450 (25.2)	
2008 – 2009	847 (24.9)	502 (21.4)	1,349 (23.5)	
2010 - 2011	1519 (44.6)	212 (9.1)	1,731 (30.1)	
Changes in viral load and CD4				
Supressed (VL<1,000) at 4-months, n(%)				
Supressed	2,136 (62.7)	2,102 (89.8)	4,238 (73.8)	<0.001
4-month CD4, (cells/µl)				
Median (IQR)	244 (156-337)	237 (164-323)	241 (160-330.5)	0.258
4-month change in CD4 (4-month - pre-ART), n(%)				
<100	1,050 (49.1)	922 (43.7)	1,972 (46.4)	<0.001
≥100	1,087 (50.9)	1,189 (56.3)	2,276 (53.6)	
12-month CD4, (cells/µl)				
Median (IQR)	286 (191-391)	297 (213-390)	293 (204-391)	0.001
12-month change in CD4 (12-month - pre-ART), n(%)				
<100	479 (30.7)	440 (21.9)	919 (25.8)	<0.001
≥100	1,079 (69.3)	1571 (78.1)	2,650 (74.3)	
CD4 under 200, n(%)				
Always <200	938 (28.2)	72 (3.1)	1,010 (17.8)	<0.001
≥200	2383 (71.8)	2,268 (96.9)	4,651 (82.2)	

There was no difference in the unadjusted risk of LTFU between the Green Clinic and treatment-initiation site patients (HR 0.95, 95% CI 0.80-1.12) (Table 6.4, Figure 6.1A & Figure 6.1C). In the multivariate model, Green Clinic patients had a slightly increased of risk of LTFU (aHR 1.36, 95% CI 1.09-1.69) compared to treatment-initiation site patients (Figure 6.1B). The increased risk of LTFU in Green Clinic patients after adjustment persisted when restricting to patients who survived beyond 4 and 12-months after ART initiation (Table 6.4, Figure 6.1D). LTFU was also associated with male gender, younger age, high CD4 cell count and low haemoglobin at baseline and time updated laboratory values (results not shown). An increasing association with year of ART initiation and LTFU was also observed; those initiating ART in 2008-2009 had 5 times the risk of LTFU (aHR 5.22, 95% CI 2.80-9.75) and those initiating ART in 2010-2011 had 10 times the risk of LTFU (aHR 9.73, 95%CI 5.16-18.37) compared to those who initiated ART in 2002-2003. In unadjusted analysis, Green Clinic patients with a high CD4 cell count or in WHO stage I and II had a decreased risk of LTFU compared to those at the treatment-initiation site (CD4 ≥200 cells/μl: HR 0.57, 95% CI 0.36-0.88; WHO Stage I and II: HR 0.66, 95% CI 0.48-0.91) (Supplementary Table 6.2). After adjustment, an increased risk of LTFU was observed for Green Clinic patients who were men, aged 25-34, initiated ART with a CD4 cell count <50 cells/μl or in WHO clinical stage III or stage IV, or initiated ART before 2006 compared to treatment-initiation site patients.

6.4.4 Viral rebound

Rates of viral rebound were defined as a viral load measure >1,000 copies/mL were lower in the Green Clinic compared to the treatment-initiation site (8.1 vs. 11.3/100 person-years) (Table 6.3). The highest rates of rebound were observed in those less than 25 years of age compared to patients 45 years and older in both sites (14.7 vs. 6.4/100 person-years and 19.5 vs. 7.3/100 person-years, respectively). In unadjusted analysis, Green Clinic patients were 23% less likely to experience viral rebound compared to patients in the treatment-initiation site (HR 0.77, 95% 0.66-0.91) (Table 6.4). After adjustment, there was no difference in the risk of viral rebound (HR 0.94, 95% CI 0.78-1.13).

Table 6.2 Incidence rates of mortality and loss to follow-up, at the treatment-initiation site and after down-referral to the Green Clinic*

	Person-time (years)	Mortality Events	Mortality Rate per 100 PY (95% CI)	Loss to follow-up Events	Loss to follow-up Rate per 100 PY (95% CI)
Overall incidence rates from ART initiation[+](n=5154)					
0-6 months	2,250.6	240	10.7 (9.4-12.1)	325	14.4 (13.0-16.1)
6-12 months	1,881.9	60	3.2 (2.5-4.1)	158	8.4 (7.2-9.8)
12-18 months	1,599.5	33	2.1 (1.5-2.9)	129	8.1 (6.8-9.6)
18-24 months	1,355.6	17	1.3 (0.8-2.0)	77	5.7 (4.5-7.1)
24-36 months	2,211.1	38	1.7 (1.3-2.4)	132	6.0 (5.0-7.1)
36-48 months	1,678.2	26	1.6 (1.1-2.3)	97	5.8 (4.7-7.1)
48-60 months	1,236.4	13	1.1 (0.6-1.8)	74	6.0 (4.8-7.5)
60+ months	1,531.1	17	1.1 (0.7-1.8)	89	5.8 (4.7-7.2)
OVERALL	13,744.4	444	3.2 (2.9-3.6)	1081	7.9 (7.4-8.4)
Treatment-initiation site incidence rates from ART initiation until censoring or down-referral[§] (n=5147)					
0-6 months	2,224.4	240	10.8 (9.5-12.2)	323	14.5 (13.0-16.2)
6-12 months	1,717.2	55	3.2 (2.5-4.2)	145	8.4 (7.2-9.9)
12-18 months	1,304.7	29	2.2 (1.5-3.2)	104	8.0 (6.6-9.7)
18-24 months	973.9	14	1.4 (0.8-2.4)	52	5.3 (4.1-7.0)
24-36 months	1,259.1	24	1.9 (1.3-2.8)	76	6.0 (4.8-7.6)
36-48 months	693.8	11	1.6 (0.9-2.9)	46	6.6 (5.0-8.9)
48-60 months	377.4	7	1.9 (0.9-3.9)	27	7.2 (4.9-10.4)
60+ months	385.6	6	1.6 (0.7-3.5)	24	6.2 (4.2-9.3)
OVERALL	8,936.0	386	4.3 (3.9-4.8)	797	8.9 (8.3-9.6)
Green Clinic incidence rates from date of down-referral[±] (n=1740)					
0-6 months	825.5	11	1.3 (0.7-2.4)	53	6.4 (4.9-8.4)
6-12 months	726.7	8	1.1 (0.6-2.2)	42	5.8 (4.3-7.8)
12-18 months	677.6	8	1.2 (0.6-2.4)	28	4.1 (2.9-6.0)
18-24 months	600.9	6	1.0 (0.5-2.2)	26	4.3 (3.0-6.4)
24-36 months	943.7	13	1.4 (0.8-2.5)	60	6.4 (4.9-8.2)
36-48 months	723.8	9	1.2 (0.7-2.4)	47	6.5 (4.9-8.6)
48-60 months	156.5	3	1.9 (0.6-5.9)	18	11.5 (7.3-18.3)
60+ months	7.4	0	0	1	13.6 (1.9-96.2)
OVERALL	4,662.1	58	1.2 (1.0-1.6)	275	5.9 (5.3-6.6)

*Restricted to patients who have a date of down-referral or who were never down-referred

[+]Reports the rates of events among all patients from ART initiation until analysis closure or censoring

[§]Reports the rates of events among patients from ART initiation until down-referral, analysis closure, or censoring

[±] Reports the rates of event from date of down-referral until analysis closure or censoring

Table 6.3 Crude rates of progression to death, loss to follow-up and viral rebound by pre-ART characteristics and model of care*

	Event rates (per 100 person-years, 95%CI)					
	Death		Loss to follow-up		Viral Rebound±	
	Treatment-initiation site	Green Clinic§	Treatment-initiation site	Green Clinic§	Treatment-initiation site	Green Clinic$^{\alpha}$
All patients	4.3 (3.9-4.8)	1.2 (1.0-1.6)	8.9 (8.3-9.6)	5.9 (5.2-6.6)	11.3 (10.5-12.3)	8.1 (7.2-9.1)
Age (years)						
Less than 25	5.1 (3.7-7.0)	0.6 (0.1-2.3)	14.5 (12.0-17.5)	7.3 (4.9-10.8)	19.5 (15.3-24.7)	14.7 (10.5-20.6)
25-34	3.0 (2.6-3.6)	1.1 (0.8-1.7)	8.9 (8.0-9.8)	6.1 (5.2-7.2)	11.4 (10.1-12.8)	8.6 (7.4-10.1)
35-45	4.7 (3.9-5.6)	0.6 (0.3-1.2)	8.3 (7.3-9.5)	5.6 (4.5-7.1)	11.3 (9.8-13.2)	6.4 (5.0-8.1)
45 and above	7.8 (6.3-9.5)	3.6 (2.4-5.6)	7.1 (5.7-8.8)	4.9 (3.3-7.0)	7.3 (5.6-9.5)	6.4 (4.5-9.2)
Gender						
Males	5.9 (5.1-6.9)	2.1 (1.4-3.0)	10.6 (9.4-11.8)	7.1 (5.8-8.6)	10.9 (9.4-12.7)	8.6 (7.0-10.5)
Females	3.6 (3.1-4.1)	0.9 (0.6-1.3)	8.2 (7.5-8.9)	5.4 (4.6-6.2)	11.5 (10.5-12.7)	7.8 (6.8-9.0)
CD4 (cells/µl)						
<50	8.6 (7.3-10.0)	1.4 (0.8-2.5)	8.4 (7.2-9.9)	5.0 (3.7-6.8)	14.4 (12.2-17.0)	9.8 (7.6-12.6)
50-99	4.2 (3.4-5.3)	1.0 (0.5-1.8)	7.6 (6.4-8.9)	6.5 (5.1-8.2)	11.3 (9.5-13.5)	8.3 (6.5-10.6)
100-199	2.6 (2.1-3.2)	1.5 (1.0-2.1)	8.3 (7.4-9.3)	6.6 (5.6-7.8)	10.2 (8.9-11.7)	8.0 (6.7-9.6)
≥200	2.9 (2.1-4.0)	0.9 (0.4-2.1)	12.9 (11.0-15.0)	4.8 (3.3-6.9)	9.1 (7.2-11.5)	6.8 (4.9-9.6)
WHO stage						
Stage I and II	1.8 (1.4-2.4)	0.8 (0.4-1.4)	10.2 (9.0-11.5)	4.1 (3.1-5.4)	11.2 (9.5-13.1)	7.8 (6.4-9.7)
Stage III	4.4 (3.8-5.0)	1.4 (1.0-2.0)	8.5 (7.7-9.4)	5.2 (4.3-6.3)	12.0 (10.8-13.5)	8.8 (7.5-10.3)
Stage IV	7.9 (6.7-9.3)	1.4 (0.9-2.4)	8.0 (6.8-9.5)	4.2 (3.0-5.8)	10.0 (8.2-12.1)	6.9 (5.3-9.1)
Year of initiation						
2002 - 2003	3.8 (2.6-5.4)	0.6 (0.2-2.5)	1.4 (0.8-2.6)	5.7 (3.6-9.1)	7.2 (5.3-9.8)	3.8 (2.0-7.1)
2004 - 2005	4.2 (3.5-5.1)	1.5 (1.0-2.2)	3.9 (3.2-4.7)	4.8 (3.9-5.8)	8.9 (7.5-10.6)	7.3 (6.0-9.0)
2006 – 2007	5.3 (4.5-6.3)	1.4 (0.9-2.0)	8.7 (7.6-10.0)	6.3 (5.3-7.6)	13.5 (11.7-15.7)	9.6 (8.2-11.3)
2008 – 2009	4.3 (3.5-5.3)	0.4 (0.1-1.6)	11.0 (9.7-12.6)	8.0 (5.9-10.8)	14.2 (12.1-16.6)	7.7 (5.5-10.8)
2010 - 2011	3.0 (2.2-4.2)	-	20.7 (18.3-23.3)	9.9 (4.7-20.9)	11.1 (8.8-14.0)	6.1 (2.3-16.4)

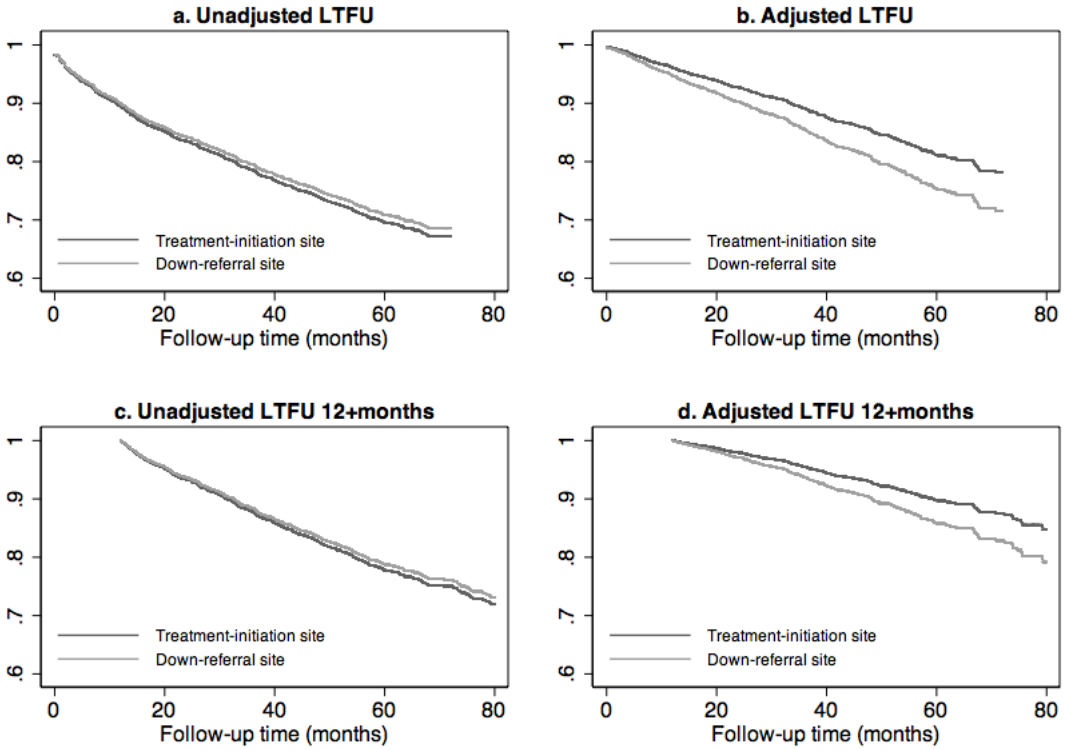
*Restricted to patients who were never in the down-referral site or have a date of referral.
§Patients who were down-referred to the Green Clinic contributed analysis time to the treatment-initiation site until referral.
± All patients suppressed (VL<1,000) at 4-months included in this analysis. Viral rebound defined as a viral load ≥1,000 after suppression.
$^{\alpha}$ Restricted to eligible patients who have a down-referral date that precedes their date of failure

Table 6.4 Relative hazard of mortality, loss to follow-up and viral rebound from Cox's proportional hazards models

	Mortality		LTFU		Viral rebound±	
Model of Care	Univariate HR (95% CI)	Multivariate* aHR (95% CI) (n=4 088)	Univariate HR (95% CI)	Multivariate* aHR (95% CI) (n=4 088)	Univariate HR (95% CI)	Multivariate§ aHR (95% CI) (n=2 981)
OVERALL						
Treatment-initiation site	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Green Clinic	0.71 (0.50-1.00)	1.51 (0.90-2.55)	0.95 (0.80-1.12)	1.36 (1.09-1.69)	0.77 (0.66-0.91)	0.94 (0.78-1.13)
FROM 4-MONTHS$^{\alpha}$						
Treatment-initiation site	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Green Clinic	0.72 (0.51-1.01)	1.41 (0.82-2.41)	0.96 (0.81-1.13)	1.33 (1.06-1.66)	0.77 (0.66-0.91)	0.94 (0.78-1.13)
FROM 12-MONTHS$^{\beta}$						
Treatment-initiation site	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Green Clinic	0.70 (0.48-1.01)	1.29 (0.72-2.33)	0.95 (0.80-1.13)	1.41 (1.11-1.79)	0.79 (0.66-0.93)	0.97 (0.80-1.18)

±All patients suppressed (VL<1,000) at 4-months included in this analysis. Virological failure defined as a viral load ≥1,000 after suppression.
*Multivariate: Includes all demographic (age, sex) and baseline characteristics (CD4, WHO stage, viral load, haemoglobin, year of initiation) + time-updated CD4 and viral load
§Multivariate: Includes all demographic (age, sex) and baseline characteristics (CD4, WHO stage, viral load, haemoglobin, year of initiation) + time-updated CD4
$^{\alpha}$ Restricted person-time from 4-months after ART initiation
$^{\beta}$ Restricted person-time from 12-months after ART initiation

Figure 6.1 Post-estimation plots of loss to follow-up by site of care, for: (a) Unadjusted LTFU, (b) Adjusted LTFU, (c) Unadjusted LTFU restricted to person-time from 12-months after ART initiation, (d) Adjusted LTFU restricted to person-time from 12-months after ART initiation*



*Adjusted includes demographic (age, sex) and baseline characteristics (CD4, WHO stage, viral load, haemoglobin, year of initiation) and time-updated CD4 and viral load

6.5 DISCUSSION

There is a growing need for decentralised models of ART care to deliver services in high-burden settings across sub-Saharan Africa. We evaluated a nurse-driven down-referral service for maintenance of stable patients on ART. Over 5 years, 41% of patients were successfully down-referred to the Green Clinic. Overall, we found the risk of mortality and viral rebound was similar in patients at the Green Clinic and treatment-initiation site. However, LTFU is a significant challenge under both models of care, with rates increasing with each successive calendar year of initiation. The Green Clinic was associated with an increased risk of LTFU compared to the treatment-initiation site among men.

We found that mortality rates were highest in older patients, men, and patients with advanced HIV disease at ART initiation while LTFU was highest among younger patients, men and patients who initiated ART in recent calendar years. Findings are consistent with previous research [56, 117]. After adjusting for clinical and demographic variability between patients, no difference in mortality or viral rebound was observed between patients at the Green Clinic and treatment-initiation site. Taken together, these findings support previous research suggesting that decentralised programmes can have comparable outcomes for stable patients [165, 174, 178, 250].

The adjusted risk of LTFU was slightly higher in patients at the Green Clinic compared to those attending the treatment-initiation site. This difference appears to be driven by subgroups of male patients, patients 25-34 years of age and those with advanced HIV disease. Patients who initiated ART between 2002-2005 started at the facility when the staff to patient ratio had sufficient capacity for individualised counselling and support. It is possible that the change between the level and type of care patients received early in the ART programme and the Green Clinic led to increased disengagement and the higher risk of LTFU.

Growing evidence highlights LTFU as a ubiquitous challenge facing ART programmes in resource-limited settings [56]. Our data support this concern, with the risk of LTFU increasing with each calendar year of ART initiation in both models of care. In adjusted models there was a five and ten-fold increase in the risk of LTFU among patients initiating ART between 2008-2009 and 2010-2011, respectively, compared to patients initiating ART before 2004. Innovative models of care with decentralised ART management and task shifting of responsibilities are required to address the challenge of growing ART programmes and long-term retention in care [42, 151]. While the benefits of such models include offering ART services closer to home, by lower cadres of staff, there may be risks involved. As with the Green Clinic, many of these models incorporate less frequent visits, with fewer opportunities for individualised counselling and adherence support that could negatively impact long-term retention.

There is some evidence suggesting that patients who initiate ART at higher CD4 cell counts may be at greater risk of LTFU and the high rates of LTFU observed in our study

among patients at the treatment-initiation site with high baseline CD4 cell counts support this [134, 136]. Patients initiating ART with a CD4 cell count above 200 cells/μl were 43% less likely to be LTFU at the Green Clinic compared to the treatment-initiation site. These results suggest that specialised, doctor-managed clinics may not be the most appropriate model of care for patients with high CD4 cell counts at ART initiation. Given that the Green Clinic offered shorter and less frequent visits, the model may be especially beneficial to patients who initiate with less advanced disease. Expanding and accelerating access to decentralised models of care may be especially important as ART programmes expand eligibility criteria and initiate patients at progressively higher CD4 cell counts.

This study has several strengths and limitations. The data come from a large, well-maintained cohort from a public sector South African ART clinic that is in many ways representative of primary care services in the region. There are relatively good ascertainment of outcomes, but LTFU may be overestimated through inclusion of patients who are dead, transferred out, or otherwise disengaged from care [53, 87, 203, 211]. However, whether such over-reporting of LTFU could be systematically different between the two models of care is unclear. The early establishment of the down-referral site allows for substantial follow-up time and the ability to assess the long-term impact of the model. The major weakness of this analysis is the potential for selection bias in terms of who was eligible and referred for the down-referral model of care. To account for this, we adjusted for pre-ART characteristics and laboratory data. Although we cannot rule out the possibility of residual confounding effects, in the absence of the ability to randomise patients, data from this operational research programme provides valuable evidence on the impact of different models of care on patient outcomes.

The 2013 WHO guidelines include specific recommendations for decentralisation and task shifting to assist in expanding ART access and improving retention [28]. These data suggest that good outcomes can be achieved in such models of care but that the challenge of LTFU requires on-going attention. There is a need for further research to determine effective models of care that successfully can deliver ART at a community level in high-prevalence, resource-limited settings [42, 151, 176, 183, 245, 247, 251]. In

particular, more data are necessary to determine the cost-effectiveness of these models, as well as to understand the potential risks and benefits and trade-offs that may exist in offering out-of-clinic ART maintenance. Any alternative model of care needs to consider that ART programmes are maturing and initiating patients at progressively higher CD4 cell counts.

In conclusion, in these data a large proportion of stable ART patients were successfully down-referred for treatment maintenance. While no differences in the risk of mortality or virological failure were observed, there was a slight increase in the risk of LTFU at the Green Clinic compared to the treatment-initiation site. Overall these data suggest relatively good outcomes achieved under this down-referral service. Further research is necessary to determine models of care that incorporate task shifting and decentralised ART care potentially targeting specific types of patients to effectively support the maturing and expanding ART programmes in resource-limited settings.

6.6 ACKNOWLEDGEMENTS

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6.6.1 Author contributions

RK and LGB were responsible for establishing and maintaining the cohort. AG and LM conceived the design and plan for analysis. AG was responsible for the analysis and the draft of the manuscript. All authors agreed with the final results and approved the final version of the manuscript.

Chapter 7. Implementation of community-based Adherence Clubs for stable antiretroviral therapy patients

Grimsrud A, Sharp J, Kalombo C, Bekker LG, Myer L. Implementation of community-based Adherence Clubs for stable antiretroviral therapy patients. *Submitted December 2014 to the Journal of the International AIDS Society*

7.1 ABSTRACT

Background

Community-based models of antiretroviral therapy (ART) delivery have been recommended to support ART expansion and retention in resource-limited settings. However, the evidence base for community-based models of care is limited. We describe the implementation of community-based Adherence Clubs (CACs) at a large, public-sector facility in peri-urban Cape Town, South Africa.

Methods

Starting in May 2012, stable ART patients were down-referred to CACs. Eligibility was based on self-reported adherence, >12 months on ART, and viral suppression. CACs were facilitated by four community health workers (CHWs) and met every eight weeks for group counselling, a brief symptom screen and distribution of pre-packed ART. The CACs met in community venues for all visits including annual blood collection and clinical consultations. CAC patients could send a patient-nominated treatment supporter ("buddy") to collect their ART at alternate CAC visits. Patient outcomes [mortality, loss to follow-up, and viral rebound (>1,000 copies/mL)] during the first 18-months of the programme are described using Kaplan-Meier methods.

Results

From June 2012 to December 2013, 74 CACs were established, each with 25-30 patients, providing ART to 2,133 patients. CAC patients were predominantly female (71%) and lived within 3km of the facility (70%). During the analysis period, 9 patients in a CAC died (<0.1%), 53 were up-referred for clinical complications (0.3%) and 573 CAC patients sent a "buddy" to at least one CAC visit (27%). After 12 months in a CAC, 6% of patients were lost to follow-up and fewer than 2% of patients retained experienced viral rebound.

Conclusion

Over a period of 18 months, a community-based model of care was rapidly implemented decentralising more than 2,000 patients in a high prevalence, resource-limited setting. Further research is needed to support down-referral sooner after ART initiation and to describe patient experiences of community-based ART delivery.

7.2 INTRODUCTION

Models of care for ART delivery have evolved considerably over the last decade of ART provision in resource-limited settings. Services have been decentralised from hospitals to primary care facilities and tasks shifted from doctors to nurses and community health workers (CHWs) [6]. However, we are dependent on a limited number of models of care with 95% of HIV services provided within health facilities [3, 225]. To support the ambitious targets and accelerated pace of ART expansion, further adaptations are needed [3]. Health system changes are also necessary to improve retention in care especially where severe congestion of health facilities is occurring [7]. To this end, decentralising at least 30% of HIV services into communities has been recommended [3].

Community-based models of care for stable patients present one such model, designed to make ART delivery more efficient for the health system and provide appropriate support to encourage long-term retention of patients [151]. However, the evidence from community-based models of care is limited. In the recent review on decentralisation, the three community-based models of care were limited to programs providing home-based ART delivery [153, 167, 168, 171, 174]. While the results suggest that community-models can have comparable outcomes to facility-based models, the scalability of home-based ART models is debatable and such models do not encourage patient self-management, a key level of task shifting required for retention in care [41].

The adherence club model of care was designed to support ART maintenance for groups of stable patients in a CHW-facilitated model with peer-support and increased patient self-management [43, 143]. The success of an early pilot project in Cape Town [178], led to the model of care being adopted by the City of Cape Town and Western Cape Government Department of Health (DOH) [143]. From 2011, facility-based Adherence Clubs were implemented across Cape Town [43, 143]. The Gugulethu adapted the adherence club model to local conditions by shifting the service away from health facilities to be community based. Stable patients were down-referred to community-based adherence clubs (CACs) and managed by CHWs. Adherence clubs are expected to have advantages both for patients and the health system [252]. For patients, they are trying to reduce costs, both in the time it takes to receive treatment and support, and in money reducing transport costs by providing care closer to home and taking less time away from work and family commitments. For the health system, adherence clubs aim to empower the patient to manage their condition, which thus decreases the workload on the health system and improves patient outcomes. By supporting increased patient self-management, the clinically trained staff has more time to deal with new and complicated ART patients and facilitates are not crowded by patients who do not require clinical care. Here we describe the early outcomes and lessons learned from our experience implementing the CACs given the limited evidence base for community-based models and the push to further decentralise ART delivery.

7.3 METHODS

Adherence clubs were implemented within the Hannan Crusaid Treatment Centre (HCTC) at the Gugulethu CHC in Cape Town, South Africa. The ART programme at the HCTC is a well-characterised, large, public-sector service that has been described in detail previously [16, 249, 253]. The HCTC receives support from the Desmond Tutu HIV Foundation and peer counsellor support from the Sizophila programme [16, 57]. In Table 7.1, key features of the standard of ART care at the CHC is compared with the CAC model. Implementation of the CACs is described in detail covering the six core components of the WHO health systems framework [254].

7.3.1 CAC eligibility and referral

ART Adherence Clubs were designed to decongest facilities and support stable ART patients [43, 143]. Stable patients were voluntarily down-referred to the CACs. Patients were considered "stable" if they have been adherent on the same ART regimen for >12 months, had two consecutive undetectable (<400 copies/mL) viral loads, and did not have any other medical conditions requiring more frequent follow up. Individual patient counselling at the time of referral described the benefits of CAC model, a description of the visit schedule and how to access clinical care outside of CAC visits as necessary.

Table 7.1 Comparison of Standard of Care and CACs for the management of ART patients

	Standard of Care (CHC)	Community-based Adherence Clubs (CACs)
Setting	Clinic based	Community based
Patient profile	All ART patients	Stable patients
Key personnel	Doctors/nurses	CHW
Frequency of visits	2 monthly	2 monthly
Frequency of clinical consultations	2 monthly (every visit)	12-monthly
Location of clinical consultations	CHC	Community-based
Emphasis of patient contacts	Detecting clinical complications	Treatment adherence, patient wellness
Units of care	Individual patient	Groups of 25-30
Peer-based support	No emphasis	Strong emphasis
Patient self-management	Minimal emphasis	Strong emphasis
Frequency of laboratory monitoring	6-12 monthly	12-monthly
Management of clinical complications	On-site	Up-referral to CHC
ART packing and dispensing	Packed at the CHC pharmacy, dispensed from pharmacy	Pre-packed by central dispensing unit, dispensed at CAC visit
Treatment buddy	Patients attend the CHC and collect ART themselves	ART can be collected by a treatment buddy

7.3.2 Community-based Adherence Clubs (CACs) venues

The adherence club model was adapted to reduce congestion in the CHC deliver care in the local community as a result of congestion in the CHC and to provide ART within the community. The first clubs met in a separate building at the CHC. Starting in May 2013, Adherence Clubs were transitioned from being facility-based to being located at community venues. From June 2013, the Clubs were all CACs meeting at a community-based organisation (CBO) facility approximately 300 meters m from the CHC. From April 2014, CACs relocated to a room within the municipal community centre located approximately 450 meters m from the CHC. Daily transportation by one of the CHC vehicles is provided for the CAC CHWs, the pre-packed ART, the CAC registers and, on a phlebotomy or clinical club day, the CAC nurse.

7.3.3 CAC operations

Recruitment for CACs began in May 2012 and the first club met in June 2012. Initially there was one Club per day expanding to two Clubs per day as the programme grew. Each club had approximately 25-30 patients who met every two months (eight-weeks). At each CAC visit, there was a group counselling session, a brief symptom screening and distribution of ART. The group counselling sessions focused on content relevant to stable patients on ART such as safe conception and was facilitated by the CHW. The CHW weighed all patients and asked administered a brief screening questionnaire on systemic well-being. CAC sessions were facilitated by a CHW with a standard Club visit lasting approximately 60 minutes. Annual visits for phlebotomy and clinical consultations took longer (maximum three hours) due to the time taken for each patient to be seen by the club nurse. At the four-month Club visit monitoring blood samples were drawn and this was repeated annually. A clinical consultation with a nurse occurred at the 6-month Club visit and was then repeated annually.

All of the CAC ART was pre-packed off-site at a central pharmacy. Patients received 2-months of pre-packed ART at their CAC visit. During the October/November visit, four-months of pre-packed ART was distributed to CAC members to support migration over

the holiday period [255]. Therefore, most CACs met five times per year. and 6 monthly prescriptions were provided in August/September and February/March. The group counselling session in the October/November CAC visit focused on how to ensure adherence to ART when travelling and how to access ART elsewhere should a patient not return to Gugulethu for any reason.

Patients who were late for their CAC visit had a grace period of five working days to collect their ART and remain in a club. CAC patients who were late for their CAC would return to the CAC CHWs at the CHC for either collection of their ART if they were within the grace period or up-referral to the CHC is they were later than five working days. Patients were also up-referred if they were no longer stable. This includedInstability included development of a condition that required more frequent clinical consultations (e.g. tuberculosis), the need to switch regimens or viral rebound.

A patient-nominated treatment supporter or "buddy" could be sent to every alternate CAC visit to collect the CAC patient's ART. The buddy would arrive at the CAC with the patient's clinic card, collect their ART and the visit would be recorded in the CAC register as a buddy collected visit in place of where the patient's weight and symptom screen would typically be captured. Patients could nominate more than one buddy and the specific details of who the buddy was were not routinely collected.

7.3.4 CAC Monitoring & Evaluation

CAC data were recorded in a paper register with one register per CAC. At each CAC visit, the weight of each patient and results of the brief symptom screen were recorded. A summary of the CAC data (number of patients attended, number of patients up-referred, number of patients who sent a buddy) was completed by the CHW following each CAC visit and monthly group level reports were compiled for the DOH. Standard individual patient files at the CHC of CAC members were only used at the annual clinical visit. When a patient was down-referred to a CAC, the CAC number was placed on the CHC patient file so that clinicians could determine where the patient was receiving ART.

7.3.5 Human resources and management

CACs were CHW-managed with support from clinical staff at the CHC. The CHWs had varying levels of education and experience as part of the Sizophila peer-counselling programme [16, 57]. Each of the four CHW's were responsible for managing between 12 and 18 CACs. The specific responsibilities of a CAC CHW included calling all CAC patients before their first CAC visit, completing club registers, compiling CAC statistics monthly, completing the brief assessment of CAC patients (weighing and symptom screening) on their CAC day, facilitating the group counselling session on CAC days, checking with the pharmacist that pre-packed ART was ready for each CAC patient, tracing any CAC patients who did not arrive, and recording blood results in the CAC registers.

A professional nurse was assigned as the CAC nurse rotating on a monthly basis. The CAC nurse was at the community venue for blood and clinical CAC visits approximately two days per week. If a CAC patient needed to see a clinician on their CAC visit date, the patient was referred to the CHC and had priority access to the CAC nurse.

One of the pharmacists at the CHC was responsible for the CACs. The CAC Pharmacist ensured that there was a valid script for each CAC patient and that the scripts included the CAC number and first visit date for dispensing. The central pharmacy delivered the pre-packed medication parcels to the CHC pharmacy three days before the CAC visit date to the CHC pharmacy. On the day of the CAC, the pharmacist provided all the pre-packed ART for the CAC to the CAC CHW for distribution to CAC patients.

Management of the CACs was integrated within the CHC management. The CHC clinical manager provided oversight with support from the CHC facility manager. No additional financing was required during the implementation of CACs. In December 2013, a clubs manager was appointed from the existing CAC CHW team and a new CHW was recruited to join the CAC. This position was created to support the growing programme and alleviate the administrative CAC responsibilities previously completed by the clinical manager of the CHC.

7.3.6 Analysis

Ethical approval for the collection of routine clinic data and data on adherence clubs was obtained from the Human Research Ethics Committee in the Faculty of Health Sciences at the University of Cape Town. Data were analysed using STATA 13.0 (STATA Corporation, College Station, Texas, USA). All patients down-referred to an adherence club between May 2012 and December 2013 were included in the analysis. Patients entered the analysis on the date of their first club visit. Patient outcomes were assessed at the end of 2013 (analysis closure). The primary outcome of interest was loss to follow-up (LTFU) with secondary outcomes of mortality and viral rebound also reported. LTFU was defined as having no contact at a CAC or the CHC in the first 12 weeks of 2014. For patients defined as LTFU, the date of last contact was the LTFU date. Viral rebound was defined as having a single viral load measure of >1,000 copies/mL after suppression. Patients were censored at the date of death, transfer or LTFU.

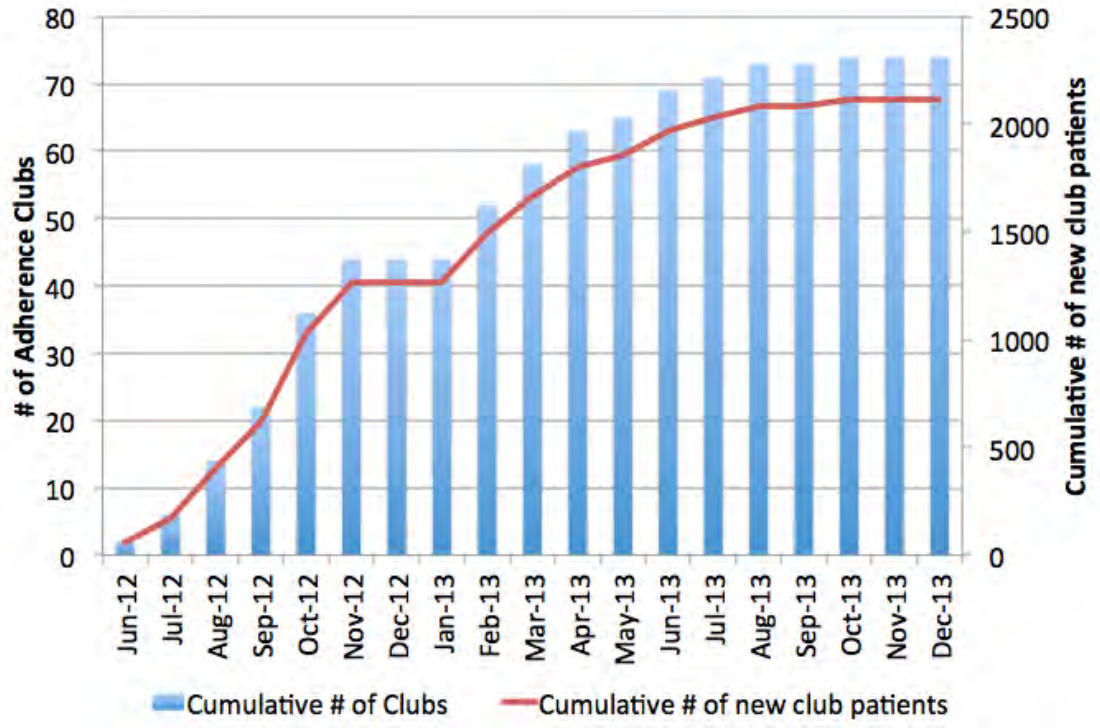
The number of new CAC patients and CACs were reported by month. Median year of club initiation is reported biannually and described by pre-ART characteristics. Patient characteristics at ART initiation (sex, age, CD4 cell count, viral load and year of initiation), CAC initiation (age, CD4 cell count, time on ART) and demographics (distance from clinic, employment status) at CAC initiation are described and summarised using appropriate summary statistics, continuous variables with medians and inter-quartile ranges (IQRs) and categorical variables as proportions. Median time to CAC initiation was calculated by pre-ART characteristics with IQRs and Wilcoxon rank-sum tests used to investigate associations with pre-ART characteristics. Time to event analysis was conducted using Kaplan-Meier methods. Kaplan-Meier graphs of the outcomes (mortality, LTFU, and viral rebound) are presented and proportions reported every three months.

7.4 RESULTS

Over an 18-month period, 2,113 patients were decentralised to one of 74 Community-based Adherence Clubs (Figure 7.1). During this same period, 2,776 patients were

initiated onto ART at the CHC. By December 2013, approximately one-third of the CHC patients were managed in a CAC. CAC patients were predominantly female (71%), lived within three kilometres of the CHC (72%) and unemployed (58%) (Table 7.2). The median pre-ART CD4 cell count was 134 cells/μl and 32% of CAC patients had been on ART for 6 years or longer at the time of joining a CAC. At the time of joining a CAC, the median age was 39 years and the median CD4 cell count was 517 cells/μl.

Figure 7.1 Implementation of Community-based Adherence Clubs between June 2012-December 2013.



The median time from ART initiation to CAC uptake was 4.4 years (IQR 2.5-6.6) (Table 7.3). For CAC patients who initiated ART in 2011 and 2012 when ACs were available, time to CAC initiation was 1.6 (IQR 1.4-1.9) and 1.2 (IQR 1.1-1.3) years, respectively. The median year of ART initiation among CAC patients increased from 2007 (IQR: 2005-2009) among those joining a CAC during 2012, to 2009 (IQR: 2006-2011) in the first half of 2013 and 2011 (IQR: 2010-2012) and in the latter half of 2013 (results not shown).

During the study period, nine patients in a CAC died (<0.1%) (Figure 7.2A), 53 were up-referred to the CHC for clinical conditions (0.3%) and 573 CAC patients sent a "buddy" to at least one club visit (27.1%). LTFU among CAC patients was 2.6% (95% CI 2.0-3.4), 3.9% (95% CI 3.1-4.8) and 6.2% (95% CI 5.1-7.4) at months 6, 9 and 12, respectively (Figure 7.2B, Table 7.4). Kaplan-Meier estimates of viral rebound were 1.4% (95% CI 1.0-2.0) at 6-months and 1.7% (95% CI 1.2-2.4) at 12-months (Figure 7.2C, Table 7.4). Overall retention on ART was 97.2% (95% CI 95.4-97.8) at 6-months and 93.5% at 12-months (95% CI 92.2-94.5). In Chapter 8, further outcomes from CACs are presented.

Table 7.2 Characteristics and demographics of Community-based Adherence Club patients pre-ART and at time of Club start

	Adults (≥16 years) n = 2,113
Gender, *n* (%)	2,113 (100)
Female, n(%)	1,489 (70.5)
Age at Club start (years), median (IQR)	38.8 (34.0-44.5)
Age categories at Club start (years), *n* (%)	
16-24	38 (1.8)
25-34	593 (28.1)
35-44	974 (46.1)
≥45	508 (24.0)
CD4 cell count at Club start (cells/μl), *n* (%)	2,109 (99.8)
Categorical, *n* (%)	
<200	49 (2.3)
200-399	502 (23.8)
400-599	846 (40.1)
600-799	439 (20.8)
≥800	272 (12.9)
Median (IQR)	517 (396-669)
Pre-ART Viral load, $\log_{10}$ copies/mL, *n* (%)	1,588 (75.2)
Median (IQR)	4.8 (4.3-5.2)
Years on ART at Club start, median (IQR)	4.6 (2.5-6.6)
Categorical, n (%)	
<1.5 years	211 (10.0)
1.5 – 3 years	465 (22.0)
3 – 4.5 years	407 (19.3)
4.5 – 6 years	347 (16.4)
6 – 7.5 years	407 (19.3)
≥7.5 years	276 (13.1)
Distance from the CHC, n(%)	1,392 (65.9)
<1 km	463 (33.2)
1-3 km	540 (38.9)
3-5 km	254 (19.0)
>5 km	12 (9.1)

Table 7.3 Median time to Community-based Adherence Club initiation by pre-ART characteristics

	Median time,	p-value
Overall	4.4 (2.5-6.6)	
Gender		
Females	4.5 (2.5-6.7)	0.262
Males	4.3 (2.4-6.5)	
Age, (years)		
16-24	4.1 (2.5-6.4)	0.013
25-34	4.8 (2.6-6.7)	
35-44	4.2 (2.5-6.6)	
≥45	3.8 (2.3-6.2)	
CD4, (cells/μl)		
<49	5.9 (3.5-7.2)	<0.001
50-99	5.4 (2.3-7.1)	
100-199	4.8 (2.9-6.5)	
≥200	2.7 (1.7-4.8)	
Missing	*3.7 (1.8-6.6)*	
Year of initiation		
2002 - 2004	8.6 (8.2-9.2)	<0.001
2005 - 2007	6.4 (5.7-7.1)	
2008 – 2010	3.3 (2.6-4.0)	
2011 – 2012	1.4 (1.2-1.7)	

Figure 7.2 Kaplan-Meier plots of Community-based Adherence Clubs (a) Morality, (b) Loss to follow-up, and (c) Viral rebound

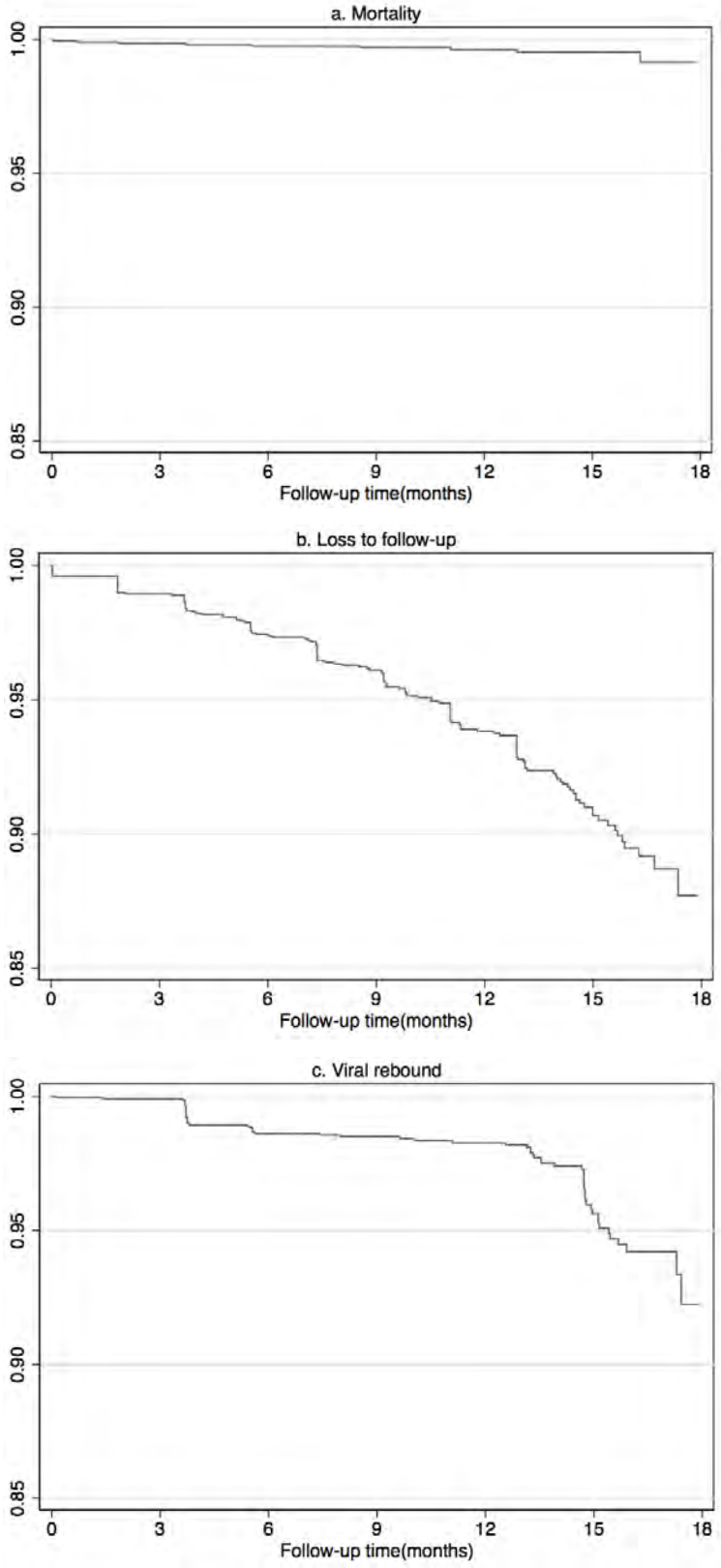


Table 7.4 Kaplan-Meier estimates of mortality, loss to follow-up and viral rebound by duration of follow-up after Community-based Adherence Club initiation±

Duration of follow-up	n (%)	Mortality % (95% CI)	Loss to follow-up % (95% CI)	Viral rebound§ % (95% CI)
3 months	2,078 (98.3)	0.1 (0.1-0.4)	1.0 (0.7-1.6)	0.1 (0.1-0.4)
6 months	1,925 (91.1)	0.2 (0.1-0.6)	2.6 (2.0-3.4)	1.4 (1.0-2.0)
9 months	1,602 (75.8)	0.3 (0.1-0.7)	3.9 (3.1-4.8)	1.5 (1.1-2.1)
12 months	1,170 (55.4)	0.4 (0.2-0.8)	6.2 (5.1-7.4)	1.7 (1.2-2.4)
15 months	572 (27.1)	0.5 (0.2-1.0)	9.3 (9.9-11.0)	4.4 (3.3-5.8)
18 months	63 (3.0)	0.9 (0.3-2.2)	12.3 (9.7-15.5)	7.8 (5.2-11.6)

±Estimates are from time of Community-based Adherence Club initiation
§ Viral rebound is defined as a single viral load measure above 1,000 copies/mL

7.5 DISCUSSION

Over a period of 18 months, more than 2,000 stable ART patients were successfully decentralised from a doctor-driven primary health care clinic to a community-based model of care where they were managed by four CHWs. We adapted the adherence club model to be community-based with all visits occurring out of the facility. CAC patients accessed ART and received annual clinical consults in the community, thus decongesting the primary health care facility. The size and scale-up of the CAC model is unprecedented, with implementation occurring more rapidly and the volume of patients much larger than previous models of care described [177, 178].

This model of care exemplifies the substantial paradigm shift in ART delivery over the past decade from doctor-led facility-based care towards decentralisation of care and task shifting of patient care responsibilities. When ART became publically available in 2004, programs were largely individualised, hospital-based and doctor-led [42]. In South Africa, task shifting has included increasing the number of nurses trained to initiate ART from 250 in February 2010 to 23,000 by May 2013 [256]. Concurrently, ART services have been increasingly decentralised with the more than 3,500 facilities supporting ART provision by mid-2013 [15, 256]. The findings of our study highlight that further decentralised community-based models with task shifting to CHWs can successfully support ART maintenance and encourage patient self-management.

Increasing patient self-management is crucial for ART programs to expand and for HIV to be successfully managed as a chronic condition [257].

Patients in the CACs had high levels of retention and virologic suppression. At 12-months, retention on ART was 94%, LTFU was 6% and 2% of patients had experienced viral rebound. These are promising outcomes and demonstrate that the majority of patients retained in the community model were adherent and virally suppressed. Retention in care was less than the 97% reported from the pilot study of facility-based Adherence Clubs [178]. Limited outcome data are available from other community-based programs with most community-models providing home-based ART delivery [154, 155]. The exception is the community adherence group (CAG) model in Mozambique with 98% retention in care after 12-months [177].

Our findings should be considered in light of a number of limitations. It is difficult to determine the generalizability of our findings as the context in which these innovative models of care are implemented is of critical importance. We implemented a novel model of care in a high-prevalence site with an existing peer-counselling programme with considerable NGO support. In addition, the site had a well functioning pharmacy and logistics system without ART stock-outs during the study period. It is difficult to gauge the transferability of our model to other settings, but our results highlight that its feasibility should be considered elsewhere. Furthermore, flexibilities within the model allow for adaptations to local contexts. Models of ART delivery are not a one-size-fits-all solution [151]. Adaptations to local context will therefore be necessary for broader implementation. The focus of this analysis was limited to early outcomes and more research is necessary to assess factors associated with retention in this model of care delivery with long-term outcomes of decentralized patients. In addition, the impact of decentralizing patients on the workload of the CHC is not assessed.

We present key factors and challenges that contributed to implementation success based on our experiences (Table 7.5). A cohesive team comprising the CHW, pharmacist and clinic management team worked as a collective despite having different line managers. It was essential that all clinic staff bought into the benefits of the model and trusted that patients could be successfully managed outside of the traditional

model of care and clinic facility. Second, policies allowing ART to be distributed within the community were agreed by the provincial, sub-district and facility teams and could therefore be used. Furthermore, CACs received a reliable supply of ART. Without a reliable drug supply, patients may not trust a community model of care [43]. The CHWs involved in CACs were part of a well-established cadre of staff at the CHC and played a pivotal role in providing quality treatment support to CAC members.

A fundamental factor to the success of the CACs was that patients receiving ART within the community were regarded as an extension of the CHC with the facility continuing to assume full responsibility and accountability for AC patients' care [151]. Since the CHC did not routinely see the patients receiving ART in the community-based model, these patients could become easily forgotten and dismissed as not the responsibility of the CHC. It was difficult to engage staff that were not dedicated CAC staff to support CAC patients in CAC activities such as rescripting. This echoes challenges previously described in the literature where health personnel are trained within a hierarchical framework of health care delivery and do not provide a supportive environment for CHWs [46, 258]. Ongoing and sustained efforts are needed to emphasise that CAC patients .

Our experience of implementing community-based ART delivery was not without challenges (Table 7.5). The location of the CACs within the community had to shift between a CBO facility to a municipal community centre. A long-term standing agreement with the municipal venue is still underway requiring negotiation at the level of the city and the community. While in principal the DOH is supportive of expanding community-based ART delivery, in practice there have been significant barriers to overcome. A unique challenge of community-based delivery models is the physical location outside of existing health facilities. Any upgrades or maintenance at community venues is not covered within the DOH budgeting and it is unclear if extending responsibilities of staff to outside of the CHC is within their contractual agreements. Being located outside of the primary care facility also provides daily logistical challenges due to transportation of materials between the community facility and the primary care facility. In addition, with limited resources available at the

community facility, CAC CHWs frequently use their personal cell phones to follow-up with patients and contact the CHC.

Table 7.5 Key factors and challenges to implementation success of the CAC model

	Factor for implementation success	Challenge for implementation success
Community-based models as an extension of the facility	Strong bi-directional referral pathways between facility and community-based models	Patients in community-based models not viewed as the responsibility of the facility (i.e. reluctance to assist with rescripting of CAC patients)
Location	Stable patients managed outside of health care facility	Ensuring access to a clean and appropriate community-based facility
Staffing	Cohesive, multidisciplinary team	All staff have separate line managers
ART distribution within the community	ART distribution by CHWs supported by the pharmacy	Policies regarding dispensing and distribution
ART supply	Reliable, uninterrupted supply	Frequent shortages in many areas of the country
Resources for community-based ART delivery	CHWs using their personal cell phones	Limited resources within the community venue and distance to CHC for supplies

Adaptation of the CAC model will be necessary for further implementation. The frequency of CAC visits, the window period for late ART collection by CAC patients and the type of symptom screening completed at CAC visits can all be adapted to align with local policy. While we utilised a central pharmacy for the CAC ART, this component of the model could be adapted and ART packing done at the facility level. It is recommended that the CAC model be implemented over time, allowing for both patients and staff to see the benefits while being reassured that the model can adequately support stable patients without undue risk. It is crucial that the CACs and all community-based delivery models be viewed not just as a response to the high patient volume but as beneficial and even preferable to patients [151]. Community-based models of care allow patients to return to normal life and increase their self-management increasing the effectiveness of ART delivery [42, 134].

While there is an urgent need for ongoing research to optimise community-based ART delivery, our implementation findings support continued expansion of community-

based ART delivery in high prevalence, resource-limited settings. The adherence club model was successfully adapted, decentralised and implemented to provide community-based care, and it is novel that our model supported ART maintenance exclusively in the community. Additional data and shared experiences from innovative community-based models of care are needed to support long-term ART retention as ART cohorts in resource-limited settings continue to expand and mature.

7.6 ACKNOWLEDGEMENTS

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7.6.1 Author contributions

AG was responsible for the statistical analysis and writing of the manuscript. AG, JS, CK, LGB and LM contributed to the plan of analysis and interpretation of the data. All authors commented on drafts of the manuscript and approved the final version.

Chapter 8. Community-based Adherence Clubs for stable antiretroviral therapy patients: Outcomes from Gugulethu, South Africa

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8.1 ABSTRACT

Background

There are few data on patient outcomes from community-based models of antiretroviral therapy (ART) delivery. We describe outcomes of ART patients decentralised to community-based Adherence Clubs (CACs) and compare these to patients on ART at the community health centre (CHC).

Methods

The analysis included 8,150 adults initiating ART from 2002-2012 at a public sector clinic in Gugulethu, South Africa followed until the end of 2013. From June 2012, stable patients (ART >12 months, supressed viral load) were referred to CACs. Kaplan-Meier methods estimated time to outcomes stratified by gender and age (youth: 15-24 years of age and older patients: >25 years of age). LTFU was compared between CACs and facility-based care using proportional hazards models with time-varying covariates and inverse probability weights of CAC participation.

Results

Of the 2,113 patients (68.8% female, 7.4% youth) decentralised to a CAC, 94% were retained on ART after 12-months. In multivariate models of CAC patients, LTFU [(adjusted hazard ratio) aHR: 2.17, 95% CI 1.26-3.73] and viral rebound (aHR 2.24, 95% CI 1.00-5.04) were twice as likely in youth compared to older patients. Among CAC patients, no difference in the risk of LTFU or viral rebound was found by gender (p-values 0.613 and 0.278, respectively). CAC participation reduced LTFU by 67% (aHR: 0.33, 95% CI 0.27-0.40) compared to facility-based care, and this reduction persisted when stratified by patient demographic and clinic characteristics.

Conclusion

Community-based Adherence Clubs appear to be associated with a decreased risk of LTFU compared to facility-based care. More research is needed on how to expand the role of community-based ART services to support long-term retention.

8.2 INTRODUCTION

The scale-up of antiretroviral therapy (ART) to 13.6 million people in resource-limited settings in the past decade has been unprecedented [3]. Despite this, treatment coverage in adults is estimated at only 38% [3]. South Africa's ART programme exemplifies these trends of rapid implementation and unmet treatment needs. Between 2010 and 2013 a third of all new ART patients globally were in South Africa [26] and today the programme provides ART to more than 2 million people [4]. However, with 6.4 million people in the country living with HIV [4], further scale-up of ART is needed.

In addition to the challenge of accelerating ART expansion, attrition on ART represents a substantial hurdle [3, 77]. Loss to follow-up (LTFU) is a considerable threat to the success of ART programmes with 20-30% of patients estimated to be lost from the programme after 3-years [24, 39, 56]. The risk of LTFU varies across sub-groups with higher rates generally higher in men [132, 144-146] and younger patients [131, 132, 135, 147].

Against this background, the 2013 World Health Organization (WHO) guidelines recommended earlier ART initiation [28, 29]. To facilitate this expansion and improve retention in care, reorientation of ART delivery through decentralisation of services into communities and the shifting of specific tasks related to ART provision to different cadres of health care workers has been proposed [28]. Recent systematic reviews from models with task shifting concluded that patients supported by nurses or community health workers (CHWs) have comparable outcomes to those supported by doctors [152, 154]. Evidence from models where treatment is decentralised into communities is limited with most models providing home-based ART delivery [153, 155].

There is burgeoning interest in community-based ART delivery with pilot studies reporting favourable outcomes [43, 151, 177]. Community-based Adherence Clubs (CACs) facilitated by CHWs were implemented to provide effective ART support to stable ART patients. They were designed both to decongest the local primary health

care facility and reduce attrition by decreasing the frequency and intensity of patient visits and providing support within the community. This study describes outcomes [LTFU and viral rebound] over the first 18-months of CAC implementation in Cape Town, South Africa, and compares patient outcomes under the CAC model of care to those of patients managed in facility-based primary care.

8.3 METHODS

8.3.1 Study setting

The Gugulethu Community Health Centre (CHC) is a large primary health care facility, typical of urban public sector ART services across the region. It serves a community of predominantly low socioeconomic status with a high HIV seroprevalence. The local ART service has been described in detail previously and in Chapters 6 and 7 [57, 63, 249, 253]. Briefly, the service began providing ART in 2002 based on South African national programme criteria for ART initiation and regimens. CD4 cell count and viral load were monitored before ART initiation, after 4 months on ART and then repeated annually. At each visit patients had a clinical consultation with either a medical doctor or professional nurse followed by adherence support from a counsellor before proceeding to the pharmacy to collect their ART. Each patient was assigned to a peer counsellor who conducted pill counts at each clinic visit and provided individual and group sessions to promote high levels of adherence. For patients who defaulted, their counsellor followed up via phone or home visit. The ratio of counsellors to ART patients increased from 2006 onwards from when the total number of counsellors was limited to approximately 30 [63].

8.3.2 Community-based Adherence Clubs

The Adherence Club model of care [43, 143] and details of the implementation of community-based Adherence Clubs (hereafter referred to as CACs) in Gugulethu have been discussed in Chapter 7. Briefly, from June 2012, patients classified as stable on

ART were recruited from the CHC for down-referral or decentralisation to the CAC programme. Specific eligibility criteria were: adherent to ART based on self-report, on ART for >12 months, two consecutive suppressed viral loads (<400 copies/ml) and no active opportunistic infections. CACs met every 2 months (8 weeks) for group counselling, a brief symptom screening and distribution of pre-packed ART.

Beginning in May 2013, Adherence Clubs were relocated to a community venue where all CAC visits, including clinical consultations and blood collection, took place. A team of 4 CHWs supported CACs with a professional nurse available at the community venue for annual monitoring bloods (CD4, viral load and creatinine as necessary) and clinical consultation. CAC patients could send a patient-nominated treatment supporter or "buddy" to collect their ART at alternating CAC visits.

8.3.3 CAC evaluation

This analysis focuses on the outcomes of patients referred to CACs and compares these to outcomes of patients receiving facility-based care. Data were obtained from the prospectively collected CHC clinical database, the CAC database and the National Health Laboratory Service database. Ethical approval for collection of routine clinical data and data from CACs was obtained from the Human Research Ethics Committee at the University of Cape Town Faculty of Health Sciences. Data were analysed using STATA 13.0 (STATA Corporation, College Station, Texas, USA).

8.3.4 Definitions of outcomes

Patients were eligible for inclusion if they initiated ART before the end of 2012. Patients entered the analysis on the date of ART initiation in the CHC, contributing person time to the facility-based model of care. Patients decentralised to the CACs contributed person time to the CAC model from their first CAC visit. Patient outcomes were assessed as of the end of 2013 (analysis closure); the database closure was the 21st of March 2014 [207].

As the long-term programmatic goals of ART services are to retain patients in care and virologically suppressed over time, the outcomes of interest in this analysis were loss to follow-up (LTFU) and viral rebound. Loss to follow-up was defined as having no visit in the first 12-weeks of 2014 and patients were censored at the date of last contact with either health care service. Viral rebound was defined as a single viral load measurement >1000 copies/ml after previous suppression (<1000 copies/ml).

8.3.5 Statistical analysis

Pre-ART characteristics of all patients by model of delivery were summarised; continuous variables are reported with medians and inter-quartile ranges (IQRs) and categorical variables as proportions with 95% confidence intervals (CI). Time-updated CD4 and viral load values were available at each patient contact, defined as the closest measure within a 2-month window of each patient contact. P-values from Pearson's chi-squared and Wilcoxon rank-sum tests were calculated to investigate differences between patients in facility-based care at the CHC versus those attending CACs.

Time to LTFU and viral rebound from first CAC visit were analysed by gender and age [youth (16-24 years) and adults (≥25years)] and differences investigated with the log-rank test. A series of proportional hazards models were used to model relative hazards of different patient outcomes adjusting for demographic, programmatic and clinical variables including time-updated laboratory values. Results are presented as hazard ratios (HR) or adjusted hazard ratios (aHR) with 95% CI.

Since allocation to the CAC model of care was not randomly assigned, a number of approaches were undertaken to compare LTFU with the CHC. In the primary results (Approach 1), we used proportional hazards models with the treatment (being in a CAC versus CHC) and time-updated laboratory values as time-varying covariates to model time to LTFU [253, 259]. In addition, we modelled the probability of CAC participation using inverse probability weighting (IPW) [260] and incorporated this weight into the proportional hazards models. To calculate the IPW we used a dataset restricted to patients for whom a CAC was available after 12 months on ART (i.e. patients initiating

after June 2011). Stratified hazard ratios by age, gender, year of initiation and CD4 cell count at ART initiation were also generated to assess if LTFU differed by subgroup.

We ran a series of secondary analyses to examine different methods of accounting for selection biases when examining the association between model of care and LTFU. In Approach 2, proportional hazards models without IPW adjusting for the probability of being in a CAC were used. Further, Cox's models without (Approach 3) and with the IPW (Approach 4) were restricted to patients who were in care 12 months after ART initiation. We also used the IPW with logistic regression to model LTFU (Approach 5) [178]. Approach 6 generated propensity scores and the average effect of the treatment on the treated was assessed [165, 261, 262].

8.4 RESULTS

8.4.1 Description of Adherence Club patients

A total of 2,113 patients were decentralised to a CAC between May 2012 and December 2013 contributing a total of 2098 years of person-years of follow-up to CACs [median 1.1 years, interquartile range (IQR) 0.75-1.26]. CAC patients represented a quarter of all patients ever initiated onto ART at the site (26%). The time in the CAC was 6.5% of the total person-years of follow-up in the analysis. Patients referred to CACs had similar pre-ART demographic and clinical characteristics to patients retained in facility-based care (Table 8.1). However systematic differences between the two groups were apparent following ART initiation: before down-referral, CAC patients were more likely to achieve viral suppression (viral load >1000 copies/mL) after 4 and 12 months on ART compared to patients managed in facility-based care at the CHC (p-values <0.001). After 12-months on ART, the median CD4 cell count was higher in CAC patients versus CHC patients (320 cells/μl vs. 295 cells/μl, p-value <0.001)(Table 8.1).

8.4.2 Outcomes of patients referred to CAC's

Loss to follow-up from CACs

Loss to follow-up among CAC patients was 5.6% and 6.4% at 12-months after the first CAC visit, for men and women respectively (Figure 8.1A; p-value 0.961). LTFU was higher for youth (ages 16-24) than adults (patients ≥ 25), with 9.1% and 5.9% LTFU at 12 months after referral to CACs, respectively (Figure 8.1B, p-value 0.022). When stratified by gender and age, youth had higher LTFU than adults for both men and women (12 month LTFU: 7.7% vs. 5.5% for men and 9.2% vs. 6.1% for women) (results not shown).

In proportional hazards models of patients referred to CACs, the hazard of LTFU was higher in youth vs. adults (HR: 1.67, 95% CI 1.00-2.79), and in patients who initiated ART in 2002-2004 vs. after 2008 (HR: 1.64, 95% CI 1.00-2.69) (Table 8.2). In adjusted models of CACs, youth were twice as likely to be LTFU compared to adults (aHR: 2.17, 95% CI 1.26-3.73). An increased risk of LTFU was also found for patients who initiated ART with a CD4 cell count ≥200 cells/μl (aHR 2.25, 95% CI 1.36-3.72) and a decreased risk in patients with a CD4 cell count <50 cells/μl (aHR: 0.52, 95% CI 0.29-0.93) compared to patients initiating with a CD4 cell count between 50-199 cells/μl in CACs. Patients in CACs who initiated ART between 2011-2012 had a 58% decrease in the risk of LTFU (aHR: 0.42, 0.22-0.86) compared to those initiating between 2008-2010. No difference in the risk of LTFU was found by gender (aHR: 0.90, 95% CI 0.61-1.34) or in patients who sent a buddy to collect medications (aHR 0.89, 95% CI 0.59-1.36).

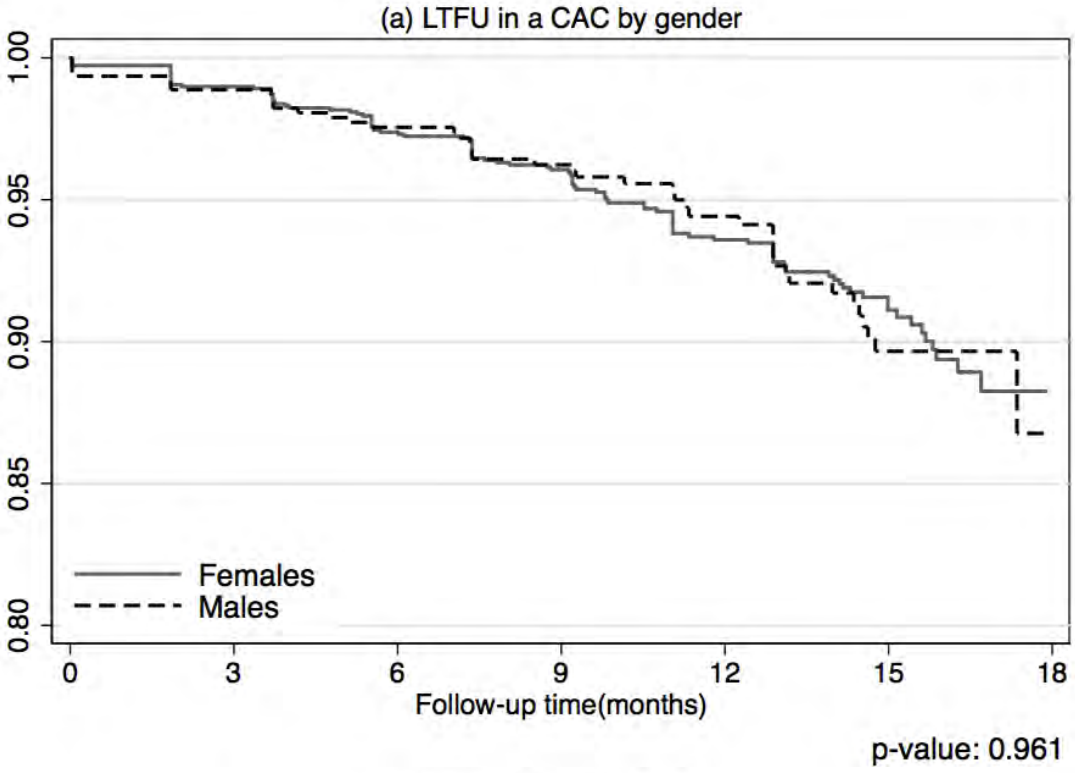
Viral rebound in CACs

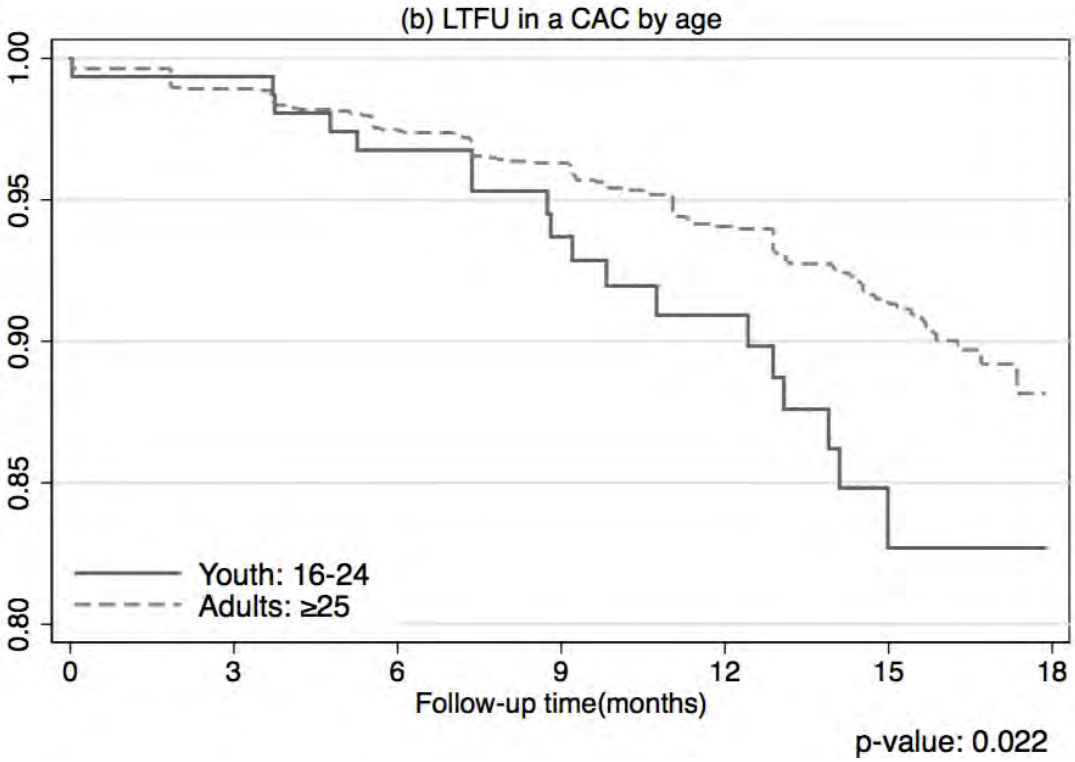
No difference in viral rebound was found by gender (Figure 8.2C, p-value 0.173) or age (Figure 2D, p-value 0.194). After 12 months in a CAC, 2.2% (95% CI 1.3-3.9) and 1.5% (95% CI 1.0-2.3) of males and females had experienced viral rebound (results not shown). No associations were found between pre-ART characteristics and risk of viral rebound in univariate models (Table 8.2). In final models of CACs, youth were twice as likely to experience viral rebound compared to adults (aHR: 2.24, 95% CI 1.00-5.04).

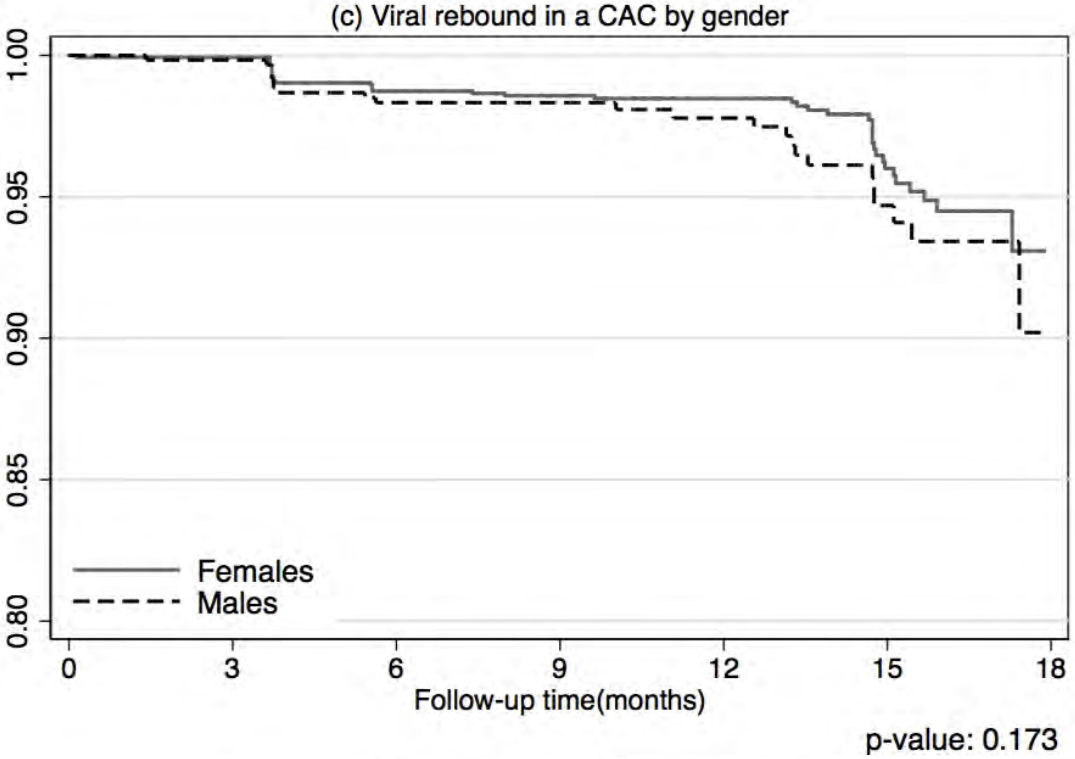
Table 8.1 Description of patients by pre-ART characteristics and changes to viral load and CD4 cell count over 12-months by model of care

	Community Health Centre only (n=6,037)	Community Health Centre + CAC (n=2,113)	Total (n=8,150)	p-value
Pre-ART characteristic				
Gender				
Females, n(%)	4,091 (68.8)	1,489 (70.5)	5,580 (68.5)	0.021
Age (years), n(%)				
16-24	728 (12.1)	156 (7.4)	884 (10.9)	<0.001
25-34	2,803 (46.4)	1,026 (48.6)	3,829 (47.0)	
35-44	1,664 (27.6)	656 (31.1)	2,320 (28.5)	
≥45	842 (14.0)	275 (13.0)	1,117 (13.7)	
Median (IQR)	33.2 (28.0-39.8)	33.9 (29.4-39.8)	33.4 (28.4-29.8)	<0.001
CD4 cell count (cells/μl), n(%)				
<50	893 (20.3)	275 (16.2)	1,168 (19.2)	<0.001
50-99	837 (10.0)	336 (19.8)	1,173 (19.2)	
100-199	1,589 (36.1)	688 (40.6)	2,227 (37.3)	
≥200	1,083 (24.6)	397 (23.4)	1,480 (24.3)	
Median (IQR)	128 (61-198)	134 (73-195)	130 (64-197)	0.277
Missing, n(%)	*1,635 (27.1)*	*417 (19.7)*	*2,052 (25.2)*	
Viral load, log_{10} copies/mL				
Median (IQR)	4.9 (4.4-5.3)	4.8 (4.3-5.2)	4.8 (4.4-5.3)	<0.001
Missing, n(%)	*2,405 (39.8)*	*525 (24.8)*	*2,930 (36.0)*	
Year of initiation, n(%)				
2002 - 2004	372 (6.2)	191 (9.0)	563 (6.9)	<0.001
2005 - 2007	1,818 (30.1)	758 (35.9)	2,576 (31.6)	
2008 – 2010	1,847 (30.6)	803 (38.0)	2,650 (32.5)	
2011 – 2012	2,000 (33.1)	361 (17.1)	2,361 (29.0)	
Changes in viral load and CD4				
Viral suppression at 4-months, n(%)				
Supressed (VL<1,000)	3,595 (59.6)	1,781 (84.3)	5,376 (66.0)	<0.001
Viral suppression at 12-months, n(%)				
Supressed (VL<1,000)	2,677 (44.3)	1,762 (83.4)	4,439 (54.5)	<0.001
4-month CD4, (cells/μl)				
Median (IQR)	249 (159-349.5)	254 (180-341)	251 (166-347)	0.045
4-month change in CD4 (4-month - pre-ART), n(%)				
<100	1,054 (47.9)	529 (44.9)	1,583 (46.8)	0.096
≥100	1,148 (52.1)	650 (55.1)	1,798 (55.1)	
12-month CD4, (cells/μl)				
Median (IQR)	295 (198-411)	319.5 (234-422)	304 (210-416)	<0.001
12-month change in CD4 (12-month - pre-ART), n(%)				
<100	558 (29.8)	236 (20.1)	794 (26.1)	<0.001
≥100	1,316 (70.2)	936 (79.9)	2,252 (73.9)	
CD4 under 200 cells/μl, n(%)				
Always <200	1,194 (20.5)	6 (0.3)	1,200 (15.1)	<0.001
≥200	4,623 (79.5)	2,102 (99.7)	6,725 (84.9)	

Figure 8.1 Kaplan-Meier plots over the first 18-months in a Community-based Adherence Club (a) LTFU by gender, (b) LTFU by age, (c) Viral rebound by gender, (d) Viral rebound by age






(c) Viral rebound in a CAC by gender
1.00
0.95
0.90
0.85
0.80
Females
Males
0
3
6
9
12
15
18
Follow-up time(months)
p-value: 0.173

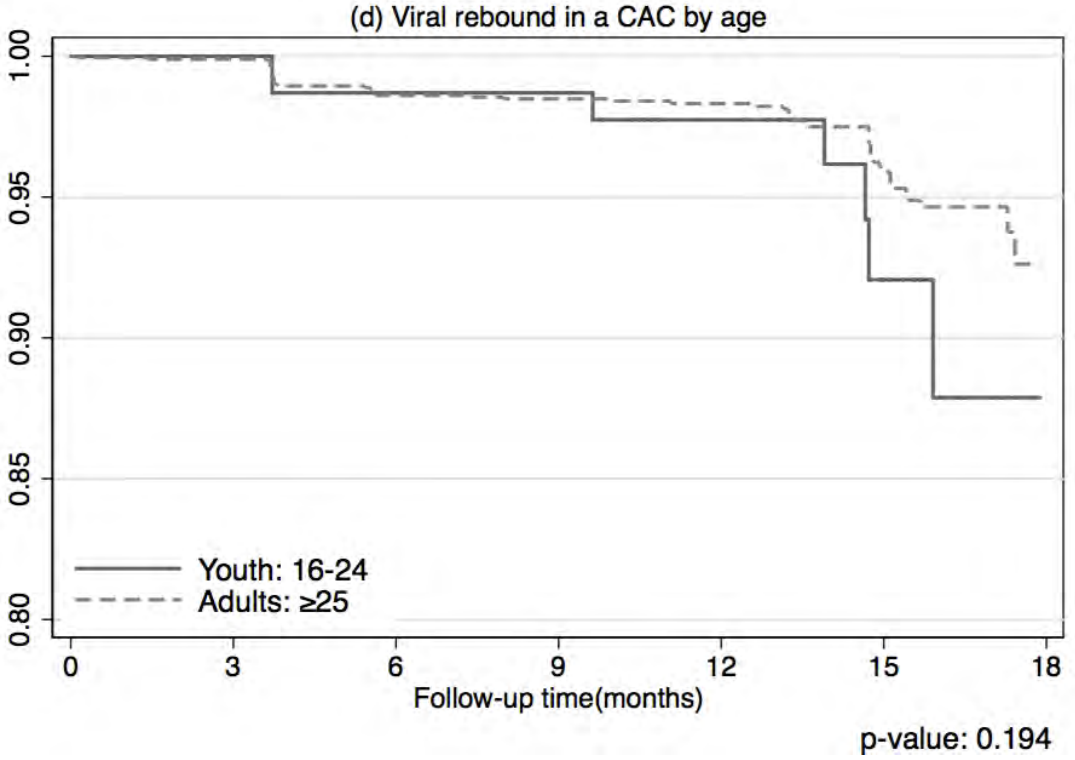

(d) Viral rebound in a CAC by age
1.00
0.95
0.90
0.85
0.80
Youth: 16-24
Adults: ≥25
0
3
6
9
12
15
18
Follow-up time(months)
p-value: 0.194

Table 8.2 Relative hazard of loss to follow-up, viral rebound and programme attrition among Community-based Adherence Club patients

Characteristic	LTFU		Viral Rebound		Programme attrition	
	Univariate HR (95% CI)	Final Model aHR (95% CI) n = 2,083	Univariate HR (95% CI)	Final Model aHR (95% CI) n = 2,088	Univariate HR (95% CI)	Final Model aHR (95% CI) n = 2,083
Age when starting ART						
Youth - 16-24 years	1.67 (1.00-2.79)	2.17 (1.26-3.73)	1.67 (0.76-3.67)	2.24 (1.00-5.04)	1.75 (1.09-2.83)	2.15 (1.27-3.64)
Adults - ≥25 years	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Gender						
Male	1.01 (0.71-1.43)	0.90 (0.61-1.34)	1.42 (0.86-2.36)	1.35 (0.79-2.30)	1.08 (0.77-1.52)	0.95 (0.65-1.39)
Year of ART initiation						
2002-2004	1.64 (1.00-2.69)	1.28 (0.70-2.32)	1.50 (0.67-3.37)	1.88 (0.78-4.51)	1.50 (0.92-2.43)	1.16 (0.65-2.09)
2005-2007	1.14 (0.79-1.64)	1.19 (0.79-1.79)	1.17 (0.66-2.05)	1.50 (0.83-2.72)	1.07 (0.75-1.53)	1.13 (0.77-1.68)
2008-2010	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2011-2012	0.77 (0.41-1.45)	0.44 (0.22-0.86)	1.16 (0.49-2.76)	0.66 (0.26-1.69)	0.82 (0.47-1.48)	0.48 (0.26-0.91)
Ever sent a buddy						
Yes	0.72 (0.49-1.04)	0.89 (0.59-1.36)	0.56 (0.30-1.02)	0.68 (0.37-1.27)	0.67 (0.46-0.96)	0.84 (0.55-1.27)
CD4 cell count at ART initiation, (cells/μl)						
<50	1.06 (0.62-1.81)	0.52 (0.29-0.93)	0.69 (0.28-1.69)	0.49 (0.19-1.25)	0.96 (0.57-1.62)	0.47 (0.26-0.83)
50-99	1.19 (0.74-1.93)	0.66 (0.40-1.10)	1.27 (0.64-2.52)	0.95 (0.47-1.94)	1.16 (0.73-1.84)	0.64 (0.40-1.04)
100-199	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
≥200	1.16 (0.72-1.84)	2.25 (1.3,-3.72)	1.06 (0.52-2.14)	1.56 (0.74-3.27)	1.08 (0.69-1.70)	2.07 (1.26-3.38)
Missing	1.27 (0.80-2.01)	0.80 (0.35-1.81)	1.03 (0.50-2.12)	1.39 (0.60-3.22)	1.18 (0.76-1.84)	0.73 (0.32-1.65)
Time-updated CD4, (per 50-unit increase)	0.67 (0.63-0.72)	0.70 (0.63-0.77)	0.84 (0.78-0.90)	0.81 (0.74-0.88)	0.67 (0.63-0.71)	0.70 (0.63-0.76)
Time-updated viral load, (copies/mL)						
Suppressed (<1,000)	1.0 (ref)	1.0 (ref)	-	-	1.0 (ref)	1.0 (ref)
Not supressed (≥1,000)	19.1 (12.8-28.7)	3.13 (1.82-5.39)	-	-	20.74 (13.95-30.84)	3.42 (2.02-5.80)

8.4.3 Comparison of LTFU in CACs versus CHC

Patients referred to CACs had a reduced risk of LTFU compared to patients managed in facility-based care in all crude and adjusted models (Table 8.3). We report on Approach 1, using inverse probability weights to estimate CAC participation and included in proportional hazard models with time-varying covariates. The inverse probability weighting model correctly classified 91% of patients (results not shown). In unadjusted models, CAC patients were 62% less likely to be LTFU compared to patients managed in facility-based care (HR: 0.38, 95% CI 0.32-0.45) (Table 3). In the final model (Model 2) also adjusting for time-updated CD4 and viral load, the CAC patients were 67% less likely to be LTFU compared to patients in facility-based care (aHR: 0.33, 95% CI 0.27-0.40). The hazard ratios of covariates in Approach 1 can be found in Supplementary Table 8.1.

In stratified models, LTFU was reduced for all patients managed in a CAC compared to facility-based care irrespective of age, gender, year of ART initiation or CD4 cell count at ART initiation (Table 8.4). The exception was for youth 16-24 years of age whose adjusted hazard of LTFU in a CAC was not significantly different from the hazard of LTFU observed under facility-based care (aHR: 0.68, 95% CI 0.37-1.22, p-value 0.197).

In secondary analyses, CACs decreased in the risk of LTFU (Table 8.3). Under Approach 3, the most conservative scenario, models were restricted to patients on ART after 12 months and the hazard of LTFU in CACs compared to facility-based care was 0.25 (95% CI 0.21-0.31) (Table 8.3). When inverse probability weights to estimate CAC participation were incorporated into this model with further restriction (Approach 4) the adjusted hazard of LTFU was 0.47 (95% CI 0.39-0.56). Propensity scores were also generated adjusting for age, gender, rate of scale-up and programme size. In all matching methods, the average treatment on the treated effect (ATT) was reduced, ranging from -0.141 to -0.641 (results not shown).

Table 8.3 Risk of LTFU in Community-based Adherence Clubs compared to the Community Health Centre

	Univariate	Model 1*	Model 2 (Final Model)±
	HR (95% CI)	aHR (95% CI)	aHR (95% CI)
Approach 1§			
Cox's model with IPW**	0.38 (0.32-0.45)	0.21 (0.17-0.25)	0.33 (0.27-0.40)
Approach 2			
Cox's model	0.38 (0.32-0.45)	0.19 (0.16-0.22)	0.29 (0.24-0.35)
Approach 3			
Cox's model with further restriction±±	0.50 (0.42-0.60)	0.16 (0.13-0.19)	0.25 (0.21-0.31)
Approach 4			
Cox's model with IPW** & further restriction±±	0.50 (0.42-0.60)	0.17 (0.14-0.21)	0.29 (0.24-0.36)
Approach 5			
Logistic regression with IPW**	0.06 (0.05-0.07)	0.08 (0.06-0.09)	0.07 (0.06-0.09)

* Adjusted for age, gender and year of ART initiation

±Adjusted for age, gender, year of ART initiation, time-updated CD4 and viral load

§Approach 1 is reported as the primary results. Restriction was done in the IPW predicting CAC participation

**IPW denotes inverse probability weighting to predict CAC participation

±±Further restriction limited the models to patients for who were retained in care after 12-months on ART

Table 8.4 Stratified hazard ratios of LTFU among Community-based Adherence Club patients vs. patients at the Community Health Centre

Characteristic		Univariate HR (95% CI)	Final Model* aHR (95% CI)
Age pre-ART			
	16-24	0.59 (0.36-0.98)	0.68 (0.37-1.22)
	25-34	0.37 (0.29-0.47)	0.32 (0.24-0.42)
	35-44	0.35 (0.25-0.48)	0.33 (0.23-0.48)
	≥45	0.35 (0.21-0.57)	0.35 (0.23-0.54)
Gender			
	Male	0.38 (0.28-0.52)	0.36 (0.25-0.51)
	Females	0.38 (0.31-0.47)	0.32 (0.25-0.41)
Year of ART initiation			
	2002-2004	0.34 (0.20-0.55)	0.30 (0.16-0.56)
	2005-2007	0.23 (0.17-0.31)	0.42 (0.31-0.59)
	2008-2010	0.14 (0.11-0.19)	0.34 (0.24-0.47)
	2011-2012	0.05 (0.03-0.09)	0.10 (0.05-0.21)
CD4 cell count pre-ART (cells/μl)			
	<50	0.35 (0.21-0.58)	0.33 (0.19-0.55)
	50-99	0.41 (0.27-0.63)	0.35 (0.22-0.55)
	100-199	0.34 (0.25-0.47)	0.30 (0.22-0.41)
	≥200	0.34 (0.23-0.51)	0.30 (0.20-0.44)

* Adjusted for inverse probability weighting of CAC participation, age, year of ART initiation, time-updated CD4 & viral load

8.5 DISCUSSION

This analysis suggests that the community-based Adherence Club model may achieve favourable programmatic outcomes for stable patients on ART in resource-limited settings. For most patient groups, the risk of LTFU was substantially reduced in the CAC model compared to facility-based care. The exception was youth; patients 16-24 years of age at ART initiation experienced no reduction in the risk of LTFU in CACs compared to facility-based care and had an increased risk of LTFU and viral rebound in the CACs compared to adults 25 years or older. Within CACs, differences in the risk of LTFU were observed by CD4 cell count and year of ART initiation while men and women had comparable LTFU, viral rebound and retention.

The CACs appeared to reduce the risk of LTFU compared to facility-based care with a two-thirds reduction in the hazard of LTFU. The hazard ratio in the final adjusted

model of 0.33 is similar to that from facility-based Adherence Clubs reporting 0.43 in modelling the hazard of LTFU or death [178]. These are novel data as previous results for models of care labelled as "community-based" are actually models of home-based care for individual patients. [167, 168, 171-175].

There is a particular concern about how to effectively provide ART to men who represent more than 40% of the HIV epidemic in South Africa [4] but have inequitable access to ART [149, 263-265]. Community-based models of ART delivery may be uniquely positioned to support men on ART [151]. Among CAC patients, outcomes did not differ by gender; a promising finding given that men consistently have worse outcomes on ART in primary care facilities [56, 226, 266]. Recent evidence from community-based drug dispensing programmes also found no difference in retention between men and women [267]. By contrast, men in the community-based adherence group model in Mozambique had twice the risk of attrition compared to women [177]. Further research into what components of community models of care can support the retention of men, whether it is being out of the health care facilities, decreasing visit frequency or some other factor, is warranted.

Youth were the only sub-set of patients that did not have a decreased risk of LTFU in CACs compared to the CHC. This finding is crucial since 40% of new infections occur in this age group [268] and adds to the current discussion of the need for managed health care transition from adolescent to adult type services [269, 270]. A renewed focus on strategies to successfully retain youth in care, both for their own health and given the potential benefits of ART as prevention in this age group, is required.

CAC patients initiating ART with higher CD4 cell counts ≥200 cells/μl had an increased risk of LTFU compared to patients with CD4 cell counts between 100-199 cells/μl at ART initiation. However, rates of LTFU in CACs among patients with CD4 cell counts ≥200 cells/μl at initiation were less than a third of those observed under facility-based care. These findings highlight that retention of patients initiating ART at higher CD4 cells is a challenge in both models of care. As the guidelines encourage healthier patients to be initiated onto ART, there must be a concurrent shift away from the common perception that ART is for sick patients [271]. Our findings of decreased LTFU

in CACs regardless of CD4 cell count at baseline and year of ART initiation calls for community-based models of care to be expanded towards achieving optimistic treatment targets and supporting long-term retention in care [3, 151].

A number of strengths and limitations must be considered in the interpretation of our findings. Our data are from a large cohort that decentralised a previously described model into the community. Data was available for comparing the CAC with facility-based care including data on time-varying laboratory values [132]. We were limited to reporting short-term outcomes over the first year of the programme. We acknowledge that the outcome LTFU represents all patients with an unknown outcome: including unascertained deaths and transfers [211], administrative LTFU and those currently interrupting treatment [239]. Further, our data are from a cohort with considerable research support and an established counsellor programme that may impact the generalizability of our findings. To assess data quality during the recent scale-up at the CHC, a random sample of patients identified to be LTFU among those initiating ART in 2011 and 2012 were selected for a folder review. Of the patients classified as LTFU, two thirds were confirmed to be LTFU, while approximately 20% were administrative LTFU and 15% were unascertained transfers. The effect of CACs on reducing LTFU is therefore likely overestimated but not entirely explained by issues of data quality.

These observational data do not provide a direct comparison of outcomes between the CACs and facility-based models of care. The major limitation is selection bias into the intervention (CACs). We used different methods to adjust for this bias [165, 178, 253, 262]. Our main results incorporated the probability of being in a CAC into models of time to LTFU thereby adjusting for this confounding. In the absence of trial data, we are dependent on the methods of observational epidemiology, which are limited by the quality of the data and measurement of factors that determine entry into a CAC and outcomes; we cannot rule out residual confounding that was unmeasured or measured with imprecision. This is a fundamental challenge of observational evaluations of models of health service delivery. In this light, it may be more appropriate to compare novel models of care such as CACs to predetermined targets for outcomes as opposed to attempting to overcome the methodological challenges of comparing them to increasingly heterogeneous patients in facility-based care. LTFU from CACs at 12

months was 6% and 98% of these patients were virally suppressed. These figures, even without comparison to other programmes, represent successful ART provision and support the CAC model of care.

Our findings on the benefits of CACs are relevant as countries look to expand ART eligibility in line with the 2013 WHO guidelines [28]. Nevertheless, questions remain about how community-based models of ART delivery can best support service expansion and retention in care. Patients were only eligible to join the programme after a year on ART, but the model is of potential benefit to patients sooner after treatment initiation especially as healthier patients access ART. Expansion of the model to include patients who previously have had inequitable access and outcomes on ART, such as women who initiate ART in pregnancy, should be considered. Since sending a buddy reduced the visit frequency for the patient and we found no difference in the outcomes for patients who sent a buddy and those who did not, further reducing the visit frequency could be desirable to patients without negatively impacting outcomes [255]. More data are needed to determine the long-term outcomes of CACs. In addition, documenting patient experiences and preferences and conducting cost-effectiveness analyses would be beneficial to scaling up the model. Further investigation into how community-based programmes could support ART at different stages of the treatment cascade, such as testing and ART initiation, are also needed.

From a policy perspective, community-based models raise questions about how to integrate ART provision allowing for patients to return to normal life and minimise the disruptions from ART delivery [42, 134]. In the context of increased availability of fixed-dose combination therapy and point of care viral load testing, policies regarding who can distribute ART and the frequency of rescripting and clinical consultations need to be reconsidered.

In summary, we found that stable patients were successfully managed by CHWs within a community-based model of ART delivery. Higher rates of retention and viral suppression were maintained in both men and women. More long-term data are needed to understand how best community-based models of care can improve retention in care with particular attention given to supporting youth. Given that ART

cohorts in high-prevalence, resource limited settings are continuing to expand and mature, community-based models of care represent a promising alternative to promote patient self-management and community involvement within ART delivery.

8.6 ACKNOWLEDGEMENTS

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8.6.1 Author contributions

AG, ML, LGB and LM contributed to the plan of analysis and interpretation of the data AG was responsible for the statistical analysis and writing of the manuscript. All authors commented on drafts of the manuscript and approved the final version.

Chapter 9. Discussion and recommendations

This chapter provides a synopsis of key findings in relation to the thesis aim and objectives. Three underlying themes are presented, summarising what we know as we enter the second decade of ART delivery in resource-limited settings. Recommendations for research, policy, programmes and services are made based on the thesis results as a combined body of work.

9.1 SYNOPSIS OF KEY FINDINGS

9.1.1 Definitions of LTFU impact estimates of outcomes

In Chapter 3, a series of different analytic approaches of LTFU were used to estimate programme outcomes addressing the first objective of this thesis. This thesis found that variations in the definition of LTFU can have an appreciable impact on estimates of outcomes. For conclusions to be drawn about ART programme effectiveness, standardisation of an approach and definition of LTFU is needed. Chapters 4-8 adopted the recommended definition of LTFU from Chapter 3.

9.1.2 Increasing LTFU observed by calendar year of ART initiation

Data from MSF cohorts in eight resource-limited countries was analysed in Chapter 4. The risk of LTFU increased with each calendar year of ART initiation, addressing objective 2a, and confirming the association previously found in South African cohorts [56]. Year of ART initiation was associated both with early LTFU in the first 12 months of ART and late LTFU over 12-72 months of follow-up. The strength of the association persisted in final models adjusted for pre-ART characteristics and programme expansion. Year of ART initiation was included in multivariate analyses in Chapters 5-8.

9.1.3 Pace of scale-up more important the programme size in relation to LTFU

To address objective 2b, two variables were used to quantify programme expansion. Programme size and rate of expansion were both related to increased risk of early (0-12 month) and late LTFU (12-72 month) among the MSF cohorts in Chapter 4. After adjusting for baseline characteristics and year of initiation, the association between programme size and LTFU was attenuated. However, the association between rate of expansion and LTFU persisted in final multivariate models. This suggests that it is not simply cohort size that is related to programme outcomes, but the pace of scale-up.

9.1.4 Higher CD4 cell counts associated with increased risk of early LTFU

The focus of Chapter 5 was on objective 2c to determine if patients initiating ART at higher CD4 cell counts had a greater risk of LTFU. Using the South African adult cohorts contributing to the IeDEA-SA collaboration with linkage to the National Population Register, corrected estimates of LTFU were higher among patients initiating ART at CD4 cell counts above ≥300 cells/μl compared to those with CD4 cell counts between 150-199 cells/μl at ART initiation. This increased risk of LTFU among patients initiating ART at CD4 cell counts above ≥300 cells/μl persisted after adjustment for programme size and rate of scale-up, as well as pre-ART characteristics and year of ART initiation. The relationship between CD4 cell counts above ≥300 cells/μl and LTFU was highest in the first three months on treatment. Given that countries are implementing the 2013 WHO guidelines and increasing the CD4 threshold for initiation to 500 cells/μl, programmes must acknowledge that patients with higher CD4 cell counts at initiation may need different models of care and support to be successfully retained on treatment [272].

9.1.5 Models of care delivery to support ART retention for stable patients

Stable patients were down-referred to the nurse-managed Green Clinic in Chapter 6 and community-based Adherence Clubs (CACs) in Chapters 7 and 8 and outcomes

compared to patients at the community health centre (CHC). Assessing the outcomes of these models was in line with objective 3a. Green Clinic patients had no difference in their risk of mortality or viral rebound, but LTFU was slightly higher compared to patients in the CHC, in final models. CACs were successfully implemented, down-referring more than 2,000 patients over 18 months to the decentralised model of care. The CACs reduced the risk of LTFU significantly and in final models patients in a CAC were 0.33 times as likely to be LTFU compared to the CHC.

9.1.6 Models of care offer risk and benefits to different sub-groups of patients

To address objective 3b, outcomes in the models of care were assessed in different sub-groups of patients. In both the Green Clinic and the CACs, lower rates of LTFU were observed for patients who recently initiated ART and who initiated ART at CD4 cell counts ≥200 cells/μl compared to the CHC. In the Green Clinic, the increased risk of LTFU was driven by higher LTFU among men, younger patients (25-34 years old) and those who initiated ART with advanced HIV disease or early years of the programme. CAC patients had preferable outcomes with all sub-groups having reduced risk of LTFU. The exception was youth, patients 16-24 at ART initiation, for whom the CACs offered no improvement in risk of LTFU. Men and women in CACs had similar rates of retention, a promising finding given that men consistently have worse ART outcomes than women in previous analyses focusing on facility-based models of care.

9.1.7 Strengths and limitations

While study-specific limitations are presented within the discussion section of each results chapter, there are overarching limitations that should be stated in advance of making recommendations. First and foremost, the generalisability of our findings must be considered in light of all data coming from cohorts with considerable research support. This support enables improvements in data quality and outcome ascertainment. Furthermore, contributing cohorts likely have greater resources than other sites in resource-limited settings. Previous research has found that programmes

with adherence support and tracing programmes have improved patient outcomes and hypothesised these improvements are the result of greater resources [87, 102]. Despite the data coming from research sites, we did not have access to data on human resources and other resources that may affect capacity for increasing scale-up. These resources may be related to LTFU and retention and without data on their availability there may be residual confounding in how scale-up and year of ART association are related to outcomes.

Moreover, the contributing cohorts were from well-established programmes that began providing ART relatively early in the treatment efforts in resource-limited settings. They are therefore not representative of the newer programmes in recent years, when there has been a proliferation of new ART sites and the rate of ART scale-up has been most dramatic [3]. The analyses in Chapters 4 and 5 were restricted to patients who started treatment in and before 2011 and 2012, respectively, and therefore may not accurately represent the current rate of scale-up.

Our findings and insights on models of ART delivery are also limited in that data was from a single ART site and with limited duration of follow-up (Chapter 6-8). This site has previous experience with innovating care for HIV patients [16, 57] and therefore, the successes and challenges that were observed may be different to challenges elsewhere. While the nurse-managed Green Clinic programme described in Chapter 6 was started in 2007 and had follow-up data through 2012, the community-based Adherence Clubs in Chapters 7 and 8 were limited to a maximum of 18 months of follow-up, with very small patient numbers beyond one year. Further follow-up time will be required to understand the long-term outcomes of novel models of care.

All our data were from observational cohorts by sites providing ART within the public sector. The value of using this observational data are that it will reflect some of the realties on the ground. In Chapters 6-8, the data are limited by the fundamental difference of observational compared to experimental research designs. The central challenge is one of selection bias to the intervention compared to the control group. Allocation into the novel models of care was not at random, but informed by subjective measures of adherence as defined by clinicians and factors associated with improved

LTFU and retention. These analyses adjusted for this confounding, but were limited by the type and quality of data available.

There are outstanding questions regarding LTFU and models of care to support retention that were beyond the scope of this thesis. As outlined in Section 2.1, this thesis only addressed one step in the treatment cascade, losses after ART initiation. This thesis did not address losses along other stages of the cascade such as after a positive HIV test (linkage to care) or from eligibility for treatment and initiation. Beyond the cascade, this thesis did not endeavour to document the patient and health care provider experiences. The analyses of models of care delivery did not extend to measure cost-effectiveness or efficiency [250]. This thesis was limited to adult ART programmes. However, LTFU is a considerable challenge for other populations such as those with inequitable access to ART including paediatric, adolescent and key populations.

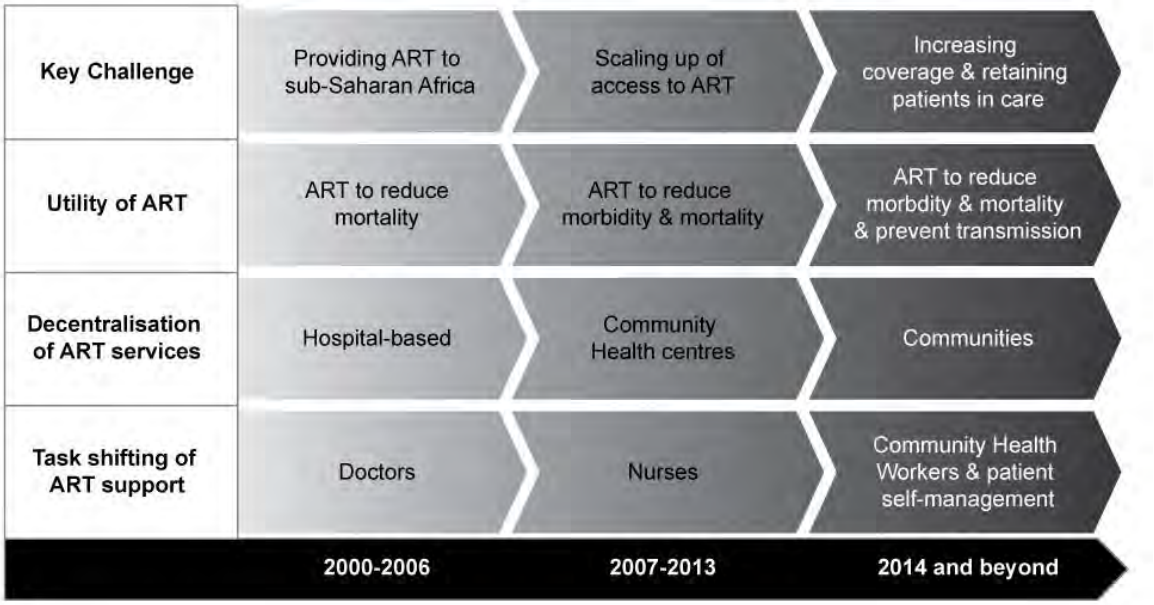
The thesis utilised the most conservative approach to defining LTFU as per the recommendations from Chapter 3. However, patients classified as LTFU are indeed patients with three distinct outcomes as drawn out in Section 2.2, including unascertained deaths, unascertained transfers and patients currently disengaged from care. With the exception of Chapter 5, where LTFU was adjusted for unascertained deaths through linkage with the National Population Register, we did not trace patients to disaggregate those classified as LTFU into the three discrete groups. As highlighted in a recent systematic review of tracing studies, rates of unascertained transfers or self-transfers are increasing with scale-up [91]. Given that the data did not link to data from other ART facilities, estimates of LTFU are likely overestimates of programme loss, with a considerable proportion of patients being in care elsewhere [211]. The classification of LTFU also included a considerable proportion of patients who were in a treatment interruption and will re-engage with care at a later stage. Potentially, treatment interruptions occur at different rates across the treatment lifetime, with patients who have more recently initiated ART more likely to be in an interruption and therefore classified as LTFU [239]. This thesis also did not assess risk factors for patients in an interruption compared to those who are permanently LTFU.

The importance of context when assessing risk factors for LTFU and the outcomes of models of care delivery for ART cannot be overstated. The thesis findings come from a specific a geographical context, as well as a temporal context. Chapter 7 focussed specifically on the implementation of CACs providing the detailed context necessary for programme managers and policy makers to understand, before extending the model to their setting. Given the pace of change over the first decade of ART provision in resource-limited settings, factors associated with LTFU and models of care to support retention are placed within a specific time context as well. Effective community interventions in one context may not work in all contexts and detailed compendium of heuristics is necessary to tailoring the model to the setting [19, 273]. The recommendations that follow are presented with an overall caveat that implementation must be contextualised and consider the local resources, size of the ART programme and targets for scaling up access to ART [43, 151].

9.2 WHAT WE KNOW GOING INTO THE SECOND DEACDE OF ART DELIVERY IN RESOURCE-LIMITED SETTINGS

Acknowledging the transitional context over the first decade of ART provision in resource-limited settings, as represented in Figure 1.1 and re-presented below, is important ahead of making recommendations for the next decade. Further adaptations are necessary, given the ambitious treatment targets and call for quickening the pace of ART scale-up [3]. Before presenting recommendations, three underlying themes summarising what we know about the HIV response and ART programmes to date are given to provide the current context: LTFU is a significant and pervasive challenge, the composition of the ART cohort will be increasingly heterogeneous and the focus should be on how to support effective ART delivery.

Re-presentation of Figure 1.1 Evolution over the first decade of ART in sub-Saharan Africa



9.2.1 LTFU is a significant and pervasive challenge

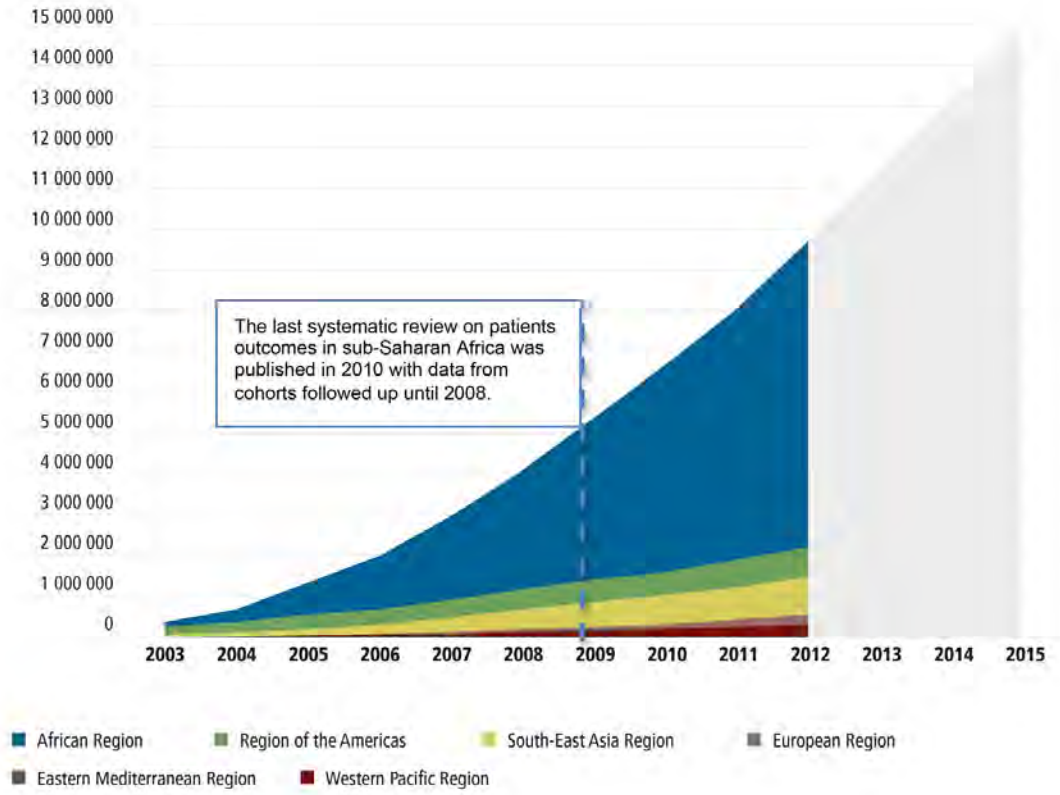
LTFU is a significant and pervasive challenge threatening the effectiveness of ART programmes. Data from Chapter 4 suggested that while estimates of mortality decreased, 36-month LTFU nearly doubled from 11% to 21% between patients initiating in 2003 or earlier and those initiating in 2008. As a result, the contribution of LTFU to overall programme losses increased dramatically. Further, rates of LTFU increased with each successive year of ART initiation (Objective 2a). An increase in LTFU by year of ART initiation was also observed in Chapters 5-7.

Figure 9.1 is a frequently cited graph representing the impressive rate of ART scale in resource-limited settings over the past decade [24]. The slope of the curve representing the rate of scale-up and the number of patients accessing ART is striking, but we know very little about the outcomes of patients starting ART during the most rapid scale-up period over the last five years. Outcome data available from cohorts is largely from observations in 2008 and earlier [56, 90, 139, 195, 274]. The last systematic review on retention on ART in sub-Saharan Africa was published in 2010 with a meta-analysis of outcomes from cohorts under observation in 2008 and earlier [38]. The dotted line in

Figure 9.1 highlights the end of the observation time of contributing cohorts in this review, drawing attention to how estimates of programme outcomes is limited to before the majority of patients initiated ART (2009 onwards).

Figure 9.1 Actual and projected numbers of people receiving ART in low- and middle -income countries, and by WHO region, 2003-2015.

Reprinted from Global update on HIV treatment 2013: Results, impact and opportunities [24]



In addition to having limited data on outcomes among patients initiating ART in recent years, many of the cohorts providing data for previous estimates of outcomes were large, established research cohorts supported by academic and non-governmental partners and not likely to be representative of the national cohorts. Further, patients initiating ART in recent years have done so at new, decentralised and nurse-managed sites. In South Africa, more than 3,500 sites were providing ART by mid-2013 and the number of nurses trained to initiate ART had increased from 250 in February 2010 to 23,000 [15, 256]. Given the trend of increasing LTFU that we observed in Chapters 4, 6

and 7, it is likely that recent estimates of LTFU presumed from earlier cohorts may be overestimating the proportion of ART patients retained in care. LTFU is therefore a significant and pervasive challenge, given that conservative estimates from Chapter 4 have only two thirds of patients retained in care after five years on treatment.

9.2.2 The composition of the ART cohort will be heterogeneous

UNAIDS recently redefined the narrative around HIV treatment targets calling for acceleration of ART to ensure 90% of HIV patients know their status, 90% of patients have access to ART and that 90% of patients are achieving viral suppression by 2030 or "90-90-90" [3]. Efforts to meet these ambitious treatment targets combined with implementation of the 2013 WHO guidelines, will see both an increase in the volume of patients, as well as a change in the composition of the cohort [237]. The 2013 Guidelines support earlier initiation, expanding the CD4 cell count thresholds from <350 cells/μl to <500 cells/μl and thus increasing the number of patients eligible for ART who do not have an illness experience from their HIV. In addition, healthier patients, including women who initiate in pregnancy regardless of CD4 cell count and HIV-positive patients in serodiscordant relationships, are also recommended to initiate ART. At the same time, the current ART cohort is aging and there will be an increase in the number of complex patients on ART. These complex patients will include patients with chronic conditions associated with aging, comorbidities more likely in those with HIV co-infection, ART complications due to long-term exposure and toxicities, and more patients on second- and third-line regimens [47, 275].

In contrast to the healthier patients accessing ART, there will still be a significant and continued number of patients who are initiating with low CD4 cell counts, less than 100 cells/μl, who require substantial clinical resources [210, 216, 276, 277]. As shown in Chapter 4, despite a rise in the median CD4 cell count at ART initiation, a consistent 30% of patients are starting ART with a CD4 cell count <100 cells/μl. The high burden of low CD4 cell count patients was also observed in Chapter 5. This dichotomy of a

rising median CD4 cell count of the cohort combined with a substantial burden of low CD4 cell count patients has been observed in many regions [277].

9.2.3 The focus should be on how to support effective ART delivery

In the past decade, determining when to start ART in the course of HIV disease or the optimal CD4 threshold for ART initiation has been the centre of a number of large trials, analyses of observational cohorts and considerable debate [29, 236, 278-285]. The current discourse on ART delivery needs to be reframed from *when to* start ART to *how to* efficiently and effectively provide ART. At present, the focus remains on scale-up, as reflected in the UNAIDS document *Fast-track: Ending the AIDS epidemic by 2030 [3]*. While *Fast-track* outlines the benefits of accelerated scale-up of ART and presents the ambitious targets for "90-90-90" by 2030, there is no mention of how to support retention or decrease LTFU, despite the reality that retaining patients in care will be essential to reaching the targets. Given the threat of LTFU to ART programme effectiveness, it is high time that some of the focus on when to start be shifted to how to provide ART.

The substantial resources leveraged to provide ART to millions of patients worldwide and the size and scale of the response has been one of exceptionalism [25, 286, 287]. Shifting attention to support the effective delivery of ART would be in line with this exceptionalism. Exceptionalism is reflected in the human rights approach to the disease, whereby patients are autonomous. It is further affirmed in how adaptations to the provision of ART were implemented in parallel with research to support their effectiveness [42].

An underlying tenet of the public health approach to HIV is that HIV-positive patients on ART can to return to normal life and that models of care for accessing ART should cause as little disruption as possible [42, 134]. This tenant is held by the findings of this thesis, where models of care delivery outside of the traditional in-facility model provided effective provision of ART (Chapters 6-8). Community-based models of care are not just as a response to the need to expand ART and overburdened facilities, but also as preferable models providing ART closer to patients' homes [288, 289].

It is the opportune time to leverage some of the resources from when to start ART to investigate how to effectively support ART provision. Following on from decentralisation to community health centres and task shifting to nurses, community-based models of care with provision of ART by CHWs and increased patient self-management are needed [290]. More gravitas is needed in the discussions on how to support effective ART provision if we are to achieve the grand targets of "90-90-90".

9.3 RECOMMENDATIONS

This section outlines recommendations for research and policy, and programmes and services based on the findings of the thesis. An overarching recommendation is made for the expansion of community-based models of care to support retention [57-61].

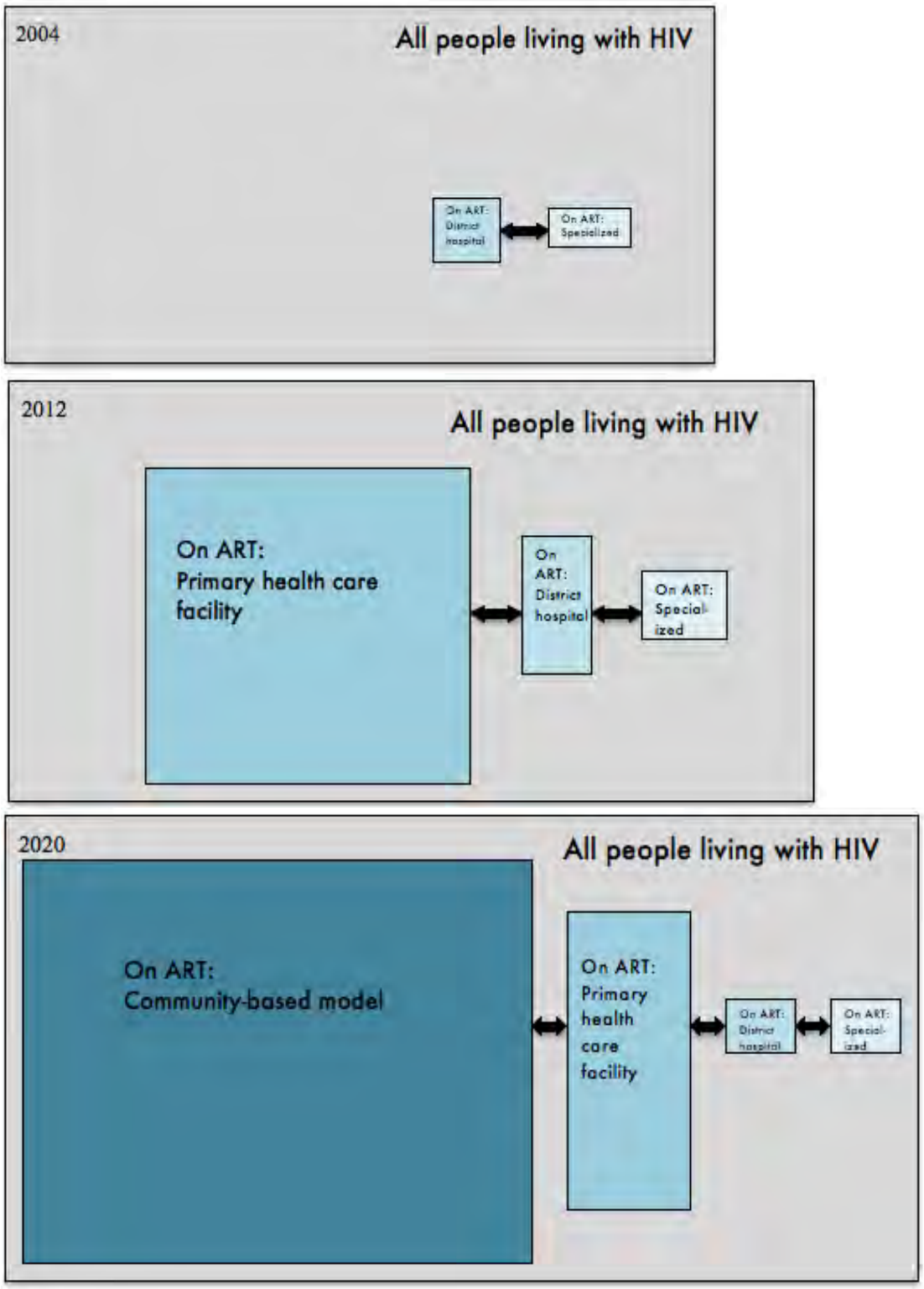
The primary model of care for delivery of ART has shifted from being within specialised and hospital facilities to primary care facilities. Figure 9.2 depicts the delivery of ART within South Africa in 2004, 2012 and a hypothetical scenario for 2020. At each time-point, the HIV-positive population is represented and those accessing ART are depicted within different boxes, representing where they receive treatment. In 2004, when public sector roll-out of ART began, access was restricted to within specialised and district hospitals to only 55,000 patients [291]. By 2012, the ART cohort had grown dramatically, with more than 2 million patients on treatment [4] and the majority of patients were accessing ART in primary care facilities. While this scenario represents the ART cohort in South Africa, it is likely representative of the situation in other resource-limited settings where it estimated that at present, 95% of ART delivery is facility-based [3].

In 2020, the size of the on-ART population will expand; treatment coverage will increase will the total number of patients living with HIV (bottom box, Figure 9.2). This is a hypothetical scenario whereby the majority of patients are accessing ART within community-based models of care. The size of the community-based cohort is higher

than the 30% of the treatment cohort that has been recommended by UNAIDS and others [3, 143]. Given that healthier patients accessing ART earlier may benefit from earlier engagement with community-based models, at least 50% of patients should access treatment in community-based models of care. We are currently dependent on a limited number of models of care, most of which are dependent on doctors and nurses [25, 237, 292]. Given the changes in the treatment cohort, the human resource constraints and challenges with retention innovations are required in service delivery to maximise efficiency [225]. Further decentralisation into communities is needed and support by the findings of community-based Adherence Clubs in Chapters 7 and 8. For millions of HIV patient to be managed in sustainable, chronic disease care [7], we need to extend ART delivery into communities.

In Figure 9.2, the black arrows between boxes represent the bi-directional referral pathways between models of care delivery. Just as patients moved between hospitals and primary care facilities, it is envisioned that patients will move between community-based and facility based models as their needs change throughout their treatment lifetime.

Figure 9.2 Models of care delivery within the South African primary health care system: 2004 [291], 2012 and 2020



The number of PLWHIV are represented by the grey box and this number increases from 2004 to 2012 and to 2020 as the HIV-positive population increases. Patients on ART are represented within the blue boxes proportional to the number of patients on ART at each time point. The black arrows between each ART service point represent referral patterns between the models of care.

9.3.1 Expansion of community-based models of care

Expansion of community-based models of ART delivery follows on logically from previous evolutions over the first decade of ART in resource-limited settings (Figure 1.1). Community-based models of care are an extension of the Alma Ata definition of primary health care, by providing health care as close as possible to where people live [293]. They also importantly employ decentralisation and patient and community participation, as recommended by the public health approach to ART delivery in resource-limited settings [237]. The premise is that community-based models of care are an extension of, and not a replacement for, the health care system. As evidenced in community-based approaches for reducing childhood mortality, community interventions need well-functioning local health facilities and are not stand alone services [294].

A key to community-based models being an extension of the formal health services is the acknowledgement of the role of the staff within the community-based model. As highlighted in Chapter 7, a key factor to the implementation of CACs was the CHC viewing the CAC patients and staff as part of the health service, despite being based in the community. Removing the hierarchy from traditional facility-based models is necessary to engage the multidisciplinary staff required for successful community-based provision of services [295]. There are examples of this in ART programmes in resource-poor areas in developed countries [40] and from community-based models with CHWs to address childhood diseases [294].

9.3.2 Recommendations for research and policy

Questions remain about how to support long-term retention in care while facilitating expansion of ART provision. The research agenda therefore focuses on gaps in our understanding revealed from the results of this thesis.

More research on LTFU and programme retention

A primary recommendation is that the programme outcomes of LTFU and retention need continual research with updated estimates published regularly. As highlighted in Section 9.2, LTFU represents a substantial challenge to ART effectiveness and cohort data on outcomes from the last five years are limited. It is also critical that the assessment of LTFU and programme outcomes utilise a standardised definition of LTFU (Chapter 3, Objective 1). Furthermore, given the relationship between LTFU and temporal factors of year of ART initiation (Chapter 4, Objective 2a), programme expansion (Chapter 4, Objective 2a) and CD4 cell count (Chapter 5, Objective 2b), there is a need for continual updates to our estimates of LTFU. Analyses of programme outcomes thus need to include multivariate models that adjust for temporal and individual factors.

Neglecting to present updated estimates of programme outcomes may lead to overstating the success of ART programmes. If we continue to focus on simply the number of people ever initiated onto ART we will not have an understanding of who is presently on treatment, what proportion of the HIV-positive population is suppressed and therefore the community viral load. The ability of ART to act as prevention will be exaggerated. There will also be no systems in place to support transitions within and between HIV programmes to have accurate numbers of patients retained in care.

As delivery of ART services adapts and novel models of care are utilised (Chapter 6-8, Objective 3), published programme outcomes should include a description of the delivery model. This description should include staffing patterns, details of the community health worker cadre in regards to their role and training, the counselling and support provided at the time of ART initiation, the protocol around pre-ART support and how patients who are late or miss visits are followed up. A standardized tool to collect this information would be beneficial to ensure consistency between sites. In addition to describing the model of ART delivery, additional data surrounding the process of design and implementation should be encouraged. One such tool that could be utilized is the Consolidated Framework For Implementation Research, which defines specific constructs related to process and supports building the knowledge base for broader implementation in multiple contexts [296].

Further research on models of care delivery is needed, especially on long-term outcomes [25, 251, 297-300]. While the notion that community-based models of care delivery can support retention is not new, there is a pressing need for more evidence [12, 107]. In addition, research into patients' experiences within models of care is necessary to support expansion of novel models. It will also be advantageous to engage with health care workers around their experiences of models of delivery including community health workers as well as facility-based staff. The cost-effectiveness of different community-based models of care provision also warrants further research [301].

What study design should be used to investigate models of care presents an interesting dilemma. As mentioned within the strengths and limitations section, the data in this thesis was limited to observational studies with selection bias of patients into the novel models of care. It may be necessary for randomized control trial methodology to be used to generate sufficient quality of evidence to change policy, despite a growing evidence base from observational studies. This would parallel the generation of evidence for changing the policy around doctors versus nurses for ART initiation. While many programmes had moved to nurse-led models as the result of resource constraints, it was the evidence generated from the CIPRA-SA randomized trial that facilitated the policy shift to nurse initiated management of antiretroviral treatment (NIMART).

Further research is needed for a model of care delivery that provides ART effectively to youth

Youth represent a significant and growing challenge to our ART programmes given their poor treatment outcomes [146, 147, 267, 302-305] and that the numbers of youth in our cohorts is likely to increase. In this thesis, youth had an increased risk of LTFU in community-based Adherence Clubs (Chapter 8, Objective 3b) and in the MSF cohorts in Chapter 4. They also had higher rates of viral rebound than other age groups in all three models of care, the CHC, Green Clinic and CACs (Chapters 6 and 8). The higher rates of LTFU and viral rebound we observed are similar to findings from a recent analysis of ART cohorts from Kenya, Mozambique, Tanzania and Rwanda [306].

Delivering ART to young people also represents a particular opportunity, given that early treatment in this age group has the most potential for reducing transmission. The youth included in this thesis were most likely to be behaviourally infected as opposed to perinatally infected since they were initiating ART in young adulthood. While considerable resources and interventions have been targeted to perinatally infected children who are maturing into adolescents, the behaviourally infected youth are less acknowledged. Youth are a blind spot within our ART service delivery most commonly grouped into the adult cohort without tailored support or interventions that recognise their unique challenges [269]. This age group is in a critical developmental stage transitioning from childhood to adulthood.

Youth pose a substantial challenge to our programmes given their high rates of LTFU. However, our systems are failing them and our approaches not working, evidenced by their high rates of LTFU and viral rebound. Further research is needed to elucidate what models of care can effectively support ART provision for youth.

Optimal implementation of community-based models of ART delivery

Community-based ART should not be just for stable ART patients

A paradigm shift underscoring the utility of community-based models beyond only stable patients is needed. At present, most community-based models for ART are focused on delivery and support for stable patients but the definition of "stable" is not standardised. It is unknown what proportion of the global ART cohort is stable and therefore eligible for existing stable models of care [151]. Community-based models of care should also be considered for patients who are struggling with adherence and may currently not qualify [54]. Such adherence problems may be caused by limited time available to attend the clinic and may benefit the peer-support in out-of-facility models. However, these non-stable patients may require closer and more regular clinical oversight. Another area of future research is how community-based models of care can support patients who default from treatment while in the community-based models. At present, defaulting patients would be up-referred to the CHC. Depending on why the

patient is defaulting, an increase in counselling support within the community-based model of care may be preferable to up-referring the patient.

Earlier transition to community-based models

Further research is warranted to investigate if patients can be transitioned to community-based models of care sooner after ART initiation. With patients initiating treatment at higher CD4 cell counts, viral suppression can be achieved within a few months of initiating ART, and therefore waiting a year (as in the case of CACs) until decentralisation may be unnecessary. Support for earlier transition to community-based models was found in Chapters 4-7. In Chapter 4, patients with recent ART initiation had the highest rates of LTFU and in Chapter 6 and 8 patients with recent ART initiation had an increased risk of LTFU in the traditional in-facility model and benefitted most from down-referral. The question of how soon patients can be effectively down-referred to community-based models of ART warrants further research.

Supporting HIV testing and pre-ART patients

Community-based models may also have benefits at other stages in the HIV "treatment cascade". This thesis was limited to assessing their effectiveness in supporting ART provision after a year or more on treatment, but they may also be effective in initiating patients onto treatment. With the challenges in retaining patients along the "treatment cascade" [76], community-based models may also support linkage between HIV testing and treatment. Community-based models could be equipped to provide HIV testing as well as CD4 and viral load monitoring for patients not yet eligible to start ART. Point-of-care (POC) viral load and CD4 cell count testing within community-based models could provide further innovation [307].

The frequency of viral load monitoring for ART patients is changing. Potentially, if viral load monitoring was done using POC technology or with pooled viral loads in dried blood spots, different frequencies may be cost-effective for community models, especially if community models are restricted to stable patients.

The need to adapt the ART supply chain

Adaptations of the ART supply chain are also needed to support community-based models. In the CACs in Chapter 7, pre-packaged ART was transported daily from the CHC to the community venue. Direct delivery of ART to the community venues should be considered as should direct delivery from pharmaceuticals. Simplification of regimens will assist in expanding opportunities for community-based models of delivery [237]. Another option or model that requires further investigation is that of community pharmacies or community distribution points [43]. Research into what components of community-based models support retention in care, whether it is decreased visit frequency, shorter visits, peer support or some other factor, is necessary [308]. This work will help to inform how community distribution points compared with Adherence Clubs may support ART provision.

Strengthening referral pathways

The pathways between models of care are bi-directional, supporting movement both in and out of primary care (Figure 9.2). While acutely ill patients need to be timeously up-referred to ensure appropriate disease management, the systems and transition of down-referral into community models also requires attention. In both the Green Clinic in Chapter 6 and the Community-based Adherence Clubs in Chapter 8, patients who initiated ART in the early years of the programme had a higher risk of being LTFU in the down-referred models compared to patients who initiated treatment more recently. Furthermore, patients in the Green Clinic who had advanced HIV disease had an increased risk of LTFU compared to the CHC. This suggests that patients who initiated treatment in the early years of the programme and those who had an illness experience may value the CHC model of care and require a more active transition when they are down-referred. Potentially increasing the counselling and support is needed for these patient groups so that they understand the rationale for the decentralisation. It is important that they not only have the right to choose to stay at the primary care facility, but also that with being down-referred they do not feel as though they are being pushed out of the health care system. Appropriate support of referrals both into and out of the primary care setting are therefore needed to ensure retention across models of care.

Policies can impede community-based models of care

A key policy in the ability of programmes to decentralise ART delivery is around ART dispensing versus ART distribution. Dispensing and distributing are not synonymous, and there must be balance between oversight and provision of ART while allowing reasonable distribution by CHWs.

The amount of ART that can be collected at one time affects the number of patient visits within a year. Decreased visit frequency offers huge potential benefits both to the patient and the health system. At the Gugulethu CHC, the amount of ART that is dispensed per visit ranges from 4 weeks to 16 weeks. National policy in South Africa is for 8 weeks, or a maximum of 2 months of ART to be distributed. However, data from Community-based Adherence Clubs found no difference in retention or viral rebound among patients who were given four months vs. two months of ART [255]. While dispensing of four months of ART is against policy, the policy should be reconsidered and revised to be evidence-based.

In South Africa, patients are rescripted every six months by a nurse or a doctor. With the ART programme providing treatment to more than 2 million South Africans, this equates to high volume of administration due to prescriptions. In addition, with simplified regimens, the majority of stable patients are on the same regimen. With decentralisation of ART into communities, patients in the Community-based Adherence Clubs are rescripted blindly; the patient does not sit with the clinician while the script is written. Therefore, the frequency of this process should be reconsidered and if possible amended. Electronic scripting or other ways of reducing the administrative burden should be considered.

Beyond ART towards integration

A large component of the research agenda for community-based models of ART delivery revolves around how to integrate with other services. While originally implemented as an emergency response, ART programmes in resource-limited settings

have adapted and been transformed towards supporting sustainable chronic care [40, 309]. In recent years, there have been moves to combine ART programmes with one other programme, often tuberculosis (TB) or maternal health, creating integrated diagonal programmes [25, 310, 311]. The dominant paradigms are shifting away from horizontal and vertical approaches and treatment versus prevention [273] towards full integration and the Integrated Management of Adult Illnesses (IMAI) [312]. This in part is due to the successes of Integrated Management of Childhood Illnesses (IMCI), where the move is towards full integration.

There is a renewed interest in operational models of primary care delivery following the thirtieth anniversary of the Alma Ata Deceleration of "health for all" [25, 293, 312-315]. This approach is very much aligned with the public health approach of ART programmes in resource-limited settings. In addition, there has been a simultaneous shift away from communicable and non-communicable diseases, towards health systems for acute and chronic diseases and HIV care exemplifies this shift [312]. Health systems research regarding ART originally focussed on whether or not ART programmes were beneficial or detrimental to other services [309]. Today, it is recognised that ART programmes in many resource-limited settings were the first successful, large-scale chronic care programmes [46]. Therefore, there are many lessons that can be learned and further research into how systems that can be leveraged for wider improvement of the health system [35, 40, 46, 47, 49, 289, 316, 317]. In line with the revitalisation of Alma Ata and the public health approach, calls have been made to capitalise on the systems implemented for ART provision and expand them to other services [41].

There is a unique opportunity for strengthening links between community-based models of ART delivery and existing programmes for IMAI and IMCI [310]. IMAI and IMCI were a response to fragmented vertical programmes, the result of disease-specific programming, such as HIV-specific programmes, that were focussed on achieving short-term measurable targets [318]. Utilising existing ART programmes to build IMAI echoes how systems of outreach that were implemented for immunisation were the foundation for IMCI [294, 310]. However, in contrast to IMCI, there has been very little uptake of IMAI and resultantly limited evidence of its effectiveness [310]. Lessons from

IMCI can therefore lend insight into how to expand implementation of IMAI and define the research agenda. Within the campaigns for IMCI expansion, the importance of extending the health systems out of facilities and into health spaces was identified as a key factor for uptake [319]. To date, the guidelines and policies for IMAI have mirrored those for IMCI and been integrated with HIV services. A noteworthy difference is the paucity of guidance around community level delivery of services for IMAI [310]. Therefore, to support the broader implementation of IMAI necessary for research on its effectiveness, increasing the guidelines regarding community-based programmes is recommended.

In summary, there is a large and exciting future research agenda into how community-based models of care utilised for ART delivery can be expanded to other services [309]. In order to support expanding IMAI, further guidelines in regards to community delivery are needed [49]. Despite the sizable interest in global health and focus on health systems strengthening, limited data on actual delivering health services in resource-limited settings has received little academic interest [273].

9.3.3 Recommendations for programmes and services

Programmes and services need to adapt to the current challenge of LTFU and the growing and changing cohort as new initiation guidelines are implemented. Based on findings of this thesis, recommendations are for triaging of patients at ART initiation, an overhaul of the approach and delivery of ART for healthier ART patients and simplification of monitoring and evaluation (M&E) systems.

Improving ART effectiveness may mean revisiting the public heath approach to ART provision

To date, a public health approach to the provision of ART in resource-limited settings has supported the rapid scale-up of ART. However, with the increase in the heterogeneity of ART patients and the challenge of LTFU, it may be time to reconsider some elements of the “one-size-fits-all” approach [41]. While the principles of simplification, decentralisation, equity and patient and community participation are

still very relevant, the increased heterogeneity of the ART cohort demands that the standardisation principle is revisited. Our findings that the ART cohort consists of a considerable group of acutely ill patients, as well an increasing number of patients who are healthy and without an illness experience, leads to a recommendation of triaging patients at the time of ART initiation. This recommendation is based on the findings of the thesis and supports many of the public health principles while highlighting that we need to do better to improve ART effectiveness and support retention in care.

Designating resources for those in need of clinical support

As outlined above and evidenced in Chapter 4, a large proportion and absolute number of patients are still initiating ART with a low CD4 cell count, <100 cells/μl. This group of patients requires substantial clinical resources and timely initiation onto ART to prevent mortality. Counselling of this group should be specific to their needs, focussing on how ART can reduce mortality and addressing underlying reasons for late initiation. The model of care more appropriate to this group of patients may be the traditional in-facility model given its ability to provide significant clinical support. While it is discouraging that such a large number of patients are still accessing ART so late in their disease progression, it is also promising that increasing the treatment threshold is not squeezing these patients out of care [19]. WHO guidelines specify that provision to this group remain a priority and this can be achieved within parallel innovative models of care to be implemented for other patient groups [283]. Given that timely ART is necessary to prevent mortality in this patient population, it is essential that there is a model of care for them to access with appropriate resources. The model of care is also needed for the complex patients (aging cohort, chronic co-morbidities, patients with treatment failure, etc.) as described in Section 9.2. Designating resources for patients accessing ART with low CD4 cell counts can be supported by triaging healthier patients at ART initiation and stable patients out of facilities and into community-based models of care [237].

Appropriate services for healthier ART patients

As highlighted in Section 9.2, implementation of the 2013 WHO guidelines will lead to a healthier group of patients accessing treatment. These healthy patients are unlikely to be acutely ill or feel as though they have a chronic condition. Put another way, they are HIV patients without an illness experience. It is crucial to therefore consider how best services can support their initiation and retention on ART. As a first step, the healthier patients must be separated from the <100 cells/μl patients.

Separate healthier patients at ART initiation

In Chapter 5, patients accessing ART at higher CD4 cell counts had an increased risk of LTFU (Objective 2c). The primary care facilities we analysed in Gugulethu, the IeDEA-SA collaboration and the MSF sites were designed for acutely ill patients but are increasingly utilised by this healthier group of patients. The facilities are congested, have long queues in waiting areas and increasingly have patients wearing masks to prevent transmission of TB. The exposure of the HIV patient without an illness experience to this clinic experience may be detrimental to their motivation to be retained in care. Patients without an illness experience may feel "too healthy" to be on ART and could be deterred by long queues for medication for a disease for which they have yet to experience [271]. Continuing to offer services in the same physical space for patients with low CD4 cell counts <100 cells/μl and those without an illness experience may be reinforcing the common perception that ART is treatment for sick patients [63]. We observed that rates of LTFU were higher in the CHC for patients initiating at higher CD4 cell counts (Chapters 6 and 8) compared to down-referred models.

Change ART initiation counselling for healthier patients

How to initiate patients with higher CD4 cell counts onto ART is also of critical importance. In Chapter 5, the highest risk of LTFU was in the first year on ART and peaked in the first three months for patients initiating at high CD4 cell counts. The counselling support and information provided to patients around initiation is therefore critical. ART needs to be rebranded as something not just for sick patients [271].

Initiation materials are out-dated and require an overhaul to reflect the changes in first line regimens, the scientific advances on the role of ART as prevention and the benefits of earlier initiation. The focus needs to be on the benefits of life long viral suppression, how ART can be prevention and why daily adherence is crucial. Without an overhaul to the messaging provided to patients without an illness experience at initiation, we risk them disengaging from care early and a perpetuation of the out-dated view that ART is just for treatment.

Move healthier patients at ART initiation into community models of care sooner

The timing of decentralisation into communities was raised as a key area for further research in Section 9.3.1. However, given that historically with ART provision changes to operational models have been made concurrently with research to evaluate their effectiveness [42], our findings support that programmes should proceed with earlier decentralisation into communities. When patients with high CD4 cell counts accessed either the nurse-managed Green Clinic (Chapter 6) or community-based Adherence Clubs (Chapter 8), they had substantially reduced LTFU compared to the traditional community health centre. With increases to the CD4 cell count threshold for ART initiation, programmes should consider fast-tracking patients without an illness experience who are healthy to community-models of care delivery that may more effectively support retention. We acknowledge that retention in care is not the same as adherent on treatment and being virally supressed [48]. However, data from the CACs did support that retained patients were adherent. Viral rebound at 6-months and 12-months was less than 2%, evidence that patients retained in care were adherent.

There are risks to transitioning patients to out of facility-models earlier in their treatment cycle. Decentralisation may be viewed as being pushed out of the health care system and not give patients sufficient time to develop a relationships with CHC staff. It may also give the impression that their HIV is not a serious condition, as it does not warrant frequent clinical consultations. To address these concerns, the messaging around decentralisation and when and how to access primary care as necessary, is critical.

Simplified and modernised monitoring and evaluation

LTFU appears to be increasing with each calendar year as concluded Chapter 4, observed in the IeDEA-SA cohort in Chapter 5 and suggested in the Gugulethu ART cohort in Chapters 7 and 8. As discussed in the strengths and limitations section in 9.1, all of these cohorts were research cohorts, with support and resources provided by academic or non-governmental partners. Significant external resources are provided to ensure high levels of data quality. However, even in these well-resourced sites, retention in care appears to be deteriorating and the volume and rate of scale-up presents challenges to obtaining good quality monitoring data. If LTFU is increasing at these sites, it is likely that the situation is even worse elsewhere and that efforts are necessary to support simplified monitoring of patients.

One reason for the poor outcomes in existing ART programmes is high rates of administrative LTFU, whereby monitoring and evaluation systems are overwhelmed by patient volume and unable to accurately record basic patient-level data. The number of key variables at the individual level that need to be collected should be limited in favour of quality [237]. As we saw in Chapter 3, the analytic approach to defining LTFU can affect estimates of patient outcomes. Therefore, it is essential for the approach to be harmonised across programmes, including standardisation of the type and methods of data collected.

Setting targets for evaluating innovative models of care

For programmes, one solution is to change the way in which innovative models of care are evaluated. While conventionally new interventions are judged against the standard of care, this may be increasingly difficult and irrelevant for ART models of care. Outcomes from pre-existing services providing ART or the standard of care are deteriorating, as evidenced by the increasing rates of LTFU and challenges due to poor data quality. If the outcomes from the standard of care models are below a level that would be recommended, comparing novel models to existing models is futile. Further, given that patients are selected into new models of care based on factors related to better outcomes, it is a substantial methodological challenge to find comparable patient populations as a reference group. Potentially, targets for retention and sustained viral

suppression should be set and used as benchmarks for comparing the outcomes from innovative models of care. This would serve to simplify analysis and expedite evidence of ways in which health services could adapt to support expanding ART access and retaining patients on care.

A growing need to track patients across programmes and between models of care

Higher rates of transfers between programmes are documented as the number of sites providing ART continues to grow [91]. With the expansion of the number of ART sites and moves afoot for greater decentralisation, the ability to track patients between and across programmes is increasingly important to accurately assess patient outcomes [211, 289]. To account for patient mobility, systems need to consider unique identifiers, the sharing of information between facilities and more modern biometric identifiers [91, 212, 251, 320]. The potential impact of improved systems for tracing patients between sites is huge; both to patients and health systems. Patients are given flexibility to move between and across models ensuring they have an uninterrupted ART supply and that at the time of ART collection the person dispensing can see the patients most recent viral load measure and regimen. For the system, patient outcomes are accurately and timeously collected allowing for effective programme monitoring, the ability to accurately forecast ART needs and identification of patients who are in need of support to re-engage with care [237]. Considerable and ongoing efforts to improve the monitoring of ART patients highlight that in resource-limited settings where health systems are severely constrained in financial and human resources as well as technical infrastructure, the substantial challenge of making patient-level monitoring a reality [251, 289, 321, 322].

9.4 CONCLUSIONS

This thesis has addressed the challenge of LTFU from ART programmes in South Africa and other high prevalence resource-limited settings. It investigated the impact of the definition of LTFU on programme outcomes before describing temporal factors,

including year of ART initiation, programme expansion and increasing CD4 cell count at ART initiation, and their impact on LTFU. Lastly, it assessed models of care for improving retention among stable ART patients.

The first contribution of this thesis was demonstrating that how the definition and analytic approach to LTFU can have an appreciable impact on programme outcomes. Given that LTFU is a reflection of programme effectiveness, having a standardised definition will be necessary to compare outcomes within and between programmes.

The second novel finding of this thesis was confirmation of the increasing trend of LTFU with calendar year of ART initiation. Looking at data from twenty-five cohorts from 8 low and middle-income countries, calendar year of ART initiation was persistently associated with an increased risk of LTFU, with adjustment for individual level factors and measures of programme expansion. This finding corroborated a concerning trend that LTFU is a growing challenge. Our research also suggests that it is the pace of scale-up and not programme size that may be associated with increases in LTFU.

Thirdly, we provided evidence that healthier patients initiating ART at higher CD4 cell counts, above 300 cells/μl, were at an increased risk of LTFU in the first year on ART. Given the trend towards earlier ART initiation, we must acknowledge that patients initiating ART without an illness experience may require different support and systems to effectively delivery ART.

The final contribution of this thesis was in the assessment of models of care for ART delivery to stable patients. The implementation experience and early outcomes from the community-based Adherence Clubs support continued decentralisation and task shifting for effective ART provision. Investigating patient sub-groups and their outcomes in novel models of care confirmed that not all patients benefit equally. Patients who initiated ART in the early years of the programme or with advanced disease need increased support during down-referral. Patients who have recently initiated ART had large improvements in outcomes with down-referral, suggesting earlier decentralisation may lead to additional risk reduction.

The findings of this thesis draw attention to the growing challenge of LTFU in a time when ART programmes are encouraged to increase the pace of scale-up. Globally, millions of HIV patients require ART for effective management of their chronic condition. However, ART expansion must be accompanied by changes to the health system to support retention of patients in care. Based on the results of this thesis, the recommendation for expanding community-based models of care is presented as a strategy to provide ART more efficiently and to alleviate clinical capacity to assist late presenters and complex ART patients. While the challenges and context of ART provision in resource-limited settings have evolved over the past decade, new challenges have arisen. ART was first provided in resource-limited settings without evidence of its effectiveness in this context and no implementation experience. Now, we must once again proceed with limited data, as it is our responsibility to expand access and encourage retention.

Health systems adaptions with approaches that support patient self-management and ART delivery closer to home need to be expanded. Recommendations include expanding community-based models of ART delivery and further research into how community-based models can be integrated to support management of other adult illnesses. With the knowledge that ART can provide benefits beyond the individual it is our collective imperative to improve how ART is provided in support of an AIDS free world.

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APPENDICES

Appendix 1: Ethics documents

Ethics document 1.1 Ethical approval for the Observational Antiretroviral Studies in Southern Africa Collaboration

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E53-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • Facsimile [021] 406 6411
e-mail: preaward@curie.uct..ac.za

12 April 2006

REC REF: 084/2006

Dr. A Boulle
Public Health and Family Medicine

Dear Dr. Boulle

THE OBSERVATIONAL ANTIRETROVIRAL STUDIES IN SOUTHERN AFRICA (OASIS) COLLABORATION

Thank you for submitting your study to the Research Ethics Committee for review. It is a pleasure to inform you the Ethics committee has formally approved the above mentioned study.

Please quote the REC. REF in all your correspondence.

Yours sincerely

DR. M BLOCKMAN
CHAIRPERSON

Ethics document 1.2 Current ethical approval for the International epidemiological Databases to Evaluate AIDS Southern Africa Collaboration

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

23 MAY 2014
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	15.5.2015
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	23/5/2014

Principal Investigator to complete the following:

1. Protocol information

Date form submitted	21 May 2014		
HREC REF Number	084/2006	Current Ethics Approval was granted until	15 May 2014
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	20 May 2014
Signature of Supervisor (if PI is a student)		Date	

Ethics document 1.3 Ethical approval for the analysis of Chapter 5

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/research/humanethics/forms

15 August 2013

HREC REF: 459/2013

Ms A Grimsrud
c/o A/Prof L Myer
Public Health & Family Medicine
Falmouth Building
CIDER, Office 5.36

Dear Ms Grimsrud

PROJECT TITLE: TEMPORAL TRENDS IN MORTALITY AND LOST TO FOLLOW-UP ASSOCIATED WITH SCALING UP OF ANTIRETROVIRAL THERAPY OVER A 10-YEAR PERIOD: MULTICOHORT STUDY OF AFRICAN AND ASIAN HIV PROGRAMS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 30th August 2014

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/research/humanethics/forms)

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.
The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

s.thomas

Ethics document 1.4 Ethical review board exemption from Médecins Sans Frontières for the analysis of Chapter 5

OPERATIONAL RESEARCH STUDY
University of Cape Town & Medecins Sans Frontieres

PRINCIPAL INVESTIGATOR: ANNA GRIMSRUD

COUNTRY: SOUTH AFRICA

SITE: CAPE TOWN

TITLE: **Temporal changes in baseline characteristics and antiretroviral therapy outcomes among adults treated in MSF ART programmes**

COLLABORATING PARTNERS

1 University of Cape Town, Cape Town, South Africa – Grimsrud A, Myer L, Van Cutsem G, Ford N
2 Medecins Sans Frontieres, Cape Town, South Africa – Van Cutsem G
3 Medecins Sans Frontieres, Geneva, Switzerland – Lujan J, Ford N
4 Medecins Sans Frontieres, Amsterdam, Holland – Casas E
5 Medecins Sans Frontieres, Paris, France – Balkan S
6 Epicentre, Paris, France – Pujades M, Poulet E, Pinoges L

The study is based on routinely collected programmatic data and meets the following criteria for exemption from the MSF ERB review:

1. Studies/articles are based on routinely-collected program data
The study is based on the analysis of routine program data collected to ensure the clinical monitoring of patients and the evaluation of HIV programs supported by Medecins Sans Frontieres (MSF). The present study will describe trends in patient characteristics at antiretroviral therapy (ART) initiation and outcomes of patients treated with antiretroviral therapy in MSF-supported ART programs between 2003 and 2012.

2. They are either descriptive/evaluative or targeted evaluations
This is a descriptive study.

3. Confidentiality is respected; no individual patient identifiers are revealed or used.
All data will be held in strict confidence. Paper-based data had been entered prospectively into the Follow-up and Care of HIV Infection and AIDS (FUCHIA) monitoring software (Epicentre, Paris, France) in each site. The data are centralised anonymously in Epicentre - Paris- France, the epidemiological support office of MSF. Databases are password-protected and only identified personnel (e.g. data entry clerks, data managers, epidemiologists or program coordinators) have access to the information. Each patient is assigned a unique identity number and most projects do not enter the patients' names in the database. In places where this is done to facilitate the clinical follow-up of the patients, databases are automatically anonymised before making any copies of the database that are transferred to the Epicentre central team for data cleaning and analysis.

No names or identifying information will be used in any publication or presentation.

4. Harm is minimal but acknowledged where relevant
MSF has provided ART in the 8 participating countries since 2001. All MSF programs provide medical care free of charge, including antiretroviral drugs and laboratory investigations, with clinical consultations performed by doctors, clinical officers, or nurses. All HIV services are aimed to provide comprehensive HIV care and treatment and care for patients is organised in such a way as to ensure patient confidentiality and minimal harm in each specific context.

5. Potential benefits to both the program and the community are described. Since the goal is publication, the relevance to a wider audience is described

Specific patient benefits and community benefits are likely to arise from this study because it will assess how retention in ART programs changes over time and what are the factors that are associated with high retention. The results will highlight how interventions should address loss to follow-up. Necessary improvements can be made in the sites when results are made available.

6. Collaborative involvement and, if applicable, authorship from a local authority or partner (Ministry of Health, DHO, other NGO) is encouraged. If relevant and possible, consultation with a body representing the community is desirable.
The study will involve collaborating partners of MSF/Epicentre and the University of Cape Town. Representatives from of all sections contributing data will be represented on the study manuscript and any eventual publication.

This is to certify that the study entitled "Temporal changes in baseline characteristics and antiretroviral therapy outcomes among adults treated in MSF ART programmes" satisfies the MSF ERB's ethics criteria for analysis of routinely-collected program data.

Signature
Dr Jean Rigal MD
Medical Director
17/10/2012

MSF Operational Centre Paris

MSF France
8 Rue St. Sabin
F-75012, Paris, France

Ethics document 1.5 Ethical approval for the Monitoring and Evaluation of models of care for stable ART patients

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences
Faculty of Health Sciences Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: sumayah.ariefdien@uct.ac.za

07 August 2012

HREC REF: 383/2012

Ms A Grimsrud
School of Public Health & Family Medicine
FHS

Dear Ms Grimsrud

PROJECT TITLE: MONITORING AND EVALUATION OF MODELS OF CARE FOR STABLE ART PATIENTS

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study.

Approval is granted for one year till the 15 August 2013.

Please submit a progress form, using the standardised Annual Report Form, if the study continues beyond the approva period. Please submit a Standard Closure form if the study is completed within the approval period.

Please add the UCT FHS HREC contact details to the I/C form as well as the PI's contact details.
Please add how long the interview will take to the I/C form.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please cuote the HREC.REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA),

Appendix 2: Supplementary tables

Supplementary Table 2.1 Characteristics of systematic reviews on decentralisation and task shifting

Study *Author, date, publication*	**Type of review**	**Objective**	**Criteria for included studies** *Study design, date range, region*	**Description of included studies** *# of publications, programs, countries, patients*	**Key findings related to improving LTFU/retention/adherence**
Models of care - Decentralisation					
Decroo et al 2013 [155]	Systematic review	Describe evidence of community models of care in sub-Saharan Africa	Quantitative and qualitative, Sub-Saharan Africa	18 studies [168, 170-176, 323-329], 6 programs, 3 countries	Programs were for home-based ART delivery in Uganda & Kenya, and the CAGs in Mozambique No key findings related to LTFU
Kredo et al 2013 [153]	Systematic review and meta-analysis	Assess the effects of models of decentralised ART treatment and care for initiating and maintaining ART	Quantitative, 1996-31 March 2013	16 studies (2 RCTs, 14 cohorts; 6 partial decentralisation [163-165, 246, 330, 331], 7 full decentralisation [36, 204, 332-336], 3 CBART [168, 171, 174]), 1 from outside of Africa	Partial decentralisation led to less LTFU after 12-months (RR: 0.55, 95% CI 0.45-0.69), full decentralisation led to less LTFU after 12-months (RR: 0.30, 95% CI 0.17-0.54), insufficient data for community
Suthar et al 2014 [152]	Rapid systematic review*, meta-analysis	Summarise reviews of ART decentralisation (one of four objectives)	Quantitative	10 studies (4 partial decentralisation [163, 165, 171, 174, 246, 330], 4 full decentralisation [36, 204, 332, 334], 2 CBART [168, 174])	Partial decentralisation had improved retention (RR: 1.05, 95% CI 1.01-1.09), full decentralisation had improved retention (RR: 1.12, 95% CI 1.01-1.17), comparable retention in CBART to hospital based (RR: 1.01, 95% CI 0.99-1.03)
Models of care - Task shifting					
Callaghan et al 2010 [159]	Systematic review	Review evidence of task shifting in HIV care in Africa	Quantitative and qualitative and grey literature, until 2009, Africa	84 articles, 51 on outcomes (25 original articles), 15 reviews, 12 opinion pieces, 13 describing models, 6 policy analysis studies	Reduced waiting times and LTFU in task shifted models

Study *Author, date, publication*	**Type of review**	**Objective**	**Criteria for included studies** *Study design, date range, region*	**Description of included studies** *# of publications, programs, countries, patients*	**Key findings related to improving LTFU/retention/adherence**
Emdin et al 2014 [160]	Systematic review and meta-analysis	"Determine if non-physician provided HIV care does result in equivalent outcomes to physician-provided care"	RCTs, non-randomized control trials, cohorts, and case-control studies, excluding lay workers and CHWs, including conference abstracts	12 studies (3 qualitative only, 9 for meta-analysis [44, 45, 164, 165, 332, 334, 337-339] including 5 non-physician initiated ART and 4 non-physician ART maintenance))	No difference in LTFU in non-physician ART maintenance (HR 0.98, 95%CI 0.59-1.66), less LTFU in non-physician ART initiation (HR 0.63, 95% CI 0.45-0.87), Overall in non-physician models, LTFU was reduced (HR 0.72, 95% CI 0.56-0.94)
Kredo et al 2014 [154]	Systematic review and meta-analysis	Describe the quality of ART initiation and maintenance in models that task shift care from doctors to non-doctors	Quantitative	10 studies (4 RCTs, 6 cohorts) [44, 45, 164, 165, 168, 173, 332, 334, 339, 340], all sub-Saharan Africa Assessed nurse initiated and maintenance model, doctor initiated nurse maintenance model, and community maintenance model – looked at outcomes as 12-months by study design	In nurse initiated and maintenance model vs. doctor, lower LTFU from RCTs (RR 0.73, 95% CI 0.55-0.97) and no difference in cohorts; in doctor initiated and nurse maintenance model, no difference in LTFU from RCTs or cohorts; in community maintenance model, no difference in LTFU.
Mdege et al 2013 [161]	Systematic review	Assess the effectiveness and impact on cost of task shifting	RCTs, quasi-experimental studies and modelling studies for costing	8 studies, 6 on effectiveness (4 on clinicians to CHWs [168, 171, 174, 341], 2 on doctors to nurses [44, 45]) and 3 evaluating cost impact	Task shifting from clinicians to CHWs led to comparable adherence and LTFU, task shifting from doctors to nurses led to comparable LTFU.
Mwai et al 2013 [162]	Systematic review	Describe the role and outcomes of CHWs	Quantitative and qualitative, until Dec 2012, sub-Saharan Africa	23 studies, 21 programs (5 qualitative, 7 cohort, 6 mixed methods, 3 RCTs), 9 countries	CHWs provided adherence support, improved ART retention, reduced waiting times

Supplementary Table 2.2 Models of care included in systematic reviews of task shifting and decentralisation

Model of care	Kredo et al 2013, Decentralisation [153]	Kredo et al 2014, Task shifting [154]	Suthar et al 2014 [152]	Callaghan et al 2010 [159]	Emdin et al 2014 [160]	Mdege et al 2013 [161]	Mwai et al 2013 [162]	Decroo et al 2013 [155]
Assefa et al. 2012 [332]	✔	✔	✔	✖	✔	✖	✖	✖
Balcha et al. 2010 [333]	✔	✖	✖	✖	✖	✖	✖	✖
Bedelu et al. 2007 [334]	✔	✔	✔	✔	✔	✖	✖	✖
Brennan et al. 2011 [165]	✔	✔	✖	✖	✔	✖	✖	✖
Chan et al. 2010 [163]	✔	✖	✔	✖	✖	✖	✖	✖
Decroo et al. 2014 [177]	✖	✖	✖	✖	✖	✖	✖	✔
Fairall et al. 2012 [45]	✖	✔	✖	✖	✔	✔	✖	✖
Fatti et al. 2010 [246]	✔	✖	✔	✖	✖	✖	✖	✖
Humphreys et al. 2010 [164]	✔	✔	✖	✖	✔	✖	✖	✖
Jaffar et al. 2009 [168]	✔	✔	✔	✔	✖	✔	✔	✔
Kipp et al. 2012 [172]	✔	✔	✖	✖	✖	✔	✔	✔
Luque-Fernandez et al. 2013 [178]	✖	✖	✖	✖	✖	✖	✖	✖
Massaquoi et al. 2009 [36]	✔	✖	✔	✖	✖	✖	✖	✖
McGuire et al. 2012 [204]	✔	✖	✔	✔	✖	✖	✖	✖
Sanne et al. 2010 [44]	✖	✔	✖	✖	✔	✔	✖	✖
Selke et al. 2010 [174]	✔	✖	✔	✖	✖	✔	✔	✔
Sherr et al. 2010 [339]	✖	✔	✖	✖	✔	✖	✖	✖

Supplementary Table 4.1 Kaplan–Meier estimates of mortality, loss to follow-up and programme retention in care by duration of follow-up, programme size and rate of programme expansion

	n (%)	Mortality % (95% CI)	LTFU % (95% CI)	Retention in care % (95% CI)
Duration of follow-up				
6 months	102,289 (77.3)	6.0 (5.9-6.2)	7.7 (7.6-7.9)	86.7 (86.6-86.9)
12 months	85,249 (64.4)	7.6 (7.5-7.8)	10.8 (10.6-11.0)	82.4 (82.2-82.7)
24 months	61,005 (46.1)	9.3 (9.2-9.5)	15.1 (14.9-15.4)	76.9 (76.7-77.2)
36 months	41,801 (31.6)	10.5 (10.3-10.7)	18.6 (18.4-18.9)	72.8 (72.5-73.1)
48 months	25,835 (19.5)	11.6 (11.3-11.8)	21.7 (21.4-22.0)	69.2 (68.9-69.6)
60 months	14,747 (11.1)	12.5 (12.3-12.8)	24.4 (24.1-24.8)	66.1 (65.8-66.5)
Programme size (patients)	**n (%)**	**12-month mortality % (95% CI)**	**12-month LTFU % (95% CI)**	**12-month retention in care % (95% CI)**
<500	3,512 (2.7)	12.1 (11.1-13.3)	2.7 (2.2-3.3)	85.5 (84.3-86.6)
500-999	7,398 (5.6)	10.6 (9.9-11.3)	5.3 (4.8-5.8)	84.7 (83.9-85.5)
1,000-2,499	25,348 (19.2)	9.4 (9.0-9.7)	7.8 (7.5-8.2)	83.5 (83.1-84.0)
2,500-4,999	37,001 (28.0)	8.1 (7.8-8.4)	10.3 (10.0-10.7)	82.4 (92.0-82.8)
5,000-7,499	22,153 (16.7)	5.5 (5.2-5.9)	14.7 (14.2-15.2)	80.6 (80.1-81.2)
7,500 – 9,999	14,530 (11.0)	5.8 (5.4-6.2)	12.7 (12.1-13.3)	82.3 (81.6-82.9)
10,000-14,999	13,314 (10.1)	6.3 (5.8-6.7)	13.9 (13.3-14.5)	80.7 (80.0-81.4)
15,000-19,999	3,885 (2.9)	4.7 (4.1-5.5)	10.6 (9.7-11.7)	85.2 (84.0-86.3)
≥20,000	5,193 (3.9)	5.6 (4.9-6.4)	12.2 (11.2-13.3)	82.9 (81.6-84.0)
Rate of expansion (patients/month)	**n (%)**	**12-month mortality % (95% CI)**	**12-month LTFU % (95% CI)**	**12-month retention in care % (95% CI)**
<25	23,445 (17.7)	10.0 (9.6-10.4)	5.6 (5.3-6.0)	84.9 (84.5-85.4)
25-60	23,214 (17.5)	9.3 (8.9-9.7)	9.6 (9.2-10.0)	82.0 (81.5-82.5)
60-90	27,009 (20.4)	7.3 (7.0-7.6)	12.6 (12.2-13.1)	81.0 (80.5-81.5)
90-125	27,375 (20.7)	6.7 (6.4-7.1)	11.6 (11.2-12.0)	82.5 (82.0-82.9)
≥125	31,291 (23.7)	5.3 (5.0-5.6)	13.3 (12.9-13.7)	82.1 (81.6-82.6)

Supplementary Table 4.2 Sensitivity analysis: Cox proportional hazards estimates of mortality including patients with missing data*

	0-12 months (n=132,334)				
	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.67 (0.61-0.74)	0.69 (0.63-0.76)	0.82 (0.72-0.93)	0.81 (0.73-0.91)	0.89 (0.78-1.01)
2005	0.53 (0.48-0.58)	0.60 (0.54-0.66)	0.74 (0.65-0.85)	0.76 (0.68-0.86)	0.82 (0.70-0.95)
2006	0.51 (0.47-0.56)	0.65 (0.59-0.71)	0.85 (0.74-0.98)	0.87 (0.77-0.99)	0.96 (0.82-1.12)
2007	0.36 (0.33-0.40)	0.53 (0.48-0.59)	0.82 (0.69-0.96)	0.74 (0.65-0.84)	0.92 (0.77-1.10)
2008	0.34 (0.31-0.38)	0.57 (0.51-0.62)	0.94 (0.79-1.11)	0.84 (0.73-0.97)	1.09 (0.91-1.31)
2009	0.29 (0.26-0.32)	0.50 (0.45-0.55)	0.87 (0.73-1.05)	0.76 (0.65-0.88)	1.03 (0.84-1.24)
2010	0.27 (0.24-0.29)	0.47 (0.43-0.52)	0.79 (0.66-0.96)	0.72 (0.63-0.84)	0.93 (0.76-1.14)
2011	0.28 (0.24-0.32)	0.49 (0.43-0.57)	0.81 (0.65-1.00)	0.75 (0.63-0.90)	0.93 (0.74-1.16)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.90 (0.79-1.03)		0.95 (0.83-1.09)		0.94 (0.82-1.08)
1,000-2,499	0.64 (0.57-0.72)		0.87 (0.75-1.00)		0.87 (0.75-1.00)
2,500-4,999	0.51 (0.45-0.57)		0.77 (0.65-0.91)		0.81 (0.68-0.96)
5,000-7,499	0.31 (0.27-0.35)		0.55 (0.44-0.67)		0.58 (0.47-0.72)
7,500 – 9,999	0.26 (0.23-0.30)		0.43 (0.35-0.54)		0.50 (0.39-0.63)
10,000-14,999	0.22 (0.19-0.25)		0.54 (0.43-0.69)		0.66 (0.50-0.86)
15,000-19,999	0.15 (0.12-0.18)		0.43 (0.32-0.57)		0.53 (0.38-0.73)
≥20,000	0.18 (0.15-0.22)		0.56 (0.42-0.75)		0.70 (0.50-0.96)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.64 (0.59-0.69)			0.86 (0.79-0.94)	0.85 (0.78-0.93)
60-89	0.43 (0.40-0.47)			0.69 (0.62-0.78)	0.74 (0.65-0.83)
90-124	0.37 (0.34-0.41)			0.67 (0.59-0.77)	0.79 (0.68-0.91)
≥125	0.21 (0.20-0.24)			0.54 (0.47-0.63)	0.63 (0.52-0.77)
Sex		Sex			
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref	1.0 (ref)
Male	1.61 (1.54-1.68)	1.30 (1.25-1.36)	1.31 (1.25-1.37)	1.31(1.25-1.37)	1.31 (1.25-1.37)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	1.07 (0.99-1.17)	1.13 (1.05-1.24)	1.14 (1.05-1.24)	1.14 (1.05-1.24)	1.14 (1.05-1.24)
35-44	1.16 (1.07-1.26)	1.23 (1.13-1.34)	1.22 (1.12-1.33)	1.23 (1.13-1.34)	1.22 (1.12-1.33)
45+	1.33 (1.22-1.46)	1.49 (1.36-1.63)	1.48 (1.35-1.62)	1.49 (1.36-1.62)	1.48 (1.35-1.62)
Body Mass Index					
Underweight	3.58 (3.40-3.76)	2.57 (2.44-2.70)	2.58 (2.45-2.71)	2.57 (2.44-2.70)	2.57 (2.44-2.70)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.59 (0.50-0.70)	0.74 (0.62-0.87)	0.73 (0.62-0.86)	0.74 (0.62-0.87)	0.73 (0.62-0.86)
Obese	0.91 (0.69-1.20)	1.20 (0.90-1.58)	1.18 (0.89-1.56)	1.20 (0.90-1.59)	1.18 (0.89-1.57)
Missing	7.21 (6.75-7.70)	6.18 (5.78-6.60)	6.39 (5.98-6.83)	6.24 (5.84-6.67)	6.45 (6.04-6.90)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.60 (0.56-0.65)	0.70 (0.65-0.75)	0.70 (0.65-0.76)	0.70 (0.65-0.76)	0.70 (0.65-0.76)
50-99	0.38 (0.36-0.41)	0.50 (0.47-0.54)	0.51 (0.47-0.55)	0.51 (0.47-0.55)	0.51 (0.47-0.55)
100-149	0.26 (0.24-0.28)	0.39 (0.36-0.43)	0.40 (0.36-0.43)	0.40 (0.37-0.43)	0.40 (0.37-0.43)
150-199	0.19 (0.17-0.21)	0.34 (0.31-0.37)	0.34 (0.31-0.37)	0.34 (0.31-0.37)	0.34 (0.31-0.37)
200-349	0.14 (0.13-0.16)	0.28 (0.25-0.30)	0.28 (0.26-0.31)	0.28 (0.26-0.31)	0.28 (0.26-0.31)
≥350	0.24 (0.21-0.28)	0.38 (0.32-0.44)	0.38 (0.33-0.44)	0.38 (0.33-0.44)	0.38 (0.33-0.44)
Missing	0.45 (0.42-0.48)	0.51 (0.48-0.54)	0.52 (0.48-0.55)	0.52 (0.49-0.56)	0.52 (0.49-0.56)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	2.60 (2.42-2.79)	1.79 (1.66-1.93)	1.74 (1.61-1.87)	1.75 (1.62-1.88)	1.72 (1.60-1.86)
IV	5.70 (5.31-6.11)	3.09 (2.87-3.33)	3.00 (2.78-3.23)	3.01 (2.79-3.24)	2.96 (2.74-3.19)
Missing	2.04 (1.72-2.43)	1.53 (1.28-1.82)	1.49 (1.25-1.77)	1.51 (1.26-1.79)	1.48 (1.24-1.76)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.2(continued) Sensitivity analysis: Cox proportional hazards estimates of mortality including patients with missing data*

	12-72 months (n=85,171)				
	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.77 (0.66-0.91)	0.77 (0.65-0.90)	0.88 (0.72-1.08)	0.88 (0.74-1.05)	0.91 (0.74-1.12)
2005	0.69 (0.59-0.81)	0.72 (0.61-0.84)	0.88 (0.71-1.09)	0.85 (0.71-1.03)	0.88 (0.71-1.11)
2006	0.58 (0.50-0.68)	0.63 (0.54-0.74)	0.78 (0.63-0.98)	0.78 (0.64-0.95)	0.81 (0.64-1.02)
2007	0.53 (0.46-0.62)	0.63 (0.53-0.74)	0.80 (0.62-1.04)	0.78 (0.64-0.97)	0.83 (0.63-1.09)
2008	0.46 (0.38-0.54)	0.56 (0.47-0.66)	0.74 (0.56-0.98)	0.72 (0.57-0.92)	0.78 (0.58-1.04)
2009	0.43 (0.35-0.52)	0.52 (0.42-0.63)	0.70 (0.51-0.96)	0.68 (0.52-0.88)	0.73 (0.53-1.00)
2010	0.50 (0.35-0.72)	0.61 (0.42-0.87)	0.93 (0.60-1.45)	0.79 (0.53-1.17)	0.97 (0.62-1.52)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.83 (0.69-1.00)		0.97 (0.80-1.19)		0.98 (0.80-1.19)
1,000-2,499	0.77 (0.65-0.91)		1.03 (0.84-1.27)		1.05 (0.96-1.29)
2,500-4,999	0.59 (0.49-0.71)		0.83 (0.65-1.06)		0.89 (0.69-1.14)
5,000-7,499	0.42 (0.34-0.52)		0.65 (0.48-0.90)		0.69 (0.50-0.96)
7,500 – 9,999	0.38 (0.29-0.51)		0.58 (0.40-0.85)		0.63 (0.41-0.96)
10,000-14,999	0.42 (0.33-0.54)		0.81 (0.55-1.19)		0.88 (0.57-1.34)
15,000-19,999	0.35 (0.25-0.50)		0.80 (0.49-1.32)		0.93 (0.531.61)
≥20,000	0.18 (0.06-0.55)		0.29 (0.08-1.02)		0.34 (0.10-1.19)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.74 (0.65-0.84)			0.84 (0.73-0.97)	0.87 (0.75-1.00)
60-89	0.56 (0.49-0.65)			0.72 (0.60-0.86)	0.81 (0.67-0.99)
90-124	0.52 (0.45-0.61)			0.75 (0.61-0.92)	0.92 (0.72-1.17)
≥125	0.39 (0.32-0.47)			0.66 (0.50-0.86)	0.79 (0.56-1.12)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.77 (1.64-1.91)	1.59 (1.47-1.72)	1.59 (1.47-1.72)	1.59 (1.47-1.72)	1.59 (1.47-1.72)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.94 (0.81-1.09)	0.95 (0.82-1.10)	0.95 (0.81-1.10)	0.95 (0.82-1.10)	0.95 (0.81-1.10)
35-44	1.10 (0.92-1.27)	1.07 (0.91-1.24)	1.06 (0.91-1.24)	1.07 (0.91-1.24)	1.06 (0.91-1.24)
45+	1.66 (1.42-1.95)	1.60 (1.37-1.88)	1.60 (1.36-1.87)	1.61 (1.37-1.88)	1.60 (1.37-1.88)
Body Mass Index					
Underweight	1.64 (1.51-1.78)	1.46 (1.34-1.58)	1.46 (1.35-1.59)	1.45 (1.34-1.58)	1.46 (1.34-1.59)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.85 (0.70-1.04)	0.96 (0.79-1.18)	0.96 (0.78-1.17)	0.97 (0.79-1.18)	0.96 (0.79-1.17)
Obese	0.95 (0.64-1.43)	1.11 (0.74-1.66)	1.10 (0.73-1.64)	1.11 (0.74-1.67)	1.10 (0.73-1.65)
Missing	3.83 (3.31-4.43)	3.68 (3.18-4.27)	3.80 (3.28-3.41)	3.70 (3.19-4.29)	3.84 (3.31-4.45)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.92 (0.78-1.09)	0.96 (0.81-1.14)	0.96 (0.81-1.14)	0.96 (0.81-1.14)	0.96 (0.81-1.14)
50-99	0.86 (0.73-1.00)	0.95 (0.81-1.11)	0.95 (0.81-1.11)	0.95 (0.82-1.11)	0.95 (0.81-1.11)
100-149	0.63 (0.54-0.75)	0.75 (0.63-0.89)	0.75 (0.64-0.89)	0.75 (0.64-0.89)	0.75 (0.64-0.89)
150-199	0.64 (0.44-0.61)	0.82 (0.70-0.97)	0.82 (0.70-0.97)	0.83 (0.70-0.98)	0.82 (0.70-0.97)
200-349	0.52 (0.44-0.61)	0.69 (0.58-0.81)	0.69 (0.58-0.81)	0.70 (0.59-0.82)	0.69 (0.59-0.82)
≥350	0.79 (0.60-1.05)	0.95 (0.72-1.26)	0.96 (0.72-1.27)	0.85 (0.72-1.26)	0.95 (0.72-1.26)
Missing	0.90 (0.78-1.03)	0.95 (0.82-1.09)	0.97 (0.83-1.12)	0.96 (0.83-1.11)	0.97 (0.84-1.12)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.54 (1.38-1.72)	1.27 (1.13-1.43)	1.26 (1.12-1.42)	1.26 (1.12-1.42)	1.25 (1.12-1.41)
IV	2.26 (2.01-2.53)	1.68 (1.49-1.90)	1.65 (1.46-1.87)	1.66 (1.46-1.87)	1.64 (1.45-1.85)
Missing	1.43 (1.10-1.86)	1.29 (0.99-1.68)	1.28 (0.98-1.68)	1.28 (0.98-1.67)	1.27 (0.97-1.66)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.3 Sensitivity analysis: Cox proportional hazards estimates of LTFU including patients with missing data*

	0-12 months (n=132,334)				
	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.62 (1.40-1.88)	1.59 (1.37-1.84)	1.06 (0.88-1.27)	1.42 (1.21-1.66)	1.04 (0.87-1.25)
2005	1.69 (1.46-1.95)	1.76 (1.52-2.03)	1.16 (0.97-1.39)	1.55 (1.32-1.82)	1.12 (0.92-1.35)
2006	1.62 (1.41-1.86)	1.86 (1.62-2.14)	1.21 (1.01-1.45)	1.58 (1.34-1.87)	1.12 (0.92-1.35)
2007	2.04 (1.78-2.34)	2.55 (2.22-2.92)	1.48 (1.23-1.80)	2.12 (1.80-2.50)	1.40 (1.14-1.71)
2008	2.26 (1.98-2.59)	2.83 (2.47-3.24)	1.70 (1.40-2.06)	2.25 (1.90-2.66)	1.46 (1.27-1.92)
2009	2.14 (1.87-2.45)	2.72 (2.37-3.12)	1.56 (1.27-1.90)	2.07 (1.75-2.46)	1.35 (1.09-1.67)
2010	2.99 (2.62-3.42)	3.84 (3.35-4.40)	2.15 (1.75-2.63)	2.86 (2.41-3.39)	1.90 (1.53-2.36)
2011	3.64 (3.15-4.21)	4.77 (4.12-5.53)	2.63 (2.12-3.27)	3.51 (2.93-4.20)	2.44 (1.94-3.06)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.71 (1.29-2.26)		1.93 (1.45-2.56)		1.80 (1.35-2.39)
1,000-2,499	3.02 (2.33-3.92)		2.81 (2.13-3.72)		2.60 (1.97-3.44)
2,500-4,999	3.29 (2.54-4.27)		2.90 (2.16-3.88)		2.54 (1.89-3.41)
5,000-7,499	4.36 (3.36-5.67)		3.29 (2.42-4.48)		2.86 (2.10-3.90)
7,500 – 9,999	4.60 (3.53-5.99)		2.92 (2.13-4.00)		2.13 (1.54-2.95)
10,000-14,999	6.17 (4.73-8.04)		3.95 (2.79-5.32)		2.34 (1.67-3.30)
15,000-19,999	5.97 (4.49-7.93)		4.50 (3.18-6.38)		2.79 (1.94-4.01)
≥20,000	7.35 (5.55-9.73)		3.78 (2.66-3.67)		2.26 (1.56-3.27)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.57 (1.41-1.75)			1.32 (1.17-1.49)	1.27 (1.12-1.44)
60-89	1.94 (1.73-2.18)			1.34 (1.16-1.54)	1.30 (1.12-1.51)
90-124	2.16 (1.92-2.4)			1.40 (1.20-1.63)	1.46 (1.24-1.73)
≥125	3.09 (2.74-3.48)			1.79 (1.52-2.10)	2.04 (1.68-2.46)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.31 (1.27-1.36)	1.29 (1.24-1.33)	1.28 (1.24-1.33)	1.28 (1.23-1.33)	1.28 (1.23-1.33)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.72 (0.69-0.76)	0.76 (0.72-0.80)	0.76 (0.72-0.80)	0.76 (0.72-0.80)	0.76 (0.72-0.80)
35-44	0.60 (0.57-0.64)	0.62 (0.59-0.66)	0.62 (0.59-0.66)	0.62 (0.58-0.66)	0.62 (0.59-0.66)
45+	0.60 (0.56-0.64)	0.61 (0.57-0.65)	0.61 (0.57-0.65)	0.61 (0.57-0.65)	0.61 (0.57-0.65)
Body Mass Index					
Underweight	1.69 (1.63-1.76)	1.50 (1.44-1.57)	1.50 (1.44-1.56)	1.50 (1.44-1.57)	1.50 (1.44-1.56)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.91 (0.83-0.99)	1.00 (0.91-1.09)	1.00 (0.91-1.08)	1.00 (0.91-1.09)	0.99 (0.91-1.09)
Obese	1.13 (0.96-1.32)	1.28 (1.10-1.50)	1.28 (1.09-1.50)	1.29 (1.10-1.51)	1.28 (1.09-1.50)
Missing	2.91 (2.76-3.07)	2.70 (2.55-2.85)	2.72 (2.57-2.88)	2.69 (2.54-2.84)	2.73 (2.58-2.88)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.81 (0.75-0.88)	0.89 (0.82-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)	0.88 (0.81-0.96)
50-99	0.62 (0.58-0.67)	0.73 (0.68-0.79)	0.72 (0.67-0.78)	0.72 (0.67-0.78)	0.72 (0.67-0.78)
100-149	0.57 (0.53-0.61)	0.70 (0.65-0.75)	0.69 (0.64-0.75)	0.69 (0.64-0.75)	0.69 (0.64-0.75)
150-199	0.48 (0.44-0.51)	0.60 (0.56-0.65)	0.60 (0.55-0.65)	0.60 (0.55-0.65)	0.60 (0.55-0.65)
200-349	0.52 (0.48-0.55)	0.60 (0.56-0.65)	0.59 (0.55-0.63)	0.60 (0.55-0.63)	0.59 (0.55-0.63)
≥350	0.79 (0.71-0.87)	0.75 (0.67-0.83)	0.75 (0.67-0.83)	0.75 (0.68-0.84)	0.75 (0.68-0.84)
Missing	0.83 (0.78-0.89)	0.92 (0.86-0.98)	0.93 (0.87-0.99)	0.92 (0.86-0.98)	0.92 (0.86-0.98)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.10 (1.05-1.14)	1.17 (0.11-1.22)	1.17 (1.12-1.23)	1.18 (1.13-1.24)	1.18 (1.12-1.23)
IV	1.51 (1.44-1.59)	1.54 (1.46-1.62)	1.55 (1.48-1.64)	1.57 (1.49-1.65)	1.57 (1.49-1.65)
Missing	1.01 (0.88-1.17)	1.05 (0.91-1.21)	1.04 (0.90-1.20)	1.05 (0.91-1.21)	1.03 (0.89-1.18)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.3 (continued) Sensitivity analysis: Cox proportional hazards estimates of LTFU including patients with missing data*

	12-72 months (n=85,171)				
	Univariate HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)	Model 4 HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.31 (1.16-1.49)	1.30 (1.15-1.47)	1.07 (0.90-1.26)	1.15 (1.00-1.31)	1.02 (0.87-1.21)
2005	1.19 (1.05-1.35)	1.21 (1.07-1.37)	0.99 (0.83-1.18)	0.96 (0.84-1.11)	0.84 (0.70-1.00)
2006	1.47 (1.31-1.66)	1.56 (1.39-1.76)	1.30 (1.10-1.54)	1.16 (1.00-1.34)	1.00 (0.84-1.20)
2007	1.82 (1.62-2.05)	2.00 (1.77-2.26)	1.74 (1.43-2.11)	1.46 (1.26-1.70)	1.37 (1.11-1.69)
2008	2.44 (2.15-2.75)	2.68 (2.37-2.04)	2.33 (1.89-2.86)	1.86 (1.58-2.19)	1.80 (1.45-2.24)
2009	3.60 (3.16-4.10)	3.96 (2.47-4.51)	3.59 (2.88-4.46)	2.67 (2.25-3.18)	2.61 (2.06-3.29)
2010	6.50 (5.45-7.76)	7.07 (5.92-8.46)	6.61 (5.11-8.55)	4.87 (3.95-6.00)	4.94 (3.77-6.47)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.64 (1.34-2.00)		1.60 (1.31-1.96)		1.55 (1.27-1.89)
1,000-2,499	2.35 (1.94-2.86)		1.75 (1.41-2.16)		1.69 (1.27-2.10)
2,500-4,999	2.66 (2.19-3.22)		1.87 (1.48-2.36)		1.64 (1.29-2.08)
5,000-7,499	3.80 (3.11-4.65)		1.65 (1.26-2.15)		1.37 (1.3-1.79)
7,500 – 9,999	5.47 (4.42-6.77)		1.67 (1.26-2.21)		1.07 (0.79-1.45)
10,000-14,999	4.06 (3.22-5.12)		1.49 (1.09-2.04)		1.02 (0.74-1.43)
15,000-19,999	4.89 (3.69-6.48)		1.16 (0.80-1.67)		0.84 (0.57-1.23)
≥20,000	7.03 (4.30-11.48)		0.95 (0.54-1.67)		0.67 (0.38-1.20)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.48 (1.33-1.64)			1.27 (1.14-1.42)	1.21 (1.08-1.35)
60-89	1.96 (1.75-2.18)			1.47 (1.28-1.68)	1.49 (1.29-1.72)
90-124	2.79 (2.48-3.14)			1.81 (1.56-2.11)	1.98 (1.68-2.34)
≥125	3.72 (3.25-4.27)			1.69 (1.41-2.03)	2.28 (1.84-2.82)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.16 (1.11-1.21)	1.21 (1.16-1.27)	1.21 (1.16-1.27)	1.21 (1.15-1.27)	1.21 (1.16-1.27)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.63 (0.59-0.67)	0.64 (0.60-0.69)	0.64 (0.60-0.69)	0.64 (0.60-0.69)	0.64 (0.60-0.69)
35-44	0.50 (0.47-0.54)	0.51 (0.47-0.55)	0.50 (0.47-0.54)	0.51 (0.47-0.55)	0.50 (0.47-0.54)
45+	0.51 (0.47-0.56)	0.50 (0.46-0.55)	0.50 (0.46-0.55)	0.51 (0.47-0.55)	0.50 (0.46-0.55)
Body Mass Index					
Underweight	1.12 (1.06-1.17)	1.05 (1.00-1.11)	1.06 (1.00-1.11)	1.05 (1.00-1.11)	1.05 (1.00-1.11)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.99 (0.90-1.09)	1.07 (0.97-1.17)	1.06 (0.97-1.17)	1.07 (0.97-1.18)	1.07 (0.97-1.17)
Obese	0.87 (0.70-1.07)	0.98 (0.79-1.121)	0.97 (0.79-1.20)	0.98 (0.79-1.21)	0.97 (0.79-1.20)
Missing	2.00 (1.84-2.18)	1.97 (1.81-2.14)	2.00 (1.84-2.18)	1.99 (1.83-2.17)	2.07 (1.90-2.25)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.93 (0.84-1.04)	1.00 (0.90-1.11)	1.00 (0.90-1.12)	0.99 (0.89-1.11)	1.00 (0.90-1.12)
50-99	0.86 (0.78-0.95)	0.95 (0.86-1.05)	0.96 (0.87-1.05)	0.94 (0.86-1.04)	0.95 (0.86-1.05)
100-149	0.84 (0.77-0.93)	0.94 (0.85-1.03)	0.95 (0.86-1.04)	0.93 (0.84-1.02)	0.94 (0.85-1.03)
150-199	0.87 (0.79-0.96)	0.96 (0.87-1.06)	0.97 (0.88-1.07)	0.95 (0.86-1.05)	0.96 (0.87-1.06)
200-349	0.91 (0.83-1.00)	0.91 (0.82-1.00)	0.92 (0.84-1.01)	0.90 (0.82-0.99)	0.92 (0.83-1.01)
≥350	1.15 (0.98-1.34)	1.04 (0.89-1.23)	1.06 (0.90-1.24)	1.02 (0.87-1.20)	1.03 (0.88-1.21)
Missing	1.02 (0.94-1.12)	1.08 (0.99-1.18)	1.08 (0.98-1.18)	1.04 (0.96-1.14)	1.05 (0.96-1.14)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.05 (0.99-1.11)	1.19 (1.12-1.26)	1.18 (1.11-1.25)	1.18 (1.11-1.25)	1.16 (1.10-1.23)
IV	1.11 (1.04-1.18)	1.29 (1.20-1.38)	1.28 (1.20-1.37)	1.29 (1.21-1.38)	1.29 (1.20-1.37)
Missing	1.06 (0.89-1.25)	1.14 (0.96-1.35)	1.12 (0.94-1.33)	1.11 (0.94-1.32)	1.08 (0.91-1.29)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.4 Sensitivity analysis: Competing risks estimates of mortality*

	0-12 months				
	Univariate	Model 1 (n=94,571)	Model 2 (n=94,571)	Model 3 (n=94,571)	Model 4 (n=94,571)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.65 (0.59-0.71)	0.66 (0.57-0.76)	0.53 (0.46-0.62)	0.64 (0.56-0.74)	0.54 (0.46-0.63)
2005	0.56 (0.51-0.61)	0.60 (0.53-0.69)	0.51 (0.44-0.59)	0.61 (0.53-0.69)	0.53 (0.46-0.62)
2006	0.54 (0.49-0.59)	0.55 (0.49-0.61)	0.47 (0.29-0.38)	0.55 (0.49-0.62)	0.48 (0.42-0.55)
2007	0.36 (0.33-0.40)	0.41 (0.36-0.46)	0.33 (0.29-0.38)	0.40 (0.35-0.45)	0.34 (0.29-0.39)
2008	0.34 (0.31-0.38)	0.48 (0.43-0.55)	0.38 (0.33-0.44)	0.45 (0.39-0.51)	0.39 (0.34-0.45)
2009	0.29 (0.27-0.32)	0.47 (0.42-0.53)	0.39 (0.34-0.45)	0.43 (0.38-0.49)	0.39 (0.33-0.45)
2010	0.26 (0.24-0.29)	0.48 (0.43-0.54)	0.36 (0.31-0.42)	0.43 (0.38-0.49)	0.37 (0.32-0.43)
2011	0.25 (0.21-0.28)	0.44 (0.38-0.52)	0.32 (0.26-0.38)	0.39 (0.33-0.47)	0.32 (0.27-0.39)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.85 (0.76-0.96)		1.10 (0.92-1.31)		1.10 (0.92-1.31)
1,000-2,499	0.74 (0.67-0.82)		1.53 (1.29-1.80)		1.49 (1.26-1.77)
2,500-4,999	0.64 (0.58-0.71)		1.47 (1.24-1.73)		1.35 (1.10-1.64)
5,000-7,499	0.44 (0.39-0.49)		1.35 (1.12-1.62)		1.23 (0.98-154)
7,500 – 9,999	0.41 (0.36-0.46)		1.32 (1.08-1.61)		1.00 (0.77-1.29)
10,000-14,999	0.43 (0.38-0.48)		1.97 (1.62-2.39)		1.33 (0.99-1.77)
15,000-19,999	0.36 (0.30-0.43)		1.61 (1.26-2.07)		1.08 (0.78-1.49)
≥20,000	0.43 (0.36-0.50)		2.13 (1.69-2.69)		1.39 (1.01-1.92)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.91 (0.86-0.97)			1.14 (1.05-1.24)	1.09 (0.99-1.20)
60-89	0.69 (0.65-0.73)			1.02 (0.94-1.12)	1.05 (0.91-1.21)
90-124	0.64 (0.60-0.690			1.09 (1.00-1.20)	1.16 (1.01-1.34)
≥125	0.49 (0.46-0.53)			1.41 (1.28-1.56)	1.55 (1.25-1.92)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.56 (1.50-1.63)	1.21 (1.14-1.28)	1.22 (1.15-1.29)	1.21 (1.15-1.28)	1.22 (1.15-1.29)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	1.10 (1.01-1.19)	1.11 (0.99-1.24)	1.10 (0.98-1.23)	1.11 (0.99-1.24)	1.10 (0.98-1.23)
35-44	1.19 (1.09-1.29)	1.23 (1.10-1.38)	1.22 (1.08-1.36)	1.22 (1.09-1.37)	1.21 (1.08-1.36)
45+	1.37 (1.26-1.50)	1.60 (1.42-1.80)	1.56 (1.39-1.76)	1.57 (1.39-1.77)	1.56 (1.38-1.76)
Body Mass Index					
Underweight	3.49 (3.32-3.66)	2.47 (2.33-2.63)	2.49 (2.34-2.65)	2.48 (2.33-2.64)	2.49 (2.34-2.65)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.58 (0.49-0.68)	0.72 (0.60-0.87)	0.72 (0.60-0.87)	0.73 (0.60-0.88)	0.72 (0.60-0.87)
Obese	0.86 (0.65-1.13)	1.13 (0.83-1.55)	1.15 (0.84-1.57)	1.16 (0.85-1.58)	1.14 (0.84-1.56)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.64 (0.59-0.69)	0.73 (0.67-0.80)	0.73 (0.66-0.79)	0.73 (0.67-0.79)	0.73 (0.67-0.79)
50-99	0.43 (0.40-0.46)	0.57 (0.53-0.62)	0.57 (0.52-0.62)	0.57 (0.52-0.62)	0.57 (0.52-0.62)
100-149	0.29 (0.27-0.32)	0.46 (0.42-0.51)	0.46 (0.42-0.50)	0.46 (0.42-0.50)	0.46 (0.42-0.50)
150-199	0.21 (0.20-0.23)	0.39 (0.35-0.43)	0.38 (0.35-0.43)	0.39 (0.35-0.43)	0.38 (0.35-0.43)
200-349	0.17 (0.15-0.18)	0.35 (0.31-0.38)	0.34 (0.31-0.37)	0.34 (0.31-0.38)	0.34 (0.31-0.37)
≥350	0.28 (0.24-0.32)	0.53 (0.45-0.62)	0.52 (0.45-0.61)	0.52 (0.44-0.61)	0.52 (0.45-0.61)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	2.43 (2.27-2.61)	1.50 (1.37-1.63)	1.55 (1.42-1.69)	1.58 (1.43-1.71)	1.58 (1.45-1.73)
IV	5.41 (5.05-5.79)	2.45 (2.23-2.69)	2.55 (2.32-2.81)	2.61 (2.37-2.87)	2.61 (2.37-2.87)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.4 (continued) Sensitivity analysis: Competing risks estimates of mortality*

		12-72 months			
	Univariate	Model 1 (n=62,080)	Model 2 (n=62,080)	Model 3 (n=62,080)	Model 4 (n=62,080)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	0.82 (0.70-0.96)	0.80 (0.65-0.99)	0.89 (0.71-1.11)	0.95 (0.77-1.18)	0.91 (0.73-1.14)
2005	0.82 (0.71-0.96)	0.79 (0.65-0.96)	0.97 (0.78-1.19)	0.90 (0.74-1.10)	0.92 (0.74-1.15)
2006	0.69 (0.60-0.80)	0.69 (0.58-0.83)	0.82 (0.67-0.99)	0.78 (0.65-0.95)	0.78 (0.64-0.95)
2007	0.60 (0.51-0.69)	0.69 (0.57-0.83)	0.80 (0.65-0.98)	0.80 (0.66-0.97)	0.75 (0.61-0.93)
2008	0.48 (0.40-0.56)	0.61 (0.50-0.75)	0.73 (0.57-0.92)	0.71 (0.57-0.89)	0.71 (0.56-0.90)
2009	0.43 (0.35-0.51)	0.60 (0.48-0.75)	0.72 (0.55-0.95)	0.67 (0.53-0.86)	0.68 (0.51-0.89)
2010	0.46 (0.32-0.66)	0.76 (0.52-1.12)	1.02 (0.67-1.55)	0.86 (0.58-1.28)	0.97 (0.64-1.47)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	0.86 (0.73-1.02)		1.01 (0.80-1.26)		1.04 (0.83-1.30)
1,000-2,499	0.82 (0.70-0.95)		1.13 (0.91-1.39)		1.23 (0.99-1.52)
2,500-4,999	0.57 (0.49-0.67)		0.74 (0.60-0.92)		0.91 (0.70-1.19)
5,000-7,499	0.39 (0.32-0.46)		0.64 (0.49-0.84)		0.80 (0.59-1.11)
7,500 – 9,999	0.35 (0.27-0.44)		0.63 (0.45-0.89)		0.78 (0.51-1.18)
10,000-14,999	0.57 (0.47-0.70)		1.09 (0.83-1.44)		1.38 (0.94-2.02)
15,000-19,999	0.46 (0.34-0.64)		1.02 (0.67-1.55)		1.43 (0.84-2.43)
≥20,000	0.22 (0.07-0.70)		0.38 (0.11-1.27)		0.52 (0.15-1.82)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	0.69 (0.63-0.77)			0.76 (0.66-0.86)	0.80 (0.69-0.93)
60-89	0.52 (0.47-0.58)			0.58 (0.50-0.67)	0.73 (0.58-0.90)
90-124	0.57 (0.51-0.64)			0.75 (0.64-0.87)	0.91 (0.72-1.16)
≥125	0.45 (0.39-0.53)			0.76 (0.62-0.93)	0.72 (0.51-1.03)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.80 (1.67-1.94)	1.56 (1.42-1.72)	1.51 (1.37-1.67)	1.50 (1.36-1.66)	1.50 (1.36-1.66)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.98 (0.84-1.14)	0.87 (0.72-1.05)	0.88 (0.73-1.06)	0.88 (0.73-1.07)	0.88 (0.73-1.06)
35-44	1.13 (0.98-1.32)	1.03 (0.85-1.25)	1.06 (0.87-1.28)	1.07 (0.88-1.29)	1.06 (0.88-1.29)
45+	1.66 (1.42-1.94)	1.54 (1.27-1.88)	1.62 (1.33-1.98)	1.64 (1.35-2.00)	1.64 (1.34-2.00)
Body Mass Index					
Underweight	1.67 (1.54-1.81)	1.54 (1.39-1.71)	1.51 (1.36-1.67)	1.50 (1.35-1.66)	1.50 (1.36-1.66)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.85 (0.69-1.03)	1.01 (0.80-1.27)	1.01 (0.80-1.28)	1.01 (0.80-1.28)	1.01 (0.80-1.28)
Obese	0.95 (0.64-1.43)	0.75 (0.42-1.33)	0.76 (0.43-1.35)	0.77 (0.43-1.36)	0.77 (0.43-1.36)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.95 (0.80-1.12)	1.01 (0.84-1.21)	0.98 (0.82-1.18)	0.99 (0.83-1.19)	0.98 (0.82-1.18)
50-99	0.87 (0.74-1.01)	1.04 (0.88-1.22)	1.02 (0.86-1.21)	1.04 (0.88-1.23)	1.03 (0.87-1.21)
100-149	0.64 (0.54-0.75)	0.82 (0.68-0.98)	0.82 (0.68-0.98)	0.83 (0.69-1.00)	0.82 (0.69-0.99)
150-199	0.64 (0.55-0.76)	0.92 (0.77-1.10)	0.91 (0.76-1.08)	0.93 (0.78-1.12)	0.91 (0.76-1.10)
200-349	0.53 (0.45-0.62)	0.79 (0.66-0.94)	0.76 (0.64-0.92)	0.79 (0.66-0.95)	0.77 (0.64-0.93)
≥350	0.78 (0.59-1.03)	1.01 (0.74-1.37)	1.02 (0.75-1.39)	1.02 (0.75-1.39)	1.02 (0.75-1.39)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III		1.49 (1.33-1.66)	1.14 (0.99-1.31)	1.11 (0.97-1.27)	1.13 (0.99-1.30)
IV		2.28 (2.04-2.55)	1.46 (1.26-1.69)	1.43 (1.24-1.66)	1.45 (1.25-1.68)

*All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.5 Sensitivity analysis: Competing risks estimates of LTFU*

	0-12 months				
	Univariate	Model 1 (n=94,571)	Model 2 (n=94 ,571)	Model 3 (n=94,571)	Model 4 (n=94,571)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.66 (1.44-1.93)	1.45 (1.16-1.82)	0.89 (0.70-1.12)	1.02 (0.81-1.28)	0.91 (0.72-1.15)
2005	1.59 (1.38-1.83)	1.75 (1.43-2.16)	0.99 (0.79-1.23)	1.24 (1.00-1.53)	1.11 (0.89-1.40)
2006	1.45 (1.26-1.66)	1.72 (1.42-2.10)	0.95 (0.77-1.16)	1.20 (0.98-1.47)	1.02 (0.83-1.26)
2007	1.89 (1.65-2.16)	2.57 (2.12-3.10)	1.15 (0.94-1.41)	1.69 (1.40-2.06)	1.34 (1.09-1.65)
2008	2.13 (1.86-2.44)	2.94 (2.43-3.55)	1.31 (1.07-1.61)	1.82 (1.50-2.21)	1.50 (1.22-1.85)
2009	1.90 (1.66-2.17)	2.71 (2.24-3.28)	1.23 (1.00-1.51)	1.77 (1.46-2.15)	1.44 (1.16-1.78)
2010	2.66 (2.33-3.04)	4.00 (3.32-4.82)	1.79 (1.47-2.20)	2.56 (2.11-3.10)	2.15 (1.74-2.65)
2011	2.90 (2.51-3.35	3.90 (3.19-4.76)	1.76 (1.42-2.19)	2.50 (2.04-3.06)	2.14 (1.71-2.67)
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.99 (1.58-2.52)		2.52 (1.82-3.50)		2.39 (1.72-3.32)
1,000-2,499	3.03 (1.58-2.52)		3.22 (2.36-4.39)		2.54 (1.89-3.48)
2,500-4,999	4.21 (3.40-5.20)		5.21 (3.83-7.07)		2.67 (1.93-3.70)
5,000-7,499	6.09 (4.86-7.44)		7.13 (5.23-9.74)		3.21 (2.29-4.49)
7,500 – 9,999	5.21 (4.20-6.46)		5.84 (4.26-7.99)		2.36 (1.67-3.33)
10,000-14,999	5.55 (4.47-6.88)		6.88 (5.03-9.42)		2.51 (1.77-3.57)
15,000-19,999	4.35 (3.45-5.48)		6.28 (4.50-8.77)		2.25 (1.56-3.26)
≥20,000	5.25 (4.19-6.59)		5.14 (3.72-7.13)		1.79 (1.24-2.48)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.76 (1.64-1.89)			1.91 (1.75-2.10)	1.71 (1.53-1.91)
60-89	2.40 (2.25-2.57)			2.88 (2.64-3.15)	2.32 (2.03-2.66)
90-124	2.18 (2.04-2.33)			2.41 (2.21-2.64)	2.12 (1.84-2.43)
≥125	2.57 (2.41-2.75)			2.74 (2.50-3.00)	2.86 (2.39-3.34)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.17 (1.13-1.21)	1.11 (1.06-1.16)	1.18 (1.12-1.23)	1.18 (1.12-1.23)	1.18 (1.13-1.24)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.70 (0.66-0.74)	0.70 (0.65-0.75)	0.70 (0.65-0.75)	0.70 (0.65-0.75)	0.70 (0.65-0.75)
35-44	0.60 (0.56-0.63)	0.61 (0.56-0.66)	0.59 (0.55-0.64)	0.59 (0.55-0.64)	0.59 (0.55-0.64)
45+	0.62 (0.58-0.66)	0.63 (0.58-0.69)	0.59 (0.54-0.64)	0.59 (0.54-0.64)	0.59 (0.54-0.64)
Body Mass Index					
Underweight	1.46 (1.40-1.52)	1.36 (1.30-1.43)	1.40 (1.33-1.47)	1.41 (1.34-1.48)	1.40 (1.34-1.47)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	0.96 (0.83-0.99)	0.93 (0.84-1.03)	0.94 (0.85-1.05)	0.94 (0.85-1.04)	0.94 (0.84-1.04)
Obese	1.20 (0.88-1.04)	1.14 (0.94-1.39)	1.15 (0.95-1.39)	1.14 (0.94-1.38)	1.13 (0.93-1.37)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.81 (0.75-0.88)	0.85 (0.78-0.93)	0.87 (0.80-0.95)	0.87 (0.80-0.96)	0.88 (0.81-0.96)
50-99	0.62 (0.58-0.67)	0.76 (0.70-0.83)	0.75 (0.69-0.81)	0.76 (0.70-0.82)	0.76 (0.70-0.82)
100-149	0.57 (0.53-0.61)	0.76 (0.70-0.83)	0.74 (0.68-0.81)	0.75 (0.69-0.81)	0.75 (0.69-0.81)
150-199	0.48 (0.44-0.51)	0.65 (0.60-0.71)	0.64 (0.58-0.70)	0.64 (0.59-0.70)	0.64 (0.59-0.70)
200-349	0.52 (0.48-0.55)	0.66 (0.61-0.72)	0.64 (0.59-0.70)	0.65 (0.60-0.70)	0.65 (0.60-0.70)
≥350	0.79 (0.71-0.87)	0.92 (0.82-1.03)	0.86 (0.77-0.96)	0.87 (0.77-0.97)	0.86 (0.77-0.97)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.10 (1.05-1.14)	1.04 (0.98-1.10)	1.09 (1.03-1.16)	1.12 (1.06-1.19)	1.12 (1.05-1.18)
IV	1.51 (1.44-1.59)	1.22 (1.14-1.31)	1.37 (1.28-1.46)	1.39 (1.30-1.49)	1.40 (1.31-1.50)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 4.5 (continued) Sensitivity analysis: Competing risks estimates of LTFU*

		12-72 months			
	Univariate	Model 1 (n=62,080)	Model 2 (n=62 ,80)	Model 3 (n=62,080)	Model 4 (n=62,080)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Year of ART initiation					
≤2003	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2004	1.44 (1.27-1.63)	1.30 (1.11-1.53)	0.81 (0.68-0.97)	0.98 (0.84-1.16)	0.94 (0.78-1.12)
2005	1.17 (1.04-1.32)	1.23 (1.06-1.44)	0.71 (0.60-0.84)	0.95 (0.81-1.11)	0.85 (0.71-1.02)
2006	1.41 (1.26-1.59)	1.58 (1.37-1.83)	0.96 (0.82-1.12)	1.14 (0.98-1.32)	1.03 (0.87-1.21)
2007	1.73 (1.54-1.94)	2.17 (1.88-2.51)	1.48 (1.27-1.74)	1.55 (1.34-1.80)	1.65 (1.40-1.95)
2008	2.20 (1.95-2.49)	2.85 (2.46-3.31)	1.83 (1.55-2.17)	2.21 (1.89-2.58)	2.13 (1.78-2.54)
2009	2.95 (2.60-2.25)	3.76 (3.21-4.40)	2.50 (2.10-2.98)	3.06 (2.60-3.60)	2.91 (2.42-3.50)
2010	4.72 (3.97-5.61)	5.70 (4.61-7.04)	3.91 (3.11-4.92)	4.67 (3.78-5.77)	4.85 (3.80-6.15)
2011	-	-	-	-	-
Programme size (patients)					
<500	1.0 (ref)		1.0 (ref)		1.0 (ref)
500-999	1.93 (1.62-2.30)		1.88 (1.51-2.33)		1.83 (1.47-2.27)
1,000-2,499	2.03 (1.73-2.39)		1.78 (1.44-2.19)		1.45 (1.16-1.81)
2,500-4,999	3.26 (2.79-3.83)		3.55 (2.89-4.36)		1.82 (1.43-2.31)
5,000-7,499	3.84 (3.26-4.52)		3.10 (2.50-3.85)		1.52 (1.18-1.95)
7,500 – 9,999	5.33 (4.49-6.33(		3.38 (2.68-4.25)		1.52 (1.16-1.01)
10,000-14,999	1.96 (1.63-2.35)		1.54 (1.21-1.95)		0.72 (0.54-0.95)
15,000-19,999	2.19 (1.72-2.78)		1.34 (1.00-1.80)		0.66 (0.46-0.93)
≥20,000	3.11 (1.95-4.97)		1.15 (0.66-2.01)		0.53 (0.29-0.97)
Rate of expansion (patients/month)					
<25	1.0 (ref)			1.0 (ref)	1.0 (ref)
25-59	1.58 (1.46-1.70)			1.71 (1.56-1.88)	1.59 (1.42-1.78)
60-89	2.09 (1.95-2.25)			2.76 (2.08-2.49)	2.04 (1.77-2.34)
90-124	2.42 (2.25-2.60)			2.63 (2.40-2.88)	2.58 (2.22-2.99)
≥125	1.85 (1.69-2.03)			1.33 (1.18-1.49)	2.12 (1.74-2.56)
Sex					
Female	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Male	1.06 (1.01-1.10)	1.05 (0.99-1.11)	1.11 (1.05-1.18)	1.13 (1.07-1.19)	1.12 (1.06-1.19)
Age group (years)					
16-25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-34	0.65 (0.61-0.70)	0.70 (0.64-0.77)	0.68 (0.63-0.75)	0.69 (0.63-0.75)	0.68 (0.62-0.74)
35-44	0.55 (0.52-0.60)	0.59 (0.53-0.64)	0.55 (0.50-0.61)	0.55 (0.50-0.61)	0.55 (0.50-0.60)
45+	0.60 (0.55-0.65)	0.61 (0.55-0.68)	0.56 (0.50-0.62)	0.55 (0.49-0.61)	0.55 (0.49-0.61)
Body Mass Index					
Underweight	0.98 (0.94-1.03)	0.93 (0.87-0.99)	0.98 (0.92-1.04)	0.98 (0.92-1.04)	0.99 (0.93-1.05)
Normal	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Overweight	1.09 (0.99-1.20)	1.16 (1.04-1.29)	1.12 (1.01-1.25)	1.14 (1.02-1.27)	1.12 (1.00-1.25)
Obese	1.00 (0.81-1.23)	1.12 (0.87-1.43)	1.05 (0.82-1.35)	1.06 (0.83-1.36)	1.02 (0.80-1.31)
CD4 cell count (cells/µl)					
<25	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
25-49	0.86 (0.77-0.96)	0.87 (0.78-0.98)	0.93 (0.83-1.04)	0.92 (0.81-1.03)	0.94 (0.84-1.06)
50-99	0.83 (0.75-0.91)	0.86 (0.77-0.95)	0.90 (0.81-0.99)	0.88 (0.79-0.97)	0.91 (0.82-1.00)
100-149	0.83 (0.76-0.92)	0.90 (0.81-1.00)	0.93 (0.84-1.03)	0.90 (0.81-1.000	0.94 (0.84-1.04)
150-199	0.85 (0.77-0.93)	0.88 (0.79-0.97)	0.92 (0.83-1.02)	0.89 (0.80-0.98)	0.93 (0.84-1.03)
200-349	0.81 (0.74-0.89)	0.76 (0.68-0.84)	0.83 (0.75-0.92)	0.78 (0.71-0.86)	0.84 (0.76-0.93)
≥350	1.00 (0.86-1.18)	0.92 (0.77-1.09)	0.95 (0.80-1.13)	0.88 (0.75-1.05)	0.92 (0.77-1.09)
WHO stage					
I and II	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
III	1.02 (0.96-1.07)	1.23 (1.15-1.32)	1.15 (1.07-1.24)	1.20 (1.11-1.28)	1.15 (1.07-1.24)
IV	0.99 (0.93-1.05)	1.22 (1.12-1.32)	1.21 (1.12-1.32)	1.26 (1.16-1.37)	1.23 (1.13-1.33)

* All models accounted for site heterogeneity using random effects. Model 1 – demographics and baseline variables, Model 2 - Model 1 + programme size, Model 3 – Model 1 + rate of expansion, Model 4 – Model 1 + programme size and rate of expansion

Supplementary Table 5.1 Hazard ratios of overall, 0-3 month, 3-12 month and 12-24 month observed LTFU by CD4 cell count at ART initiation±

	OVERALL (0-24 months)	**0-3 months**	**3-12 months**	**12-24 months**
	n=17,038	n=17,038	n=15,470	n=12,728
		Observed LTFU		
Crude HR				
<50 cells/µl	1.62 (1.44-1.83)	2.35 (1.87-2.95)	1.64 (1.35-2.00)	1.15 (0.93-1.42)
50-99 cells/µl	1.25 (1.10-1.41)	1.75 (1.38-2.23)	1.18 (0.96-1.46)	1.00 (0.81-1.24)
100-149 cells/µl	1.11 (0.98-1.26)	0.98 (0.75-1.28)	1.22 (0.99-1.49)	1.10 (0.90-1.34)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.96 (0.83-1.10)	0.88 (0.65-1.18)	1.03 (0.81-1.29)	0.94 (0.75-1.18)
250-299 cells/µl	1.29 (1.06-1.58)	1.29 (0.87-1.92)	1.36 (0.99-1.87)	1.25 (0.89-1.75)
≥300 cells/µl	1.45 (1.22-1.73)	1.57 (1.13-2.19)	1.58 (1.20-2.07)	1.28 (0.93-1.76)
Adjusted* - aHR				
<50 cells/µl	1.55 (1.37-1.75)	2.24 (1.78-2.81)	1.60 (1.32-1.95)	1.08 (0.87-1.33)
50-99 cells/µl	1.21 (1.06-1.37)	1.70 (1.34-2.17)	1.15 (0.94-1.42)	0.96 (0.77-1.19)
100-149 cells/µl	1.09 (0.96-1.24)	0.96 (0.73-1.26)	1.20 (0.98-1.46)	1.07 (0.88-1.31)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.92 (0.80-1.06)	0.87 (0.64-1.17)	0.96 (0.77-1.22)	0.92 (0.73-1.16)
250-299 cells/µl	1.18 (0.97-1.45)	1.31 (0.88-1.96)	1.17 (0.85-1.62)	1.15 (0.82-1.61)
≥300 cells/µl	1.33 (1.12-1.59)	1.61 (1.15-2.25)	1.34 (1.02-1.76)	1.18 (0.85-1.62)

±All estimates are stratified by cohort

*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Supplementary Table 5.2 Description of patients at baseline and hazard ratios of overall *corrected* LTFU by CD4 cell count at ART initiation by cohort

	Cohort 1 Hlabisa	**Cohort 2 Khayelitsha**	**Cohort 3 Themba Lethu**
CD4 cell count at ART initiation			
Median (IQR)	142 (72-199)	151 (82-205)	105 (40-176)
Year of ART initiation, n(%)			
2008	2,003 (24.2)	1,354 (23.5)	1,360 (45.6)
2009	1,872 (22.6)	1,695 (29.4)	1,577 (52.9)
2010	2,116 (25.5)	1,902 (33.3)	9 (0.3)
2011	1,856 (22.4)	813 (14.1)	36 (1.2)
2012	443 (5.3)	0 (0)	2 (0.1)
	Hazard ratio of overall corrected LTFU		
Crude HR, HR (95% CI)			
<50 cells/μl	1.39 (1.12-1.75)	1.22 (0.99-1.52)	0.60 (0.43-0.83)
50-99 cells/μl	1.02 (0.80-1.29)	1.16 (0.94-1.44)	0.67 (0.48-0.95)
100-149 cells/μl	0.89 (0.70-1.13)	1.19 (0.98-1.45)	0.82 (0.58-1.14)
150-199 cells/μl	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/μl	0.99 (0.72-1.35)	1.05 (0.86-1.28)	0.64 (0.43-0.97)
250-299 cells/μl	1.45 (1.03-2.03)	1.46 (1.09-1.97)	1.10 (0.51-2.39)
≥300 cells/μl	1.66 (1.28-2.16)	1.89 (1.38-2.57)	0.93 (0.51-1.70)
Adjusted*, aHR (95% CI)			
<50 cells/μl	1.28 (1.02-1.61)	1.17 (0.94-1.45)	0.60 (0.43-0.82)
50-99 cells/μl	0.99 (0.78-1.25)	1.12 (0.90-1.38)	0.65 (0.46-0.92)
100-149 cells/μl	0.89 (0.70-1.13)	1.14 (0.93-1.39)	0.82 (0.58-1.15)
150-199 cells/μl	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/μl	0.88 (0.64-1.21)	1.00 (0.82-1.22)	0.59 (0.39-0.89)
250-299 cells/μl	1.20 (0.85-1.69)	1.27 (0.94-1.71)	1.07 (0.49-2.34)
≥300 cells/μl	1.41 (1.08-1.83)	1.59 (1.16-2.17)	0.84 (0.45-1.57)

*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Supplementary Table 5.3 Sub-group analyses, stratified hazard ratios of corrected LTFU by covariates from multivariate models

Baseline characteristic	<50 cells/µl	50-99 cells/µl	100-149 cells/µl	150-199 cells/µl	200-249 cells/µl	250-299 cells/µl	≥300 cells/µl
Year of ART initiation±							
2008	1.00 (0.74-1.34)	0.91 (0.67-1.25)	0.97 (0.72-1.32)	1.0 (ref)	0.88 (0.61-1.28)	0.43 (0.16-1.18)	1.70 (1.01-2.85)
2009	0.95 (0.74-1.21)	0.88 (0.69-1.14)	0.94 (0.74-1.20)	1.0 (ref)	0.80 (0.61-1.06)	0.85 (0.46-1.58)	1.23 (0.81-1.87)
2010	1.12 (0.85-1.49)	1.16 (0.89-1.52)	1.08 (0.83-1.40)	1.0 (ref)	0.97 (0.73-1.29)	1.48 (1.07-2.05)	1.68 (1.23-2.28)
2011	1.42 (1.02-1.99)	0.96 (0.68-1.36)	0.97 (0.69-1.36)	1.0 (ref)	0.89 (0.63-1.24)	1.35 (0.90-2.03)	1.16 (0.78-1.71)
2012	-			1.0 (ref)			
Gender§							
Female	1.04 (0.86-1.26)	0.92 (0.76-1.12)	0.94 (0.78-1.12)	1.0 (ref)	0.86 (0.71-1.04)	1.24 (0.97-1.59)	1.35 (1.09-1.68)
Male	1.15 (0.92-1.42)	1.07 (0.96-1.34)	1.10 (0.88-1.38)	1.0 (ref)	0.97 (0.75-1.26)	0.92 (0.58-1.48)	1.24 (0.84-1.82)
Age*							
16-24	0.80 (0.51-1.24)	0.62 (0.39-0.99)	0.63 (0.41-0.97)	1.0 (ref)	1.02 (0.68-1.54)	1.49 (0.95-2.36)	0.99 (0.61-1.58)
25-34	1.02 (0.83-1.26)	1.04 (0.84-1.29)	0.99 (0.80-1.22)	1.0 (ref)	0.92 (0.74-1.15)	1.20 (0.87-1.65)	1.38 (1.21-2.08)
35-44	1.17 (0.90-1.52)	1.07 (0.83-1.39)	1.14 (0.88-1.46)	1.0 (ref)	0.74 (0.55-1.00)	0.96 (0.61-1.50)	1.23 (0.84-1.80)
≥45	1.40 (0.95-2.08)	0.92 (0.61-1.41)	1.10 (0.76-1.60)	1.0 (ref)	1.08 (0.70-1.67)	0.70 (0.30-1.63)	1.24 (0.69-2.22)

± Adjusted for gender, age, programme size and rate of expansion

§ Adjusted for year of ART initiation, age, programme size and rate of expansion

* Adjusted for year of ART initiation, gender, programme size and rate of expansion

Supplementary Table 5.4. Patient characteristics among those with and without South African civil ID numbers

Baseline characteristic	SA ID not available (n=16,161)	SA ID available (n=17,038)	TOTAL (n=33,199)
Cohort			
Gugulethu	2,377 (13.2)	0 (0)	2,377 (7.2)
Hlabisa (1)	2,715 (15.1)	8,290 (47.0)	11,005 (33.2)
Khayelitsha (2)	1,676 (9.3)	5,764 (32.7)	7,440 (22.4)
Themba Lethu (3)	8,157 (45.4)	2,984 (16.9)	11,141 (33.6)
Tygerberg	1,236 (6.9)	0 (0)	1,236 (3.7)
Gender			
Female	9,846 (60.9)	11,243 (66.0)	21,089 (63.6)
Age			
Median (IQR)	35.9 (30.0-43.0)	35.2 (29.6-42.2)	35.5 (29.8-42.6)
16-24	1,313 (8.1)	1,320 (7.8)	2,633 (7.9)
25-34	6,152 (38.1)	7,059 (41.4)	13,211 (39.8)
35-44	5,426 (33.6)	5,531 (32.5)	10,957 (33.0)
≥45	3,270 (20.2)	3,128 (18.4)	6,398 (19.3)
Year of ART initiation			
2008	2,173 (13.5)	4,717 (27.7)	6,890 (20.8)
2009	2,672 (16.5)	5,144 (30.2)	7,816 (23.5)
2010	4,511 (27.9)	4,027 (23.6)	8,538 (25.7)
2011	4,025 (24.9)	2,705 (15.9)	6,730 (20.3)
2012	2,780(17.2)	445 (2.6)	3,225 (9.7)
WHO stage			
I and II	2,748 (39.3)	4,727 (43.0)	7,475 (41.5)
III	3,021 (43.1)	4,797 (43.6)	7,818 (43.4)
IV	1,233 (17.6)	1,470 (13.4)	2,703 (15.0)
Missing	*9,159 (56.7)*	*6,044 (35.5)*	*15,203 (45.8)*
Cohort size at initiation (patients)			
<7,500	6,585 (40.6)	2,448 (14.4)	9,033 (27.2)
7,500-7,999	610 (3.8)	3,226 (18.9)	3,836 (11.6)
8,000– 9,899	947 (5.9)	3,476 (20.4)	4,423 (13.3)
9,900-11,499	6,685 (41.4)	4,130 (24.2)	10,815 (32.6)
≥11,550	1,334 (8.3)	3,758 (22.1)	5,092 (15.3)
Rate of scale-up (patients/month)			
<130	2,943 (24.4)	3,542 (20.8)	7,485 (22.6)
130-159	589 (3.6)	3,296 (19.3)	3,885 (11.7)
160-179	1,407 (8.7)	3,516 (20.6)	4,923 (14.8)
180-199	2,065 (12.8)	3,700 (21.7)	5,765 (17.4)
≥200	8,157 (50.5)	2,984 (17.5)	11,141 (33.6)

Supplementary Table 5.5 Sensitivity analysis of weighted hazard ratios of overall, 0-3 month, 3-12 month and 12-24 month corrected LTFU by CD4 cell count at ART initiation±§

	OVERALL (0-24 months)	**0-3 months**	**3-12 months**	**12-24 months**
	n=26,955	n=26,955	n=24,244	n=18,551
Crude HR				
<50 cells/µl	1.11 (0.96-1.29)	1.11 (0.81-1.53)	1.28 (1.01-1.63)	0.96 (0.75-1.22)
50-99 cells/µl	1.04 (0.89-1.22)	1.37 (0.95-1.99)	1.02 (0.79-1.30)	0.89 (0.70-1.13)
100-149 cells/µl	1.03 (0.89-1.20)	0.64 (0.45-0.92)	1.22 (0.94-1.58)	1.06 (0.85-1.32)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	1.00 (0.83-1.20)	1.21 (0.75-1.97)	1.01 (0.77-1.32)	0.87 (0.68-1.11)
250-299 cells/µl	1.27 (1.00-1.61)	1.35 (0.79-2.29)	1.31 (0.88-1.95)	1.18 (0.83-1.68)
≥300 cells/µl	1.40 (1.13-1.75)	1.83 (1.15-2.92)	1.35 (1.00-1.83)	1.12 (0.80-1.57)
Adjusted* - aHR		Adjusted* - aHR		
<50 cells/µl	1.03 (0.89-1.20)	1.02 (0.74-1.41)	1.21 (0.95-1.54)	0.88 (0.69-1.13)
50-99 cells/µl	1.01 (0.86-1.18)	1.32 (0.93-1.87)	0.99 (0.78-1.27)	0.86 (0.68-1.09)
100-149 cells/µl	1.01 (0.87-1.18)	0.63 (0.44-0.90)	1.20 (0.93-1.55)	1.05 (0.85-1.31)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.94 (0.79-1.12)	1.11 (0.71-1.72)	0.93 (0.71-1.22)	0.85 (0.67-1.09)
250-299 cells/µl	1.07 (0.84-1.37)	1.18 (0.69-2.02)	1.09 (0.73-1.63)	1.05 (0.74-1.48)
≥300 cells/µl	1.17 (0.93-1.47)	1.55 (0.94-2.55)	1.10 (0.80-1.51)	1.00 (0.71-1.40)

±All estimates are stratified by cohort

§Weighted to represent all patients regardless of SA civil ID number availability

*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Supplementary 5.6 Sensitivity analysis with imputed CD4 cell counts at ART initiation. Corrected hazard ratios of overall, 0-3 month, 3-12 month and 12-24 month corrected LTFU by CD4 cell count at ART initiation±§

	OVERALL (0-24 months)	**0-3 months**	**3-12 months**	**12-24 months**
	n=22,495	n=22,495	n=20,374	n=16,599
Crude HR				
<50 cells/µl	1.05 (0.91-1.20)	1.01 (0.77-1.32)	1.16 (0.91-1.47)	0.96 (0.79-1.18)
50-99 cells/µl	0.98 (0.85-1.14)	1.07 (0.82-1.40)	0.99 (0.74-1.32)	0.93 (0.76-1.13)
100-149 cells/µl	1.00 (0.88-1.14)	0.73 (0.52-1.02)	1.08 (0.88-1.34)	1.05 (0.85-1.31)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	1.01 (0.83-1.21)	0.95 (0.68-1.33)	1.06 (0.74-1.52)	0.98 (0.79-1.22)
250-299 cells/µl	1.22 (1.01-1.48)	1.25 (0.82-1.92)	1.26 (0.88-1.79)	1.16 (0.84-1.58)
≥300 cells/µl	1.32 (1.09-1.59)	1.34 (0.92-1.93)	1.35 (1.03-1.78)	1.26 (0.90-1.77)
Adjusted* - aHR				
<50 cells/µl	1.08 (0.94-1.24)	1.02 (0.78-1.34)	1.21 (0.95-1.54)	0.98 (0.80-1.20)
50-99 cells/µl	0.97 (0.84-1.14)	1.07 (0.81-1.40)	0.98 (0.73-1.32)	0.92 (0.76-1.12)
100-149 cells/µl	0.99 (0.87-1.13)	0.72 (0.51-1.01)	1.08 (0.87-1.33)	1.04 (0.84-1.30)
150-199 cells/µl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/µl	0.87 (0.72-1.06)	0.81 (0.58-1.14)	0.92 (0.64-1.30)	0.86 (0.69-1.07)
250-299 cells/µl	1.05 (0.86-1.28)	1.22 (0.78-1.90)	1.02 (0.70-1.49)	0.99 (0.73-1.35)
≥300 cells/µl	1.24 (1.04-1.49)	1.50 (1.04-2.18)	1.18 (0.90-1.56)	1.19 (0.86-1.65)

±All estimates are stratified by cohort

§Weighted to represent all patients regardless of SA civil ID number availability

*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Supplementary Table 5.7 Sensitivity analysis of competing risks hazard ratios of overall, 0-3 month, 3-12 month and 12-24 month corrected LTFU by CD4 cell count at ART initiation§

	OVERALL (0-24 months)	**0-3 months**	**3-12 months**	**12-24 months**
	n=17,038	n=17,038	n=15,431	n=12,697
Crude HR				
<50 cells/μl	0.98 (0.85-1.13)	1.05 (0.78-1.42)	1.25 (1.00-1.56)	0.89 (0.71-1.13)
50-99 cells/μl	0.06 (0.83-1.11)	1.11 (0.82-1.50)	1.02 (0.80-1.29)	0.89 (0.71-1.11)
100-149 cells/μl	0.99 (0.86-1.14)	0.66 (0.47-0.93)	1.13 (0.91-1.41)	1.07 (0.86-1.32)
150-199 cells/μl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/μl	1.05 (0.90-1.22)	0.97 (0.69-1.36)	1.12 (0.87-1.43)	1.03 (0.81-1.30)
250-299 cells/μl	1.38 (1.12-1.71)	1.48 (0.96-2.27)	1.40 (0.99-1.98)	1.31 (0.92-1.86)
≥300 cells/μl	1.45 (1.20-1.74)	1.56 (1.09-2.25)	1.57 (1.17-2.10)	1.26 (0.90-1.75)
Adjusted* - aHR				
<50 cells/μl	0.99 (0.86-1.14)	1.05 (0.77-1.42)	1.27 (1.01-1.60)	0.88 (0.70-1.11)
50-99 cells/μl	0.96 (0.83-1.10)	1.11 (0.82-1.50)	1.01 (0.80-1.29)	0.87 (0.69-1.10)
100-149 cells/μl	0.98 (0.85-1.12)	0.65 (0.46-0.92)	1.12 (0.89-1.39)	1.05 (0.85-1.30)
150-199 cells/μl	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
200-249 cells/μl	0.89 (0.76-1.03)	0.79 (0.56-1.12)	0.95 (0.74-1.21)	0.90 (0.71-1.14)
250-299 cells/μl	1.17 (0.94-1.45)	1.40 (0.91-2.16)	1.13 (0.80-1.60)	1.11 (0.78-1.57)
≥300 cells/μl	1.34 (1.11-1.63)	1.69 (1.16-2.48)	1.34 (0.99-1.80)	1.17 (0.84-1.65)

§Weighted to represent all patients regardless of SA civil ID number availability
*Adjusted for year of ART initiation, gender, age, programme size and rate of expansion

Supplementary Table 6.1 Median time to down-referral by baseline characteristics

Baseline characteristic	Median time to down-referral, years (IQR) (n=1,749)	p-value
Overall	1.6 (0.9-2.6)	
Gender		
Females	1.7 (0.9-2.6)	0.643
Males	1.6 (1.0-2.5)	
Age		
16-24	1.5 (0.9-2.2)	0.030
25-34	1.7 (1.0-2.7)	
35-44	1.7 (1.0-2.7)	
45+	1.5 (0.8-2.4)	
CD4 (cells/µl)		
<50	2.1 (1.3-3.1)	<0.001
50-99	2.0 (1.1-2.8)	
100-199	1.5 (0.9-2.5)	
≥200	1.2 (0.7-2.1)	
Missing	*1.8 (1.0-2.4)*	
Viral load, log_{10} copies/mL		
Supressed (≤ 200)	1.3 (1.0-3.2)	0.008
201-24,999	1.5 (0.9-2.5)	
25,000-99,999	1.9 (1.0-2.7)	
100,000+	1.6 (0.9-2.7)	
Missing	*1.5 (0.8-2.2)*	
Haemoglobin, g/dL		
<10	1.6 (1.0-2.7)	0.463
10-12	1.6 (0.9-2.7)	
12+	1.5 (0.9-2.6)	
Missing	*1.9 (1.0-2.2)*	
WHO stage		
Stage I and II	1.3 (0.7-2.2)	<0.001
Stage III	1.8 (1.1-2.6)	
Stage IV	2.0 (1.1-3.1)	
Missing	*0.8 (0.6-1.1)*	
Year of initiation		
2002 - 2003	4.4 (4.2-4.8)	<0.001
2004 - 2005	2.5 (2.1-3.1)	
2006 – 2007	1.3 (0.9-1.7)	
2008 – 2009	1.0 (0.6-1.7)	
2010 - 2011	0.8 (0.5-1.1)	

Supplementary Table 6.2 Stratified hazard ratios of LTFU among down-referred patients versus patients at the treatment-initiation site

	LTFU	
	Univariate HR (95% CI)	Multivariate* aHR (95% CI)
Gender		
Males	1.03 (0.78-1.37)	1.80 (1.22-2.66)
Females	0.90 (0.73-1.11)	1.19 (0.91-1.56)
Age - categorical		
16-24	0.81 (0.49-1.35)	1.11 (0.60-2.05)
25-34	0.98 (0.77-1.24)	1.67 (1.22-2.29)
35-44	1.07 (0.78-1.48)	1.10 (0.71-1.69)
≥45	0.68 (0.40-1.15)	0.84 (0.41-1.76)
CD4 (cells/µl)		
<50	1.02 (0.67-1.58)	1.76 (1.02-3.03)
50-99	1.18 (0.82-1.70)	1.49 (0.92-2.40)
100-199	0.98 (0.76-1.26)	1.32 (0.95-1.82)
≥200	0.57 (0.36-0.88)	0.75 (0.40-1.41)
WHO stage		
Stage I & II	0.66 (0.48-0.91)	1.04 (0.69-1.56)
Stage III	1.11 (0.88-1.40)	1.40 (1.04-1.88)
Stage IV	1.05 (0.70-1.57)	1.88 (1.05-3.37)
Year of ART initiation		
2002 - 2003	1.58 (0.62-4.02)	4.04 (1.03-15.78)
2004 - 2005	1.06 (0.73-1.55)	2.20 (1.29-3.78)
2006 – 2007	0.77 (0.59-1.01)	1.08 (0.77-1.51)
2008 – 2009	0.71 (0.50-1.00)	1.27 (0.80-2.00)
2010 - 2011	0.73 (0.38-1.39)	1.27 (0.55-2.95)

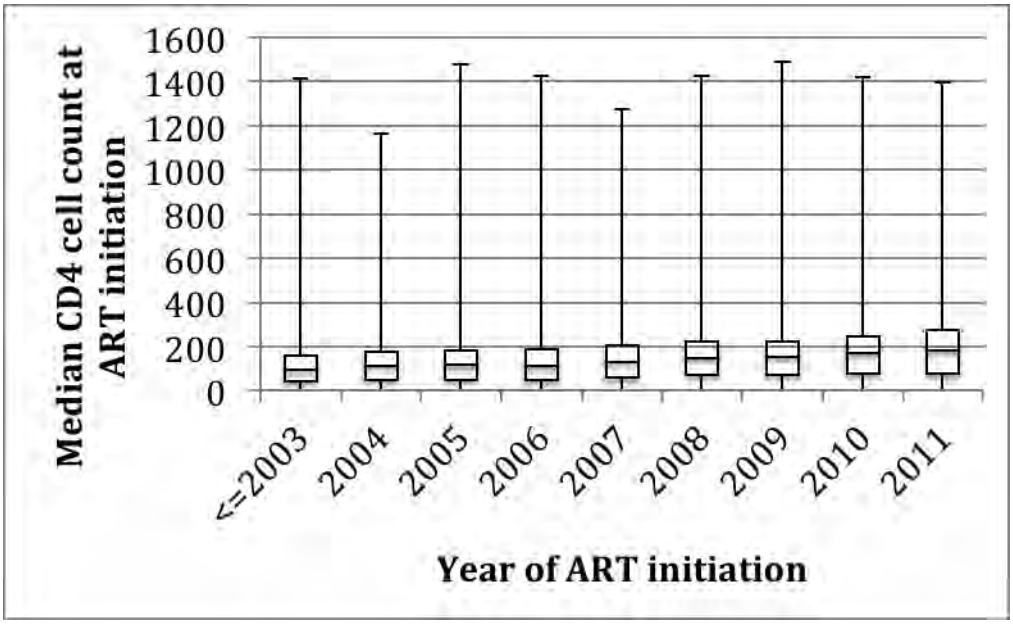
*Multivariate: Includes Model of Care, all demographic (age, sex) and baseline characteristics (CD4, WHO stage, viral load, haemoglobin, year of initiation) + time-updated CD4 and viral load

Supplementary Table 8.1 Approach 1 (Primary results) - Relative hazards of loss to follow-up including probability of being in a Community-based Adherence Club

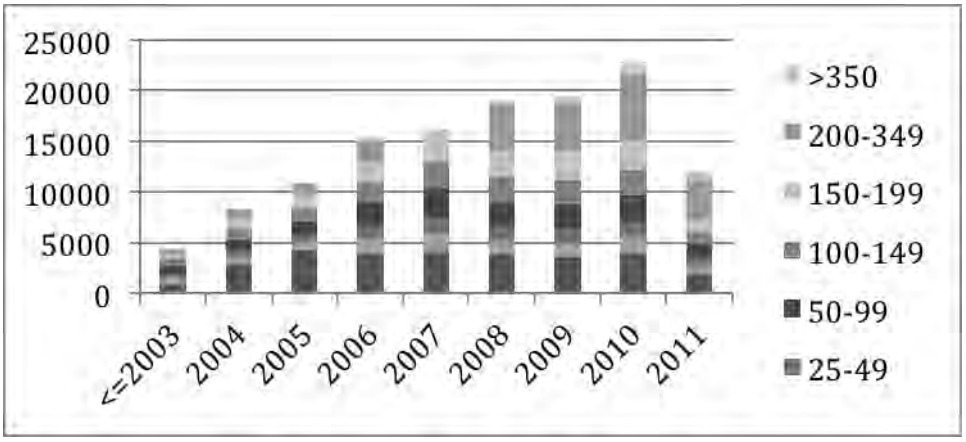
Characteristic	Univariate HR (95% CI)	Model 1 aHR (95% CI) n=5 755	Model 2 Final Model aHR (95% CI) n=5 753	Model 3 aHR (95% CI) n = 5 753
Model of Care				
CHC	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
CAC	0.38 (0.32-0.45)	0.21 (0.17-0.25)	0.33 (0.27-0.40)	0.32 (0.26-0.39)
Age when starting ART				
16-24	1.41 (1.27-1.56)	1.38 (1.21-1.57)	1.19 (1.05-1.36)	1.26 (1.10-1.43)
25-34	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
35-44	0.94 (0.87-1.01)	0.87 (0.79-0.95)	0.92 (0.83-1.01)	0.92 (0.83-1.02)
≥45	0.94 (0.85-1.04)	0.75 (0.66-0.85)	0.88 (0.77-1.00)	0.81 (0.71-0.93)
Gender				
Male	1.09 (1.02-1.17)	1.12 (1.06-1.26)	0.95 (0.87-1.04)	1.01 (0.92-1.10)
Year of ART initiation				
2002-2004	0.13 (0.11-0.16)	0.12 (0.10-0.16)	0.18 (0.14-0.23)	0.22 (0.17-0.28)
2005-2007	0.40 (0.36-0.44)	0.44 (0.39-0.50)	0.41 (0.36-0.46)	0.43 (0.39-0.49)
2008-2010	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
2011-2012	3.39 (3.10-3.71)	3.22 (2.87-3.60)	3.21 (2.87-3.58)	2.83 (2.53-3.17)
CD4 at ART initiation, (cells/μl)				
<50	0.90 (0.80-1.01)	-	-	0.50 (0.45-0.57)
50-99	0.94 (0.84-1.04)	-	-	0.68 (0.60-0.76)
100-199	1.0 (ref)	-	-	1.0 (ref)
≥200	1.55 (1.41-1.71)	-	-	2.06 (1.85-2.30)
Time-updated CD4 (per 50-unit increase)	0.74 (0.73-0.75)	-	0.79 (0.78-0.81)	0.72 (0.71-0.74)
Time-updated viral load, (copies/mL)				
Suppressed (<1,000)	1.0 (ref)	-	1.0 (ref)	1.0 (ref)
Not supressed (≥1,000)	7.30 (6.77-7.87)	-	3.16 (2.84-3.51)	2.50 (2.25-2.78)

Appendix 3: Supplemental figures

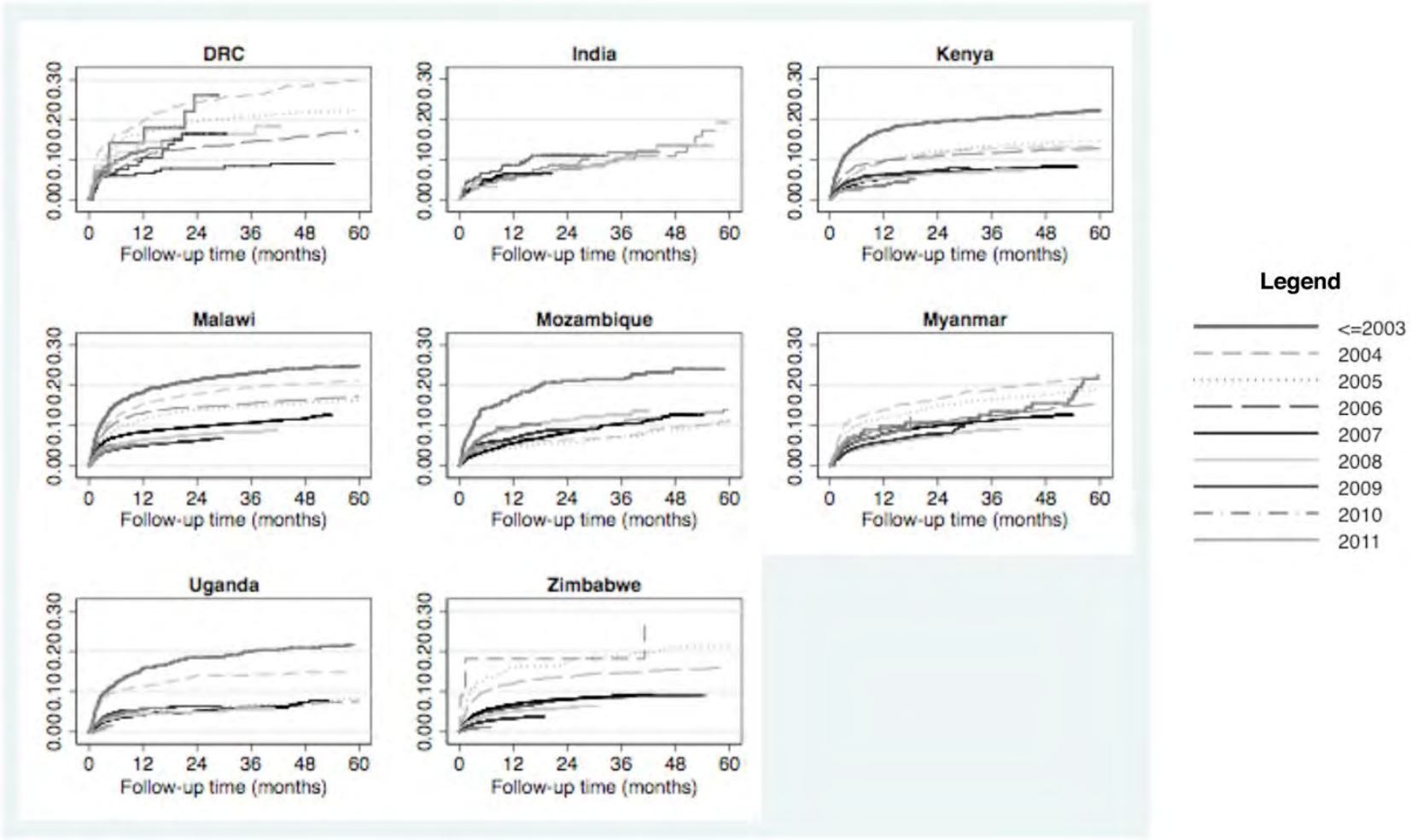
Supplementary Figure 4.1 Median CD4 cell count by year of ART initiation



Supplementary Figure 4.2 Baseline CD4 cell count level by year of ART initiation



Supplementary Figure 4.3 Kaplan-Meier cumulative estimates of mortality by country and year of ART initiation



Supplementary Figure 4.4 Kaplan-Meier cumulative estimates of LTFU by country and year of ART initiation