Assessing the effectiveness of the ART programme in the Western Cape Province of South Africa through triangulation of context-appropriate population level routine monitoring and surveillance systems

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Declaration

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 on which this thesis is based 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 included multi-authored papers is further delineated in the preface to the thesis and in the introduction to each included paper as appropriate. These manuscripts have been formatted uniformly for the purposes of this thesis, with referencing combined into a single section at the end. The content of each published manuscript remains substantively unchanged, with only minor stylistic edits for consistency such as the standardisation of the terms used for referring to men and women.

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Preface

Inclusion of papers and the candidate`s own scientific work

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. I confirm that I have been granted permission by the University of Cape Town's Doctoral Degrees Board to include the following publication(s) in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publication(s):

1. **Osler M**, Hilderbrand K, Hennessey C, Arendse J, Goemaere E, Ford N, Boulle A. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. JIAS 2014; 17(1):18908. DOI: 10.7448/IAS.17.1.18908
2. **Osler M**, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G, Kruger J, Govender N, Boulle A. 2018. The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. CID 2018. 66:S118-S125. DOI: 10.1093/cid/cix1140
3. **Osler M**, Cornell M, Ford N, Hilderbrand K, Goemaere E, Boulle A. Population-wide differentials in HIV service access and outcomes in the Western Cape for men as compared to women, South Africa: 2008 to 2018: a cohort analysis. JIAS 2020, 23(S2):e25530; DOI: 10.1002/jia2.25530

The publications are included alongside an additional three results chapters which while unpublished, are also presented in manuscript format.

The title page for each results chapter details my contribution to the relevant manuscript. In general terms, I contributed extensively to data acquisition and consolidation, conducted all analyses myself, and was responsible for the drafting of all manuscript versions. With respect to the data acquisition contribution, from the start of the ART services, I personally implemented and trained facilities in the use of the paper-based monitoring system throughout the Western Cape ART services, stewarded the development of information systems for HIV management (the eKapa online electronic medical health record and the TIER.Net electronic register) from their infancy, and worked extensively alongside government to implement these systems. The information systems underpinned the establishment of the province-wide clinical health data initially implemented in the

Western Cape Province and on which this thesis is based, and later, the scale-up of the TIER.Net offline health information application nationally.

Signature…… Date: 12 June 2023

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- To my family, I am deeply grateful to you for providing me the time, endless amounts of coffee and space, as well as continuous encouragement to finish this thesis.

Abbreviations

AHD advanced HIV disease
aHR adjusted hazard ratio
AIDS acquired immunodeficiency syndrome
aOR adjusted odds ratio
ART antiretroviral therapy
ARV antiretroviral
BMI body mass index
CACE complier average causal effect
CBS case-based surveillance
CD4 CD4+ T-lymphocyte count
CDC Centers for Disease Control and Prevention
CrAg cryptococcal antigen test
CVRS civil vital registration statistics
d4T stavudine
DES data exchange standard
DHSs Demographic Health Surveys
DRC Democratic Republic of Congo
DR-TB drug resistant tuberculosis
DS-TB drug sensitive tuberculosis
DSMB data safety and monitoring board
DTR dynamic treatment regimen
EAC enhanced adherence counselling
EFV efavirenz
EKAPA database application used in the Khayelitsha antiretroviral cohort
EMR electronic medical record
FRIL fine grain record linkage software
FDC fixed-dose combination
HIS health information system
HIV Human Immunodeficiency Virus
HDSSs Health and Demographic Surveillance Systems
HPRS Health patient registration system
HSRC Health Sciences Research Council
IQR interquartile range
ITT intention to treat analyses
IV instrumental variable
LAM Lipoarabinomannan
LTF lost to follow-up (lost to care)
M&E monitoring and evaluation
MCH mother child health services
MeSH Measurement & Surveillance of HIV Epidemics
MSM marginal structural model (statistical method)
NGOs non-governmental organisations
NHLS National Health Laboratory Services

NICD National Institute for Communicable Diseases
NNRTI non-nucleoside reverse transcriptase inhibitors
NPR national population register
NRTI nucleoside reverse transcriptase inhibitors
NVP nevirapine
OI opportunistic infection
PEPFAR President's Emergency Plan for AIDS Relief
PHC primary health care
PHDC provincial health data centre
PHIA population- based HIV impact assessment
PI protease inhibitor
PMI patient management index
PMTCT prevention of mother-to-child transmission
PYO person-years observed
RD risk difference
RLS resource limited setting
SA ID South African Identification number
SA NDoH South African National Department of Health
SAMRC South African Medical Research Council
SHIMS Swaziland HIV Incidence Measurement Survey
SMR standardised mortality ratio
SNM structural nested model (statistical method)
TB tuberculosis
TIER.Net Three Inter-linked Electronic Registers (software application)
TDF tenofovir
UCT University of Cape Town
UNAIDS The Joint United Nations Programme on HIV/AIDS
USAID United States Agency for International Development
UTT universal testing and treatment
WHO World Health Organization

Glossary of key terms

Advanced HIV disease refers to an HIV-infected person presenting with a CD4 cell count below 200 cell/μL. The WHO definition also includes people with WHO clinical stage 3 or 4, however due to the high level of CD4 count monitoring before ART initiation in South Africa, the WHO clinical stages are not as commonly referred to.

ART (antiretroviral therapy) refers to the use of a combination of drugs for treating HIV infection and is a lifelong therapy at the current time.

ARV (Antiretroviral) drugs refer to the medicines used to treat HIV

Clinicians in South Africa refer to both doctors and nurses.

A cohort is a group of people defined by a specific characteristic(s) who are followed over time. For this thesis, all data included were from HIV positive people and cohorts were either defined by a person's first-ever CD4 count (entry to HIV care services) or the date they initiated ART. People were categorised into different cohorts by years for some of the analyses and by the time between eligibility guideline implementation dates for other analyses.

Electronic medical records (EMRs) are most often comprehensive online software applications used to collect information across the health services regardless of where the service is delivered.

Electronic registers refer to digital software applications that are set up to quickly and easily digitise paper registers or specific prioritised health services at a health care facility and facilitates tracking patient data longitudinally over time

Generalized HIV epidemic refers to a geographic area where HIV is established in the general population, and not only among one or a few defined populations.

HIV care is defined in these analyses as the time from a person getting their first CD4 count to the time a person initiates HIV treatment (ART).

Linkage refers to the process of using data algorithms to merge recorded data from many different digital health sources to the correct patient record. The health sources can include clinical, demographic, laboratory and pharmacy data as well as hospital and primary health care data.

Lost to follow up (LTF) is defined in this set of analyses as people who have not attended any health care services for 180 days or longer.

Retention rates refer to the proportion of a population enrolled in HIV or ART services who attended health care appointments or had drugs in hand during the period being monitored. It is a snapshot in time.

A Three Tier Monitoring and Evaluation System refers to a seamless monitoring system designed to enable the use of a mix of paper registers, offline and online systems (one per facility) across a geographic region. The reports are standardised across the systems providing patient and service delivery management tools at facility level, with data that can be exported and combined centrally (district, province or nationally) to fulfil reporting requirements at a national and international level.

Universal test and treat (UTT) refers to a time after ART eligibility guidelines removed CD4 cell count threshold criteria. This change allowed ART initiation on the same day as an HIV diagnosis or as soon as possible thereafter, without the need of meeting a CD4 count threshold. However, baseline CD4 cell count testing was still recommended.

ABSTRACT

Background

After a decade of free antiretroviral therapy (ART) provision, countries continued facing challenges both in trying to meet the ever-increasing pool of eligible people needing HIV treatment, and efficiently monitoring programme effectiveness to improve patient care and service delivery. Concerns about the feasibility of further treatment expansion were being debated with trials showing benefit, but with ongoing uncertainty as to whether those benefits would be realised in resource-limited settings with fragile health systems. Key questions underpinning this thesis were how to robustly develop, implement, monitor and use routine health information systems to explore pertinent epidemiological questions, including real-world effectiveness of the ART programme, determinants of ongoing morbidity and mortality, and the impact of guideline changes.

Methods

The thesis includes a health systems review of the implementation of person-level information systems for HIV care, followed by a number of cohort analyses based on the public-sector health services in the Western Cape, South Africa. The study population consists of people living with HIV, who had at least one CD4 test or HIV-care visit, and who were ≥16 years of age. The cohort analyses utilized a population-wide linked dataset containing all available digital data from fixed health facilities, laboratory, pharmacy, and death registry systems. The first analysis described temporal trends in the CD4 distributions over 10 years, with longitudinal categorization of ART status of people with extremely advanced HIV disease (AHD). Two analyses used a regression discontinuity design to consider the causal impact of guideline changes, while the last two analyses explored important longer-duration determinants of morbidity and mortality in a survival analysis cohort framework, including through the use of flexible parametric survival models.

Results

Developing a tiered suite of interoperable information solutions enabled each health facility to independently evolve from paper to offline and then hybrid/online electronic registers when dependencies such as electricity, stable networks and resources allowed them to. The largest proportion of people with severe AHD (CD4 <50 cells/μL) came from those already on ART in more recent years, in comparison to people first presenting or not eligible for ART. Of those on ART with severe AHD, more than three-quarters had a confirmed treatment interruption (>3 months) and/or viraemia within the previous year. The biggest benefits (based on24-month survival) when increasing eligibility thresholds for ART were seen during earlier guideline changes which expanded access at

lower CD4 count thresholds (from CD4 <200/µL to CD4 <350/µL); however, at a patient level, benefits from ART were seen at all three eligibility threshold changes (200, 350 and 500 cells/µl). Deferring treatment for people ineligible lead to, on average, >2 years delay prior to starting ART, increasing risk of AHD and death. The greatest increases in ART initiations and decreases in mortality happened between guideline changes, reflecting large increases in ART access prior to formal expansion of access through guideline changes. As the ART programme has matured, men living with HIV continue to have poorer access to ART, a greater risk of TB, are more likely to interrupt treatment and have inferior clinical outcomes compared to woman, especially between diagnosis and the first five years on ART. Women, however, carried the larger absolute mortality burden, due to the greater numbers living with HIV. Almost two-thirds of the ART cohort interrupted treatment for >4 months at least once, increasing their risk of death by 27%, compared to people who had never interrupted ART. Each additional interruption was associated with further increases in mortality.

Conclusions

Pragmatic interoperable offline/hybrid/online health information systems can be successfully implemented at scale in lower resource settings to improve patient care, provide information on interventions and inform policy and resource allocation. Programmatic ART outcomes did improve during expansion of ART eligibility including into the time-period of the treat-all policy when CD4 count criteria were removed. More people accessed ART over time, independent of guideline changes, improving population HIV outcomes. The guidelines changes were nonetheless shown to be effective at an individual level. The number of people with AHD has not decreased however due to ART experienced patients returning to care after interruptions with considerable immune deterioration. Recommendations focused on improving systems for retention, re-engagement, and AHD and are most likely applicable to similar public-sector settings in Southern Africa.

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Chapter 1: Introduction and literature review

INTRODUCTION

This thesis was conceived following the first decade of the antiretroviral therapy (ART) services in the public health sector of South Africa. At that time, in early 2014, there was uncertainty as to how the public sector would continue to monitor program effectiveness as the program grew in size and complexity (1, 2). This was coupled with a number of epidemiological questions around population-level outcomes (3). Up until then there had been a strong reliance on the monitoring of facility-based cohorts to address clinical and program questions, but these cohorts were difficult to maintain, and were biased to those who remained in care (4, 5, 6). This was compromising both the completeness and fidelity of program monitoring, and the robustness of epidemiological inferences, when reliant on these data alone. Key questions underpinning the framing of this thesis, were how to robustly describe population-wide outcomes in a growing program, and to use these systems to explore pertinent epidemiological questions related to the program at a population level. Examples of questions being asked at the time included the real-world effectiveness of the program as a whole (by analysing routing programme data rather than data collected from experimental studies), determinants of ongoing morbidity and mortality which was often presenting in acute care in patients not formally part of monitored primary care cohorts, and the real-world impact of guideline changes.

The antiretroviral therapy programme has contributed to slowly regaining the average life expectancy to levels reached prior to the first diagnosis of human immunodeficiency virus (HIV) in South African in 1982 (7). Globally, by 2014 the spread of HIV was slowing down with a 33% decrease in new HIV infections from 2001 to the beginning of 2013. Despite all the gains in antiretroviral therapy scale-up and care, morbidity and mortality remained high with 35.3 million people worldwide living with HIV in 2012. There were 1.6 million new HIV infections and 1.2 million deaths in sub-Saharan Africa alone in 2012 (8). In 2013, the World Health Organization (WHO) recommended countries implement new guidelines to provide ART to all individuals living with HIV who had met WHO clinical stage 3 or 4 criteria and all individuals with a CD4 count ≤500 cells/μL (9). Although applauded, this recommendation would double the number requiring ART in South Africa (10), a goal that seemed ambitious amid operational complexities and significant gaps in resources and equity, despite the unprecedented rapid scale-up of the programme over the previous 10 years.

More locally, in South Africa, it was estimated that 5.3 million people were HIV infected in midyear 2013, and 15.9% of the adult population were HIV positive (11). The free ART services in South

Africa first launched in 2004 and rapidly scaled up at unprecedented rates. By 2014, the public-sector facilities were providing antiretroviral therapy to more than 2 million people (12) . The service had operationally evolved from a health service offered by doctors in designated tertiary hospitals to a largely nurse-driven health service offered in primary health care (PHC) facilities (13). It had also transitioned from a siloed acute health programme to a lifelong chronic programme within the South African National Department of Health (SA NDoH) (14). In the Western Cape, HIV clinicians started integrating other health services with ART care. The reverse, full integration of ART patients into routine services, continued to be discussed as an important topic but without implementation by the end of 2013.

During this time (2012-2014), provinces were having difficulty setting up or maintaining monitoring services, and data used to measure ART uptake and impact were coming from larger research affiliated health facilities with additional donor supported staff and resources. An electronic offline register, TIER.Net, was introduced to try and maintain complete program monitoring as paper-based systems became unmanageable. The offline register enabled near complete individuated data for patients accessing ART, which was essential for more detailed epidemiological analyses.

As the Western Cape government scaled up the Three-Tier Monitoring and Evaluation (M&E) System several years ahead of national adoption, the province was well placed to answer population-level questions of effectiveness within the ART programme (please see Chapter 2a for more information on the Three-Tier M&E System comprising paper registers, offline electronic registers and online medical records). As the ART scale-up matured, cohort monitoring above facility level became increasingly difficult due to patient movement across facilities and information on deaths not being reported back to the ART services. However, in the Western Cape, routine laboratory and hospital data flowed centrally, with data linkage available per patient, regardless of facility access. This was initially carried out by the author and later through the Provincial Health Data Centre (PHDC). Over the time that the studies included in this thesis were conducted, the PHDC progressively linked all public-sector digital health data in one online system, including clinical, laboratory, hospital, pharmacy, mobile and vital registry data. The PHDC does not yet incorporate data from the private sector; however, about 25% of the Western Cape population have health insurance, and it is anticipated that the proportion accessing HIV services is much lower given the higher prevalence in lower income communities. The Western Cape was the only province in the country and one of the few settings in the region that had all digital health and death data linked per patient, enabling more accurate population-level reports and analyses. The individuated patient-linked central database allowed the author to consider programme effectiveness and determine associations with mortality, with data spanning the entire public-sector health population.

LITERATURE REVIEW

The purpose of the literature review which builds on that in the original thesis protocol, is to cover what was known at the time of the thesis conception with respect to questions of population-wide effectiveness and impact. There is a vast literature on clinical and epidemiological aspects of HIV interventions, and it would not be possible to comprehensively cover all of this. The focus instead is on studies that had addressed at the time, questions of population-wide monitoring, effectiveness or impact, in the same or similar contexts. Due to several breaks in the research (owing to work commitments related to the digitisation of the primary health care services in South Africa), relevant studies published after the original thesis protocol submission are referenced in the results chapters and not in this section. While I have attempted to be systematic in the sourcing of studies related to key thesis questions, the intention was not to conduct a series of formal systematic reviews, but rather to take reasonable measures to find the studies related to key areas of interest. Inclusion and exclusion criteria were carefully thought through, in order to find context-appropriate publications relevant to the Western Cape cohort. This included global publications on timing for optimal ART initiation and publications from Southern Africa on programme-wide outcomes, predominant associations with morbidity and mortality and on the impact of guideline changes. In all instances, the referencing by later studies has also been used to identify further studies of interest.

This literature review therefore summarizes relevant literature published from January 1990 to end December 2013 and retrieved in the PubMed database, providing a narrative synthesis of the most relevant studies related to key thesis focus areas.

Pre-existing data on ART effectiveness at different ART-eligibility thresholds

There was no debate on the benefits of closely monitored uninterrupted ARV drugs for the individual living with HIV, but questions remained regarding real world effectiveness of expanded access and the impact of guideline changes. In 1987, zidovudine was the first antiretroviral (ARV) drug to gain approval for treatment of AIDS as a mono-drug therapy. In 1997, after the development of new classes of ART drugs, including protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), clinical trials demonstrated superior efficacy of 3-drug ART regimens (15). Triple therapy compared to dual therapy was demonstrated to reduce acquired immunodeficiency syndrome (AIDS) and death events by 38% in patients with a CD4 count <200 cells/µL, as reported by a meta-analysis of 9 trials (16). As triple therapy was proven more beneficial to mono or dual therapy, it was considered unethical to run clinical trials to measure the efficacy of

the drug regimen combinations compared to no therapy. However, complex statistical modelling based on emergent causal inference methods estimated a reduction in progression to AIDS or death by 86% compared to no therapy and by 96% in those with a CD4 cell count <200 cells/µL (17).

Clinical trials on when to start ART

Clinical trials on when to start HIV treatment paused for several years until ethical clearance was given to measure the optimal timing during the progression of HIV infection to initiate ART in asymptomatic people (18). In the early days of ART therapy scale-up, treatment regimens were complex and had serious side effects and limited durability. It was perceived that difficulty with adherence could potentially drive viral resistance eliminating the benefits of the small handful of ART drugs available (19). Prior to clinical trials and observational studies measuring optimal initiation timing, guidelines favoured delaying treatment to preserve drugs for later use when they were more effective, weighing risks against benefit, as well as available resources (20).

The SMART trial beginning in 2002 was the first of the clinical trials to receive approval to test strategies which involved earlier ART initiation (Table 1). The SMART trial compared continuous ART versus deferred ART whenever patients reached a CD4 count above 350 cells/µL. The hypothesis was that intermittent antiretroviral drugs would lesson drug toxicity; however, after 15 months of follow-up the data and safety monitoring boards (DSMB) recommended the trial be halted due to double the risk of disease progression in those with episodic (or deferred) treatment. Unexpectedly, the SMART trial also showed an increased rate of other serious events in those who had treatment deferred (21). Although the trial was predominantly designed to test treatment preservation through interruptions when CD4 counts were higher, it also enabled the randomized evaluation of early versus deferred ART initiation in treatment-naïve individuals. In a secondary analysis the risk ratio for death in the SMART trial was 0.26 (95%CI: 0.11-0.63) in those with early ART initiation at CD4 cell count above 350 cells/µl compared to those in whom ART was delayed until they had a CD4 cell count below 250 cells/µl (22).

The only other trial which at the time had formally evaluated earlier ART initiation versus operative thresholds (Table 1) was a trial conducted in Haiti which randomized patients to initiate ART when their CD4 counts fell to below 350 cells/µl versus the operative threshold at the time of 200 cells/µl (23). The risk ratio for mortality in the earlier ART group was 0.3 (95%CI: 0.01-7.31) (22). The START trial was still underway at the time of thesis conception and would not report until mid-2015.

Table 1: Included clinical trials determining the optimal time to initiate ART

Study [ref]	Location	Sample (N)	Date of study	CD4 count thresholds	Primary outcome
SMART Trial [12]	USA	5472	2002- 2006	<250 vs >350	Death or OI
CIPRA [14]	Haiti	816	2005-2009	<200 vs 200 to 350	Death

Observational studies on when to start ART

In the absence of randomised trials on optimal timing of ART initiation, cohorts around the world were measuring differences in mortality in individuals initiating ART at different CD4 count strata, but with important limitations, including lead-time and selection bias as well as time-varying confounding (24, 25, 26, 27, 28, 29, 30). An HIV-infected individuals' CD4 cell count is changing over time and is affected by the presence or absence of exposure to ART. Therefore, the CD4 count is a time-dependent confounder on the effect of ART on mortality. Some studies sought to overcome these biases through the application of causal methods designed to mitigate lead time and time-varying confounding issues such as marginal structural models (MSMs), and g-estimation of structural nested models (SNMs) (31). No studies were identified during this review which used a regression discontinuity approach to mimic randomisation of patients around a threshold as another way to apply causal methods to data from observational studies with time-varying confounding.

Observational studies making use of causal methods (Table 2) had demonstrated protection from progression to AIDS and death at higher CD4 cell counts (32), when compared to ART initiation at <200 cells/µL. The NA-ACCORD and the Cascade Collaboration studies were able to find protection against death at higher CD4 stratum compared to those initiating ART above 500 cells/µL (33, 34), although there were some differences in both these studies compared to the first two mentioned above. The results of the NA-ACCORD study were counter-intuitive and resulted in some debate around the statistical methods, whereas the Cascade Collaboration study suggested that patients who were deferred had a higher proportion of drug abuse and hepatitis infections potentially biasing results.

An additional observational study by Shepherd and colleagues considered a composite metric score as the primary outcome (excluding it from these search results, see Annexure 2) which included death, AIDS events, non-AIDS events, and CD4 cell count at 1 year. The causal methods employed were proposed by Robins (35) and were the same methods used by the NA-ACCORD study but modified to include a rule per CD4 cell count initiation value (550 separate rules for those who started ART with a CD4 cell count between 200 and 750 cells/µL) instead of dividing all participants into two categories as the NA-ACCORD study did. In effect, the Shepherd study design was an effort to mimic a randomised controlled trial with multiple arms. The study results suggested starting people on ART within three months of their CD4 cell count dropping below 495 to maximise health and 354 to maximise the quality-of-life metric used in the study (36).

Predating these causal studies were methodological papers which proposed tools and methods in order to use observational data in a causal way. Although these publications were not focussed on

clinical outcomes, their rigor to improve the methodological approach were important to the debate of when to start ART, while their publications contained examples with datasets from observational cohorts showing how to apply the methods. Hernán first introduced the dynamic treatment regimens (DTR) approach to the debate in trying to deduce the optimal timing of ART initiation in 2006, comparing ART initiation at 200 versus 500 cells/µL. DTRs are a list of individually tailored rules, one per time interval, which when used together with G-estimation, parametric G-formula, MSMs or NSMs can compare the survival of individuals to estimate results similar to a clinical trial (37, 38, 39). A later paper by Cain modifies the DTR approach by applying a new rule per CD4 cell count initiation value (in increments of 10 cells) between 200 and 500 cells/µL (40). Both publications suggested better survival when starting ART earlier (Hernan's study result had a HR of 0.5 (95%CI: 0.2-1.1) when comparing initiating ART at 200 versus 500 cells/µL and Cain's study, although acknowledged as imprecise, suggested starting ART above 350 cells/µL as being most optimal) (37, 40).

By 2013, guidelines in the United States (US) recommended ART initiation for all HIV diagnosed individuals (41), whereas WHO recommended ART for all individuals with a CD4<500 (9), and in South Africa guidelines recommended ART initiation when the CD4 cell count dropped below 350 cells/µL (42). The US recommendations were based on higher potency drugs, lower toxicity and studies showing both decreased transmission in discordant couples on ART and decreased morbidity from non-AIDS-defining illnesses when starting ART early (43, 44). Although there was strong evidence that starting ART at higher CD4 cell counts lead to less morbidity and mortality, the optimal timing (or CD4 cell count threshold) for ART initiation in high burden settings – where different ART regimens were being used – was still debated. There remained a paucity of data and appropriate analyses on the individual (relative risk) and population (risk difference) effectiveness of ART initiation at different thresholds in these resource limited settings. The costs and program implications in areas with resource-constrained health service capability were also expected to differ from the settings where eligibility had already been expanded (43, 45, 46, 47, 48, 49).

Table 2: Included observational studies determining the optimal time to initiate ART

Cohort [reference]	Sample	Study years	Analysis	CD4 count thresholds	Death (AHR, RR)
NA-ACCORD Investigators [24]	17,517	1996-2005	MSM	deferred vs 351-500	RR 1.69 (95%CI 1.26-2.26)
				deferred versus >500	RR 1.37 (95%CI 1.37-2.79)
HIV-causal collaboration [23]	20,971	1996-2009	MSM	<350 vs >500	AHR 1.01 (95%CI 0.84, 1.22)
				<200 vs >500	AHR 1.20 (95%CI 0.97, 1.48)
Cascade collaboration [25]	9,455	1996-2009	SNM	200–349 vs immed start	AHR 0.71(95%CI 0.44, 1.15)
				350–499 vs immed start	AHR 0.51 (95%CI 0.33, 0.80)
				500–799 vs immed start	AHR 1.02 (95%CI 0.49, 2.12)

Systems for monitoring ART programme effectiveness

In this section of the literature review I sought to explore published approaches for monitoring HIV and associated interventions at a population level in similar settings to South Africa.

Monitoring approaches to estimating population-level ART coverage and outcomes

There are several commonly described approaches to assessing ART programme uptake and effectiveness. The main categories include population-based household surveys (50), case-based surveillance (51, 52), and monitoring and evaluation systems within HIV care and ART treatment health services (53). All the above monitoring approaches make use of individuated data which is consolidated to try and ascertain population level estimates on disease incidence, prevalence, interventions, and outcomes.

Household surveys

Comparable multi-country household surveys can be country-wide (Demographic and Health Surveys [DHS]) or restricted to a smaller area (Health and Demographic Surveillance Systems [HDSS]). A third type of survey is similar in design to the DHS but is generally a more localised sampling-based survey taking place within a country (for example the Swaziland HIV Incidence Measurement Survey (SHIMS) (54)). HDSS projects typically follow every household within a demarcated area, whereas once-off or repeated surveys, which could be for a large (country/multi-country) or smaller jurisdiction (localised sampling-based surveys), are based on a sample which is representative of all households. All surveys are made up of interview questions on demographics and clinical information for all residents within the households taking part and some surveys may also include taking biomedical samples for analyses to measure disease and/or treatment prevalence (54, 55, 56).

The multi-country Demographic and Health Survey (DHSs) programme was established by the United States Agency for International Development (USAID) in 1984. These nationally based surveys take place in over 85 countries including South Africa and many Southern African countries. DHSs are periodic national cluster samples collecting cross-sectional data including questions on marriage, fertility, family planning, reproductive health, child health and HIV/AIDS. However, prior to 2014, the DHS implementation guidance only collected testing and prevalence data related to HIV and did not cover treatment access or current HIV viral load status (56, 57).

In many high-HIV-prevalence settings, dedicated in-country national household HIV impact assessment surveys that collect blood specimens in addition to interview type questions have been

conducted additional to the DHSs survey, in order to estimate ART uptake and viral load suppression in HIV positive participants. In South Africa, the South African National HIV Prevalence, Incidence and Behaviour Survey has been repeatedly implemented by the Human Sciences Research Council (HSRC). In 2008 and 2012, this survey measured the presence of antiretroviral drugs in dried blood samples from people who tested positive for HIV, using a high-performance liquid chromatography matched to a tandem mass spectrometry. The survey utilises a multi-stage cluster sampling design, and in 2012 projected country estimates from a sample size of 13,083 households. Between 2008 and 2012, the prevalence of HIV, as measured by the survey, increased from 10.6% to 12.3% (6.4 million people) and by 2012 over 2 million people were exposed to antiretroviral therapy. A greater proportion of women (34.7%) were exposed to ART in comparison to men (25.7%) (58).

Different from the above cross-sectional DHSs and stand-alone health impact assessment surveys, the Health and Demographic Surveillance Systems (HDSSs) gather comprehensive longitudinal data from a cohort consisting of the total population within a specific area. HDSSs are often implemented in countries where there is a lack of effective or accessible national civil (birth and death) registries and monitors births, deaths, causes of death and other social and economic determinants of health (59). HDSSs mitigate concerns around sampling error and recall biases often found in DHSs. However, results of an HDSS cannot be interpreted as representative of a national population. The population covered under an HDSS is usually under constant monitoring over a long period of time and contains a larger dataset inclusive of disease specific information. HDSSs are useful in reporting trends and can possibly extrapolate causal mechanisms of disease as well (55). However, it is important to note that HDSSs are not intended to replace vital registries but rather provide a stepping stone to evolve national civil registry systems (59). The Alpha and INDEPTH Networks are examples of HDSS networks which operate in over 20 countries in Africa, Asia and Oceania (59). They perform population surveillance at all households within a geographically defined adult population, capturing HIV sero-testing for HIV prevalence and verbal autopsy interviews for all HIV related mortality.

One of the sites in South Africa participating in the HDSS project collected data on all 12,000 households within a rural population in Kwa-Zulu Natal, starting in 2000 (60). Using the surveillance data over time, Herbst and colleagues were able to show a significant decline both in population mortality and HIV-related adult mortality following the scale-up of free ART services and were also able to demonstrate a decline in HIV incidence correlated to increasing ART coverage (43, 61). The cause-specific mortality fractions for HIV-related causes declined from 56% in 2002 to 39% in 2009, with the largest decline in 2004 coinciding with the rollout of the free ART services. The all-cause age-standardized mortality rate (SMR) declined over the same period from a high of 174 (95%CI:

165-183) deaths per 10,000 person-years observed (PYO) in 2003 to a low of 116 (95% CI: 109-123) in 2009 (62). Verbal autopsy methods showed substantial agreement with physician coding, post-mortem and hospital diagnoses (63) and can be used to measure changing trends in cause-specific mortality. In a separate publication, the same surveillance project reported a 38% less likely risk of HIV transmission to an HIV-negative individual in a high ART coverage area in comparison to someone living in a low ART coverage area. This study demonstrated significant decline in HIV incidence in areas where ART coverage is high (43). The concept for this study was ideated after seeing results from a landmark prevention clinical trial which demonstrated that ART substantially decreased risk of HIV-transmission in sero-discordant couples (44).

A second HDSSs site, the Agincourt HDSS located in rural Northeast South Africa was established in 1992 and contained upwards of 90,000 people in 2012. The Agincourt team use the survey process not only to promote HIV prevention but also to collect and elucidate causal pathways and test interventions over the entire health cascade. There are nested cohorts within the Agincourt cohort to measure HIV prevalence and risk factors which started post 2009. One focus is measurement of the impact of decentralised ART delivery through the public and private health sector and another HIV-related research project is validation of verbal autopsy interviews for causes of death with clinical diagnoses (64). One publication from this team, demonstrating high concurrence between verbal autopsy interviews, clinician diagnoses and probabilistic determination, illustrated the rise in ranking of HIV as a top cause of death, from number 3 in the 5-14 age bracket in 1992-1994 to the number one cause across all ages by 2002-2005 (65).

Household surveys have strengths and limitations that need to be understood when considering implementing or interpreting data from them. DHSs and HDSSs have been widely implemented and are generally regarded as being robust methods for estimating population parameters. Results derived from the different types of household surveys (DHSs and HDSSs) have been shown to be comparable, with caveats, in regard to common data indicators and could prove very beneficial if data from the different surveys were triangulated to approximate national estimates, and to inform policy (55, 66). Household surveys have also provided a great platform for research and research capacity building, can generate indicators required for international reporting and may have provided the insight needed to develop enthusiasm for future routine, nationally established, longitudinal information systems (56, 59, 67).

A key advantage specifically of HDSSs is the inclusion of everyone, whether diagnosed or not, and whether in care or not, mitigating concerns about selection and recall bias. HDSSs triangulated with clinical data from HISs can provide a more complete picture of a populations health, creating

estimates for those who do and do not access health care (43, 59). This is especially important in communities with low health care coverage. HDSSs can also provide excellent insight to how well health interventions are working and/or impacting a population(59). Whereas disadvantages of HDSSs with respect to population-level HIV monitoring include generalisability concerns given the intentional focus on a small area, challenges in integrating data when patients move out of the area under surveillance, and challenges in the availability of and access to clinical data from health services. HDSSs are also resource intensive and require stability over time in both the data elements and population (59).

Key advantages of DHSs include national representation whereby population-level estimates can be extrapolated. DHSs report high response rates and deploy highly trained interviewers (56). Usually, the questions and procedures are standardised across multiple countries and use consistent content over time. This enables repeated cross-sectional designs for temporal trend tracking, geospatial and cross-comparative analyses (56, 68, 69, 70). A critical disadvantage of the DHS approach is the inability to look for associations with outcomes as the data are inherently cross-sectional from a sampled population. Some measures are also based on self or proxy reporting (such as maternal proxy for children, or head of household reporting) and can be confounded by recall bias (56).

Case-based surveillance

Case-based surveillance (CBS) systems usually consist of centrally located databases or collection tools that record information usually reported from a clinician, health facility or laboratory on an individual (case) with markers of a specific infectious disease (often called notifiable diseases and conditions)(71). The notifiable cases focus on diseases that pose potential serious health threats to others in the population. The often-challenging goal of a CBS system is to comprehensively collect data on the individuals with the specified condition, with intention to follow up, ensure proper clinical management and collect data on status and outcomes, while limiting or preventing further spread (72, 73, 74).

Every few years, debates arise questioning whether HIV should be a notifiable disease (75, 76). Currently, HIV is not a notifiable disease in South Africa, but it is in many other countries. In 1999, the Minister of Health strongly advocated to make AIDS notifiable, stating better statistics were needed and relatives and partners needed to be notified (76). However, there was strong opposition by human rights advocates, people living with HIV, non-governmental organisations (NGOs) and researchers. The law was never passed (77, 78). Typically, the justification for a notification system is to alert authorities of diseases that may require immediate intervention, to get a better grasp on statistics and to evaluate changing patterns or key populations affected by the disease. However,

South Africa already had well established statistics on HIV from both DHSs and HDSSs, antenatal surveys, and the death registry, paired with very capable researchers and modellers (58, 79). As HIV is highly prevalent in South Africa, one of the primary objectives – to visit every case reported via the notification system – would have over-burdened an already resource-constrained health care system. In addition, due to the sexual nature of transmission and delayed onset of fully recognizable symptoms for several years, outbreak responses would be ineffective (80). Mass screening campaigns would be needed in order to supply the data the government was hoping to glean from a notification system, but this was not seen as affordable or feasible (81). Although South Africa suggested anonymous case reporting, human rights advocates and others doubted the confidentiality such a system could provide, without which there would be the risk of stigma and the possibility that individuals would be discouraged from seeking care (80, 82, 83). Despite the numerous arguments against making HIV a notifiable disease in South Africa, there has been enthusiasm for unlinked sentinel surveillance systems, which was later followed by case-based surveillance lifted from digital linked health records for a more targeted and data-informed response (80, 84).

In settings where the disease services are uniform and the disease is of high prevalence (like HIV in South Africa), many of the objectives which have resulted in CBS being promoted for HIV can be achieved using the same data already collected by the health services via the electronic registries, laboratories or health information systems. In this case, there would be no need for separate collection systems or parallel data flow (52). In high HIV prevalence settings without robust monitoring systems, CBS is promoted, in addition to supporting an outbreak response, to provide individuated longitudinal data on HIV by requiring sentinel events to be reported by services to a dedicated CBS system, in a manner that enables linkage, allowing estimation of population-wide parameters for treatment services or monitoring interventions in a manner that is more regular and ongoing than periodic surveys (72, 73).

The National HIV/AIDS case-based surveillance system in Haiti has proven to be successful with an estimated 95% completeness of reporting and further ongoing iterations to the system to improve estimates (85). The system was implemented in December of 2008 and collects data in a centralised web database, with data imported from both an electronic medical record (EMR) system and a laboratory (86). The system was built with the intention to monitor the epidemic trends and better allocate HIV prevention resources and HIV/AIDS services. The case-based surveillance system collects data on the HIV cascade which appears to be heavily pre-ART focussed but also includes information on ART initiation and date of death (85). In 2011, there were an estimated 500 case reports a week (86). Although the implementers tried to use a unique patient health identification

number, that approach did not work and now the system matches on several indicators including name and demographics. Cascade reporting dashboards depict the gaps in access at the different stages of health care access and shows comparable estimates when looking at modelled estimates (85).

Routine health information systems

Monitoring and evaluation (M&E) systems ideally should deliver concrete evidence on programme successes and failures, inform policy interventions, and guide the delivery of continuously improving prevention and treatment services (87). M&E systems can be paper-based or digital tools to help collect and aggregate patient demographics, clinical assessment data, health service burden and delivery statistics and can also map individuated longitudinal data, creating alerts and temporal trends. The data in M&E systems ideally should be transformed and triangulated with other data in a HIS (83).

Many HIV M&E systems in resource limited settings (RLSs) were set up in health contexts that previously had very rudimentary M&E systems such as tick sheets for counting services provided and some RLSs had no M&E systems in place at all (87). With the scale-up of free ART services, RLSs were required to quickly implement M&E services in order to report to donors on their programme successes to secure subsequent tranches of funding (88). Therefore, sending data centrally became the most important objective, with leaders and programme managers often forgetting that data should first and foremost be used to improve the care of the patient providing the data (89).

The ear-marked donor funding for HIV care and treatment enabled rapidly scaled HIV and ART services, but also influenced siloed M&E systems that only serviced HIV care and ART initially (88). In the beginning, the majority of public health facilities offering ART services used paper-based M&E systems with guidance on tools from the World Health Organization (53). Paper registers allowed for the collection and aggregation of patient demographics, and clinical assessment statuses. Most registers were set up in a way that programme managers could see at a glance how many people were missing routine labs (such as viral loads and CD4 cell counts) and appointments, enabling recall if necessary (53). The data from the registers were aggregated and submitted in a format that was usually standardised across a specific area or country, enabling uniform numerators and denominators for transformation into indicators and estimates (85). While most facilities were using paper-based registers, some of the research affiliated or NGO supported sites were using sophisticated online systems collecting and analysing individuated data (87). Both approaches proved unsustainable: ART treatment is for life making paper registers too unwieldy, and countries in RLSs did not have stable online networks and large enough bandwidth at the majority of their

health facilities (53, 87). In some countries, this lead to the implementation of digital registers which were often offline software applications that allowed HIV care and ART services to collect individuated clinical assessment data for more efficient use of data at the facility and ease of reporting centrally (87, 90). A well designed digital system, although originally built with ear-marked HIV funding, could incorporated other health services as well (87).

For clinical assessment records to be used for population-level treatment uptake and mortality estimates, patients lost to the health services would need to be followed-up in the community to ascertain outcomes among those lost to care (86). This becomes increasingly difficult in high prevalence regions, specifically where treatment is for life, as scale-up compounds the number of people requiring follow-up. In these scenarios, the most accurate and beneficial estimates for population estimates can be established when patients' health data are linked to unique identifiers and the demographic and clinical assessment data are triangulated with laboratory results, referral data and death registry data (51, 83, 86, 88).

Life expectancy methods and estimates, and burden of disease studies

Life expectancy estimates are important indicators of health burden, cost and future demographic and socio-economic impact of the HIV epidemic. Data on the life expectancy of people on ART is lacking across most resource limited settings, with one of the few countries able to estimate such figures being South Africa. This is due to the ability to link ART data to the death registry, of which 90% of all adult death records were recorded in 2012 (91). A study by Johnson and colleagues used relative survival models to estimate excess mortality attributable to HIV stratified by age and for different baseline CD4 categories; they estimated a life expectancy of 33.3 additional years overall in 2010 for individuals living with HIV, who initiated ART at 20 years of age. This is in comparison to 52.9 years in uninfected people. The life expectancy for men on ART at 20 years of age was 27.6 additional years (95%CI: 25.2-30.2) while the life expectancy for women was 36.8 additional years (95%CI: 34.0-39.7). People starting ART with CD4 cell counts higher than 200 cells/µL had near-normal life expectancy (91). Other countries in Sub-Saharan Africa have been able to determine life expectancy through methods using abridged life tables, stratified by sex and baseline CD4 cell count. Patients on ART who were lost to the services were followed up in the community to determine mortality rates, imputing mortality in the small proportion that could not be found. A study following this method in Uganda found an overall life expectancy of 26.7 additional years (95%CI: 25.0-28.4) if starting ART at 20 years of age (92).

The above studies are focussed on measuring life expectancy in patients already enumerated in cohorts, which might be biased due to selective care access. Whole population life expectancy

trends have also been used to explore the population-level impact of HIV (93, 94) and subsequently of HIV interventions, using mortality surveillance data. The South African Medical Research Council (SAMRC) cleans, and analyses deaths recorded in the National Population Register to determine trends in life expectancy and impact disease and treatment interventions have on population level mortality. In 2000, prior to the free ART rollout, the SAMRC reported that the probability of a 15-year-old woman dying before the age of 25 was about 43 per 1000 and dropped to 23 per 1000 in 2012, with decreases largely due to the provision of to HIV treatment to mothers. The life expectancy at birth was 61.2 years in 2012, an increase of more than 7 years since 2005 and was most likely related to drops in child mortality as well as young adult mortality due to access to ART (95).

The national burden of disease study in South Africa is another way to measure population level premature mortality. The first burden of disease study was published in 2003 and triangulated three sources of data plus utilised a modelling approach to incorporate AIDS estimates. The three sources of data included data from Statistics South Africa, the National Injury Mortality Surveillance System, and the National Department of Home Affairs for causes of death. This study demonstrated that the top cause of mortality was related to HIV/AIDS (38% of years of life lost), followed by homicide, tuberculosis, road traffic accidents and diarrhoea. This seminal study suggested the stark reality that premature mortality due to HIV/AIDS would more than double by 2010 (96). In 2013, the Global Burden of Disease study reported a 354% increase in HIV/AIDS burden from 1990 to 2010 (97). Cause of death data is a cornerstone to burden of disease studies; however, this data is not available in many high burden settings. In South Africa, where the collection of this data is fairly good, there is possibility that this data will be sealed and confidential to researchers.

Predominant associations with advanced HIV disease and mortality

The impact of HIV in South Africa has been profound but since the rapid expansion of the ART programme, morbidity and mortality rates have decreased in HIV-infected people who were able to access ART (62, 98, 99). Regardless, some strong predictors of early mortality remained which included initiating ART with a low baseline CD4 cell count, being male, pregnancy, tuberculosis (TB) and becoming lost to care (91, 99, 100).

Mortality remained highest during the first 6 months of ART, although this rate did decrease by 50% between 2001 and 2005. The decreasing mortality rate was closely correlated with a drop in the proportion of patients initiating treatment with advanced HIV disease (defined by the WHO as having a baseline CD4 cell count below 200 cells/µL in adults or WHO clinical stage 3 or 4) and severe advanced HIV disease (CD4 cell count below 50 cells/µL) (9, 99). However, despite ART scale-

up, a sizable proportion of individuals were still initiating ART with severe advanced HIV disease, greatly increasing the risk of early mortality (4, 91). South Africa had one of the highest TB burdens in the world, and TB is a major cause of mortality among people with HIV. Due to the HIV epidemic, and accompanying compromised immune systems in those with HIV, the TB case load in South Africa had increased 4-fold between 1986 to 2006 (101) to 628 per 100,000 people. TB continued to be the most common cause of death in HIV-infected patients (100). Pregnancy to a lesser extent, also had an impact on mortality for HIV-infected individuals. CD4 cell counts tend to decline faster when women are pregnant (102) and according to a global systematic review, a higher proportion of pregnant women on ART were adherent during the antepartum period (75.7%, 95%CI: 71.5-79.7%) to protect their baby, but those rates declined to just over 50% during the postpartum period (53.0%, 95%CI: 32.8-72.7%) (103). Becoming loss to care (or loss to follow-up (LTF)), indicative of treatment interruption, had also been shown to be closely associated with mortality. In a comprehensive study of 7,323 treatment naïve adults who started ART between 2001 and 2007, 6.7% (95%CI: 6.1-7.4) were reported to be LTF by the first year on ART, and mortality was 7.0% (6.4-7.7). However, after linking patients reported as LTF to the national death registry, a more accurate weighted estimate of mortality was found to be 9.9% (95%CI: 8.9-10.9) (4).

Most of these studies of associations with HIV treatment outcomes in high HIV burden settings by 2014 had been based on relatively short follow-up times. It was unclear how these associations would change over time as programs grew, or how this could be continuously assessed given the challenges to routine monitoring discussed above.

Population-wide effectiveness studies

Individual level benefits from the ART programme translate into population-level benefits through viral suppression and decreased transmission, morbidity, and mortality. However, apart from the trends in overall life-expectancy discussed above, accurately estimating this impact remained difficult for most RLSs due to operational challenges with digitising health records and issuing unique identifiers to link data across health services and to vital registries. Despite there being a dearth of information on population-level impact of the ART programme in Southern Africa, the few projects that had been able to report on outcomes of all patients on ART within their geographic locations had remarkable heterogeneity in outcomes, when taking into account the increasing baseline CD4 cell counts over time. In this section, studies were sought in Southern Africa which comprehensively reported on jurisdiction-wide health outcomes for patients in HIV or ART care, in spite of the challenges to routine reporting discussed above.

Outcomes of population level cohorts

There were 4 studies within South Africa (2 from the Western Cape, and one each from Free State and KwaZulu-Natal), one within Zambia (Lusaka) and a country level study in Malawi which met the criteria of reporting on all patients within the ART programme across a specified region ((sub)district, province, or country). The baseline median/mean CD4 cell counts were low across all studies (43 to 143 cells/µL) signifying advanced HIV disease; however, this is expected given participants represent the first of those receiving ART services within the Southern African countries. Reported retention at 1 year after starting ART was 85.3% in the Western Cape population, 84% in the KwaZulu-Natal population and 70% in Malawi (99, 104, 105). The Free State study reported a Pre-ART mortality of 26.2% (95%CI: 25.6-26.9%) over two years (106). Several studies reported the first 3 months as being the duration after initiating ART with the highest mortality. The reported 1-year ART mortality proportion for all studies (except the Free State study which did not report on ART mortality) ranged from 6.9% in Lusaka, Zambia to 12.2% in Malawi (4, 99, 104, 105, 107). Common risk factors for mortality across all studies included a low baseline CD4 cell count, low weight (body mass index (BMI)) and earlier year of initiation. A few studies also included low haemoglobin and low creatinine levels at baseline as additional risk factors. Male sex was a risk factor for mortality in some studies and not a significant risk factor in others. Poor adherence was reported in one study as a strong risk factor for mortality and was not measured in the other studies (107).

The only population-level study that demonstrated triangulation of data across health facilities and with other data sources was the study published from Khayelitsha. This study considered those lost to care and used laboratory results (tracking across facilities) and the death registry to classify the individuals absent from care as in care but at a different facility, truly lost to the ART services, or as having died (with high mortality among those truly lost to care (33%))(4).

The reviewed studies had all been conducted in the early years following ART service establishment in the respective jurisdictions and were likely possible due to exceptional investments in electronic monitoring solutions aligned with new services. By 2014 it was already apparent that most of these systems were not sustainable, and there was a drop-off in robust and comprehensive reporting of outcomes as programs expanded. The Joint United Nations Programme on HIV/AIDS (UNAIDS) global report from 2013 identified the lack of systems for monitoring retention in care as a key challenge (108).

Table 3: Observational studies reporting population-level ART initiation and outcome estimates

	Study code	Sample	Year of study	Primary assessments	Duration	Results
1	Western Cape, South Africa [89]	12,587	2001-2006	CD4<50cells/µL	baseline	51.3% in 2001
				CD4<50cells/µL	baseline	21.5% in 2005
				Retention	1 year	85.3% (95%CI 84.5-86.1)
				Retention	4 years	72.0% (95%CI 68.0-75.6%)
				Mortality	1 year	8.8%
				Mortality	4 years	23.1%
2	Khayelitsha, WC, South Africa [91]	7,323	2001 - 2007	Median CD4	baseline	43 cells/µL in 2001; 131 cells/µL in 2006
				LTF	5 years	9.8%
				Mortality	1 year	9.9% (95%CI 8.9-10.9%)
				Mortality	5 years	20.9% (95%CI 17.9, 24.3)
				Risk factors for death	5 years	CD4<200,low baseline weight
3	Free State, South Africa [97]	44,844	2004-2007	Median CD4	baseline	87 cells/µL in 2004; 101 cells/µL in 2007
				Pre-ART mortality	2 years	26.2% (95%CI 25.6-26.9%)
				Started ART	2 years	67.7% (67.1-68.4%)
				Risk factors for death	2 years	CD4<100, male, age>50, low weight, low
4	Hlabisa, KZN, South Africa [95]	5,719	2004-2008	Median CD4	baseline	116 cells/µL (IQR 53-173)
				Retention	1 year	84.0% (82.6-85.3)
				LTF	1 year	3.7% (95%CI 3.0, 4.4)
				Mortality	1 year	10.9% (95%CI 9.8-12.0)
				Risk factors for death	1 year	CD4<50, male, weight, Hb<8, creat>120
5	Malawi [96]	117,945	2004 - 2007	Retention	1 year	69.50%
				Mortality	1 year	12.20%
				LTF	1 year	10.00%
				Risk factors for death	1 year	WHO III&IV, Age(15-24), male, region
6	Lusaka, Zambia [98]	21,755	2004-2005	Mean CD4	baseline	143 cells/µL
				Mortality	<90 days	4.50%
				Mortality	1 year (acc)	6.90%
				Mortality (CD4 <50)	2 years	AHR 2.2 (95%CI 1.5-3.1)
				Mortality(CD4 50-199)	2 years	AHR 1.4% (95%CI 1.0-2.0)
				Risk factors for death	2 years	CD4<200, low BMI, Hb<8, adherence

Assessments of the impact of guideline changes

Guideline changes and temporal associations

The WHO recommended ART eligibility guideline changes prior to 2014 were based on the learnings from the major clinical and observational studies (9). The 2006 and 2010 WHO ART guidelines updates simplified ARV regimens, and in addition the 2010 guidelines also included recommendations to increase the CD4 cell count thresholds. The 2013 WHO guidelines also recommended an increased CD4 cell count threshold for ART initiation (109). The Western Cape ART eligibility guidelines, following WHO recommendations, were revised over time with some lag in adoption to allow time to procure drugs and prepare for increased numbers of people accessing the ART services. The original guidelines stipulated a CD4 cell count of less than 200 cells/µL which was later increased in 2011 to include all with a CD4 cell count <350 cells/µL (110).

The higher WHO CD4 cell count threshold recommendations enabled more people to access ART in earlier stages of their HIV infection, and over 80 RLS countries adopted the guidelines by the end of 2011 (111). About 9.7 million people in RLSs were on ART by 2012, which was an increase of 1.6 million in one year (109). Globally, the increase in ART access had been correlated with both a declining HIV incidence rate and HIV mortality rate. The United Nations General Assembly had set a target of 15 million people on ART by 2015 of which 65% of this target had already been reached by the end of 2011 due to the great increases in ART enrolment (112). Despite all of these achievements, there remained high attrition rates along all the points in the HIV care cascade (109).

The improved ART regimens and increased CD4 cell count thresholds were applauded by most; however, the country-level implications of these guideline changes meant overcoming multiple challenges. As ART is lifelong, the health services needed to care for a quickly compounding number of people on ART each year, large sustainable investments in health resources and staff were needed, and more space and further task sharing needed to be considered. In addition, operational challenges such as drug procurement and distribution, limited laboratory services, and the potential spread of drug resistance also needed to be overcome. Finally, however, one of the most critical challenges identified to the continued ART scale up was that of patient retention (109).

There was a concern that with limited resources and weak health systems, more expansive access to ART for patients with less advanced disease might compromise access to care for those with more advanced disease where coverage was still suboptimal and the potential to benefit was greater. While there were studies as discussed above which demonstrated that ART scale-up within current guidelines was associated with improved program (4, 99, 113) and population-level (94, 114, 115) survival, there were no identifiable studies which formally assessed the population-level impact of changing ART eligibility guidelines in the context of limited resources. A number of community-randomized trials were being planned to test the impact of expanded ART access on HIV incidence (116, 117).

PROBLEM STATEMENT

There are very few high-HIV-burden settings where population level estimates of ART effectiveness and impact can be comprehensively assessed without being heavily influenced by selection or information bias, as programs expand and increase in clinical and operational complexity. Key uncertainties in these settings include how to ensure data are available to continue to assess and improve HIV interventions, how the effectiveness and impact of ART might evolve as guidelines change and access to care increases, and how the associations with poor HIV outcomes might change. Specific concerns aligned with program maturation and long-term chronic disease management relate to retention in care, the impact of recurrent treatment interruptions, potential de-prioritisation of sicker patients, and the evolution of gender disparities in care access and outcomes.

The Western Cape of South Africa provides an important opportunity to measure the population-level impact of the ART programme, given the widespread use of unique health identifiers, near complete coverage of individuated electronic health registers in public sector health services, and with the death registry containing upwards of 90% of all deaths (91). The triangulation of clinical assessment data regardless of where health care is accessed, laboratory results and death registration data provide the opportunity to more accurately analyse population-level estimates of ART uptake, important associations with morbidity and mortality, and how policies have impacted treatment access and outcomes.

The framework for this thesis was to review information systems and data availability for addressing HIV treatment programme effectiveness, and then to utilise available data to address key areas of epidemiological uncertainty which had emerged in high burden settings, in large part due to data challenges.

AIM AND OBJECTIVES

The overall aim of this thesis is to describe, based on population level routinely collected data, access to treatment, retention and outcomes for HIV patients in the Western Cape province over time, exploring the impact of scale-up and the changing treatment eligibility criteria.

Specific objectives are the following:

1. Describe the ART monitoring system and the critical factors that have enabled the health information system used in South Africa to generate comprehensive individuated HIV treatment program data
2. Explore the population-wide evolution of advanced HIV disease presentation irrespective of ART access
3. Describe the real-world effectiveness of ART in patients initiating treatment at newly introduced ART eligibility CD4 cell count thresholds
4. Describe outcomes of patients presenting before and after ART eligibility criteria policy changes, and the effectiveness of the guideline changes
5. Describe important associations with mortality, with a particular focus on gender and patient treatment interruptions, over time

CHAPTER ONE ANNEXURES

Annexure 1

Search methods and results for clinical trials on optimal time to start ART

Objective

- To assess evidence for the best timing during the course of HIV infection to initiate ART

Dates

- 1 Jan 1990 to 31 December 2013

Who

- HIV-infected, treatment naive Adults (>14 years of age)

Type of study

- Randomised clinical trial

Primary outcome measured

- Serious non-AIDS event, AIDS or death

Electronic searches

- Medline, papers referenced in downloaded publications

Language

- English language publications only

Inclusion criteria

- Comparing CD4 count thresholds at ART initiation with associated mortality
- Randomised Clinical Trials

Exclusion criteria

- Children, adolescents less than 15 years of age
- Subset of cohort
- Primary outcome not death or AIDS and death
- Studies other than RCT
- Biased or ongoing trials
- Primary objective not considering optimal timing of ART initiation

No.	Search Filters	Hits
5	Search: #1 AND (#2 OR #3) AND #4 AND 1990/01/01:2013/12/31[dp]	71
4	Search: (“CD4”[tiab] AND “eligibility" [tiab]) OR ("CD4”[tiab] AND “threshold"[tiab]) or OR (“Optimum tim*” AND “ART”) OR (“ART initiation” AND “CD4”) or “Deferred therapy” OR “early ART” OR (“early initiation” AND “ART”) OR “Deferred ART”) OR (“Early therapy” AND “CD4”) NOT Children NOT paediatric NOT pediatric AND 1990/01/01:2015/12/31[dp]	2,631
3	Search: (Antiretroviral therapy[MeSH] OR anti-retroviral therapy [MeSH] OR antiretroviral drugs [MeSH] OR HAART[tw])]) AND 1990/01/01:2015/12/31[dp]	41,673
2	Search: (HIV[MeSH] OR HIV infection[MeSH] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] human immune-deficiency virus[tw] OR ((human immune*) AND (deficiency virus[tw]))]) AND 1990/01/01:2015/12/31[dp]	297
1	Search: (Randomized controlled trial [pt]) AND 1990/01/01:2015/12/31[dp]	379,651

Supplementary table 1: Search strategy, clinical trials

Annexure 2

Search method and results for observational studies on optimal time to start ART

Objective

- To assess evidence for the best timing during the course of HIV infection to initiate ART

Dates

- 1 Jan 1990 to 31 December 2013

Who

- HIV-infected, treatment naive Adults (>14 years of age)

Type of study

- Observational cohort studies

Primary outcome measured

- Serious non-AIDS event, AIDS or death

Electronic searches

- Medline, papers referenced in downloaded publications

Language

- English language publications only

Inclusion criteria

- Comparing CD4 count thresholds at ART initiation with associated mortality
- Observational cohort studies

Exclusion criteria

- Children, adolescents less than 15 years of age
- Subset of cohort
- Primary outcome not death or AIDS and death
- Randomised controlled trials & clinical trials

No.	Search Filters	Hits
5	Search: #1 AND (#2 OR #3) AND #4 AND 1990/01/01:2013/12/31[dp]	102
4	Search: (“CD4”[tiab] AND “eligibility" [tiab]) OR ("CD4”[tiab] AND “threshold"[tiab]) or OR (“Optimum tim*” AND “ART”) OR (“ART initiation” AND “CD4”) or “Deferred therapy” OR “early ART” OR (“early initiation” AND “ART”) OR “Deferred ART”) OR (“Early therapy” AND “CD4”) NOT Children NOT paediatric NOT prevention AND 1990/01/01:2015/12/31[dp]	1,397
3	Search: (Antiretroviral therapy[MeSH] OR anti-retroviral therapy[MeSH] OR antiretroviral drugs [MeSH] OR HAART[tw])]) AND 1990/01/01:2015/12/31[dp]	41,673
2	Search: (HIV[MeSH] OR HIV infection[MeSH] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] human immune-deficiency virus[tw] OR ((human immune*) AND (deficiency virus[tw]))]) AND 1990/01/01:2015/12/31[dp]	297
1	Search: ("observational cohorts" OR "cohort studies" OR "Regression Discontinuity") AND 1990/01/01:2015/12/31[dp]	351,269

Supplementary table 2: Search strategy, observational cohorts

Annexure 3

Search methods and results for population-level estimates on the ART programme

Objective

- To assess population-level estimates of ART uptake, advanced disease and mortality

Dates

- 1 Jan 1990 to 31 December 2013

Who

- HIV-infected, treatment naive Adults (>14 years of age)

Type of study

- Consolidated linked ART clinical database

Primary outcome measured

- Serious non-AIDS event, AIDS or death

Electronic searches

- Medline, papers referenced in downloaded publications

Language

- English language publications only

Inclusion criteria

- ART uptake and mortality estimates
- Population level studies inclusive of everyone on ART
- In a Southern African country

Exclusion criteria

- Children, adolescents less than 15 years of age
- Subset of population
- Primary outcome not death or AIDS and death
- Sampled sites within a region

No.	Search Filters	Hits
5	Search: #4 AND (#3 OR #2) AND #1 AND 1990/01/01:2013/12/31[dp]	123
4	Search: ("ART"[All Fields] AND ("risk factors"[MeSH Terms] OR "outcomes"[All Fields]) AND ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "mortality"[MeSH Terms])) AND 1990/01/01:2013/12/31[Date - Publication]	849
3	Search: (Antiretroviral therapy[MeSH] OR anti-retroviral therapy [MeSH] OR antiretroviral drugs [MeSH] OR HAART[tw])]) AND 1990/01/01:2013/12/31[dp]	37,059
2	Search: (HIV[MeSH] OR HIV infection[MeSH] OR human immunodeficiency virus[tw] OR human immune deficiency virus[tw] human immune-deficiency virus[tw] OR ((human immune*) AND (deficiency virus[tw]))]) AND 1990/01/01:2013/12/31[dp]	253
1	Search: (Angola OR Botswana OR Lesotho OR Mozambique OR Namibia OR South Africa OR Swaziland OR Zambia OR Zimbabwe OR Southern Africa)	209,279

Supplementary table 3: Search strategy, population-wide outcomes

Chapter 2: Results

CHAPTER 2a

A THREE-TIER FRAMEWORK FOR MONITORING ANTIRETROVIRAL THERAPY IN HIGH BURDEN SETTINGS

Associated publication(s)

Osler M, Hilderbrand K, Hennessey C, Arendse J, Goemaere E, Ford N, Boulle A. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. J Int AIDS Soc. 2014 Apr 28;17(1):18908. doi: 10.7448/IAS.17.1.18908. PMID: 24780511; PMCID: PMC4005043.

This paper is a copy of the version of the above paper in PubMed Central® (PMC) with a few post-publication modifications, including formatting of references, figures, tables, appendices, and supplementary material for consistency throughout the thesis. The content remains substantively unchanged although there are a few additional sentences added for clarification, and minor stylistic edits such as the standardisation of the terms used for referring to men and women.

Alignment with the related thesis objective

A key challenge the doctoral research sought to address was how maturing and expanding ART programs in high HIV-burden settings could be monitored. Robust program data would be a pre-requisite to being able to explore any of the emergent clinical or operational questions. The first thesis objective was therefore to detail the program monitoring approach which formed the basis for the rest of the thesis; theorising it as a multi-tiered, flexible and pragmatic solution; reflecting on critical success factors and challenges; and presenting a case study demonstrating system-wide cohort outcomes.

Candidate`s contributions

The candidate designed and planned the research. The candidate wrote the first draft of the manuscript, distilling principles learnt from implementing the ART M&E system in the Western Cape and South Africa, acquired, processed, and analysed the data for the case study, integrated comments from co-authors and submitted the manuscript for peer review.

Abstract

The provision of antiretroviral therapy in low- and middle-income countries is a chronic disease intervention of unprecedented magnitude and is the dominant health systems challenge for high burden countries, many of which rank among the poorest in the world. Substantial external investment, together with the requirement for service evolution to adapt to changing needs, including the constant shift to earlier antiretroviral therapy initiation, makes outcome monitoring and reporting particularly important. However, there is growing concern at the inability of many high-burden countries to report on the outcomes of patients who have been in care for various durations, or even the number of patients in care at a particular point in time. In many instances, countries can only report on the number of patients ever started on antiretroviral therapy. Despite paper register systems coming under increasing strain, the evolution from paper directly to complex electronic medical record solutions is not viable in many contexts. Implementing a bridging solution, such as a simple offline electronic version of the paper register, can be a pragmatic alternative. This paper describes and recommends a three-tiered monitoring approach in low and middle-income countries based on the experience implementing such a system in the Western Cape Province of South Africa. A three-tier approach allows Ministries of Health to strategically implement one of the tiers in each facility offering antiretroviral therapy services. Each tier produces the same nationally required monthly enrolment and quarterly cohort reports so that outputs from the three tiers can be aggregated into a single database at any level of the health system. The choice of tier is based on context and resources at the time of implementation. As resources and infrastructure improve, more facilities will transition to the next higher and more technologically sophisticated tier. Implementing a three-tier monitoring system at country level for pre-antiretroviral wellness, antiretroviral therapy, tuberculosis and mother and child health services can be an efficient approach to ensuring system-wide harmonization and accurate monitoring of services during the scale-up of digital solutions, including long term retention in care.

Introduction

The provision of antiretroviral therapy (ART) in low and middle income countries is a chronic disease intervention of unprecedented magnitude (118, 119, 120), and is the dominant health systems challenge for high burden countries, many of which rank among the poorest countries in the world. ART provision is characterised by its scale, the accumulation of numbers on treatment given the requirement for lifelong therapy, and associated burden on health services, and national and international funding (121).

Substantial external investment, together with the requirement for service evolution to adapt to changing needs, including the constant shift to earlier ART initiation (118, 122, 123), makes outcome monitoring and reporting particularly important. However, there is growing concern at the inability of many high-burden countries to report on the outcomes of patients who have been in care for various durations, or even the number of patients in care at a particular point in time (87, 121, 124, 125, 126). In many instances, countries can only report on the number of patients ever initiated on ART.

For chronic disease care, the preferred means of monitoring progress is through cohort monitoring, which follows groups of patients over time and reports on key baseline and outcome variables (127, 128), which in the case of HIV care may include immunological, clinical, and virological indicators (99, 129). Typically, data are aggregated per cohort at standard treatment durations measured from the start of care.

Monitoring of primary care interventions has often been based on tallying the numbers of services rendered to inform the allocation of resources, with pervasive concerns on the reliability of these data(130). Against this backdrop, there are many reasons for the failure to establish and maintain robust country-level HIV cohort monitoring systems in many high burden countries. Chief amongst these are the rapid scale-up of ART, limited human and monetary investment in monitoring, and limited appreciation of the value of cohort monitoring both for policy and facility management.

In addition, monitoring may be done by different actors and services with poor co-ordination between sites. In many settings ART provision has involved a collaborative effort by many actors, including the public and private sector, national and international non-governmental organizations (NGOs), academic research groups and external donors. Varied and complex electronic medical record (EMR) systems have been created either with particular research interests in mind or in order to fulfil parallel reporting requirements stipulated by donor agencies (126, 131). Most of these tools are not, however, simple or robust enough for use at scale, and depend on facility-based

infrastructure, network capacity and stability, leaving individual treatment sites and health authorities without viable standardised tools to monitor the ART programme.

There have been notable exceptions in terms of country-level or regional reporting. The government of Malawi has an impressive track record of peer-reviewed outputs based on their national monitoring system for ART (132, 133, 134, 135). The Western Cape province of South Africa, on a smaller scale, has maintained cohort reporting for over 10 years during which time over 160,000 patients have been initiated on ART. The common themes for both programmes have been a single monitoring system, strong system stewardship, and a phased evolution which began with paper-based systems that then guided the cautious development of electronic data capture (99).

In this paper we describe a pragmatic, multi-tier and fully inter-operable technology mix that limits dependencies and points of system failure, offering a viable and context-appropriate framework for ART monitoring in resource-constrained settings. This three-tier approach was developed in the Western Cape of South Africa, which has experienced rapid scale up of ART over the last decade and today manages over 150,000 patients on ART across 208 sites (case study). Paper-based registers, electronic registers and EMR solutions are combined in a unified system to produce common nationally required indicators, and rapid migration options between tiers as resources or monitoring needs change.

Case study

South Africa rolled out a free ART service in the public health sector beginning in April 2004 (136). Through close collaboration with academic centres and donor agencies, the Western Cape started the same free services from May of 2001 (137). The Western Cape has an estimated population of just fewer than 6 million people and is the fourth most populous province out of a total of 9 in South Africa. By mid-2012, the Actuarial Society of Southern Africa HIV model projections estimated that 260,000 adults were living with HIV in the Western Cape Province and there would be an estimated 13,000 new infections in the 2012-2013 financial year. At the end of December 2013, a reported 132,279 people remained in care within the ART services. Monthly reporting is from all public health facilities offering ART services.

*The Western Cape monitoring and evaluation programme for ART services started as a combination of paper registers at the facilities scaling up ART services and electronic medical record software called EKAPA (**E**valuation of the **K**hayelistsha **A**IDS **P**rogr**A**m) in the initial Khayelitsha sentinel sites. This two-tier system, with the majority of sites using paper-based registers, was successfully*

monitoring outcomes for the entire cohort up to 2008, during a period when the programme was still young and enrolment was relatively low (99). The paper registers provided for patients to be followed for up to 4 years on treatment within a single register. It was envisaged that by the time the first patients completed the register, electronic solutions would be in place. A number of delays in the provision of adequate networking infrastructure, computer hardware, and software development (EKAPA was being redeveloped as a Provincial system), together with the constant program expansion, resulted in a failure to migrate sites onto an electronic system as originally envisaged. Despite creative adaptations of the paper-based system to cope with ever increasing patient numbers and durations on ART, clerical staff in large or mature sites began to take increasing strain maintaining the paper-based registers and extracting monthly and quarterly cohort reports.

*A standalone electronic HIV register had been developed by the University of Cape Town Centre for Infectious Disease Epidemiology and Research as a potential digitization option for paper registers, and in line with WHO guidance was intended to eventually encompass multiple priority HIV-linked interventions which required outcome reporting (HIV treatment, tuberculosis treatment and mother and child health services incorporating the prevention of mother-to-child transmission of HIV). This application (TIER.Net for the **T**hree **I**nterlinked **E**lectronic **R**egisters) became the middle tier of the Three-Tier Monitoring and Evaluation System and enabled the rapid digitization of the paper registers, in many cases obviating the need to go back to source folders.*

The quality of data improved when migrating from paper to electronic solutions, particularly in the reporting of patients lost to care where large sites using paper registers struggled to identify and account for all losses distributed across multiple registers. In addition to improving accuracy, the auto-calculation of the cohort reports after migration to electronic registers obviated the need to reserve dedicated clerical time to extract reports, thereby improving the timeliness of reporting.

Table 1 reflects routine cohort data from the Western Cape Antiretroviral therapy programme with follow-up data to the 31 December 2013. Information reflects naïve patients and is based on a combination of reports from paper antiretroviral therapy registers, TIER.Net (the offline tier-2 software) and EKAPA (the 3rd tier networked electronic medical record). These data are predominantly collected by facilities using TIER.Net (201 of 231 facilities), but a substantial proportion (20%) of patients are followed by the larger sites using EKAPA; only a few sites remain on paper-based systems. Just over 87% of the facilities offering ART reported cohort outcomes for inclusion in the presented data (Table 1).

Table 1 describes the baseline characteristics, clinical status and outcomes of yearly cohorts (columns) per duration of time on antiretroviral therapy (rows). Each grouped set of rows reports on

indicators per duration on ART for that particular cohort, with duration or time on ART increasing as one scrolls down the column. When the programme first started in 2001, over 78% of those initiating ART had a CD4 count < 100 cells/µl. This proportion dropped over time, with only 19% initiating ART with such low CD4 counts in 2013. Mortality during the first year on ART (first 3 months more specifically) has dropped over time and is correlated with the increase in CD4 counts at ART initiation within each cohort. Retention (number remaining in care at the same facility they initiated ART) at 12 months was greater than 85% until 2009; however, with each year this figure decreased slightly. The drop in retention over time is related to the ever-increasing number of patients enrolling in care. As the programme grows, the proportion of people lost to ART care increases, forcing policy makers and innovators to think about changes to the traditional models of care in order to decongest the ART services.

Discussion

Rationale for a multi-tier solution

Over the past decade of ART scale up, many countries have recognized the need to transition from paper to EMR systems in order to manage ever increasing patient numbers. This transition has been mainly driven by high patient burden or the length of follow-up where extracting data from patient records or aggregating paper registers have become unwieldy and unsustainable. One study in Malawi reported that high burden clinics managing in excess of 2,000 patients on ART need up to 5 days to extract quarterly cohort reports directly from patient records, with facilities sometimes obliged to halt services during this period, despite the support of a team from the National Aids Office (138). Implementing a collection tool such as a paper ART register can make extracting routine quarterly reports less burdensome. Nonetheless, with time a multitude of registers accumulate, and patient follow-up duration exceeds what the registers were designed for, making the storage, recording and aggregation of data more cumbersome.

Despite paper register systems coming under increasing strain, the evolution from paper directly to an EMR solution is not viable in many contexts. Most EMR systems require wide area networks, facility-level infrastructure including computers and local networks, and structured helpdesk support. Well designed and context appropriate systems might still fail due to their dependency on infrastructure and support.

Transitioning from paper directly to EMR systems is often not immediately feasible, and implementing a bridging solution can be a pragmatic alternative. These middle tiers or bridging

solutions include electronic implementation of the paper registers through off-line or online solutions, or a hybrid of the two. Figure 1 illustrates the potential increments in sophistication in disease monitoring solutions, which are candidate tiers in a multi-tier implementation.

It is not practical to implement and support all potential levels depicted in Figure 1. Implementing one middle tier can however make the evolution from paper to EMR solutions more viable. Digitisation can happen more rapidly via direct back-capture from the paper registers already in place, whilst the infrastructure requirements and overheads are minimal in comparison to networked EMR solutions. A simple offline electronic version of the paper register has relatively few barriers to installation, only requiring a computer and a stable power source.

A three-tiered monitoring approach allows Ministries of Health to strategically implement one of the tiers in each facility offering HIV and/or ART services. The choice of tier is based on context and resources at the time of implementation, as resources and infrastructure improve, more facilities will transition to the next higher and more technologically sophisticated tier.

In South Africa, the 3 Tier Monitoring and Evaluation System for ART (Figure 2) was adopted by the National Department of Health in December 2010. The Three-Tier Monitoring and Evaluation System allows for data to be reported centrally but has the patient and programme management by facility as the main focus. As a facility moves up in tiers, the number of reports to improve facility management of the health service increases. These reports are required to be used locally and are mandated and supported by national standard operating procedures for the monitoring of ART. In addition to the monthly patient totals and quarterly cohort reports, the paper-based system can be used to extract missed appointment lists for tracing patients via community health workers; the middle tier offline system automates the generation of missed appointment and defaulter lists, can generate staff work load reports (for burden, accountability and recognition) and missing laboratory result reports amongst others; the third tier or networked EMR in addition allows for centralised data linkage and quality control and has more built in clinical validations.

Key principles of a three-tier solution

Each tier produces the same minimum set of reports

Each tier should produce the same nationally required monthly enrolment and quarterly cohort reports so that outputs from the three tiers can be aggregated into a single database at any level of the health system, giving programme managers a better understanding of the burden of care, equity of access, quality of service, retention in care, and other outcomes of the programme (Figure 3).

Although each tier produces the same monthly and quarterly cohort reports, reports and modules to facilitate service management at a facility or district improve as facilities migrate to the next tier. For example, an offline computerised implementation of the registers can provide listings of patients who have missed appointments, defaulted, transferred out, are on second-line medication or are clinically eligible for but not yet on ART. EMR solutions typically offer more comprehensive functionality in addition to these reports such as detailed appointment systems, workload management tools, access to laboratory, pharmacy and vital status data, and closer tracking of patient movement through the system.

Standardisation and interoperability

An import/export data exchange standard (DES) enables the transfer of data from one software system to another. In addition to allowing interoperability between tiers, a DES can provide an interoperability solution in countries which have a multitude of existing software applications of similar functionality which evolved organically, ensuring data from each application is imported into a single national dataset. Criteria such as DES compliance and validated nationally required reports can then be set by governments as prerequisites for the continued sanctioning of software solutions. Multiple solutions can in some instances create healthy competition and reduce risk of failure by preventing dependence on a single system which might not scale well or fail to meet future functionality requirements, or for which contractual complications may be encountered.

The DES for ART in South Africa has been based on the HIV Cohorts Data Exchange Protocol (139), which is well documented and further facilitates rapid analyses of exported data to address queries which are not catered for by routine reports.

Using a middle tier as a migration strategy towards an EMR

A DES also provides a 'steppingstone' for expedited back capture of patient histories directly from paper ART registers without the extra burden of finding, drawing, re-capturing and re-filing every physical patient folder. In our experience in South Africa, back capturing data for a patient who started ART in 2004 from a paper register into a middle tier system takes 2-3 minutes in comparison to 5-20 minutes if capturing from a patient folder depending on the location of the patient files and whether or not standard clinical stationery was used by clinicians. Once a site is fully back-captured, a DES export can be created for direct import into EMR software if resources and management capacity warrant it.

Practical considerations in determining the optimal alignment of solutions

Paper-based systems are likely to remain used in facilities for years to come, especially for small rural clinics and those without stable electricity, as well as new ART services. The opening of a new

ART service should not be delayed due to procurement of hardware or cabling, and paper systems allow for immediate implementation of a monitoring system with rapid migration to an electronic register as resources become available.

Choice of tier does not reduce data staff requirements or necessarily impact on data quality

Regardless of tier, dedicated staff time is required to transcribe patient data on a daily basis and to extract and compile required data for monthly, quarterly and ad hoc reports. Except in very small services, dedicated data staff are essential irrespective of tier, although depending on clinic size they may also have other administrative responsibilities at busier times of day. The key function of abstracting specific parameters from the structured clinical record of each patient seen each day, and then capturing this in a paper register or electronic system cuts across solutions. The integrity of this process in terms of source clinical record-keeping, completeness of folder processing and accuracy of capture are what ultimately determines the quality of data rather than the choice of system into which data are captured. Managing the integrity of reports is however easier with electronic solutions, although errors in manually extracted reports can be readily identified through rule-based consistency checks on the aggregate data.

Not all sites need to have an EMR at the outset

Smaller services with low monthly enrolment may not need to move to an electronic system; however, larger more mature sites with multiple registers could benefit substantially from appropriate electronic solutions. Ministries of Health should also consider establishing a small number of sentinel sites during the early stages of digitisation that are supported by implementing partners or academic groups that collect a larger set of more closely interrogated data. These few sentinel sites can help to answer questions raised by a Ministry regarding clinical or operational issues without burdening all facilities in the country with collection of an expanded data set (99).

There are some criteria that could be considered as requirements for moving to the next level:

A successful lower tier as a pre-requisite to moving to the next tier

With each higher tier comes added complexity and the need for additional support. The second-tier solutions require computer literate staff, computer availability, and software and hardware support in addition to the training and protected staff time which are common requirements of all tiers. Third tier solutions additionally require central database and system control and network maintenance. Therefore, if a lower tier is not successfully working (given certain workload parameters), moving to a higher tier is unlikely to be successful. Digitization of registers into a tier-2 solution which resembles the tier-1 paper registers is a far more efficient digitization strategy than comprehensive back-capture of physical patient folders into an EMR system.

Ensuring ability to benefit from added functionality of EMR systems

Ultimately, tier-3 solutions can offer additional functionality beyond routine monitoring and patient listings, including linking to laboratory or pharmacy data and software systems. To benefit from the added functionality requires availability of additional infrastructure (networking and hardware at more service points), staff, and management capacity. In particular, support systems need to be in place and reliable so that faulty equipment is rapidly replaced, network bandwidth is sufficient, and network stability is guaranteed.

Extensive support for clinical governance is potentially available from high-end EMR systems, including real-time or asynchronous decision support and tools to improve service efficiency. Both require committed clinical and management champions who will use these tools to iteratively improve services. Some of the largest sites with the greatest potential to benefit from EMR systems are also the most challenging sites to ensure stability of infrastructure, staff and management processes.

System-wide uniformity may trump facility considerations

Early stages of evolution to an electronic monitoring platform may be driven by resources, patient burden, and equity considerations. However, if a country has finished transitioning to a multi-tier system with the majority of sites on tiers 2 or 3, it does not make sense to continue with paper registers at the smallest facilities. Electronic monitoring systems can provide patient-level data to higher levels which brings additional programme knowledge when combined with other health data (in comparison to aggregate numbers from paper systems). Similarly, if networks are in place and most sites are already using a tier-2 system, it may make sense to further scale up tier-3 solutions. The true benefits of an EMR will only be realised once a large area is fully utilising a single networked solution. Patient movements can be comprehensively tracked, patient histories are available to referral or emergency centres, and laboratory data and most recent clinic visits and outcomes can be linked or imported.

Consolidating an electronic register platform across priority programmes

While middle tier electronic registers are proving to be a rapidly scalable solution for HIV and ART monitoring in some settings, including in South Africa as part of the three-tier approach, another example where electronic registers have been widely implemented is for monitoring tuberculosis control. ETR.Net™ (Electronic Tuberculosis Register) has been implemented in 8 countries and collects and reports on demographic, case finding and outcome data for patients receiving tuberculosis treatment. This simple offline middle-tier approach could also provide important benefits to services such as maternal and child health services (MCH) in developing countries, where

longitudinal outcome data are necessary but rolling out EMR software to all facilities offering these services would be too expensive and resource intensive; services for the prevention of mother-to-child transmission (PMTCT) of HIV, another global health priority, could also benefit from such an approach. With the WHO 2013 guidelines for antiretroviral therapy now promoting the integrated provision of ART through TB, antenatal care, and MCH sites, the need for such platforms across different clinic settings will become increasingly important(108). Using a tiered platform across HIV, TB and MCH health services will give a common data platform for outcome reporting of priority programs for use at facility level. It could provide service managers with a better understanding of co-infection rates and multiple health services access, and improved tools for targeting interventions.

There are many overlapping challenges in providing robust program monitoring and treatment provision for HIV/ART, tuberculosis and MCH services. Patients may attend more than one service at any given time as well. Deploying a middle-tier software solution incorporating these three linked priority disease programmes could be the catalyst to natural integration at facility level including reception staff, data staff, counsellors and clinicians. An integrated priority disease approach to these three dynamic and rapidly changing service domains requiring outcome reporting would maintain focus on these diseases and at the same time slowly merge the vertical and separate monitoring approaches that were initially taken.

Regardless of the combination of tiers chosen, evolving to digital monitoring solutions requires substantial time and resources at all levels of health

High-level political buy-in and support is necessary to ensure adequate funding for tools and an appropriate staff complement for the implementation and operationalisation of any monitoring system. In addition to staff discussed in above sections performing daily roles within the monitoring and evaluation (M&E) service (data and reception staff, and information technology teams), clinical, information, and programme management staff also need to routinely use the data and standardised reports both at ground level and centrally. These different levels of staff hold each other accountable for the collection and use of the data, as well as overcoming technical or operational obstacles. The actionable tasks (pulling reports, calling patients on alert lists, cleaning data, providing support, manually merging identified links, identifying backlog) need to be clearly defined and assigned to specific named positions with routine timelines for completion. Another layer of staff management needs to sign off on actions that were accurately completed or ensure tasks not completed at the appropriate time are attended to, with solutions provided so the tasks can be completed on time in future. These tasks should be documented and easily accessible within

a standard operating procedure (SOP) or guideline that is improved upon with time and as tiers evolve.

The implementation of new M&E systems takes a substantial amount of time for processes to solidify into stable routines, with backlog capturing taking precedent in the beginning. The use of data follows thereafter but often only if people believe the data to be credible and if the data is being actively used at higher levels for things like policy improvement, resource allocation and feedback to the ground (together with recognition for the work being done to collect decent data). Using data centrally requires a high calibre team to process, link, analyse and feedback well thought through analyses with appropriate methodologies. It is often the lack of routine training and data use (adhering to a strong SOP) along with the lack of data evaluation centrally that contributes to the demise of a well implemented M&E system.

Conclusions

Implementing a three-tier monitoring and evaluation system at country level for HIV and ART services can be an efficient approach to ensuring system-wide harmonization and accurate monitoring of services, including long term retention in care. The different tiers allow for rapid roll out of services while maintaining a single national dataset that includes data from all sites regardless of size or context. The inclusion of a uniform data exchange standard in the second and third tier gives added flexibility, allowing different software solutions to co-exist and rapid migration between tiers. The middle-tier electronic register assists with rapid digitisation of paper treatment registers and can facilitate eventual migration to EMR systems through the uniform data exchange standard. The second and third tier provide added management reports and additional functionality and can provide the platforms required for integrated monitoring and evaluation of TB, MCH and PMTCT services. EMR systems already in place or implemented in sites meeting country-stipulated criteria can play a vital role initially in providing more detailed data from sentinel sites and some may evolve into more comprehensive solutions when resources and infrastructure allow facility evolution to networked EMR systems.

Tables and Figures

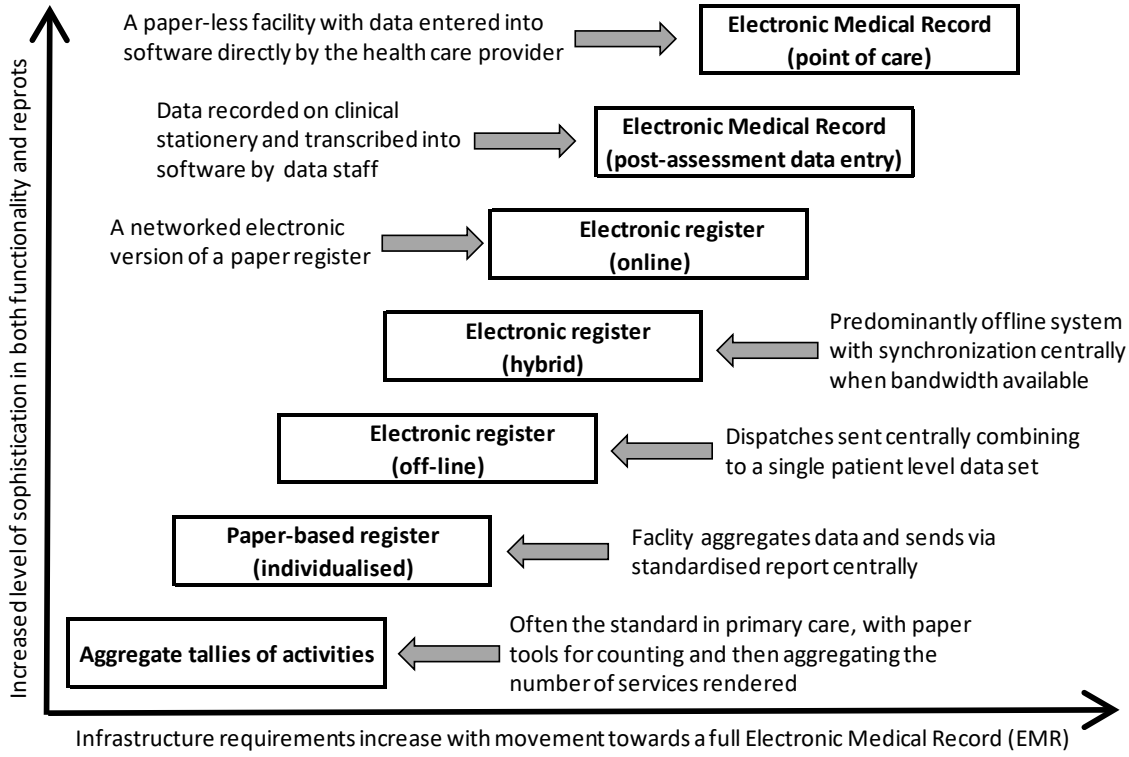


Figure 1: **Different candidate tiers of a multi-tier monitoring system**

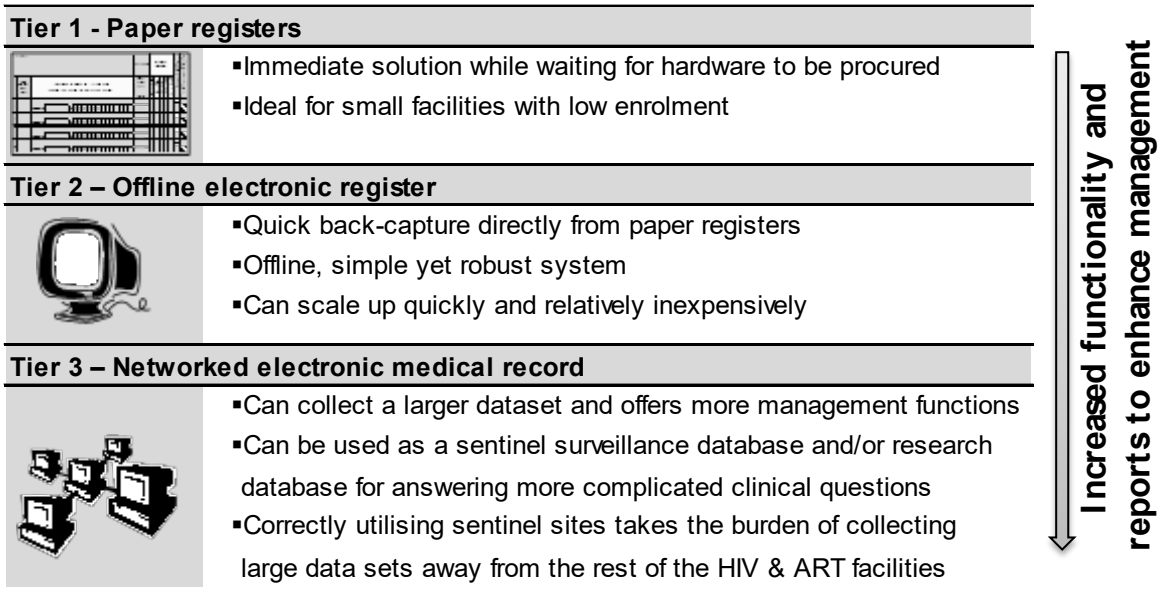
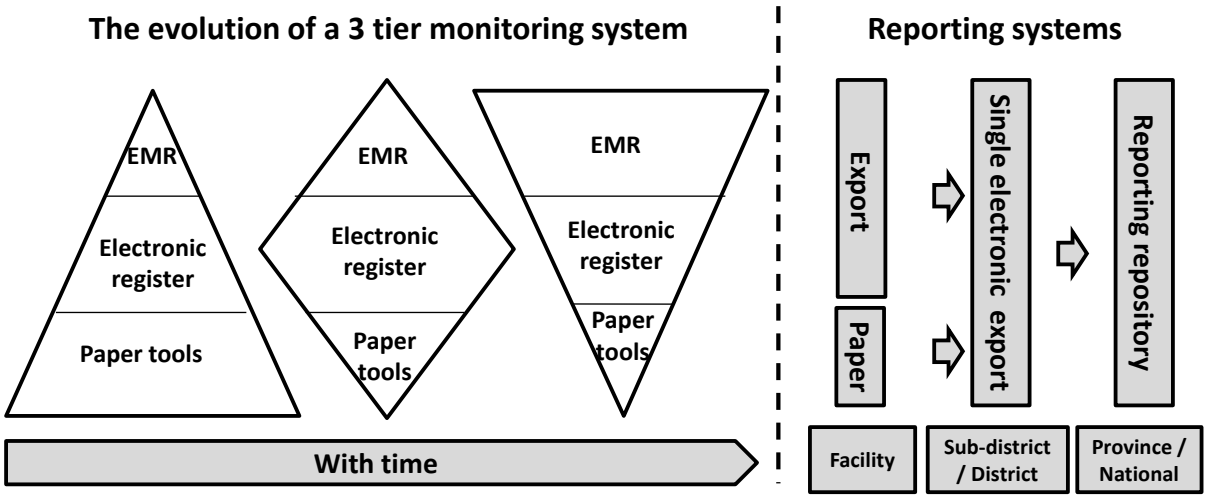


Figure 2: **A three tier monitoring and evaluation system capable of working together in a health region (one choice per facility) to ensure all contexts have an appropriate and viable way to monitor their health services**



The triangles and diamond represent the mix of tiers within a health region (one per facility) and how that mix changes over time as resources and infrastructure improve. EMR stands for electronic medical record, and usually represents a networked monitoring and evaluation software system.

Figure 3: **Evolution from paper systems to full EMR systems over time**

Table1: **Western Cape ART programme reporting from routine monitoring and evaluation systems**

	Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Grand Total
	Number starting ART (Naïve)	**88**	**308**	**596**	**2,811**	**5,637**	**8,140**	**9,606**	**15,069**	**19,018**	**23,915**	**26,732**	**31,014**	**142,934**
Baseline information	Male %	27.7%	30.7%	29.7%	31.1%	32.3%	34.4%	36.0%	34.3%	35.9%	34.9%	35.6%	35.6%	35.1%
	Paediatric %	5.7%	31.2%	27.0%	10.6%	8.2%	7.8%	6.1%	5.1%	4.5%	4.0%	3.1%	2.6%	4.5%
	ART experienced %	7.4%	1.9%	2.1%	3.8%	3.4%	3.4%	4.2%	5.2%	6.0%	5.8%	5.5%	4.2%	5.0%
	CD4 < 100 cells/µl %	78.6%	72.5%	61.3%	51.2%	45.4%	43.1%	40.2%	34.8%	35.1%	29.8%	23.8%	18.9%	30.2%
	CD4 >= 200 cells/µl %	0.0%	5.2%	6.5%	6.2%	6.7%	8.9%	12.0%	16.3%	18.1%	28.2%	38.5%	50.2%	28.8%
ART status after 1 year on ART	**Remaining in care %**	**85.1%**	**87.9%**	**89.7%**	**88.0%**	**87.2%**	**86.2%**	**84.9%**	**86.4%**	**83.7%**	**81.1%**	**77.0%**		**82.7%**
	LTF (cumulative %)	0.0%	2.0%	1.7%	5.1%	6.2%	8.3%	9.9%	10.0%	13.0%	15.6%	20.0%		13.4%
	Mortality (cumulative %)	14.9%	10.2%	8.6%	7.0%	6.5%	5.5%	5.3%	3.6%	3.4%	3.2%	3.1%		4.0%
	Second line %	0.0%	0.0%	0.8%	0.9%	0.7%	0.8%	0.6%	0.9%	0.9%	1.2%	1.3%		1.0%
	Viral load suppression %	82.4%	74.4%	87.0%	87.3%	89.0%	87.7%	88.7%	87.9%	85.8%	85.0%	87.0%		86.8%
	Viral load completion %	**91.9%**	**74.3%**	**66.7%**	**76.8%**	**81.3%**	**76.9%**	**72.0%**	**71.3%**	**67.4%**	**67.0%**	**59.5%**		**68.5%**
ART status after 4 years on ART	**Remaining in care %**	**76.5%**	**79.4%**	**75.6%**	**73.5%**	**72.1%**	**70.1%**	**67.5%**	**64.5%**					**68.3%**
	LTF (cumulative %)	1.2%	5.5%	10.5%	14.2%	16.3%	20.3%	23.2%	28.4%					22.3%
	Mortality (cumulative %)	22.4%	15.1%	13.9%	12.2%	11.6%	9.6%	9.3%	7.1%					9.3%
	Second line %	10.8%	16.5%	12.2%	9.3%	8.1%	8.6%	9.3%	10.0%					9.3%
	Viral load suppression %	87.1%	82.7%	89.9%	89.7%	88.5%	82.2%	84.6%	84.6%					85.2%
	Viral load completion %	**95.4%**	**70.1%**	**66.5%**	**74.6%**	**78.7%**	**74.9%**	**72.6%**	**62.1%**					**70.8%**
ART status after 8 years on ART	**Remaining in care %**	**66.3%**	**64.7%**	**60.8%**	**56.6%**									**58.3%**
	LTF (cumulative %)	8.8%	14.3%	21.6%	26.6%									24.2%
	Mortality (cumulative %)	25.0%	21.1%	17.5%	16.8%									17.6%
	Second line %	20.8%	28.5%	14.2%	16.3%									17.3%
	Viral load suppression %	100.0%	82.5%	87.4%	89.5%									89.1%
	Viral load completion %	**64.2%**	**36.6%**	**59.3%**	**68.0%**									**63.2%**

Please note: ART: Antiretroviral therapy; LTF: Lost to follow-up.

The proportion remaining in care decreased over time due to the inherent unknown classification in offline unlinked M&E systems of patients lost to care into categories of truly lost, self-transfers and deaths. As the ART services matured the recording of viral load results also became less reliable reflecting as a declining proportion of patients with viral load completion.

CHAPTER 2b

THE CONTINUING BURDEN OF ADVANCED HIV DISEASE OVER 10 YEARS OF INCREASING ANTIRETROVIRAL THERAPY COVERAGE IN SOUTH AFRICA

Associated publication(s)

Osler M, Hilderbrand K, Goemaere E, Ford N, Smith M, Meintjes G, Kruger J, Govender NP, Boulle A. The Continuing Burden of Advanced HIV Disease Over 10 Years of Increasing Antiretroviral Therapy Coverage in South Africa. Clin Infect Dis. 2018 Mar 4;66(suppl_2):S118-S125. doi: 10.1093/cid/cix1140. PMID: 29514233; PMCID: PMC5850025.

This paper is a copy of the version of the above paper as it appears in PubMed Central® (PMC), to which consistent formatting of references, figures, tables, appendices, and supplementary material has been applied. The manuscript remains substantively unchanged, with only minor changes based on examiner comments, and stylistic edits for consistency such as the standardisation of the terms used for referring to men and women.

Alignment with the related thesis objective

One of the reasons for the thesis focusing on population-wide outcomes is due to concerns that on-program monitoring might not reflect the true HIV associated morbidity and mortality, including in those who have not accessed care or ART. The focus on advanced HIV presentations is premised on the assumption that whether or not patients are formally in disease-specific care and part of monitored cohorts, when they present acutely ill due to advanced disease, they are likely to be diagnosed and have their CD4 counts measured.

The second objective sought to explore trends in advanced disease to be inclusive of pre-ART clinical outcomes as well as those in patients falling out of care and no longer monitored by treatment services and cohorts.

Candidate's contribution

The candidate designed the study, acquired and processed all data, performed the analyses, and wrote the first draft of the manuscript, integrated comments from co-authors and submitted the manuscript for peer review. The candidate also oversaw the implementation of the monitoring system in the Western Cape, enabling the collection of clinical data. With support from data scientists, the candidate linked the CD4 count data to the patient-linked clinical assessment dataset,

which formed the dataset which the Provincial Health Data Centre (PHDC) originally used to validate linkage algorithms.

Abstract

Background

Antiretroviral therapy (ART) has been massively scaled up in order to decrease HIV-related morbidity, mortality and HIV transmission. However, despite documented increases in ART coverage, morbidity and mortality have remained substantial. This study describes trends in the numbers and characteristics of patients with very advanced HIV disease in the Western Cape, South Africa.

Methods

Annual cross-sectional snapshots of CD4 distributions were described over 10 years from January 2008 to the end of 2017, derived from a province-wide cohort of all HIV patients receiving CD4 count testing in the public sector. Patients with a first CD4 <50 cells/µl in each year were characterised with respect to prior CD4 and viral load testing, ART-access and retention in ART care.

Results

Patients attending HIV care for the first time initially constituted the largest group of those with CD4 <50 cell/µl, dropping proportionally over the decade from 60.9% to 26.7%. By contrast, the proportion who were ART-experienced increased from 14.3% to 56.7%. In patients with CD4 counts <50 cells/µl in 2016, 51.8% were ART-experienced of whom 76% could be confirmed to be off ART or had recent viraemia. More than half who were ART-experienced with a CD4 <50 cells/µl in 2016 were men, compared to approximately one-third of all patients on ART in the same year.

Conclusions

Ongoing HIV-associated morbidity now results largely from treatment-experienced patients not being in continuous care or not being fully virologically suppressed. Innovative interventions to retain ART patients in effective care are an essential priority for the ongoing HIV response.

Introduction

In the last decade, the massive scale-up of antiretroviral therapy (ART) services in sub-Saharan Africa has increased access to treatment, aiming to decrease HIV-related morbidity and mortality and more recently HIV transmission (140). The initial focus of ART scale-up was to reduce severe morbidity and mortality; patients with an AIDS-defining condition or a CD4+ T-lymphocyte count (CD4) <200 cells/µl were therefore considered eligible for ART (120). In response to successes in ART scale-up globally as well as increasing evidence of the benefits of earlier ART initiation, CD4 count eligibility thresholds have increased (9, 141) culminating in the current guidance to 'Treat All', enabling HIV-infected people to start treatment regardless of CD4 count (142, 143). South Africa implemented this guidance on 1 September 2016 (144). As the proportion of ART-eligible patients who are on ART increases, we would expect decreases in morbidity and mortality at a population level. In resource-limited settings, HIV-associated morbidity and mortality have nevertheless remained considerable (145).

Around 420,000 people out of a total population of 6.3 million were projected to be living with HIV in the Western Cape Province of South Africa in 2016. Approximately half of all HIV-infected individuals and over 85% of those with a CD4 <200 cells/µl were estimated to be on ART (146). The current study was prompted by HIV clinicians reporting anecdotal concern that the number of hospitalised cases of cryptococcal meningitis, typically associated with late presentation and advanced immunodeficiency (147), was not declining over time as would be expected given increasing ART coverage (Figure 1) (148). There is a concern that at a population level, the decline in the number of patients presenting for the first time with advanced immunodeficiency could be offset by an increasing number of patients on long-term ART who have interrupted, stopped or failed on therapy (149).

This study describes temporal trends in the ascertainment of very advanced HIV disease in the Western Cape Province of South Africa, evidenced by CD4 counts below 50 cells/µl (advanced HIV disease (AHD)), and trends in the HIV treatment history of those with very advanced HIV disease.

Methods

Setting and data sources

The Western Cape is one of nine provinces in South Africa. One in five pregnant women have HIV. The vast majority of people living with HIV seek care in the public-sector, which first offered ART in 2001, accelerating coverage after 2004 when ART provision became national policy (150). CD4 monitoring of all patients and viral load monitoring once on ART have been provided since program inception, but since 2006, baseline viral loads were no longer recommended among ART-naïve adult

patients. From mid-2013, continued CD4 count monitoring among virologically-suppressed and clinically-well patients with CD4 ≥200 cells/µl at one year on ART was no longer recommended. The first-line regimen consists of 2 nucleoside reverse-transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor. Full details of the ART program evolution are described elsewhere (151).

All public-sector laboratory testing is done by the National Health Laboratory Service (NHLS) and the digitised results have been available to the province since 2007. The province has successfully established a patient registration system which shares a unique health identifier and Patient Master Index (PMI) across both hospital and ambulatory services, which reached near-complete coverage as of 2013 (152). This has facilitated the linkage of data from hospital, laboratory and pharmacy sources, as well as electronic disease registers such as those for HIV and tuberculosis (153). The process of linking all data to the PMI is now formalised through the Provincial Health Data Centre (PHDC) from which all data provided for analyses are pre-anonymised but still linkable based on a privacy-preserving random key. Cases of cryptococcosis were ascertained through routine laboratory-based surveillance for communicable diseases (GERMS-SA) conducted by the National Institute for Communicable Diseases (NICD) based on NHLS data (154).

Analysis

Annual cross-sectional snapshots of CD4 distributions were described from a derived province-wide HIV cohort of all patients receiving CD4 testing from 1 January 2008 to the end of 2017. Further longitudinal analyses focussed on CD4 testing and ART treatment history in adults (≥16 years old) who were identified with CD4 <50 cells/µl in each period.

The cohort is based on data linkage between the National Health Laboratory Services (recorded CD4 and viral load tests), and HIV treatment information systems (TIER.Net and PHCIS). Data which had been previously linked for HIV operational reporting purposes using all available identifiers were used for analyses until the end of 2012. Analyses for subsequent years were based on anonymised extracts from the PHDC. In this period, 98.7% of CD4 counts could be linked to the PMI.

In the manually-linked database, the CD4 and viral load data had been linked to each other and to the HIV treatment database, using a combination of probabilistic and deterministic linkage based on: name, surname, date of birth, sex, facility, sub-district, district and clinic folder number. Fine Grain Record Linkage (FRIL) software (v2.1.5, Emory University) and STATA (v13.0, StataCorp) were used for linkage and analysis. A random sample of linkages was manually validated. These data were anonymised prior to use for this analysis. Data from both sources combined were available from 2007 until 20 September 2017, and for 2017, all counts were upweighted to represent a full year's

worth of data to retain comparability with previous years (based on analyses of 2016 data in which 76% of CD4 counts had been ascertained by 20 September 2016).

The data are presented in annual cohorts based on the year the CD4 was taken. Results from 2007 are omitted as prior CD4 count testing could not be determined. Province-wide CD4 counts are described as absolute counts of tests performed as well as by counts of unique individual patients receiving testing in each year. Unique patients per year with CD4 <50 cells/µL were further stratified into the following categories in relation to ART status: late presenters (presenting for their first ever CD4 test with CD4 <50 cells/µl); previously not eligible for ART (inadequate pre-ART care); previously eligible for ART (failed linkage to or initiation of ART care); and those with a low CD4 count after ART initiation. ART initiation was determined by an ART start date recorded in the provincial electronic HIV registers or a viral load result, in which case the ART treatment start date was estimated as four months prior to the first recorded viral load (clinical guidelines prescribe the first viral load 4 to 6 months after treatment initiation). Patients were deemed eligible for ART if their CD4 was <200 cells/µL prior to 1 May 2010 or <350 cells/µL after 1 May 2010 as per operative national guidelines.

ART-experienced patients in whom visit-level treatment records were available were further stratified into four categories: lost to follow-up (no antiretroviral medicines for 90 days or more) prior to their low CD4 count ('LTF'), including those who returned to care within 30 days prior to the low CD4 count but otherwise met this definition; those in care prior to the low CD4 count but who had had a recent (ending in the previous year) gap of >90 days without antiretroviral medicines; or continuously in care (no gaps >90 days without antiretroviral medicines in the year prior to the low CD4). Patients without medicine information linked to their visit were assumed to have been given 30 days of treatment and therefore were counted as lost to care at 120 days after their last appointment.

Within those in care (with or without gaps), patients were further stratified by those without viral load data, those with suppressed viral loads, those with viraemia (one viral load >1000 copies/ml) and those failing (defined as two consecutive viral loads >1000 copies/ml prior to the low CD4 count).

Throughout, count data are presented both as counts and proportions. Results of hypothesis testing for highlighted differences in proportions or tests for trend are not presented due to the large numbers of patients involved and universally low p-values (all <0.001). Age, duration on ART and time between tests were described as medians and interquartile ranges.

The study was approved by the University of Cape Town Human Research Ethics Committee (421/2016).

Results

Over the ten-year period from 2008 through 2017, the total number of patients estimated to be living with HIV in the Western Cape increased to over 400,000, with the proportion estimated to be on ART increasing from 16% in 2008 to 52% in 2016 (Table 1). CD4 counts performed annually in adults rose over time, reaching close to 300,000 tests per year in 2015, declining thereafter as routine annual CD4 monitoring for patients who are virally suppressed was stopped, however, guidelines included reflexive CD4 testing in people on ART with deteriorating health or viraemic. Clinical cryptococossis cases remained above 400 per year from 2005-2015 (Figure 1).

The number of unique patients per year with a lowest CD4 count test result below 50 cells/µl varied between 6164 and 8133, remaining relatively constant over time (Table 1, Figure 2). These patients were more likely to be men when compared to all patients receiving CD4 count testing, consistent overall years (Table 2).

Patients presenting for the first time initially constituted the largest group of those with very low CD4 counts, dropping proportionally over time from 60.9% in 2008 to 26.7% in 2017 (Figure 2, Table 2). By contrast, the proportion of ART experienced among those with a CD4 cell count <50/µL increased from 14.3% to 56.7% during the time span of the study. Throughout there was an appreciable proportion of patients with very low CD4 cell counts who should have started ART as they had previously met ART eligibility criteria based on prior CD4 count testing; this declining from 20.4% to 14.2% from 2008 to 1017. A much smaller proportion of patients with very low CD4 cell counts were known to the services but were previously not ART eligible.

Of those ART naive with previous CD4 count testing prior to the index CD4 test (first CD4 < 50 cells/µl per patient per year), the median time from the previous value to the index CD4 count increased over time. The median time between consecutive CD4 counts was much longer in those who had previously been ART ineligible (>5 years in 2015) than those who had been eligible for ART (>2 years in 2015, Table 2).

By 2014, more than half of those who had previously been on ART prior to the index CD4 had either dropped out of care (45.6%) or had had a substantial gap in care (10.3%) in the previous year, 2016 (Table 2). The remainder had evidence suggesting they were on ART continuously for at least the year prior to the index CD4. For all groups previously on ART the median duration between ART initiation and the index CD4 increased over time, approaching 4 to 5 years since ART initiation by

2018, and being consistently shorter in those continuously on ART. Of those who had been LTF prior to the index CD4 test, a substantial proportion (close to a third in recent years) were detected at hospitals rather than ART clinics.

For patients on ART at the time of the index CD4 test, those with a gap in care in the preceding year were less likely to have a viral load result available from the preceding 15 months (58.8% in 2008 vs. 43.6% in 2016), and less likely to be virologically suppressed if tested (8.8% in 2008 vs. 8.5% of those tested in 2016). A higher number of those on ART with viraemia (>1000 copies) had evidence of sustained viraemia over two or more occasions (27% in 2016).

Looking across all patients with CD4 counts <50 cells/µl in 2016, 51.8% were ART experienced of whom 76% could be confirmed to be off-ART or had viraemia at the time of the index CD4 test, 7% could be confirmed to be on suppressive ART, and the virologic status of the remaining 17% was not known (Figure 3). The total number of patients with a CD4 <50 cells/µl known to the services and lost to care or with viraemia prior to the index CD4 test substantially exceeded the number not known to the services and presenting for the first time.

Discussion

This analysis has demonstrated how in a high burden HIV setting, ascertainment of very advanced HIV disease is not declining despite the successful scaling up ART. This is reflected clinically by the relatively stable number of cases of cryptococcosis during the last decade, despite a considerable increase in access to ART. The proportion of patients initially presenting with very advanced HIV disease is reducing, reflecting increased access to treatment; however, this reduction is being offset by an increasing number of patients who have previously started ART and are re-presenting with advanced HIV following a period without effective ART. Most often this is due to predictable reasons such as stopping ART, poor adherence or virological failure, many of which are amenable to intervention.

Ongoing HIV-associated morbidity

The initial interest from hospital-based clinicians in the province in the pattern of presentation with very low CD4 counts was in response to ongoing morbidity from conditions such as cryptococcal meningitis which are associated with advanced immunodeficiency. Clinician-triggered and more recently laboratory-triggered reflex screening for cryptococcal antigenaemia was introduced in 2014 and 2016 respectively for all patients with CD4 counts <100 cells/µl. Although this likely prevents cryptococcal meningitis in some patients (155), there has been a disconcertingly high ongoing incidence since the alarm was first raised (148). This is corroborated by surveys of HIV-associated morbidity in inpatient wards, where tuberculosis has been a major contributor to clinical

presentation (156). There is growing evidence that the successes of HIV treatment access are resulting in a sizeable population of individuals on ART who are vulnerable to rapid deterioration as they cycle in and out of care, as many do, due to both service and personal challenges (149, 157).

Where to focus interventions

The 90-90-90 strategy has successfully focussed energy on identifying patients with HIV and linking them to care, bolstered by 'Treat-all' guidelines. Many organisations have, as a result, concentrated in recent years on the identification of those with undiagnosed HIV and on improved linkage to care. The declining number of patients presenting for the first time in this study with advanced HIV disease points to the success of expanded access to HIV testing, care and treatment. In many settings, the 90% target for diagnosing HIV in those infected is close to achievement (158). The dominant contribution of ART-experienced patients to advanced disease in this study cautions against complacency and suggests similar efforts be directed to ensuring adherence and retention within ART programmes. Modelling suggests that even for transmission, the variable most associated with future transmission is ensuring virologic suppression in those already on ART (159).

Identifying in which patients to intervene

Our findings point to extensive missed opportunities for intervention in patients who had started ART and at some point thereafter had declining CD4 cell counts resulting in AHD. The majority had either fallen out of care where re-engagement interventions could have been triggered by missed appointments or formally defined LTF, or had previously had viraemia or had missed viral load testing. Of those with viraemia, half had been confirmed to be so on more than one consecutive occasion. Clinical governance and quality-improvement processes could address the efficient implementation of guidelines for virologic testing, and adherence promotion and regimen switching in patients fulfilling virological failure criteria. The increasing affordability and tolerability of new regimens should remove concerns around premature switching, and the balance should shift to more aggressive intervention to ensure suppressive ART. The study also corroborated previous findings of excess mortality risks in men (160), which might guide the design of some of the interventions.

Surveillance of advanced disease

"Community viral load" tracks transmission potential (161, 162), but does not describe the immunological status of patients. Routine CD4 monitoring is no longer recommended in virologically suppressed patients (163), undermining the validity of CD4 count distribution from routine data as a population-level barometer of treatment success. The absolute numbers of patients with very low CD4 counts might however remain a sensitive barometer, where patients will often still be tested for

advanced immunodeficiency for clinical reasons. Specific HIV-associated morbidities, hospital admissions or mortality could also be used as measures of advanced disease. The advantage of a laboratory marker is that it may be easier to secondarily derive at scale across whole jurisdictions, as digitizing and centralising laboratory data is in any case operationally required. We propose that "community CD4 count" represented by the absolute numbers of patients with very low CD4 counts, may be an accessible and reliable indicator of advanced HIV disease.

Limitations

There are several limitations to this study. Two separate data linkage exercises were stitched together to create a ten-year trend history, and while they aligned remarkably well at the seam, it would have been preferable to have a single approach. There may have been residual failures to link observations due to incomplete data for patient matching, either missing antecedent CD4 count histories or subsequent ART initiation. In terms of the major findings from this study however, both biases if present would result in under-estimation rather than over estimation of the trends towards fewer presentations in newly diagnosed patients and more in care- or treatment-experienced patients. Some of the trends may further be artefact of the availability of data only from 2007 onwards, especially durations since previous measures which by design should get longer with increasing calendar time due to the lack of prior data in the early years of the analysis.

Conclusion

This study has demonstrated that ongoing HIV-associated morbidity now results largely from treatment-experienced patients not being in continuous care or not maintaining virologic suppression. Attention of health care services will need in future to focus much more aggressively on the innovation and investment in and quality of ART services in order to avert transmission, morbidity and mortality. In this study we have shown that monitoring the absolute numbers of very low CD4 counts at a population level over 10 years provided a readily accessible, durable and sensitive integrated indicator of overall program performance and identified specific program deficiencies.

Tables and Figures

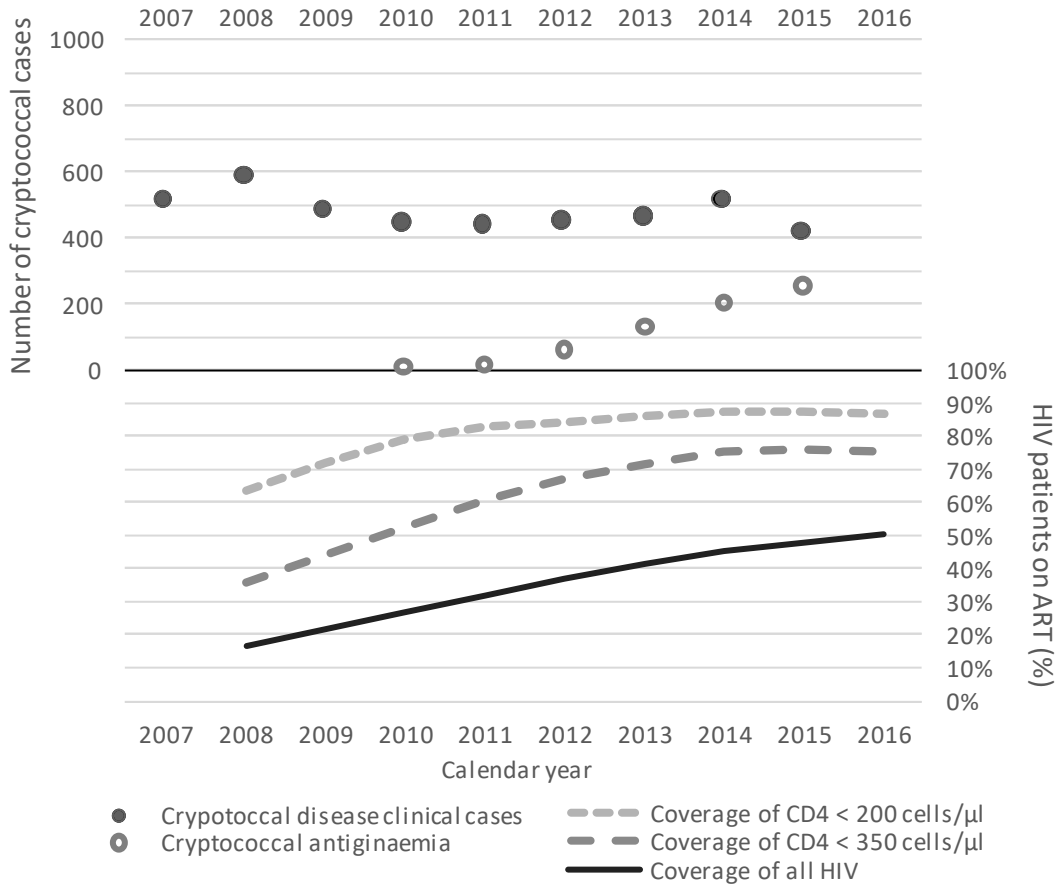


Figure 1. Temporal trends in the number of cases of laboratory-confirmed cryptococcosis and antiretroviral therapy coverage, Western Cape province, South Africa, 2007-2016

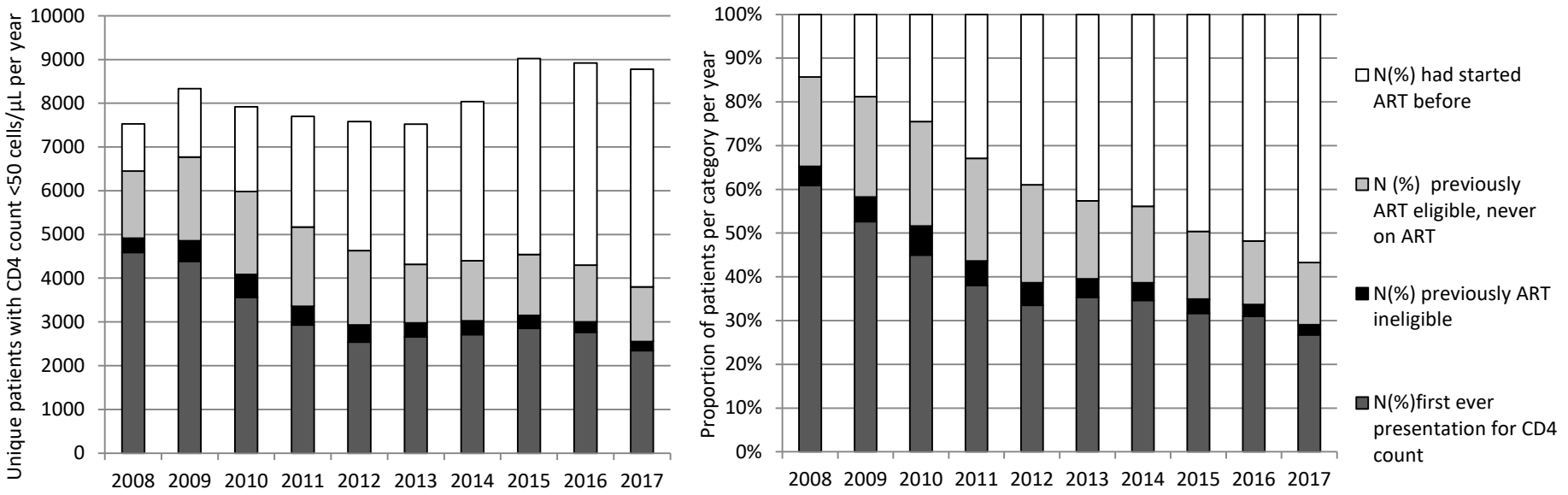


Figure 2: Presentation of unique patients with CD4 counts < 50 cells/µl by previous ART access, eligibility and previous CD4 count testing, stratified by year, in the Western Cape province, South Africa

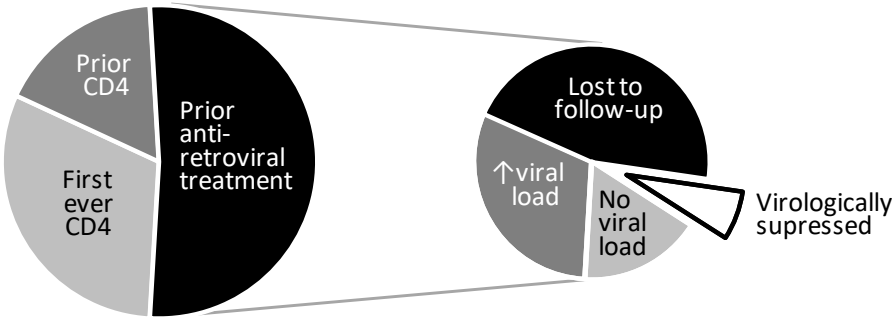


Figure 3: Distribution of prior CD4 count testing, ART, ART retention and recent virologic status in patients presenting in 2016 with a CD4 < 50 cells/µl

Table 1: Western Cape HIV prevalence, treatment coverage and counts of CD4 assessments and patients assessed in adults

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
WC Population[1]	5 514 490	5 614 809	5 714 506	5 814 411	5 947 198	6 016 926	6 116 300	6 200 100	6 293 200	6 510 300
HIV prevalence in the Western Cape[2], N(%)	278 084 (5.0%)	298 139 (5.3%)	317 133 (5.5%)	334 927 (5.8%)	353 578 (5.9%)	371 546 (6.2%)	388 786 (6.4%)	405 532 (6.5%)	421 751 (6.7%)	
ART Coverage based on CD4<200; >14 years old[2], %	63.4%	72.1%	78.9%	83.1%	84.4%	86.0%	87.5%	87.6%	86.9%	*Not available*
ART Coverage based on CD4<350; >14 years old[2], %	35.9%	44.3%	52.5%	60.8%	67.3%	72.1%	75.7%	76.2%	75.6%	
ART coverage (UTT); adults and children[2] , %	16.6%	21.5%	26.6%	32.1%	37.0%	41.5%	45.2%	48.3%	50.5%	
Total cases of cryptococcosis	591	489	460	460	519	598	729	677	*Not available*	*Not available*
Number of CD4 counts done (>=16 years)	172 618	215 425	226 435	258 381	258 547	251 030	269 833	296 282	207 058	183 384
Number of unique patients with CD4 counts done	117 758	142 397	161 396	185 601	191 587	201 280	213 616	213 388	177 356	166 822
Median age (N, [IQR])	33 [28-39]	34 [27-39]	34 [27-40]	34 [28-41]	34 [29-41]	39 [33- 45]	38 [32-45]	37 [31- 44]	36 [30-43]	35 [29-42]
Proportion male, %	30.2%	31.2%	31.3%	31.7%	31.9%	32.8%	33.3%	34.0%	35.3%	35.9%
Lowest CD4 value (cells/µl) in unique patients, N(%)										
CD4 ≤ 50	7 530 (6.4%)	8 333 (5.9%)	7 921 (4.9%)	7 702 (4.1%)	7 583 (4.0%)	7 523 (3.7%)	8 040 (3.8%)	9 019 (4.2%)	8 921 (5.0%)	8 779 (5.3%)
CD4 51 -100	6 747 (5.7%)	7 611 (5.3%)	7 667 (4.8%)	6 642 (3.6%)	6 668 (3.5%)	7 746 (3.8%)	8 202 (3.8%)	8 829 (4.1%)	8 606 (4.9%)	8 608 (5.2%)
CD4 101-200	24 872 (21.1%)	27 903 (19.6%)	29 185 (18.1%)	27 163 (14.6%)	24 869 (13.0%)	20 249 (10.1%)	20 824 (9.7%)	22 385 (10.5%)	20 620 (11.6%)	20 467 (12.3%)
CD4 201 - 350	35 687 (30.3%)	43 723 (30.7%)	50 004 (31.0%)	52 304 (28.2%)	51 522 (26.9%)	46 293 (23.0%)	46 148 (21.6%)	45 641 (21.4%)	37 913 (21.4%)	35 268 (21.1%)
CD4 351 - 500	22 447 (19.1%)	29 082 (20.4%)	34 755 (21.5%)	43 826 (23.6%)	47 295 (24.7%)	49 859 (24.8%)	51 669 (24.2%)	51 897 (24.3%)	39 091 (22.0%)	34 561 (20.7%)
CD4 >500	20 475 (17.4%)	25 745 (18.1%)	31 864 (19.7%)	47 964 (25.8%)	53 650 (28.0%)	69 610 (34.6%)	78 733 (36.9%)	75 617 (35.4%)	62 205 (35.1%)	59 139 (35.5%)

[1] Census data and STATSSA mid-year population estimates; [2] Thembisa Model (2017 omitted as not calibrated); N=number; IQR=Inter quartile range; ART=Antiretroviral Therapy

Table 2: Characteristics of adults presenting each year with a CD4 count <50 cells/µl in the Western Cape province, South Africa, 2008-2017

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017
Unique patients with CD4 counts <50 , N(%)	7530	8333	7921	7702	7583	7523	8040	9019	8921	8779
Median age (N, IQR)	34.3 [29-40]	34.4 [29-40]	34.7 [29-42]	35.1 [30-42]	35.3 [30-42]	3748 [34-45]	38 [33-45]	38 [32-44]	37 [32-43]	36 [31-43]
Men, %	45.6%	46.6%	46.7%	47.1%	49.3%	49.8%	51.0%	51.2%	51.1%	51.9%
CD4 testing and ART history, N(%)										
A. first ever presentation for CD4 count	4587 (60.9%)	4387 (52.6%)	3563 (45.0%)	2931 (38.1%)	2541 (33.5%)	2659 (35.3%)	2710 (35.7%)	2855 (31.7%)	2764 (31.0%)	2346 (26.7%)
B. Previously ART ineligible	326 (4.3%)	467 (5.6%)	524 (6.6%)	429 (5.6%)	388 (5.1%)	317 (4.2%)	316 (4.2%)	294 (3.3%)	240 (2.7%)	205 (2.3%)
C. Previously ART eligible, never on ART	1539 (20.4%)	1913 (23.0%)	1893 (23.9%)	1809 (23.5%)	1700 (22.4%)	1340 (17.8%)	1371 (18.1%)	1396 (15.5%)	1293 (14.5%)	1248 (14.2%)
D. Started ART prior to low CD4	1078 (14.3%)	1566 (18.8%)	1941 (24.5%)	2533 (32.9%)	2954 (39.0%)	3207 (42.6%)	3643 (48.0%)	4474 (49.6%)	4624 (51.8%)	4980 (56.7%)
Days since last CD4, median (IQR)										
B. Previously ART ineligible	276 [144-394]	379 [182-657]	594 [325-899]	859 [443-1218]	1023 [520-1442]	1624 [1141-1973]	1699 [1199-2248]	2085 [1345-2514]	2416 [1767-2909]	2706 [2078-3126]
C. Previously ART eligible, never on ART	210 [75-348]	270 [102-512]	357 [138-694]	402 [173-854]	539 [247-914]	667 [281-1134]	740 [292-1285]	736 [264-1434]	878 [355-1676]	890 [340-1644]
Available ART visit-level records, N(%)	524 (48.6%)	850 (54.3%)	1116 (57.5%)	1495 (59.0%)	1883 (63.7%)	3206 (100.0%)	3643 (100.0%)	4474 (100.0%)	4623 (100.0%)	2231 (44.8%)
Retention in ART care prior to presentation in (D), N(%)										
1 Considered LTF at last visit	118 (22.5%)	186 (21.9%)	297 (26.6%)	407 (27.2%)	593 (31.5%)	1275 (39.8%)	1514 (41.6%)	1936 (43.3%)	2109 (45.6%)	977 (43.8%)
2 In care but with gap (>180 days) in last year	34 (6.5%)	66 (7.8%)	106 (9.5%)	124 (8.3%)	137 (7.3%)	255 (8.0%)	339 (9.3%)	499 (11.2%)	477 (10.3%)	244 (10.9%)
3 Continuously in ART care during past year	372 (71.0%)	598 (70.4%)	713 (63.9%)	964 (64.5%)	1153 (61.2%)	1676 (52.3%)	1790 (49.1%)	2039 (45.6%)	2037 (44.1%)	1010 (45.3%)
Months since ART initiation in (D), median (IQR)										
1 Considered LTF at last visit	21.8 [14.6-33.4]	27.9 [16.0-37.6]	29 [17.3-43.0]	32 [19.5-48.9]	32.6 [19.2-51.2]	36.5 [22.2-58.0]	42.2 [23.7-64.8]	44.8 [25.0-69.3]	49.6 [27.9-73.8]	51.7 [28.8-78.1]
2 In care but with gap (>180 days) in last year	28.1 [19.3-36.7]	26 [18.6-35.7]	31.3 [21.2-42.7]	34.8 [23.0-51.2]	38.6 [24.4-54.9]	39.2 [26.2-61.2]	43.4 [29.2-66.9]	49.4 [32.1-73.4]	51.2 [32.2-79.6]	57.4 [34.5-79.1]
3 Continuously in ART care during past year	12.1 [6.0-24.0]	14 [6.0-28.3]	17.7 [6.5-34.7]	17.2 [7.1-37.2]	20.3 [8.5-43.2]	25.4 [10.7-51.3]	33.3 [12.4-58.8]	37.2 [13.2-68.1]	43 [15.5-76.2]	46.8 [18.2-83.0]
Presentation in hospital in those LTF (1), %	47.5%	36.0%	31.0%	29.2%	33.1%	31.1%	28.8%	26.6%	29.5%	30.7%
Virologic status in those with a gap in care (2), %										
No data in the previous 15 months	20 (58.8%)	40 (60.6%)	51 (48.1%)	71 (57.3%)	67 (48.9%)	91 (35.7%)	125 (36.9%)	203 (40.7%)	208 (43.6%)	84 (34.4%)
Supressed < 1000 copies/mL	3 (8.8%)	9 (13.6%)	13 (12.3%)	5 (4.0%)	11 (8.0%)	21 (8.2%)	30 (8.8%)	41 (8.2%)	26 (5.5%)	18 (7.4%)
Viraemic just on previous test	6 (17.6%)	11 (16.7%)	28 (26.4%)	37 (29.8%)	38 (27.7%)	83 (32.5%)	76 (22.4%)	136 (27.3%)	114 (23.9%)	74 (30.3%)
Viraemic on previous two or more tests	5 (14.7%)	6 (9.1%)	14 (13.2%)	11 (8.9%)	21 (15.3%)	60 (23.5%)	108 (31.9%)	119 (23.8%)	129 (27.0%)	68 (27.9%)
Virologic status in those in continuous ART (3), %										
No data in the previous 15 months	210 (56.5%)	322 (53.8%)	336 (47.1%)	414 (42.9%)	462 (40.1%)	469 (28.0%)	499 (27.9%)	600 (29.4%)	571 (28.0%)	254 (25.1%)
Supressed < 1000 copies/mL	68 (18.3%)	113 (18.9%)	120 (16.8%)	129 (13.4%)	150 (13.0%)	245 (14.6%)	336 (18.8%)	389 (19.1%)	286 (14.0%)	120 (11.9%)
Viraemic just on previous test	58 (15.6%)	93 (15.6%)	141 (19.8%)	243 (25.2%)	275 (23.9%)	448 (26.7%)	425 (23.7%)	476 (23.3%)	508 (24.9%)	281 (27.8%)
Viraemic on previous two or more tests	36 (9.7%)	70 (11.7%)	116 (16.3%)	178 (18.5%)	266 (23.1%)	514 (30.7%)	530 (29.6%)	574 (28.2%)	672 (33.0%)	355 (35.1%)

N=number; IQR=Inter quartile range; ART=Antiretroviral therapy

CHAPTER 2c

IMPACT OF ART ELIGIBILITY THRESHOLDS ON 24 AND 36-MONTH MORTALITY IN THE WESTERN CAPE, SOUTH AFRICA.

Manuscript

This study is prepared in manuscript format but has not yet been submitted for publication.

Alignment with related thesis objective(s)

With the ability to track mortality outcomes irrespective of ART initiation, one of the key questions which had not been answered in African settings was the effectiveness of ART when ART is initiated at higher CD4 cell count thresholds. This is encapsulated in the third objective.

This study uses causal methods to mimic a randomised controlled trial, providing estimates of impact of changing guideline thresholds in a 'real world' setting. The study examines both the mortality rates and potential loss to the HIV services of individuals who do and do not initiate ART within six months of their first CD4 cell count, estimating impact by looking at associations of ART initiation with mortality.

Candidate's contribution

The candidate helped develop and support the clinical monitoring system in the Western Cape, enabling the collection of the clinical data. The candidate designed the study, acquired and processed the linked data, performed the analyses, and prepared the results in manuscript format.

Abstract

Introduction

Clinical trial results informed the evolution of ART eligibility threshold changes but there have been limited population-wide estimates of effectiveness in "real-world" settings. This study considers the impact of the changing eligibility thresholds on ART uptake and associated mortality within the public sector HIV care and treatment services in the Western Cape Province of South Africa.

Methods

This study employed a regression discontinuity design to mimic a randomised trial within the cohort of HIV-diagnosed individuals in the Western Cape, South Africa, from 2008 to 2018. For successive guideline periods (CD4 cell count thresholds of 200, 350 and 500 cells/µl) we described the proportion initiating ART within a given duration post CD4 cell count testing, and the proportion dying, in those eligible (hereafter termed "compliers") and ineligible for ART, based on having measurements above and below operative CD4 cell count eligibility threshold. The effect of ART eligibility on mortality was estimated for all eligible patients at each threshold, as well as for those who were treated in strict compliance of the guideline.

Results

A total of 244,748 individuals were included. People who deferred ART due to ineligible CD4 cell results, deferred a median 807 days (IQR 422, 2485). The proportion initiating ART within 3 months with advanced HIV disease, increased from 42% to 66% during the study. More than three-quarters of participants had initiated ART at some point (78%, 80% and 82% respectively). Amongst compliers (an individual-level measure), mortality by two years was lower in individuals eligible for ART compared to ineligible, most notable when the CD4 cell count threshold was <200 cells/µl (-13.3 risk difference [RD] (95%CI: -26.2 – (-0.4))), and <350 cells/µl (-4.2 RD (95%CI: -10.2 - 1.8)). The intention to treat (ITT) analyses (a population level measure) showed a reduction in mortality during the lowest threshold period (-1.1 RD (95%CI: -2.1 – (-0.1))) which becomes less discernible at later guideline changes. A high proportion of ineligible-presenters initiated ART regardless of eligibility guidelines, and many eligible did not start ART within 6 months.

Conclusions

At an individual level, benefits due to increasing eligibility thresholds were seen at all guideline changes in those eligible who accessed ART. Deferring treatment for ineligible individuals resulted in losing patients to the HIV&ART services for long durations, increasing their risk of death. This highlights the balance between clinical considerations (who is likely to benefit the most from a given intervention) and health service considerations (what will happen if a given opportunity to initiate care is missed in a weak health care system).

Introduction

Eligibility thresholds are ethically designed to get those most in need onto treatment first, or to ensure that treatment is only used when of proven benefit. In the antiretrotherapy (ART) services, the eligibility thresholds are based on CD4 cell count test results, which is one way to measure the state of a deteriorating immune system due to the human immunodeficiency virus (HIV). These thresholds are also thought of as efficacious, as they are determined by previous studies which measured morbidity and mortality outcomes based on different CD4 cell count strata at ART initiation (164, 165, 166, 167, 168). Several randomized controlled trials measured the benefits and risks of enrolling HIV-infected people onto treatment sooner in comparison to deferring ART initiation until a lower CD4 cell count threshold is met, with results supporting an increase in the eligibility thresholds (169, 170). However, few studies have considered the real-world effectiveness of providing treatment at these recommended thresholds in non-trial settings.

Although clinical efficacy of increased CD4 cell count thresholds is not debated, the effectiveness of threshold policies in public-sector facilities operating with limited resources remains largely unexplored, both in comparing the effect of ART at different thresholds as well as the consequences of eligibility guidelines which assigned people peri-threshold to immediate versus deferred ART. Clinical trials place high priority on retaining both those starting and deferring ART but individuals deferring ART in public-sector services may not get the same intensity of follow-up. Observational studies have documented ineffective pre-ART services, with high attrition rates and poor adherence to health care appointments, resulting in initiating ART late with low CD4 cell counts or death (171, 172, 173, 174). A large systematic review found less than a third remain in pre-ART care continuously until initiating ART (175) . It may be that these documented results reflect a selection bias rather than causal effect of ART on survival, with more motivated and engaged people starting ART. Our study set out to take a closer look at both the effectiveness of increased CD4 cell count thresholds and the effect deferring treatment had on people at both an individual and population level.

We used a regression discontinuity design to assess the causal impact of initiating ART at different eligibility thresholds in a non-trial setting (176, 177, 178, 179, 180, 181). The regression discontinuity design enabled us to consider all public health sector data from HIV positive individuals across the Western Cape Province receiving care in a real-world environment with constrained resources, heavy caseloads and a limited ability to trace people lost to care.

Methods

Study design

To determine the effect of rapid versus deferred ART on mortality, this study uses a fuzzy regression discontinuity design within a cohort of all individuals accessing HIV care and treatment services in the Western Cape, South Africa. Due to random measurement error of the laboratory test (CD4 cell count), and the similarity in immunological status for individuals within a narrow CD4 cell count range either side of a threshold, individuals with CD4 cell counts close to eligibility thresholds are assigned to immediately initiate or defer treatment in an effectively random way. CD4 cell count measurements have high variability, and can be impacted by instrument precision, specimen test timing or the blood specimen collection. External factors such as exercise and smoking can also affect the accuracy of the CD4 cell count test, resulting in substantial variability in the CD4 cell count measurements. Individuals with CD4 cell counts just below and above the eligibility thresholds are expected to be similar in both observed and unobserved characteristics as long as the CD4 cell count results have not been manipulated in any way (177, 182, 183, 184, 185, 186). The CD4 cell counts used in this study come from the National Health Laboratory Service (NHLS) database and are digitally linked to the routine health information data set, therefore manipulation of CD4 cell count results by the clinicians or data staff at the facility is not plausible.

The study population consists of all individuals seeking HIV treatment and care in the Western Cape public-sector health services with a first pre-ART CD4 cell count between 1 January 2007 through to 31 August 2016 and assessment and outcome data up to 30 June 2020. Due to the requirement of a South African identification number (SA ID) number for linkage with data from the death registry, individuals without a SA ID were excluded. Other exclusions included children and adolescents less than 16 years of age on the date of their pre-ART CD4 cell count, people without a CD4 cell count test result prior to the ART initiation date, individuals who died within 1 month of their first CD4 cell count test and anyone recorded as having an unnatural death in the death registry (Figure 2).

Setting and data sources

The Western Cape is one of nine provinces in South Africa, with a population of 6.9 million (2021), an estimated 569,713 people with HIV and over 306,000 people on ART (187). The vast majority of people living with HIV seek care in the public-sector, which first offered ART in a few NGO supported facilities in 2001, accelerating coverage after 2004 when ART provision became national policy (99). CD4 cell count monitoring of all HIV positive individuals has been provided since program inception. In March 2013, continued follow-up CD4 cell count monitoring after 1 year on ART among virologically suppressed and clinically-well individuals with CD4 ≥200 cells/µL was no longer recommended (153).

Since the inception of the free ART services in 2004, the South African policy guidelines for ART eligibility have changed multiple times, each time increasing the population eligible to initiate ART. At the start of the free ART services national guidelines stipulated that an adult's CD4 cell count needed to be ≤200 cells/µL or have a WHO stage IV illness in order to be eligible for ART (188). In April 2010, guidelines changed to allow pregnant women and those with active tuberculosis (TB) who also had a CD4 cell count of <350 to be eligible (189). In August of 2011, the Western Cape included all individuals with a CD4 cell count <350 cells/µL with the National Department of Health following suit in April 2013 (42). Again in January 2015, guidelines were changed to raise the eligibility thresholds to all individuals with a CD4≤500 cells/µL (190). Lastly, in September 2016, all HIV infected people were eligible to initiate ART regardless of CD4 cell count (Figure 1) as per WHO guidelines.

All public-sector laboratory testing is done by the NHLS with the digitised results being available since 2007. The province established a patient registration system which shares a unique health identifier across all health services. This has facilitated the linkage of data from digital hospital, laboratory and pharmacy sources, as well as electronic disease registers (191). Information on deaths from natural causes within the provincial HIV population seeking care was extracted from the death registry (192). The process of linking all digital health data to the unique patient health identifier is now formalised through the Provincial Health Data Centre (PHDC) from which all data provided for analyses are already de-identified but still internally linkable based on a privacy-preserving random key (191).

Exposures

This study analysed data from 1 January 2007 to end of June 2020, with the data divided into study periods aligning to gaps between policy changes in CD4 cell count eligibility thresholds for initiating ART. Individuals were categorized into study periods based on the date of their first ever pre-ART CD4 cell count specimens. we concentrated on three specific times periods; study period 1 (SP1) prior to 1 April 2011 when the CD4 cell count eligibility threshold was set to <200 cells/µL, study period 2 (SP2) from 1 April 2011 to 31 March 2015 when the eligibility threshold was set to <350 cells/ µl, and study period 3 (SP3) from 1 April 2015 to 1 January 2017 when the eligibility threshold was set to <500 cells/ µl (Figure 2). As per protocol during these study periods, individuals were expected to return for their CD4 cell count result within a week and people eligible to initiate ART were expected to start within 4-6 weeks during which time they went through multiple counselling sessions (151). For the remainder of this paper, the term eligible or eligibility refers the CD4 cell count thresholds used to determine if someone is eligible for ART. However, there were other reasons to initiate someone on ART including WHO Stage 4 defining conditions, and during different

protocol periods, pregnancy and co-infection with TB. First line drug regimens also improved during the study, starting with a preferred first line regimen that included stavudine or zidovudine, both later being replaced by tenofovir, and ultimately changing to a fixed dose combination for adults without complications, comprising tenofovir, emtricitabine and efavirenz (Figure1).

Based on these policies, we looked at two exposures for this study. The first exposure was defined as being eligible for ART during any of the three specified time periods defined by the CD4 cell count guideline changes. The pre-ART CD4 cell count is the running or forcing variable in this study, playing a role in part in determining whether a patient is eligible to initiate ART. The second exposure was defined as initiating ART within 6 months of the first CD4 cell count. Although by protocol, individuals should initiate within 2 months of their first eligible CD4 count, we set a 6-month initiation time-period due to national guidelines stipulating that a new baseline CD4 cell count was required if the original was more than 6-months old (188). For the remainder of this paper, we will use the term "6m ART" to describe initiating ART within 6 months of an individual's first CD4 cell count.

Outcomes

Our primary outcome was death within 2 years of their first pre-ART CD4 count, with the secondary outcome being death within 3 years. All individuals had potential for at least three years of follow-up data.

Statistical analysis

We note a sizable proportion of individuals initiated 6m ART despite their cell CD4 count being above the eligibility threshold (against recommended guidelines) and not all individuals initiated ART when their CD4 cell count met the eligibility thresholds, which determined a fuzzy instead of sharp regression discontinuity design.

After exploratory and descriptive analyses, we evaluated the relationship between the value of an individual's first pre-ART CD4 count and the probability of treatment initiation in a logistic regression model, allowing for discontinuity at the specified CD4 cell count eligibility threshold for each study period. Without policy changes, we would assume this association to be smooth, therefore any discontinuity along this CD4 cell count distribution at the threshold value is interpreted as evidence of the causal effect of eligibility (181). Due to the fuzzy regression discontinuity design, the next analyses employed an intention-to-treat (ITT) perspective to consider the impact of CD4 cell count threshold changes on mortality. The ITT effects result in risk differences in mortality for individuals assigned to immediate versus deferred ART based on their CD4 cell count, at the threshold, regardless of whether they initiated ART. The final set of analyses used an instrumental variable

approach to determine the effect of initiating (or not initiating) ART on mortality for those adhering to the threshold policy in place at the time of their CD4 cell count. We estimated the effect of ART uptake on 24-month mortality among those who initiated ART because they had a CD4 cell count that made them eligible (compliers), and among those whose ART was deferred because their CD4 cell count determined they were ineligible (control compliers). Under assumptions that having an eligible CD4 cell count affected mortality only through the uptake of ART, the instrumental variables estimates are known as the complier average causal effect (CACE) or the causal effect of ART initiation on mortality among compliers.

A priori knowledge regarding clinical characteristics and immune status determined the use of 50 CD4 cell count bandwidths on either side of the threshold to ensure characteristics were as similar as possible in the eligible and ineligible individuals.

Sensitivity analyses were performed using data-driven mean squared error (MSE-two) optimal bandwidths with a triangular kernel that assigns linear down-weighting to the same observations. However, real-world application is obfuscated with multiple different CD4 cell counts on either side of the threshold. Sensitivity analyses were also performed using an exposure variable of initiating ART within 3-months and 12-months of their first eligible CD4 cell count, compared to the primary exposure which is 6 months. We also considered mortality at 36-months, compared to the primary outcome of 24-month mortality. The last sensitivity analyses excluded individuals with TB (tuberculosis) or pregnancies during the time of their initial CD4 cell count per study period if their co-infection was recorded during times when CD4 thresholds were different from the general HIV population (1st April 2010 to 1st September 2011 and 1st April 2013 to 1st September 2016).

Lastly, we calculated cumulative mortality and risk ratios for ART eligibility to compare our study outcomes with earlier trials and studies exploring the optimal time for people to initiate ART.

This study was approved by the Western Cape Department of Health and UCT Human Research Ethics Committee (HREC 421/2016).

Results

A total of 244,748 (69.7%) of the 350,912 HIV positive individuals aged 16 or older with a SA ID recorded in a Western Cape digital health database were included in this study. Individuals without a CD4 cell count test before or within the first 30 days after initiating ART (29.2%), individuals with a first CD4 cell count above 2000 cells/μL (0.04%) and individuals who died within 30 days of their first CD4 cell count test (1.0%) were excluded from the analyses. Of all study participants, just over 30% initiated ART within 6 months of their first CD4 cell count during the study (Figure 2).

Individuals without a SA ID (49% of cohort) were excluded from the study as they did not have an identifier to link them to the death registration data. Those excluded were broadly similar to the those included the study, with exception that those excluded were more likely to be men. Individuals not in the study also had lower ART initiation and death rates but this may be due to a high proportion leaving the province (migrating for work or other reasons) and therefore we were not able to access or link their follow-up clinical assessment or death data (Supplemental material: Table S1).

Close to 130,000 patients are included in SP1, when the CD4 cell count eligibility threshold was <200 cells/μL, almost 80,000 in SP2 and close to 40,000 in SP3. The number of patients in each study period is aligned with the duration of time the eligibility criteria were operative, with SP1 covering the longest length of time and SP3 the shortest. Men made up about a third of the study cohort, with proportions per period being similar to the men initiating ART in the full Western Cape cohort. The age (median 28, 28, and 27) across the 3 study periods was very similar, while the median CD4 cell count in SP1 (317 cells/μL) was lower than the second and third periods (338 and 340). The proportion with advanced HIV disease (a CD4 cell count <200 cells/μL) initiating ART within 3 months of their first CD4 cell count rose from 42% in SP1 to almost 66% by SP3. By the end of the study, more than three-quarters had initiated ART at some point in time across all study periods (78%, 80%, and 82% respectively). The proportion of deaths by 24 months was between 5% and 6% across the three study periods (Table 1).

The proportion of first-time presenters initiating ART within 6 months of their qualifying CD4 cell count increased for those below each operative CD4 cell count threshold over time (Figure 3a and 3b and Table 2a), with a modelled mortality risk increase compared to those above the threshold of 8.1% (95%CI: 5.6 - 10.5), 18.5% (95%CI: 15.2 - 21.8) and 18.3% (95%CI: 12.7 - 23.9) in SPs 1, 2 and 3 respectively (Figure 3b and Table 2a). In all study periods, the lower the eligible CD4 cell count was the greater the probability of starting ART (Figure 3a and 3b).

Amongst compliers, mortality two years after the first-ever CD4 cell count was similarly lower in those eligible for ART (below the CD4 cell count threshold) compared to those ineligible around each operative threshold, most notable in SPs 1 and 2 (-13.3% RD, 95%CI: -26.2 – (-0.4); -4.2% RD, 95%CI: -10.2 - 1.8; and -1.0 RD, 95%CI: -8.4 - 6.5) in SPs 1,2,3 respectively (Figure 3c and Table 2b). The intention to treat (ITT) analyses shows a discontinuity in mortality during SP1 (-1.1% RD (95%CI: -2.1 – (-0.1))) at the threshold which becomes less discernible in SP2 and SP3 (Figure 3d and Table 2b). In all three study periods, there is a high proportion of ineligible (above threshold) first time presenters

initiating ART regardless of eligibility criteria, in addition there are also many eligible presenters who do not start ART within 6 months (Figure 3a and 3b).

Due to large confidence intervals and lack of precision, we re-ran the complier average causal effect (CACE) estimates filtering for ineligible individuals who did not initiate ART within 3 years of their first CD4 test, rather than the stricter 6-month ART-initiation definition used in the primary study. These sensitivity analyses in SP1 and SP2 showed slightly higher estimates in magnitude but with much greater precision, with the RD being -12.6% (95%CI: -15.9 – (-9.3)) in eligible compliers compared to control compliers in SP1, and -6.9% (95%CI: -10.1- (-3.6)) in SP2 (Table 2b, last row in each study period). As we did not have more than 3 years of follow-up data for the last study period, this validation could not be performed.

Control compliers presenting for the first time to the HIV services and having treatment deferred due to ineligible CD4 cell count results, deferred the initiation of ART for a median of more than two years (807 days (IQR 422-1485) in SP1. Deferral time (delay to ART initiation) for control-compliers (people ineligible and wait to become eligible to initiate ART) decreased over time although delays were still longer than the 6 months suggested by ART protocols in place at the time (SP2 control-compliers deferred ART for a median 798 days (IQR 401-1342) and 541 days for SP3 (IQR 300-903) (Table 2a).

The risk ratios comparing mortality, showed ineligible individuals who deferred ART until eligible were 1.4 times as likely to die (95%CI: 1.2-1.7) by 24 months than those who were eligible and started ART when eligibility thresholds were set at a CD4 cell count of 200 cells/μL. The risk of mortality by 36 months was also increased by 40% (1.4 RR; 95%CI: 1.1-1.8) for those who were deferred ART treatment when eligibility thresholds were set at a CD4 count of 350 cells/μL. The effects on 24-month mortality were less discernible when the CD4 cell count was 350 cells/μL or higher (Table 2b and 2c).

Discussion

During all three ART-eligibility guideline periods, the risk of death by 24 months was less likely in compliers who started ART (due to being just below the threshold) compared to those who did not (due to being above the threshold), in keeping with ART being beneficial at these thresholds, more marked the lower the threshold. Individuals who were deferred ART due to being slightly above the threshold, on average, were deferred by more than 2 years, resulting in significant CD4 cell count decline and worse outcomes. The intention to treat estimates were diluted through non-compliers on both sides of the thresholds, with support for a modest risk difference during SP1, and less certain and smaller population level mortality reductions at the higher thresholds.

Real world health service ART eligibility considerations

Unlike in clinical trials with active follow-up, a missed opportunity to initiative ART in an individual in a highly constrained service setting, could result in disease progression without appropriate identification and intervention (such as subsequent ART initiation) (174, 175, 193, 194). This is in addition to differences in event rates in untreated versus treated individuals with CD4 cell counts around each threshold, potentially accentuating differences which would be seen in a trial setting.

Any delays in accessing treatment results in worsening CD4 cell count trajectories and the possibility of opportunistic infections (OIs) and death. HIV treatment protocols in SP1 and SP2, prior to universal test and treat, were to provide the next CD4 cell count test appointment date within 6 months if not yet eligible for ART (42), however our study showed ineligible individuals deferring ART by a median of 807 days during SP1 (798 in SP2, and 541 in SP3). The delays in initiating ART described in this study correlate with outcomes described by the Africa Health Research Institute (AHRI) in which retention within the health services by 12 months increased by 70% for individuals who initiated ART within 3 months compared to similar individuals who didn't due to CD4 results that were slightly above the threshold (177). Initiating ART soon after diagnosis may be effective in both mitigating losses to care and decreasing mortality through ART clinical effectiveness.

ART initiation

Although guidelines offer definitive CD4 cell count eligibility thresholds, clinicians were understandably sometimes more aggressive than allowed for by guidelines in initiating individuals onto ART, especially during the first two study periods when the CD4 cell count thresholds were set at 200 and 350 cells/µL. On average, across the three study periods, a third of ineligible individuals with a CD4 cell count within 50 cells/µL above each threshold were initiated by 6 months on ART. The high number of ineligible individuals initiating ART diluted or masked the true effects of ART at each threshold as an intervention to mitigate mortality. Interestingly, the percentage initiating ART among eligible individuals within 6 months of their first CD4 cell count test only surpassed the ineligible ART initiation figures by 10% in SP1 and just under 20% in the last two study periods, reaching 57% of the eligible cohort in the last study period. The health services have struggled to increase ART initiation among eligible patients; however, this cohort is known to the health facilities with a high likelihood of the individuals' addresses and contact details recorded in their patient files. These individuals should in theory be as important if not more important to encourage initiation onto ART as they are inexpensive to locate and somewhat motivated to seek care in comparison to individuals diagnosed during HIV testing campaigns in the communities, but not yet linked to care.

Mortality in ineligible compliers

Regression discontinuity designs require large sample sizes and a substantial number of events to achieve enough statistical power (182). Our study contains a relatively small number of deaths within the 50-cell bandwidth on either side of the threshold, and therefore we lacked precision in estimating the effect sizes at higher CD4 cell count thresholds. In addition, our estimates were further diluted by ineligible people often initiating ART after the study defined 6-month period (but being categorised as not having started ART for the entire respective analysis period). In order to validate our CACE estimates, we ran additional sensitivity analyses where we only included ineligible compliers who did not initiate ART for at least 3 years after their first CD4 cell count. Although the sensitivity analyses were reassuring, this remains a major limitation, as ineligible compliers who remain off ART for so long may differ systematically from those who went on to start ART between 6m and 3y after enumeration. Methods for applying censoring within a regression discontinuity design are not yet commonly implemented and require further development and dissemination (195). As such our estimates might be considered lower bound effectiveness estimates.

Validation of early clinical trials motivating for increasing ART eligibility thresholds

This study and the SMART and START trials showed benefits of starting ART at higher CD4 cell count thresholds, although the estimates from this study and those of the randomised control trials (RCTs) are not directly comparable due to different controls groups and treatment strategies. The RCTs exploring optimal timing of ART initiation compared strategies which involved starting ART at different eligibility thresholds, while the study presented in this thesis compared those immediately above and below each CD4 cell count eligibility threshold to each other. The SMART trial found a 3-fold increased risk of death for those starting ART with a CD4<200 cells/µL compared to those with a CD4 count >350 cells/µL (196). The START trial compared individuals initiating ART with CD4 counts <350 cells/µL to those with CD4 cell counts >500 cells/µL and found a 28% increased risk of serious AIDS-related events or death when initiating ART at a CD4 cell count threshold of 350 (170).

Although it is difficult to compare estimates from this study to those from RCTs, comparisons to other causal analyses of routine data are possible. A study in 2009 by the When To Start Consortium used causal methods to compare ART initiation within 100 cells above and below different thresholds and found weak evidence (HR 1.13, 95% CI 0.80-1.60) of increased risk of death if ART was delayed to below a CD4 cell count of 350 cells/µL (164). Another study in 2011 by the HIV Causal Collaboration had similar results finding no evidence of increased mortality when ART was delayed until the CD4 cell count dropped to below 350 cells/µL, and weak evidence (HR 1.20, 95% CI 0.97-1.48) of increased mortality when delayed until the CD4 cell count dropped to below 200 cells/µL,

when compared to 500 cells/µL (32). However, both studies did find increased risk for a combined endpoint of AIDS defining events or death when deferring treatment to below 350 cells/µL.

The study presented in this paper found evidence of increased mortality for those above the threshold and ineligible to initiate ART at both the 200 and 350 CD4 cell count thresholds, within 24 and 36 months after the first CD4 cell count test, respectively. The risk ratios were less discernible for the 500 CD4 cell count threshold. Results from all the above studies found benefits to initiating ART earlier with higher CD4 cell counts.

Potential unintended consequences of expanded eligibility

Increasing eligibility thresholds did not negatively affect the percentage of people initiating ART who were presenting to the HIV services for the first time with advanced HIV disease. A main concern when debating the merit of increasing ART eligibility thresholds was that healthier people initiating ART would overwhelm the health facilities while the sickest would be side-lined and left potentially without treatment (197, 198, 199). This study shows an increase in the proportion of people in the lowest CD4 cell count categories initiating ART, with each successive guideline implementation.

Clinician agency versus strict guideline adherence

At the start of the free ART services, eligibility thresholds were necessary to ensure the sickest individuals had access to medication, and the benefits of ART initiation at higher CD4 cell counts were at the time less-well established. ART treatment was closely monitored and provided only by doctors due to concerns about adverse drug reactions, unknown long-term outcomes and expensive drugs. Experience was gained over the years, and drug regimens became more robust and user friendly as well as less expensive. In the Western Cape, where access to doctors is reasonably good compared to many similar settings, it is clear that clinicians exercised agency to initiate patients they thought could benefit, guided by but not always in strict compliance with the operative clinical policy. At a population level initiating ART based on clinician agency was very effective in bringing down mortality in those close to but above eligibility thresholds. However, other clinicians may not have been as empowered to interpret or implement guidelines as flexibly. In a more recent experience, during the COVID epidemic, thresholds were also applied, triaging vaccinations based on age categories. There are times when eligibility thresholds for health interventions are critical, for example when medication supply is limited and/or future procurement is precarious or unknown. However, when drug supply is no longer a concern, allowing flexible triaging by services may alleviate some complexity, expense and future client morbidity and deaths.

Strengths & limitations

A strength of this study was the use of a regression discontinuity (RD) design to estimate real-world ART effectiveness at guideline thresholds, with the potential for causal interpretation (177, 200, 201). In addition to the potential information bias mentioned above (that ineligible compliers might have still accessed ART outside the 6-month window), there was also a risk of selection bias in that we could only include patients within the provincial dataset who had a South African identification number recorded (51%) in order to reliably link clinical data to the death registry, although it is reassuring that the patients with and without SA IDs were comparable on most available measures.

Conclusions

ART was found to be effective at averting mortality at all the eligibility thresholds of historical guidelines, with the greatest impact in earlier years when the only patients eligible were patients with lower CD4 cell counts. In addition to the clinical benefits of ART, deferring treatment in people with CD4 cell counts slightly above eligibility thresholds resulted in loss to the ART services for long periods. Ineligible patients for whom ART was deferred had worsening health outcomes through disease progression, and potentially increased risk of HIV transmission to others. This highlights the balance between clinical considerations (who is likely to benefit the most clinically from a given intervention) and health service considerations (what will happen if a given opportunity to initiate care is missed in a weak health care system). The relatively modest ITT effects compared to the effects in compliers, demonstrates both the agency of clinicians in initiating treatment in patients who have not yet fully met eligibility criteria if they perceive benefit, as well as the failure of the health care system to ensure everyone who is eligible gets the treatment that is indicated for them.

Tables and Figures

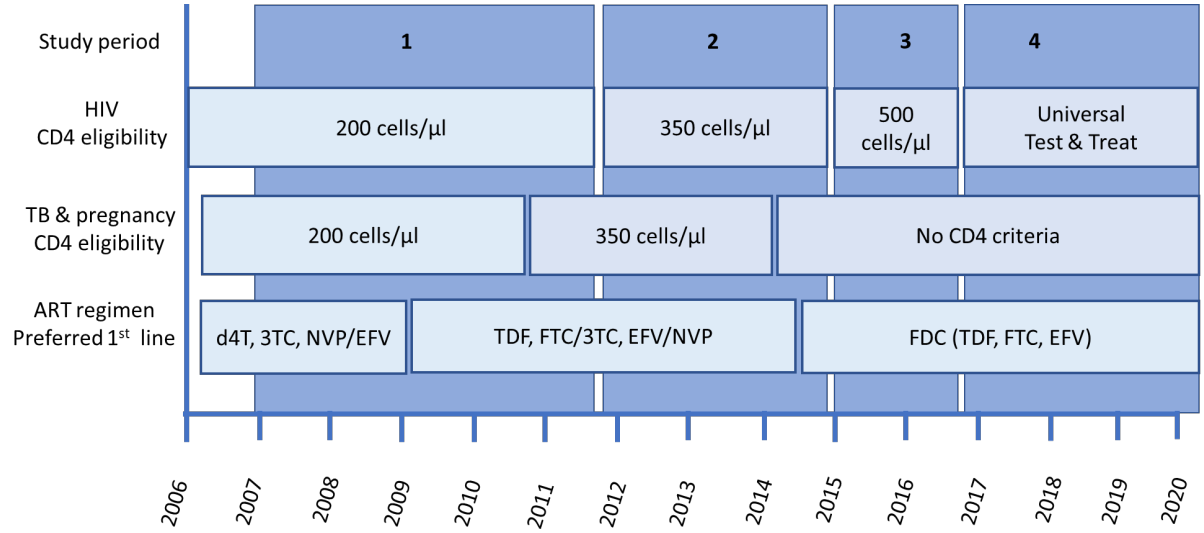


Figure 1: Study time periods based on CD4 count eligibility.
Notes: HIV = Human Immunodeficiency Virus, CD4 = CD4+ T cell count per microlitre, TB = tuberculosis, d4T = stavudine, 3TC = Lamivudine, NVP = nevirapine, EFV = efavirenz, TDF = tenofovir, FTC = emtricitabine, FDC = fixed dose combination

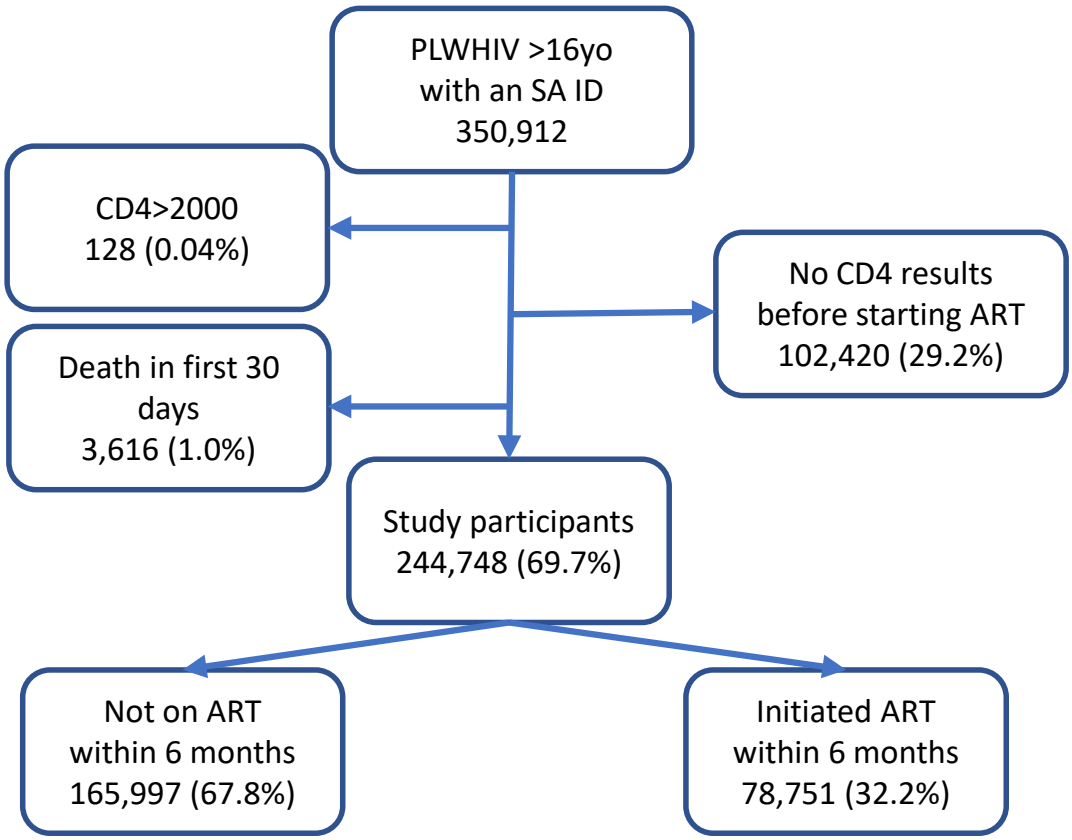


Figure 2: People considered for the study (Western Cape public sector health care)
Notes: PLWHIV=People living with HIV; yo= years old; SA ID = South African identification number; CD4=CD4 cell count per microlitre; ART= antiretroviral therapy

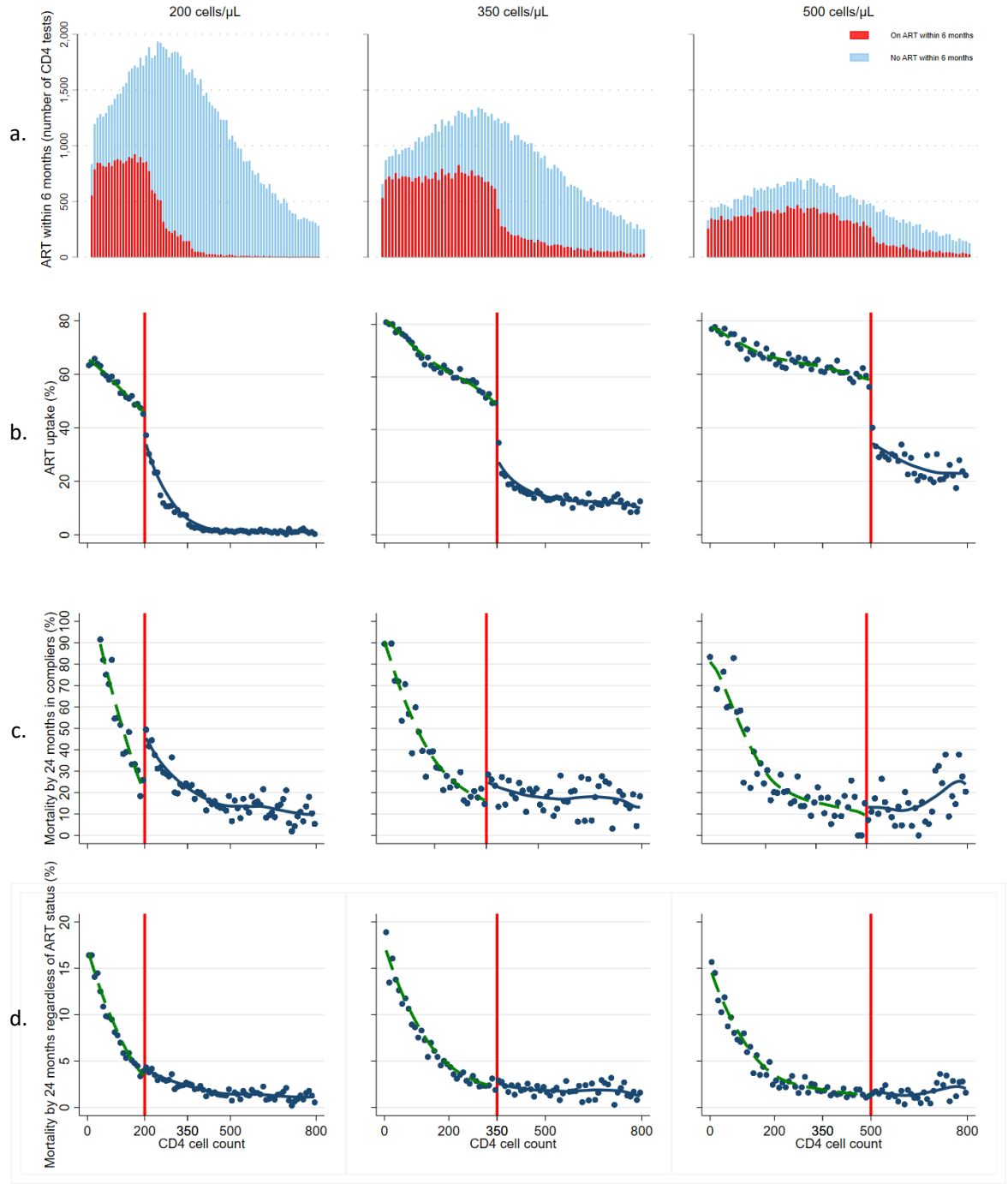


Figure 3: ART initiation and impact on mortality at 24 months after the first CD4 count per eligibility time-period.
ART= antiretroviral therapy, RD= risk difference. The y-axis maps proportions of the sample, while the x-axis plots the mean CD4 cell count (10 cell bins per point estimate). Each of the three columns illustrates separate analyses done at mutually exclusive time periods, based on the changing ART eligibility threshold policy dates. The red vertical bar indicates the CD4 count threshold within each study period (column), with eligible being to the left of the red bar and ineligible to the right. The first row of stacked bar graphs illustrates people who started ART within 6 months after their first CD4 count (shaded) versus those who did not start within 6 months (clear bars). The second, third and fourth rows are two-way scatter plots depicting separate linear regressions.

Table 1: Baseline characteristics and mortality status of individuals with HIV in the Western Cape.

Study periods Dates of study periods ART CD4 count eligibility criteria	Study period 1 1 Jan 2007-31 July 2011 <200 cells/µl	Study period 2 1 Aug 2011-31 Dec 2014 <350 cells/µl	Study period 3 1 Jan 2015-31 Aug 2016 <500 cells/µl
Total patients, N	128992	77825	37931
Males, N (%)	36157 (28 %)	26909 (34.6 %)	13686 (36.1 %)
Age, Median (IQR)	28 (23, 35)	28 (23, 36)	27 (22, 35)
15-24	43732 (33.9 %)	28155 (36.2 %)	14949 (39.4 %)
25-54	83179 (64.5 %)	47884 (61.5 %)	22083 (58.2 %)
55+	2081 (1.6 %)	1786 (2.3 %)	899 (2.4 %)
CD4 (cells/µl), Median (IQR)	317 (180, 488)	338 (189, 522)	340 (191, 521)
0-99	15885 (12.3 %)	9319 (12 %)	4375 (11.5 %)
100-199	20777 (16.1 %)	11408 (14.7 %)	5610 (14.8 %)
200-349	34924 (27.1 %)	19576 (25.2 %)	9565 (25.2 %)
350-499	26761 (20.7 %)	16229 (20.9 %)	8000 (21.1 %)
500+	30645 (23.8 %)	21293 (27.4 %)	10381 (27.4 %)
ART by 3 months, $N^{sum.}$	19802	26980	18724
0-199, N (%)	15548 (42.4 %)	13114 (63.3 %)	6551 (65.6 %)
200-349, N (%)	3706 (10.6 %)	9497 (48.5 %)	5627 (58.8 %)
350-499, N (%)	328 (1.2 %)	2325 (14.3 %)	4411 (55.1 %)
UTT, N (%)	220 (0.7 %)	2044 (9.6 %)	2135 (20.6 %)
ART by 6 months, $N^{sum.}$	26778	31280	20693
0-199, N (%)	20220 (55.2 %)	14487 (69.9 %)	7083 (70.9 %)
200-349, N (%)	5653 (16.2 %)	11097 (56.7 %)	6168 (64.5 %)
350-499, N (%)	556 (2.1 %)	3176 (19.6 %)	4885 (61.1 %)
UTT, N (%)	349 (1.1 %)	2520 (11.8 %)	2557 (24.6 %)
ART by 12 months, $N^{sum.}$	33931	36240	23098
0-199, N (%)	22981 (62.7 %)	15503 (74.8 %)	7542 (75.5 %)
200-349, N (%)	8875 (25.4 %)	12281 (62.7 %)	6647 (69.5 %)
350-499, N (%)	1471 (4.8 %)	4860 (29.9 %)	5296 (66.2 %)
UTT, N (%)	601 (2 %)	3596 (16.9 %)	3613 (34.8 %)
ART before end of study, $N^{sum.}$ (% of tot)	100847 (78.2 %)	62489 (80.3 %)	31044 (81.8 %)
Mortality status*			
Death by 30 days, $N^{sum.}$ (% of total)	1644 (1.3 %)	1376 (1.8 %)	596 (1.6 %)
Death by 24 months, $N^{sum.}$ (% of total)	6642 (5.1 %)	4595 (5.9 %)	1829 (4.8 %)
Death by 36 months, $N^{sum.}$ (% of total)	8346 (6.5 %)	5382 (6.9 %)	2194 (5.8 %)
Death by end of study, $N^{sum.}$ (% of total)	19409 (15 %)	8762 (11.3 %)	2843 (7.5 %)

Notes: Jan=January; Aug=August; Dec= December; ART=antiretroviral therapy; CD4 = CD4+ T cell count per microlitre, N= number; %=percentage; IQR= inter-quartile range; N^{sum} = summative number; tot=total; *Individuals who died within 30 days of their first CD4 are excluded from all tables and analyses, with exception to the mortality status figures above.

Table 2: Intention to treat effects and predicted outcomes of ART eligibility on ART initiation and mortality; bandwidths of 50 cells/ µl were applied to either side of the threshold limiting the number of individuals in the regressions.

Columns	a	b	c
ART uptake		**Predicted outcomes (months after first CD4)**	
	Baseline	**24**	**36**
SP1: 200 cells/µL threshold, bandwidth 150 to 250 cells/µL			
Patients, N	23,212	Total deaths (sum)	927	1,312
ART uptake, RD (95% CI)	8.1 (5.6, 10.5)	Eligible complier deaths, N (% of tot. deaths)	152 (16.4 %)	218 (16.6 %)
Eligible started ART, % (95% CI)	45% (42.7, 46.3)	Ineligible complier deaths, N (% of tot. deaths)	344 (37.1 %)	482 (36.7 %)
Ineligible started ART, % (95% CI)	36% (34.8, 38.2)	Effect of ART eligibility, RD (95% CI)	-1.1 (-2.1, -0.1)	-1.0 (-2.1, 0.2)
Time to ART (days), eligible, M (IQR)	127 (56, 616)	Effect of ART in compliers (6m), RD (95% CI)	-13.3 (-26.2, -0.4)	-11.9 (-26.7, 2.9)
Time to ART (days), ineligible compliers, M (IQR)	807 (422, 1485)	Effect of ART in compliers (>3y), RD (95% CI)	-12.6 (-15.9, -9.3)	-14.5 (-18.1, -10.8)
		Risk ratio of compliers	1.4 (1.2, 1.7)	1.4 (1.2, 1.6)
SP2: 350 cells/µL threshold, bandwidth 300 to 400 cells/µL			
Patients, N	12,421	Total deaths (sum)	298	382
ART uptake, RD (95% CI)	18.5 (15.2, 21.8)	Eligible complier deaths, N (% of tot. deaths)	64 (21.5 %)	76 (19.9 %)
Eligible started ART, % (95% CI)	50% (47.3, 52.1)	Ineligible complier deaths, N (% of tot. deaths)	106 (35.6 %)	143 (37.4 %)
Ineligible started ART, % (95% CI)	31% (28.9, 33.5)	Effect of ART eligibility, RD (95% CI)	-0.8 (-1.9, 0.3)	-1.1 (-2.3, 0.2)
Time to ART (days), eligible, M (IQR)	76 (27, 567)	Effect of ART in compliers (6m), RD (95% CI)	-4.2 (-10.2, 1.8)	-5.7 (-12.5, 1.1)
Time to ART (days), ineligible compliers, M (IQR)	798 (401, 1342)	Effect of ART in compliers (>3y), RD (95% CI)	-6.9 (-10.1, -3.6)	-8.4 (-11.9, -4.9)
		Risk ratio of compliers	1.2 (0.9, 1.7)	1.4 (1.1, 1.8)
SP3: 500 cells/µl threshold, bandwidth 450 to 550 cells/µl			
Patients, N	4,575	Total deaths (sum)	72	108
ART uptake, RD (95% CI)	18.3 (12.7, 23.9)	Eligible complier deaths, N (% of tot. deaths)	18 (25 %)	22 (20.4 %)
Eligible started ART, % (95% CI)	57% (52.7, 60.5)	Ineligible complier deaths, N (% of tot. deaths)	21 (29.2 %)	33 (30.6 %)
Ineligible started ART, % (95% CI)	38% (34.1, 42.3)	Effect of ART eligibility, RD (95% CI)	-0.2 (-1.5, 1.2)	-1.0 (-2.7, 0.8)
Time to ART (days), eligible, M (IQR)	36 (9, 204)	Effect of ART in compliers (6m), RD (95% CI)	-1.0 (-8.4, 6.5)	-5.2 (-14.8, 4.4)
Time to ART (days), ineligible compliers, M (IQR)	541 (300, 903)	Effect of ART in compliers (>3y), RD (95% CI)	NA	NA
		Risk ratio of compliers	1.2 (0.7, 2.3)	1.6 (0.8, 2.4)

ART=antiretroviral therapy, N=number, %=proportion, RD=risk difference, CI=confidence interval, tot.=total, M=median, IQR=interquartile range. The risk differences show the regression coefficient and heteroskedasticity-robust 95% confidence intervals (95% CI). The three sets of grouped rows each report results at mutually exclusive time periods, based on the changing ART eligibility criteria policy dates. Column a displays regression results for ART uptake and statuses at baseline, column b and c represent intention to treat (effect of ART eligibility) and complier average causal effect (effect of ART in compliers) analyses and status at 24 and 36 months after the first CD4 cell count. Each linear regression discontinuity model has different slopes and 50 cell bandwidths on either side of the threshold.

Supplement table 1: Baseline characteristics of individuals with and without a South Africa identification number (required for linking to the death registry)

Study periods ART CD4 count eligibility criteria	All study periods Aggregate total (with SA ID)	All study periods Aggregate total (without SA ID)
Total patients, N	244748	233200
Males, N (%)	76752 (31.4 %)	91775 (39.4 %)
Age, Median (IQR)	28 (23, 35)	30 (24, 36)
15-24	86836 (35.5 %)	64044 (27.5 %)
25-54	153146 (62.6 %)	164792 (70.7 %)
55+	4766 (1.9 %)	4364 (1.9 %)
CD4 (cells/µl), Median (IQR)	317 (180, 488)	305 (167, 477)
0-99	29579 (12.1 %)	32563 (14 %)
100-199	37795 (15.4 %)	39005 (16.7 %)
200-349	64065 (26.2 %)	62521 (26.8 %)
350-499	50990 (20.8 %)	46415 (19.9 %)
500+	62319 (25.5 %)	52696 (22.6 %)
ART by 3 months, $N^{sum.}$	65506 (26.8 %)	48430 (20.8 %)
ART by 6 months, $N^{sum.}$	78751 (32.2 %)	58656 (25.2 %)
ART by 12 months, $N^{sum.}$	93269 (38.1 %)	68824 (29.5 %)
ART before end of study, $N^{sum.}$ (% of tot)	194380 (79.4 %)	123546 (53 %)
Mortality status*		
Death by 30 days, $N^{sum.}$ (% of total)	3616 (1.5 %)	4365 (1.9 %)
Death by 24 months, $N^{sum.}$ (% of total)	13066 (5.3 %)	11631 (5 %)
Death by 36 months, $N^{sum.}$ (% of total)	15922 (6.5 %)	13338 (5.7 %)
Death by end of study, $N^{sum.}$ (% of total)	31014 (12.7 %)	18921 (8.1 %)

Notes: ART=antiretroviral therapy; CD4 = CD4+ T cell count per microlitre, SA ID= South Africa identification number, N= number; %=percentage; IQR= inter-quartile range; $N^{sum.}$ = summative number; tot=total; *Individuals who died within 30 days of their first CD4 cell count are excluded from all tables and analyses, with exception to the mortality status figures above.

CHAPTER 2d

DID ART ELIGIBILITY POLICY CHANGES OR SUPPLY AND DEMAND DRIVE ART SCALE-UP IN THE WESTERN CAPE, SOUTH AFRICA? ASSESSING THE IMPACT OF CHANGING GUIDELINES ON ART ACCESS AND MORTALITY USING A REGRESSION DISCONTINUITY DESIGN.

Manuscript

This study is prepared in manuscript format but has not yet been submitted for publication.

Alignment with thesis objective(s)

Results from clinical trials are not always replicated when an intervention is applied in operational settings. The fourth objective of the thesis was to try to assess the impact on mortality of guideline changes which increased ART eligibility. This builds on the previous objective which explored the Impact of different ART eligibility thresholds on mortality.

Among the many concerns raised in the lead up to each guideline change, and the questions this study tries to answer, is whether the sickest patients presenting to ART services would be pushed aside amid an overwhelming number people who were eligible to initiate ART, and whether the adoption of new guidelines would immediately change patterns of initiation and mortality when an increasing number of people who were getting access to ART were clinically asymptomatic.

This paper uses causal methods to mimic a randomised controlled trial, providing estimates of impact at a population-wide level.

Candidate's contribution

The candidate helped develop and support the clinical monitoring systems in the Western Cape, enabling the collection of the clinical data used for this thesis. The candidate designed the study, acquired and processed the linked data, performed the analyses, and prepared the results in manuscript format.

Abstract

Introduction

The results of clinical trials have informed ART eligibility guideline changes but the population-wide guideline effectiveness in "real-world" settings has been difficult to evaluate. This study considers the impact of guideline CD4 cell count eligibility changes on ART uptake and associated mortality in the Western Cape, South Africa.

Methods

We used a regression discontinuity design to mimic a randomised trial within the cohort of HIV-diagnosed individuals from 2007 to 2017, with outcomes followed through to June 2020. The main analyses consider the CD4 cell count closest to the date of guideline change and measures the effect on antiretroviral therapy (ART) uptake, and on mortality within 2 and 3 years.

Results

The proportion of patients accessing ART increased by 4.4% when the CD4 threshold was increased from 200 to 350 cells/µl; 3.9% when the CD4 cell count threshold was increased 350 to 500 and 2.9% when the CD4 threshold was removed. When examining the entire HIV study cohort regardless of CD4 cell count there were no easily discernible population level impacts of the guideline changes. By 2017, over 60% of people were initiating ART within 6 months of their first CD4 cell count (up from 25% in 2009) and less than 2.5% were dying within 2 years (down from 4%).

Conclusions

The greatest gains in ART enrolment and decreased mortality occurred between guideline changes instead of immediately after guideline implementation. These results suggest that, compared to the release of new guidelines, pre-existing improvements in the supply of ART and related services, patient demand, and clinical agility in anticipation of guideline changes may have had the greatest influence of ART access.

Introduction

Guidelines issued by the World Health Organization (WHO) have successfully raised the threshold for CD4 cell count guided antiretroviral therapy (ART) initiation, and this has informed guideline changes in South Africa. However, few studies have measured the effectiveness of these changes on access to ART and the health of population needing HIV care and treatment. Clinical trials have demonstrated the benefits of starting ART at higher CD4 cell counts (170, 196, 202), and most national guidelines now recommend starting ART regardless of CD4 cell count (203, 204). However, results from clinical trials cannot estimate the effectiveness of guideline implementations in real-life contexts due to the extra resources employed in trial settings to implement interventions and closely monitor and trace study participants (205).

Early studies compared outcomes of patients initiating treatment at different CD4 cell counts, found that earlier treatment at higher CD4 counts led to less morbidity and mortality. The Strategies for Management of Antiretroviral Therapy (SMART) trial outcomes suggested that those starting with a CD4 cell count <250 cells/µL had a 3-fold increased risk of AIDS or death when compared to people who started ART with a CD4 cell count >350 cells/µL (196). The Strategic Timing of Antiretroviral Treatment (START) trial showed a reduction in mortality of 72% between those who started ART immediately (CD4 count >500 cells/µL) and those who deferred treatment until their CD4 cell count dropped below 350 cells/µL, but these findings were not significant (170). The WHO decision to recommend ART regardless of CD4 cell count was a landmark decision (142), enabling individuals to get onto ART sooner and with less steps in the process. WHO guideline changes over two decades (206) were based on the learnings of these clinical trials and other major studies; however, many questions remained regarding operational impact. Would ART uptake among the sickest continue to increase in parallel to offering ART to all with HIV, and would mortality rates continue to fall over time?

Causal evidence on real-world effectiveness of policy change on health outcomes using individuated population-wide longitudinal data in RLSs is still limited (207). Following WHO recommendations, the Western Cape ART eligibility guidelines had three major revisions since the free ART services began in 2004, leading to the current guidelines to treat all with HIV regardless of CD4 cell count. These three discreet guideline changes provide an opportunity to evaluate the impact of guideline changes on mortality for the full cohort of people receiving an HIV diagnosis in public-sector health facilities across the Western Cape Province using a regression discontinuity design (180, 181).

Methods

This study takes advantage of the natural randomisation of patients around a threshold (date of a guideline change) enabling a causal interpretation of intervention uptake and outcome comparisons either side of the threshold.

Setting and data sources

The Western Cape is one of nine provinces in South Africa, with a population of 6.9 million, an estimated 506,202 people with HIV and over 322,128 people on ART as of June 2021 (187). The vast majority of people living with HIV seek care in the public-sector, which first offered ART in 2001, accelerating coverage after 2004 when ART provision became national policy (99). CD4 cell count monitoring of all HIV positive patients has been provided since program inception. Full details of the ART program evolution are described elsewhere (151).

All public sector laboratory testing is done by the National Health Laboratory Service and the digitised results have been available since 2007 (208). The province has successfully established a patient registration system which shares a unique health identifier and Patient Master Index (PMI) across both hospital and ambulatory services. This has facilitated the linkage of data from hospital, laboratory and pharmacy sources, as well as electronic disease registers such as TIER.Net for HIV and tuberculosis (153, 191). Information on deaths within the provincial HIV population was extracted from the death registry.

The process of linking all digital data from the public health services to the PMI is now formalised through the Provincial Health Data Centre. All data provided for analyses are pre-anonymised but still linkable based on a privacy-preserving random key (191). De-identified, linked CD4 cell count results, ART and TB clinical appointment data, and mortality data were provided by the Provincial Health Data Centre for the purposes of this study as approved by the Western Cape Department of Health and UCT Health Research Ethics Committee (HREC 421/2016).

Study population

The study population for these analyses consisted of all patients presenting for HIV care and treatment in the Western Cape public-sector health services with a pre-ART CD4 cell count between January 2007 through to January 2017. Follow-up visit, laboratory and outcome data for individuals were extracted up to the end of June 2020. Patients without a South African identification (SA ID) number were excluded. Other exclusions included children and adolescents less than 16 years of age on the date of their first CD4 cell count, individuals with no CD4 cell count test date prior to 30 days after their ART start date, and any record linked to an unnatural death in the death registry (Figure

1). We further excluded individuals who died within one month of their CD4 cell count test as these were very sick patients who most likely would not have benefitted from the guideline changes and the possibility of ART when they first presented to the HIV services.

Study Design

To determine the effect of immediate versus deferred ART on mortality, this study uses a fuzzy regression discontinuity design (180, 181, 209, 210) applied to a cohort of individuals accessing HIV services in the Western Cape, South Africa. The ability to initiate ART is determined, in part, on whether an individual seeks HIV care services, and has a CD4 cell count test analysed before or after the date of a guideline change (the threshold).

The precise date of the CD4 cell count test was influenced by a set of random factors: the decision of the individual to access transport and seek an HIV diagnosis, return to HIV services to be assessed for treatment eligibility, and ability to get an appointment (clinic congestion) (176). As long as the forcing variable (the date to seek a CD4 cell count) is not manipulated in order to gain access to ART, patients with CD4 cell counts on either side and proximal to the cut-off (or threshold) date will be similar (including unmeasured confounders), simulating the assignment of a randomised exposure in a controlled trial (181).

We assessed the association between access to ART within 6 months of the first CD4 cell count and mortality within 24 and 36 months after the CD4 cell count test date. Comparisons of outcomes in those treated and untreated are observed just before and after the guideline changes were implemented (177, 179, 181, 211).

Exposures

Since the inception of the free ART services in South Africa, the policy guidelines for ART eligibility have changed multiple times, each time extending services to a larger pool of individuals who meet the criteria to initiate ART. Based on these policies, we looked at two exposures for each set of analyses. We considered the date of the CD4 cell count test as the primary exposure (the running or forcing variable in this study) whilst the secondary exposure was initiating ART within 6 months. Having a first-ever CD4 cell count on a date proximal to the implementation of one of the 3 major guideline changes (GC) regardless of CD4 cell count result enabled their inclusion in the analyses, with the CD4 cell count test date falling before or after the guideline change being the exposure (those testing after the guideline change having potential to benefit from the guideline change).

This study focussed on the dates of new guideline implementation with the first guideline change (GC#1) raising the CD4 cell count eligibility threshold from <200 to <350 cells/µL on 1 August 2011,

the second guideline change (GC#2) raised the threshold to <500 cells/µL on 1 January 2015, and the last guideline change (GC#3) removed all CD4 cell count eligibility criteria - a universal test and treat scenario- on 1 September 2016 (144, 188, 190). For ease of describing the times between the guideline changes, we have named these study periods SP1, SP2, SP3 and SP4 (Figure 2). Exposure to ART was defined as initiating ART within the 6-month time-period from first CD4 cell count, due to national guidelines stipulating that a new baseline CD4 cell count was required if the original was more than 6-months old.

Outcome measures

Our primary outcomes looked at death within 2 and 3 years of the first pre-ART CD4 cell count. All patients had potential for at least 24 months of follow-up, but the majority were followed for at least 3 years.

Death was ascertained via the death registry database in South Africa, which was determined to be 96% complete in 2017 (212). A South African identification was required in order to link people to data within the death registry, therefore, anyone with a CD4 cell count who did not have a South African identification recorded in any of the routine health system data was not included in the study.

Statistical analysis

We first explored the data to ensure the assumptions required to perform regression discontinuity analyses were met. Using a histogram to plot the CD4 cell count test dates on either side of the guideline change, we could determine that there was no bunching of tests just after implementation to indicate manipulation of treatment eligibility. In order to further consider manipulation, we looked at the CD4 cell count test dates separately for those who initiated ART within 6 months versus those who deferred ART, ensuring a smooth distribution. We note that some patients started ART despite their CD4 cell count not being within the guideline's eligible threshold and, conversely, not all individuals started ART when their CD4 cell count met the dates of eligibility; as such, a fuzzy instead of sharp regression discontinuity design was chosen.

Prior to multi-variable analyses, we looked at the individual fields to observe outliers, plot variable form, and consider any further data processing required. We regressed each baseline variable individually in separate RD models to ensure characteristics within each variable were similar on either side of the cut-off (guideline implementation dates). This was used to support the assumption that treatment was quasi-randomly assigned and no co-variates are required in the final regression models (176, 211). We also assessed the remaining assumptions to ensure we could use a regression discontinuity and found the study to meet all assumptions and validity concerns including a

continuous assignment variable, continuous outcomes at the threshold, known thresholds, and monotonicity (200).

We then ran several regressions on the restricted and unrestricted datasets (described below) looking at the effects of ART eligibility on ART uptake and mortality, using local linear regression models with heteroskedasticity-robust standard errors. We allowed for separate slopes estimating the effects of ART uptake and mortality on either side of the cut-off date (guideline change). For illustrative purposes, we plotted the regressions lines overlaid by scatterplots binned in monthly intervals, displaying averages in each bin.

The first regression evaluated the relationship between the date of the patients first CD4 cell count relative to starting ART within 6 months, allowing for discontinuity at the date of each guideline change.

Due to the fuzzy regression discontinuity design, the next regression in the set utilised an intention-to-treat (ITT) perspective to consider the impact of guideline changes on mortality. The ITT effects result in risk differences in mortality for patients assigned to immediate versus deferred ART based on the date of their CD4 cell count on the date of guideline change.

The final regression was only performed on the restricted dataset as it inherently considered CD4 cell count results and eligibility (which was not applicable when considering the entire cohort regardless of CD4 cell count result). This final regression used an instrumental variable method to determine impact. We estimated the effect of ART uptake on 24-month and 36-month mortality among those who initiated ART because they had an eligible CD4 cell count result taken after the guideline change, making them treatment compliers, and those whose ART was deferred because their ineligible CD4 cell count result test date was before the guideline change determining them to be control compliers. Under assumptions that having a CD4 cell count test after the guideline change affected mortality only through the uptake of ART, the instrumental variables estimates are known as the complier average causal effect (CACE) or the causal effect of ART initiation on mortality among compliers.

Data exploration and robustness checks

After running our models in STATA (213), we ran sensitivity tests using data-driven bandwidths for all regressions using the mean squared error (MSE-two) and chose a triangular kernel that assigns linear down-weighting to the same observations (214). The data-driven bandwidths were varied and wide, but the results were similar to the regressions illustrated in this paper. We also ran several sensitivity analyses to look at risk differences by removing times (6 months prior to new guideline

implementation) when health providers may be aggressively initiating patients on ART due to known imminent changes in ART guidelines, and regressions removing those with TB and/or pregnancy during times when guidelines were different for this subgroup. Both would resolve some dilution due to information bias in estimating true differences in eligible and non-eligible individuals. After confirming that that there were minimal changes to the presented findings, the presented outputs did not include any of these further restrictions.

Two datasets: a restricted and an unrestricted cohort

Both the restricted and unrestricted sets of analyses compared individuals whose first CD4 cell count was taken proximal to the date of the three different eligibility criteria guideline changes over time. The bandwidths were determined *a priori* to provide enough data for power, yet maintain assurance that people were similar in observed and unobserved characteristics.

For the restricted cohort analyses, the bandwidths included individuals whose first-ever CD4 cell count test date was taken in a study period directly before or after each specific guideline change being measured (Figure 2). In addition, we restricted the dataset to people who would directly benefit from the guideline change (between 200 and 349 cells/µL for individuals with first-ever CD4 cell counts taken proximal to GC#1, between 350 and 499 cells/µL for individuals with CD4s cell counts proximal to GC#2, and a CD4 result of 500 cells/µL and above for individuals with CD4 cell counts proximal to GC#3).

For the unrestricted cohort analyses, the entire Western Cape dataset of individuals with a first-ever CD4 cell count test date proximal to each guideline change was taken into account. As the number of individuals in this dataset was much greater in comparison to the restricted dataset, the variance in the sample decreased enabling the use of tighter bandwidths for more precision (215). All individuals with CD4 cell count tests taken within a year before or after the three guideline changes being studied were included in the study, regardless of CD4 cell count result.

Results

Characteristics of Western Cape population

A total of 248,564 individuals from the Western Cape were included in this study, with a greater proportions of individuals (and follow-up time) in SP1 and SP2 compared to SP3 and SP4 (Table 1). Observable trends over the ten years include an increase in the proportion of men (29% in SP1 to 37% in SP4), younger populations accessing HIV services, and a decrease in deaths by 24 months from SP2 onwards (5.9% of the cohort in the SP2 compared to under 4% in SP3). The breakdown into CD4 cell count strata among individuals first ever presenting for a CD4 cell count, remained similar across the study periods with mild fluctuations (notably an increase in individuals with a first

CD4>500 cells/µL in SP2, SP3 and SP4 compared to SP1). In all CD4 cell count strata there was an increase in the proportion starting ART with each successive study period. During the last two years of the study (SP4), since the removal of CD4 cell count eligibility criteria, just over 70% of HIV patients accessing CD4 cell counts were being referred and initiated on ART within 12 months of their first CD4 cell count test.

Impact of guideline changes on a restricted cohort of individuals with the potential to benefit from guideline changes

The restricted cohort analyses looked at a subset of people who would be in line to directly benefit by the change in CD4 cell count eligibility criteria. We filtered for individuals with a CD4 cell count result within the range of those who would be newly eligible for ART under the incoming guideline, and taken proximal to the three guideline changes. The cut-off being measured is the date of each guideline implementation and not the CD4 cell count threshold.

The proportion of patients initiating ART (within the restricted CD4 cell count cohort) displayed strong discontinuities (increases) at the dates of all 3 guideline changes. There was a 13.2% risk difference (95%CI: 11.1-15.3) in ART uptake measured at GC#1, a 17.6% RD (95%CI: 14.8-20.3) at GC#2 and a 13.1% ART uptake RD (95%CI: 10.2-16.0) at GC#3. The smaller than expected risk differences in ART uptake are due to many ineligible patients being given access to initiate ART prior to the implementation date of the guideline change, with 35.6% RD (95%CI: 34.1-37.1) in SP1, 40.6% RD (95%CI: 39.0-42.2) in SP2, and 29.5% RD (95%CI: 27.6-31.3) in SP3 having started ART when guidelines suggested they should not initiate ART due to not meeting CD4 cell count criteria (Table 2). At the same time, a large proportion of individuals who were eligible also did not start ART (between 42% and 57% across the study).

ART uptake differences, summarized in Table 2 and Figure 3, show an increase in the absolute number of people initiating ART leading up to the guideline change; numbers fluctuate but tend to plateau after the guideline change is implemented. The increases in ART uptake leading up to implementation of a new guideline change (Figure 3b) are also reflected in the upward slopes of the solid lines of the scatter plot on the left side of each guideline change. The regression lines on the right side of the guideline implementation date (cut-off) in the scatter plot continue to have an increasing slope (albeit flatter than the left side) that is not seen in the bar graphs. This is due to a similar number starting ART per month compared to the number before the guideline change, but a slight decrease in total individuals with first-ever CD4 cell count within the CD4 cell count range being considered, hence a proportionate increase. For those with CD4 cell counts below 200 cell/µl, there is no evidence of declines in access as new guidelines were introduced.

In intention to treat (ITT) analyses, measuring the effect of having a CD4 cell count test taken proximal to but after GC#1 (and within the restricted CD4 cell count range) compared to those with their first CD4 cell count test taken before, there was a stronger association with lower mortality (-0.9% RD, 95% CI: -1.6 – (-0.1)) by 36 months than for GC#2 and GC#3. Changes in guideline criteria to a CD4 cell count <500cells/µL (-0.3% RD, 95%CI: -1.0 - 0.3) and universal test and treat time periods (-0.2% RD, 95% CI: -0.9 - 0.4) had smaller effect sizes and confidence intervals which included the possibility of no mortality benefit. Stronger associations with similar magnitudes were seen in the ITT sensitivity analyses where no bandwidth around the guideline date changes were implemented (between -1.0% RD (95%CI: -1.6 - (-0.3)) at GC#1, and -0.8% RD (95%CI: -1.4 – (-0.2)) at GC#3). These declining trends in ITT effects over successive GCs are reflected visually for 24m mortality (Figure 3c).

The last regression in the restricted cohort was a complier average causal effect (CACE), which compares ART uptake and mortality among compliers of guidelines before and after guideline changes. Among compliers, immediate eligibility reduced mortality within the first 36 months after a first-ever CD4 cell count test by a risk difference of 5.1% (95%CI: 0.8 - 9.4) at GC#1, by 1.9% (95%CI: -1.8 - 5.7) at the second, and a decrease of 2.3% RD (95%CI: -4.0 - 8.9) when having a CD4 cell count proximal to the last guideline change (Figure 3d and Table 2).

Impact of each guideline change on the entire population (unrestricted cohort) accessing HIV treatment services

When considering all individuals with a first ever CD4 cell count test at population level and within one year of the three guideline changes being measured, regression estimates become more abstract. Guideline changes were effective at increasing ART uptake across the HIV population, although these effects were modest and most pronounced with earlier guideline changes (4.4% RD, 95%CI: 2.6-6.2; 3.9% RD, 95%CI: 1.9-5.9; 2.9% RD, 95%CI: 1.4-4.5 at GC#1, 2 and 3 respectively, Table 3). The intention to treat analyses resulted in no discernible population level impact on mortality ascribed to the implementation date of guideline changes, when considering the Western Cape HIV population with applicable first CD4 cell count dates but ignoring CD4 cell count values (Table 3).

When plotting ART uptake and mortality proportions over time, regardless of CD4 cell count result, there is a clear continuous increase in ART uptake and decline in mortality (Figure 4). The proportion of individuals initiating ART within 6 months of first attending HIV services increased from just over 22% to almost 70% during the 10-year study period from 2008 through 2018 (Figure 4a and b). Mortality from 2009 to 2012 was close to 4% by 24 months but from 2012 onwards there was a decline down to close to 2.5% in 2015 (Figure 4c). This same trend is validated when plotting

mortality against ART uptake, in a scatter plot (Figure 5). The lower ART initiation proportions have higher mortality rates, with a notable downward slope in mortality as proportions increased over time from 2012 to 2015.

Discussion

What we found

Although mortality benefits attributable to guideline changes were evident, these were modest and especially in later periods, uncertain. The largest gains in ART initiations and associated decreases in mortality were between 2012 to 2015, when no guideline changes in ART criteria were being implemented (Figure 5), suggesting operational supply (ART medication and clinician availability) and patient demand (health service attendance) may drive mortality declines. There was no evidence of patients with low CD4 cell counts being denied access to ART as a result of increased access for patients with higher CD4 cell counts.

Operational access versus operative policy

At a population level our study showed sharper decreases in mortality for individuals presenting for the first time to HIV services between guideline changes, rather than just after new guidelines were implemented (the steepest declines being in SP2). The WHO published new ART guidelines in June of 2013 suggesting raising the ART CD4 cell count cut-off to individuals with a CD4 count<500 cells/µL (9). The Western Cape implemented these guidelines in January of 2015. Several prominent HIV clinicians from the Western Cape and South Africa took part in helping develop the changing WHO guidelines during the year prior to its publication. Discussions from WHO expert working meetings were being relayed to the Western Cape ART Monthly Meetings and may have driven a level of confidence in clinicians to initiate people who were close to but above the CD4 cell count cut-off prior to guidelines changing. It is also possible that as more and more health care facilities opened ART services and individuals stable on ART received their care and treatment in adherence groups outside of health facilities, there were more ART initiation appointments available in comparison to the number meeting the ART criteria in place. This allowed facilities to triage and initiate patients with CD4 cell counts above the cut-off, but importantly also resulted in higher ART access for those already eligible for ART but many of whom had struggled to access ART due to previous service capacity constraints. Although it is not clear which were the most impactful factors leading to increased ART initiations and decreased mortality, it is clear that ART access was not driven by a specific change in guidelines alone but more by a continuous increase over time in ART availability, this in itself being a factor in the guideline deliberation process. In some ways the guideline changes

to promote wider ART eligibility were premised on increased accessibility which was already impacting operationally by the time of guideline release.

Increases in CD4 count eligibility criteria provided modest benefit without harm

Policy makers were concerned that widening the pool of people able to access ART might overwhelm facilities and resources, resulting in the sickest who most needed and would most benefit from treatment unintentionally waiting for longer or not being prioritised (198, 216). However, this study shows ART uptake proportions among the sickest CD4 cell count strata continue to remain the highest throughout the study.

Implementing universal test and treat services regardless of CD4 cell count result showed limited benefits over the previous guideline period in terms of 24-month mortality. Although no one would argue the benefits of universal ART test and treat services in mitigating mortality and transmission, the results from this study are consistent with results from the modelling study presented by Johnson and colleagues in 2015 suggesting that the timing of test and treat service implementation was less important than optimising retention and viral suppression of those already on ART (159).

ITT and CACE estimates diluted

Health providers were (correctly) somewhat aggressive in getting patients onto ART despite CD4 cell count threshold guidelines, this was especially true during SP2 when almost 41% RD (95%CI: 39.0-42.2) of individuals ineligible according to CD4 cell count criteria were nevertheless initiated onto ART. While some patients were eligible for ART because of other clinical criteria such TB co-infection, pregnancy and presenting with a stage IV-defining illnesses, clinicians were able to exercise agency appreciating the potential missed opportunities for patients if waiting for further CD4 cell count declines before initiating ART.

The intention to treat estimates were diluted due to the substantial number of patients who started ART when ineligible and by those who did not start ART when eligible. Whereas the fuzzy design and CACE estimates provide some insight into the potential effectiveness of the intervention, there was additional dilution of both estimates due to individuals who did not initiate ART within 6 months subsequently starting ART, biasing the analysis exposure and diluting the effect estimates through increased survival in those classified as not being on ART. This could either be due to re-assessment in those who were always eligible, or due to re-assessment post guideline changes in those who were initially ineligible but subsequently eligible. The findings in this study therefore represent lower bound estimates of the effectiveness of guideline changes.

Limitations

Although there are many strengths to this study, including provincial sample size and linkage of all digital data including the death registry information, there are a number of limitations. In addition to the point that that people who were not eligible may have subsequently accessed ART after 6 months, an analysis which censored people as they re-engaged care and started ART would be of value. In addition, the data included in the analyses is limited to individuals we could successfully link to the death registry, and that can only be done via a South African National Identification number (SAID). SAIDs are thankfully not compulsory for treatment but individuals are encouraged to provide them when registering for care. Just under 50% of the individuals in the cohort had SAID numbers recorded in the health information systems. It is possible that people who attend more often or for longer periods of time have more opportunity to be prompted for and provide a SAID, which could introduce a survival bias. Although this study meets all assumptions necessary to make the regression discontinuity an appropriate design to measure causal effects (182), the assumption of association of treatment assignment (initiating ART) with the threshold indicator (date of guideline change) is weak, causing ITT estimates to be diluted. To further complicate this, regression discontinuity analyses need very large data sets to robustly detect associations (215). Although our numbers were large (>10,000), the relatively small number of events (deaths) contributed to a lack of precision in effect estimates

Conclusions and future research

This study showed that the greatest increase in ART initiations and greatest decreases in mortality occurred outside of guideline changes, suggesting operational supply (ART medication and clinician availability) and patient demand (attending health services) may drive access in advance of changes to eligibility guidelines. Observational cohorts provide a wealth of insights into service delivery access and impact, with regressions discontinuity designs being powerful methods to measure impact when ethical or financial reasons would not make randomised trials viable. Statistical methods that enable assessment of patient trajectories and changing ART status over time within regression discontinuity designs would provide further refinement to and confidence in these estimates.

Tables and figures

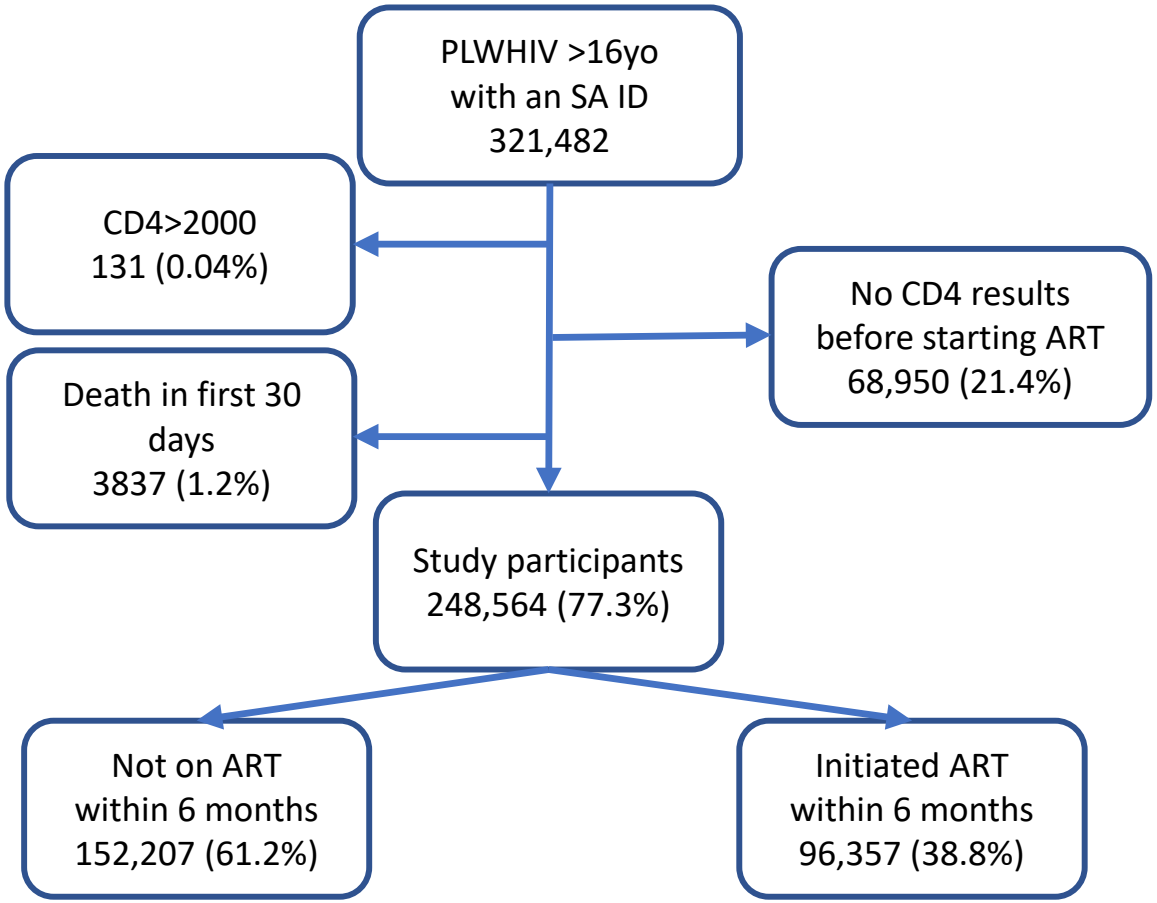


Figure 1: People included in the population wide analyses for this study (Western Cape public health sector)

Notes: PLWHIV=People living with HIV; yo= years old; SA ID = South African identification number; CD4=CD4 cell count per microlitre; ART= antiretroviral therapy

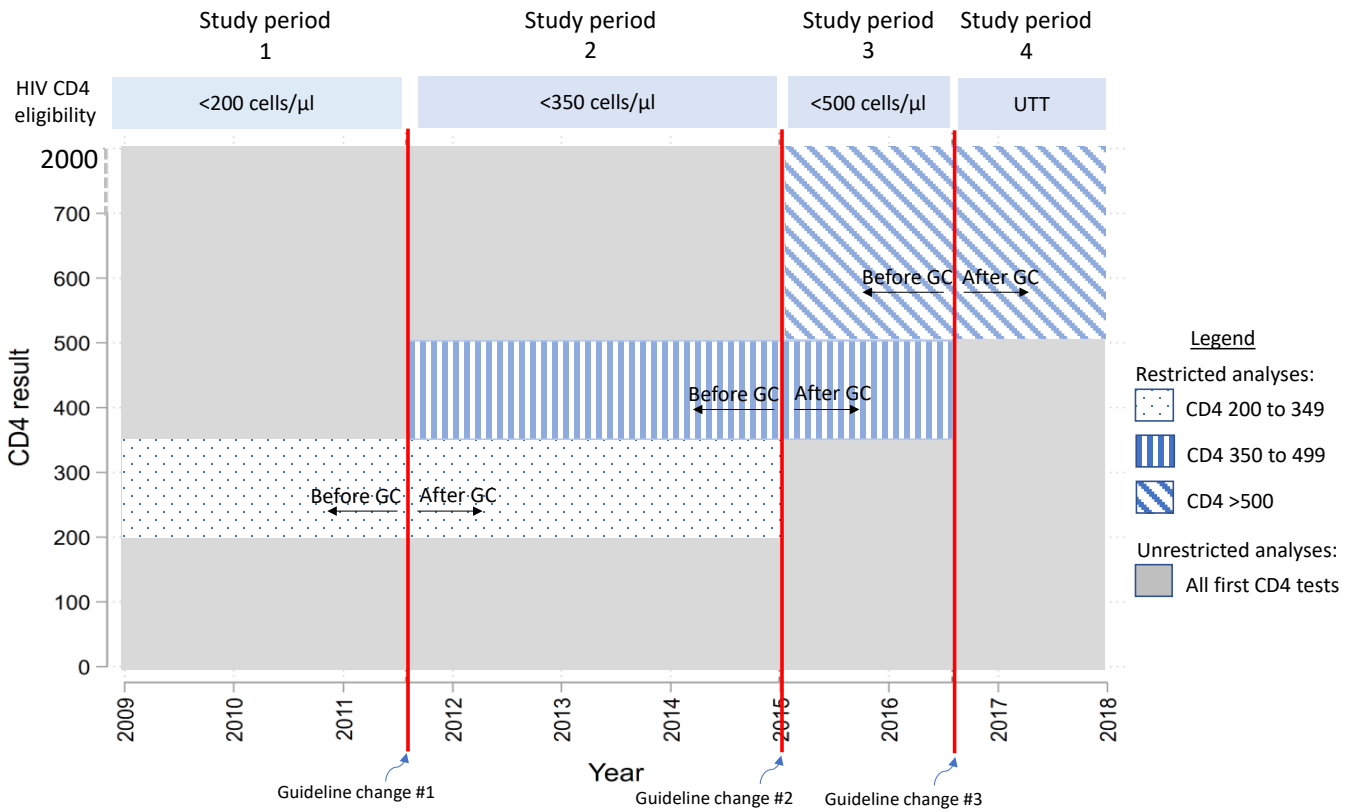


Figure 2: Study time periods and guideline changes

Notes: HIV = Human Immunodeficiency Virus, CD4 = CD4+ T cell count per microlitre, GC = guideline change

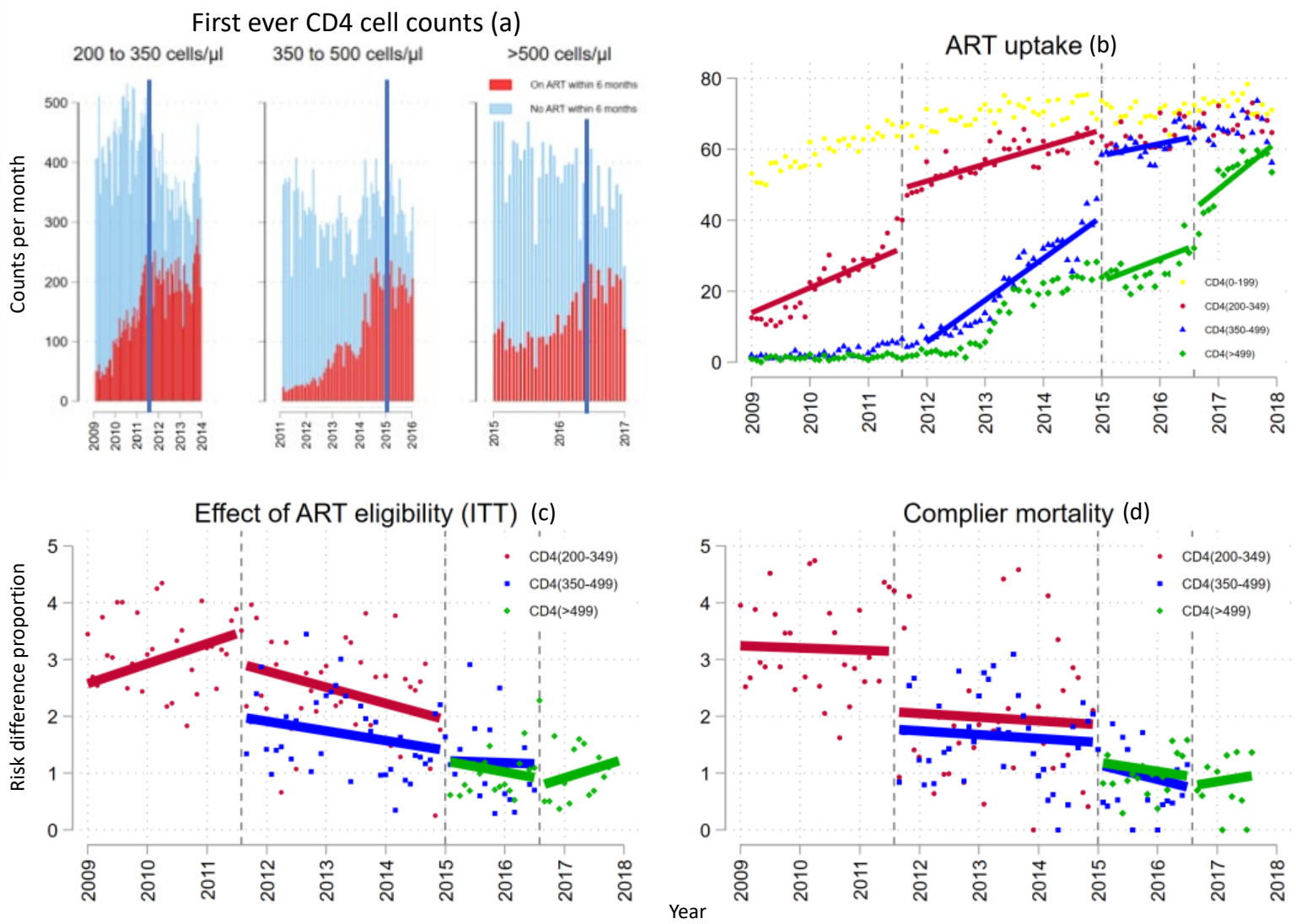


Figure 3: ART uptake and mortality (restricted cohort); compliments table 2

ART= antiretroviral therapy, CD4 = CD4 cell count, ITT = intention to treat analysis. The stacked bar graphs (a) illustrate people who initiated ART within 6 months after their first CD4 count (red) versus those who did not start within 6 months (blue bars). The total first-ever CD4 counts per month are represented by each stack (red plus blue) and the guideline change date is represented by the thick vertical blue line in each graph (separating study periods). The two-way scatter plots (b, c, d) have a different thick coloured sloping horizontal line depicting separate linear regressions based on different CD4 cell count strata. Each scatter point represents the average proportion (ART initiation (a), mortality (b, c)) per CD4 cell count category binned by month. The dashed vertical lines in the scatter plots indicate the date of each guideline change, with newly accessible being to the right of the vertical lines.

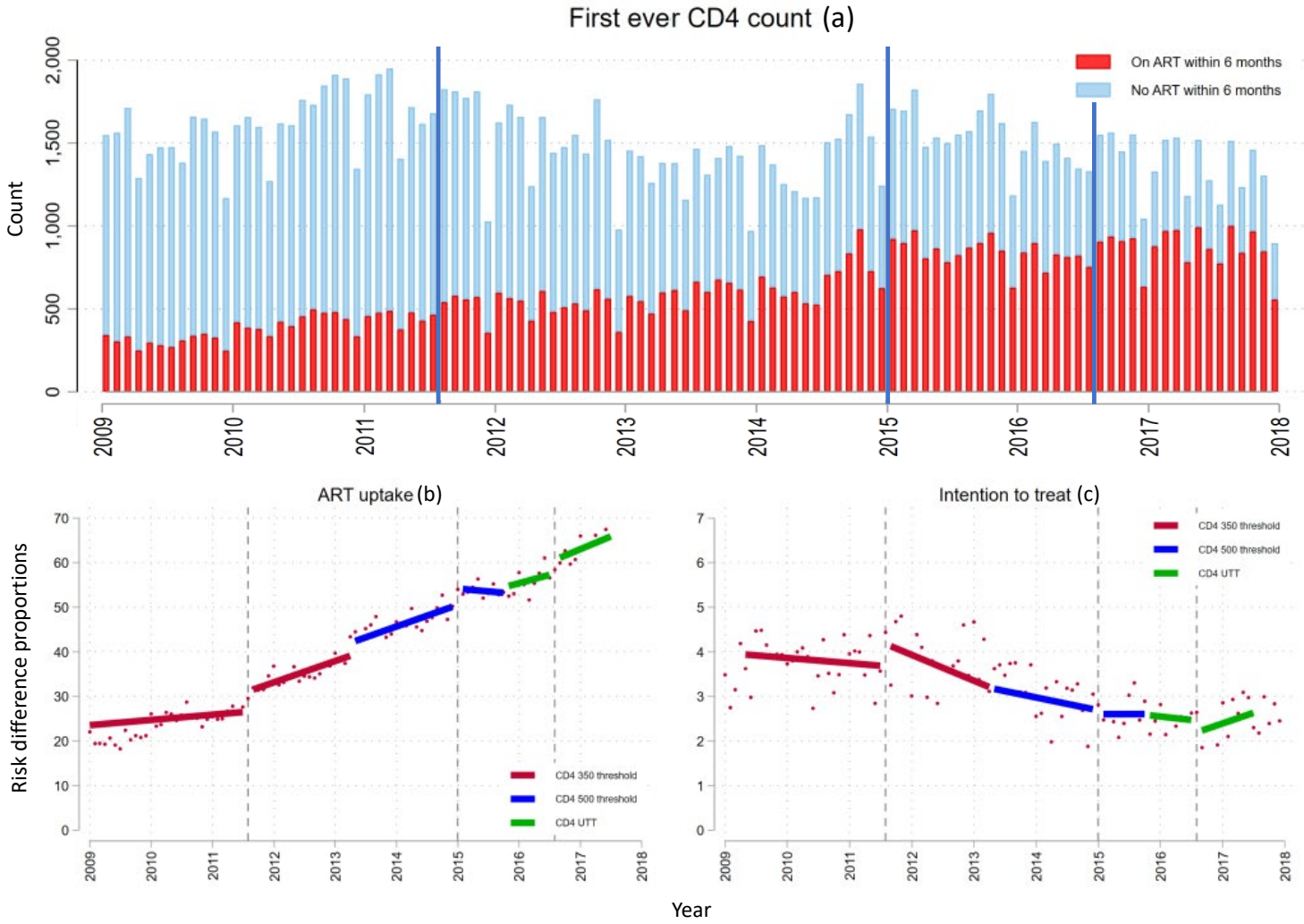


Figure 4: ART uptake and mortality for entire study population (unrestricted cohort); compliments table 3

Notes: ART= antiretroviral therapy, CD4 = CD4+ T cell count per microlitre, ITT = intention to treat analysis. The stacked bar graphs (a) illustrate people who initiated ART within 6 months after their first CD4 count (red) versus those who did not start within 6 months (blue bars) with the total first-ever CD4 counts per month represented by each stack (red plus blue). The bottom row illustrations are two-way scatter plots with each colour depicting separate linear regressions based on different CD4 cell count strata. Each scatter point (b, c) represents the average proportions (ART initiation (b) and intention to treat impact on mortality (c)) per CD4 count category binned together by month. The thick blue vertical lines (a), and the dashed vertical lines (b, c) mark the dates of each guideline change.

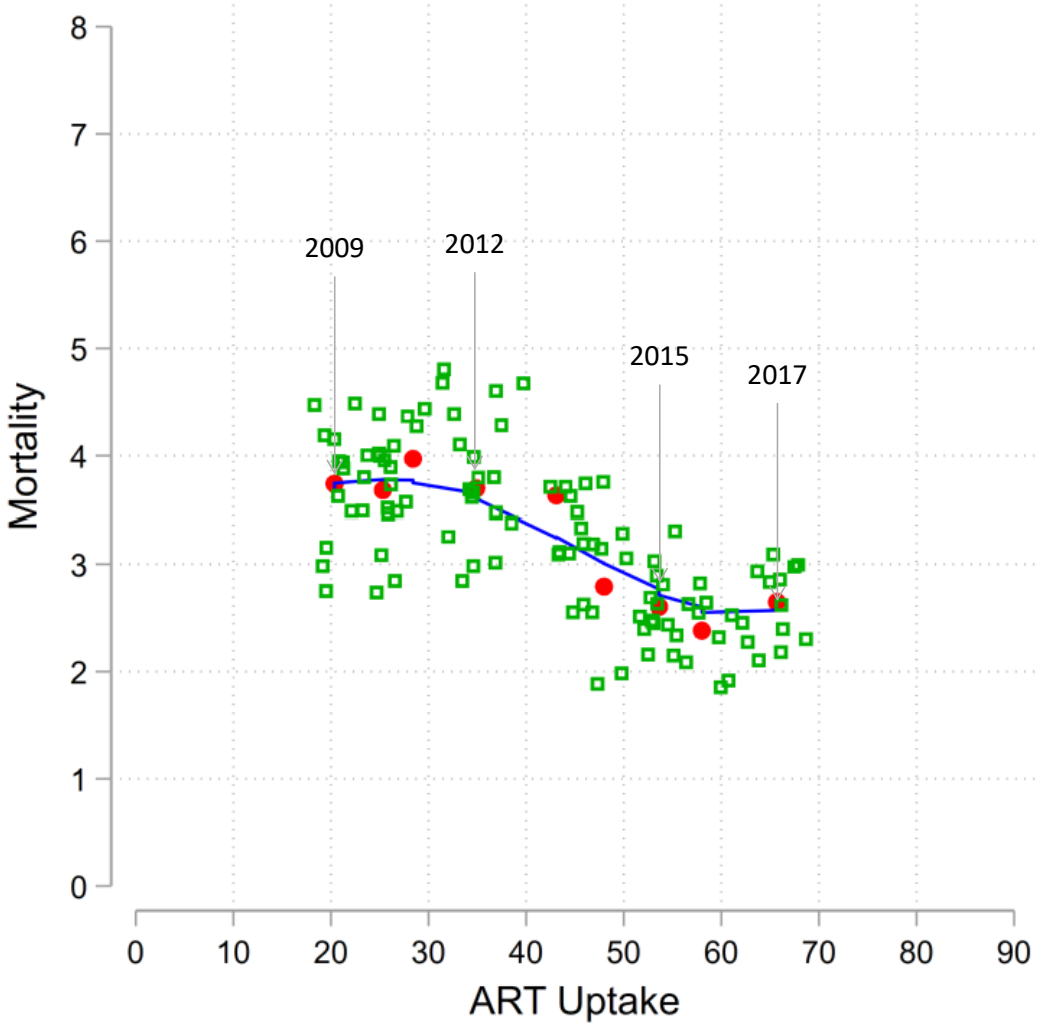


Figure 5: ART initiation proportion within 6 months against mortality proportion within 24 months, from 2009 to 2017

Table 1: Baseline characteristics of individuals in the study

Study periods Dates of study periods ART CD4 count eligibility criteria	Study period 1 1 Jan 2008-31 July 2011 <200 cells/µl	Study period 2 1 Aug 2011-31 Dec 2014 <350 cells/µl	Study period 3 1 Jan 2015-31 Aug 2016 <500 cells/µl	Study period 4 1 Sep 2016-1 Jul 2018 Universal test & treat
Total patients, N	99856	77825	37931	32952
Males, N (%)	29269 (29.3 %)	26909 (34.6 %)	13686 (36.1 %)	12069 (36.6 %)
Age, Median (IQR)	28 (23, 35)	28 (23, 36)	27 (22, 35)	27 (22, 34)
15-24	33947 (34 %)	28155 (36.2 %)	14949 (39.4 %)	13467 (40.9 %)
25-54	64189 (64.3 %)	47884 (61.5 %)	22083 (58.2 %)	18749 (56.9 %)
55+	1720 (1.7 %)	1786 (2.3 %)	899 (2.4 %)	736 (2.2 %)
CD4 (cells/µl), Median (IQR)	310 (175, 478)	338 (189, 522)	340 (191, 521)	337 (186, 516)
0-99	12745 (12.8 %)	9319 (12 %)	4375 (11.5 %)	4132 (12.5 %)
100-199	16661 (16.7 %)	11408 (14.7 %)	5610 (14.8 %)	4810 (14.6 %)
200-349	27183 (27.2 %)	19576 (25.2 %)	9565 (25.2 %)	8189 (24.9 %)
350-499	20598 (20.6 %)	16229 (20.9 %)	8000 (21.1 %)	7011 (21.3 %)
500+	22669 (22.7 %)	21293 (27.4 %)	10381 (27.4 %)	8810 (26.7 %)
ART by 3 months, $N^{sum.}$	17119	26980	18724	20130
0-199, N (%)	13213 (44.9 %)	13114 (63.3 %)	6551 (65.6 %)	6206 (69.4 %)
200-349, N (%)	3430 (12.6 %)	9497 (48.5 %)	5627 (58.8 %)	5240 (64 %)
350-499, N (%)	290 (1.4 %)	2325 (14.3 %)	4411 (55.1 %)	4339 (61.9 %)
UTT, N (%)	186 (0.8 %)	2044 (9.6 %)	2135 (20.6 %)	4345 (49.3 %)
ART by 6 months, $N^{sum.}$	22679	31280	20693	21705
0-199, N (%)	16838 (57.3 %)	14487 (69.9 %)	7083 (70.9 %)	6603 (73.8 %)
200-349, N (%)	5066 (18.6 %)	11097 (56.7 %)	6168 (64.5 %)	5617 (68.6 %)
350-499, N (%)	490 (2.4 %)	3176 (19.6 %)	4885 (61.1 %)	4687 (66.9 %)
UTT, N (%)	285 (1.3 %)	2520 (11.8 %)	2557 (24.6 %)	4798 (54.5 %)
ART by 12 months, $N^{Sum.}$	28158	36240	23098	23291
0-199, N (%)	18915 (64.3 %)	15503 (74.8 %)	7542 (75.5 %)	6930 (77.5 %)
200-349, N (%)	7513 (27.6 %)	12281 (62.7 %)	6647 (69.5 %)	5962 (72.8 %)
350-499, N (%)	1241 (5.5 %)	4860 (29.9 %)	5296 (66.2 %)	4977 (71 %)
UTT, N (%)	489 (2.2 %)	3596 (16.9 %)	3613 (34.8 %)	5422 (61.5 %)
ART before end of study, $N^{sum.}$ (% of tot)	78029 (78.1 %)	62489 (80.3 %)	31044 (81.8 %)	27219 (82.6 %)

Mortality status*				
Death by 30 days, $N^{sum.}$ (% of total)	1368 (1.4 %)	1376 (1.8 %)	596 (1.6 %)	497 (1.5 %)
Death by 24 months, $N^{sum.}$ (% of total)	5432 (5.4 %)	4595 (5.9 %)	1829 (4.8 %)	1529 (4 %)
Death by 36 months, $N^{sum.}$ (% of total)	6763 (6.8 %)	5382 (6.9 %)	2194 (5.8 %)	N/A
Death by end of study, $N^{sum.}$ (% of total)	14588 (14.6 %)	8762 (11.3 %)	2843 (7.5 %)	1916 (5.8 %)

Notes: Jan=January; Aug=August; Dec= December; ART=antiretroviral therapy; CD4 = CD4+ T cell count per microlitre, N= number; %=percent; IQR= inter-quartile range; N^{sum} = summative number; *Individuals who died within 30 days of their first CD4 are excluded from all tables and analyses, with exception to the mortality status figures above.

Table 2: ART uptake and mortality for those with potential to benefit from each guideline change.

ART uptake		Predicted mortality (months after first CD4)			Sensitivity analysis	
	Baseline		24	36	24	36
GC#1 (350 cells/ul threshold); restricted to first CD4 ≥200 & <350 cells/µl; Bandwidth is defined by study period 1&2					**No BW, restricted to CD4≥200 & <350**	
Patients, N in bandwidth (Total)	28,778 (43,855)	Cumulative deaths, N (% of all patients)	800 (2.8 %)	1,030 (3.6 %)	1,065 (2.4%)	1,390 (3.2%)
Eligible, N (%)	15,181 (52.7 %)	ITT: Effect of ART eligibility, RD* (95% CI)	-0.5 (-1.2, 0.1)	-0.9 (-1.6, -0.1)	-0.7 (-1.3, -0.1)	-1.0 (-1.6, -0.3)
Ineligible, N (%)	13,600 (47.3 %)	Mortality on right of TH, % (95% CI)	2.9 (2.4, 3.4)	3.5 (3.0, 4.0)	2.8 (2.4, 3.1)	3.4 (3.0, 3.8)
ART uptake, RD* (95% CI)	13.2 (11.1, 15.3)	Mortality on left of TH, % (95% CI)	3.5 (3.0, 4.0)	4.4 (3.8, 4.9)	3.5 (3.0, 3.9)	4.4 (3.9, 4.9)
Eligible started ART, % (95% CI)	48.8% (47.3, 50.3)	CACE: Effect of ART in compliers, RD* (95%CI)	-3.2 (-7.1, 0.7)	-5.1 (-9.4, -0.8)	-3.6 (-6.4, -0.7)	-4.9 (-8.1, -1.7)
Ineligible started ART, % (95% CI)	35.6% (34.1, 37.1)					
GC#2 (500 cells/ul threshold); restricted to first CD4 ≥350 & <500 cells/µl; Bandwidth is defined by study period 2&3					**No BW, restricted to CD4≥350 & <500**	
Patients, N in bandwidth (Total)	19,263 (42,244)	Cumulative deaths, N (% of all patients)	293 (1.5 %)	389 (2.0 %)	602 (1.4%)	872 (2.1%)
Eligible, N (%)	6,622 (34.4 %)	ITT: Effect of ART eligibility, RD* (95% CI)	-0.2 (-0.8, 0.4)	-0.3 (-1.0, 0.3)	-0.7 (-1.1, -0.2)	-0.6 (-1.2, -0.1)
Ineligible, N (%)	12,641 (65.6 %)	Mortality on right of TH, % (95% CI)	1.2 (0.8, 1.6)	1.7 (1.3, 2.1)	1.2 (0.8, 1.6)	1.7 (1.3, 2.1)
ART uptake, RD* (95% CI)	17.6 (14.8, 20.3)	Mortality on left of TH, % (95% CI)	1.4 (1.0, 1.8)	2.0 (1.5, 2.5)	1.9 (1.6, 2.2)	2.3 (2.0, 2.6)
Eligible started ART, % (95% CI)	58.1% (55.9, 60.4)	CACE: Effect of ART in compliers, RD* (95%CI)	-1.1 (-4.3, 2.1)	-1.9 (-5.7, 1.8)	-2.1 (-3.7, -0.6)	-2.0 (-3.8, -0.2)
Ineligible started ART, % (95% CI)	40.6% (39.0, 42.2)					
GC#3 (Universal test and treat (UTT)); restricted to first CD4 >500 cells/µl; bandwidth is defined by study period 3&4					**No BW, restricted to CD4 >500**	
Patients, N in bandwidth (Total)	15,546 (50, 082)	Cumulative deaths, N (% of all patients)	208 (1.2 %)	303 (1.8 %)	616 (1.2%)	893 (1.8%)
Eligible, N (%)	7,335 (47.2 %)	ITT: Effect of ART eligibility, RD* (95% CI)	-0.2 (-0.7, 0.3)	-0.2 (-0.9, 0.4)	-0.8 (-1.3, -0.3)	-0.8 (-1.4, -0.2)
Ineligible, N (%)	7,816 (50.3 %)	Mortality on right of TH, % (95% CI)	0.7 (0.2, 1.2)	1.3 (0.7, 1.8)	0.7 (0.2, 1.2)	1.3 (0.7, 2.3)
ART uptake, RD* (95% CI)	13.1 (10.2, 16.0)	Mortality on left of TH, % (95% CI)	0.9 (0.6, 1.2)	1.5 (1.2, 1.8)	1.5 (1.3, 1.7)	2.1 (1.9, 2.3)
Eligible started ART, % (95% CI)	42.6% (40.3, 44.8)	CACE: Effect of ART in compliers, RD* (95%CI)	-2.0 (-7.5, 3.5)	-2.3 (-8.9, 4.0)	-4.7 (-7.9, -1.5)	-5.1 (-8.8, -1.3)
Ineligible started ART, % (95% CI)	29.5% (27.6, 31.3)					

Notes: ART=antiretroviral therapy, CD4 = CD4+ T cell count per microlitre, GC= guideline change, N=number, %=percent, RD=risk difference, *=displayed as a percentage; CI=confidence interval. Each column and section represent a separate linear regression discontinuity model, based on the changing ART eligibility criteria policy dates (rows) and changing mortality assessment durations (24 and 36 months). The risk differences show the regression coefficient and heteroskedasticity-robust 95% confidence intervals (95% CI).

Table 3: ART uptake and mortality for the entire study population

ART uptake			Predicted outcomes (months after first CD4 count)		
	Baseline			24	36
GC#1 (350 cells/ul threshold); bandwidth (-1 year,+1 years)					
Patients, N in bandwidth (Total)	39,807	197,450	Cumulative deaths, N (% of all patients)	1,517 (3.8%)	1,880 (4.7%)
Right of threshold, N (%)	19,006	(47.7%)	ITT: Effect of guideline change, RD* (95% CI)	0.6 (-0.1, 1.4)	0.3 (-0.5, 1.1)
Left of threshold, N (%)	20,801	(52.3%)	Mortality on right of TH, % (95% CI)	4.3 (3.8, 4.9)	5.0 (4.3, 5.5)
ART uptake, RD* (95% CI)	4.4	(2.6, 6.2)	Mortality on left of TH, % (95% CI)	3.7 (3.2, 4.2)	4.6 (4.1, 5.2)
Right of TH, started ART, % (95% CI)	31.0%	(29.7, 32.2)			
Left of TH, started ART, % (95% CI)	26.6%	(25.3, 27.8)			
GC#2 (500 cells/ul threshold); bandwidth (-1 year, +1 year)					
Patients, N in bandwidth (Total)	36,157	197,450	Cumulative deaths, N (% of all patients)	974 (2.7%)	1,268 (3.5%)
Right of threshold, N (%)	19,154	(53%)	ITT: Effect of guideline change, RD* (95% CI)	-0.2 (-0.9, 0.4)	-0.2 (-1.0, 0.5)
Left of threshold, N (%)	17,003	(47%)	Mortality on right of TH, % (95% CI)	2.6 (2.2, 3.0)	3.5 (3.0, 4.0)
ART uptake, RD* (95% CI)	3.9	(1.9, 5.9)	Mortality on left of TH, % (95% CI)	2.8 (2.3, 3.3)	3.7 (3.2, 4.3)
Right of TH, started ART, % (95% CI)	54.1%	(52.9, 55.6)			
Left of TH, started ART, % (95% CI)	50.4%	(48.9, 51.8)			
GC#3 (Universal test and treat); bandwidth (-2 year, +2 year)					
Patients, N in bandwidth (Total)	66,192	197,450	Cumulative deaths, N (% of all patients)	877 (1.3%)	1,135 (1.7%)
Right of threshold, N (%)	29,189	(44.1 %)	ITT: Effect of guideline change, RD* (95% CI)	-0.3 (-0.8, 0.2)	-0.1 (-0.6, 0.5)
Left of threshold, N (%)	37,003	(55.9 %)	Mortality on right of TH, % (95% CI)	2.2 (1.8, 2.6)	3.1 (2.7, 3.6)
ART uptake, RD* (95% CI)	2.9	(1.4, 4.5)	Mortality on left of TH, % (95% CI)	2.5 (2.2, 2.8)	3.2 (2.8, 3.5)
Right of TH, started ART, % (95% CI)	60.4%	(59.3, 61.6)			
Left of TH, started ART, % (95% CI)	57.5%	(56.5, 58.4)			

Notes: ART=antiretroviral therapy, CD4 = CD4+ T cell count per microlitre, GC= guideline change, N=number, %=percent, RD=risk difference, TH=threshold, *=displayed as a percentage; CI=confidence interval. Each column and section represent a separate linear regression discontinuity model, based on the changing ART eligibility criteria policy dates (grouped rows) and changing mortality assessment durations (24 and 36 months). The risk differences show the regression coefficient and heteroskedasticity-robust 95% confidence intervals (95% CI).

CHAPTER 2e

POPULATION-WIDE DIFFERENTIALS IN HIV SERVICE ACCESS AND OUTCOMES IN THE WESTERN CAPE FOR MEN AS COMPARED TO WOMEN, SOUTH AFRICA: 2008 TO 2018: A COHORT ANALYSIS

Associated publication(s)

Osler M, Cornell M, Ford N, Hilderbrand K, Goemaere E, Boulle A. Population-wide differentials in HIV service access and outcomes in the Western Cape for men as compared to women, South Africa: 2008 to 2018: a cohort analysis. J Int AIDS Soc. 2020 Jun;23 Suppl 2(Suppl 2):e25530. doi: 10.1002/jia2.25530. PMID: 32589367; PMCID: PMC7319137.

This paper is a copy of the version in PubMed Central® (PMC), to which consistent formatting of references, figures, tables, appendices, and supplementary material has been applied. The content remains substantively unchanged, with minor edits made in response to examiner comments.

Alignment with the thesis objective(s)

Poorer access and outcomes for men have been reported globally in several studies, with this concept gaining further attention when, in 2017, both the UNAIDS and the World Health Organization highlighted gender differences in HIV testing and outcomes within their respective reports. This study tries to address where in the HIV care and treatment cascade there are differences in outcome by gender and includes a look at pregnancy and TB service access and how they impact an individual's ART uptake and outcomes. A quantitative look at points within the care continuum may highlight where interventions should be considered to ensure health services are equally responsive to the needs of men and women.

Candidate's contribution

The candidate designed and planned the study. The candidate also oversaw the development and implementation of the monitoring system in the Western Cape, enabling the collection of clinical data. The candidate processed all data, performed the analyses, wrote the first draft of the manuscript, integrated comments from co-authors and submitted the manuscript for peer review.

Abstract

Introduction

Men living with HIV have inferior outcomes at various steps in the HIV care cascade. Few studies have systematically described population-level gender differences in access to care and mortality outcomes across the continuum of routine HIV care.

Methods

We analysed population-wide linked anonymised data, including vital registration linkage, for the Western Cape Province of South Africa. Temporal trends across antiretroviral therapy guideline eligibility periods were described by gender for disease-severity at presentation, ART access and mortality. The bandwidths used for all regressions were 100 CD4 count cells/µl on either side of the threshold The effectiveness of ART around each successive CD4 eligibility threshold was explored based on regression discontinuity analyses by gender.

Results

Adult men make up 49% of the Western Cape population and account for 37% of the HIV prevalence. Men contributed <35% of all CD4 counts over 10 years and presented with more advanced disease than women overall (CD4 counts <50 cells/µl increasing from 50% to 55% between 2008 and 2018). ART access was lower (adjusted hazard ratio [AHR] ranging from 0.73-0.76) and mortality after presentation (AHR 1.34-1.53), pre-ART (AHR 1.13-1.26) or after ART start (AHR 1.33-1.65) was higher in men across all ART eligibility periods. Being eligible for ART when eligibility was based on a CD4 count of 200 cells/µl resulted in a 2.0% RD (95%CI: 0.7-3.3) absolute risk reduction in 24-month mortality in women presenting with CD4 counts close to the threshold, but no difference in men.

Conclusions

Compared to women, men presented with more advanced disease, were less likely to initiate ART, had higher pre-ART and on-ART mortality, and benefited less from guideline-guided ART access. Our findings point to missed opportunities for improving access to and outcomes from interventions for men along the entire HIV cascade.

Introduction

South Africa has the largest antiretroviral therapy (ART) programmes in the world (98, 217). Coverage of those eligible for ART is improving year-on-year, but retention on ART is declining (153, 218). Improvements in mortality are slowing, and a large number of patients continue to present with advanced HIV disease in spite of the widespread access to ART (219). Identifying patients who are less likely to test, present to care, start ART and remain on effective ART, provides opportunities to adjust service delivery models to be more responsive to the needs of these patients.

A range of studies have shown that HIV-infected men in South Africa are less likely to access care than women, and present with more advanced disease (98, 107, 220). Across the region, men on ART have had higher mortality than women once accessing HIV care (160, 221).

Any exploration of differential access to care requires consideration of the changing eligibility criteria for ART access. While patient cohorts and randomized trials have demonstrated reduced morbidity and mortality risks in patients accessing ART at higher CD4 counts (170), the population-level impact of progressive expansion of ART availability through guideline changes is difficult to evaluate. There is even less data from high HIV-burden countries exploring the differential impacts of treatment guidelines by individual patient characteristics such as gender.

Regression discontinuity analysis provides an opportunity to explore differences in the impact of ART availability by gender, around the CD4+ T-lymphocyte (CD4) count eligibility criteria operative in different guideline eras, in a non-trial setting. Since the advent of public sector ART in SA in 2004, eligibility for treatment has incrementally expanded from <200 cells/µl to universal access in 2016.

The aim of this analysis is to describe in the Western Cape Province of South Africa, population-wide differences by gender in presentation with HIV, access to ART, mortality on ART, and the impact on mortality of ART availability around the successive CD4 count eligibility thresholds as guidelines evolved.

Methods

Setting and data sources

The Western Cape is one of nine provinces in South Africa, with a population of 6.8 million, an estimated 434,533 people with HIV and over 190,000 people on ART in 2015 (222). The vast majority of people living with HIV seek care in the public sector. ART was first available in pilot projects from 2001, and coverage was accelerated after 2004 when ART provision became national policy (99). CD4 count monitoring of all HIV positive patients has been provided since program

inception. In March 2013, CD4 count monitoring after one year on ART among virologically-suppressed and clinically-well patients with CD4 ≥200 cells/µl was no longer recommended.

Full details of the ART program evolution are described elsewhere (99, 151, 223). From 2004 to March 2010, an adult was eligible for ART with a CD4 cell count ≤200 cells/µL or a WHO stage IV illness. In April 2010, national guideline revisions increased ART eligibility to include a CD4 count of 350 cells/µL for pregnant women and those with active tuberculosis (TB) (188). In August 2011, eligibility was expanded to include all patients with a CD4 count <350 cells/µL (224). In April 2013, all TB patients and pregnant women were eligible regardless of their CD4 count (189). In January 2015, guidelines were changed again to expand eligibility to all patients with a CD4 ≤500 cells/µL (190). Finally, in September 2016, universal access was introduced, and all HIV infected people were eligible to start ART regardless of CD4 count as per WHO guidelines (217, 225). These changes for patients without other health conditions conferring ART eligibility are summarised into three CD4 count ART-eligibility eras in Table 1 and referenced throughout this paper.

All public-sector laboratory testing was done by the National Health Laboratory Service and province-wide digitised results were available from 2007 onwards. The province has successfully established a patient registration system which shares a unique health identifier and Patient Master Index (PMI) across both hospital and ambulatory services (152). This has facilitated the linkage of data from hospital, laboratory and pharmacy sources, as well as electronic disease registers such as those for HIV and tuberculosis (153). Information on deaths within the provincial HIV population seeking care was extracted from the National Population Register (NPR) (91), which classified deaths as natural or unnatural. The process of linking all data to the PMI is formalised through the Provincial Health Data Centre (191). All data provided for analyses are pre-anonymised but linkable based on a privacy-preserving random key.

The study was approved by the Western Cape Department of Health and the University of Cape Town Human Research Ethics Committee.

Study population

The study population consisted of all patients seeking HIV treatment and care in the Western Cape public-sector health services with a pre-ART CD4 count between January 2007 and January 2017. We excluded children and adolescents less than 16 years of age on the date of their pre-ART CD4 count, people without a CD4 test result prior to the ART start date, any record with a first CD4 specimen taken at hospital, anyone recorded as having an unnatural death and any patients with recorded TB or pregnancy indicated anytime between their first CD4 count result and their ART start date. We intentionally excluded patients tested in hospital, and those pregnant or with TB to focus

on patients with ambulatory-care CD4 counts who would be evaluated for ART eligibility based on CD4 count rather than co-morbidities or pregnancy status (Figure 1).

Study design and key variables

The study comprises a cohort analysis by gender of time to ART and time to death from natural causes. In addition, we undertook fuzzy regression discontinuity analysis of the impact of ART eligibility on mortality in each guideline era (179), around the operative CD4 count eligibility threshold. The regression discontinuity and survival analyses were restricted to patients with a South African identification (SA ID) number (40% of the total cohort), a requirement for linkage with data from the NPR (91).

ART eligibility was defined as having an initial CD4 count below the operative CD4 count threshold for the guideline era. First presentation with HIV was defined as the first ever CD4 count. ART access for the risk difference (RD) was defined as starting ART within six months of the initial CD4 count. Data from the NPR distinguish natural from non-natural causes. Mortality was defined as death from natural causes, and for the RD analysis within one and two years of the first presentation with HIV.

We included age, guideline era and CD4 count as baseline variables in adjusted models for the survival analyses of time to ART and time to death after presentation or ART initiation. We added one day to death dates if the patient was recorded as being dead on the date of entry into the analyses.

Statistical analysis

The baseline characteristics of the Western Cape HIV population and of those linkable to mortality data with a SA ID were described by gender with summary statistics (absolute number, proportions, medians and interquartile ranges (IQR)).

Time to ART and time to death were analysed from the date of the first CD4. Time to death for those on ART was analysed from their ART initiation date. We used Cox proportional hazards models to assess crude and adjusted associations between baseline characteristics and mortality. Results are presented as adjusted hazard ratios with 95% confidence intervals.

We applied a regression discontinuity design to look at the impact of changing eligibility criteria. (226). In each era we described the frequency distribution of those starting and not starting ART within 6-months. We then estimated the discontinuity at the threshold for both ART initiation (first-stage) and mortality (both 12 and 24-month, the intention-to-treat estimates) on a risk-difference scale. We used a linear regression of the outcome accounting for the slopes in the relationship between CD4 count and outcome pre- and post the discontinuity, allowing these slopes to differ

through interaction terms (176). As the outcome was binary, we also performed sensitivity analyses using a logistic regression with adjusted risk differences on the margins with comparable results. The bandwidths used for all regressions were 100 CD4 count cells/µl on either side of the threshold (214). The final set of analyses treated the eligibility-threshold as an instrumental variable (IV), and used standard linear IV methods to determine the complier average causal effect (CACE), considered the effect in those estimated to have started ART because of the eligibility criteria (215).

Data were analysed using STATA 14.2 (STATA Corporation).

Results

Men 15 years of age and older comprised 49% the population and 37% of the HIV prevalence of the Western Cape from 2008 through August 2016. In the total cohort, the proportion of men newly diagnosed with HIV (first ever CD4 cell count) out of all men projected to have HIV (HIV prevalence) was lower than women newly diagnosed with HIV by the health services, although more recently the gender distribution of first-ever CD4 counts has tracked population prevalence more closely. Over time men presented with more advanced HIV disease than women (50% to 55% of all CD4 counts <50 cells/µl were in men over the three time-eras). The increase in median CD4 at presentation was less among men than women (59 versus 95 cells/µl increase in CD4). After presentation, men were also less likely than women to initiate ART at some future time point (64 – 68% of newly diagnosed men versus 73-75% for women across all three time-eras) (Table 1).

Among HIV-positive individuals with a SA ID, the proportion of patients first ever presenting to HIV care across all eligibility eras was substantially lower among men than women (35% versus 65% in the last era) (Table 2). Compared with women, at first visit men were older (median age 35 years versus 29 years) and had a lower median CD4 count (307 cells versus 392 cells in the last eligibility era). Over time, access to care was greater in women than men (Median CD4 count increasing from 329 to 392 cells/µl versus 256 to 307). Men were also twice as likely as women to be co-infected with TB (11% versus 4% in total). Across all three eligibility eras, men were less likely to start ART than women. Overall, 67% of men and 74% of women with a recorded CD4 test result started ART.

Men were more likely to die regardless of whether they started ART (Table 3). After adjusting for age and CD4 count, men were 24% less likely to start ART in comparison to woman (adjusted hazard ratio [aHR] 0.76, 95%CI: 0.74-0.77) during the 200 cell/ul era and this remained stable over the successive eligibility eras. Men had higher mortality overall (aHR 1.34, 95% CI 1.27-1.42 in the 200 cell/ul threshold to aHR 1.53, 95% CI 1.39-1.69 at the 500 cell/ul threshold), higher mortality prior to ART (aHR 1.26, 95% CI 1.19-1.34 in the first era) and higher mortality on ART (aHR 1.41, 95% CI 1.28-1.55 in the first era).

Comparing the CD4 count distributions of those who do and do not start ART within 6 months of the first CD4 count (Figure 2a), a discontinuity at the operative eligibly threshold (red line) is clearly visible, reflected by the RD at the threshold (Figure 2b), and more pronounced in later eras. Restricting to compliers (those not treated above the threshold and those treated below the threshold) there is a clear mortality RD at the threshold in favour of those on ART, attenuating over successive eras (Figure 2c). This translates into a much smaller mortality RD at the threshold when considering everyone irrespective of ART access (intention-to-treat (ITT) representation, Figure 2d).

In the first two ART-eligibility guideline eras, eligible men and women presenting peri-threshold but below the threshold, had reduced mortality by 12 and 24 months after their first CD4 count compared to those above the threshold (Table 4), except for 24-month mortality in men in the first era. Fewer ineligible people started ART as the cut-off thresholds increased (33-20% ineligible men and 36-30% ineligible women initiated ART over the 3 guideline eras). A smaller proportion of eligible men accessed treatment in comparison with women (43% men to 49% women in the 200 cell/µl era and 48% men to 59% women in the 500 cell/µl era). Among ART-eligible patients presenting with first CD4 counts close to the cut-off thresholds, men had at least a 2-fold or greater increase in mortality compared to women. Among women with a first ever CD4 count close to the threshold in the 200 cell/ul era, there was an ITT mortality RD of -2.00% (95%CI: -3.29 – (-0.71)) in those eligible for ART peri-threshold. Men did not see the same benefits (ITT RD -0.07, 95% CI -2.20, 2.06). This pattern was repeated, though attenuated, in the 350 cells/µl era in woman, with the benefit in men increasing. The mortality reductions assuming perfect guideline compliance (CACE estimates) were as high as a 18.9% RD in 12-month mortality at the threshold in women in the first era, with the impact dropping over time to little effect in the last guideline era.

Discussion

Using clinical, laboratory, pharmaceutical and vital registry data linked at patient level for all people with HIV in the Western Cape, we analysed gender differences in the HIV cascade over the past decade. Men were less likely to present for HIV care than women, represented in this analysis by their first recorded CD4 count, and more likely to be diagnosed due to concurrent tuberculosis infection. In analyses limited to patients with SA IDs, across all three eligibility eras, men consistently had lower enrolment on ART and higher mortality across the entire cascade. Mortality reductions due to being eligible for ART were present in women but not men in the first guideline era.

Presenting with HIV and accessing HIV care

Late presentation has been cited as one of the main reasons for ongoing HIV-associated morbidity and for mortality after starting ART, especially in men (160, 219, 221). Although women surpassed

men in gains to accessing care at earlier stages of HIV disease over time, both genders presented earlier to HIV care over time. This trend in earlier ART access is validated by the gains in median CD4 counts for first presenters for both men and women.

Whereas our findings in the earlier periods concur with other studies which have found men less likely to access HIV care in similar settings (227, 228), we observed a narrowing of this gender differential in later periods of this study, approaching what would be expected based on HIV prevalence estimates. Men continued to present with lower CD4 counts. This may be partially explained by underlying biological differences in CD4 count trajectories (229). In addition, numerous studies have found that women, via reproductive health services, have more opportunities to test for HIV and therefore present earlier for care and treatment while not otherwise symptomatic (228, 230, 231). Recently scaled-up interventions that increase uptake of HIV testing and care by men, such as mobile community-based mobile testing units, may be contributing to the gains in access to HIV care seen in men in recent eligibility eras of this study (228, 232, 233). Changes may also be due to a saturation effect being reached in women earlier than in men, due to the higher proportion of women who already know their HIV status (222).

Antiretroviral therapy access

Men continue to have lower rates of ART enrolment after their first eligible CD4 count. Men, across all three time periods, were 25% less likely to start antiretroviral therapy and that estimation held relatively stable regardless of eligibility era. Poorer access for men to treatment has been widely noted (228, 234). This study provides strong evidence of the need for clinical service interventions specifically oriented to assisting men in accessing ART after initial presentation.

Mortality after initial CD4 count assessment

Men had increased pre-ART mortality compared to women, noting a narrowing of this difference over time. As men continue to present to HIV services with more advanced HIV disease (219), specific diagnostic interventions for co-morbidities associated with advanced HIV disease are needed, targeting men. These include a Lipoarabinomannan (LAM) antigen tests for TB and cryptococcosis antigen (CrAg) tests, which could be guided by immunodeficiency represented by CD4 count testing. Alternatively, in countries where routine CD4 counts are not done at baseline, interventions could be based on algorithms for advanced disease risk in which gender may play a role.

Mortality after ART initiation

Men continue to have inferior mortality outcomes on ART, shown by both the survival and regression discontinuity analyses in this study. Similar results have been widely published (107, 160,

234, 235) and deficits in life expectancy are largely related to HIV and TB (235), with men showing higher rates of TB co-infection in this study across all eligibility eras. Although similar or greater all-cause mortality differentials are observed even in those of similar ages who are HIV-uninfected (160), interventions targeting men, their retention in care, and the co-morbidities associated with their advanced disease at ART initiation, are warranted.

Impact of ART availability on mortality

Assessing the causal impact of ART on mortality is complicated by time-varying confounding in which sicker patients with higher mortality risk are also those most likely to get onto ART. Some observational cohort studies have addressed this through causal inference cohort approaches (236). The RD approach of exploring causal impact at the ART eligibility thresholds, as implemented in this study, has not been widely utilised due to the paucity of robust mortality data in high-burden HIV settings where eligibility guidelines based on CD4 count are strictly applied at scale. Our study was able to use linkages to explore the population-level impact of ART availability at these thresholds, integrating issues of access to ART and outcomes pre- and on-ART.

In broad terms the RD analyses demonstrated that ART access is profoundly linked to operative guidelines, in keeping with other recent RD analyses (237). All estimates confirmed the higher mortality in men at all CD4 counts in all eras on and off ART. The ITT causal estimates were modest due to small RDs at the threshold in ART access in the earliest era, or due to small RDs in mortality in those accessing or not accessing ART at the threshold in the later eras, in spite of a more discernible risk difference in ART access. The smaller RDs in ART access in the first era likely reflect patients with CD4 counts above the threshold started on ART due to symptoms or less rigid guideline application.

Women who started ART due to the guidelines and with CD4 counts close to the threshold of 200 cells/µl during this era were estimated to have a substantial reduction in 12 and 24-month mortality in keeping with other RD analyses exploring non-mortality outcomes (177), whereas the analysis could not substantiate a similar benefit in men. This could be due to the smaller number of events and associated uncertainty but could also be impacted on by the differences in treatment outcomes. In the subsequent era however, the attenuated morality gains appear similar in men than women. One possible speculative explanation could be that in the era when ART was only available to those with more advanced disease, the later presentation and inferior ART outcomes in men was more impactful. In contrast asymptomatic men and women starting ART in ambulatory care at the higher threshold may be better placed to benefit similarly.

Strengths and limitations

The population-wide linked dataset with mortality data from vital registration is a strength of this study. A potential weakness is that the study was restricted to those with vital registry linkage (45% of the cohort). However, in supplementary analysis we showed similarity in patients with and without available civil identifiers, suggesting that these results may be generalizable more broadly (Supplement table 1). A further limitation is that in the early era of this study, it is uncertain if CD4 counts were from first presentation to HIV services, as linked CD4 count data were only available from 2007 and some patients would have been in care prior to the first CD4 count available for the analysis. Finally, ineligible patients presenting just prior to guidelines may have benefited from re-assessment under different operative guidelines following the change, potentially attenuating the effect of the eligibility threshold.

Conclusions

Free ART services have been rapidly scaled-up in unprecedented magnitude globally, reducing HIV incidence and mortality. However, men do not seem to have benefited from these services as much as women. Exploring the HIV cascade over 10 years, men continued to present with more advanced disease overall, were less likely to initiate ART, were less impacted by guideline provisions and had inferior on-ART outcomes. Our findings point to missed opportunities for improving access to and outcomes from interventions for men along the entire HIV cascade.

Tables and Figures

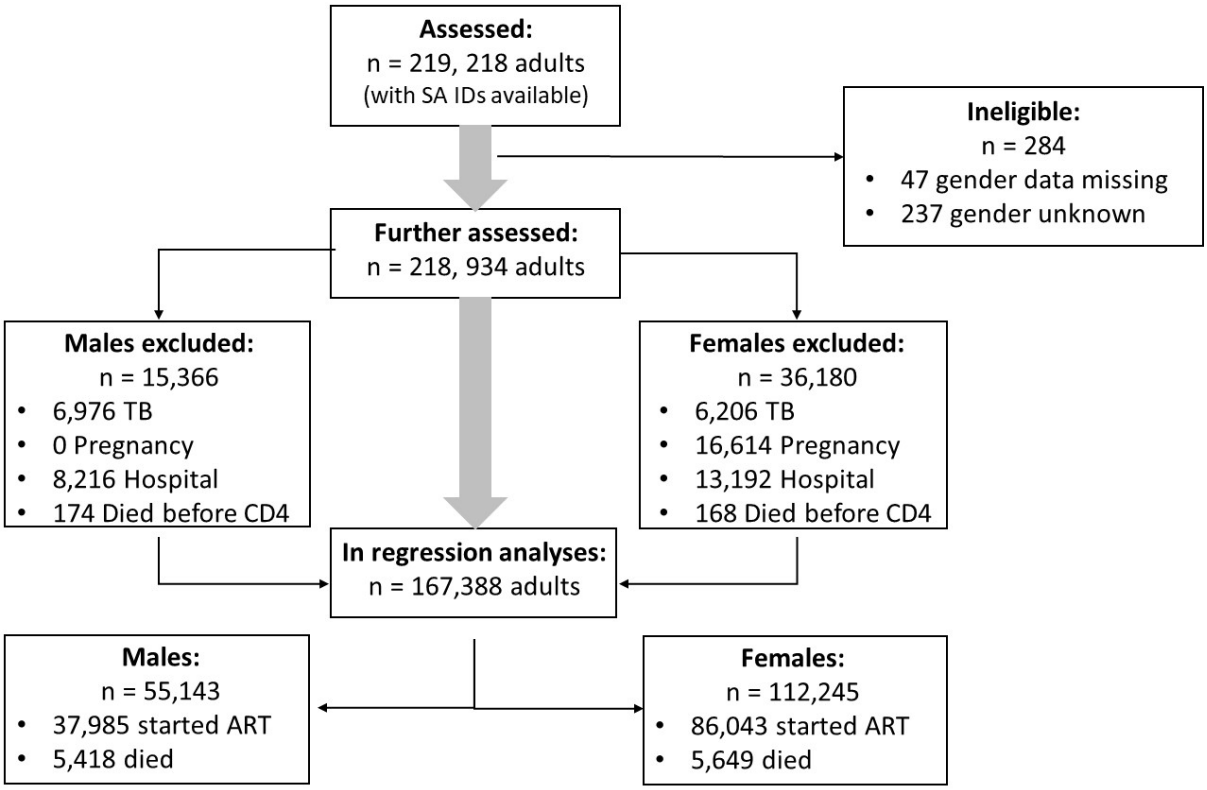


Figure 1: Patient flow chart describing the cohort of patients included in the regression and survival analyses

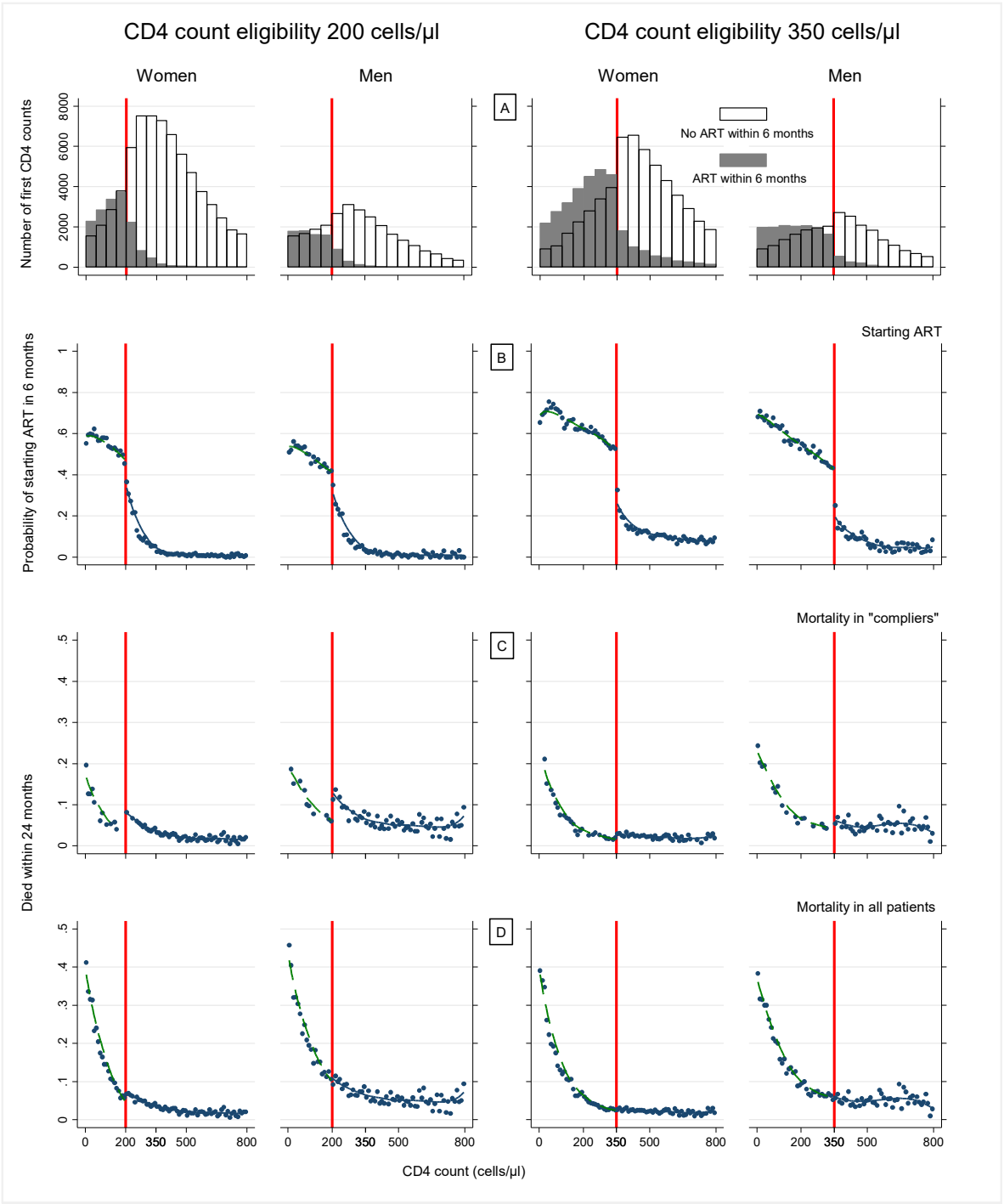


Figure 2: Impact of eligibility criteria thresholds on mortality within 24 months in men and women with a first-ever CD4 count recorded

A: Frequency distributions of first CD4 counts in those who did (shaded) and did not go on to initiative ART within 6 months of presentation, B: Probability of initiating ART within 6-months in 10-cell CD4 count bands, C: Mortality within 24 months by initial CD4 count, in those who did (below the threshold) and did not (above the threshold) start ART within six months; D: Mortality within 24 months by initial CD4 count

Table 1: Western Cape HIV statistics and CD4 count results

Enrolment cohorts	1 Jan 2008 - 31 Jul 2011			1 Aug 2011 - 31 Dec 2014			1 Jan 2015 - 31 Aug 2016		
CD4 count eligibility threshold	<200 cells/µl			<350 cells/µl			<500 cells/µl		
Gender	Male, N (%)	Female, N(%)	Total	Male, N (%)	Female, N(%)	Total	Male, N (%)	Female, N(%)	Total
Western Cape population(>14)[1]	2,039,580 (48)	2,169,400 (52)	**4,208,980**	2,157,870 (49)	2,288,600 (51)	**4,446,470**	2,298,600 (49)	2,439,760 (51)	**4,738,360**
Annual HIV incidence (>14) [1]	9,219 (39)	14,180 (61)	**23,399**	8,491 (40)	12,882 (60)	**21,373**	7,874 (40)	11,826 (60)	**19,700**
Annual HIV prevalence (>14) [1]	103,334 (37)	173,366 (63)	**276,700**	123,565 (37)	210,192 (63)	**333,757**	143,662 (37)	246,777 (63)	**390,439**
All CD4 counts	231,939 (32)	483,765 (68)	**715,704**	287,016 (33)	595,723 (67)	**882,739**	219,388 (34)	417,687 (66)	**637,075**
First ever CD4 count, per person	58,314 (35)	106,927 (65)	**165,241**	71,253 (35)	130,576 (65)	**201,829**	72,524 (37)	124,984 (63)	**197,508**
First ever CD4 count categories†									
0-49	5,962 (10)	6,033 (6)	**11,995**	5,337 (7)	4,803 (4)	**10,140**	5,450 (8)	4,381 (4)	**9,831**
50-99	5,418 (9)	6,112 (6)	**11,530**	4,918 (7)	4,821 (4)	**9,739**	4,905 (7)	4,619 (4)	**9,524**
100-199	11,052 (19)	15,864 (15)	**26,916**	10,694 (15)	12,939 (10)	**23,633**	11,028 (15)	12,178 (10)	**23,206**
200-349	15,772 (27)	29,255 (27)	**45,027**	18,495 (26)	29,700 (23)	**48,195**	18,711 (26)	26,652 (21)	**45,363**
350-500	9,819 (17)	22,941 (21)	**32,760**	14,867 (21)	31,355 (24)	**46,222**	15,017 (21)	28,962 (23)	**43,979**
>500	10,291 (18)	26,722 (25)	**37,013**	16,942 (24)	46,978 (36)	**63,920**	17,413 (24)	48,192 (39)	**65,605**
Median CD4 (IQR)	259 (129, 421)	329 (193, 500)	**305**	319 (172, 489)	409 (257, 410)	**377**	318 (171, 491)	424 (261, 612)	**384**
New ART enrolment† N (%)	33,529 (57)	62,021 (58)	**95,550**	46,737 (66)	93,585 (72)	**140,322**	44,944 (62)	87,839 (70)	**132,783**

[1] Thembisa Model outputs version 4.2 (population, HIV incidence and prevalence estimates are for June 2009, June 2012, June 2015 and June 2018)(238); proportions in the first five population level rows used total of males and females as denominator, †CD4 count categories and ART enrolment proportions have the first ever CD4 count as the denominator.

Table 2: Baseline characteristics stratified by gender, of those with a recorded South African identification

Enrolment cohorts		1 Jan 2008 - 31 Jul 2011			1 Aug 2011 - 31 Dec 2014			1 Jan 2015 - 31 Aug 2016		
CD4 count eligibility threshold		<200 cells/µl			<350 cells/µl			<500 cells/µl		
Gender		Male	Female	total	Male	Female	Total	Male	Female	Total
First CD4 count presentation		29,028 (30)	68,673 (70)	**97,701**	29,055 (34)	56,756 (66)	**85,811**	12,528 (35)	22,894 (65)	**35,422**
First CD4 count, age categories										
16 to <25	N(%)	2,553 (9)	18,785 (27)	**21,338**	2,806 (10)	15,694 (28)	**18,500**	1,324 (11)	6,589 (29)	**7,913**
25 to <35	N(%)	12,062 (42)	32,152 (47)	**44,214**	11,513 (40)	24,219 (43)	**35,732**	4,966 (40)	9,201 (40)	**14,167**
35 to <45	N(%)	9,332 (32)	12,367 (18)	**21,699**	9,260 (32)	10,777 (19)	**20,037**	3,741 (30)	4,139 (18)	**7,880**
>45	N(%)	5,081 (18)	5,369 (8)	**10,450**	5,476 (19)	6,066 (11)	**11,542**	2,497 (20)	2,965 (13)	**5,462**
median age		35 (29, 42)	29 (25, 35)	**31**	35 (29, 42)	29 (24, 37)	**31**	35 (29, 43)	29 (24, 38)	**31**
First CD4 count result										
0-49	N(%)	2,658 (9)	2,999 (4)	**5,657**	2,274 (8)	2,198 (4)	**4,472**	667 (5)	706 (3)	**1,373**
50-99	N(%)	2,822 (10)	3,924 (6)	**6,746**	2,309 (8)	2,584 (5)	**4,893**	837 (7)	852 (4)	**1,689**
100-199	N(%)	5,782 (20)	10,985 (16)	**16,767**	5,163 (18)	7,085 (12)	**12,248**	2,199 (18)	2,636 (12)	**4,835**
200-349	N(%)	8,066 (28)	18,764 (27)	**26,830**	7,881 (27)	14,031 (25)	**21,912**	3,531 (28)	5,568 (24)	**9,099**
350-500	N(%)	5,045 (17)	15,153 (22)	**20,198**	5,613 (19)	13,044 (23)	**18,657**	2,540 (20)	5,425 (24)	**7,965**
>500	N(%)	4,655 (16)	16,848 (25)	**21,503**	5,815 (20)	17,814 (31)	**23,629**	2,754 (22)	7,707 (34)	**10,461**
median CD4 count, (IQR)		256 (132, 410)	329 (194, 495)	**307**	289 (153, 453)	376 (228, 554)	**346**	307 (175, 473)	392 (245, 572)	**361**
Tuberculosis	N(%)	3,756 (13)	3,640 (5)	**7,396**	3,220 (11)	2,566 (5)	**5,786**	439 (4)	356 (2)	**795**
Pregnant	N(%)	NA	12,265 (18)	**12,265**	NA	4,364 (8)	**4,364**	NA	550 (2)	**550**
First CD4 count, location type										
Hospital	N(%)	4,153 (14)	8,050 (12)	**12,203**	4,050 (14)	6,487 (11)	**10,537**	1,587 (13)	2,128 (9)	**3,715**
Primary Health Care	N(%)	24,875 (86)	60,623 (88)	**85,498**	25,005 (86)	50,269 (89)	**75,274**	10,941 (87)	20,766 (91)	**31,707**
ART starts ever	N(%)	19,680 (68)	51,167 (75)	**70,847**	19,829 (68)	42,632 (75)	**62,461**	8,035 (64)	16,691 (73)	**24,726**

Please note: proportions are of total unique CD4 counts in time period, stratified by gender. Jan-January; Jul-July; Aug-August; Dec-December.

Table 3: Male versus female mortality, baseline characteristics and adjusted hazard ratios.

Analysis	Threshold time period	Hazard Ratio (HR) (95% CI)*	Number (% female)	Median CD4 (M:F)	Median Age (M:F)	Started ART N (%)
Time to ART; starting ART HR	200 cells/ul	0.76 (0.74, 0.77)	68,576 (68)	280:339	34:29	31,395 (46)
	350 cells/ul	0.73 (0.71, 0.74)	65,626 (68)	309:388	34:29	40,192 (61)
	500 cells/ul	0.74 (0.72, 0.76)	30,088 (69)	310:397	34:29	21,080 (70)
Analysis	**Threshold time period**	**Hazard Ratio (HR) (95% CI)***	**Number (% female)**	**Median CD4 (M:F)**	**Median Age (M:F)**	**Deaths N (%)**
Time to death, pre-ART; mortality HR	200 cells/ul	1.26 (1.19, 1.34)	68,576 (68)	280:339	34:29	5,189 (8)
	350 cells/ul	1.24 (1.15, 1.34)	65,626 (68)	309:388	34:29	2,869 (4)
	500 cells/ul	1.13 (0.97, 1.31)	30,088 (69)	310:397	34:29	751 (2)
Time to death on ART; mortality HR	200 cells/ul	1.41 (1.28, 1.55)	51,491 (70)	252:318	35:29	1,814 (4)
	350 cells/ul	1.33 (1.21, 1.45)	49,854 (69)	271:360	35:29	2,071 (4)
	500 cells/ul	1.65 (1.46, 1.88)	22,683 (68)	275:368	35:29	1,024 (5)
Time to death, irrespective of ART; mortality HR	200 cells/ul	1.34 (1.27, 1.42)	68,789 (68)	280:339	34:29	5,126 (7)
	350 cells/ul	1.43 (1.34, 1.52)	66,952 (67)	309:388	34:29	4,162 (6)
	500 cells/ul	1.53 (1.39, 1.69)	31,631 (66)	310:397	34:29	1,763 (6)

(HR) Hazard ratio; (ART) antiretroviral therapy; (M:F) male versus female. Adjusted for baseline CD4 count and age categories. Hazard ratio unit is 1 month. The end time is 3 years.

Table 4: Intention to treat effects of ART eligibility on ART initiation and mortality (year bandwidths)

Men Women

Outcome	Males: ART initiation by 6 months	Males: Mortality by 12 months	Males: Mortality by 24 months	Females: ART initiation by 6 months	Females: Mortality by 12 months	Females: Mortality by 24 months
200 cells/µl threshold	**Bandwidth (100, 300)**			**Bandwidth (100, 300)**		
Number	10,448	10,448	10,448	19,712	19,712	19,712
Number died, cumulative		548	933		729	1,185
Eligible for ART, (%) ^†	42.94%^	4.17%†	8.29%†	47.91%^	1.87%†	3.90%†
Not eligible for ART, (%)^†	33.36%^	4.80%†	8.36%†	36.41%^	4.04%†	5.90%†
ART, RD (95% CI)	9.58 (6.05, 13.11)			11.51 (8.88, 14.14)		
CACE, RD (95% CI)		-6.59 (-23.96, 10.78)	-0.75 (-22.99, 21.49)		-18.90 (-28.37, -9.43)	-17.38 (-28.83, -5.88)
ITT, RD (95% CI)		-0.63 (-2.30, 1.03)	-0.07 (-2.20, 2.06)		-2.18 (-3.19, -1.16)	-2.00 (-3.29, -0.71)
350 cells/µl threshold	**Bandwidth (250, 450)**			**Bandwidth (250, 450)**		
Number	7,721	7,721	7,721	15,141	15,141	15,141
Number died		190	345		194	355
Eligible for ART, (%) ^†	41.18%^	1.98%†	3.72%†	52.21%	0.95%†	1.86%†
Not eligible for ART, (%)^†	18.23%^	2.73%†	5.24%†	27.17%^	1.36%†	2.47%†
ART, RD (95% CI)	22.96 (19.15, 26.77)			25.04 (22.12, 27.95)		
CACE, RD (95% CI)		-3.25 (-9.23, 2.74)	-6.64 (-14.62, 1.35)		-1.66 (-4.46, 1.13)	- 2.44 (-6.25, 1.37)
ITT, RD (95% CI)		-0.75 (-2.12, 0.63)	-1.52 (-3.35, 0.30)		-0.42 (-1.12, 0.28)	-0.61 (-1.56, 0.34)
500 cells/µl threshold	**Bandwidth (400, 600)**			**Bandwidth (400, 600)**		
Number	2,346	2,346	2,346	5,620	5,620	5,620
Number died		188	302		162	243
Eligible for ART, (%) ^†	47.54%^	3.65%†	5.12%†	58.61%^	0.76%†	1.07%†
Not eligible for ART, (%)^†	20.00%^	4.07%†	4.67%†	30.49%^	0.44%†	1.02%†
ART, RD (95% CI)	27.54 (20.27, 34.80)			28.12 (23.12, 33.11)		
CACE, RD (95% CI)		-1.51 (-11.76, 8.73)	1.62 (-10.46, 13.71)		1.18 (-2.16, 4.47)	0.16 (-4.21, 4.53)
ITT, RD (95% CI)		-0.41 (-3.23, 2.40)	0.45 (-2.89, 3.78)		0.32 (-0.61, 1.26)	0.04 (-1.18, 1.27)

^ART uptake, †Predicted outcome, %proportion, ART=antiretroviral therapy, RD=risk difference, CACE=complier average causal effect, ITT=intention to treat. Each section under the bold sub-titled rows reports the results of separate analyses done at mutually exclusive dates of guideline changes. The risk differences show the regression coefficient and heteroskedasticity-robust 95% confidence intervals (95% CI). Each column represents a separate linear regression discontinuity model.

CHAPTER 2f

EXPLORING THE CYCLICAL NATURE OF SERVICE ATTENDANCE AND ART INTERRUPTIONS ON MORTALITY IN THE WESTERN CAPE, SOUTH AFRICA, 2008 TO 2020

Manuscript

This study is prepared in manuscript format but has not yet been submitted for publication.

Alignment with thesis objective(s)

Managing HIV well, means taking treatment for life. However, treatment interruptions and becoming lost to the services continues to be reported as a major determinant of poor outcomes on ART globally. Digital visit data linked to death registry data has proven challenging in resource limited settings, making it difficult to get an in-depth understanding of the cyclic nature of interruptions, the frequency, and the impact of longer treatment interruptions (4 months+) on mortality.

Using a cohort design based on a flexible semi-parametric survival analysis, and using a population-wide dataset of patient-level longitudinal data, this paper focuses on ARV treatment interruptions and how they impact outcomes after 5 years on ART. This study's secondary objective examines the temporal treatment interruption patterns and frequency of interruptions over a decade of free public sector ART provision.

Candidate's contribution

The candidate designed the study based on the topical questions regarding treatment interruptions. The candidate helped develop and support the clinical monitoring system in the Western Cape, enabling the collection of the clinical data. The candidate processed the linked data, performed the analyses, wrote the manuscript draft.

Abstract

Introduction

An important challenge in realising the full benefits of ART remains the phenomenon of patients cycling in and out of treatment services. The measurement of interruptions and the impact on overall mortality is not well quantified, partly due to unlinked health information systems and a lack of digital pharmacy data. A better understanding of treatment interruption patterns and impact could inform interventions to improve ART retention and outcomes.

Methods

We considered associations with mortality in a cohort-designed survival analysis with restricted cubic splines of adults (>15 years old) attending ART services, focussing specifically on interruptions as a time-varying covariate. A visit interruption was defined as a 6-month+ gap between ART visits, equating to a 4-month+ treatment interruption. The models were stratified by sex to determine if baseline and time-varying risk factors were homogenous across men and women. Additional Cox models considered prior interruptions as a risk for additional interruptions.

Results

This study included 261,625 people initiating ART in the Western Cape between 2008 and 2018. Over half (57%) interrupted ART treatment at least once, with a median time between ART initiation and the first interruption of 307 days (IQR 117-794). People with one treatment interruption were 27% (aHR 95%CI: 1.21-1.33) more at risk of death than those with no interruptions. Having 4 or more interruptions led to a 3-fold increased risk of death (aHR 3.09 95%CI: 2.79-3.41). Post-model visualisations show mortality rates for men due to interruptions peaking higher and earlier than women, with both converging to similar rates by 10 years on ART.

Conclusions

Over half of people interrupted ART care at least once, with the risk of mortality increasing with the increasing number of interruptions. People out of care and returning to care after interrupting treatment should be considered at high risk for AHD and death. Indicators which measure cyclic interruptions are needed to focus attention on the need for programmes to support retention and reengagement in care.

Introduction

Antiretroviral therapy prevents HIV transmission, and HIV-related morbidity and mortality in individuals, as well as viral burden at a population level. A key challenge to realising the full benefits of ART remains the phenomenon of patients cycling in and out of care, incurring interruptions in treatment. the characteristics and impact of interruptions are not currently well described in resource-limited settings (239, 240, 241, 242), partly due to unlinked health information systems and a lack of digital pharmacy data (243, 244, 245, 246). A better understanding of interruption patterns and mortality risk may enable targeted interventions to minimize their occurrence.

Retention in care is commonly measured at a single point in time, creating average estimates for population level retention, losses from care and death (247). Based on such measures, the published percentages of patients LTF from HIV care range between 19% to 54% with up to 46% to 73% of people reported as lost to follow-up (LTF), returning to care after varying lengths of time (242, 248, 249, 250, 251, 252, 253). As such, interruptions in treatment and care, as opposed to LTF, more accurately reflect the cyclical nature of service attendance.

The ART service scale-up has been highly effective at initiating the sickest people on treatment, but as current ART is for life, maintaining consistent long-term adherence to medication is proving difficult. Whereas historically, advanced HIV disease (AHD) – defined in adults as having a CD4 cell count <200 cells/mm^3 – has been understood as a challenge among individuals diagnosed late in their HIV disease progression, increasingly, programmes report that the greater proportion of people with advanced HIV disease are ART experienced, having started ART and subsequently interrupted treatment (219). Treatment interruptions are associated with higher risk of death and opportunistic infections, declines in CD4 cell counts, and increases in viral loads (248, 253). Neurocognitive impairment, lower quality of life, and suboptimal immune recovery have been reported after resuming treatment (254). Periods of interruption can also contribute to the development of drug resistance and the need to transition to more expensive regimens (255).

Using routinely collected data from the Western Cape, South Africa, we describe the pattern and impact on mortality of single and repeated treatment interruptions.

Methods

Study population and data sources

We performed a province-wide analysis of all patients aged 15 years or older who initiated ART in the public sector of the Western Cape, South Africa between January 2008 and 2018. Interruptions and outcomes were followed to 31 June 2020. Patient eligibility criteria for study inclusion included an ART initiation date (existing or calculated), a birthdate, sex, manually captured ART visit data

(versus automatically populated visit attributes), and a South African ID recorded in one of the routine health information systems for monitoring HIV care. Patients whose first 5 or more digitally recorded ART visits were consistent with back-capture protocol for the quick digitisation of paper-registers (automated insertion of assumed visits on the same numeric day of the month, each month) were excluded, as treatment and care interruptions (non-attendance) during the time of back capture were not able to be ascertained.

Exposures and outcomes

A causal diagram was drawn to consider which variables were most likely moderators and which were in the causal pathway. We used the DAGitty software (256) to create a directed acyclic graph (DAG) to identify whether to adjust for the following demographics while looking for the impact of interruptions on mortality for all who started ART: year of starting ART, age at the start of ART, sex, baseline CD4 cell count, TB diagnosis prior to starting ART and pregnancy or TB co-infection at ART initiation (Supplemental Figure 1). Age at ART initiation, baseline CD4 cell count and year starting ART were all categorised into a priori categories, with an additional category coded to capture missing measures.

Viral load results are a mediator in the path between treatment interruptions and mortality (Supplemental Figure 1). Viral loads and health care visits gaps are both proxies for treatment interruptions; however, health care visits gaps are a better tool for enabling proactive interventions to improve patient outcomes. This is in part due to viral load tests only being required once a year per national guidelines and only a proportion (~75%) of viral load specimens were taken in the correct window of time and had the results appropriately recorded in the information system (153).

For the main analysis, an interruption was marked by a gap of six months or longer (6m+) between health care facility visits. As per ART protocol during the study, patients stable on ART were given two months of medication at each visit, making a 6m+ gap between facility visits equating to a 4-month+ treatment interruption. The date of interruption was assigned on the date of ascertainment, six months after the last visit, six months after the last visit, regardless of whether the length of the interruption extended beyond the six months.

People dying on the day they started ART were given a date of death equal to their ART initiation date plus one day; people dying during the study were given a visit date on the date of death to force ascertainment of a possible interruption prior to death. People who became lost to care and never returned were assumed to be alive (due to the 96% completion rate of the death registry (212)) and given a visit date at the end of the study (30th June 2020) so that their survival and interruption in care would be included in the analyses. Patient records without an ART start date

recorded but with viral load results, indicating high confidence of the patient being on ART, were given a proxy ART start date as 4 months prior to the first ever viral load date.

Baseline CD4 cell counts were included if measured between one year before and 15 days after starting ART. Where there were multiple counts prior to ART, the date of the closest CD4 cell count prior to commencement was flagged for the analyses.

Statistical Analysis

All data processing and analyses were conducted using StataCorp 16.1 and 17 (College Station, Texas). For processing of the data, we merged clinical assessment tables with episode, lab, pharmacy, demographic and death registry tables using an anonymised unique patient number provided by the Western Cape provincial data health centre (191). Time zero was the date of ART initiation. Measures of engagement included clinical assessment visits, emergency care visits, CD4 test dates and results and pharmacy dispensing dates. Patients were not censored at the time of their last LTF but remained in the data set until the end of the study or until the date of their death.

Baseline characteristics were described using counts, proportions, medians, and interquartile ranges. These were explored using Pearson's Chi-Squared and Wilcoxon rank-sum tests.

We performed long rank tests of equality for categorical variables and Cox tests of equality for continuous variables (181). Kaplan-Meier estimates were used to look at the shape of the survival function and to illustrate time to event graphs for crude associations with mortality (hazard ratios). Interruptions were summed per patient over time. Heat plots were computed to illustrate the summed number of interruptions per patient based by year of ART start and duration on ART.

Visually, the log-log survival curve and Schoenfeld residual plots illustrated the interruptions variable violated the proportional hazard assumption. Because of this violation and to consider repetitive interruptions longitudinally, we used Royston-Parmar flexible parametric survival regressions to check for interactions and explore interruptions as a time-varying covariate. Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) were estimated for each model using restricted cubic splines to decide on the most ideal number of spline knots for the overall model and for the time-varying covariate (257). Additionally, we stratified based on sex to determine if interruptions and baseline risk factors were homogenous across the categories when comparing men and women.

We elected to display the full model hazard ratio (HR) estimates for the interruption variable, which was estimated flexibly by duration on ART, at 5 years after initiating ART alongside the hazard ratio

estimates of the other variables measured at baseline. Sensitivity analyses were performed for 3-month clinical visit gaps (1-month treatment interruptions on average).

All data were received as de-identified data and stored on encrypted drives. The study was approved by the University of Cape Town Health Research Ethics Committee [#421/2016] and research permission was received from the Western Cape Government Department of Health.

Results

A total of 284,858 individuals starting ART between 2008 and 2018 were included in this study. Of these 23,025 (8.1%) were excluded based on missing date of birth, sex, or the inability to ascertain interruptions due to initial back-capture from paper-based registers. Of the remaining 261,625, over 63% (165,574) were in care at the end of the study, encompassing 1,492,352 person-years of follow-up. Seven percent (18,430) of the individuals in the study died prior to the closing date. Most deaths (7,680 (98.1%) in the group with one or more treatment interruptions occurred beyond the first year on ART; while the majority of deaths in the non-interrupter group (6,004 (56.7%)) occurred in the first year on ART, with (4,594 (43.3%) occurring in the first six months)(Figure 1). Among individuals who could not be linked to the death registry due to lack of an SA ID number (198,769; 43%), there was a larger proportion of people with treatment interruptions and a higher proportion of men (Supplementary table 1).

A total of 148,141 (56.6%) people interrupted ART care at least once for six months or longer (Table 1), resulting in a 4 months or longer treatment interruption. Those who interrupted ART tended to have initiated in earlier years and a younger age compared to those who never had a 6m+ interruption. The median time to the first ART interruption was 331 days (IQR, 123-855) for patients with only one ART interruption recorded during the study period, for patients with two interruptions, the median time to first interruption was 199 days (IQR, 39-521), for patients with three and four interruptions, their median time to first interruption was 177 (IQR, 45-439) and 162 days (IQR, 45-337) respectfully (Table 1).

Interruptions were aggregated per individual over time. A heat map (Figure 2) was used to illustrate the average number of interruptions per year and per duration on ART. According to average numbers, interruptions do not seem to be changing in people initiating ART in more recent years, but rather similar patterns can be seen year-on-year when stratified by duration on ART. In the cohort that remained alive during the study period, the average number of interruptions just surpassed 1 after 4 years on ART, compared to 3 years on ART in the cohort that died during the study.

The univariable time to death graphs (Figure 3) show stronger trends of death among people with more treatment interruptions, men, people with lower baseline CD4 cell counts, older age and with multiple episodes of TB prior to starting ART. Although there is a time-lag from starting ART to accumulation of interruptions, each successive interruption results in a more rapid rise in mortality than the previous.

In multivariable analysis, there are strong trends of increasing hazard ratios for interruptions at five years on ART (Table 2). Those with one 6-month interruption were 27% (aHR 1.27; 1.21-1.33) more at risk of death than those who have not interrupted treatment and those with 4 or more interruptions were at a 3-fold (aHR 3.09; 2.79-3.41) increased risk of death. Men, older patients, those with lower CD4 cell counts and people starting in earlier years of the ART service were all at increased risk. Pregnancy at the start of ART was found to be protective (aHR 0.64; 0.58 – 0.69) while people with TB co-infection at ART initiation (aHR 1.72; 1.67-1.78) were at higher risk of death, as were those with past episodes of TB: 1.78 (1.91-1.85) for 1 episode to 3.53 (2.93-4.27) for 3 or more episodes. Sensitivity analysis with interruptions between health facility visits of 3 months (or longer) showed similar trends for all baseline variables in risk for death as the 6-month (or longer) interruption regression models. When stratifying the regression models by sex, the effect size for all baseline variables and time-varying interruptions were greater for women than men.

Post model mortality rate and hazard ratio visualisations demonstrate the delay in time required to register each consecutive increase in interruptions as well as the increased risk of death per increase in number of interruptions (Figure 4). The models also show a non-multiplicative effect per successive interruption but with similar patterns displaying a fairly steep rise to a peak mortality and then risk declining slowly for up to 12 years after starting ART. The mortality rates per 1000 patient years for men peak more rapidly and with higher peak incidence than in women for all interruption categories, declining thereafter to similar levels as women by 12 years after ART initiation. Hazard ratios for each successive interruption in men are lower than in women in spite of higher mortality rates for each group, due to the higher mortality rate in men in the comparison group with no interruptions.

Discussion

What we found

Patterns for and frequency of interruptions in a cohort of adults on ART in the Western Cape have remained similar over the 10 years of follow-up. We have estimated the impact of serial interruptions on mortality, with increased frequency strongly associated with increased hazard of death. More than half the people who initiated ART interrupted care for at least 6 months (resulting

in a treatment interruption of at least 4 months), increasing their risk of death by a third in comparison to people with no interruptions, while more than one interruption doubles the risk of death. Gender disparities in on-ART mortality are also reflected in mortality differences following treatment interruptions, especially in the first few years on ART.

Interruption Patterns and risk factors

Previous studies from well-resourced settings suggest interruption patterns are changing over time, with less interruptions within the first year of ART in more recent years (249); however, we did not pick up on similar patterns within the ART cohort in the Western Cape. The heat maps showed similar interruption averages per year and duration on ART over time, with an average of 1 interruption by 3 years. However, our primary analyses looked at treatment interruptions of 4 months or longer (6-month clinical visit gaps). It is possible that analysing shorter interruptions might provide a more precise account of changing patterns within the first year, given a more granular number of interruptions can be accounted for.

Concern has been expressed that earlier ART initiation could lead to an increased risk of treatment interruptions and the development of multidrug resistance as people would initiate ART in a healthier state and not realise the importance of adherence to ART on their health (258). More recent studies have also found that higher CD4 counts (>350 cells/µL) are a risk factor for ART interruptions (242, 247, 249). Reassuringly, that our study did not find a strong summative temporal trend in interruptions after considering duration on ART and multiple interruptions over time in the same individuals.

Interruptions are a valuable health service hook to improve outcomes

Treatment interruptions are not unique to South African cohorts and are recurrent events among ART patients locally and globally (145, 218, 248, 249, 251, 252, 259, 260), with each interruption conferring additional mortality risk. Cycling in and out of care, which inherently leads to interruptions in treatment, undermines the potential ability of antiretroviral drugs to mitigate morbidity, mortality and reduce HIV transmission at a population level (4, 240, 248).

A study carried out among hospitalised HIV patients in South Africa found that people who self-reported missing previous primary HIV care appointments were 30% more likely to be readmitted to hospital or die (RR 1.3, 95%CI: 1.0 - 1.8) compared to those who self-reported not missing appointments (261).

In this study, over half of people on ART in the Western Cape interrupted treatment at least once for 4 months or longer, increasing their risk of AHD and death. Patients with multiple interruptions were

likely to begin their first interruption within the first two hundred days on ART, marking people with breaks in treatment, especially those within the first year of ART, as being at high risk for further interruptions and adverse clinical outcomes.

Mortality risk for men versus women due to interruptions

Another study from South Africa found higher mortality for men in the first few years on ART in comparison to women; differences in age-standardized mortality still persisting after several years on ART were explained by the higher mortality for men in the general population (160, 262). Late presentation to ART with more advanced HIV disease, initiating ART at older ages, and higher LTF rates have been cited as reasons for higher mortality in men during the earlier years on ART (107, 219, 220). The current study found similar associations with a higher hazard ratio for mortality in men in the full model and higher mortality rates for men per interruption (per person years) in the stratified models. The higher HR effect of interruption in women than men could in part be a dilution effect due to the higher overall risk of death in men at baseline and including during the early period prior to any interruptions.

Interruption measurement definitions and proxies

Adherence is inherently difficult to measure, and proxies are used including pill counts, months of medication prescribed, and gaps in visit attendance. In this study we used 3+ and 6+ month gaps between ART service visits, as markers for 1+ and 4+ months of treatment interruption, given the majority of patients are dispensed two months of treatment (263, 264, 265). Exceptions to 2 monthly dispensing schedule include prescribing 1 month of treatment to newly enrolled ART patients and, more recently, dispensing 4 months of treatment to stable patients during the December holidays. Digitised pharmacy data triangulated with clinical data is critical to improving our understanding of the impact of shorter interruptions and the cyclic nature of the ART cascade.

Strengths and limitations

Strengths of this study include the analyses of linked public sector health data from the entire province (191). Together with linking the province-wide clinical dataset to the death registry data, which in South Africa was determined to be 96% complete in 2017 (212), the dataset provides comprehensive and accurate measures for death, facility transfers and numbers lost to care. As we could accurately ascertain the vital status of those lost to care that never returned during the study time, we did not censor them in the analysis until the study end date, counting them as having one interruption (at the 3 or 6-month mark after their last visit). Unfortunately, 43.2% of the clinical patient records had to be excluded due to lack of an SA ID needed to link to the death registry data. Records not linked were similar in baseline characteristics to the linked dataset but contained a

larger proportion of interrupters. but contained a larger proportion of interrupters. This is most likely due to the inability to distinguish between deaths and interrupters in the unlinked dataset as well as some migrant workers such as seasonal fruit pickers arriving in the province for a short period of time before moving to other provinces. Whereas the use of a missing category for missing CD4 count data at baseline could have created a heterogenous group and in many analyses would best be approached through multiple imputation, the health service significance of not having a baseline CD4 count was felt to be an important attribute to explore.

Conclusion

Whereas many analyses have included treatment interruptions as a risk factor for mortality in patients on ART, few have attempted to quantify the impact of multiple interruptions. In addition to patients currently lost to care, those who have returned to care after a previous interruption should be prioritized for retention support given the increasing risk of death associated with subsequent interruptions. Multifaceted approaches to retain people in continuous care and encourage interrupters back into care are important areas of research needing more focus and investment and go hand-in-hand with longer prescription durations for those who are established on treatment and differentiated models of care. Community support groups, tracing and support to return back to care for treatment interrupters – including “welcome back” clinics for returning interrupters – are all interventions proven to work (266, 267, 268). The results of this study contribute to a better understanding of the impact of varying frequency and durations of treatment interruptions on mortality in order to prioritize retention support.

Tables and Figures

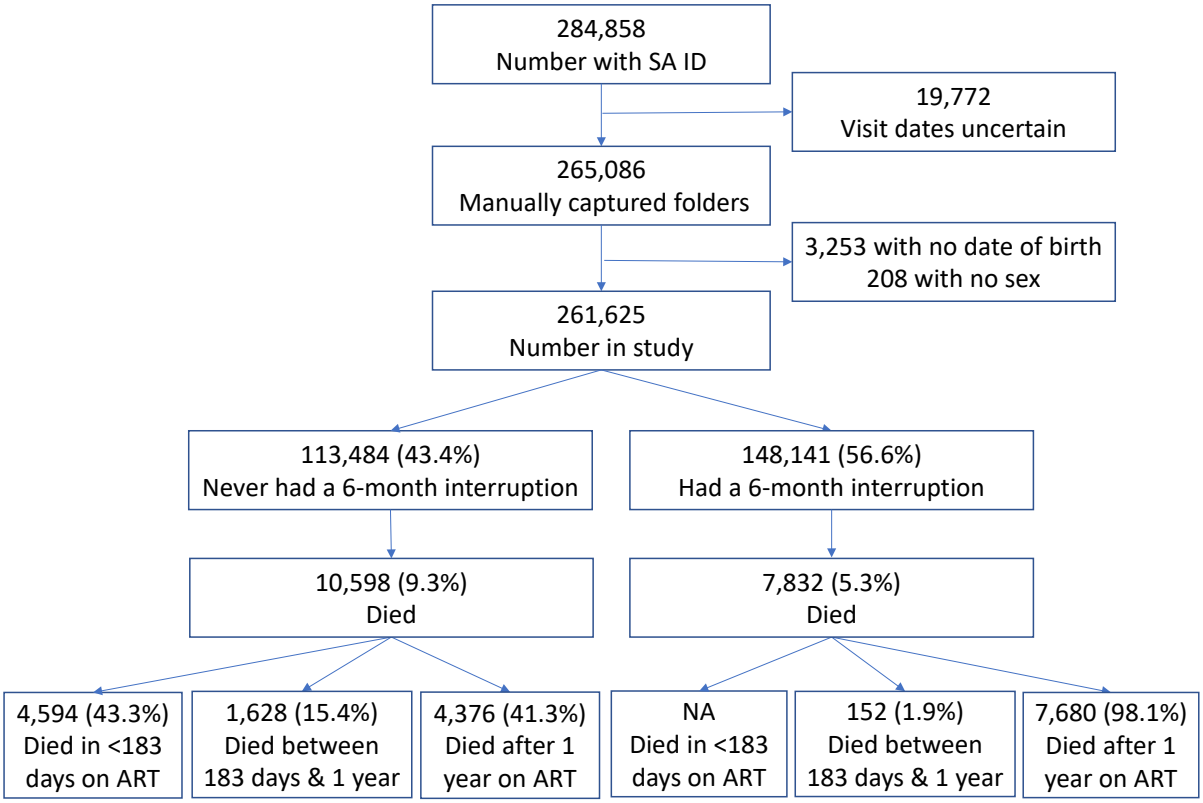


Figure 1: Study inclusions, exclusions, interruptions, and mortality

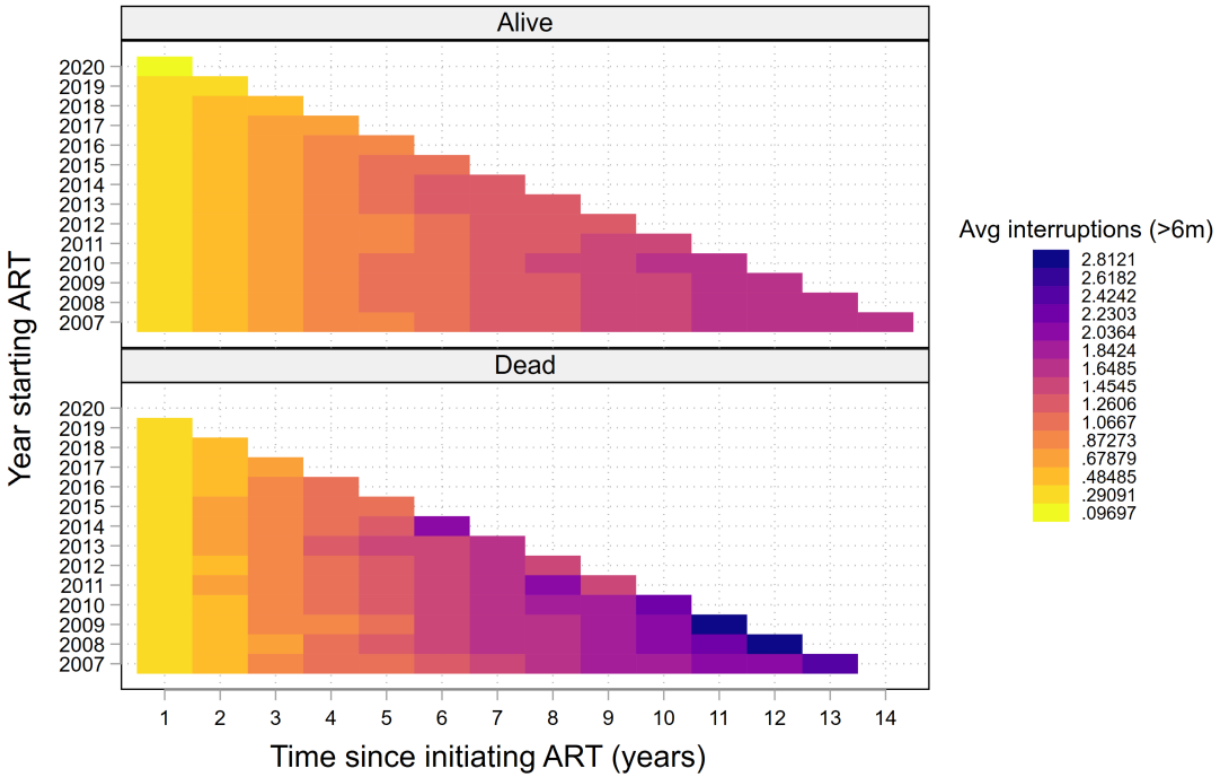


Figure 2: A heat map illustrating interruption frequency and patterns (average per year and duration) stratified by those who were alive or dead by the end of the study.

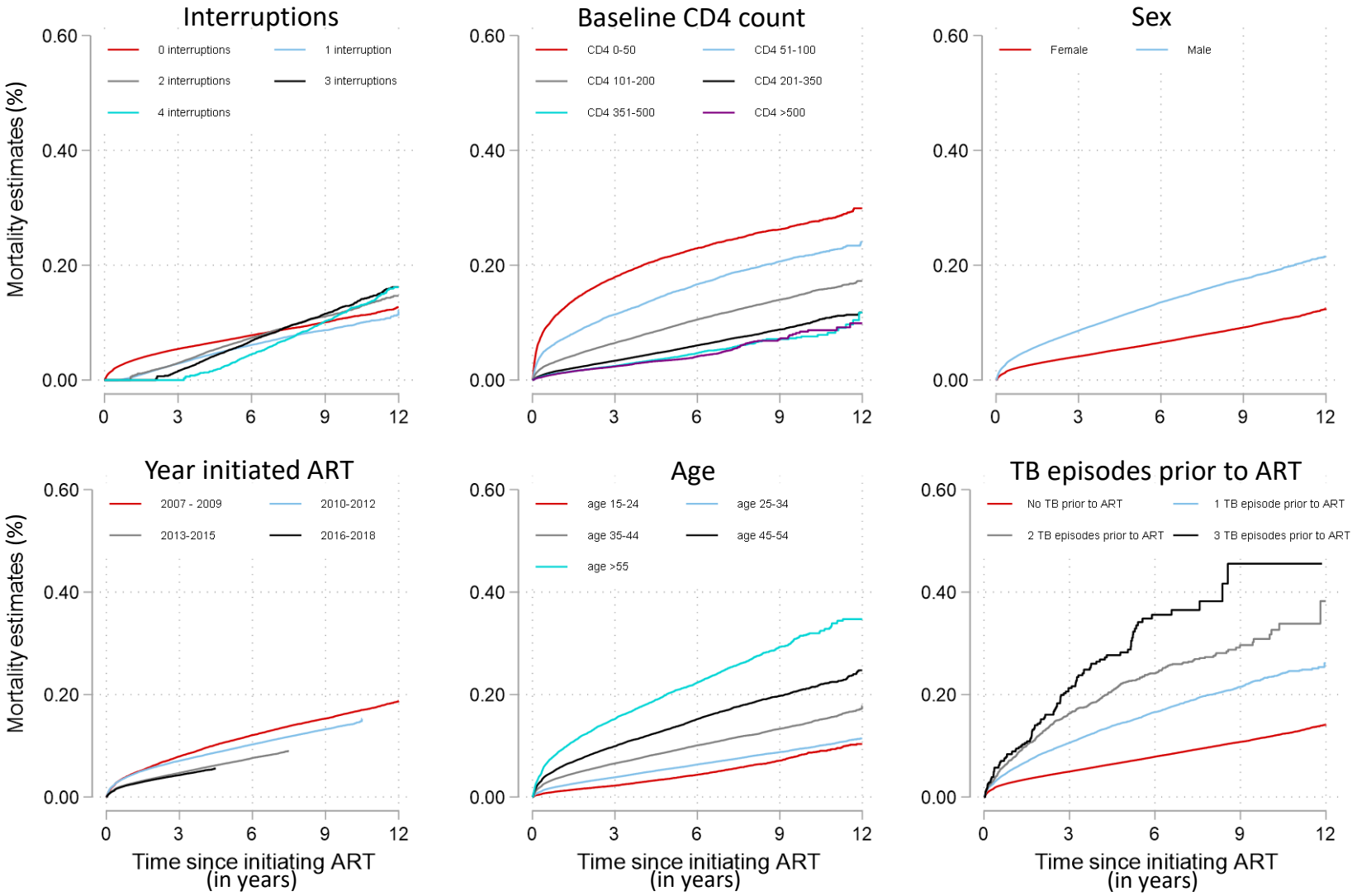


Figure 3: Kaplan Meier time to event graphs for univariable models

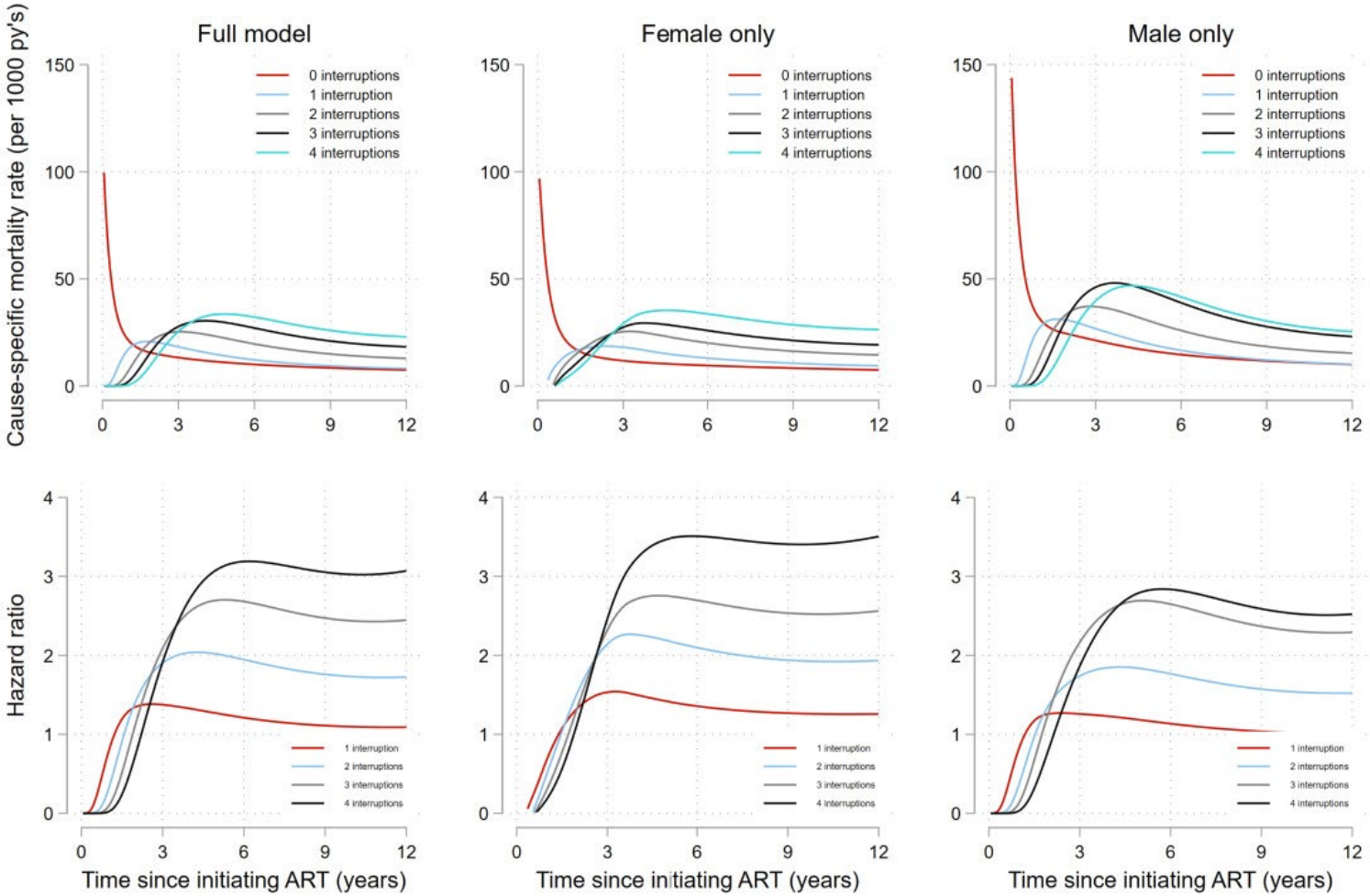


Figure 4: Post-model visualisations

Table 1: Baseline characteristics (total, and stratified by 6-month gaps in attendance at health facility)

	Total		Interrupted ART		Never interrupted ART	
Characteristics	**Number**	**% of baseline**	**Number**	**% of baseline**	**Number**	**% of baseline**
Baseline	261,625		148,141	(56.6%)	113,484	(43.4%)
Age (year), median (IQR)	33	(27, 40)	31	(26, 38)	34	(28, 41)
15-24	36,180	(13.8%)	25,314	(17.1%)	10,866	(9.6%)
25-34	112,415	(43.0%)	66,625	(45.0%)	45,790	(40.3%)
35-44	70,572	(27.0%)	35,977	(24.3%)	34,595	(30.5%)
45-54	28,633	(10.9%)	13,343	(9.0%)	15,290	(13.5%)
55+	10,572	(4.0%)	5,091	(3.4%)	5,481	(4.8%)
unknown	3,253	(1.2%)	1,791	(1.2%)	1,462	(1.3%)
Sex						
Female	184,053	(70.3%)	103,258	(69.7%)	80,795	(71.2%)
Male	77,572	(29.7%)	44,883	(30.3%)	32,689	(28.8%)
Year started ART						
2007-2009	22,865	(8.7%)	15,377	(10.4%)	7,488	(6.6%)
2010-2012	60,339	(23.1%)	38,023	(25.7%)	22,316	(19.7%)
2013-2015	89,885	(34.4%)	53,603	(36.2%)	36,282	(32.0%)
2016-2018	79,665	(30.5%)	39,602	(26.7%)	40,063	(35.3%)
2019-2020	8,871	(3.4%)	1,536	(1.0%)	7,335	(6.5%)
CD4 count at ART start, mdian (IQR)	228	(128, 344)	218	(124, 336)	236	(132, 351)
<=50	17,528	(8.5%)	8,475	(8.0%)	9,053	(9.1%)
51-100	18,499	(9.0%)	9,628	(9.0%)	8,871	(9.0%)
101-200	43,192	(21.0%)	23,449	(22.0%)	19,743	(20.0%)
201-350	64,050	(31.2%)	33,516	(31.5%)	30,534	(30.9%)
351-500	33,634	(16.4%)	16,621	(15.6%)	17,013	(17.2%)
501-1000	28,576	(13.9%)	14,848	(13.9%)	13,728	(13.9%)
Unknown (not in cat. proportions)	56,146	(21.5%)	41,604	(28.1%)	14,542	(12.8%)
TB at ART start						
yes	41,670	(15.9%)	23,354	(15.8%)	18,316	(16.1%)
no	219,955	(84.1%)	124,787	(84.2%)	95,168	(83.9%)
Pregnancy at ART start (% of females)						
yes	13,896	(7.5%)	8,920	(8.6%)	4,976	(6.2%)
no	170,157	(92.5%)	94,338	(91.4%)	75,819	(93.8%)
TB episodes before ART						
0	241,970	(92.5%)	137,421	(92.8%)	104,549	(92.1%)
1	17,202	(6.6%)	9,405	(6.3%)	7,797	(6.9%)
2	2,065	(0.8%)	1,108	(0.7%)	957	(0.8%)
3	388	(0.1%)	207	(0.1%)	181	(0.2%)
Follow-up						
Follow-up in years, median (IQR)	5	(3, 7)	6	(4, 8)	4	(2, 6)
Time to 1st int. (1 int. only), N (median, IQR)			75,066	(331, 123-855)		
Time to 1st int. (2 int. only), N (median, IQR)			40,808	(199, 39-521)		
Time to 1st int. (3 int. only), N (median, IQR)			18,888	(177, 45-439)		
Time to 1st int. (4 int. only), N (median, IQR)			7,940	(162, 45-337)		

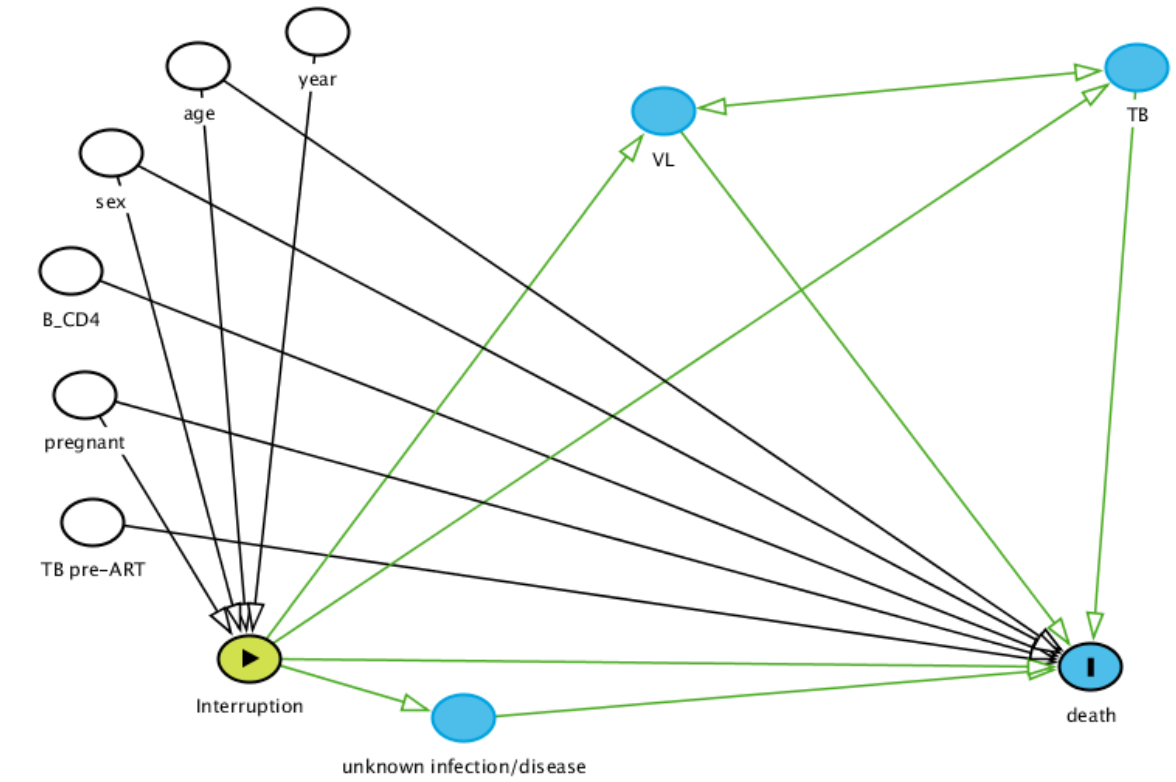
Notes: ART=antiretroviral therapy; %=percentage; IQR= inter-quartile range; CD4=CD4+ T cell count per microlitre, cat.=category, TB=tuberculosis, int.=treatment interruption, N=number.

Table 2: Univariable and multivariable parametric survival analysis

	Unadjusted HR		Adjusted HR		Adjustd hazard ratio					
Characteristic	6 m visit gap		6 m visit gap		3 m visit gap		6m visit male gap		6m visit female gap	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Age (years)										
15-24	0.71	(0.68, 0.76)	0.88	(0.83, 0.93)	0.89	(0.84, 0.94)	0.89	(0.79, 1.00)	0.87	(0.87, 0.98)
25-34	1.00	ref	1.00	ref	1.00	ref	1.00	ref	1.00	ref
35-44	1.61	(1.56, 1.66)	1.38	(1.33, 1.42)	1.37	(1.33, 1.42)	1.20	(1.14, 1.26)	1.51	(1.44, 1.58)
45-54	2.48	(2.39, 2.58)	2.11	(2.03, 2.19)	2.11	(2.03, 2.20)	1.82	(1.72, 1.92)	2.32	(2.20, 2.45)
55+	3.90	(3.72, 4.09)	3.48	(3.32, 3.65)	3.54	(3.37, 3.71)	2.81	(2.62, 3.01)	4.08	(3.81, 4.36)
Male sex	2.06	(2.00, 2.11)	1.30	(1.27, 1.34)	1.31	(1.27, 1.35)	NA		NA	
Year started ART										
2007 - 2009	1.13	(1.08, 1.17)	1.09	(1.05, 1.14)	1.13	(1.08, 1.17)	1.07	(1.01, 1.14)	1.10	(1.05, 1.16)
2010-2012	1.00	ref	1.00	ref	1.00	ref	1.00	ref	1.00	ref
2013-2015	0.72	(0.70, 1.17)	0.83	(0.8, 0.86)	0.82	(0.80, 0.85)	0.83	(0.79, 0.87)	0.84	(0.80, 0.88)
2016-2018	0.62	(0.60, 0.65)	0.75	(0.72, 0.78)	0.74	(0.71, 0.78)	0.74	(0.70, 0.79)	0.76	(0.72, 0.81)
2019	0.87	(0.77, 0.99)	0.90	(0.79, 1.02)	0.90	(0.79, 1.02)	0.90	(0.76, 1.08)	0.90	(0.76, 1.07)
CD4 count at ART start										
<=50	6.13	(5.71, 6.59)	3.74	(3.47, 4.03)	3.72	(3.46, 4.01)	2.70	(2.40, 3.04)	4.51	(4.09, 4.97)
51-100	4.26	(3.95, 4.58)	2.73	(2.53, 2.95)	2.73	(2.53, 2.94)	2.05	(1.82, 2.31)	3.14	(2.84, 3.47)
101-200	2.65	(2.47, 2.85)	1.97	(1.83, 2.12)	1.96	(1.82, 2.11)	1.48	(1.32, 1.66)	2.25	(2.05, 2.47)
201-350	1.53	(1.42, 2.64)	1.32	(1.23, 1.43)	1.31	(1.22, 1.41)	1.08	(0.96, 1.22)	1.43	(1.30, 1.57)
351-500	1.09	(1.00, 1.19)	1.03	(0.95, 1.13)	1.03	(0.95, 1.13)	0.91	(0.79, 1.04)	1.08	(0.97, 1.21)
501-1000	1.00	ref	1.00	ref	1.00	ref	1.00	ref	1.00	ref
unknown	1.77	(1.65, 1.90)	1.46	(1.36, 1.57)	1.48	(1.37, 1.59)	1.26	(1.12, 1.42)	1.50	(1.37, 1.65)
Interruptions (6-month)										
1	1.07	(1.03, 1.11)	1.27	(1.21, 1.33)*	1.07	(1.02, 1.14)*	1.18	(1.10, 1.27)*	1.42	(1.33, 1.51)*
2	1.50	(1.43, 1.58)	2.02	(1.91, 2.13)*	1.37	(1.28, 1.47)*	1.83	(1.68, 2.00)*	2.18	(2.02, 2.36)*
3	1.95	(1.82, 2.09)	2.68	(2.50, 2.91)*	1.83	(1.70, 1.96)*	2.69	(2.41, 3.01)*	2.75	(2.50, 3.04)*
4+	2.25	(2.06, 2.45)	3.09	(2.79, 3.41)*	2.40	(2.25, 2.57)*	2.80	(2.39, 3.28)*	3.47	(3.05, 3.95)*
TB episodes before ART										
1	2.16	(2.07, 2.25)	1.78	(1.71, 1.85)	1.77	(1.70, 1.85)	1.62	(1.53, 1.71)	1.95	(1.84, 2.07)
2	3.26	(2.97, 3.58)	2.50	(2.28, 2.74)	2.48	(2.26, 2.72)	2.33	(2.06, 2.63)	2.68	(2.32, 3.09)
3+	4.70	(3.89, 5.67)	3.53	(2.93, 4.27)	3.45	(2.86, 4.17)	3.07	(2.39, 3.94)	4.17	(3.13, 5.55)
TB at ART start										
yes	2.78	(2.70, 2.85)	1.72	(1.67, 1.78)	1.74	(1.69, 1.79)	1.50	(1.44, 1.57)	1.95	(1.87, 2.04)
Pregnancy at ART start										
yes	0.37	(0.33, 0.40)	0.64	(0.58, 0.69)	0.64	(0.59, 0.7)	NA		0.67	(0.62, 0.74)

*Hazard ratio estimates provided at time equivalent to each person having completed 5 years on antiretroviral therapy, to ensure interruption events have taken place and are included in the model estimations.

HR, hazard ration; m, month; ref, reference; NA, not applicable; ART, antiretroviral therapy; CD4 count, CD4 count cells/µl; TB, tuberculosis



Supplementary figure 1: Causal diagrams (directed acyclic graph (DAG))

Characteristics	Total with SA ID		Interrupted ART		Never interrupted ART		Total without SA ID		Interrupted ART		Never interrupted ART	
	Number	% of baseline	Number	% of baseline	Number	% of baseline	Number	% of baseline	Number	% of baseline	Number	% of baseline
Baseline	261,625		148,141	(56.6%)	113,484	(43.4%)	198,769		134,101	(67.5%)	64,668	(32.5%)
Age (year), median (IQR)	33	(27, 40)	31	(26, 38)	34	(28, 41)	32	(26, 39)	31	(25, 38)	34	(27, 40)
15-24	36,180	(13.8%)	25,314	(17.1%)	10,866	(9.6%)	24,999	(12.6%)	19,119	(14.3%)	5,880	(9.1%)
25-34	112,415	(43.0%)	66,625	(45.0%)	45,790	(40.3%)	79,790	(40.1%)	55,346	(41.3%)	24,444	(37.8%)
35-44	70,572	(27.0%)	35,977	(24.3%)	34,595	(30.5%)	54,558	(27.4%)	34,359	(25.6%)	20,199	(31.2%)
45-54	28,633	(10.9%)	13,343	(9.0%)	15,290	(13.5%)	19,825	(10.0%)	11,995	(8.9%)	7,830	(12.1%)
55+	10,572	(4.0%)	5,091	(3.4%)	5,481	(4.8%)	5,944	(3.0%)	3,754	(2.8%)	2,190	(3.4%)
unknown	3,253	(1.2%)	1,791	(1.2%)	1,462	(1.3%)	13,653	(6.9%)	9,528	(7.1%)	4,125	(6.4%)
Sex												
Female	184,053	(70.3%)	103,258	(69.7%)	80,795	(71.2%)	122,665	(61.7%)	83,858	(62.5%)	38,807	(60.0%)
Male	77,572	(29.7%)	44,883	(30.3%)	32,689	(28.8%)	76,104	(38.3%)	50,243	(37.5%)	25,861	(40.0%)
Year started ART												
2007-2009	22,865	(8.7%)	15,377	(10.4%)	7,488	(6.6%)	26,776	(13.5%)	22,003	(16.4%)	4,773	(7.4%)
2010-2012	60,339	(23.1%)	38,023	(25.7%)	22,316	(19.7%)	47,705	(24.0%)	35,521	(26.5%)	12,184	(18.8%)
2013-2015	89,885	(34.4%)	53,603	(36.2%)	36,282	(32.0%)	61,272	(30.8%)	41,846	(31.2%)	19,426	(30.0%)
2016-2018	79,665	(30.5%)	39,602	(26.7%)	40,063	(35.3%)	57,458	(28.9%)	33,517	(25.0%)	23,941	(37.0%)
2019-2020	8,871	(3.4%)	1,536	(1.0%)	7,335	(6.5%)	5,558	(2.8%)	1,214	(0.9%)	4,344	(6.7%)
CD4 count at ART start, mdian (IQR)	228	(128, 344)	218	(124, 336)	236	(132, 351)	241	(134, 375)	231	(128, 360)	251	(141, 387)
<=50	17,528	(8.5%)	8,475	(8.0%)	9,053	(9.1%)	11,915	(8.8%)	6,837	(8.5%)	5,078	(9.3%)
51-100	18,499	(9.0%)	9,628	(9.0%)	8,871	(9.0%)	12,672	(9.4%)	7,820	(9.7%)	4,852	(8.9%)
101-200	43,192	(21.0%)	23,449	(22.0%)	19,743	(20.0%)	28,783	(21.3%)	18,067	(22.4%)	10,716	(19.7%)
201-350	64,050	(31.2%)	33,516	(31.5%)	30,534	(30.9%)	40,742	(30.2%)	24,321	(30.1%)	16,421	(30.2%)
351-500	33,634	(16.4%)	16,621	(15.6%)	17,013	(17.2%)	20,753	(15.4%)	11,811	(14.6%)	8,942	(16.5%)
501-1000	28,576	(13.9%)	14,848	(13.9%)	13,728	(13.9%)	20,203	(15.0%)	11,943	(14.8%)	8,260	(15.2%)
Unknown (not in cat. proportions)	56,146	(21.5%)	41,604	(28.1%)	14,542	(12.8%)	63,701	(32.0%)	53,302	(39.7%)	10,339	(16.0%)
Died by end of study	18,430	(7.0%)	7,832	(5.3%)	10,598	(9.3%)	11,679	(4.5%)	4,084	(3.0%)	7,595	(11.7%)

Supplementary table 1: Comparing baseline characteristics of those in the study to those who were excluded due to not having an SA ID recorded in the digital health databases

Notes: ART=antiretroviral therapy; %=percentage; IQR= inter-quartile range; CD4=CD4+ T cell count per microlitre, cat.=category, TB=tuberculosis, int.=treatment interruption, N=number.

Chapter 3: Discussion

SUMMARY

The main findings of this thesis have been discussed in detail in Chapter 2. This chapter will discuss the findings as they relate to each other and to a wider context, as well as consider additional evidence from other publications since the beginning of 2014, after the inception of this research project.

Prior to this research project, little was known about population-level estimates of ART effectiveness in RLSs given the difficulties countries were having setting up health information systems. The few RLSs that did have an HIV health information system operational, did not necessarily have the data linked per patient across health facilities or to a country death registry, with outputs subject to selection and information bias.

The findings of this research project show that it is feasible in a high prevalence, resource-constrained setting to implement an information system using individuated data to improve patient care and evaluate population-level estimates of ART impact. Despite the immense scale-up of ART services during this time period, advanced HIV disease is a persistent challenge among those first presenting in care and in those who have initiated ART. Successive guideline changes expanding ART access likely provided individual benefit to those who met the changing eligibility criteria, but the greatest overall benefit continued to be in individuals with advanced HIV disease.

The proportion of ART uptake within each CD4 cell count stratum increased over time. Anticipated guideline changes and expanded ART services most likely resulted in an increasing number of individuals who were sick but not yet meeting CD4 cell count threshold criteria gaining access to ART prior to being eligible, alongside increasing coverage for those who were eligible for ART. Poorer access to health care and poorer outcomes for men continued throughout this past decade, whilst treatment interruptions were found to be an important driver of morbidity and mortality.

INTERPRETATION OF FINDINGS

The following sections will reflect on the findings under four thematic areas: health information systems, advanced HIV disease, evolution of guidelines and evolving associations with mortality.

Health information systems

One of the requirements of the country-wide rapid scale-up of the free ART services was the implementation of systems to monitor individuals in care, report on service delivery, monitor quality and report on impact and temporal epidemic trends. The first paper in this thesis concluded that a pragmatic, incremental evolution from paper to hybrid and then online systems, guided by available resources and infrastructure, is feasible, even if completely offline.

Evolution of HIV monitoring systems within South Africa

Since writing the paper on the three-tier framework for health information systems, the monitoring systems discussed have continued to evolve in South Africa. As infrastructure continued to improve over time, the use of the offline TIER.Net application continued scaling to include prisons and expanded its monitoring modules to include tuberculosis, pre-ART care and pre-exposure prophylaxis (PrEP) services (269, 270). The digitisation project using the offline application continues collecting and reporting on data at over 4,000 health care facilities and cascading individuated data centrally to district, provincial and national databases. TIER.Net exceeded expectations explored within the Three Tier Framework paper, as the original intention was to provide a temporary bridging solution for evolution to a full hybrid/online HIS.

Challenges existed in spite of this scale up. The availability of individuated data was not really capitalised on, with ongoing reliance on aggregate data in spite of individuated data being sent by facilities to provinces and the national ministry. Therefore, at higher levels of health management, there was no way to accurately account for people who left care at their primary facility, exaggerating estimates of loss to follow-up, although a large proportion were still in care after self-transferring to other facilities, and an important proportion had died (4, 271, 272). As the linkage functionality developed for TIER.Net in 2016 was never implemented, data on patients who had self-transferred or had died were unknown and could not be shared back to facility level, bloating recall lists and creating an overwhelming burden when trying to trace patients in the community.

Another major challenge was not knowing which HIV patients were coinfected with drug resistant TB (DR-TB), or vice versa. The DR-TB module within the TIER.Net software, which was technically interoperable with the parallel online software implemented within DR-TB hospitals, was also not made available to facilities when DR-TB care decentralised from TB hospitals to PHC facilities.

Studies looking at patient records in the health facilities, determined co-infection was sometimes not known to the health care provider or facility, with patients separately receiving ART and drug sensitive TB or drug resistant TB care and medication from different facilities (272, 273, 274).

The reasons for not activating these additional linkage and interoperability tools at higher levels of health within the national HIV and TB HIS (TIER.Net) is not known but may have included a lack of research into and confidence in the linkage algorithms and a parallel strategy by the SA NDoH to build an EMR and national data warehousing infrastructure as a broader digital health strategy (275, 276). During the course of completing this study there were few examples of outputs or tools in use by services to improve patient care based on nationally consolidated and de-duplicated individuated HIV and TB data, although there had been extensive investments made into building infrastructure to potentially support this (277).

Due to better resources, infrastructure and collaborations with partners in academia, the Western Cape Province was however able to leverage the availability of individuated digital HIV data as part of a broader provincial health data centre (PHDC) for person-level health data. The PHDC was established in late 2015 with the aim to import health data from all digital sources and from vital registries, link data per patient and enable all reporting from the centre. The reporting includes patient alerts and case-based surveillance, service delivery statistics, epidemiologic trends, disease burden, and the development of an interface for patient access to their own longitudinal record (191). There have been numerous publications on the Western Cape health services (not limited to HIV) due to the linked patient records in the PHDC, including adverse events, treatment impact and epidemic trends that have informed national and international policy, and continue to do so (191, 219, 278, 279, 280, 281, 282, 283). As has been detailed in Chapter 2, over time this resource became the dominant data source for the analyses included in this thesis.

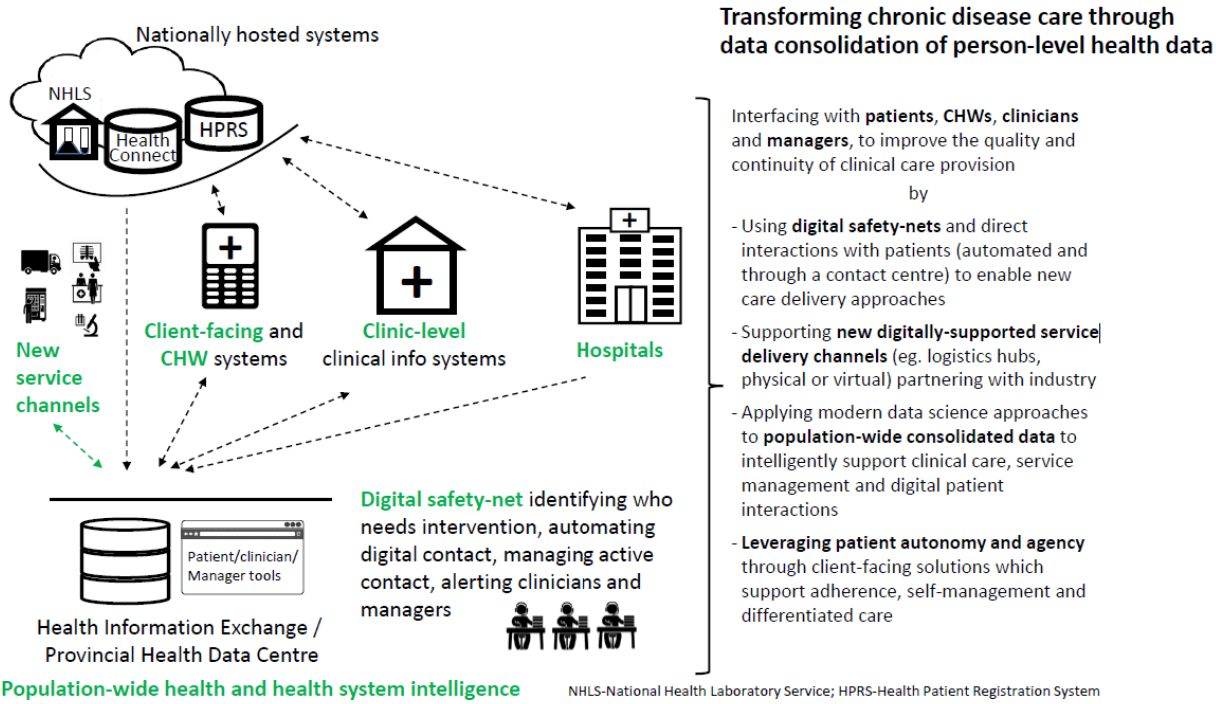


Figure 4: Conceptual model for how consolidated person-level health data can support service delivery. Source: Boulle, AfroPHC conference, November 2021 (284)

At a similar time as the above evolution of HIS improvements in the Western Cape, WHO guidelines were also revising recommendations from previously promoting aggregate data to recommending individuated data, and ultimately to consolidated linked individuated data. In 2015, WHO released guidelines recommending that RLSs implement HIS solutions that can collect individuated digital data, with the work in South Africa being referenced as a case study (285). In 2017, the newly revised WHO guidelines recommended a consolidated approach where case-based surveillance (CBS), provincial, national and international reporting requirements could be lifted from the same clinical records if paired with laboratory and death registry data (53, 152). The WHO 2022 Consolidated guidelines on person-centered HIV strategic information further solidifies guidance on digital patient-level data collection, data use and the development of digital health ecosystems (243).

Unique health identifiers

Although the WHO and Western Cape Province HIS approaches are similar, one area where WHO recommendations and the Western Cape PHDC implementation diverge is in the necessity for a unique identifier. Where available, a jurisdiction-wide unique health identifier (or with some privacy concerns, the national civil identification number) makes linking data across health platforms easier, but it is not an absolute requirement for linkage (286). The PHDC collects a variety of data from patients (demographics, geographic location, and clinical indicators such as ART start date,

pregnancy information or other) which can be used to de-duplicate patients even in the absence of a unique identifier, or where a unique identifier still contains many duplicates (284). Others in South Africa have also been able to achieve workable de-duplication in the absence of a well-functioning unique identifier (287, 288). Although patient data is potentially linked with less confidence when a unique identifier is not supplied at the health care service point, using algorithms centrally to build a unique health identification backbone enables data linkage for a multitude of use cases including case-based surveillance, service delivery management and for ascertaining population-wide treatment uptake and impact estimates.

While implementing unique identifiers can be done via fairly sophisticated inference and linkage algorithms in a central database, most countries in RLSs have opted for trying to provide unique identifiers at facility level (289, 290). If implemented well, unique identifiers that are provided at the location of health care delivery can improve linkage rates overall and enable data from multiple digital sources (lab and pharmacy) to be imported and linked for improved patient management and care (289, 291). This can be implemented in facilities that have offline or online software. For example, in South Africa there is a dedicated attempt to implement a unique identifier centrally via the Health Patient Registration System in order to maximise the wealth of information from collected clinical health data (288, 292). The Health Patient Registration System uses pre-allocated temporary numbers for offline facilities which can be changed to permanent unique health identifiers when a patient visits an online facility (292). However, South Africa is still early in the journey to ensuring the patient and health services benefit from and therefore use the unique health identifier for all laboratory samples, patient forms and data collection purposes. Rwanda is also in early stages of rolling out a unique health identifier, piloting a centralized client repository for allocation of numbers which are sent to local hospitals. Although Rwanda has an OpenMRS health information systems in 195 PEPFAR supported sites (of the 417 facilities offering HIV services (293)), many are offline and there may be challenges scaling up unique identifiers at these sites (294).

Evolution of HIV monitoring systems outside of South Africa

A second major challenge alongside implementing unique identifiers in RLSs is bringing multiple, organically grown, disparate systems together, making use of standardised data elements and interoperable platforms. Uganda uses a mix of electronic-based HISs (OpenMRS/ UgandaEMR, ICEA and DHIS2) at the larger sites (just over 50% of all sites in 2020) and paper-based ART cards and registers at other sites (295, 296, 297). Patient information for clinical assessment history is shared within and between facilities using paper-based methods, whereas aggregate data is shared to district and higher levels in DHIS2 (297, 298). It is unknown what proportion of patients recorded as lost to follow-up (LTF) have actually transferred to other facilities or have died due to the unlinked

nature of the data (295). Mozambique, Botswana and Kenya have also had a similar experience as Uganda with multiple separate monitoring platforms implemented depending on which donor partner was working within each facility (paper, OpenMRS, DHIS2 or an SQL-based information system) (299, 300, 301, 302). Facilities in Mozambique, whether paper or digital, submit aggregate statistics to the MOH, with over half the digital sites manually aggregating reports from paper registers in order to meet data indicator requirements in a format which was not supported by the digital systems (300). Malawi's HIS includes a mix of paper and online software, with data being submitted in various disparate formats to districts and each district creating their own database for aggregation of reports and submission centrally. As such, the district databases are not harmonised making data sharing difficult (303).

Interestingly, Zambia is the most similar in terms of vision and scale-up to the model put forward in the Three-Tier Framework paper, making use of a software application called SmartCare as the middle and top tier offline/online digital platforms while the remaining rural and remote sites are on paper. SmartCare has similar attributes as TIER.Net, built as a context-appropriate solution for digitising health care (304, 305). Advantages include enhanced patient records, improved patient follow-up and reduction in patient waiting times (306), although several disadvantages have been noted including the burden of the amount of data being collected, the fact that only HIV data are collected, and lack of evidence of the use of collected data for ART service planning or policy, resulting in underutilised data (304, 306). As far as could be determined, Zambia does not have population-wide estimates generated from individuated data, but do produce many publications based on the health care facilities using the hybrid digital solutions (304, 305, 307, 308).

As with Zambia, Rwanda also seems to have successfully digitised a majority of healthcare sites using a singular software application, although the number of sites not digitised is difficult to ascertain. Rwanda uses an OpenMRS system called TRACnet in the PEPFAR supported sites (309, 310) and triangulates the data with the Rwanda population-based HIV impact assessment (PHIA) to project population-wide estimates (311).

In most of the above country examples (with exception to Zambia and Rwanda), the multiple disparate information systems and the lack of data standards and IT system interoperability results in the data not being optimally linked to better inform patient care or enable population-wide programme estimates (297, 298, 301, 303, 312).

Challenges in completeness of mortality data

A third major challenge in providing population-wide treatment uptake and mortality estimates in RLSs is the lack of comprehensive civil and vital registration statistics which are able to provide

individuated death details for triangulation with clinical assessment data (301, 312). This means that population level mortality estimates, and epidemic control cannot be measured unless every death in an HIV person is reported back to the primary care facility and linked in a central database. Interestingly, in Nairobi, Kenya, researchers together with the US Centers for Disease Control and Prevention (CDC) piloted an HIV mortuary surveillance system to measure HIV-positivity among cadavers as the country utilises an incomplete paper system for their national civil death registry (301) and digital EMRs are only in the larger HIV care facilities (312). Although measuring annual cause-specific mortality rates was not possible in this study due to lack of records on cause of death, there was success in determining HIV-positive mortality among all deaths sampled. The researchers suggested this as an inexpensive approach to measuring HIV-proportional mortality trends in RLSs in the absence of well-documented digital civil registries (301). Other researchers have done similar minimally invasive autopsy surveys to look for disease specific conditions to answer questions which cannot be done via cohorts, as these surveys can cover people unknown to the health services and test for conditions (such as tuberculosis) which were previously undiagnosed (313).

Comprehensive published data on the status of civil registration across African countries is hard to find. In the context of understanding reported mortality due to COVID-19, journalists estimated that only eight of more than 50 countries in Africa have functioning, compulsory, digital civil registries; this includes Egypt, South Africa, Tunisia, Algeria, Cape Verde, São Tomé and Príncipe, Seychelles and Mauritius (314) . Rwanda and Malawi have stated that the development of digital viral registries is a key deliverable in their most recent national digital health strategy documents (294, 315), while the death registry in South Africa is estimated to be 96% complete for deaths in patients on ART (316). Most of the analyses in this thesis relied on vital registration linkage, which could only be done for those with national identifications numbers recorded in the health records.

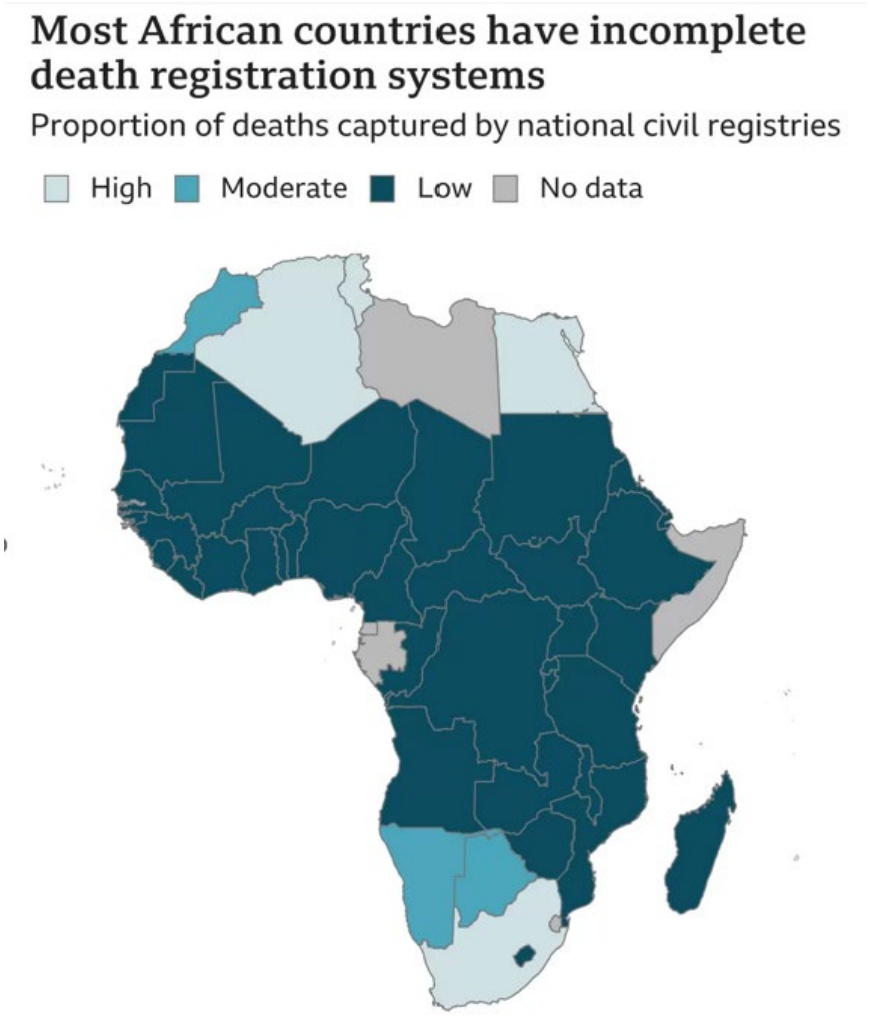


Figure 5: Digital death registries in Africa. Source: UN, BBC Research

Data on COVID-19 as a barometer of broader HIS maturity in African settings

The COVID-19 pandemic was a litmus test of whether health services and health information systems could rapidly respond in emergency situations. Most HISs in Southern African countries were too fragile with systems too disparate to be able to respond as efficiently as is necessary to monitor individual cases and population trends of an emergent epidemic (289, 317). Publications on HIV infected and non-infected COVID-19 patients demonstrated (or were proxy of) a healthy HIS with the ability to quickly add new data elements for emergent diseases, link data per patient across services, and rapidly use the data to inform policy and health service delivery (278, 282, 289). A systematic review looking at hospitalisation and mortality of COVID-19 infected people with and without HIV by October 2021, included 44 English publications world-wide, with 10 from African countries (318). Twenty-eight of the included studies were multi-centre and five of the multi-centre studies were from African countries but only one - from the Western Cape, in South Africa - used data from all health care facilities within a region (282, 318). Other RLSs needed to rely on

population estimates based on small research studies, and extrapolation of outcome estimates from surveillance systems within households, and excess mortality estimate studies, all of which can be delayed and are not always able to link potential associations to disease outcomes (319, 320, 321, 322).

Summative reflections on health information system architecture in high HIV burden settings

Although there are very few coherent examples of country-wide HIV information systems in RLSs, a search of publications highlighted three countries that have successfully deployed fairly well-working, interoperable HIS throughout a majority of HIV sites. Rwanda, Zambia and South Africa all have deployed a type of two or three-tier monitoring framework for their HIV HIS, with Zambia and Rwanda still having a sizable number of facilities using paper-based systems (294, 304, 305, 323). It can be surmised that there are not many publications on patient-record derived population-wide HIV impact and mortality estimates from these countries, as unique identifiers have not been deployed yet at scale, and civil registries may not be digitised; this results in data-linkage challenges including the deduplication of patient records, overestimation of the number of people reported as lost to care and an unknown number of deaths.

The paper on a three-tier framework for monitoring HIV recommended a pragmatic mix of evolving systems which send standardised data centrally to generate population-wide estimates. However, not many countries have taken this approach and are left trying to implement complex online or offline systems in larger facilities while others without stable networks or stable donor partners remain with the various systems originally put in place during ART services scale-up. Health information systems require substantial continuous investments, as can be seen in the Western Cape of South Africa and Rwanda (191, 294). Countries in RLSs need to ring-fence ample funds for developing and maintaining context-appropriate health information and unique identifier systems, to digitise civil registries, to link data across services and facilities, and to ensure the collected data is being used to improve patient care and inform policy.

Advanced HIV Disease

In this thesis, using population-wide HIV and ART clinical and laboratory data linked via unique patient identifiers within the PHDC, it was possible to demonstrate that people with advanced HIV disease (AHD) are not only from the pool of people who have not initiated ART but that the majority are from those who have already initiated ART. AHD is an ongoing challenge and reflects both those starting treatment late and those falling off treatment. As a result, AHD continues to be a major driver of morbidity and mortality in the HIV services. Our analyses reflect on and measure AHD in

two ways, by focussing on both patients presenting with low CD4 cell counts and focussing on mortality.

AHD is an ongoing challenge

Other researchers worldwide have also confirmed AHD (<200 cells/µL) as an ongoing challenge in their cohorts, and a strong driver of mortality (324, 325, 326). A large proportion of individuals living with HIV still present very late with advanced HIV disease. Over 60% of the initiating cohort in rural Tanzania had AHD at diagnosis between 2013 and 2018 and more than 50% after implementation of test and treat guidelines (327). In Mozambique, 70% of the TB-index diagnosed individuals and 16% of the contacts had AHD in 2018, while 6 month mortality among the TB-index cases was 21% and 0% among the contacts (324). In South Africa, constructing patient longitudinal records via laboratory results, 33% of those entering HIV care had AHD and men were twice as likely as women to have very advanced HIV diseases (<100 cells/µL) (328). In Botswana the proportion presenting late to HIV services is much smaller in comparison, however this proportion increased from 15% prior to the introduction of the test-and-treat policy, to 24.7% after (326).

AHD is predominantly a challenge among people who are ART-experienced

There is a persistent burden of advanced HIV disease among individuals in the ART services. In cohorts from Kenya and Democratic Republic of Congo (DRC), 66% and 78% of HIV infected patients admitted to in-patient hospital care with ADH were people who had already initiated ART, with a median duration of 44 and 56 months on treatment. Of those, 17% from Kenya and 30% from DRC died (329). In Malawi, 53% of those admitted to hospital with AHD had already started ART (330). The University Teaching Hospital in Lusaka, Zambia reported that 92% of their AHD patients to have been on ART previously with 58% on ART for more than 12 months (331).

These latter studies of AHD in people who already initiated ART, resonates with the research in this thesis which illustrated a larger proportion of patients with ADH coming from the cohort already on ART. The different studies above demonstrate that AHD continues to remain high in RLSs, representing a burden of morbidity that could be addressed through service delivery improvements (328).

The scale-up in treatment coverage and viral suppression has driven country progress towards reaching 95-95-95 HIV epidemic treatment targets. However, it is also important to focus on targets that measure the number of people who cycle in and out of care and treatment to achieve the goal of ending AIDS (240, 301). These missing AHD and mortality measures may be better understood if the number and frequency of patients stopping and re-starting HIV care and ART treatment at each point along the HIV care cascade are measured.

Drivers of AHD

Understanding what drives AHD is important when trying to recommend interventions for mitigating risk or decreasing the number of people affected. Researchers globally have found delayed initiation of ART, drug resistance, interruptions, suboptimal viral load testing, being a man, older age, and injecting drug use influences a person's risk of AHD (295, 326, 332, 333, 334), while the leading causes of death remain tuberculosis, cryptococcal meningitis and severe bacterial infections (330, 335).

The study presented as part of this thesis (Chapter 2b) finds a continuing steady proportion of initiators (naïve or experienced) are presenting late to ART services with opportunistic infections and AHD. This trend has not changed dramatically and is not unique to South Africa. As discussed in the section above, between 24% and 50% of the initiating cohorts in Southern Africa initiate ART with AHD (326, 327, 328, 335). It is important to measure CD4 cell counts in order to know what further screening tests (TB-LAM, CrAg) and prophylaxis are required to appropriately manage a new patient, yet studies have reported that test and treat policies have significantly reduced the number of CD4 cell count tests done at baseline in new ART enrolees (336).

Ongoing viraemia and drug resistance as a driver of AHD

Interruptions emerged strongly as a driver of AHD in the last analyses of this thesis. Drug resistance has been reported as associated with the progression to AHD but prior interruptions are likely often the precursor. In the smaller proportion of patients who had AHD in spite of having been on continuous ART treatment, it is possible that transmitted drug resistance or exposure to a single ARV drug prior to the current ART regimen could have precipitated virologic failure.

Drug resistance, in earlier years of the ART programme occurred in as high as 80% of patients with virologic failure (viral load >500 copies/mL) and in some individuals with prior exposure to single ART drugs (337, 338, 339, 340, 341). However, drug resistance has largely decreased with the scale-up of dolutegravir as part of the first line ARV regimen, which has a higher genetic barrier to drug resistance (342). Interruptions, however, are in the pathway between viral load suppression and acquired drug resistance, and the number of interrupters continue to increase as the number of individuals enrolled in ART services continues to increase. A systematic review of studies from South Africa suggested that 11% of all enrolled in ART for a year and as much as 25% by 5 years become lost to follow-up (interrupting treatment for 1 month or longer). Our research validates these numbers but suggests that many return to care and some become LTF repeatedly (343). During times of treatment absence, viral loads increase, and prolonged viremia can lead to AHD and potentially drug resistance, so it is important to monitor missed appointments and repeat viral loads

(or monitor for clinical deterioration when VLs are not available) when patients return to care after extended periods off ART. If viral loads are unsuppressed, enhanced adherence counselling (EAC) and potentially drug regimen switching can mitigate further disease progression. A study from Lesotho showed EAC to be associated with achieving viral load re-suppression (adjusted odds ratio [aOR] 7.2, 95%CI: 1.9-27.0) and could potentially mitigate a proportion of AHD, drug resistance, and death (340). EAC has been part of the South African HIV guidelines since quite early in the free ART service scale-up.

A study from KwaZulu-Natal in South Africa found that routine viral load monitoring was not happening as per protocol, with only 41% getting viral loads by 6 months, and 26% by 2 years on ART. However only 11.7% received their viral load tests per protocol at 6, 12 and 24 months. Of those with a viral load above 1000 copies/mL, 38% had a second one within 6 months, and only 18% of those successfully managed to decrease their viral load through better adherence or via regimen change. A survey of sampled health facilities in Uganda found similar results, with only 50% of health centres monitoring >70% of patients' viral loads at 12 months (295). Suboptimal viral load testing and poor management of people with unsuppressed viral loads may have a significant impact on morbidity and contributes to higher numbers of people with AHD and possible death. Suboptimal virologic testing may also lead to an underestimation of the problem, and inaccurate decisions on resource needs and programme effectiveness (344).

AHD drives mortality among people living with HIV globally

As described above and in our research, as HIV prevalence increases due to new infections and an increasing number of people receiving ART treatment, the absolute number of people with AHD also increases, creating a persistent burden of morbidity and mortality that is not being managed well. This remains true even when programmes perform consistently well or improve in terms of health and mortality metrics. In 2018 there were still 770,000 deaths related to HIV globally (325), of which over 60,000 deaths due to AIDS were in South Africa. The more striking figures though, are AIDS deaths in patients on ART in South Africa. The number of deaths in patients on ART stopped decreasing after 2014 and have remained stable at around 38,000 (95% CI 37672, 39179 in 2014) fluctuating by +/- 1000 during the subsequent 5 years according to THEMBISA modelled estimates (187). Globally, the same trend has been recognised, with a relatively constant proportion of people with a CD4 cell count <200 cells/µL or WHO Stage 3 or 4 disease (331, 335).

Recommendations to mitigate AHD and potential mortality from AHD

Most of the recommendations from PHC studies reported on interventions for late first time presenters to HIV services (324, 327, 328, 345, 346); however, our research and more recent

publications from hospitals reported on and suggested interventions for patients coming from the cohort already on ART (329, 330, 331, 335). In both scenarios (with the exception of those with drug resistance) the recommended package for those with AHD are very similar. The most frequently reported recommendations include a package of screening for comorbidities, providing prophylaxis, initiating or re-initiating ART and providing enhanced adherence support (330, 334, 335, 347, 348, 349, 350). In addition, studies on initiating cohorts suggest interventions to bring people to ART services earlier (328, 335), while additional interventions for people on ART include retention in care, optimal viral load testing and rapid tracing and re-engagement of those who have interrupted treatment (266, 268, 329, 331, 343, 344).

To highlight the importance of the package of screening and prophylaxis in those already on ART, a study from the US reported on the rapid decline of screening for coinfections in people with known high viral loads and low CD4 cell counts; tuberculosis, cryptococcosis and severe bacterial infections are the leading causes of death in people with HIV, yet less than 3% of those eligible (with AHD) and on ART for over 3 years received screening for these opportunistic infections (334). In Uganda, Tanzania and Nigeria, more than 80% with AHD, at ART initiation or while on ART, never received screening for OIs yet were eligible according to protocols (351). The South African 2019 guidelines suggest CrAg screening in ART-experienced individuals who have been lost to care for >3 months, and it has been suggested that this should be implemented globally (334, 352). A study by May and colleagues demonstrated that individuals who initiated ART with severe AHD (cd4 count<50 cells/µL) and survived 5 years on ART converge to similar mortality risk of people who initiated ART with high baseline CD4 cell counts. People with AHD who are screened and treated for coinfection can overcome their associated high risk of mortality when properly managing treatment (353).

Many studies also touched upon differentiated service delivery (varying times, medication delivery in the community or within private pharmacies, adherence groups) to facilitate more easily accessible care and treatment options such as less frequent health care visits for individuals stable on ART (81, 349, 354) and closer initial follow-up of individuals starting ART or re-starting ART after being diagnosed and treated for AHD (349, 355). Offering less frequent clinical visits, differentiated service delivery and closer support after administering the AHD screening and prophylaxis package of care is anticipated to bring down costs by focusing resources to be more equitably distributed to those in need (335).

Some of the less frequently mentioned but still potentially important interventions include those to attract men to early ART initiation (328), non-judgement and friendly staff welcoming patients who

have previously disengaged and are now returning to care (266, 335, 354) and point of care tests to easily and rapidly screen for coinfections such as TB and meningitis (348).

Conclusions with respect to AHD

In summary, this thesis highlighted both the extent of ongoing AHD and associated mortality, and that it is increasingly predominantly occurring in patients who have already started ART, frequently in patients who have had an interruption to their HIV care. These observations align with those from other high-HIV-burden settings. Aside from recommendations for optimal clinical management in patients with AHD, strengthening the HIV care cascade to provide improved case-holding and clinical guideline compliance, and better systematic health service interventions for those at risk of care interruption can help lesson morbidity and mortality due to AHD. Simplifying HIV care and providing a flexible range of service delivery options aligned to patient needs, especially for those who are doing well, ought to provide the best chance of retaining patients in care and preserving scarce resources for early intervention for those who need them.

Evolution of guidelines

Summary of thesis findings

In this research project, we evaluated guideline changes and their impact on mortality within the ART programme from two perspectives. One perspective considered the CD4 count guideline thresholds that increased over time enabling people living with HIV to initiate ART in progressively earlier stages of infection, and the second perspective looked at how implementation of new policy guidelines impacted the same population. The greatest impact of ART on mortality was seen at the lowest CD4 cell count thresholds at both a population level (intention to treat analysis) and in terms of individual benefit. There was less benefit at higher thresholds, although still noticeable at the individual level when comparing outcomes for those who initiated ART according to new and old guideline thresholds. Thresholds no longer apply today in the test and treat era but it still makes sense to triage the sickest first, regardless of whether they are ART naïve or are re-starting ART after a treatment interruption.

Looking at the impact of new guideline implementation on the ART naïve population, the analyses detailed increasing access to ART which ran ahead of guideline implementation dates, diluting the impact on mortality the new guidelines could have made had access to new eligibility groups been delayed until the guidelines were in place. We saw the greatest increases in ART access between guideline changes instead of just after each implementation date. This likely resulted from both increased accessibility and coverage of ART for those who were already eligible and the agility of

clinicians to act in anticipation of guideline changes helping the sickest get onto ART (regardless of CD4 cell count), knowing their next visit may not be for several months or years.

Guideline changes since 2014

The WHO recommendation that countries initiate people with a CD4 cell counts between 350 and <500 cells/µL was made with some caution in their 2013 guidelines. Although evidence pointing to clinical benefit was moderate, it was unknown if implementation was feasible and if retention and adherence would be high enough to realise the benefits in RLSs (9). WHO guidelines were updated again in 2015 recommending that countries start all people with an HIV diagnosis on ART, regardless of clinical stage or CD4 cell count. The 2015 WHO guideline update was largely informed by data from 3 clinical trials: TEMPRANO, INSIGHT START and HPTN 052 (285).

Trials and observational studies measuring impact of changing CD4 cell count threshold guidelines

Subsequent to the WHO 2015 clinical guideline review group meeting, results from the START, TEMPRANO and HPTN trial were published. The START trial tested benefits and risk of raising the CD4 cell count threshold to >500 cells/µL compared to <350 cells/µL and resulted in a hazard ratio of 0.43 (95%CI: 0.3 - 0.6) for serious and non-serious AIDS-related events or death (170). The TEMPRANO trial had results showing the risk of death or severe HIV-related illness was lower when starting ART earlier with a CD4 cell count >500 cells/µL (aHR 0.56, 95%CI: 0.33 - 0.94). Although the HPTN 052 clinical trial did not look at long term ART outcomes, it also supported removing thresholds, demonstrating early ART to be highly effective in stopping transmission of HIV (356).

Results from this thesis considering ART uptake and mortality at different CD4 cell count thresholds using a quasi-randomised experiment did not demonstrate hazard ratios as strong as the above clinical trials but there are several explanations for this. First, the results from our study are from a real-world setting and included all data from the HIV services in the public sector of the Western Cape province. The public health services do not have the same resources to closely manage and follow-up patients as a clinical trial, and clinicians in the public-sector initiated people on ART outside of guideline recommendations when their knowledge supported doing so. In addition, we only considered mortality and not serious AIDS and non-AIDS-related events. Regardless, the outputs from this real-world setting also support the effectiveness of starting ART early, but also emphasized the effectiveness of starting ART in those with most advanced disease.

A number of observational studies measured the impact of the above guideline changes, including one from Uganda which measured the impact with a before and after study design around the guideline implementation date, looking at the CD4 cell count threshold increase from <350 cells/µL to <500 cells/µL among youth aged 15-24 years old (357). A second one from Australia measured the

impact of both recent guideline changes using a before and after design, from <350 cells/µL to <500 cells/µL and then the change to removal of all CD4 cell count thresholds (358). Both studies reported positive benefits from the CD4 cell count threshold guideline changes: the Ugandan study found a 30% reduction (adjusted odds ratio 95%CI: 0.58 - 0.85) in OIs at 12 months duration on ART and no significant differences in survival, whilst the study in Australia found a strong decreasing trend in time to initiating ART for men and women over the two guideline changes (357, 358), which can decrease the risk of acquiring a potentially fatal opportunistic infection (143, 326, 348, 357). The study from Australia was descriptive and performed in a low-prevalence setting (358).

There have also been a number of trials looking at the effect of expanded early access to ART on incidence, which some hoped would be the tool to contain the epidemic. The Botswana Combination Prevention Project showed a 30% decrease in HIV incidence per annum resulting from their universal testing and treatment (UTT) community trial held from 2013-2018 (359). The ANRS TasP trial could not demonstrate a reduction in HIV incidence due to the offer of UTT not increasing the ART coverage in the trial intervention arms, possibly due to slow linkage to care (360, 361). The PopART trial in Zambia and South Africa showed a 30% reduction of HIV incidence when initiating ART per local guidelines with intervention support. Surprisingly, the UTT arm only showed a 7% decrease, although this arm reached the greatest proportion of viral suppression. The results were confusing but did show evidence that UTT can reduce incidence within a population regardless of the mixed results (362). Although these trials all show benefits of UTT, and some showed a decrease in incidence, it is argued that it is unlikely that UTT will rapidly end the epidemic (361).

Conclusion with respect to the impact of guideline changes

Subsequent to the thesis initiation, there has been a rapid evolution towards universal test and treat. It will no longer be possible or ethical to experimentally test the effectiveness of initiating ART at different CD4 cell count thresholds. The quasi-experimental studies in this thesis provide a rare retrospective review of the effectiveness of ART initiation at defined thresholds, as well as the impact of guideline changes, but are unlikely to further impact policy given the current standard of care.

Evolving associations with poor retention, morbidity, and mortality

Summary of thesis findings

The research in this thesis on AHD a priori focused on gender and interruptions as important drivers of both AHD and mortality. There have been longstanding concerns that clinical outcomes for men with HIV are worse than for women. Interruptions emerged as one likely reason in the analysis of ongoing AHD. The first of the last two studies in this thesis validated higher mortality overall among

men even when adjusting for tuberculosis; however, this risk did decrease over time from 2008 to 2018. The study also highlighted that men were 20% less likely to initiate ART than women. People coinfected with tuberculosis were 70% more likely to die, with the risk increasing over time. Men had twice the proportion of TB prevalence compared to women. The last research paper looking at interruptions also noted the higher risk of death for men, although when limiting to age categories over 34 years old, women were at greater risk for death. Over 56% of people on ART in the Western Cape had a least one treatment interruption of 4 months or longer, while 44% had two interruptions or more. Those with a 4-month treatment interruption were 27% more at risk of death, while those with 4 or more interruptions had a 3-fold increased risk of death compared to people with no treatment interruptions. Both studies also noted the overall higher risk associated with mortality of older age, lower CD4 cell counts and tuberculosis. Pregnancy, in both studies, was found to be protective for risk of mortality.

It is important to note that our measurement for treatment interruptions was 6 months without an ART visit to a health care facility. In the Western Cape, the majority of people have a visit to an ART facility every other month and receive 2 months of treatment, with those new to ART attending more often until stable. The stable patients may get 4 months of treatment in November or December for the December holidays if they are going away and require it. Therefore, a treatment interruption in this study was on average equivalent to 4 months without treatment. In other research the most frequently used measurement for LTF is 3 months, although definitions vary and are as diverse as 2 days beyond an appointment date to a year without a visit.

Gender: What other researchers have found

Although a higher proportion of women are infected with HIV in Southern African countries, men within the HIV services are frequently reported as presenting late, more likely to be lost to the services and having worse outcomes than women (363, 364, 365). The increase in adult life expectancy in South Africa due to the ART treatment scale up in 2011 was 9.0 years for men and 13.2 years for women. In the same year, 57% of HIV-related deaths in men and 41% of HIV-related deaths in women occurred in those who never started ART, despite the free ART services (363). A study using a causal design (g-computation) from Zambia found higher rates of mortality in HIV infected men <30 years of age (concurring with our results), but similar rates in men ≥50 years when compared to women of the same ages (366). Tuberculosis is one of the top causes of death in people living with HIV if left untreated. The research included as part of this thesis, and other studies, describe a higher proportion of TB in men with HIV (235, 367, 368). A study from KwaZulu Natal, South Africa found 8.4 life expectancy years gained in men and 12.8 in women just from reductions in deaths related to HIV co-infection with pulmonary TB since the scale-up of the free ART

programme (235). Age standardised death rates in 2018 in South Africa due to HIV for men was 468 per 100,000 people and 391 per 100,000 for women (364). Interestingly, a study by Johnson and colleagues modelling HIV incidence from 2000-2019 in South Africa showed a substantial decrease in 15–24-year-olds regardless of gender, but a slightly greater decrease in HIV incidence in men (37% to 24%) compared to women (55% to 44%); these reductions were largely attributed to volunteer male medical circumcision and ART (369). This thesis concentrated on mortality within the HIV population, but any reduction in HIV incidence rates will correlate to decreases in HIV-related mortality at a population level. Although men in Southern Africa tend to present later, have slightly worse ART attendance and higher mortality rates, the absolute burden remains greater for women as a substantially larger proportion are living with HIV infection (235).

Interruptions: What other researchers have found

The research included in this thesis and many other studies have described the increasing challenge of retention within the ART programme and its inverse association with treatment interruptions, AHD and mortality (267, 370, 371, 372). A study in Nigeria, following patients from 1 to 3 years on ART, reported 56% of patients as having a least one treatment interruption (>90 days since last visit) and 35% having greater than one interruption (250). A study in Zambia followed people initiating ART over two years and found that 19% who were reported as being LTF had actually died, while 18% of people in care and 71% of people lost to care and traced were viraemic (>1000 copies/ml) (371). The viraemia measurements are discussed here as a proxy for potential AHD in the absence of CD4 cell counts post-ART initiation. Life-long retention continues to be challenging in the high HIV prevalence and resource constrained countries in Sub-Saharan Africa. Most studies are still reporting on treatment interruptions cross-sectionally and categorizing people missing clinical visits as LTF in population-level averages (149, 267, 365, 371). This approach does not allow for an understanding of patterns of engagement, or frequency and length of interruptions. Results do, however, show the clear association of interruptions with AHD and mortality (371, 373, 374). An additional challenge in places without digital CRVS is ascertaining if those not in care are actually LTF, have transferred or have died (375).

What drives interruptions?

As with AHD, although the research presented here did not look into associations with becoming a treatment interrupter or LTF, it is important to understand predictors in order to consider ways to intervene. As many countries do not have digital civil vital registration systems (CVRSs) in place, the following studies may be misclassifying some deaths as treatment interruptions, demonstrating certain characteristics as being associated with treatment interruptions when in fact they are associated with mortality.

A systematic review of 30 studies from sub-Saharan Africa determined the following as associated with becoming LTF (or having a treatment interruption): being a man, between 15 and 35 years of age, unmarried, unemployed, living in a rural setting, identified as having risk behaviours or predisposing conditions (alcohol or drug abuse, smoking, mental health conditions), having a low CD4 cell count at the last visit, TB and/or a history of OIs. Behavioural risk factors and a history of previous OIs had the strongest association with interrupting treatment and becoming lost to care (376). A couple of studies also reported being previously LTF as a significant risk factor for another treatment interruption (253, 377). Qualitative interviews reported multiple challenges to attending clinic visits including not wanting to risk disclosure, having work obligations, transport issues, feeling healthy, too long a wait at the clinic and alcohol-related issues (253, 267, 378).

The more traditional baseline characteristics that overlapped in the majority of studies looking at associations with treatment interruptions and associations with mortality include men, low baseline CD4 cell count and TB (5, 376, 379). Looking at each risk factor separately, there were some conflicting results for both male sex and baseline CD4 cell counts. A few studies found the male sex to be protective (380, 381), a few found no significant difference (382, 383) and the majority reported male sex to be a risk factor for interruptions (376, 384, 385, 386, 387). As male sex has been found associated with mortality, LTF could be a mediator in the pathway to mortality; in addition, these results may reflect the fact that women are more likely to return after a treatment interruption whereas men may remain LTF (380). The study presented in this thesis also demonstrated a link between men, interruptions, and mortality with men who interrupted having had higher rates of death due to interruptions in comparison to women but only during the first 5 years after initiating ART.

A low baseline CD4 count has been shown in a study by May and colleagues to no longer be associated with risk of death at 5 years on ART and thereafter, if the patient is adherent and managing treatment well (353). However, there are some conflicting results regarding a shorter duration on ART and the association between baseline CD4 cell count (and/or WHO Clinical Stage IV) and risk of attrition, LTF, or treatment interruption. Some studies have shown greater attrition/LTF in the higher CD4 cell count strata/WHO Stage I&II (375, 382, 383), some found no differences (149, 169) and others found increased LTF in the lower CD4 cell count strata/WHO Stage IV (383, 384, 386, 388). The research presented as part of this thesis found decreased mortality in the higher CD4 cell count strata and a fairly equal proportion of interrupters and non-interrupters in each stratum. The first six months on ART continues to have the highest mortality rates and that could be why the PopART trial in South Africa found the highest attrition (death and interrupters) from the trial during the same period, with rates peaking at 3 months on ART. However, when considering each CD4 cell

count category separately, the highest attrition in the PopART trial was in people with a baseline CD4 count>500 cells/µL (375), a stratum where one would not anticipate a lot of early deaths (169).

Tuberculosis infection and/or previous OIs have been highlighted in several studies as important drivers of interruptions, perhaps due to a high pill burden, drug-drug interactions, and mobility constraints due to feeling sick. (368, 376, 381). In addition, as tuberculosis and severe bacterial infections are also highly associated with AHD and mortality, it may be that people with severe coinfections are not interrupting treatment (or LTF) but are actually in hospital or have died. This misclassification would overestimate the association between tuberculosis and treatment interruptions. Better retention in care, and adherence support can decrease severe coinfections linked to morbidity and mortality.

Measuring treatment interruptions and LTF

The systematic review and a study by Kaplan and colleagues echoed our research concerns that defining when an individual is considered LTF (usually used in point of time or cross-sectional designs) or having a treatment interruption (recognises the sometimes-repetitive cyclic nature of leaving and returning to care) is difficult and varies widely. This makes comparing results across studies and geographic regions challenging. Within the 30 studies in the systematic review, there were 12 definitions of LTF varying by different lengths of absence (343, 376).

What recent interventions have proven successful?

A few studies noted success with tracing people who have become disengaged from the HIV care services, with 30-70% returning to care (253, 267, 268, 389, 390). Those traced in the community who had more recently interrupted treatment, had a previous interruption, were female, and were previously attending a rural PHC facility had a higher rate of returning (253, 267). However, tracing, recall and re-engagement can only be successful if the HIS can alert managers to patients needing to be traced and if the individuals who require recall have updated patient contact details in their patient health records which are easily accessible. A study performed in 7 Southern African countries could not trace over 40% of patients who were identified as LTF due to poorly captured patient details or complete lack of contact details (365).

The Welcome Back campaigns originally designed by Médecins Sans Frontiers include a training package for health care workers to improve a patient's experience when returning to care. Non-judgemental messaging, and clinics with flexible and extended hours were noted to retain a higher proportion of returning individuals (378). Differentiated service delivery that supports people in different scenarios (working, pregnant, adolescent, men) and in different stages of life to address patient barriers have also been shown to be effective (267, 371).

Some studies have reported re-enforcing adherence locally, in the communities for improved outcomes. One pooled analysis and one systematic review suggested that community-based interventions to improve adherence are successful because they "help the patient build social networks, exercise more autonomy and reduce structural barriers, such as transport cost to the facility"(391). Both studies showed higher rates of treatment adherence when interventions were community based, and in addition the systematic review found adherence clubs in the community also improve retention (391, 392).

Stopping interruptions before they happen would be most ideal and some studies have reported general education and counselling, optimal regimens, community support groups, better case management including extra care for individuals with low CD4 cell counts, and targeting specific patients with substance abuse and mental health issues can improve retention (370, 392, 393).

Conclusion with respect to associations with interruptions and mortality

Associations with outcomes change as the programme matures. In earlier years of scale-up the focus was on baseline associations with mortality. Now with more stable information systems, and a more mature ART service, it is possible to assess how gender and attendance (separately and together) influence ART uptake and outcomes. Several studies reported high return to care rates in those who were traced after a treatment interruption (390). Tracing is only possible, if HIS and clinic standard operations facilitate the capture of updated patient contact details (address and telephone) at each clinic visit and the HIS provide standardised reports of who requires tracing. In addition, in Sub-Saharan Africa, it can be challenging deciphering if individuals classified as LTF are actually LTF, have transferred or have died unless we prioritise digitising civil and vital registration and a linking person-level health data (191, 375). Interventions such as differentiated service delivery to mitigate barriers to care need to be implemented with patient input. Tracing and better management of those who do re-engage should be prioritised. Further evaluation of interventions to keep people in care are needed as interruptions within the ART services continue to remain an ongoing occurrence.

STRENGTHS AND LIMITATIONS

Strengths and limitations pertaining to each specific study within this thesis are discussed in detail in Chapter 2. This section summarizes the common themes affecting the overall thesis.

Strengths

The data used in this thesis cover all public sector health facilities and hospitals, representing estimates from 'real-world' environments with all the operational challenges that exist in resource-constrained health facilities during a time of unprecedented health services scale-up. All digital health data has been linked and consolidated centrally within the PHDC enabling patient longitudinal records, encompassing data from PHC facilities, secondary and tertiary hospitals, laboratories and pharmacies. In addition, the data has also been linked to the South African CRVS, which is over 96% complete.

The data included in this thesis covers over a decade of HIV care and treatment data, enabling an in-depth look at policy changes and temporal trends that occurred over time in this dynamic health services sector.

All aspects of this thesis benefit from the rich first-hand experience of the candidate working in the health services and stewarding relevant health information systems. This enabled an in-depth appreciation of both operational challenges and how to interpret and process data elements.

Finally, the study employed causal approaches to routine health data that improved the robustness of the findings where applicable, providing an evaluation of policy changes where trials would be unfeasible or unethical. The cohort papers also took time-varying effects into account, providing an opportunity to look at treatment interruption frequency and patterns and how they affect mortality.

Limitations

As this thesis was conducted over a long period, some of the findings are no longer policy-relevant as guidelines have further evolved; nevertheless there is considerable value in presenting findings which validate trial outcomes, demonstrating the real-world effectiveness of interventions.

Many analyses were restricted to patients who could be linked to the death registry. Although efforts were made to provide reassurance that this did not introduce a selection bias, it is possible that there might have been systematic differences between those included and those excluded based on availability of a civil identifier.

As the offline TIER software uses prescribed drug data and not dispensed data, and because this data was often poorly collected (simply re-saving the last visit instead of ensuring prescription length and

drugs remained the same), the decision to use appointment visits instead of drug days prescribed was taken. This limited more granular measurement of treatment interruption durations due to the reliance on actual visit dates in analyses of treatment interruptions.

Different analytical approaches could have overcome an important limitation of the regression discontinuity analyses. At the time of writing the papers, some methodologists were starting to look at incorporating censoring into regression discontinuity designs, but these methods were not yet accessible or refined for use.

RECOMMENDATIONS

The following recommendations are made based on the thesis findings as well as informed by the more recent published studies referenced above.

Improving and Sustaining Health Information systems

- *Ensuring divergent health information system software employs data standards*

It is not necessary to implement a single online system throughout all health facilities. What is important is a HIS that supports patient management and which is interoperable with other health information systems such as laboratory, pharmacy, hospital and central databases that provide patient-linked longitudinal records. The information system should be harmonized with other systems regionally, based on interoperability standards.

- *Unique identifiers can be simple and practical in evolving HISs*

Globally unique centrally distributed health identifiers are not necessary and don't need to be an obstacle to linking data in a region or country with many offline facilities. While a global UID system is preferable, it does not need to be perfect in order for data to be linked at scale. Most of the studies in this thesis were conducted in a jurisdiction where there are many duplicate identifiers for patients, but it was still possible to identify these duplicates and create functional virtual cohorts.

- *A tiered approach*

This thesis recommended a tiered approach to ensure countries can evolve to an online system pragmatically and when resources allow. Although South Africa moved almost universally to an offline electronic register, there is evidence that the tiered approach is organically emerging in other settings. This appears to be a pragmatic approach to ensure population-wide coverage for a harmonised health information system. Collecting and linking digital health data centrally via data standards means context-appropriate organically developed health information systems or software applications that already have a successful footprint can continue without major disruption or expensive migration to and training requirements on new systems.

- *Being able to identify patients who need attention*

The important role health information systems play in improving patient care emerged repeatedly, especially with respect to minimising interruptions and responding where people have already interrupted their care. The system needs to be able to produce reports that support improved patient management such as a list of people that need to be recalled prior to their next appointment and a list of people who missed their clinical appointment. In order to do this successfully, the

patient and clinical health details need to be updated at each visit. Standard operating procedures can outline who is responsible for routinely performing these activities and who is responsible for overseeing that the activities are carried out.

- *Sustainable investments in HISs and capacity building for better use of the data*

No matter what approach is taken, whether harmonised across multiple systems or the implementation of a single pervasive system, health information systems require adequate investment, with appropriately trained staff routinely using the data and reports to improve patient health and inform policies.

Operational activities to improve patient care and outcomes

- *Active engagement with alert reports and recalling people back to care*

This thesis demonstrated that unplanned interruptions in treatment and AHD can lead to higher risk of morbidity, death and potential HIV transmission. Active engagement with and reaction to standard alert reports from the HIS can identify people requiring recall and help trace them telephonically or through home visits. Research complimenting this thesis has indicated that tracing people soon after missing an appointment has a greater change of re-engagement than waiting for the patient to be considered lost to care (>90 days).

Multiple interruptions confer additional risk. Providing a welcoming environment where people are not judged on return is an important part of increasing re-engagement and retention.

- *Retaining a focus on advanced HIV disease*

People who present for the first time to HIV care, those returning to ART after a definitive treatment gap and those with an unsuppressed viral load should be assessed for Advanced HIV disease (CD4<200 cells/µL or WHO Stage III or IV) and provided with the WHO recommended package of screening, treatment, and prophylaxis. The health care facilities need to prioritise sicker people first, regardless of whether they have been on ART before or not.

Improving management of advanced HIV disease and optimising viral load monitoring and reaction to unsuppressed viral loads could mitigate preventable deaths. A focus on initiating new people onto treatment is not enough; people with poor laboratory results and those missing clinical appointments, need to be recalled in order to manage their advancing disease, provide counselling, and retain them in care.

- *Allowing for clinical agility where expertise and resources exist*

Over time, an increasingly larger proportion of people initiated ART with ineligible CD4 cell counts in the months and years leading up to the guideline changes that would make them formally eligible. Greatest ART access was in the months leading up to guideline changes rather than just after the new guideline implementation.

Guideline changes are often discussed in expert groups long before they are implemented, and are contemplated when accumulating evidence supports benefit to patients. In the case of ART, each successive CD4 cell count threshold guideline change offered ART to a larger pool of people, with the aim of decreasing HIV transmission in the population and decreasing morbidity and mortality. There is evidence that clinicians who knew new guidelines were in the pipeline, or who were aware of the same evidence being considered by guideline committees, started the sicker people who were soon to be eligible in anticipation of imminent changes. In addition, increasing ART availability resulted in much higher proportions of those eligible under existing guidelines gaining access to ART over time, and this increased coverage likely had a large impact on outcomes independent of guideline changes.

Where resources allow, this clinical agility and triage is likely an important contributor to improved patient outcomes.

International targets need to recognise and help minimise the cyclic nature of treatment and care

- *Add number of people entering and leaving care to international targets*

Many RLSs do not have centrally-linked population-wide datasets to accurately estimate their 95:95:95 targets set by the joint WHO UNAIDS programme to fast track the repose to HIV. As a second-best option, RLSs resort to unlinked datasets reporting ART enrolment for the second 95 and the proportion of suppressed viral load tests among those done to report the last 95. Although there are modelling efforts to validate and improve these estimates per country, this does not provide a granular understanding of where the continuum of care is most broken, and where interventions should focus. A cyclical cascade which describes those exiting and entering care at each step in the continuum could enable the development of effective interventions to target the areas of care where there could be the greatest impact.

CONCLUSIONS

This thesis looked at health information systems, ART impact, guideline effectiveness, and associations with mortality in order to better understand how to identify people on ART who may have or will be at risk of dying from AHD. Findings show that pragmatic interoperable offline/hybrid/online health information systems can be implemented in RLSs to improve patient care at both facility and higher levels of the health services, provide information on interventions and inform policy and resource allocation. Programmatic ART outcomes did improve during expansion of ART eligibility including into the time-period of the treat-all policy when CD4 cell count criteria were removed. More people accessed ART over time independent of guideline changes improving population HIV outcomes. The guidelines changes were still shown to be effective at an individual level. The number of people with AHD has not decreased however due to ART experienced patients returning to care after interruptions with AHD. Recommendations focussed on improving systems for retention and re-engagement, and are most likely applicable to similar public-sector settings in Southern Africa.

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