

**The feasibility and effectiveness of
universal antiretroviral therapy provision in adults:
The Treat-All approach
in the public-sector in rural Swaziland**

By

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Declaration

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Bernhard Kerschberger

09 March 2021

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Finally, I would like to acknowledge all patients and research participants of the Shiselweni region, Eswatini.

Preface

Inclusion of papers and the candidate`s own scientific work

This thesis includes published papers as outlined in the University of Cape Town (UCT) Rule GP 6.7.

I confirm that I have been granted permission by the UCT Doctoral Degrees Board to include the following publications in my PhD thesis, and where co-authorships are involved, my co-authors have agreed that I may include the publications:

- Kerschberger B, Schomaker M, Ciglenecki I, et al. Programmatic outcomes and impact of rapid public sector antiretroviral therapy expansion in adults prior to introduction of the WHO treat-all approach in rural Eswatini. *Trop Med Int Health*. 2019;24(6):701-714. doi:10.1111/tmi.13234
- Kerschberger B, Jobanputra K, Schomaker M, et al. Feasibility of antiretroviral therapy initiation under the treat-all policy under routine conditions: a prospective cohort study from Eswatini. *J Int AIDS Soc*. 2019;22(10):e25401. doi:10.1002/jia2.25401
- Kerschberger B, Schomaker M, Jobanputra K, et al. HIV programmatic outcomes following implementation of the “Treat-All” policy in a public sector setting in Eswatini: a prospective cohort study. *J Int AIDS Soc*. 2020;23(3):e25458. doi:10.1002/jia2.25458
- Kerschberger B, Boulle A, Kuwengwa R, Masango M, Ciglenecki I, Schomaker M. The impact of same-day antiretroviral therapy initiation under the WHO Treat-All policy. *American Journal of Epidemiology*. 2021; 12:kwab032. doi: 10.1093/aje/kwab032. Online ahead of print.
- Kerschberger B, Schomaker M, Telnov A, et al. Decreased risk of HIV-associated TB during antiretroviral therapy expansion in rural Eswatini from 2009 to 2016: a cohort and population-based analysis. *Trop Med Int Health*. 2019;24(9):1114-1127. doi:10.1111/tmi.13290

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In summary, the contribution of the candidate to establishment of the research cohorts, individual research protocols, data acquisition and preparation, analyses, and writing of the papers is detailed under Chapter II (Results). The senior co-author(s) of the University of Cape Town and of Médecins Sans Frontières, as well as other co-authors, have confirmed to the University of Cape Town Doctoral

Degrees Board that the included papers are a reflection of the candidate's own scientific work. In summary, the candidate is the lead author and primary researcher of each included publication.

Literature review

The literature review outlines the evidence as to the feasibility of universal antiretroviral (ART) provision (Treat-All) in resource-limited settings at the time of conceptualization of this thesis (September 2017). Based on the evidence existing at the time, the aims and objectives of this thesis were developed. The evolution of this evidence during this project is reflected in the literature cited in the papers as well as in the thesis in Chapter III (Discussion) that includes literature until February 2020. In addition, the description of the setting includes literature that became available after the conceptualization of this thesis, apart from the published papers included in this thesis under Chapter II (Results).

Formatting of reference style and tables

The published papers – including figures, tables, appendices, and supplementary material – are word-for-word copies of the versions in PubMed Central® (PMC).¹ This thesis applies a consistent referencing style, with the style of referencing of the publications themselves updated accordingly and presented in the References section. In addition, the tables and supplementary material have been consistently formatted.

Table of contents

Chapter I: Introduction and literature review.....	1
Introduction	2
Literature review	5
Effectiveness of Treat-All in RLS	5
Linkages from HIV testing to care enrolment.....	8
Linkages from pre-treatment care to ART initiation.....	10
Achieving and sustaining favourable ART outcomes	13
ART expansion and TB	19
Studies investigating Treat-All	20
Methodological challenges	23
Rationale	26
Aim and objectives.....	28
Setting	29
Eswatini	29
Study setting – the Shiselweni region	29
Data management.....	33
Data collection	33
Data sources.....	33
The candidate’s role in data management.....	35
Prospective Treat-All study (Objectives 2, 3, and 4)	37
Retrospective analyses of routine data (Objectives 1, 5)	37
Chapter II: Results	39
Results for Objective 1	40
Results for Objective 2.....	72
Results for Objective 3.....	102
Results for Objective 4.....	138
Results for Objective 5.....	173
Chapter III: Discussion	209
Interpretation of findings.....	211
Additional methodological considerations	226
Limitations and strengths	234
Recommendations	239
Conclusions	242
References	243

List of tables and figures (excluding those in published papers)

Table 1: Main Treat-All trials evaluating the impact of the Treat-All approach.

Table 2: Standard composition of primary care facilities in the Shiselweni region from 2010 onwards.

Table 3: Data sources used for analyses.

Table 4: Linkage to HIV care, ART initiation and ART outcomes of main Treat-All trials, and of Nhlengano health zone following the Treat-All approach.

Table 5: Treat-All trials assessing the impact of Treat-All on population-level ART coverage, viral suppression and HIV incidence.

Figure 1: Map of Eswatini and the Shiselweni region with health facilities of Nhlengano, Hlathikulu and Matsanjeni health zones.

Figure 2: The HIV care cascade and population-level impact.

Figure 3: Temporal trends in population-level outcomes along the HIV care continuum for PLHIV in the Shiselweni region.

Figure 4: Population-level outcomes along the HIV care continuum in the four regions of Eswatini in 2016/2017.

List of abbreviations

ART	Antiretroviral therapy / antiretroviral treatment
ARVs	Antiretroviral drugs
DAG(s)	Directed acyclic graph(s)
EAA	Early Access to ART
EFV	Efavirenz
HR	Hazard ratio
HRH	Human Resources for Health
HTS	HIV testing services
LTFU	Loss to follow-up
MOH	Ministry of Health
MSF	Médecins Sans Frontières
NGO(s)	Non-governmental organization(s)
NVP	Nevirapine
PLHIV	People living with HIV
POC	Point-of-care
RCT(s)	Randomized controlled trial(s)
RLS	Resource limited setting(s)
SOC	Standard of care
TB	Tuberculosis
VL	Viral load
WHO	World Health Organization

Glossary of terms

Advanced HIV disease – Refers to patients presenting with CD4 count below 200 cells/mm³ and/or WHO clinical stage III/IV to HIV care and/or ART initiation. This term is used interchangeably with the term “late presentation”.

All-cause attrition – This is attrition during the pre-treatment (pre-ART) or ART care period and combines the outcomes of death and lost to follow-up (LTFU).

Early ART – Refers to ART initiation between 1 and 14 days after HIV care enrolment.

Eswatini/ Swaziland – The Kingdom of Swaziland changed the country’s name to “The Kingdom of Eswatini” at the 50th anniversary of the country's independence in April 2018. Eswatini is used in most of the thesis unless the term Swaziland is more appropriate.

Health cluster – See Health zone.

Health zone – The terms health zone and health cluster are used interchangeable. The Shiselweni region is divided into three health zones. Each health zone is served by one secondary care facility with inpatient capacity and 8 to 10 primary care clinics.

Late presentation – See above, “Advanced HIV disease”.

Same-day ART – Refers to ART initiation on the same days as HIV care enrolment, which may or may not be on the same day as HIV diagnosis.

Standard of care (SOC) – The care that is provided as standard in the country as per national guidelines; refers to linkage procedures, ART initiation and ART follow-up care.

Treat-All – Refers to the public health programmatic approach of immediate ART initiation at the time of HIV diagnosis and/or HIV care enrolment irrespective of the immunological criteria of CD4 cell count and WHO clinical staging. Different terms are used in the literature, such as “Universal ART provision”, “Treat-All”,² “Treatment as Prevention”,³ “Test and Start” in Eswatini, “Universal ART”, and “Early Access to ART”.⁴ For this thesis, the terms universal ART and Treat-All (or treat-all) are used interchangeably.

UNAIDS 90-90-90 targets – This refers to the HIV care cascade targets established by UNAIDS: 90% of people living with HIV should know their HIV status, 90% of people knowing their HIV status should receive ART, and 90% of people receiving ART should be virally suppressed.⁵ At the population level, these targets translate to 90% of PLHIV knowing their HIV-positive status, 81% of PLHIV receiving ART, and 73% of PLHIV being virally suppressed.⁵

Abstract

The World Health Organization (WHO) recommends antiretroviral therapy (ART) initiation at the time of HIV diagnosis irrespective of immunological criteria – known as Treat-All – aiming at improving individual level health outcomes and reducing HIV transmission. However, concerns were raised about the feasibility of further treatment expansion in already fragile health systems in resource-limited settings (RLS). This thesis evaluates the feasibility of ART expansion under the Treat-All approach in a public sector setting in Eswatini. A wide range of HIV care expansion outcomes were explored at patient, programme, and population level.

The studies were conducted in outpatient departments of primary and secondary care facilities of the predominantly rural Shiselweni region of Eswatini, from 2007 to 2016. The study population consisted of people living with HIV (PLHIV) who were offered ART under Treat-All and standard of care (SOC) as well as HIV co-infected tuberculosis (TB) patients.

The result section of this thesis presents the findings through published manuscripts. The first paper describes the feasibility of rapid public sector ART expansion before the Treat-All approach became policy. The active ART cohort and treatment coverage among PLHIV expanded approximately 8-fold. Attrition decreased over time, which was most pronounced in the most recent treatment cohort. Attrition remained high for previously described higher risk socio-demographic (e.g. young age, men), clinical (e.g. higher WHO clinical stage, lower CD4 cell count), and programme factors (e.g. toxic drug regimens). The second paper investigates the feasibility of ART initiation under Treat-All compared with SOC. ART initiation was higher and quicker under Treat-All, mainly because more patients with high baseline CD4 cell count initiated treatment under the policy of universal ART. ART initiation was delayed for patients co-infected with TB disease under Treat-All, but was higher overall after 1 month compared with patients without TB. Patients presenting with advanced HIV disease ($CD4 < 200$ cells/mm³ and/or WHO III/IV clinical stage) had similar cumulative ART initiation rates with both interventions, although initiation was faster under Treat-All during the first month after care enrolment. The third paper assesses treatment outcomes of patients initiated on ART under Treat-All compared with SOC. Patients under Treat-All initiated ART with a higher median CD4 cell count and were more likely to achieve viral suppression. The risk of an unfavourable treatment outcome and viral failure was similar between both interventions. Under Treat-All, previously described higher risk socio-demographic (e.g. younger age, pregnancy) and clinical factors (e.g. low CD4 cell count, higher WHO clinical staging) increased the risk of the unfavourable outcome. The fourth paper evaluated the effectiveness and efficacy of ART initiation on the day of facility-based HIV care enrolment under Treat-All compared with patients initiated 1 to 14 days after care enrolment. Among patients initiated on treatment, same-day ART initiation increased the risk of an unfavourable outcome. This effect was mainly seen during the first months of ART after HIV care

enrolment. The fifth paper describes temporal trends in HIV-associated TB during rapid ART expansion including the time-period of Treat-All. Notifications of TB disease decreased by 5-fold over a period of 8 years, and the decline was most pronounced in HIV-associated TB disease compared with HIV-negative TB. The main population-level predictor of TB disease was HIV disease, and the decline in TB coincided with increased access to ART in PLHIV.

The thesis concludes that ART expansion and Treat-All are feasible in this RLS, by achieving favourable HIV care outcomes in terms of ART initiation and treatment, for patients with high CD4 cell counts as well for patients presenting late to HIV care. It also highlights the potential population level impact of rapid ART expansion on reducing the burden of HIV-associated TB disease over time. It cautions however against the assumption that outcomes will be improved through ART initiation on the same day as facility-based HIV care enrolment under the Treat-All approach.

Chapter I: Introduction and literature review

INTRODUCTION

In 2015 an estimated 37.7 million people lived with HIV globally and 2.1 million new infections were reported.⁶ Eastern and Southern Africa accounted for approximately half of new infections (960,000) and people living with HIV (PLHIV) (19.0 million).⁶ In Sub-Saharan Africa, HIV is intertwined with the tuberculosis (TB) epidemic, resulting in high TB incidence (275 cases per 100,000 person-years in 2015) and rates of co-infection, and 23 out of 30 high HIV/TB burden countries being in Africa.⁷

Effective antiretroviral therapy (ART) reduces HIV- and TB-related morbidity and mortality by suppressing the HIV virus and restoring immunological recovery.⁸ Although ART was mainly available in Western countries during the early years of the HIV epidemic, small vertical HIV pilot programmes demonstrated the feasibility of ART provision in resource-limited settings (RLS).⁹ Recognizing the multiple operational constraints in these settings (e.g. lack of qualified human resources, suboptimal funding, many PLHIV requiring ART), a public-health oriented approach was proposed to allow for simplification of HIV care.^{10,11}

Successive expansion of ART in RLS

In 2006, the World Health Organization (WHO) recommended a public health approach with simplified ART regimens.¹² Two years later in 2008, the decentralization and integration of HIV services was recommended,¹³ and the 2013 WHO treatment guidelines endorsed task shifting, adherence monitoring support, and HIV service decentralization and integration into TB and primary care settings.¹⁴ In parallel, ART eligibility threshold criteria were successively expanded from CD4 count ≤ 200 cells/mm³, to CD4 count ≤ 350 cells/mm³ in 2011, and to CD4 count ≤ 500 cells/mm³ in 2013.^{12,14–16} In 2013, lifelong ART was proposed for pregnant and breastfeeding women at the time of HIV diagnosis and irrespective of CD4 cell count threshold criteria, widely known as prevention of mother-to-child transmission option B+ (PMTCTB+).¹⁴ These guidelines also emphasized the need to prioritize populations in greatest need for ART, such as patients presenting late to HIV care.¹⁴

Expansion of HIV care resulted in a decline in AIDS-related mortality.⁶ In 2015, 46% of PLHIV received ART, with most gains made in Eastern and Southern Africa with ART coverage increasing from 24% to 54% (10.3 million) between 2010 and 2015.⁶ In some countries in Sub-Saharan Africa, treatment coverage increased to above 90% in patients co-infected with TB, averting an estimated 11 million deaths related to TB between 2000 and 2015.⁷

International efforts to expand HIV care continued. In September 2015, WHO announced revised early-release guidelines, for the first time recommending ART initiation for all PLHIV at the time of HIV diagnosis and irrespective of CD4 cell count and WHO clinical staging criteria.¹⁷ This

recommendation – known as Treat-All – was based on evidence from randomized controlled trials (RCTs) showing that early ART initiation when the CD4 cell counts were still high had a therapeutic benefit at the individual level.^{18,19} ART has also shown to reduce HIV transmission in sero-discordant couples,²⁰ indicating potential as an HIV prevention tool. Furthermore, ART reduces the risk of TB at the individual level²¹ and possibly decreases TB notification rates at the population level in high HIV/TB prevalence settings.^{22,23} The operational benefits of immediate ART were recognized too.²⁴ The separation of pre-ART and ART care was no longer required and ART initiation became possible irrespective of availability of CD4 cell count measurements, possibly resulting in a shortened pre-treatment period and less pre-treatment attrition.¹⁶

High-level political support for ART expansion has grown over time. It was initiated with the Millennium Development Goals in 2000, with goal 6 aiming at combatting HIV/AIDS.²⁵ It was supported by the “3 by 5” initiative aiming at providing access to ART for 3 million PLHIV in RLS by 2005,²⁶ and by the “15 by 15” initiative facilitating access to ART for 15 million by 2015.²⁷ In the same year, the newly announced Sustainable Development Goals contained two targets aiming at ending the AIDS epidemic by 2030 and achieving universal health coverage.²⁸ The 2014 UNAIDS Fast-Track implementation agenda – with a focus on the 30 low and middle income countries most affected by HIV – provides a roadmap for accelerated implementation of effective HIV prevention and treatment interventions to reduce HIV infections by 90% and avert 21 million AIDS-related deaths by 2030.²⁹ This strategy utilizes the UNAIDS 90-90-90 cascade targets, stating that by 2020, 90% of PLHIV should know their HIV-positive status, 90% of those knowing their HIV status should receive ART, and 90% of those receiving treatment should be virally suppressed.⁵ It advocates for increased focus on quality care and recognizes immediate ART for PLHIV as a key strategy.^{5,29} In addition, international TB targets were set to accelerate the TB treatment response. In high HIV/TB prevalence settings, two of these targets – 95% decline in deaths due to TB and 90% TB incidence reduction – may depend on achieving the UNAIDS 90-90-90 HIV cascade targets, given the potential of ART to reduce TB notifications and TB mortality.

Remaining gaps and real-world impact of Treat-All

Despite the introduction of policies supporting universal ART, translating them into effective action is challenging in RLS which face an underfunded health sector, inadequate medical capacity, and slow implementation of international recommendations.^{30–35} Suboptimal access to HIV services has persisted, leaving PLHIV undiagnosed and without access to ART and viral load (VL) testing.³⁶ For instance, treatment coverage in PLHIV in Eastern and Southern Africa was 60% in 2016,³⁷ with ART initiations happening late during HIV infection and the majority of AIDS-related deaths being in PLHIV not receiving ART.^{38,39} Given the complexity of challenges and uncertainty about the ability

of national HIV programmes to effectively expand Fast-Track interventions, concerns persist with regards to the feasibility and real-world impact of Treat-All in RLS.^{31–33,35,39–43}

LITERATURE REVIEW

This literature review summarizes the literature related to the operational feasibility and potential impact of implementing Treat-All strategies in RLS, with a focus on Sub-Saharan Africa. This requires an understanding of potential benefits and risks of Treat-All, as well as the current status of HIV care programming along the HIV care continuum. As the focus of this research project is on feasibility of Treat-All after the diagnosis of HIV infection, the first step in the cascade – diagnosis of HIV infection – is not elaborated. This literature review focuses on interventions for general adult PLHIV in Sub-Saharan Africa without reviewing vertical programmes targeting key populations (men who have sex with men, sex workers, transgender people, injecting drug users) and sero-discordant couples. It highlights operational and treatment priority areas that may be key to informing HIV programming and future health policy in the context of Treat-All. This literature review covers the time period until September 2017, the time of the inception of this research project.

Effectiveness of Treat-All in RLS

Experimental evidence on HIV incidence

Individual-level effectiveness

RCTs have established the evidence of the therapeutic and transmission reduction benefits of early ART.^{18–20} The TEMPRANO trial (ANRS 12136) demonstrated that early ART initiation and isoniazid preventive therapy for 6 months independently lowered the risk of severe HIV-related illness by 44% and all-cause death by 35% without an increase in grade 3 and 4 adverse events when compared with deferred treatment provision following previous WHO treatment eligibility criteria.¹⁸ The multi-country two arm START trial showed a significant reduction in serious AIDS-related and non-AIDS-related illness by 72% and 39% without increasing adverse grade 4 treatment events when ART was initiated at CD4 count >500 cells/mm³ vs CD4 count ≤ 350 cells/mm³.¹⁹ The multi-country HPTN 052 trial demonstrated a risk reduction of genetically linked HIV-1 transmission by 93% among sero-discordant couples when the HIV-infected partner initiated treatment at a CD4 count between 350 and 500 cells/mm³ (early arm) vs CD4 count <250 cells/mm³ (deferred arm).²⁰ Genetically linked HIV infections in the early arm occurred before the HIV-positive partner was virally suppressed, and one third of other HIV transmissions were genetically unlinked and thus likely occurred outside the couple.²⁰

Population-level effectiveness

With increasing ART coverage, an increasing proportion of PLHIV is virally suppressed, likely reducing HIV transmission.⁴⁴ An observational cohort from KwaZulu Natal (South Africa) between 2004 and 2011 reported a 38% reduced risk of HIV acquisition for HIV-negative individuals residing in a community with higher ART coverage (30-40%) compared with a community with lower ART coverage (<10%), with each percentage point increase in ART coverage reducing the risk of HIV acquisition by 1.4%.⁴⁵ However, limitations of the study were likely unmeasured differences in the people (e.g. sexual behavioural factors) between high and low ART coverage communities and cross-contamination respectively.⁴⁵

Measuring a potential HIV incidence reduction is the main objective of several ongoing Treat-All trials (Table 1).⁴⁶⁻⁴⁸ Interim updates from the Treat-All TasP trial, however, showed no HIV incidence reduction under Treat-All (2.13 per 100 person-years, 95% CI 1.85-2.41) compared with SOC (2.27 per 100 person-years, 95% CI 2.00-2.55).⁴⁹ According to the authors and despite high population-level awareness of HIV status, low linkage rates from community-based HTS to HIV care (47% at 12 months under Treat-All and SOC) was the likely reason as it left the majority of PLHIV without access to ART and therefore virally unsuppressed. This study was conducted in the same setting but later calendar periods (2012 to 2016) than the aforementioned observational study (2004 to 2011)⁴⁵ reporting declining HIV incidence during ART scale-up.⁴⁵

Population-level impact from modelling studies

Overall, modelling studies predict population-level benefits and cost-effectiveness of universal HIV care and ART provision. Universal access to HIV testing followed by immediate ART initiation could reduce annual HIV incidence and mortality to less than 1 case per 1,000 people, possibly resulting in HIV elimination in generalized epidemics.²⁴ A more than 60% reduction in HIV transmission was predicted for adoption of universal home-based HIV testing services (HTS) and universal ART strategies.⁵⁰ Changing the treatment eligibility criteria towards universal ART appears to be cost-effective in Sub-Saharan Africa, even under health system constraints, mainly by averting new HIV infections and decreasing loss to follow-up (LTFU) and mortality in otherwise treatment-ineligible patients.⁵¹ Although achieving the UNAIDS 90-90-90 targets requires significant investments, it is likely to be cost-effective because of reductions in mortality, HIV transmissions, and maternal orphans.⁵² Finally, the potential impact of universal ART on the TB epidemic has been acknowledged,⁵³ with a reduction in population-level TB incidence predicted during ART expansion.^{22,54,55}

Two modelling studies, however, arrived at different conclusions. Implementing Treat-All in Kenya under a weak HIV care cascade would not be cost-effective compared with the scale-up of combination interventions addressing the multiple gaps along the HIV care continuum.⁴⁰ The probability of HIV elimination and the cost-effectiveness was drastically reduced in South Africa⁵⁶

when survival time on ART was assumed to be longer than assumed in a previously mentioned modelling study.²⁴

Operational challenges and early evidence

Individual and public health benefits derived from modelling studies and from RCTs conducted under controlled conditions may lack generalizability to real-world settings. Although Treat-All showed favourable patient outcomes in concentrated epidemics in Western settings, implementation experience from RLS is limited.³⁴ Before the introduction of the 2013 WHO guidelines, under-resourced health settings were already doubted to have the ability to provide sufficient quality care to fast-growing HIV cohorts⁵⁷ and to effectively transition from an HIV emergency response to a sustainable approach,⁵⁸ given high pre-existing HIV care attrition, the gap between policy and HIV programming, the gap between the ideal and real-world situations, lack of qualified human resources for health, and frail supply chains.^{34,57,58} Other challenges include combining quality life-saving services for patients in greatest need of ART (e.g. PLHIV with advanced HIV disease) with sustainable chronic care services for patients stable on treatment.⁵⁸ In addition, the feasibility of Treat-All may be context specific. A survey found that HIV care facilities performed overall at a high standard, but significant inter- and intra-country variations were detected.⁵⁹ In 2015, WHO published early lessons learnt from countries implementing Treat-All and found inferior ART retention and viral suppression for patients with high baseline CD4 cell counts despite high acceptability of universal ART in the general HIV-infected population in Brazil.² In Sub-Saharan Africa, lessons learnt from public sector Treat-All strategies are limited to the roll-out of PMTCTB+ programmes, demonstrating high uptake of ART and high attrition thereafter.³⁴

Effectiveness of HIV care provision along the HIV care cascade

For Treat-All to have real-world impact, HIV care programmes need to perform with high quality along the HIV care cascade. Also referred to as the HIV care continuum, the cascade describes the different steps and periods that PLHIV pass through from HIV testing to diagnosis, HIV care enrolment, ART initiation, treatment retention, and viral suppression.^{60–62} The cascade is leaking at each step, with attrition during the first steps of the cascade impacting later stages.^{61,63} Various interventions aiming at overcoming these gaps and thus supporting HIV care expansion have been evaluated in RLS.^{60,62,63} For instance, decentralization and simplification of HIV care, task-shifting, and introduction of routine VL testing and new care models were found to be efficient,^{16,34,57,64,65} and combining these interventions may be key to strengthening the entire HIV care continuum.⁶²

Performance of HIV programmes using the Treat-All approach can be measured against achieving and sustaining the UNAIDS 90-90-90 cascade targets. Although an increasing number of HIV programmes utilize these indicators, the comparison between settings is limited because of

inconsistencies in data sources, definitions, and analytical methods applied.^{66,67} For instance, analyses may focus on specific elements of the cascade, consider the entire HIV care continuum, and apply different definitions for linkage, retention, and viral suppression.^{67–73}

The next sections focus on the different steps along the HIV care cascade, starting from linkage to HIV care. These steps show similarities and interventions can address multiple steps along the cascade at the same time.

Linkages from HIV testing to care enrolment

After the diagnosis of HIV infection, the next step in the HIV care cascade is linkage to HIV care, thus contributing to the second 90 of the UNAIDS 90-90-90 cascade targets.⁵ However, linkage is often suboptimal in RLS. A systematic review, which included studies from Sub-Saharan Africa conducted between 2002 and 2010, analysed combined linkage from community-based and facility-based HTS to HIV care enrolment and ART initiation.⁷³ It found that only 72% of patients received a CD4 cell count, 40% were eligible for ART according to context-specific CD4 count eligibility criteria ranging from 200 to 300 cells/mm³, and 25% started treatment.⁷³ Overall, 63% of treatment eligible patients initiated ART at a median of 22 to 95 days, while treatment ineligible patients had higher pre-treatment attrition and lower mortality.⁷³

Predictors of linkage to care

Factors affecting pre-treatment attrition and linkage to HIV care are multifactorial. They include demographic and socio-economic (e.g. costs for transportation, employment) factors, psychosocial determinants (e.g. stigma, fear of side effects of ART), and health system factors (e.g. waiting time, shortages in medical staff), as well as clinical factors (e.g. CD4 count, poor health, TB co-infection).^{73,74}

Interventions to increase linkage

Intervention-specific factors also affect linkages. Higher linkages were reported for facilitation of transportation, service decentralization and integration, point-of-care (POC) CD4 testing, facility-related interventions (e.g. shortening the time from eligibility to ART initiation by reducing pre-treatment visits), improved monitoring systems for the pre-treatment time period, task-shifting as well as specific patient support interventions (e.g. enhanced post-test counselling, support groups, treatment literacy), enhanced patient self-management, and patient escorts.^{64,73–75} Most of these interventions are recommended by WHO,¹⁶ yet HIV programmes implement them in different combinations and with varying quality.^{76,77}

Linkage to care in Eswatini

Pre-treatment linkages are also inferior in Eswatini. In 2011 and 2012, of HIV-positive patients identified through a nationwide community-based voluntary male circumcision campaign and the household Swaziland HIV Incidence Measurement Survey (SHIMS), only 14%, 24%, and 37% of HIV-positive cases were enrolled into facility-based care at 3, 12, and 24 months.⁷⁸ Adherence to the national linkage to care standard operating procedures was low, with less than half of the patients receiving recommended administrative and telephonic follow-up patient tracking procedures despite the availability of tools, phones, and airtime.⁷⁸ Decentralized HIV care settings (primary vs secondary care facilities) were more likely to engage patients, and 25% of patients linked to alternate facilities.⁷⁸

In 2013 in the Shiselweni region, only 34% of HIV-positive patients diagnosed through community-based HTS linked to facility-based care within 6 months, of whom 52% of treatment eligible patients (2010 WHO eligibility criteria) initiated ART.⁷⁹ People aged 20-29 years, and patients who tested previously HIV-negative (vs first-time testers) were less likely to link, while there was no difference by sex, community-based HTS strategy, and marital status.⁷⁹ A qualitative study from the same setting investigating barriers to timely linkage suggested that half of the patients classified as not linked self-reported successful linkage at the referral facility or elsewhere,⁸⁰ indicating a weakness in the monitoring system and possible underestimation of linkage.

From 2013 to 2014, a nationwide cluster site-randomized trial implemented streamlined interventions (facility-based POC CD4 testing at HIV diagnosis, accelerated ART for patients with CD4 count ≤ 350 cells/mm³, SMS appointment reminders, a prevention package for pre-ART patients, and telephone voucher financial incentive) at integrated and co-located HIV sites to improve intra-facility linkages and HIV care outcomes.^{70,71} Although the median time to HIV care enrolment decreased from 7.4 to 2.5 days and the median time to ART initiation from 17 to 8 days when compared with standard of care (SOC), crude HIV care enrolment and ART initiation did not improve significantly.⁷⁰ However, the 12-month probability of composite pre-ART and ART care retention was 47% higher for the streamlined intervention.⁷⁰

Linkage to care under Treat-All

The cluster-randomized TasP (ANRS 12249) trial in KwaZulu Natal, South Africa (Table 1), reported 36.9% linkage to HIV care at 3 months after referral from home-based HTS.⁸¹ While linkage was increased for patients with a known HIV-infected family member, it was lower for students (vs employed), people with some secondary or higher education (vs primary or less), residency more than one kilometre from the nearest treatment facility (vs <1 km), and for patients not previously in HIV care.⁸¹ Notably, not all patients were newly diagnosed with HIV (43%) but some were previously diagnosed without engagement into HIV care (26%) or defaulted after linkage to HIV care (31%).⁸¹

The SEARCH community cluster-randomized controlled trial in Uganda and Kenya (Table 1) linked 86% of patients to HIV care within 1 year of HIV diagnosis.⁶⁸ Enhanced patient support interventions were provided through a streamlined care model and included immediate patient tracing activities by phone and physically in case of missed linkage clinic visit.⁸¹ Factors associated with linkage to HIV care were not described, as the main outcome was retention in HIV care.

Finally, public health messaging on when to start ART⁸¹ and the belief in an effective health system may impact linkages to care under Treat-All. For instance, patients were less likely to link to care when they perceived themselves as healthy and not in need of ART, doubted the HIV-positive test results, feared drug toxicities, or believed that drug supplies were not sufficient or unavailable at the facility.^{82,83}

Linkages from pre-treatment care to ART initiation

After enrolment into pre-treatment HIV care, the next step in the cascade is timely ART initiation, contributing to the second 90 of the UNAIDS 90-90-90 cascade targets.⁵ Previous WHO treatment guidelines required patients to remain in pre-treatment care until they become eligible for ART according to CD4 count thresholds and WHO clinical staging criteria.¹⁴ This pre-treatment waiting period is associated with increased rates of LTFU varying between 23% and 88% across settings.⁸⁴

Predictors of retention in pre-treatment care

Various factors are associated with higher retention in care before ART eligibility, including age above 25 years, non-pregnant women, higher income, and free cotrimoxazol prophylaxis, while findings with regards to physical distance to the nearest facility were inconclusive.⁸⁴ Factors related to advanced HIV disease such as lower CD4 cell count, anaemia, and TB co-infection appeared to be protective against LTFU.⁸⁴

Similarly, predictors of pre-treatment losses for the time period from ART eligibility assessment to ART initiation were demographic, socio-economic (e.g. lower education, transportation costs), health system factors (e.g. human resource shortages, long waiting time), clinical (e.g. advanced HIV disease, TB co-infection), perceived good health, and psychosocial (stigma, fear of drug toxicities).^{74,85}

Notably, there appeared to be a contradiction with regards to advanced HIV disease. It appeared protective against LTFU during the pre-treatment period before ART eligibility, while it appeared to increase losses between the time of ART eligibility assessment and ART initiation. Possible explanation of these different findings could be heterogeneity of studies, different patient follow-up procedures in place, data errors, and other unmeasured factors.

Interventions to increase ART initiations

HIV care interventions can intervene during this pre-treatment period. A systematic review of studies published from settings in Sub-Saharan Africa between 2008 and 2015 concluded that various pre-treatment HIV care interventions potentially increase ART initiation, measured from the time of HIV testing, POC CD4 testing, HIV care enrolment, or treatment eligibility:⁸⁶ 1) availability of POC CD4 testing with possible integration into primary care settings and same-day CD4 cell count result; 2) home-based combination interventions providing POC CD4 testing and patient referral; 3) HIV self-testing combined with home-based ART initiation; 4) clinic operations interventions comprising HIV service integration, training of health workers, and same-day ART initiation; and 5) patient-directed packages of support services including specific pre-treatment interventions combined with task-shifting and pre-treatment counselling, SMS services to notify patients about CD4 test results, and specific linkage to care intervention packages combined with tracing interventions. In contrast, ART initiation appeared lower in the case of provider-initiated HTS for a study population mainly consisting of patients presenting with advanced HIV disease.⁸⁶ Counselling and support interventions including home visits, facilitation of facility visits, and phone follow-up by lay counsellors or peer supporters did overall not show an impact on ART initiation.⁸⁶

ART initiation in patients with high CD4 count

Patients presenting with high CD4 count need to start ART in a timely fashion under Treat-All in order for HIV programmes to achieve high ART coverage and achieve the second 90 of the UNAIDS 90-90-90 cascade targets. Several studies, however, indicated that patients are less likely to start treatment when presenting to HIV care with asymptomatic HIV disease and high CD4 count.⁸⁷⁻⁸⁹

An HIV pre-exposure prophylaxis study in Kenya reported in 2011 that only 69% of men and 58% of women infected with HIV and living in a sero-discordant sexual relationship showed willingness to start ART at CD4 count thresholds above 350 cells/mm³.⁹⁰ Reasons cited were fear of stigma, pill burden, anticipated drug side effects, and development of antiretroviral resistance.⁹⁰

The Treat-All cluster-randomized TASP trial in KwaZulu Natal (South Africa) (Table 1) reported lower cumulative 1-month ART initiation of asymptomatic non-pregnant patients with CD4 count >350 cells/mm³ (37%) compared with patients presenting with CD4 count ≤100 cells/mm³ (72%).⁹¹ In multivariable analysis, CD4 count above 350 cells/mm³ remained a predictor of non-initiation at 1 month while cumulative 6-month ART initiation was similar to that in asymptomatic non-pregnant adults (89% vs 85%), suggesting overall good but delayed ART uptake for patients with high baseline CD4 counts.⁹¹ Clinic factors (e.g. health workers capacity, low staff-patient ratio) were identified as possible reasons for lower ART initiation rates and the prioritization of patients presenting with advanced HIV disease.⁹¹

Accelerated ART initiation

The pre-treatment care period is shortened under Treat-All, with the focus shifting to how this period can be further simplified. In some settings, multiple interventions from HIV testing to HIV care enrolment and ART initiation were combined and shortened.^{68,69,92,93} Specifically in the context of ART expansion, same-day ART initiation – the start of ART on the day of HIV diagnosis and/or treatment eligibility – has emerged as one possible strategy to shorten the pre-treatment period and reduce pre-treatment attrition.

Experimental evidence of accelerated ART initiation

A RCT from Uganda evaluated streamlined combination interventions (enhanced trainings for health workers, revised counselling protocols with the possibility of same-day ART initiation, POC CD4 testing, bi-annual clinic feedback meetings) implemented under the 2010 and 2013 WHO treatment eligibility criteria.⁹³ Compared with SOC, these interventions increased same-day ART initiation (71% vs 18%), three-month ART initiation (90% vs 70%), and 12-month viral suppression (85% vs 75%), while there was no effect on overall retention in care, visit adherence and mortality.⁹³ Of note, the trial was not designed to evaluate same-day ART initiation although most patients initiated ART on the day of treatment eligibility in the intervention group.

The RapIT RCT, conducted in South Africa from 2013 to 2014, offered same-day ART initiation to treatment eligible patients (according to CD4 count ≤ 350 and/or WHO clinical stage III/IV criteria) on the day of HIV diagnosis or the day of first treatment eligible CD4 count.⁶⁹ Study specific interventions (POC CD4 testing, tuberculosis and blood testing, physical examination and accelerated patient education and counselling) were applied for the intervention arm while SOC offered several counselling session before ART initiation and treatment was deferred by 2-4 weeks.⁶⁹ There was an increase in the pace and overall proportion of ART initiation for the same-day ART intervention arm (97% vs 72% at 3 months), higher 10-month retention in composite pre-ART and ART care (81% vs 64%), and increased viral suppression below ≤ 400 copies/mL (64% vs 51%).⁶⁹ However, LTFU after ART initiation was increased (17% vs 8%).⁶⁹ Notably, 86% of all LTFU in the same-day arm occurred after ART initiation compared with 22% in the SOC, while LTFU was higher during the pre-treatment period for SOC when compared with same-day ART (28% vs 3%).⁶⁹ In both arms, a high proportion of patients defaulting from treatment did not come back for the first or second follow-up visit after ART initiation. In addition, patients who initiated ART on the day of HIV diagnoses were less likely to be retained in HIV care when compared to patients who already knew their HIV-positive status.⁶⁹ Generalizability to routine populations and settings was a weakness of this study: 1) the patient sample was restricted to non-pregnant adults in two urban public sector facilities, 2) patients were excluded for reasons such as emotional or physical stress; 3) 5% of potential participants

declined to be enrolled; and 4) 18% did not meet eligibility criteria (e.g. found unfit to complete study procedures).

An open label RCT in Haiti assigned non-pregnant ART-naïve adults with CD4 count ≤ 500 cells/mm³ and WHO clinical stage I/II at the time of completion of CD4 count measurements to rapid and deferred ART initiation.⁹² A high number of patients were excluded as they did not meet eligibility criteria (e.g. WHO clinical stage III/IV) and a few failed the ART readiness questionnaire.⁹² Compared with deferred ART initiation, interim 12 months findings indicated higher ART initiation rates in the same-day arm (100% vs 92%), higher retention in HIV care (80% vs 71%), and improved viral suppression below 1,000 copies/mL (61% vs 50%).⁹² Of note, both groups were exposed to additional study procedures including multiple counselling visits in the first month, phone and physical tracing by community health workers in case of missed appointments and transportation subsidy.⁹²

The aforementioned studies assessed same-day ART initiation in a clinic setting. In contrast, a two-arm community RCT in rural Lesotho (CASCADE trial) was recruiting HIV-positive patients during community-based HTS campaigns at the time of inception of this research project.⁹⁴ The trial compares same-day community-based ART initiation with SOC in terms of linkage to facility-based HIV care and viral suppression.⁹⁴

Accelerated ART initiation in routine settings

Findings from routine programmatic settings on same-day ART initiation are scarce and limited to PMTCTB+ interventions. Timely ART initiation is recommended in pregnant and breastfeeding women to quickly suppress the virus, therefore to protect the infant from HIV infection as well as for the women's own health.^{14,16} Although same-day ART initiation accelerated and increased ART uptake,^{95,96} PMTCTB+ cohorts reported higher rates of disengagement from ART follow-up care for patients initiated same-day,^{95,97} and for women newly diagnosed with HIV.⁹⁸

Lack of guidance on accelerated ART initiation under Treat-All

At the time of inception of this research project, international recommendations on same-day ART initiation were not clear. WHO recommended shortening the time between HIV diagnosis and ART but also stated that “... available data are currently inadequate to support a recommendation ... in favour of same-day ... ART initiation”.¹⁶

Achieving and sustaining favourable ART outcomes

After initiation of ART, the next step in the cascade is to maintain effective therapy and achieve sustained viral suppression, thus contributing to the second and third 90 of the UNAIDS 90-90-90

cascade targets.⁵ Effectiveness of ART under routine programmatic conditions can be defined as achieving and sustaining immunorecovery with low levels of morbidity and mortality. High levels of viral suppression and retention combined is also likely to reduce transmitted and acquired HIV drug resistance, thus maintaining the effectiveness of commonly used first and second-line ART regimens.⁹⁹ Yet, these benefits will only materialize if patients with advanced HIV disease are not deprioritized during expansion of ART.

Retaining patients on ART

Retention on ART

Retention on ART is suboptimal in RLS. A systematic review, which analysed 154 general adult ART cohorts in low- and middle-income countries from before 2000 to 2012, demonstrated that ART retention was 78% at 12 months, 71% at 24 months, and 69% at 36 months.¹⁰⁰ The 36-month retention was lower in Africa than in Asia (65% vs 80%) and similar to Latin America and the Caribbean (64%).¹⁰⁰ Twelve-month retention appeared higher in earlier cohorts compared with the post-2008 cohorts (78% vs 74%), and the annual rate of attrition was highest during the first 2 years on therapy.¹⁰⁰

Predictors of ART outcomes

Common predictors of mortality and/or LTFU are male gender, younger and older age, advanced HIV disease, low body-mass index, treatment regimens containing older ARVs or ARVs with more side effects (stavudine, protease inhibitors), facility-level factors (larger facility size), and socioeconomic determinants.^{96,97,101–106}

Temporal trends have also been examined, with increased rates of LTFU in more recent calendar periods^{102–104,107–110} and stable^{104,108} or decreasing^{102,104,109,110} mortality. There are several possible explanations. The rate of ART programme expansion and larger programme size appeared to be associated with increased LTFU,¹⁰⁷ with larger and rapidly expanding HIV programmes possibly having reduced ability to focus on retention.¹⁰⁰ Overburdened health facilities with inadequate human resources need to attend to increasing number of PLHIV in need of treatment initiation and follow-up care, possibly leading to suboptimal adherence and treatment follow-up support as well as deterioration in quality care and record-keeping.^{104,107,109} Analysis bias was also suggested as a possible explanation (see below).

High CD4 count and ART outcomes

Associations between high baseline CD4 counts and ART outcomes have been reported. A study from South Africa, which analysed an adult treatment cohort from 2008 to 2012 and adjusted for HIV programme expansion and potential misclassification of LTFU by linking outcome data with the

national population register, concluded that CD4 count ≥ 300 cells/mm³ was associated with increased rates of LTFU.¹¹¹ In Médecins Sans Frontières (MSF) supported programmes in 8 countries from 2001 to 2011, LTFU and mortality among adult treatment cases was reduced during the first 12 months when the baseline CD4 count was ≥ 350 vs < 25 cells/mm³, but treatment outcomes were similar between 12 and 72 months.¹⁰⁷ A large, predominantly adult cohort in Mozambique from 2004 to 2013 showed a similar probability of LTFU for CD4 count > 500 vs < 50 cells/mm³ but noticed tendencies of decreased LTFU for patients with CD4 counts between 50 and 500 cells/mm³.¹⁰²

Notably, the latter two studies did not intend to explicitly evaluate outcomes of patients initiating ART with high CD4 counts. The comparison of higher CD4 counts with the lowest CD4 count strata was not ideal because immunosuppressed patients already have a high risk of adverse outcomes. In addition, patients with higher baseline CD4 cell count (if non-pregnant and not presenting with WHO clinical stage III/IV) were likely to have started treatment earlier than national treatment eligibility criteria recommended, thus possibly presenting a self-selected sample with increased motivation to initiate and adhere to therapy. Notably, all but one cohort¹⁰² completed ART enrolments at or before the implementation of the 2010 WHO guidelines recommending ART initiation at CD count ≤ 350 cells/mm³. Finally, CD4 count is not only associated with final treatment outcomes but may also affect treatment follow-up. For instance, a systematic review found that high current and pre-treatment CD4 cell counts as well as low CD4 counts were associated with increased risk of unstructured treatment interruptions.¹¹²

The 2013 WHO guidelines recommended universal ART for pregnant and breastfeeding women infected with HIV (PMTCTB+).¹⁴ PMTCTB+ programmes were the first to gain lessons from universal ART provision for a large population of PLHIV, following a public health approach. Most PMTCTB+ programmes experienced high rates of LTFU at 6 months, ranging from 12% to 22%.^{95–97,101} The lack of comprehensive breakdown of the CD4 cell count data in these studies, however, did not allow conclusions to be drawn on possible associations between high baseline CD4 count and ART outcomes. In addition, pregnancy is an independent risk factor for disengagement from ART when compared with non-pregnant populations,^{96,101,102,105} so lessons learnt from PMTCTB+ cohorts may not be fully applicable to Treat-All cohorts in which the majority of patients are non-pregnant. Experiences on treatment outcomes of patients with high CD4 cell counts from Treat-All settings are limited. The SEARCH trial (Table 1) reported that patients with baseline CD4 counts above national SOC treatment eligibility criteria were more likely to miss clinical appointments and required tracing interventions.⁶⁸

Interventions for improved retention on ART

Interventions to improve adherence and ART retention may be key to achieving the individual and public health benefit of Treat-All. These interventions, however, are heterogeneous, their efficacy is

often uncertain, and the real-world effectiveness is poorly understood.¹¹³ Interventions believed to improve outcomes in routine settings and interventions aiming to simplifying ART follow-up are involvement of lay and community health workers in ART care provision, provision of tolerable drugs regimens and drug formulations (once-daily dosing, fixed-dose combinations), health technology interventions, counselling interventions supporting adherence, nutritional support in the context of food insecurity, and community-based ART provision following the WHO framework of differentiated care.^{113–115} For instance, several settings in Sub-Saharan Africa introduced differentiated models of care for patients stable on ART in order to reduce out-of-pocket costs that are associated with travelling to and waiting time at facilities, improve patient peer to peer support as well as to decongest busy health facilities.^{116–118} Some of the anticipated benefits were improved adherence at patient level and thus better health outcomes, time-savings for health workers that can be used to attend to sicker patients, and improved retention at programme level.^{116–118}

Similar to other settings,^{64,119,120} in Eswatini, HIV services were decentralized to decongest overburdened facilities.¹⁰⁶ Both partial decentralization (centralized ART initiation with down-referral and ART maintenance at primary care facilities) and full decentralization (ART initiation and maintenance at primary care facilities) were associated with decreased LTFU and all-cause attrition while maintaining similar mortality compared with centralized facilities.¹⁰⁶ In the context of lack of qualified human resources for health, Eswatini introduced task shifting in 2011 and allowed for the involvement of community volunteers and medical lay cadres to make health services more widely available.¹²¹ In the context of Eswatini, task shifting was defined as shifting well defined clinical or administrative tasks from one health care cadre to the other cadre in order to reduce work load and alleviate the shortages of highly qualified human resources (e.g. medical doctors).¹²¹ For instance, task shifting mainly happened from doctors to nurses, and from nurses to lay cadres (e.g. lay counsellors for HIV testing and adherence support, phlebotomists, rural health motivators).¹²¹

Patients presenting late to ART

Definitions of late presentation to HIV care and/or treatment vary, and the terms late presentation and advanced HIV disease appear to be used interchangeably.^{122–124} Another definition is aligned to clinical decision making and a minimum package of care provided, defining late presentation as patients with CD4 cell count <200 cells/mm³ and/or WHO clinical stage III/IV.¹²⁴

Predictors of late presentation

Late presentation is a complex phenomenon. Patients can present early after HIV infection to HIV diagnosis but late to HIV care enrolment, or early to HIV diagnosis and care enrolment but late to ART initiation.¹²³ Causes of late presentation are multi-factorial, including contextual-level (characteristics of the population, HIV epidemic, and national health system), clinical-level (clinic

practices, programmatic approaches) and individual-level determinants.^{14,123,125} Consequences of late presentation are increased mortality and morbidity, higher likelihood of acquiring opportunistic infections (specifically TB), and increased HIV transmission.¹²³ Improved access to ART is associated with higher CD4 cell count at treatment initiation, and countries with ART coverage above 80% had 88 cells/mm³ higher median CD4 cell count than countries with ART coverage below 40%.¹²⁶ Nevertheless, baseline CD4 cell counts remain low in Sub-Saharan Africa, highlighting the persisting challenge of late presentation despite ART expansion.^{123,127} In 2009, one quarter of patients started ART at CD4 count <100 cells/mm³ in low and lower middle income countries.¹²⁶

Prioritization of patients presenting late to HIV care

Concerns were raised that patients presenting late to HIV care may be de-prioritized in overburdened health systems.¹⁶ Acknowledging this risk in the context of treatment expansion, as well as the immediate treatment need of these patients, the 2016 WHO guidelines recommend the prioritization of patients presenting with CD4 count below 350 cells/mm³ and/or WHO clinical stage III/IV.¹⁶ In fact, the Treat-All SEARCH and TasP trials showed that patients with lower CD4 cell count were initiated more quickly and were more likely to be on ART at 6 months after the first clinic visit (96% for CD4 count ≤100 cells/mm³ vs 89% for all patients),⁶⁸ but also showed that patients with WHO clinical stage III/IV who had CD4 count >350 cells/mm³ had inferior ART initiation rates (61% vs 89% for all patients).⁹¹

Achieving viral suppression

Effective ART reduces the virus to below laboratory detection, which is associated with improved patient outcomes and likely contributes to HIV incidence reduction at the population level.^{20,44} Viral suppression is the third 90 of the UNAIDS 90-90-90 cascade targets, the ultimate goal of effective HIV programming.⁵

Routine VL testing

Routine VL testing is the preferred method to monitor the effectiveness of ART, to diagnose treatment failure, and to trigger early clinical action.¹⁶ For instance, HIV programmes with routine VL monitoring showed improved outcomes (reduced attrition, improved CD4 cell count recovery, more treatment switching) compared with programmes without access to routine VL testing.¹²⁸ These benefits were mainly seen at 6 months after ART initiation, which is the time when the first VL test is performed and results are available for clinical decision making, adherence counselling interventions, and treatment switching.¹²⁸ Therefore, VL testing is used to re-enforce adherence, and overall 70.5% of patients with viral elevation can achieve viral re-suppression after enhanced adherence counselling interventions.¹²⁹ More frequent VL monitoring is also associated with decreased risk of resistance

against nucleoside and non-nucleoside reverse transcriptase inhibitors, likely because of earlier identification of viral failure and less time spent on failing treatment regimens.¹³⁰

WHO recommends routine VL monitoring with a VL test performed at 6 and 12 months after ART initiation and yearly thereafter, and patients with an elevated VL above 1,000 copies/mL should receive enhanced adherence counselling interventions and a consecutive VL measurement within 3 months.¹⁶ If the VL is re-suppressed below 1,000 copies/mL, the patient remains on the same treatment regimen. If the VL remains elevated and adherence issues are excluded as a possible cause of an elevated VL, treatment switching to a second-line ART regimen is recommended, assuming ineffectiveness of the current treatment regimen due to transmitted or acquired HIV drug resistance.⁶⁷

Programmatic expansion of routine VL testing

Routine VL monitoring is scaled up in Sub-Saharan Africa but poses a significant challenge to HIV programmes.^{131,132} VL testing is complex, with many issues that need to be addressed from VL laboratory capacity to clinical management and patient adherence support.^{131,133} In 2016, at programme level, only two out of seven Centers for Disease Control and Prevention (CDC) and U.S. President's Emergency Plan for AIDS Relief (PEPFAR) supported countries in Sub-Saharan Africa achieved >80% VL testing coverage; the mean test turnaround was protracted to 28 to 50 days in five countries, and the viral suppression rate was below 80% in two countries.¹³² Various factors were reported to be associated with VL testing uptake, viral elevation, viral failure, and re-suppression:^{110,131,134–137} programmatic (cohort specific, ARV stock-outs, treatment provider, deferred first VL measurement, lower VL threshold), socio-demographic (age, gender), and clinical (WHO clinical stage, baseline or last CD4 cell count, duration on ART, ART interruptions, PMTCT exposure). One study also found that viral failure increased over time.¹⁰⁴

Reporting of VL outcomes

An increasing number of HIV programmes report on viral outcomes – mainly viral suppression among patients with VL test results available – as an indicator of programmatic success.^{68,110,131,135,138–}

¹⁴⁰ To assess the ability of interventions and HIV programmes to achieve viral success at cohort level, studies increasingly report on viral suppression rates among all treatment eligible patients (by combining pre-treatment and ART care patients irrespective of missing VL data, LTFU, and death). The GHESKIO trial reported among all treatment eligible patients, and irrespective of HIV care retention status, that the 12-month viral suppression was 52% (<1,000 copies/mL) in SOC compared with 61% in the same-day ART intervention arm.¹⁴¹ The RapIT trial reported viral suppression (≤ 400 copies/mL) of 51% and 64% for SOC and same-day ART at 10 months after ART eligibility (and irrespective of other patient outcomes and missing VL test results).⁶⁹ Treat-All studies also use viral suppression as a main outcome.^{3,4,47,48} The Treat-All SEARCH trial (Table 1) reported 78.5% viral suppression (≤ 500 copies/mL) and 10.7% missing VL data at 12 months after enrolment into HIV

care, compared with 89% viral suppression among patients who were retained and had VL data available.⁶⁸

ART expansion and TB

TB is the main opportunistic infection in PLHIV in Sub-Saharan Africa and is intertwined with the HIV epidemic, most pronounced in Southern Africa with HIV co-infection rates among TB cases exceeding 70%.^{7,142,143} In Southern Africa, annual TB notifications often exceeded 1,200 cases per 100,000 population,^{144,145} being most pronounced in smear-negative and sputum-negative TB cases,^{144,146} which are the main manifestation of TB in HIV co-infected individuals.⁸

Predictors of TB

Individual-level predictors of incident TB in PLHIV are advanced HIV disease (low CD4 cell count, higher WHO clinical stage), and missing CD4 cell count and/or WHO clinical stage.¹⁴⁷ High rates of TB are most pronounced in the age groups mostly affected by the HIV epidemic (20-29 years old) and lower in older populations (>50 or >60 years old), in contrast to higher rates of TB in some older non-migrant populations (>60 years old) in low HIV prevalence settings (e.g. high income countries).^{144,147,148} While men face a higher burden of TB in most settings globally, this difference is less pronounced in some high HIV prevalence settings in Sub-Saharan Africa,¹⁴⁹ where women also carry the largest burden of HIV.³⁷

Contextual factors associated with TB are facility-level determinants (facility type, location, and utilization)¹⁴⁷ and HIV prevalence at district level (districts with varying burden of HIV have varying pace and magnitude of TB decline)¹⁵⁰. At the population level, several studies demonstrated the association between higher HIV prevalence and increased rates of TB notifications during the pre-ART era or when ART was scarce in the public sector.¹⁴²⁻¹⁴⁴

Interventions reducing TB notifications

At the individual level, ART decreases the risk of TB disease across all baseline CD4 count levels and was possibly stronger in lower CD4 count strata.²¹ Overall, the risk remains elevated for PLHIV on ART when compared with the HIV-negative population.^{151,152}

At the population level, ecological studies evaluated the potential of ART expansion for TB control. In Malawi and Zimbabwe, annual TB case notifications declined with an increase in ART coverage and expansion of treatment eligibility to higher CD4 cell count thresholds,^{143,146} being most pronounced in new and/or smear-negative TB cases.^{143,146,153} The decline in TB cases occurred before or at the beginning of ART scale-up, therefore earlier than population-level benefits due to ART scale-up would be anticipated.^{143,146} In peri-urban, high HIV/TB prevalence settings in South Africa,

TB notifications started to decline at 15-20% ART coverage in PLHIV¹⁴⁵ compared with 30-40% in the urban setting of Cape Town.²³ Population-level decline in TB cases was most pronounced in PLHIV, in the age groups mostly affected by HIV, and in patients on ART.^{145,150} Less pronounced declines were documented in PLHIV not on ART and in the HIV-negative population.^{145,147,150} While the burden of TB is likely to remain higher in PLHIV, the difference between HIV-infected and HIV-negative populations may narrow during expansion of HIV/TB care.¹⁴⁷ A modelling study cautioned that a durable immunovirological protective effect of ART needs to be achieved while HIV incidence reduction alone may not be sufficient to avoid TB rebound during scale-up of ART.²² Modelling studies, however, apply different assumptions and model specifications, and they show an inconclusive picture of the impact of ART scale-up on long-term TB incidence reduction,^{22,54,55} limiting comparison across settings and with real-world data.¹⁵⁰

Factors other than ART scale-up may contribute to TB control.^{142,145-147} In high HIV/TB prevalence settings, expansion of TB programme coverage (diagnosis and effective treatment) may reduce TB prevalence and mortality, while ART expansion may reduce new TB infections in PLHIV and prevent HIV transmission, and both interventions combined may have a similar significant impact on the TB epidemic.⁵⁴ In Eswatini, TB cases rapidly increased during the pre-ART era and sharply fell during ART expansion.¹⁴² The decline was ascribed to HIV/TB service integration, a strengthened and expanded national TB programme, and earlier diagnosis of TB through increased case finding activities and new diagnostic technologies (GeneXpert).¹⁴²

Limited evidence on trends in HIV-associated TB after further ART expansion

The studies presented here have several limitations. Studies using patient-level data examined trends in TB notifications during the early scale-up of ART but before expansion of WHO treatment eligibility criteria to and beyond the CD4 count threshold of 350 cells/mm³, and at or before the time of strengthening HIV/TB collaborative activities.¹⁴⁵ Most evidence is reported from predominantly urban settings^{145,147,150} or at national level,^{142,143,146} while studies from rural settings are scarce.¹⁵³ Only a few studies used patient-level TB and/or HIV care data.^{145,147,150} Finally, all studies were completed before the introduction of Treat-All.

Studies investigating Treat-All

Several well-known Treat-All studies have been conducted in Sub-Saharan Africa and are described in more detail in Table 1 (considering the time period until September 2017). They include community RCTs (known as TasP, SEARCH, BCPP, PopART) aiming at improving the HIV diagnosis and care cascade through enhanced community-based HIV testing, linkage to HIV care interventions, and immediate ART initiation irrespective of CD4 cell count criteria.^{3,46-48} The primary

outcome measure of most studies is the effect of Treat-All on HIV incidence at the population level, and secondary outcomes include treatment uptake, ART retention, viral suppression, and cost-effectiveness.^{3,46–48} Although these studies are implemented in the context of government HIV programmes, and some of them in multiple countries,^{47,48} they appear to be different from routine settings in Sub-Saharan Africa as additional external support activities are provided: study staff deployed to study facilities,³ implementing combination interventions that are not standard of care in the public sector, and using enhanced patient follow-up intervention to ascertain patient outcomes and reduce loss to care.⁴⁸ One Treat-All study in Eswatini (MaxART) is implemented in the public sector under routine conditions with a small study team coordinating activities among stakeholders and the Ministry of Health (MOH), providing mentoring support to facilities under Treat-All, and addressing gaps discovered during the implementation.⁴

Another prospective cohort study conducted in Eswatini since October 2014 – and part of the research presented in this thesis – is known in Eswatini as Early Access to ART (EAA). It aims to assess the feasibility of Treat-All under routine conditions in the public sector and draw lessons learnt to inform the national scale-up. The latter study changed ART eligibility criteria from CD4 count ≤ 350 cells/mm³ to universal Treat-All, and continued using existing resources and overall applying the same HIV care and treatment strategies as under SOC. Of note, at the conceptualization of this thesis, the evidence on the effectiveness of Treat-All was scarce. It was the TasP trial in KwaZulu Natal (South Africa) that demonstrated a lack of reduction in HIV incidence under Treat-All compared with SOC⁴⁹ (see section above: *Population-level effectiveness*) while results from other Treat-All trials were still pending.

Table 1: Main Treat-All trials evaluating the impact of the Treat-All approach (considering the time period until September 2017).

Study title	Main objectives	Secondary objectives	Duration, design	Sample size	Setting	Intervention
Impact of Immediate vs South African recommendations guided ART initiation on HIV incidence (TasP); (ANRS 12249) ^{3,49,91,154}	- Uptake of HTS - Uptake of ART - Cumulative HIV incidence at 4 years	- ART retention, adherence - Costs - Quality of life - Sexual partnerships	- 2012-2016 - Efficacy study. - Cluster randomized trial comparing immediate vs SOC recommended ART initiation	- 22,000 participants in 22 community clusters of people ≥16 years old - Pregnant women included	- KwaZulu Natal, South Africa - Predominantly rural - 29% HIV prevalence	- Repeated rounds of community-based HTS with immediate linkage and ART initiation
Sustainable East Africa Research in Community Health (SEARCH) ^{48,68}	- Cumulative HIV incidence at population level at 3 years	- Economic and educational impact of Treat-All - Overall outcomes of HIV care cascade (linkage, ART, VL)	- 2013-2020 - Efficacy study. - Community cluster randomized trial of universal ART vs SOC	- 32 communities of ~10,000 persons aged ≥15 years	- Kenya and Uganda - Predominantly rural communities	- Multi disease mobile HTS campaigns - Streamlined care (immediate ART at facilities, fewer follow-up visits, patient centred /empathic care, telephone hotline, appointment reminders, phone and physical tracing)
Botswana Combination Prevention Project (BCPP) ⁴⁶	- Cumulative HIV incidence at population level	- Population level uptake of HTS, ART, male circumcision, PMTCT - Costs per infection averted	- 2013-2018 - Efficacy study - Cluster randomized controlled trial - Combination prevention vs enhanced care	- 30 villages of 6,000 population (16–64 yrs)	- Botswana - Rural and peri-urban communities	- Technical assistance for combination prevention intervention package: HTS, linkage, ART for high VL, PMTCTB+, VMC, support to clinical and lab data information, supply chain
Population Effects of Antiretroviral Therapy to Reduce HIV Transmission (PopART) ^{47,155}	- Cumulative HIV incidence at 3 years	- Uptake of PMTCT, ART and VMC - Retention - Viral suppression - ART toxicity - Drug resistance - TB notifications - Cost-effectiveness	- 2013-2017 - Efficacy study - Two country cluster community randomized trial in 21 communities - 3 arms (SOC, 2 intervention arms)	- 1.2 million catchment population	- Zambia, South Africa	- Home-based HTS, active referral, immediate ART initiation, and HIV prevention interventions
Early Access to ART for All in Eswatini (MaxART) ⁴	- Retention in care, on ART - Viral suppression	- ART uptake, adherence - Drug resistance - HIV incidence (modelling) - Cost-effectiveness	- 2014-2017 - Feasibility study - 3-year randomized stepped wedge design	- 4,500 patients entering HIV care	- Eswatini (Hhohho region) - Rural health facilities and communities	- Utilization of routine interventions as implemented by NGOs and MOH: HTS, ART

ART, antiretroviral therapy; HTS, HIV testing services; NGO, non-governmental organization; MOH, Ministry of Health; NA, not available at the time of review; NGO, non-governmental organization; PMTCTB+, prevention of mother to child transmission option B+; SOC, standard of care; VL, viral load; VMC, voluntary male circumcision; yrs, years.

Methodological challenges

Several methodological challenges exist in the analysis of ART data and the comparison of outcome estimates between HIV programmes. Although the focus of this section is mainly on challenges encountered with ART data, most considerations are applicable for linkage to HIV care and pre-treatment data and analyses.

Misclassification of outcomes

Misclassification of outcomes is a challenge in many HIV programmes. For instance, national civil registration systems including mortality registries are not available or of poor quality (e.g. unreliable, incomplete, not timely) in many RLS.¹⁵⁶ This makes it more difficult to differentiate between patients who died and who are lost to HIV programmes but alive. Therefore, all-cause attrition is a main programmatic outcome indicator and is the sum of counted deaths and LTFU divided by the number of patients initiated on ART, whereby patients transferred in are removed and patients transferred out are either removed or adjusted for in time-to-event analysis. In practice, deaths reflect all-cause mortality that combines different main underlying causes of deaths related to HIV or other reasons (e.g. accidents, suicide, communicable and non-communicable diseases).^{157,158} LTFU also consists of several outcomes: unstructured treatment interruptions, undocumented and silent patient self-transfer to other treatment sites, undocumented deaths, data clerical errors, and real LTFU. In Sub-Saharan Africa, among patients LTFU and traced, 18.6% (ranging from 4.5% to 54.4%) self-transferred to other treatment sites, 38.8% died and 28.6% stopped ART.¹⁵⁹ Similar findings were reported from a tracing study of patients LTFU in referral hospitals in Eswatini in 2007:¹⁶⁰ 35% were reported dead, 45% were untraceable (actual LTFU), and 20% were found alive of whom two third were non-documented transfer out and the remaining were unstructured treatment interruptions. Cohorts with larger proportions of LTFU tend to have higher proportions of self-transfers, with an increase in more recent cohorts while the proportion of deaths tended to decrease over time from 50% to 30%.¹⁵⁹ Several strategies are applied to reduce misclassification of outcomes. Some programmes use physical defaulter tracing to ascertain LTFU and to re-engage patients into care.⁶⁸ Programmes applying physical defaulter tracing report less LTFU at 12 months (7.6% vs 15.1%), increased mortality (10.5% vs 6.6%), and higher retention on ART (80.0% vs 75.8%) compared with programmes without physical tracing.¹⁶¹ Several studies from South Africa ascertained the vital status of patients reported LTFU and corrected for underreported mortality by linking them with the national population register using unique national patient identifiers.^{111,162–164}

Definitions of outcomes and analytic bias

Definitions of LTFU are context-specific and vary across programmes and treatment sites.¹⁰⁰ For instance, patients were classified LTFU when the scheduled clinic and/or ARV drugs pick-up visit was missed for a period between 1 and 12 months.^{100,165,166} Different definitions of LTFU and its execution in analyses introduce bias when comparing estimates across settings.¹⁶⁶ For instance, analyses and effect estimates vary by whether or not to exclude patients from analysis who had an ART initiation date recorded but no follow-up date, time of database and analysis closure, and the dates used to define LTFU.¹⁶⁶ The best case scenario estimated lower LTFU rates (1.3%, 8.8%, and 18.6% at 6, 12, and 24 months) compared with a more conservative approach (9.3%, 14.4%, and 22.4%)¹⁶⁶ A conservative analytic approach was proposed, adding 1 day of follow-up for patients who have no follow-up visit recorded (thus retaining them in survival analysis), LTFU defined as 6 months without contact or clinic visit and measured at the date of last recorded visit, and closing analysis 6 months before database closure to give all patients the chance to satisfy the LTFU definition.¹⁶⁶ The 6-month LTFU definition, when patient-level data across 111 health facilities from 41 countries were pooled, had the lowest probability of misclassification between LTFU and active ART status at patient level and also showed good performance when facility- and cohort-level data were used.¹⁶⁷ Providing more time for patients to return to care before classifying them as LTFU appears to be important in the context of poor ascertainment of outcomes, weak data reporting systems, unstructured treatment interruptions, and variation in appointment scheduling during treatment follow-up, and appears to reduce the gap between actual and observed LTFU.

Notably, similar limitations in definitions have been reported for linkage to HIV care. Direct comparison of linkage outcomes across settings is limited by heterogeneity of linkage definitions used, including the date of first facility visit, date of obtaining a CD4 test or test result, and date of documented WHO clinical stage or registration in pre-ART care registers.^{68,78,79,81,82} In addition, verification of linkage status varies by context. It is often based on verification through facility records but sometimes combined with patient self-reported linkage outcomes.^{78,82,83}

Transient treatment interruption bias

More recent treatment cohorts reported increased rates of attrition and LTFU during treatment expansion.^{102–104,107–110} This phenomenon can partly be explained by analysis bias. When LTFU definitions do not account for transient treatment interruptions, this may introduce a false trend of increased LTFU for recent treatment cohorts with shorter observation time.¹⁶⁸ A systematic review found that 23% of patients on ART self-initiated unstructured treatment interruptions for a median duration of 150 days, resulting in increased morbidity and mortality, decreased CD4 cell recovery, viral failure, and possible increased risk of HIV drug resistance.¹¹² Patients with treatment gaps early during therapy and short observational follow-up time have less time to re-enter HIV care and restart ART, and are therefore at increased likelihood of being classified as LTFU when compared to patients

enrolled in older cohorts with longer follow-up time and therefore higher probability of returning to care during the observation period.¹⁶⁸ Therefore, when analysing temporal trends, a prospective LTFU definition is proposed with patients assumed to be on ART until the first occurrence of the LTFU definition and removed from analysis thereafter.¹⁶⁸ For analyses comparing different patient groups, controlling for calendar time period may be sufficient.¹⁶⁸

RATIONALE

Countries in Sub-Saharan Africa have adapted health policies for universal ART (Treat-All) and started to implement it at scale. Under-resourced public sector HIV programmes are required to deliver high quality care to achieve and sustain anticipated benefits of Treat-All. Community RCTs are evaluating Treat-All approaches, with encouraging outcomes reported in one setting in East Africa (SEARCH trial) but gaps have been exposed along the HIV care cascade in South Africa (TasP trial). There is also likely a gap between achievements under research conditions and what can be achieved in public sector settings, as well the gap between supporting health policies and efficient operationalization.^{34,57} These constraints raise questions of programmatic feasibility of Treat-All under routine conditions and the ability of large HIV programmes to achieve and sustain the UNAIDS 90-90-90 cascade targets.

The importance of operational research in documenting treatment expansion has been discussed and acknowledged. Rosen et al. established research priorities to inform the acceleration of treatment access in Sub-Saharan Africa and emphasized better understanding of the baseline characteristics of the context, characteristics of patients starting ART under Treat-All, the speed of ART initiation, and treatment outcomes.¹⁶⁹ Takarinda et al. highlighted the need for operational research during the introduction of Treat-All in resource-poor real-world settings to address existing gaps along the HIV care cascade and to successfully push the universal ART agenda.³⁰ The rapid implementation of Treat-All under field conditions requires documentation on how to translate the new recommendations into practice to inform health policy makers and HIV programme managers on the best care approach for different contexts, to identify best operational practice during scale-up,³⁴ and to understand real-world effectiveness.

Gaps in knowledge related to universal ART expansion

Lessons learnt from ART programme expansion during the past decade are instructive with respect to what might happen with further programme expansion and issues related to effective operationalization of Treat-All. Despite rapidly increasing HIV/TB service coverage, utilization of new care models and task-shifting, expansion of treatment eligibility criteria, and availability of improved drug regimens in recent years,^{170,171} long-term outcome data from recent ART cohorts are scarce.¹⁷⁰ The feasibility of Treat-All should be evaluated in the context of existing health service gaps and measured by the ability of existing health settings to absorb new interventions. Therefore, descriptive epidemiology is needed on programme outcomes prior to Treat-All and on the impact of historical programme expansion on ART care outcomes.

Low pre-treatment attrition and high ART uptake are required to achieve the benefits of Treat-All. Linkages between HIV testing and HIV care enrolment and ART initiation emerged as bottlenecks for

the effective expansion of HIV care. Although some linkage interventions implemented under previous treatment guidelines increased enrolment into HIV care, the impact of Treat-All in routine public sector settings on linkages and ART uptake remains widely under-researched. In addition, the acceleration of treatment preparation (e.g. same-day ART initiation) is proposed under Treat-All to decrease pre-treatment attrition. This review, however, did not identify studies evaluating same-day ART initiation under routine programmatic conditions for populations exposed to the Treat-All approach. There is the possibility of adverse treatment outcomes during ART expansion, mostly suspected among asymptomatic patients presenting to care with high CD4 cell counts. Effective ART provision (achieving viral suppression) and reduced attrition are critical for Treat-All to improve patient-level outcomes and achieve population-level ambitions for HIV transmission reduction.

In addition, little is known about the impact of Treat-All on outcomes of patients presenting late to HIV care, with Treat-All potentially increasing the pressure on fragile health systems and therefore possibly leading to the de-prioritization of those in greatest need of ART. Finally, evidence remains scarce on how far universal ART expansion may impact TB notifications in high HIV/TB burden settings. While studies suggested a decline in TB cases, whether the decline will persist during expansion of Treat-All is unknown.

Opportunities for lessons learnt from routine public sector settings

Public sector settings introducing Treat-All before it became a WHO recommendation provide an opportunity to explore the real-world feasibility, effectiveness, and impact of Treat-All under routine conditions. Lessons learnt can help us to understand the impact of Treat-All on ART initiation and outcomes, new models of care (e.g. same-day ART), late presentation, and HIV-associated co-morbidities. There is potential to inform other public sector HIV programmes on the risks and benefits of Treat-All.

Eswatini, after a decade of scale-up of HIV/TB care in the public sector, provides a unique opportunity to describe lessons learnt and evaluate the feasibility of Treat-All. Eswatini was one of the first countries in Sub-Saharan Africa to pilot Treat-All interventions in the public sector under routine conditions, almost 2 years ahead of the 2016 WHO guidance recommending access to ART for all PLHIV. This research project aims to contribute to the body of evidence on the feasibility of Treat-All in public sector HIV programmes by evaluating the early implementation of Treat-All in one of the pilot projects in Eswatini.

AIM AND OBJECTIVES

The overall aim of this thesis is to determine the feasibility of Treat-All in the public-sector in the rural Shiselweni region of Eswatini.

The main objectives are:

- **Objective 1:** To describe the programmatic context and evaluate outcomes of ART expansion prior to the introduction of Treat-All.
- **Objective 2:** To determine the feasibility of facility-based ART initiation under Treat-All when compared with SOC.
- **Objective 3:** To determine the effectiveness of facility-based ART follow-up care under Treat-All when compared with SOC.
- **Objective 4:** To determine the effectiveness of facility-based same-day ART initiation under Treat-All when compared with early ART under Treat-All.
- **Objectives 5:** To describe temporal trends in HIV-associated tuberculosis during ART expansion.

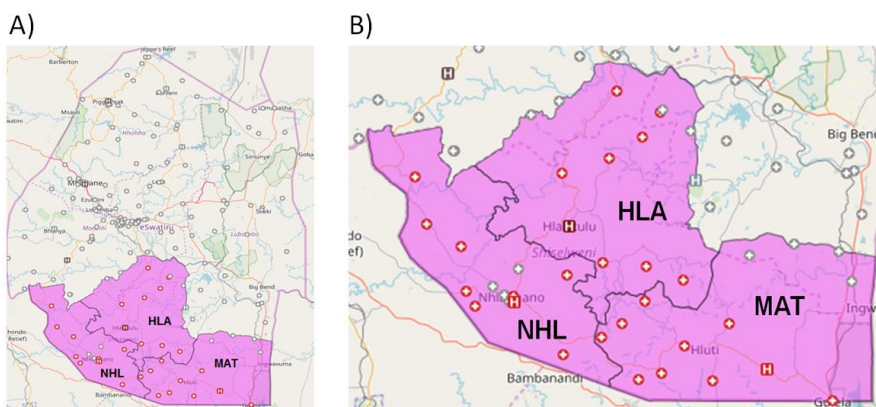
SETTING

Eswatini

Eswatini – a lower-middle-income country in southern Africa – has four administrative regions with a population of 1.1 million and an estimated life-expectancy of 58 years in 2017.¹⁷² The country has the highest HIV prevalence globally with 32% of adults aged 18-49 years living with HIV, 24% in males and 39% in females.¹⁷³ The peak of HIV prevalence in women is in 30- to 34-year-olds (54%) and in men it is in 35- to 39-year-olds (47%), and it is similar in urban and rural areas and in the four regions.¹⁷³ HIV incidence was estimated at 2.4 per 100 person-years (men: 1.7; women: 3.1) and was highest in women aged 20 to 24 years (4.3 per 100 person-years).¹⁷⁴ Eswatini also has one of the highest annual TB incidence rates, estimated at 565 cases per 100,000 population in 2015,⁷ with 73% of TB cases being HIV co-infected.¹⁷⁵ The country is affected by a human resource for health crisis with a total health staff (doctors, nurses, midwives) to population ratio of 1.7 per 1,000 population, below the WHO recommendation of 2.5 per 1,000 population.¹⁷⁶

Study setting – the Shiselweni region

The study setting is the predominantly rural Shiselweni region in southern Eswatini, bordering KwaZulu Natal in South Africa (Figure 1A). It covers almost one quarter of the country and had ~210,000 inhabitants in 2015.¹⁷⁷ Shiselweni has three health zones (Nhlanguano, Hlathikulu, Matsanjeni), each served by one secondary care facility with inpatient capacity supporting seven to eight nurse-led primary health care facilities (Figure 1B).



HLA, Hlathikulu health zone, NHL, Nhlanguano health zone; MAT, Matsanjeni health zone; Violet area: Shiselweni region with three health zones; Red crosses: primary care facilities in 2019; H: secondary care facilities (Nhlanguano Health Centre in Nhlanguano health zone, Matsanjeni Health Centre in Matsanjeni health zone, and Hlathikulu Hospital in Hlathikulu health zone). Source: MSF Map Centre, 2019.

Figure 1: Map of Eswatini and the Shiselweni region with health facilities of Nhlanguano, Hlathikulu, and Matsanjeni health zones.

The support provided by MSF includes mentoring, referrals for complicated clinical cases (e.g. HIV patients infected with drug-resistant TB or cryptococcal meningitis), drug supply, laboratory tests (e.g. supplies for POC tests or testing for TB), and monitoring and evaluation (Table 2).

Table 2: Standard composition of primary care facilities in the Shiselweni region from 2010 onwards.

Services provided	- General outpatient consultation for adults and children - Diagnostics, treatment initiation and treatment follow-up for HIV and TB - Sexual and reproductive health services: family planning, antenatal care, postnatal care, PMTCTB+ - Expanded programme on immunization - Mini-laboratories providing: 1) POC testing for HIV, biochemistry (ALAT, AST, creatinine), haemoglobin, blood glucose, urine strip testing, syphilis testing, pregnancy testing 2) Sample collection for testing at the National Reference Laboratory or health centre: sputum collection for diagnosis of TB (GeneXpert), heel prick dried blood spots for early infant diagnostic, VL plasma samples, other laboratory tests if needed
Average staffing	- One to four primary care nurses with some of them trained in nurse-led ART initiation - One HIV testing counsellor for HIV counselling and testing - One expert client for treatment adherence counselling and stepped up VL adherence counselling - One phlebotomist running the Mini-laboratory - One pharmacy assistant - 1 mobile medical doctor visiting the primary care facility one to two times per month

ALAT, alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; PMTCTB+, prevention of mother to child transmission option B+; POC, point-of-care; TB, tuberculosis; VL, viral load.

Evolution of HIV/TB care in Shiselweni

The context prior to Treat-All

In 2007, the Shiselweni region had the lowest density of treatment facilities, in-patient beds, and health workers in the country.¹⁷⁸ Co-located HIV and TB care was only available in the three centralized secondary care facilities and was physician-led. Patients from rural areas needed to travel to these facilities for the diagnosis, treatment initiation, and treatment follow-up of HIV and TB disease.

From 2008 to 2010, the MOH and MSF decentralized and integrated HIV and TB care into 22 primary care facilities in the Shiselweni region.¹⁷⁹ Task-shifting and sharing from doctors to nurses and from nurses to community-based cadres was implemented: 1) nurses performed nurse-led ART and TB treatment initiation and follow-up care; 2) HTS counsellors conducted mainly facility-based HIV testing and counselling; 3) expert clients provided treatment preparation and ART adherence support counselling; 4) pharmacy assistants supported the nurses in dispensing of ARVs and other drugs; and 5) phlebotomists performed basic laboratory tests including POC tests (Table 2). Primary care facilities were visited by a mobile doctor one to two times per month, who attended to

complicated clinical cases such as patients with co-morbidities and HIV treatment failure. Mentoring of facility staff was mainly performed by MSF doctors and MSF nurses trained in HIV/TB care. TB care provided included infection control measures, TB case finding and treatment, isoniazid preventive therapy, and ART for HIV co-infected patients.

From 2011 to 2012, the integration and decentralization of HIV and TB services was consolidated. In 2011, 62% of PLHIV knew their HIV-positive status, 36% of PLHIV received ART, and 37% of PLHIV were virally suppressed.^{180,181}

Preparation for Treat-All

In 2012, the MOH established the national “Treatment as Prevention” framework encouraging implementation research for universal ART interventions. The framework was aimed at preparing the country for Treat-All and informing health policy. As part of this strategy, the national HIV programme strengthened the diagnosis of HIV and the care and treatment cascade, and introduced provider-initiated HTS as well as standard operating procedures for linkage to HIV care, pre-ART and ART care.¹⁸²

In 2012, MSF established routine VL monitoring in the Shiselweni region to strengthen treatment and adherence support prior to Treat-All.¹⁴⁰ The Biocentric Generic HIV viral load platform was used with a lower limit of VL detection of 100 copies/mL in the early years and 416 copies/mL in later years using plasma blood samples.¹⁸³ Routine VL testing was performed at 6 and 12 months after ART initiation and annually thereafter. If the VL is higher than 1,000 copies/mL, stepped-up adherence counselling is provided and patients with persistent viral elevations are switched to a second-line treatment regimen.^{134,140,184}

In the same year, community-based HTS was expanded to increase knowledge of HIV status.⁷⁹ In 2013, an estimated 15,000 people were tested through community-based HTS, which was approximate one third of all HIV tests performed in the region (*MSF programme data*). The HIV positivity rate was approximately 4% at community-based testing,⁷⁹ compared with 6% to 8% at primary care facilities and 8% to 10% at secondary care facilities (*MSF, MOH programme data*). Only one third of HIV-positive patients linked from community-based HTS to facility-based HIV care in 2013,⁷⁹ and this increased to 50% to 60% in 2014 (*MSF programme data*), after the implementation of enhanced linkage to care strategies.

Phase-in of Treat-All

In January 2013, Nhlngano health zone introduced a PMTCTB+ implementation project that provided universal and lifelong ART to HIV-positive pregnant and breastfeeding women.¹⁸⁵ Although ART uptake was suboptimal at the beginning of the pilot (65%) and varied widely between facilities from 38% to 89%, it overall increased to 86% over a period of 1.5 years.^{185,186} Treatment outcomes,

however, remained suboptimal with 80% and 53% of women retained in care at 6 and 24 months after ART initiation.¹⁸⁶

In October 2014, universal ART for all PLHIV was introduced in Nhlangano health zone, known as “Early Access to ART” (EAA) in Eswatini. People infected with HIV aged ≥ 16 years were enrolled into HIV care and offered facility-based ART initiation irrespective of treatment eligibility criteria. This prospective cohort study with a nested qualitative study aimed to evaluate feasibility and acceptability of universal ART provision in one health zone (Nhlangano) compared with the neighbouring health zone (Hlathikulu) that followed national standard ART initiation thresholds at $CD4 \leq 350$ cells/mm³ until October 2015 and at $CD4 \leq 500$ cells/mm³ thereafter.

DATA MANAGEMENT

This section provides an overview of data sources used for this research project. A description of statistical analyses applied is provided in each of the manuscripts.

Data collection

Trained MOH and MSF data clerks extracted routine data from paper registers (pre-ART, ART, TB, VL), patient records, and referral forms (linkage forms, laboratory forms) and entered them into electronic registers. Patients' names and personal contact information were removed. To ensure that the data are accurately entered, data verification mechanisms were implemented such as automatic data checks and consistency checks, complemented by routine ongoing data cleaning.

Data sources

A summary of data sources, databases, and their use in analyses is provided in Table 3. First, databases established for the purpose of research and routine programmatic monitoring were used for most analyses. Additional databases were used to complement missing information from primary databases. Second, secondary data were used to obtain population-level estimates of the HIV infected and uninfected population.

Research database

The electronic **Treat-All Database** established in EpiData contains information on patients enrolled into facility-based HIV care under the Treat-All programmatic approach in Nhlanguano health zone and under SOC in Hlathikulu health zone from October 2014 to March 2016. Patients were followed up until October 2017. Missing baseline and follow-up data were supplemented with values from the Swaziland National AIDS Programme's ART Programme Monitoring Register (APMR), the HIV Virology Laboratory Register, the drug-sensitive and drug-resistant TB databases, and patient records. Of note, this research database did not include data from the third health zone of Matsanjeni due to practical limitations in data collection (e.g. human resources and funding). Therefore, all comparisons made between Treat-All and SOC never included data from Matsanjeni health zone.

Programmatic databases

The electronic **Community HTS/ Linkage to Care Register** maintained by MSF for programmatic monitoring contains basic individual-level information (demographics, testing dates and results) of patients tested HIV positive at community HTS, linkage to HIV care (date of linkage), and ART

initiation (date of ART initiation) from February 2013 to December 2016. This database did not use unique patient identifiers and therefore was not linked to other data sources.

The **Swaziland National AIDS Programme's ART Programme Monitoring Register (APMR)** is an electronic national ART database used for the programmatic monitoring of the national HIV/AIDS programme. It contains baseline demographic, laboratory, and clinical patient-level information from the time of ART initiation, treatment follow-up, and outcome. Although pre-treatment information was also integrated into the database, it was not reliable at the time of this research project. It covers the time period from before 2006 to August 2015. From 2014 onwards, this national register was transitioned to a newly established Central Monitoring Information System, but these data were not available for this research project. Overall, the APMR contained less baseline variables and data were less complete than in the Treat-All Database (see Table 3).

Two electronic **TB databases** containing baseline, treatment follow-up, and treatment outcome information about drug-sensitive and drug-resistant TB treatment cases were maintained by MSF for routine programmatic monitoring. These databases contain TB cases of the Shiselweni region from 2009 to until the end of this research project. This database recorded the ART number of patients co-infected with HIV and therefore was linked to the Treat-All Database.

An **HIV Virology Laboratory Register** was available electronically covering the time period from May 2012 to the completion of the studies. It collected the VL test results of all ART patients of the Shiselweni region and could be linked with the Treat-All database using the ART number. These data were used to fill gaps in the Treat-All Database during data cleaning and set-up of the Treat-All database for analysis.

Secondary data sources

Secondary, publicly accessible data sources were used to obtain population-level estimates.

The 2006 **Swaziland Population and Housing Census**¹⁷⁷ contains projected mid-year population estimates for the Shiselweni region stratified by region, year, gender, and age.

The **first (SHIMS-1, 2011) and second (SHIMS-2, 2016/2017) Swaziland HIV Incidence Measurement Surveys**^{173,180,187,188} and the **Swaziland Demographic Household Survey**¹⁸⁹ contain overall and gender- and age-stratified national and regional HIV prevalence estimates. In addition, the SHIMS studies contain population-level estimates of HIV incidence, knowledge of HIV status, ART coverage, and viral suppression.

Table 3: Data sources used for analyses.

Data source	Use for analyses	Geographic area	Comments
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covered			
Treat-All Database	Objectives 2, 3, 4	- Nhlanguano and Hlathikulu health zones	- This database contained additional variables that were not collected by the APMR (e.g. date of HIV diagnosis, TB co-infection at ART initiation, baseline laboratory test results, VL information) and it was more complete, specifically for the time period under investigation.
Community HTS/ Linkage to Care Register	Secondary objective under objective 2	- Nhlanguano and Hlathikulu health zones	- To obtain crude programmatic linkage estimates for community HTS 1) to HIV care enrolment and 2) to ART initiation
APMR	Objective 1	- Shiselweni region	
TB databases	Objective 5	- Shiselweni region	- In addition, to complete missing TB notification and treatment follow-up information in the Treat-All Database.
HIV Virology Laboratory Register	Objective 3, 4	- Shiselweni region	- To complete missing VL information in the Treat-All Database.
Swaziland Population and Housing Census ¹⁷⁷	Objective 1, 5	- Shiselweni region and national	- To obtain regionalized (Shiselweni) annual and by gender and age-group stratified denominators for population-level estimates of HIV prevalence and TB notifications
SHIMS-1 and SHIMS-2 ^{173,180,187,188}	Objective 1, 5	- Shiselweni region and national	- To obtain regionalized (Shiselweni) annual and by gender and age-group stratified population-level estimates of HIV prevalence and number of PLHIV
Swaziland Demographic Household Survey ¹⁸⁹	Objective 1, 5	- Shiselweni region and national	

APMR, Swaziland National AIDS Programme's ART Programme Monitoring Register; ART, antiretroviral therapy; HTS, HIV testing services; PLHIV, people living with HIV; SHIMS, Swaziland HIV Incidence Measurement Survey.

The candidate's role in data management

The candidate managed and supervised the MSF research, and Monitoring and Evaluation departments for most of the duration of this research project, and was thus responsible for overall data management of the MSF HIV/TB project in Eswatini. In detail, the candidate established the drug-sensitive TB database and supervised the establishment of the Treat-All Database and the Community HTS/ Linkage to Care Register. The candidate coordinated the maintenance and cleaning of the Treat-All Database, TB databases, HIV Virology Laboratory Register, and Community HTS/ Linkage to Care Register. The candidate gained access to the MOH-owned APMR database and access to the secondary data sources that were available in the public domain. The candidate set up all databases for analyses and provided interim updates about progress of the research to the MOH, non-government

stakeholders, and MSF in various platforms such as national Technical Working Groups and Research Steering Committees.

ETHICAL APPROVAL

This entire research project as presented in this thesis was approved by the Human Research Ethics Committee (HREC) at the University of Cape Town (REF 078/2018). In addition, the following approvals were obtained prior to inception of the implementation study and retrospective analyses.

Prospective Treat-All study (Objectives 2, 3, and 4)

Authorization to conduct the Treat-All study was obtained from the Ministry of Health of the Kingdom of Eswatini. The Treat-All implementation study protocol was approved by the MSF ethics review board (ID: 1336) and the Scientific Ethical Committee of Eswatini (REF: MH/599C/FWA00015267).

Written informed consent was obtained from patients who chose to initiate ART beyond national treatment eligibility criteria in place, which followed the WHO 2010 guidelines eligibility criteria until October 2015 and the 2013 WHO guidelines eligibility criteria thereafter. The consent procedure included the information sheet and the consent form, both of which were available in siSwati and English. Information about Treat-All was provided orally during routine clinic group talks and during community HTS events in the catchment area of Treat-All facilities. The patient information sheet was explained to the study participants individually during clinic consultations prior to ART initiation. The patient could also retain a copy of the information sheet. After any questions about the study had been answered, a signature (or fingerprint if illiterate) was obtained on the written consent form before prescription of ART. This study consent procedure was integrated into the general consent procedure for life-long ART initiation as done under routine care. Patients who refused to consent for study enrolment also refused routine ART initiation and thus were considered as LTFU before ART initiation.

Retrospective analyses of routine data (Objectives 1, 5)

Individual-level consent was not solicited as these data were collected routinely as part of HIV/TB care used for programmatic monitoring. Ethical approval for the use of routine data was obtained from the Scientific and Ethics Committee of Eswatini (MH/599C/FWA00015267)). This research fulfilled the exemption criteria set by the MSF Ethics Review Board for a posteriori analysis of routinely collected clinical data and thus did not require MSF ERB review.

Chapter II: Results

RESULTS FOR OBJECTIVE 1

Programmatic outcomes and impact of rapid public sector antiretroviral therapy expansion in adults prior to introduction of the WHO treat-all approach in rural Eswatini

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Paper overview

This study uses data from a cohort of patients initiated on first-line ART in the Shiselweni region in Eswatini, and describes 1) temporal programmatic trends, 2) programmatic impact of ART scale-up, and 3) the time from ART initiation to the composite unfavourable treatment outcome.

Significance of the paper

This manuscript addresses temporal trends in ART outcomes from a routine public sector setting before the introduction of Treat-All. HIV care provision changed significantly during the past decade in RLS and a variety of programmatic strategies were applied to make ART more accessible. However, suboptimal retention was reported from rapid expanding ART cohorts and there is a general lack of recent data from large public-sector ART programmes to understand recent programmatic changes. Context-specific data on the scale-up of HIV care is required to understand the baseline prior to the introduction of universal and prompt ART at the time of HIV diagnosis (Treat-All). Also, significant changes in HIV and TB programming were seen in the Shiselweni region before the introduction of Treat-All in late 2014. ART provision was centralized in 2006/2007; it was decentralized and integrated into public-sector primary care facilities between 2008 and 2010, and programmatic gains were consolidated thereafter. The main questions arising were whether this setting was ready for further ART expansion and whether lessons can be drawn to inform the introduction of Treat-All.

Candidate`s contributions

The candidate (with advice from MS and AB) designed and planned the research. The candidate acquired the data, processed all data, performed all analyses, wrote the first draft of the manuscript, integrated comments from co-authors, and submitted the manuscripts for peer review.

ABSTRACT

Objectives

To assess long-term antiretroviral therapy (ART) outcomes during rapid HIV programme expansion in the public sector of Eswatini (formerly Swaziland).

Methods

This is a retrospectively established cohort of HIV-positive adults (≥ 16 years) who started first-line ART in 25 health facilities in Shiselweni (Eswatini) between 01/2006 and 12/2014. Temporal trends in ART attrition, treatment expansion and ART coverage were described over 9 years. We used flexible parametric survival models to assess the relationship between time to ART attrition and covariates.

Results

Of 24 772 ART initiations, 6% ($n = 1488$) occurred in 2006, vs. 13% ($n = 3192$) in 2014. Between these years, median CD4 cell count at ART initiation increased (113–265 cells/mm³). The active treatment cohort expanded 8.4-fold, ART coverage increased 8.0-fold (7.1% in 2006 vs. 56.8% in 2014) and 12-month crude ART retention improved from 71% to 86%. Compared with the pre-decentralisation period (2006–2007), attrition decreased by 5% (adjusted hazard ratio [aHR] 0.95, 95% confidence interval 0.88–1.02) during HIV-TB service decentralisation (2008–2010), by 17% (aHR 0.83, 0.75–0.92) during service consolidation (2011–2012), and by 20% (aHR 0.80, 0.71–0.90) during further treatment expansion (2013–2014). The risk of attrition was higher for young age, male sex, pathological baseline haemoglobin and biochemistry results, more toxic drug regimens, WHO III/IV staging and low CD4 cell count; access to a telephone was protective.

Conclusions

Programmatic outcomes improved during large expansion of the treatment cohort and increased ART coverage. Changes in ART programming may have contributed to better outcomes.

INTRODUCTION

Because 4.1 million more people living with HIV (PLHIV) require HIV treatment for achievement of the second 90 of the UNAIDS 90-90-90 cascade targets in Eastern and Southern Africa,^{5,37} effective and universal antiretroviral therapy (ART) provision remains the backbone of successful HIV programmes.⁵ WHO recommends a public health-oriented approach for antiretroviral provision in resource-limited settings (RLS), allowing for simplification of HIV services, service decentralisation and integration into tuberculosis (TB) and primary care settings, task-shifting and expansion of treatment eligibility criteria.^{12–16} Despite the unprecedented progress in ART provision (e.g. 60% ART coverage in sub-Saharan Africa in 2017),^{37,190} achievements remain fragile as challenges persist in funding, medical capacity, slow uptake and implementation of international recommendations, health service infrastructure, healthcare staffing, laboratory monitoring services, drug supply and programme monitoring.^{30–34,171} Suboptimal ART retention has raised particular concern because large and rapidly expanding ART programmes appear to encounter greater challenges in retaining patients.^{100,107} ART retention was 78% at 12 months in low- and middle-income countries,¹⁷¹ and several studies found increased rates of loss to follow-up (LTFU) in recent years,^{102–104,107–110} while mortality remained stable^{104,108} or decreased.^{102,104,109,110} The mismatch of growing demand for ART and overburdened health facilities likely contributed to deterioration in quality of care, suboptimal adherence and treatment support and poorer record keeping.^{104,107,109} The feasibility of continued ART expansion – through the introduction of the WHO treat-all approach endorsing prompt ART initiation irrespective of immunological status – remains uncertain and has resulted in doubts about its likely impact.^{31–33,35,39–43}

Eswatini (formerly Swaziland) has the highest HIV prevalence (32% in adults aged 18–49 years)¹⁷³ and one of the highest TB notification and HIV co-infection rates in the world.¹⁹¹ Despite limited resources for the HIV response,^{106,192} estimated HIV incidence decreased by 44% (from 2.5 to 1.4 cases per 100 person-years) between 2011 and 2016.¹⁹³ Population-level viral load suppression among PLHIV was 73% in Eswatini and highest (79%) in the southern Shiselweni region,^{193,194} surpassing the international UNAIDS population-level target of 73% (1). Although the Eswatini ART response was considered a success story before the most recent guidance to drop all treatment eligibility criteria (treat-all), contemporary large ART cohort analyses with extended patient follow-up are lacking. We describe temporal trends in the growth and programmatic outcomes of the HIV treatment programme in the Shiselweni region of Eswatini, establishing a baseline against which to evaluate further treatment expansion, and drawing lessons to inform the implementation of universal treatment access.

METHODS

Setting

The predominantly rural Shiselweni region (population 210 000 (35)) in southern Eswatini has an HIV prevalence of 26% in people aged ≥ 15 years.¹⁹⁴ Several programmatic strategies were applied during ART expansion between 2006 and 2014 (Table 1). From 2006 to 2007, HIV-TB care was centralised at outpatient departments of three secondary health facilities (two health centres, one hospital) in three health clusters (Nhlangano, Hlathikulu, Matsanjeni) (period-1). In 2008, doctor-led mobile outreach teams started decentralising HIV-TB services, with physical integration into 22 nurse-led primary care clinics from 2009 to 2010 (period-2). Nurses were trained to perform ART and TB treatment initiation and follow-up. Trained lay cadres provided HIV counselling and testing, basic laboratory tests (e.g. point-of-care CD4 cell count testing, biochemistry testing), medication dispensing, pre-treatment counselling and treatment adherence support interventions. The WHO 2010 treatment guidelines were also endorsed in 2010. Thereafter, from 2011 to 2012, HIV services were consolidated, and community-based HIV testing and routine viral load monitoring were introduced^{79,140} (period-3). Then, in 2013 and 2014 (period-4), ART eligibility was further extended in Nhlangano health cluster by phasing in the prevention of mother-to-child transmission (PMTCT) option B+ approach in 01/2013^{185,186} and universal ART provision irrespective of immunological criteria (treat-all) in 10/2014. All services were provided free of charge by the Ministry of Health and Médecins Sans Frontières (MSF). A map of facilities of Shiselweni is presented in Figure S1:1.

Study design and definitions

We analysed a retrospectively established cohort of HIV-infected adults (≥ 16 years) initiated on standard first-line ART in 25 health facilities in the Shiselweni region between 01/2006 and 12/2014. Data came from the national ART treatment database used for routine programmatic monitoring by the Ministry of Health. Exclusion criteria were transfer in from outside the region, missing age or being on a non-standard first-line treatment regimen. Follow-up was from the day of ART initiation until the earliest of the composite outcome of all-cause attrition (death or LTFU), transfer out of the region and database closure (08/2015). LTFU was defined as ≥ 6 months without a clinic visit, measured on the date of last clinic visit.

Statistics

First, we described patients' baseline characteristics by calendar year and overall. Median and interquartile ranges (IQR) were used for continuous variables, and frequencies and proportions for categorical variables. Differences across categories were tested with Pearson's chi-squared test.

Second, to estimate programmatic impact, we calculated the number of patients alive and retained in care at each calendar mid-year, and obtained annual ART coverage estimates. The denominator was PLHIV, obtained by multiplying regional projected annual mid-year population estimates¹⁷⁷ by

regional HIV prevalence estimates for ≥ 15 -year-olds.¹⁹⁴ ART retention was calculated for each annual cohort separately using the Kaplan–Meier estimator.

Third, calendar years were grouped into corresponding programmatic periods (1–4) (Figure 1) for inclusion into covariate-adjusted regression analysis, where time to attrition was the outcome. Other covariates for inclusion were determined *a priori*. We used multiple imputation by chained equations for imputation of missing covariate values of sex-pregnancy status, CD4 cell count, WHO staging, body mass index (BMI), creatinine, alanine aminotransferase (ALT), haemoglobin and access to telephone, creating 20 imputed datasets.¹⁹⁵ Then we used flexible parametric survival models (Royston–Parmar models)^{196,197} to describe the association between time to attrition and the covariates, and plotted averaged survival curves based on the fitted model.¹⁹⁸ The number of internal knots for estimating the baseline spline function was based on Akaike's and Schwarz's Bayesian information criteria and on visual inspection of best fit of standardised survival and hazard curves. After assessment of the proportional hazards assumption with Schoenfeld residual statistics, we allowed the variable programmatic period to vary by duration on ART. Two regression models were built: the first included all available variables irrespective of magnitude of missingness (Model-1), and the second was restricted to covariates with $< 20\%$ imputed values (Model-2). In the sensitivity analysis, calendar year (instead of programmatic period) was allowed to interact with follow-up time. All analyses were performed with Stata 14.1 (StataCorp, College Station, Texas, US).

Ethics

This study was approved by the Scientific and Ethics Committee of the Ministry of Health of Eswatini and the Health Sciences Faculty Research Ethics Committee of the University of Cape Town, South Africa. This research fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for *a posteriori* analyses of routinely collected clinical data and thus did not require MSF ERB review. It was conducted with permission from Micaela Serafini (Medical Director, Operational Centre Geneva), MSF

RESULTS

Baseline characteristic and temporal trends

Baseline characteristics and temporal trends are presented in Tables 2, 3 and Figures 1, 2. Of 24 772 patients initiated on ART, Nhlanguano health cluster contributed 10 451 (42%) observations. Annual initiations increased from 1488 in 2006 to 3536 in 2010, coinciding with HIV-TB care decentralisation (2008–2010) and endorsement of the WHO 2010 treatment eligibility criteria. Thereafter, initiations decreased to 3039 in 2012, with a slight increase in 2013 and 2014 ($n = 3188$ and 3192), coinciding with the introduction of PMTCT option B+ and treat-all.

The median age at initiation was 33 (IQR 27–42) years with most patients being 25–34 (40%) and 35–44 (24%) years old. The proportion of young adults (16–24 years old) increased from 11% in 2006 to 21% in 2014, with a similar trend seen for 25- to 34-year-olds (2006: 36%; 2014: 43%). A reciprocal proportional decrease was seen for the age group 35–54 years, from 46% to 29%. The sex of 0.2% of patients was unknown and pregnancy status was missing in 16% of women. Most patients were non-pregnant women ($n = 11\,987$, 54%), followed by men ($n = 8493$, 38%) and pregnant women ($n = 1643$, 7%). Most patients ($n = 15\,613$, 94%) had access to a telephone.

Most patients had CD4 cell counts of ≤ 100 (28%), 101–200 (28%) and 201–350 (33%) cells/mm³, while 12% had counts ≥ 351 cells/mm³. The median CD4 cell count increased in each consecutive year, most pronounced in pregnant women (from 78 to 343.5 cells/mm³), followed by non-pregnant women (from 132.5 to 287 cells/mm³) and men (from 99 to 188 cells/mm³) (Figure 1). The absolute number of ART initiations at CD4 cell count ≤ 100 and 101–200 cells/mm³ increased until 2009 and decreased thereafter in consecutive years (Figure 1). 86% of patients had a CD4 cell count ≤ 200 cells/mm³ in 2006 vs. 37% in 2014. In the early years (2006–2009), $\leq 4\%$ had CD4 cell counts ≥ 351 cells/mm³ vs. 28% in 2014. Overall, 8389 (34%) and 1593 (6%) of patients had WHO clinical stage III and IV, respectively, decreased from 45% and 13% in 2006 to 17% and 3% in 2014 (Figure 1).

The most widely used nucleoside reverse transcriptase inhibitor drugs were zidovudine (AZT) (39%) and tenofovir disoproxil fumarate (TDF) (48%). In 2006, 80% and 18% of patients received stavudine (D4T) and AZT compared with 89% and 10% receiving TDF and AZT in 2014 (Figure 1). D4T was largely phased out between 2009 and 2010, while TDF was phased in. Abacavir (ABC) was rarely used in all calendar years ($\leq 1\%$). In 2006, the main non-nucleoside reverse transcriptase inhibitor drug was nevirapine (NVP) (68%), while efavirenz (EFV) use increased rapidly from 2011, reaching 91% in 2014.

Laboratory measures for creatinine, ALT and haemoglobin were frequently not available at baseline (60%). Among patients with complete observations (Table 3), 1349 (10%) had a BMI < 18.5 kg/m², 535 (5%) elevated creatinine ≥ 121 μ mol/L, 1551 (16%) elevated ALT ≥ 43 U/L and 2016 (20%) anaemia (haemoglobin ≤ 9 mg/dL).

Programmatic impact

The number of people active on ART increased in consecutive years from 2171 in 2006 to 18 307 in 2014 (8.4-fold increase). While the relative increase was similar for both sexes (women 8.5- vs. men 8.3-fold increase), more women ($n = 12\,210$, 67%) were on ART in 2014. In 2014, 9782 (53%) patients were followed at primary care level and 5477 (30%) at secondary care level, and 3048 (17%)

did not have the healthcare level recorded. The ART coverage among PLHIV increased 8.0-fold, from 7.1% in 2006 to 56.8% in 2014 (Figure 2).

Crude ART retention increased in consecutive annual ART cohorts (Figure 3). The 12-month retention was 71% in 2006 compared with 86% in 2014. After 9 years of follow-up of the 2006 ART cohort, 49% patients were retained in care. Improvements in retention were most pronounced comparing programmatic periods (Figure 3): retention was 66%, 74%, 80% and 82% at 2 years for consecutive periods 1–4.

Associations with attrition

The total and median follow-up times were 77 009.8 and 2.6 (IQR 1.0–4.9) years, with 1666 (7%) deaths and 5681 (23%) LTFU recorded at a rate of 9.5 (95% confidence interval [CI] 9.3–9.8) per 100 person-years. Imputation diagnostic and model selection procedures are presented in Appendices S2–S3.

While only findings of Model-1 are described here (Table 3), estimates were comparable between the models (Appendix S4, Table S4:1). Compared with the pre-decentralisation period (2006–2007, period-1), the overall risk of attrition dropped by 5% on average (adjusted hazard ratio [aHR] 0.95, 95% CI 0.88–1.02) during HIV-TB service decentralisation (2008–2010, period-2), by 17% (aHR 0.83, 0.75–0.92) during service consolidation (2011–2012, period-3) and by 20% (aHR 0.80, 0.71–0.90) during further treatment expansion (2013–2014, period-4). The effect, however, varied by duration on ART, with an absolute survival benefit seen during the first 2.5 (period-2), 4.5 (period-3) and 6.5 (period-4) years following ART initiation (Figure 4b–d). Thereafter, it remained similar for period-4 (compared with the pre-decentralisation period) while tending to decrease for period-2 and period-3. Sensitivity analysis by calendar year rather than period showed increased risk of attrition during 2007 to 2008, similar risk in 2009 and decreasing attrition thereafter (Appendix S4, Figure S4:1).

Compared with non-pregnant women, men had a 23% (aHR 1.23, 1.15–1.32) increased risk of attrition while pregnant women had a 10% increased risk (aHR 1.10, 0.98–1.23) (Appendix S4, Figure S4:2a). Compared with the reference age group 25–34 years, attrition was increased for young adults (16–24 years) and patients aged ≥ 55 years, while it was decreased for patients aged 35–54 years. The availability of a phone decreased attrition by 35% (aHR 0.65, 0.57–0.74) while BMI and health cluster did not show associations.

Compared with CD4 cell count 201–350 cells/mm³, lower CD4 strata had a higher risk of attrition (CD4 ≤ 100 : aHR 1.47, 1.38–1.57; CD4 101–200: aHR 1.18, 1.11–1.26), while higher CD4 cell counts had similar outcomes (Appendix S4, Figure S4:2b). Patients with WHO III and IV staging also

had an increased risk (WHO III: aHR 1.24, 1.17–1.31; WHO IV: aHR 2.06, 1.88–2.25), as did patients with elevated values of creatinine or ALT, or anaemia.

While Model-2 (Appendix S4, Table S4:1) showed increased risk of attrition for ABC (aHR 1.34, 95% CI 1.04–1.73) and D4T (aHR 1.57, 1.47–1.69) compared with AZT, Model-1 showed an increased risk only for D4T (aHR 1.16, 1.05–1.28).

DISCUSSION

This study describes temporal trends and outcomes of public sector ART programme expansion in a predominantly rural setting over 9 years. Crude attrition decreased over time coinciding with an 8-fold expansion of the treatment cohort and an increase in ART coverage. The same trend was seen in covariate-adjusted analysis of attrition, coinciding with programmatic changes over time.

Results in context

Crude ART retention of the 2010 annual cohort and thereafter compares favourably with retention reported from routine low- and middle-income settings (78% at 12 months, 71% at 24 months and 69% at 36 months).¹⁰⁰ In contrast to other studies suggesting higher attrition for more recent cohorts,^{100,109} attrition decreased with each consecutive programmatic period and was reduced by 20% in 2012–2014. Firstly, one study from neighbouring South Africa ceased patient follow-up during the early years of programme expansion,¹⁰⁹ possibly missing positive trends once HIV-TB programmes had been consolidated. Secondly, the implementation of combination interventions – ART provision at higher CD4 thresholds, prescription of less toxic drug combinations – may have supported ART expansion while maintaining and improving outcomes. Active defaulter tracing by phone (with possibility of physical tracing by home visits) may also have contributed, as patients with access to a phone had a 35% decreased risk of attrition. Other studies showed that programmes applying physical defaulter tracing had higher 12-month retention on ART (80.0% vs. 75.8%)¹⁶¹ and programmes using phones in combination interventions had reduced loss to care.^{161,199–201} Sensitivity analysis, however, suggested a temporary increase in risk of attrition in 2008, the year when HIV-TB care was decentralised through mobile doctor-led teams. The rapid introduction of new programmatic and clinical activities (decentralisation, task-shifting and sharing, provision of ART and TB treatment in previous ART-TB ‘naïve’ primary care clinics) facilitated access to ART but may have overwhelmed the health system and health workers. Although attrition showed a tendency of decline since 2010 (the end of the decentralisation period), the full gains became evident later during the consolidation period in 2012, when risk of attrition was reduced by 17%.

Similar to other studies, young age,^{104,135,192,202–206} sex-pregnancy status,^{101,104,105,135,192,202,204,207} pathological baseline laboratory test results,¹³⁵ more toxic drug regimens (e.g. D4T),²⁰⁶ advanced

WHO III/IV staging^{135,192,203–207} and low CD4 cell counts^{104,135,202,203,205} increased the risk of an adverse outcome. Notably, patients with CD4 cell counts above 350 cells/mm³ had similar outcomes to patients with CD4 cell count 201–350 cells/mm³, suggesting that expansion of ART eligibility through the WHO treat-all approach is feasible for healthier individuals.

Explanation of results and programmatic lessons learnt

Service decentralisation and integration, task-shifting, simplification of HIV care, viral load testing and innovative care models were found efficient to support ART expansion in RLS.^{13,57,64,65,105,204–206}

In this setting, timely identification of programmatic obstacles and overcoming them with effective combination interventions were likely contributing factors for improved programmatic outcomes.

First, the highly centralised set-up of HIV-TB care provision required decentralisation and integration of services into rural primary care clinics to increase access and facilitate the programmatic and clinical management of HIV-TB co-infection. Second, the human resources for health crisis intertwined with lack of patient support structures necessitated task-shifting and sharing. Nurses were capacitated to diagnose and treat HIV-TB with only limited doctor support. Lay people living with HIV from the surrounding communities were trained to provide basic clinic services and patient support. Third, to increase access to timely treatment, international policy changes were quickly implemented (e.g. 2010 WHO treatment eligibility recommendations) and pilot interventions for treatment expansion were introduced before becoming WHO policy (e.g. phase-in of PMTCT option B+^{185,186} and treat-all). This allowed an increasing number of PLHIV to start treatment before presenting with advanced HIV disease, possibly resulting in a less sick and clinically more easy to manage treatment cohort. In this study, however, only a limited number of patients were exposed to the most recent policy changes (PMTCT option B+, treat-all), thus making it difficult to analyse the possible impact of these changes on patient outcomes. Fourth, the establishment of phlebotomist-led mini-laboratories at primary care clinics allowed for point-of-care CD4, haemoglobin and biochemistry (creatinine, ALT) testing.²⁰⁸ This was likely to support rapid ART initiation and timely clinical decision-making by reducing turnaround time between sample collection and result delivery. Fifth, the introduction of routine viral load monitoring and enhanced adherence counselling for patients with elevated viral loads^{134,140} was likely to reduce mortality, LTFU and development of drug resistance.^{128,130}

Although the findings of this study can be considered favourable, other programmatic constraints such as suboptimal linkage to care from routine community-based (34%) and facility-based (87%) HIV testing^{79,199} may jeopardise achievement of the UNAIDS 90-90-90 targets. However, this setting reported favourable viral load outcomes, with 84% of ART patients having an undetectable viral load (<100 copies/mL)¹³⁴ and 89% of pregnant and lactating women achieving viral suppression (<1000 copies/mL).¹⁸⁶ Future programmatic changes such as simplification of ART provision under

the treat-all approach and the introduction of potent antiretroviral drugs (e.g. dolutegravir) could have the potential to further improve outcomes. The 2017 WHO recommendation on rapid and same-day ART initiation is also expected to improve rates of treatment initiation, time to viral suppression and treatment outcomes.^{209,210}

Strengths and weaknesses

Although the introduction of specific programmatic and health policy factors coincided with improved outcomes over time, this study was not designed to assess causal relationships. The efficacy and real-world effectiveness of the intervention in routine settings were discussed previously.^{113–115} Bias could have been introduced by not adjusting for other undocumented factors possibly associated with the outcome (e.g. TB co-infection, socioeconomic and facility-level factors). Treatment interruptions were not taken into account as longitudinal visit data were not available. This may have overestimated LTFU for more recent cohorts with shorter follow-up time.¹⁶⁸ Exclusion of treatment interrupters re-entering ART care may underestimate programmatic impact if the reason for return was a defaulter tracing intervention integrated into the ART programme. Because ascertainment of patient outcomes was weak and we had no access to national death registries, LTFU and death were combined into the composite outcome of all-cause attrition. Thus, we were likely to miss separate temporal trends in mortality and LTFU as reported from other settings.^{102–104,107–110} It was beyond the scope of this study to assess HIV testing, linkage to HIV care and viral load suppression, all factors crucial to estimating the overall success of large HIV programmes. Finally, despite the overall success of this HIV treatment programme, outcomes of children remained unknown as the analysis was limited to young people and adults.

A strength of the study was the use of international recommendations for definitions of LTFU and methodological approaches to ART survival analysis.^{166,167} In addition, flexible parametric survival methods allowed us to easily model programmatic period as a time-dependent factor and to understand its impact on survival over time. As this study originated from the public sector ART programme, findings are likely generalisable to other similar rural and resource-poor settings in sub-Saharan Africa.

CONCLUSIONS

Documenting and measuring previous progress in ART programming provides lessons for future treatment expansion. In this setting, public sector ART expansion was feasible and yielded improved programmatic outcomes over time. HIV-TB service decentralisation and integration, task-shifting and progressive changes in treatment eligibility were likely key factors facilitating access to ART and increasing treatment coverage. After years of ART programming, this setting appears prepared for continued treatment expansion through the WHO treat-all approach.

Table 1: Overview of main programmatic changes occurring during ART programme expansion (2006–2014)

Programmatic periods		2006	2007	2008	2009	2010	2011	2012	2013	2014
		Pre-decentralisation (period-1)	Decentralisation ^a (period-2)			Consolidation ^b (period-3)			Continued expansion (period-4)	
Decentralisation process		Centralised	Transition			Fully decentralised				
ART eligibility	General PLHIV	≤200				≤350 ^c				
	PMTCT approach	Option A							Option A & option B+ ^d	
Number of physically integrated HIV-TB facilities	Primary care clinics	0	0	0 ^e	4	21	22	22	22	22
	Secondary care facilities	3	3	3	3	3	3	3	3	3
Viral load testing availability		No testing			Targeted testing			Routine monitoring		
Expansion of community-based HIV testing services		No						Yes		

ART, antiretroviral therapy; PLHIV, people living with HIV; PMTCT, prevention of mother-to-child transmission.

a Patients established on ART were also transferred down from secondary to primary care facilities.

b Continued strengthening and streamlining of vertical integration of HIV and TB services as well as horizontal integration into routine primary care services.

c One of the three health zones (Nhlangano health zone) provided the WHO treat-all programmatic approach with ART initiation irrespective of CD4 and WHO staging criteria from October 2014.

d PMTCT option B+ was provided in Nhlangano health zone from January 2013. Thereafter, it was phased in in the other two health zones from August 2014.

e Mobile teams provided HIV-TB care in a few facilities.

Table 2: Temporal trends in ART expansion and patient characteristics from 2006 to 2014. Values are numbers (%) or median (IQR)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	Total
ART initiations	1488	1655	2354	2951	3536	3369	3039	3188	3192	24 772
Men	539 (36)	580 (35)	827 (35)	1012 (34)	1228 (35)	1187 (35)	1112 (37)	1020 (32)	988 (31)	8493 (34)
Non-pregnant women	248 (17)	462 (28)	880 (37)	1625 (55)	1959 (55)	1781 (53)	1557 (51)	1729 (54)	1746 (55)	11 987 (48)
Pregnant women	3 (0)	30 (2)	86 (4)	119 (4)	172 (5)	245 (7)	268 (9)	337 (11)	383 (12)	1643 (7)
Missing ^a	698 (47)	583 (35)	561 (24)	195 (7)	177 (5)	156 (5)	102 (3)	102 (3)	75 (2)	2649 (11)
Age, years (missing $n = 0$)	35 (28–43.5)	34 (29–43)	34 (28–43)	35 (28–45)	34 (27–43)	33 (27–42)	33 (27–42)	32 (26–41)	31 (25–39)	33 (27–42)
16–24	166 (11)	181 (11)	302 (13)	378 (13)	504 (14)	475 (14)	451 (15)	616 (19)	686 (21)	3759 (15)
25–34	543 (36)	665 (40)	876 (37)	1071 (36)	1379 (39)	1406 (42)	1261 (41)	1306 (41)	1360 (43)	9867 (40)
35–44	439 (30)	459 (28)	645 (27)	762 (26)	879 (25)	805 (24)	712 (23)	689 (22)	654 (20)	6044 (24)
45–54	234 (16)	212 (13)	346 (15)	449 (15)	476 (13)	437 (13)	382 (13)	364 (11)	291 (9)	3191 (13)
≥55	106 (7)	138 (8)	185 (8)	291 (10)	298 (8)	246 (7)	233 (8)	213 (7)	201 (6)	1911 (8)
CD4 count, cells/mm ³ (missing $n = 36$)	113 (55–174)	127 (59–191)	140 (70–213)	157 (79–236)	194 (98–289)	198 (103–294)	203 (100.5–295)	243 (125–336)	265 (136–368)	183 (91–287)
Men	99 (42–157)	102.5 (46–179)	117 (53–187)	127 (58–208)	156 (73–256)	164.5 (79–267.5)	159 (69–259)	182 (96–289)	188 (87–297)	145 (68–245)
Non-pregnant women	132.5 (71.5–185)	144.5 (66–200)	143 (76–213)	168 (92–246)	205 (107–297)	209 (117–299)	220 (118.5–304)	259 (143–345)	287 (166–403)	205 (108–303)
Pregnant women	78 (58–94)	211.5 (146–291)	225 (146–306)	231 (153–279)	237.5 (156.5–308.5)	252 (176–319)	264 (174–316)	304 (220–432)	343.5 (230–499)	272 (186–346)
0–100	651 (44)	677 (41)	824 (35)	917 (31)	911 (26)	820 (24)	759 (25)	642 (20)	616 (19)	6817 (28)
101–200	617 (42)	616 (37)	868 (37)	976 (33)	929 (26)	890 (26)	739 (24)	638 (20)	570 (18)	6843 (28)
201–350	170 (11)	292 (18)	576 (25)	929 (32)	1310 (37)	1300 (39)	1234 (41)	1224 (38)	1110 (35)	8145 (33)
351–500	32 (2)	45 (3)	66 (3)	91 (3)	268 (8)	249 (7)	226 (7)	412 (13)	473 (15)	1862 (8)
≥501	16 (1)	23 (1)	17 (1)	33 (1)	116 (3)	106 (3)	78 (3)	268 (8)	412 (13)	1069 (4)
WHO staging (missing $n = 13$)										
I+II	615 (41)	718 (43)	1027 (44)	1462 (50)	1927 (55)	2030 (60)	1989 (65)	2448 (77)	2561 (80)	14 777 (60)

III	676 (45)	754 (46)	1077 (46)	1230 (42)	1407 (40)	1159 (34)	907 (30)	637 (20)	542 (17)	8389 (34)
IV	196 (13)	183 (11)	249 (11)	258 (9)	200 (6)	177 (5)	141 (5)	101 (3)	88 (3)	1593 (6)
NRTI (missing $n = 0$)										
ABC	3 (0)	2 (0)	3 (0)	39 (1)	20 (1)	15 (0)	33 (1)	27 (1)	28 (1)	170 (1)
AZT	275 (18)	917 (55)	1664 (71)	2503 (85)	2292 (65)	659 (20)	564 (19)	352 (11)	330 (10)	9556 (39)
D4T	1192 (80)	720 (44)	664 (28)	349 (12)	181 (5)	25 (1)	20 (1)	7 (0)	9 (0)	3167 (13)
TDF	18 (1)	16 (1)	23 (1)	60 (2)	1043 (29)	2670 (79)	2422 (80)	2802 (88)	2825 (89)	11 879 (48)
NNRTI (missing $n = 0$)										
EFV	475 (32)	465 (28)	506 (21)	824 (28)	1411 (40)	2771 (82)	2456 (81)	2832 (89)	2892 (91)	14 632 (59)
NVP	1013 (68)	1190 (72)	1848 (79)	2127 (72)	2125 (60)	598 (18)	583 (19)	356 (11)	300 (9)	10 140 (41)

n, number; *IQR*, interquartile range; *WHO*, World Health Organization; *NRTI*, nucleoside reverse transcriptase inhibitor; *AZT*, zidovudine; *ABC*, abacavir; *D4T*, stavudine; *TDF*, tenofovir disoproxil fumarate; *NNRTI*, non-nucleoside reverse transcriptase inhibitors; *EFV*, efavirenz; *NVP*, nevirapine.

^aThe greatest proportion of missing values was for pregnancy status (11%), while only <1% had missing sex status.

Table 3: Baseline characteristics and predictors of all-cause attrition, Model-1

	n (%)	Univariate analysis		Multivariate analysis	
		HR	95% CI	aHR	95% CI
Programmatic period; (0)					
Period-1	3143 (12.7)	1		1	
Period-2	8841 (35.7)	0.75	(0.70–0.79)	0.94	(0.87–1.01)
Period-3	6408 (25.9)	0.57	(0.53–0.61)	0.83	(0.75–0.92)
Period-4	6380 (25.8)	0.48	(0.44–0.52)	0.80	(0.71–0.90)
Health cluster; (0)					
Nhlangano	10 451 (42.2)	1			
Hlathikulu	8187 (33)	1.02	(0.97–1.08)	1.04	(0.98–1.10)
Matsanjeni	6134 (24.8)	1.05	(0.99–1.11)	0.95	(0.89–1.02)
Sex-pregnancy status; (10.7) ^a					
Non-pregnant women	11 987 (54.2)	1		1	
Men	8493 (38.4)	1.22	(1.16–1.28)	1.23	(1.15–1.32)
Pregnant women	1643 (7.4)	0.96	(0.87–1.06)	1.10	(0.98–1.23)
Age, years; (0)					
16–24	3759 (15.2)	1.24	(1.17–1.33)	1.39	(1.30–1.49)
25–34	9867 (39.8)	1		1	
35–44	6044 (24.4)	0.87	(0.82–0.92)	0.84	(0.79–0.90)
45–54	3191 (12.9)	0.82	(0.76–0.88)	0.82	(0.75–0.89)
≥55	1911 (7.7)	1.07	(0.98–1.17)	1.11	(1.02–1.22)
CD4 cell count, cells/mm ³ ; (0.1)					
0–100	6817 (27.6)	1.99	(1.87–2.11)	1.47	(1.38–1.57)
101–200	6843 (27.7)	1.37	(1.29–1.46)	1.18	(1.11–1.26)
201–350	8145 (32.9)	1		1	
351–500	1862 (7.5)	0.92	(0.82–1.03)	0.94	(0.84–1.06)
≥501	1069 (4.3)	0.89	(0.77–1.04)	0.96	(0.82–1.12)
WHO staging; (0.1)					
I+II	14 777 (59.7)	1		1	
III	8389 (33.9)	1.55	(1.47–1.63)	1.24	(1.17–1.31)
IV	1593 (6.4)	3.03	(2.82–3.27)	2.06	(1.88–2.25)
NRTI; (0)					
AZT	9556 (38.6)	1		1	
ABC	170 (0.7)	1.46	(1.13–1.88)	0.94	(0.72–1.24)
D4T	3167 (12.8)	1.86	(1.75–1.97)	1.16	(1.05–1.28)
TDF	11 879 (48)	0.82	(0.78–0.87)	0.93	(0.84–1.02)
NNRTI; (0)					
EFV	14 632 (59.1)	1		1	
NVP	10 140 (40.9)	1.18	(1.13–1.24)	1.07	(0.99–1.15)
BMI, kg/m ² ; (47.5)					
<18.5	1349 (10.4)	1		1	
18.5–24.9	7066 (54.3)	0.74	(0.69–0.81)	0.98	(0.90–1.07)
≥25	4586 (35.3)	0.54	(0.49–0.60)	0.93	(0.82–1.06)

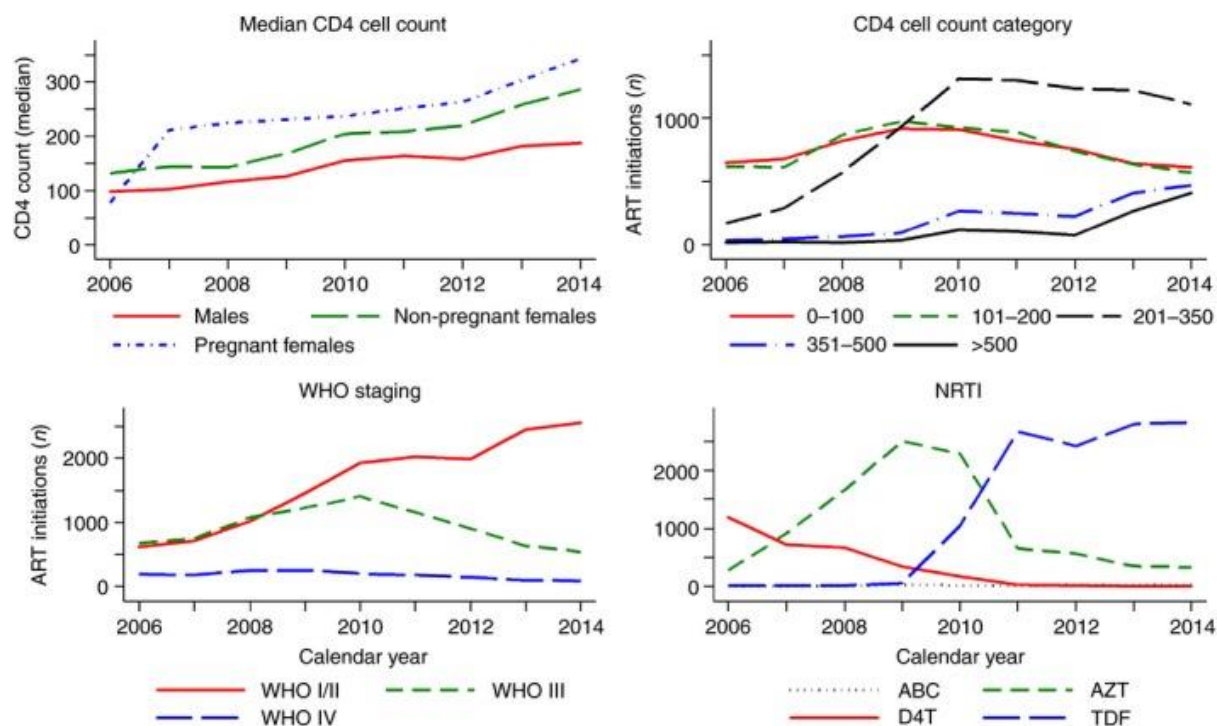
Creatinine, $\mu\text{mol/L}$; (59)					
≤ 120	9630 (94.7)	1		1	
121–240	480 (4.7)	1.16	(0.86–1.57)	0.86	(0.63–1.17)
≥ 241	55 (0.5)	2.97	(1.79–4.90)	1.77	(1.06–2.95)
ALT, U/L; (61.4)					
≤ 42	8006 (83.8)	1		1	
≥ 43	1551 (16.2)	1.19	(1.09–1.31)	1.12	(1.01–1.25)
HB, mg/dL; (59.5)					
≥ 10	8009 (79.9)	1		1	
≤ 9	2016 (20.1)	2.11	(1.98–2.26)	1.65	(1.50–1.81)
Access to telephone ^b (33.3)					
No	918 (5.6)	1		1	
Yes	15 613 (94.4)	0.62	(0.55–0.71)	0.65	(0.57–0.74)

n, number; *HR*, hazard ratio; *aHR*, adjusted hazard ratio; *CI*, confidence interval; *WHO*, World Health Organization; *NRTI*, nucleoside reverse transcriptase inhibitor; *AZT*, zidovudine; *ABC*, abacavir; *D4T*, stavudine; *TDF*, tenofovir disoproxil fumarate; *NNRTI*, non-nucleoside reverse transcriptase inhibitors; *EFV*, efavirenz; *BMI*, body mass index; *NVP*, nevirapine; *ALT*, alanine transaminase; *HB*, haemoglobin.

^a While 0.2% of patients had missing sex status, pregnancy status was missing in 16% of women.

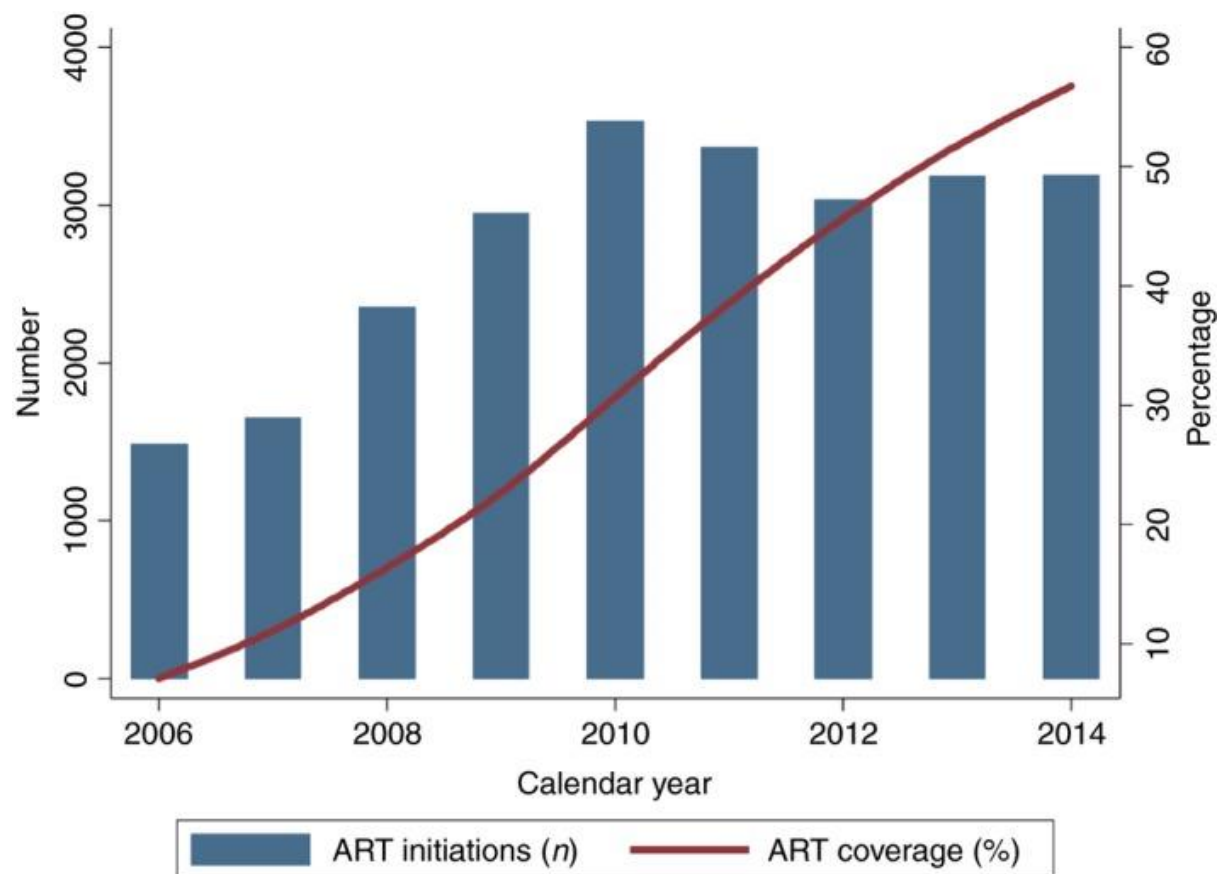
^b Access to a telephone was defined as a patient with a recorded telephone number in the database.

Multiple imputations were used in all univariate and multivariate regression analyses for the variables sex-pregnancy status, CD4 cell count, WHO staging, BMI, creatinine, ALT, HB and access to telephone. The model had 6 degrees of freedom (5 internal knots) for non-time-dependent covariates and 2 degrees of freedom (1 internal knot) for the time-dependent covariate programmatic period.



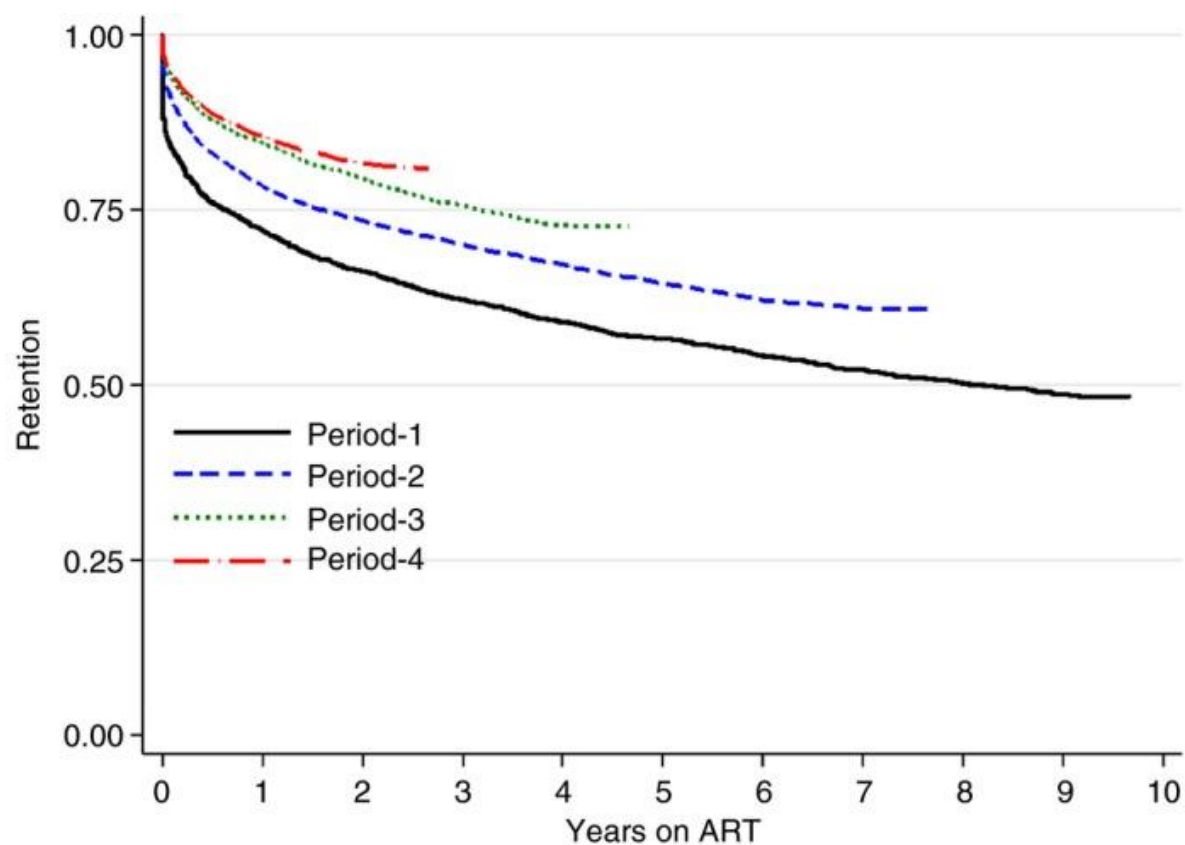
ART, antiretroviral therapy; n, number; WHO, World Health Organization; NRTI, nucleoside reverse transcriptase inhibitor; AZT, zidovudine; ABC, abacavir; D4T, stavudine; TDF, tenofovir disoproxil fumarate.

Figure 1: Temporal trends during ART programme expansion (2006–2014).



ART, antiretroviral therapy; n, number.

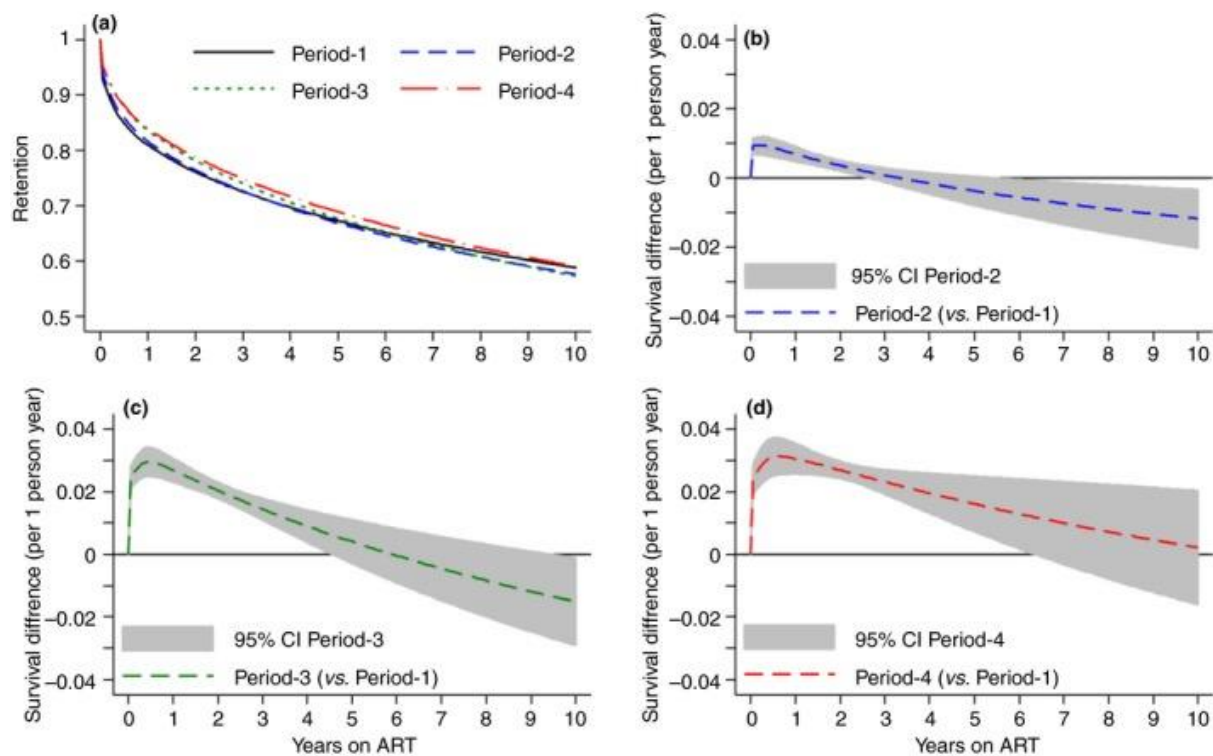
Figure 2: Annual number of ART initiations and treatment coverage during ART programme expansion (2014–2016).



	Period-1		Period-2			Period-3		Period-4	
RIC*	2006	2007	2008	2009	2010	2011	2012	2013	2014
0.5	76%	76%	80%	83%	86%	88%	88%	89%	88%
1	71%	73%	74%	78%	82%	85%	85%	86%	86%
2	65%	67%	68%	73%	78%	80%	79%	81%	
3	62%	63%	64%	70%	74%	76%	76%		
4	58%	60%	62%	67%	72%	72%			
5	56%	57%	59%	64%	69%				
6	55%	54%	56%	62%					
7	52%	52%	55%						
8	50%	50%							
9	49%								

*RIC, retention in care in years; ART, antiretroviral therapy.

Figure 3: Crude ART retention by annual and programmatic periods.



The overall 5% (aHR 0.95, 95% CI 0.88–1.02), 17% (aHR 0.83, 0.75–0.92) and 20% (aHR 0.80, 0.71–0.90) decreased risk of attrition varied by time on ART for periods 2–4 compared with period-1. An absolute survival benefit was seen during 2.5 (period-2), 4.5 (period-3) and 6.5 (period-4) years following ART initiation. Thereafter, it remained similar for period-4 (compared with the pre-decentralisation period), while it tended to decrease for period-2 and period-3. aHR, adjusted hazard ratio; CI, confidence interval.

Figure 4: Standardised (average) survival curves (a) and survival difference (b–d) curves with 95% confidence interval by programmatic period.

SUPPORTING INFORMATION

Appendix S1. Setting.

Figure S1:1: Map of facilities of the Shiselweni region in southern Eswatini.

Appendix S2. Diagnostic after multiple imputation.

Figure S2:1: Observed, imputed and completed distributions for each imputation for the continuous variable CD4 cell count.

Figure S2:2: Observed, imputed and completed distributions for each imputation for the categorical variable access to telephone.

Figure S2:3: Graphical presentation of the convergence of the mean of imputed variables.

Appendix S3. Building the flexible parametric survival model.

Table S3:1: The Akaike's (AIC) and Schwarz's Bayesian (BIC) information criteria for different number and positions of internal knots and degree of freedoms for time- and non-time-dependent covariates of Model-1 and Model-2.

Figure S3:1: Sensitivity analyses for the hazard functions of all-cause attrition of Model-1 and Model-2.

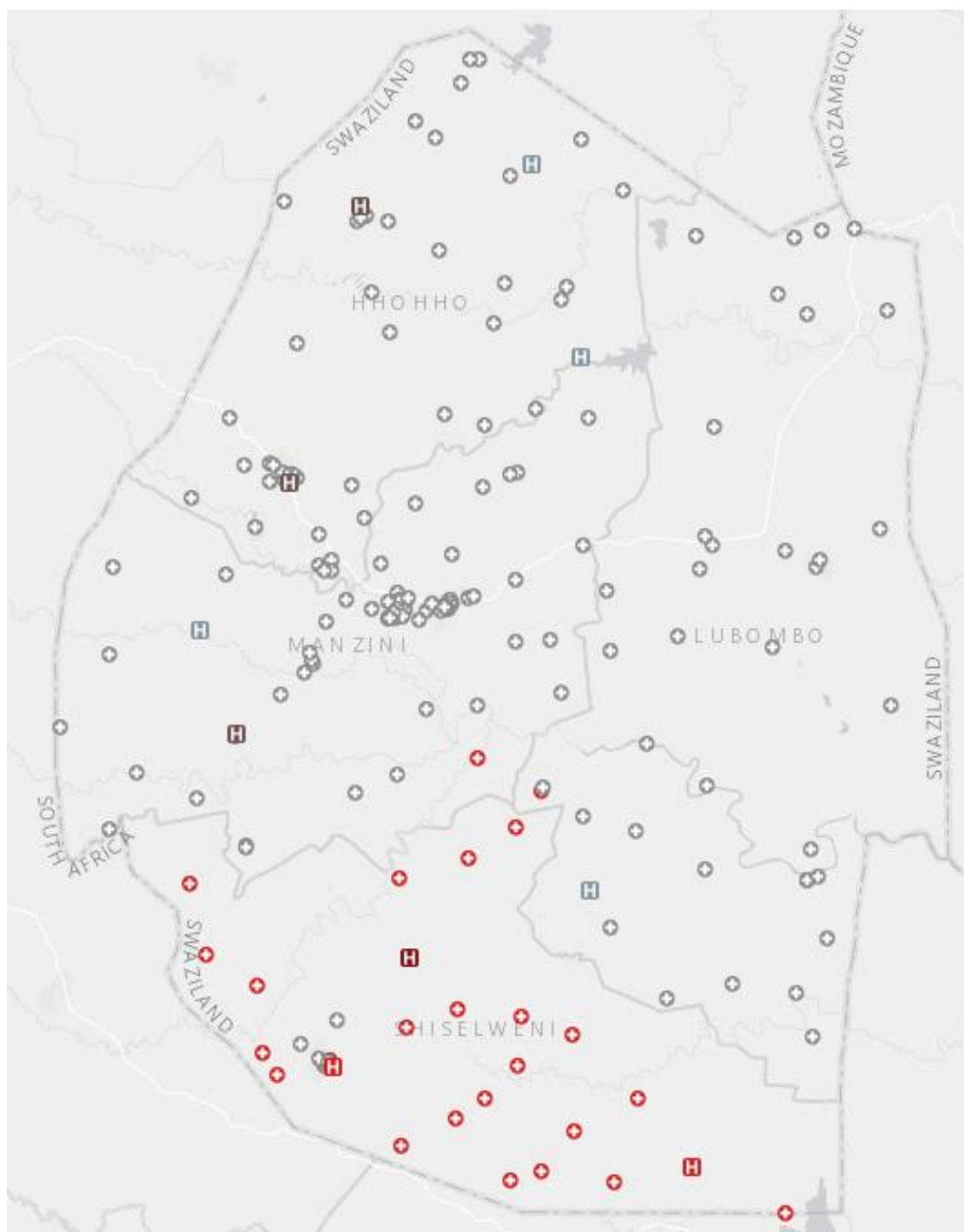
Appendix S4. Results.

Table S4:1: Baseline characteristics and predictors of all-cause attrition, Model-2.

Figure S4:1: Sensitivity analysis with adjusted hazard ratios for risk of attrition by calendar year compared with the year 2006.

Figure S4:2: Standardised (average) survival curves by sex-pregnancy status (a) and CD4 cell count category (b).

APPENDIX S1: SETTING



Red cross: primary care facilities. Red "H": health centre. Dark red "H": hospital.

Figure S1:1: Map of facilities of the Shiselweni region in southern Eswatini.

APPENDIX S2: DIAGNOSTIC AFTER MULTIPLE IMPUTATION

Several imputation diagnostics were performed. Firstly, we graphically displayed the observed, imputed and completed distributions for categorical and continuous variables for each imputation (Figure S2:1 and Figure S2:2 provide examples of the variables CD4 cell count and access to telephone). Secondly, we tested convergence of the imputation algorithm by plotting the mean of the imputed continuous and categorical variables against the cycle number (Figure S2:3). The algorithm never escaped and it converged.

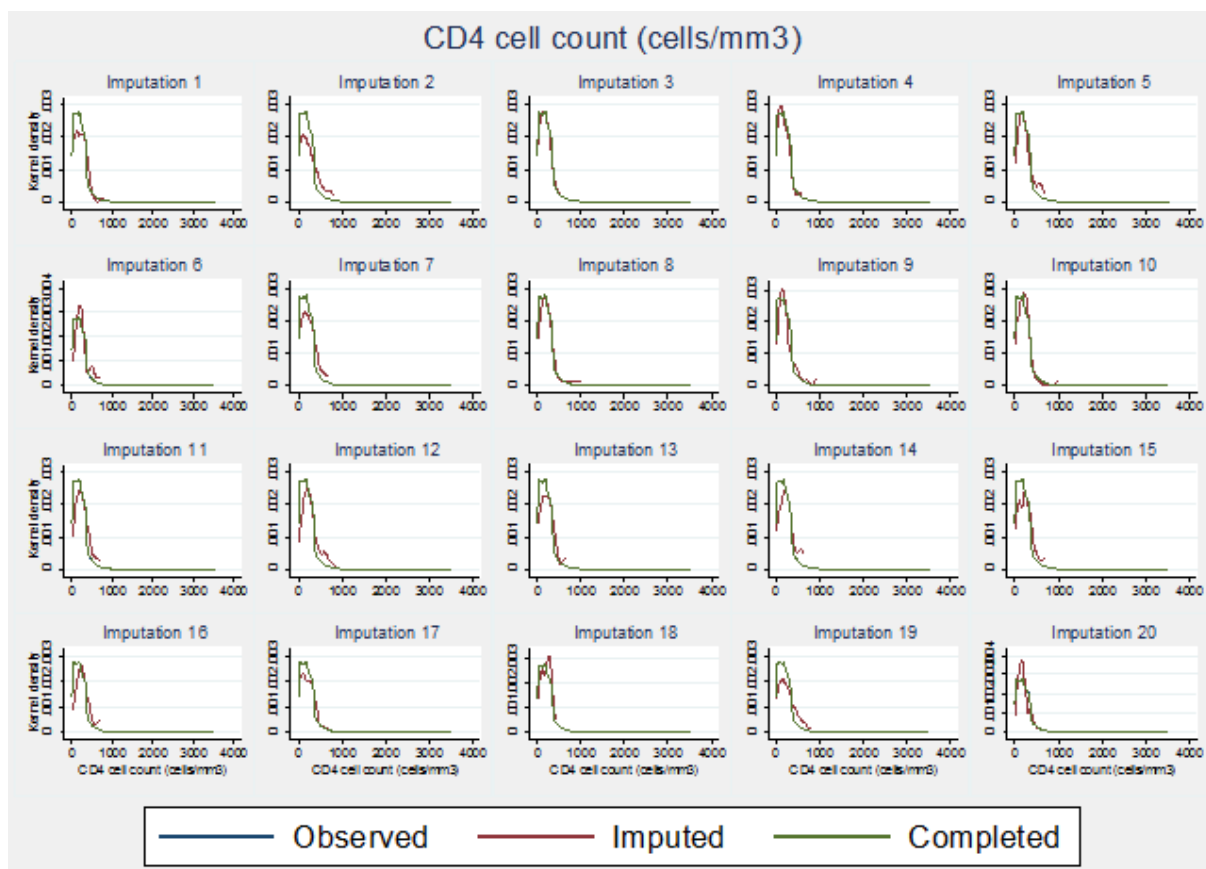


Figure S2:1: Observed, imputed and completed distributions for each imputation for the continuous variable CD4 cell count.

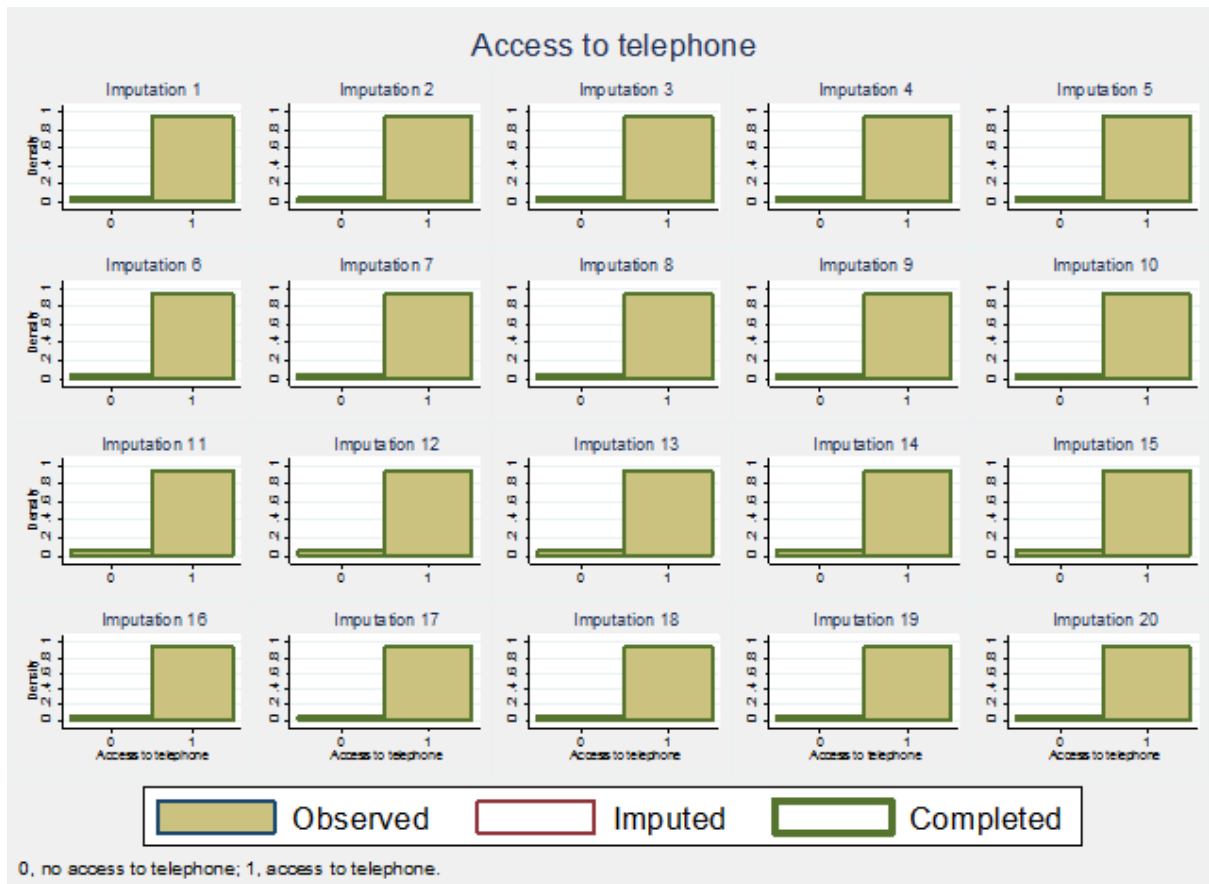


Figure S2:2: Observed, imputed and completed distributions for each imputation for the categorical variable access to telephone.

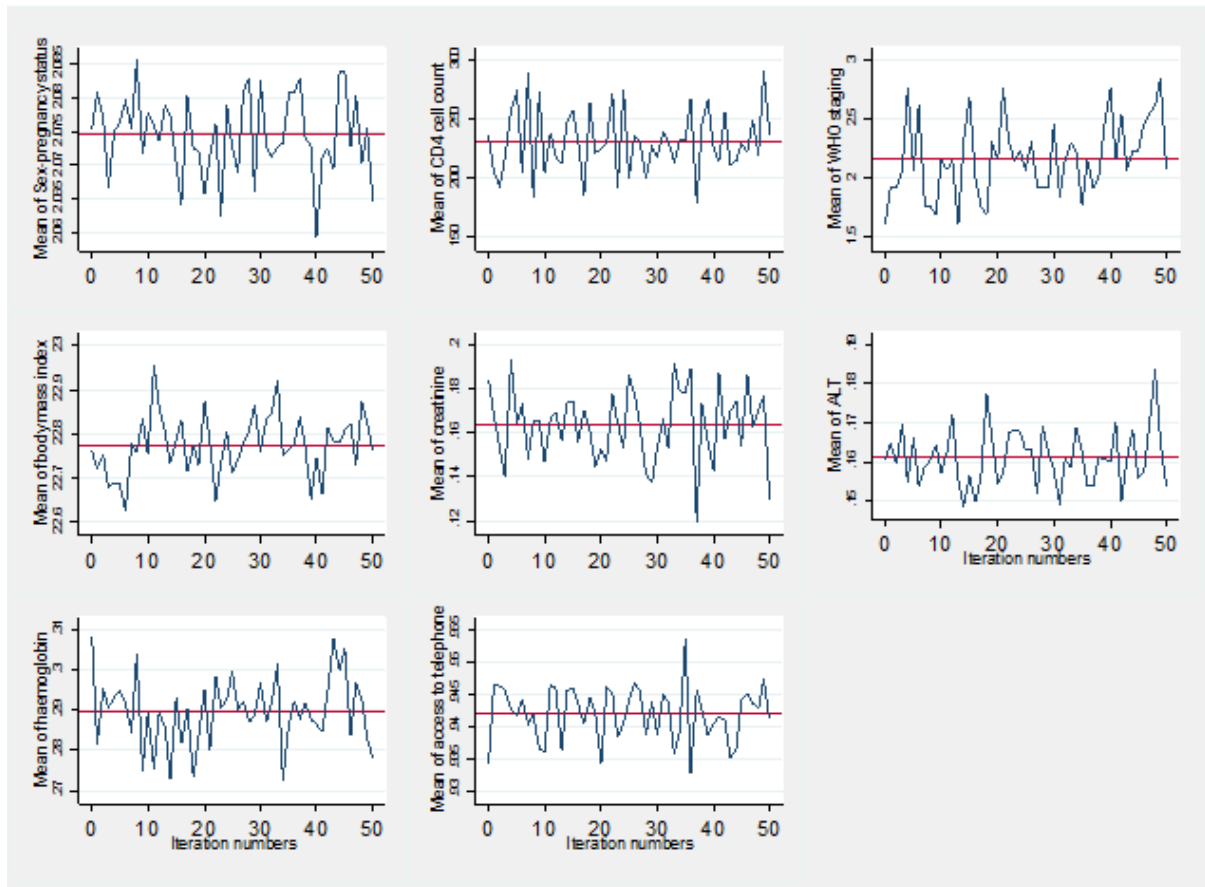


Figure S2:3: Graphical presentation of the convergence of the mean of imputed variables.

APPENDIX S3: BUILDING THE FLEXIBLE PARAMETRIC SURVIVAL MODEL.

Variables that interact with follow-up time

The Royston–Parmar model allows the inclusion of variables that interact non-linearly with follow-up time, to address violations of the proportional hazards assumption, where time is modelled via restricted cubic splines.^{196,211} Based on Schoenfeld residuals statistics, the covariate’s programmatic period, CD4 cell count, World Health Organization (WHO) staging and non-nucleoside reverse transcriptase inhibitors (NNRTI) showed some evidence of violation of the proportional hazards assumption. The inclusion of multiple time-varying effects on the log cumulative hazard scale, however, makes the interpretation of time-dependent hazard ratios difficult as the time-dependent hazard ratio of one variable may differ at different levels of the second time-varying effect.^{196,211} As the time-varying effect for most of these variables (CD4 cell count, WHO staging and NNRTI) was found to be very small and without clinical relevance, only the covariate “programmatic time period” was included as a factor that interacts non-linearly with time.¹⁹⁶ Practically, this was implemented with the “tvc” and “dftvc” options within the stpm2 command in Stata.¹⁹⁶

Determining the spline function of the flexible parametric survival model

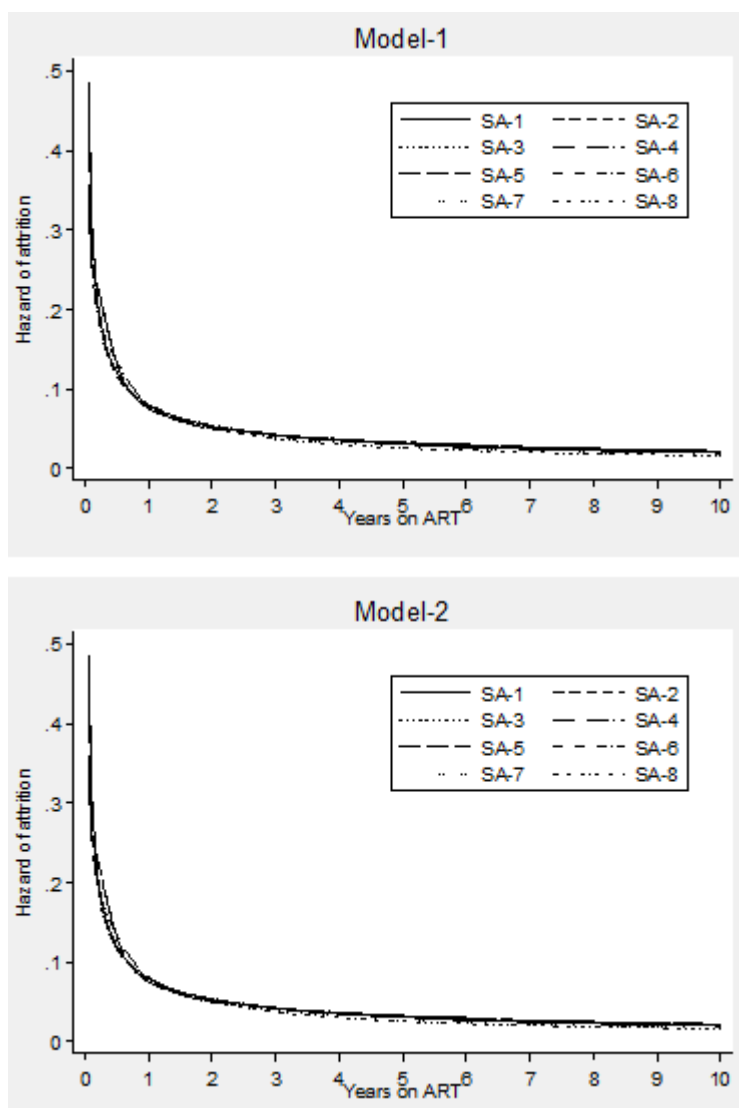
The spline function is determined by the position and number of internal knots in addition to the boundary knots. Procedures for how to select the best number and position of knots (degree of freedoms) can be found elsewhere.¹⁹⁶ We chose two approaches for the best model selection, which were performed in the first imputed dataset as the Akaike’s information criterion (AIC) and Bayesian information criterion (BIC) cannot be calculated after imputation of multiple imputed datasets.¹⁹⁵

Firstly, we used the AIC and BIC to compare optimum number of spline knots (Table S3:1). The knots’ positions are set on the uncensored log event times.¹⁹⁶ Secondly, we plotted and compared the hazard function of the standardised survival curve for each of the models (Figure S2:1). The curves appeared similar for both plots, supporting the conclusion that the number and position of knots are not critical for the final model. However, there was some evidence of overfitting of models with more than one internal knot for the time-dependent factor of programmatic period. Thus, model 6 was considered as the final model with 6 degrees of freedom (5 internal knots) for non-time-dependent covariates, and 2 degrees of freedoms (1 internal knot) for the time-dependent covariate. With 5 internal knots, the knot positions were at the 17, 33, 50, 67 and 83 centiles of uncensored log event-times¹⁹⁶.

Table S3:1: The Akaike’s (AIC) and Schwarz’s Bayesian (BIC) information criteria for different number and positions of internal knots and degree of freedoms for time- and non-time-dependent covariates of Model-1 and Model-2.

SA	DF	DF- TVC	Model-1		Model-2	
			AIC	BIC	AIC	BIC
1	2	1	58057.66	58395.84	58656.95	58925.51
2	3	1	58054.83	58402.96	58655.07	58933.57
3	4	1	58048.80	58406.88	58649.35	58937.80
4	5	1	57987.69	58355.71	58590.05	58888.45
5	6	1	57905.25	58283.22	58508.41	58816.75
6	6	2	57908.71	58316.52	58511.80	58849.98
7	6	3	57858.40	58296.05	58463.00	58831.02
8	6	4	57842.86	58310.35	58447.78	58845.65

SA, sensitivity analyses. DF, degree of freedom; DF-TVC, degree of freedom for time-dependent (time varying) covariate.



SA, sensitivity analysis.

Figure S3:1: Sensitivity analyses for the hazard functions of all-cause attrition of Model-1 and Model-2.

APPENDIX S4: RESULTS

Table S4:1: Baseline characteristics and predictors of all-cause attrition, Model-2.

		Univariate analysis		Multivariate analysis	
				Model-2	
(% missing values)	n (%)	HR	95% CI	aHR	95% CI
Programmatic period; (0)					
Period-1	3143 (12.7)	1		1	
Period-2	8841 (35.7)	0.75	(0.70-0.79)	0.95	(0.88-1.02)
Period-3	6408 (25.9)	0.57	(0.53-0.61)	0.84	(0.76-0.93)
Period-4	6380 (25.8)	0.48	(0.44 0.52)	0.81	(0.72-0.91)
Health cluster; (0)					
Nhlangano	10451 (42.2)	1		1	
Hlathikulu	8187 (33)	1.02	(0.97-1.08)	1.04	(0.99-1.10)
Matsanjeni	6134 (24.8)	1.05	(0.99-1.11)	1.02	(0.96-1.08)
Sex-pregnancy status; (10.7) ¹					
Non-pregnant women	11987 (54.2)	1		1	
Men	8493 (38.4)	1.22	(1.16-1.28)	1.18	(1.12-1.24)
Pregnant women	1643 (7.4)	0.96	(0.87-1.06)	1.12	(1.00-1.25)
Age, years; (0)					
16-24	3759 (15.2)	1.24	(1.17-1.33)	1.42	(1.33-1.52)
25-34	9867 (39.8)	1		1	
35-44	6044 (24.4)	0.87	(0.82-0.92)	0.82	(0.77-0.87)
45-54	3191 (12.9)	0.82	(0.76-0.88)	0.79	(0.73-0.86)
≥55	1911 (7.7)	1.07	(0.98-1.17)	1.09	(1.00-1.19)
CD4 cell count, cells/mm ³ ; (0.1)					
0-100	6817 (27.6)	1.99	(1.87-2.11)	1.57	(1.48-1.68)
101-200	6843 (27.7)	1.37	(1.29-1.46)	1.23	(1.15-1.31)
201-350	8145 (32.9)	1		1	
351-500	1862 (7.5)	0.92	(0.82-1.03)	0.92	(0.82-1.03)
≥501	1069 (4.3)	0.89	(0.77-1.04)	0.91	(0.78-1.06)
WHO staging; (0.1)					
I+II	14777 (59.7)	1		1	
III	8389 (33.9)	1.55	(1.47-1.63)	1.34	(1.27-1.41)
IV	1593 (6.4)	3.03	(2.82-3.27)	2.31	(2.14-2.50)
NRTI; (0)					
AZT	9556 (38.6)	1		1	
ABC	170 (0.7)	1.46	(1.13-1.88)	1.34	(1.04-1.72)
D4T	3167 (12.8)	1.86	(1.75-1.97)	1.57	(1.47-1.68)
TDF	11879 (48)	0.82	(0.78-0.87)	1.00	(0.92-1.08)
NNRTI; (0)					
EFV	14632 (59.1)	1		1	
NVP	10140 (40.9)	1.18	(1.13-1.24)	1.06	(1.00-1.13)

n, number; *HR*, hazard ratio; *aHR*, adjusted hazard ratio; *CI*, confidence interval; *WHO*, World Health Organization; *NRTI*, nucleoside reverse transcriptase inhibitor; *AZT*, zidovudine; *ABC*, abacavir; *D4T*, stavudine; *TDF*, tenofovir disoproxil fumarate; *NNRTI*, non-nucleoside reverse transcriptase inhibitors; *EFV*, efavirenz; *NVP*, nevirapine.

¹While 0.2% of patients had missing sex status, pregnancy status was missing in 16% of women.

Multiple imputations were used in all univariate and multivariate regression analyses for the variables sex-pregnancy status, CD4 cell count, WHO staging. Model-2 was restricted to covariates with <20% imputed values. The model had 6 degrees of freedom (5 internal knots) for non-time-dependent covariates and 2 degrees of freedoms (1 internal knot) for the time-dependent covariate programmatic period.

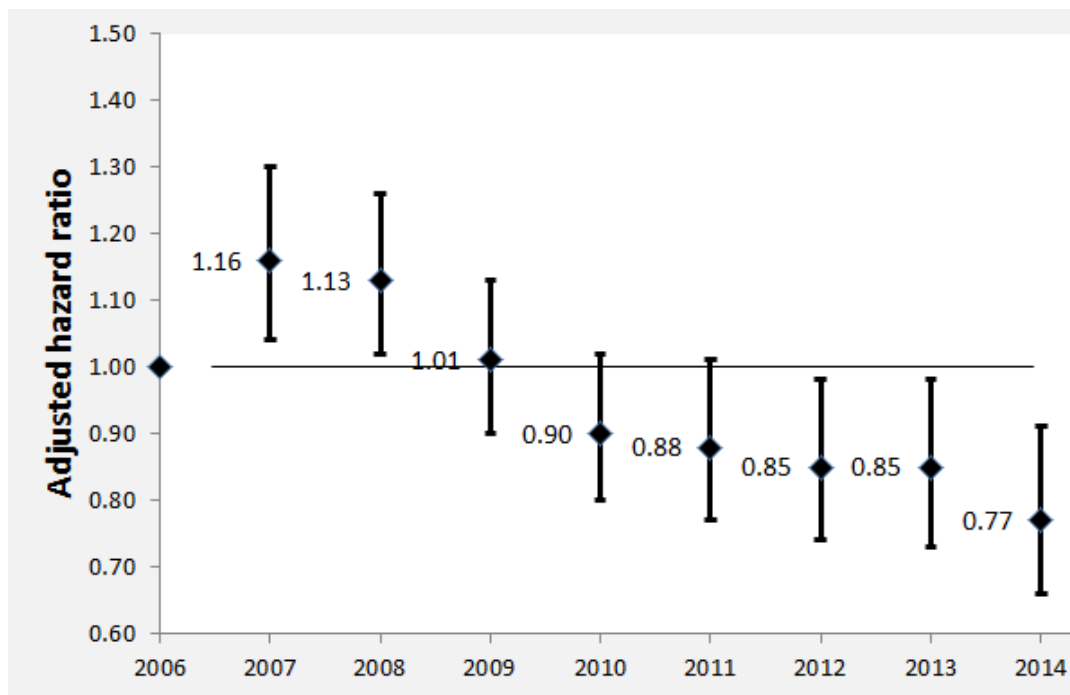
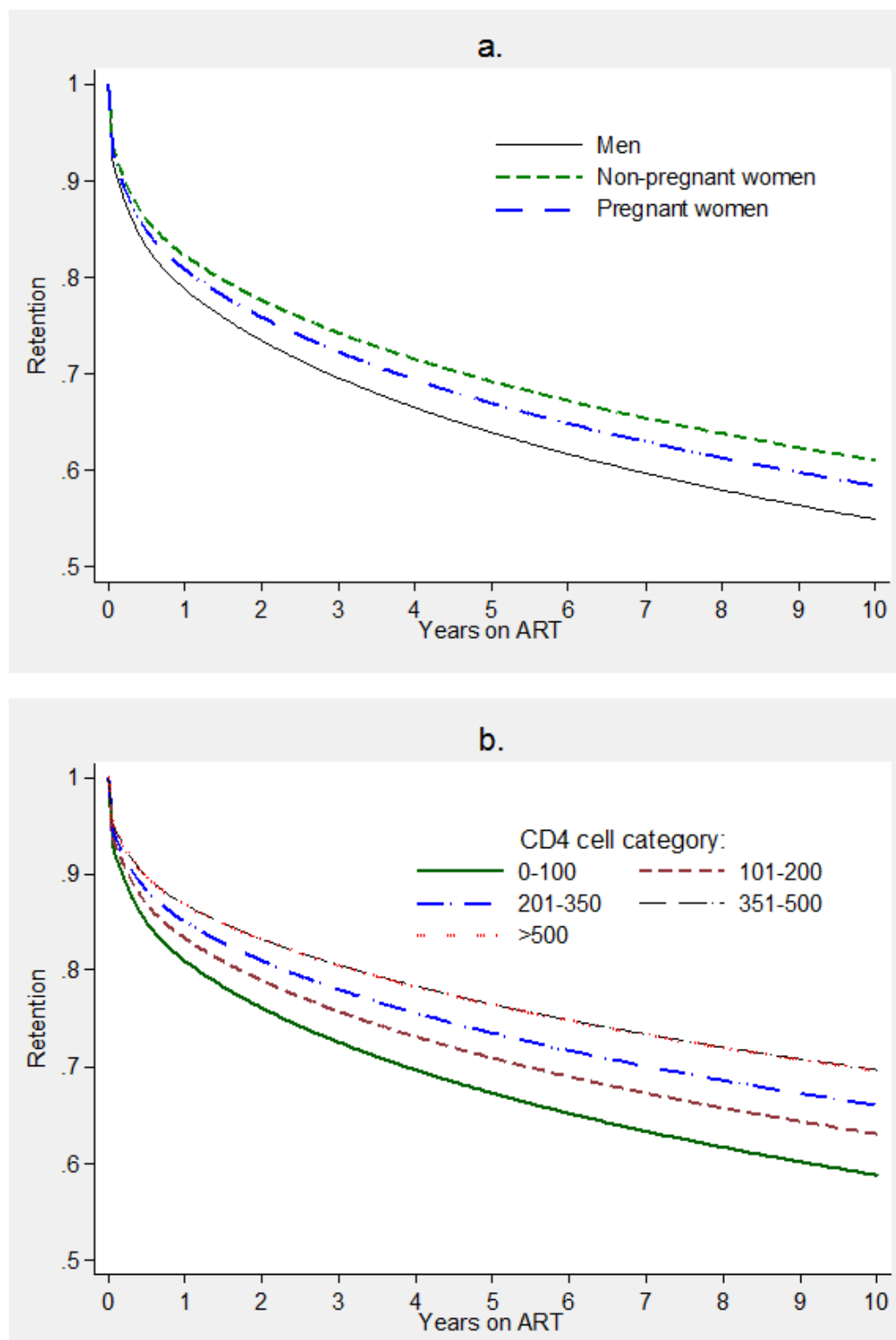


Figure S4:1: Sensitivity analysis with adjusted hazard ratios for risk of attrition by calendar year compared with the year 2006.



ART, antiretroviral therapy.

Figure S4:2: Standardised (average) survival curves by sex-pregnancy status (a) and CD4 cell count category (b).

RESULTS FOR OBJECTIVE 2

Feasibility of antiretroviral therapy initiation under the treat-all policy under routine conditions: a prospective cohort study from Eswatini

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Paper overview

This study uses data from a cohort of patients diagnosed as HIV-positive in two health zones in the Shiselweni region in Eswatini. ART initiation at the time of HIV diagnosis and irrespective of immunological criteria (Treat-All) was offered in one health zone and standard of care according to the CD4 350 and 500 cells/mm³ treatment eligibility thresholds in the neighbouring health zone. This study examines 1) the time from facility-based HIV diagnosis to ART initiation in both health zones, 2) predictors of ART initiation, and 3) linkage outcomes from the time of community-based HIV-positive diagnosis to facility-based HIV care enrolment and ART initiation.

Significance of the paper

Countries in SSA started adopting Treat-All soon after the WHO issued recommendations for the phase-in of Treat-All. However, little was known about the feasibility of universal and prompt ART initiation in the public sector at that time. There were concerns about not achieving the second 90 of the 90-90-90 UNAIDS cascade targets if ART uptake is suboptimal specifically among patients with high CD4 cell counts. There was also a lack of understanding of how many more patients initiate ART under Treat-All compared with previous WHO recommendations, which, if workload increases significantly, could impact quality of care. Also acknowledging the need for immediate ART

initiation for the sickest patients accessing HIV care in fragile health systems, the 2013 and 2016 WHO guidelines emphasized that patients presenting with advanced HIV diseases should be prioritized when treatment eligibility criteria are expanded to CD4 cell count thresholds >350 cells/mm³. Little was known about whether ART uptake would be sufficient and whether patients with advanced HIV disease would be de-prioritized under Treat-All.

In addition, community-based HIV testing has been scaled up in recent years and has become an additional important entry point into HIV care in RLS. However, patients diagnosed at community level may differ from those diagnosed at facility level and face additional barriers for facility-based HIV care enrolment. Often less than half of patients link in a timely manner to HIV care, so suboptimal linkage is a major bottleneck to achieving the second 90 of the 90-90-90 UNAIDS cascade targets. It is crucial to understand the overall impact of Treat-All on the HIV care cascade for patients diagnosed with HIV at the community level. Treat-All may reduce performance along the cascade if patients link less and delay ART initiation. However, later stages along the cascade may be improved despite low linkage to care when compared with SOC.

Candidate`s contributions

The candidate in collaboration with KJ and RT designed the study. The candidate established the cohort and was involved in data acquisition. The candidate in collaboration with MS, AB, and IC established the analysis plan. The candidate acquired and processed all data, performed all analyses, wrote the first draft of the manuscript, integrated comments from co-authors, and submitted the manuscript for peer review.

ABSTRACT

Introduction

The World Health Organization recommends the Treat-All policy of immediate antiretroviral therapy (ART) initiation, but questions persist about its feasibility in resource-poor settings. We assessed the feasibility of Treat-All compared with standard of care (SOC) under routine conditions.

Methods

This prospective cohort study from southern Eswatini followed adults from HIV care enrolment to ART initiation. Between October 2014 and March 2016, Treat-All was offered in one health zone and SOC according to the CD4 350 and 500 cells/mm³ treatment eligibility thresholds in the neighbouring health zone, each of which comprised one secondary and eight primary care facilities. We used Kaplan–Meier estimates, multivariate flexible parametric survival models and standardized survival curves to compare ART initiation between the two interventions.

Results

Of the 1726 (57.3%) patients enrolled under Treat-All and 1287 (42.7%) under SOC, cumulative three-month ART initiation was higher under Treat-All (91%) than SOC (74%; $p < 0.001$) with a median time to ART of 1 (IQR 0 to 14) and 10 (IQR 2 to 117) days respectively. Under Treat-All, ART initiation was higher in pregnant women (vs. non-pregnant women: adjusted hazard ratio (aHR) 1.96, 95% confidence interval (CI) 1.70 to 2.26), those with secondary education (vs. no formal education: aHR 1.48, 95% CI 1.12 to 1.95), and patients with an HIV-positive diagnosis before care enrolment (aHR 1.22, 95% CI 1.10 to 1.36). ART initiation was lower in patients attending secondary care facilities (aHR 0.64, 95% CI 0.58 to 0.72) and for CD4 351 to 500 when compared with CD4 201 to 350 cells/mm³ (aHR 0.84, 95% CI 0.72 to 1.00). ART initiation varied over time for TB cases, with lower hazard during the first two weeks after HIV care enrolment and higher hazards thereafter. Of patients with advanced HIV disease ($n = 1085$; 36.0%), crude 3-month ART initiation was similar in both interventions (91% to 92%) although Treat-All initiated patients more quickly during the first month after HIV care enrolment.

Conclusions

ART initiation was high under Treat-All and without evidence of de-prioritization of patients with advanced HIV disease. Additional studies are needed to understand the long-term impact of Treat-All on patient outcomes.

INTRODUCTION

The therapeutic effect of antiretroviral therapy (ART) and its preventive benefits of reducing HIV transmission are well established.^{18–20} On the basis of this evidence, the World Health Organization (WHO) established the Treat-All policy which recommends ART initiation irrespective of CD4 cell criteria and emphasizes the prioritization of patients with advanced HIV disease.^{16,209} Following these recommendations, an additional 4.1 million people living with HIV (PLHIV) required ART in Eastern and Southern Africa in 2016.³⁷

After HIV diagnosis, enrolment into HIV care, completion of pretreatment steps and ART initiation are important milestones in the care cascade.^{5,212} Before Treat-All, it was appreciated that loss to care of eligible patients between HIV diagnosis and ART initiation was high,⁷³ and predictors of pretreatment losses include patient-related, health system and clinical factors.^{74,85} Community-based linkage to care interventions, health service interventions, patient support packages and strengthened monitoring systems increased linkages and ART initiation.^{64,73–75,86,210} While these approaches will remain important, the operational simplification of ART initiation under Treat-All is expected to reduce pretreatment losses through shortening the pretreatment period.^{16,24,212}

These interventions are implemented in different combinations and with varying quality across HIV programmes,^{76,77} and operationalization of Treat-All may be challenging in weak health systems.²¹³ Despite adoption of the Treat-All policy by many countries,²¹⁴ questions remain about the feasibility of ongoing ART expansion and provision of quality care in resource-poor health settings,^{57,213} with many operational challenges anticipated.^{30,34}

In 2012, the Ministry of Health of Eswatini (former Swaziland) and collaborating non-governmental organizations agreed on a national framework for the phase-in of Treat-All, with one such project supported by Médecins Sans Frontières (MSF). We assessed the programmatic feasibility of prompt ART initiation in all HIV-infected patients in this public-sector HIV programme, implemented in a single health zone while the neighbouring health zone continued with CD4 count-based initiation criteria.

METHODS

This prospective implementation study of Treat-All was conducted in the predominantly rural Shiselweni region in southern Eswatini. HIV-positive adults aged ≥ 16 years, who were enrolled into facility-based HIV care from 20 October 2014 to 31 March 2016, were offered ART initiation irrespective of immunological criteria in the Treat-All health zone. The neighbouring health zone applied national standard of care (SOC), recommending ART initiation at the CD4 cell count

threshold criteria of ≤ 350 cells/mm³ until 31 October 2015 and ≤ 500 cells/mm³ thereafter. Pregnant and lactating women were eligible for prompt ART initiation in both health zones.

Setting

The Shiselweni region had a population of approximately 210,000 people,¹⁷⁷ 31% of adults aged 18 to 49 years were infected with HIV^{173,181} and approximately 18,000 patients received ART in 2013 (*programme data*). The region comprised three neighbouring comparable health zones, each of which had one centralized secondary care outpatient department and eight HIV-TB service integrated nurse-led primary health clinics.

Although HIV testing was mainly conducted at facilities, mobile and home-based community HIV testing was also performed routinely by MSF testing teams.⁷⁹ Linkage to care interventions included short messaging appointment reminders, up to three tracing phone calls and the possibility of a home visit for patients missing their appointment. Enrolment in HIV care occurred at facility level, with the opening of a patient file and registration in the pre-ART register. Pretreatment preparation included patient education and counselling, physical examination and screening for TB infection. Point-of-care CD4, haemoglobin and biochemistry testing was available at most primary care facilities. Under Treat-All, informed written consent for prompt ART was obtained on the day of treatment initiation for patients ineligible for ART according to national standard of care (CD4 > 350 cells/mm³ in the absence of WHO III/IV conditions). Treatment eligible patients declining ART or patients ineligible for treatment according to national eligibility criteria were not required to sign a consent form and were retained in analysis. These patients received routine pre-ART care and were offered ART at each clinic visit or when treatment eligibility criteria were met under SOC based on six-monthly CD4 count testing. Same-day ART initiation was recommended for pregnant women in both health zones. Lacking standardized operating procedures for same-day ART initiation for non-pregnant adults, it was undertaken at the clinician's discretion based on patient's readiness. Telephonic follow-up was recommended for patients who missed scheduled clinic appointments.

MSF supported both health zones similarly with respect to community-based HIV testing, linkage and facility-based HIV-TB care historically and during the study period.^{79,140,215} Because of the new concept of prompt ART initiation, sensitization events for communities and health workers started three months before the rollout of Treat-All. Information and contextualized messages about Treat-All were integrated into community-based HIV testing activities and morning clinic talks in outpatient services. Temporarily, MSF provided first line ART drug stocks for patients with CD4 > 350 cells/mm³. No other additional resources were added under Treat-All (e.g. human resources, logistics support).

Definitions and outcomes

Definitions of baseline covariates are provided in Table 1. Advanced HIV disease was defined as a patient presenting with CD4 cell counts <200 cells/mm³ and/or WHO clinical stage III/IV. The main outcome was time from facility-based HIV care enrolment to ART initiation. Patients were right censored at the earliest of the date of the last clinic visit before transfer out of the health zone, death or database closure (31 March 2017).

Several analyses were performed (Figure 1). First, we compared associations with ART initiation in each of the Treat-All and SOC zones. The analyses were done separately due to the different guidelines in operation in each, which would have made interpretation of associations and interactions with the model of care more difficult to interpret. Second, we evaluated the effect of programmatic approach (Treat-all vs. SOC) on the outcome in both zones combined for patients presenting with advanced HIV disease. Third, in supplementary analysis-1, a multivariate comparison of ART initiation between Treat-All and SOC was performed for the entire cohort of patients to estimate the overall association of programmatic approach with the outcome. In supplementary analysis-2, HIV-positive patients diagnosed through community-based HIV testing under Treat-All and SOC were followed for six months to compare facility-based care enrolment and ART initiation.

All data were collected prospectively by trained data clerks from individual patient records and facility-based pre-ART and ART registers. Data were entered into EpiData software and analyses were performed with Stata version 14.1 (College Station, Texas).

Statistics

Baseline characteristics were described using frequency statistics, proportions and medians, and compared with Wilcoxon rank-sum and Pearson's chi-square tests. Kaplan–Meier estimates were used to estimate and plot the crude cumulative hazard of ART initiation.

We used multiple imputation by chained equations to address missing values and performed imputation diagnostics thereafter (Table S1, Figure S1). The proportional-hazards assumption was assessed globally and for individual variables based on Schoenfeld residuals tests in the first imputed dataset. Using 20 imputed datasets, *a priori* determined variables identified through directed acyclic graphs were included in flexible parametric survival models (Royston–Parmar models).¹⁹⁶ The number and locations of internal knots for the restricted cubic spline function were based on clinical, the Akaike's and Schwarz's Bayesian information, and graphical criteria. Standardized failure curves and contrasts were plotted after fitting Royston–Parmar models.^{216,217}

Ethics

The findings reported here are part of a larger study assessing the feasibility of Treat-All under routine conditions. The study and analyses were approved by the Research Ethics Committees of

MSF, the Scientific and Ethics Committee of Eswatini and the University of Cape Town, South Africa.

RESULTS

Baseline characteristics

Seventeen patients were excluded from analysis as study eligibility criteria were unclear (Figure 1). Of the remaining 3013 patients enrolled into facility-based HIV care, 1726 (57.3%) were in Treat-All and 1287 (42.7%) in SOC (Table 1). Excluding missing values of covariates (Table S1), 1869 (62.0%) patients presented at primary care facilities, the median age and CD4 cell count were 30 (interquartile range (IQR) 25 to 37) years and 297.5 (IQR 153 to 467) cells/mm³, 921 (31.0%) were men, 1637 (54.9%) were diagnosed on the day of HIV care enrolment, 436 (14.7%) had WHO III/IV clinical staging, and 152 (5.1%) had TB.

Patients under Treat-All were more likely to be pregnant women (24.2% vs. 18.4%, $p < 0.001$), diagnosed HIV positive before care enrolment (48.3% vs. 40.9%, $p < 0.001$), without access to a phone (10.1% vs. 7.7%, $p = 0.027$), unmarried (67.9% vs. 56.2%, $p < 0.001$), and had higher education (e.g. secondary education 69.0% vs. 57.8%, $p < 0.001$).

Crude ART initiation

Crude outcome data and survival-time data of the main analyses are presented in Figure 1.

Most ART initiations occurred within two months after HIV care enrolment (Figure 2). Median time to ART was 1 (IQR 0 to 14) day under Treat-All and 10 (IQR 2 to 117) days under SOC. Crude cumulative three-month ART initiation was 91% and 74% respectively ($p < 0.001$). Three-month ART initiation was highest among pregnant women and similar between Treat-All (97%) and SOC (95%) ($p = 0.220$) (Figure 2, a1-a2). Crude ART initiations were similar across CD4 cell strata under Treat-All ($p = 0.075$), but lower for CD4 351 to 500 and CD4 ≥ 501 cells/mm³ under SOC ($p < 0.001$) (Figure 2b1-b2).

ART initiation on the day of HIV care enrolment (same-day ART) was similarly high for pregnant women under Treat-All (71%) and SOC (72%) ($p = 0.220$). It was higher for non-pregnant adults under Treat-All (42%) than SOC (14%) ($p < 0.001$) (Figure 2a1-a2).

Predictors of ART initiation

Treat-all

Among patients enrolling under Treat-All, the hazard of ART initiation was higher for time period-2 (adjusted hazard ratio (aHR) 1.22, 95% confidence interval (CI) 1.08 to 1.38), for pregnant women

(aHR 1.96, 95% CI 1.70 to 2.26) versus non-pregnant women, for patients with secondary education (aHR 1.48, 95% CI 1.12 to 1.95) versus no formal education, and for HIV-positive diagnoses before HIV care enrolment (aHR 1.22, 95% CI 1.10 to 1.36) (Table 2). ART initiation was lower for the secondary care facility (aHR 0.64, 95% CI 0.58 to 0.72) and tended to be lower for patients with CD4 351 to 500 cells/mm³ (aHR 0.84, 95% CI 0.72 to 1.00) versus CD4 201 to 350 cells/mm³. Although TB co-infection had a similar overall hazard of ART initiation when compared with no TB (Table 2), the effect varied over time with lower hazard during the first two weeks after HIV care enrolment and higher hazards thereafter (Figure 3).

Modelling with the facility as covariate (instead of healthcare level), the hazard of ART initiation in primary care clinics compared with the secondary facility was higher for five out of eight primary care clinics, with aHRs ranging from 1.63 to 3.22 (Figure 4).

Standard of care

Among patients enrolling under SOC, the time period-2 and timing of HIV diagnosis showed a similar increase in hazard of ART initiation to that under Treat-All, but this was more pronounced for pregnant women (aHR 3.50, 95% CI 2.87 to 4.25) (Table 2). In contrast to Treat-All, ART initiation was higher for the secondary care facility (aHR 1.39, 95% CI 1.21 to 1.59), while no association was detected for education level. Compared with CD4 cell count 201 to 350 cells/mm³ and in contrast to Treat-All, the hazard of ART initiation was higher for low CD4 ≤ 100 (aHR 1.42, 95% CI 1.14 to 1.77), and it was lower for CD4 350 to 500 (aHR 0.67, 95% CI 0.56 to 0.81) and CD4 ≥ 500 (aHR 0.48, 95% CI 0.40 to 0.59) cells/mm³. The time-varying effect of TB was less pronounced than under Treat-All (*data not shown*).

Taking the facility covariate into account, the hazard of ART initiation was lower for four out of eight primary care clinics compared with the secondary care facility, with aHRs ranging from 0.52 to 0.74 (Figure 4).

Advanced HIV disease

Of 1085/3013 (36.0%) complete observations for patients with advanced HIV disease, 631 (58.2%) presented under Treat-All and 454 (41.8%) under SOC (Table 1). The overall median CD4 cell count was 112.5 (IQR 56 to 170) cells/mm³, and 436 (40.5) had WHO III/IV clinical stage. Comparing the two interventions, differences in the distribution of baseline characteristics were seen for facility, gender and pregnancy status, marital status, WHO clinical staging and phone availability (Table 1).

Crude same-day ART initiation was higher under Treat-All (42%) than SOC (17%) while three-month ART initiation was similar (Treat-All: 92%; SOC: 91%). In multivariate analysis after multiple imputations (n = 1089) (Table 3), Treat-All had a higher hazard of ART initiation (aHR 1.75, 95% CI

1.47 to 2.08). The effect varied over time, with Treat-All initiating patients more quickly during the first month (Figure 5a1-2). As in previous analyses, ART initiation was higher for time period-2, pregnant women and HIV-positive diagnosis before HIV care enrolment while it was lower for secondary health care level. The overall hazard of ART was lower in TB cases (aHR 0.65, 95% CI 0.49 to 0.86) and the effect varied over time (*data not shown*). No associations were seen for CD4 cell count.

Supplementary analyses

Supplementary analysis-1

Considering all patients irrespective of CD4 cell and WHO clinical staging criteria, the overall hazard of ART initiation was higher under Treat-All than SOC (aHR 1.99, 95% CI 1.81 to 2.19) (Table S2). The hazard varied over time, being highest during the first three months after HIV care enrolment (Figure 5b1-2), steadily decreasing thereafter but remaining above SOC during the entire observation period. Associations of other covariates were similar as in previous analyses (Table S2).

Supplementary analysis-2

Linkage outcomes from the time of community-based HIV-positive diagnosis are presented in Figure 6. Patients known to be transferred between Treat-All and SOC were removed from the analysis ($n = 10$). Of the remaining 191 patients, 91 (47.6%) were diagnosed under Treat-All and 100 (52.4%) under SOC. The median days to HIV care enrolment were similar (Treat-All: 7, IQR 2.5 to 22; SOC: 6, IQR 3 to 21; $p = 0.651$), but the median number of days to ART initiation was lower under Treat-All (15, IQR 4 to 24) than SOC (29, IQR 18 to 67) ($p = 0.001$). Six-month HIV care enrolment was 48% under Treat-All and 57% under SOC ($p = 0.286$), and six-month ART initiation was 45% and 36% respectively ($p = 0.078$). The crude hazard of HIV care enrolment from the time of HIV-positive diagnosis was similar (HR 0.81, 95% CI 0.54 to 1.20) between Treat-All and SOC, while Treat-All tended to have a higher hazard of ART initiation (HR 1.50, 95% CI 0.96 to 2.34).

DISCUSSION

We assessed the feasibility of ART initiation under the Treat-All policy in a routine public sector setting in rural Eswatini. Overall, facility-based ART initiation was quicker and higher under Treat-All than SOC and it did not result in de-prioritisation of patients with advanced HIV disease. Despite suboptimal linkage, patients who were diagnosed with HIV in the community were also more likely to initiate ART under Treat-all.

Findings in context

We found higher ART initiation under Treat-All than SOC, overall and for patients presenting with $CD4 \geq 351$ cells/mm³. SOC restricted ART eligibility for non-pregnant adults to $CD4 \leq 350$ and ≤ 500 cells/mm³ and/or WHO III/IV clinical staging.¹⁴ The often-seen steep gradient in ART initiation by CD4 count, which was still present in SOC, was not seen under Treat-All, suggesting compliance with the new policy. When the analysis, however, was restricted to Treat-All, patients with $CD4 \geq 351$ cells/mm³ tended to have a lower hazard of ART initiation. While a Treat-All trial in South Africa reported similar three-month ART uptake across CD4 strata,⁹¹ increased patient tracking was needed for patients with higher CD4 cell counts in East Africa.⁶⁸ In this setting, there was reportedly less focus on patient tracking during the pretreatment period, possibly explaining this finding.

Men had the same hazard of ART initiation as non-pregnant women in both interventions, similar to findings from an universal ART setting in South Africa.⁹¹ Notably, pregnant women were more likely to initiate ART overall and same-day. Same-day ART initiation was emphasized in pregnant women, while ART could be deferred for non-pregnant adults depending on the patient's readiness.²¹⁸

Patients diagnosed on the same day as enrolment for HIV care were less likely to initiate treatment in both interventions, possibly related to internalized stigma when receiving an HIV diagnosis.^{80,219}

Data suggested that patients under Treat-All who have had secondary education may be more likely to initiate ART. This may be a chance finding given the lack of association in all other analyses and in other Treat-All trials.^{68,91}

The time period-2 was associated with higher ART initiation in both interventions. Associations of temporal trends with patient outcomes have been reported previously from sub-Saharan Africa.^{102–104,107–110,186} First, in our setting, expanding treatment eligibility increased the pool of treatment eligible patients, likely resulting in increasing ART initiations under SOC. In addition, patients ineligible for treatment also initiated ART under SOC, although this phenomenon was not further analysed. Second, national-level policy change on treatment eligibility allowed for increased mobilization, which may have influenced patients' and health workers' acceptance of early treatment under Treat-All.

While under Treat-All, two-thirds of primary care clinics had a higher hazard of ART initiation (vs. secondary care facility), it was lower in one-third of primary care clinics under SOC. Clinic, health worker and patient level factors have been reported to influence pre-treatment losses,^{86,219,220} possibly affecting facilities under Treat-All and SOC differently.

Advanced HIV disease

We showed that immunocompromised patients initiated ART more quickly under Treat-All, possibly due to higher rates of same-day ART initiation under Treat-All than SOC. Same-day ART initiation has been shown to decrease pretreatment losses,²¹⁰ and rapid ART initiation is recommended by WHO.²⁰⁹

ART initiation in TB cases was delayed during the first two weeks after HIV care enrolment, although overall three-month treatment initiation was higher. First, TB needs to be ruled out before ART initiation and TB diagnosis was likely delayed. Sputum samples of presumptive TB cases were sent for Xpert MTB/RIF testing to the centralized health centres, likely increasing treatment turnaround time. Second, ART initiation in TB patients is recommended after TB treatment is started due to toxicity concerns,¹⁶ preferably within two weeks of starting TB treatment in Eswatini.²¹⁸

Linkages to HIV care

Suboptimal linkage is a main weakness in the HIV care cascade.^{73,78,79} Of PLHIV diagnosed at community level under Treat-All, only 48% enrolled into care and 45% initiated ART. Comparable six-month outcomes were reported from the TasP (47.6% linkage)²²¹ and PopART (42% initiating ART)²²² trials, in contrast to the SEARCH trial with 86% of patients having had at least one clinic visit within 12 months.⁶⁸ Despite higher ART initiation under Treat-All, it remained suboptimal, potentially compromising the population-level effect of reduction in HIV incidence.²²³ However, a peer-delivered linkage case management intervention in Eswatini has shown potential for high linkage and ART initiation (96%) under routine conditions in Treat-All.²²⁴

In this context, community-based HIV testing played less of a role in diagnosing PLHIV (approximately 20% of all HIV-positive diagnoses).²²⁵ Thus, suboptimal linkages are likely to have a smaller impact on the pretreatment cascade.

Limitations and strengths

First, the treatment initiation rate was likely overestimated. As reliable patient-level data on linkage to HIV care were lacking, the analysis time started from the time of facility-based HIV care enrolment. In Eswatini, an estimated 83% to 92% of HIV-positive diagnosed patients link from facility-based HIV testing to care.¹⁹⁹ Second, we did not assess ART outcomes, which was beyond the scope of this analysis. Estimating long-term treatment outcomes is crucial to understand the feasibility of Treat-All in the wider context. Third, the intervention areas were chosen purposely to ensure comparability in clinical practice. Both zones were located in the same geographic area, received the same support and had the same number of primary and secondary care facilities. Nevertheless, the analysis indicated differences in baseline characteristics of patients and inter-facility variations in ART initiation, highlighting possible variations in patients' behaviour and clinical practice. Despite adjusting for it in

analyses, there may be still differences with respect to unobserved variables. Lastly, using data from a routine setting may compromise data quality and completeness.

External validity and generalizability is a strength of this study, as this setting has characteristics of many resource-limited settings in rural sub-Saharan Africa. Treat-All was introduced into a routine government HIV programme. The policy change towards Treat-All built on previous operational gains. For example, more than half of all patients enrolled at decentralized primary care clinics with a high degree of HIV-TB service integration. Only trainings and information were provided in addition to routine activities and the Ministry of Health started providing the additional drugs during the study period. Although this study does not address all aspects of feasibility (e.g. lack of economic evaluation), we believe it contributes to the ongoing discussion on programmatic feasibility of treatment expansion in resource-poor settings.

CONCLUSIONS

Although direct comparisons of Treat-All and SOC was limited due to possible unmeasured differences between health zones, Treat-All appeared feasible in this public-sector HIV programme. Overall, ART initiation was high and without de-prioritization of patients with advanced HIV disease. Despite suboptimal linkage to care, more PLHIV initiated ART under Treat-All than SOC.

Table 1: Baseline characteristics of patients enrolled into facility-based HIV care for the entire treatment cohort and for patients with advanced HIV disease.

(% missing values)	Entire cohort					Advanced HIV disease ^a				
	Treat-All (n, %)		SOC (n, %)		<i>p</i> value	Treat-All (n, %)		SOC (n, %)		<i>p</i> value
Health zone; (0)	1726		1287			631		454		
Implementation period; (0)										
Period-1	1320	(76.5)	945	(73.4)	0.055	473	(75.0)	340	(74.9)	0.979
Period-2	406	(23.5)	342	(26.6)		158	(25.0)	114	(25.1)	
Facility; (0)										
PHC	1068	(61.9)	801	(62.2)	0.840	393	(62.3)	243	(53.5)	0.004
SHC ^b	658	(38.1)	486	(37.8)		238	(37.7)	211	(46.5)	
Gender and pregnancy status; (1.4%)										
Non-pregnant women	807	(47.4)	598	(47.2)	<0.001	288	(46.0)	193	(42.7)	0.006
Men	484	(28.4)	437	(34.5)		266	(42.5)	228	(50.4)	
Pregnant women	413	(24.2)	233	(18.4)		72	(11.5)	31	(6.9)	
Age at HIV care enrolment, years; (0)										
16 to 24	411	(23.8)	328	(25.5)	0.560	75	(11.9)	42	(9.3)	0.379
25 to 49	1191	(69.0)	866	(67.3)		492	(78.0)	363	(80.0)	
≥50	124	(7.2)	93	(7.2)		64	(10.1)	49	(10.8)	
Marital status; (2.7)										
Married	533	(32.1)	557	(43.8)	<0.001	233	(38.3)	222	(49.2)	<0.001
Not married	1129	(67.9)	714	(56.2)		376	(61.7)	229	(50.8)	
Education; (16.6)										
None	68	(4.9)	97	(8.6)	<0.001	33	(6.4)	42	(10.6)	0.098
Primary	336	(24.2)	359	(31.9)		140	(27.3)	114	(28.9)	
Secondary	958	(69.0)	650	(57.8)		331	(64.5)	234	(59.2)	
Tertiary	26	(1.9)	18	(1.6)		9	(1.8)	5	(1.3)	
HIV diagnosis; (1.0)										
Same day as care enrolment	881	(51.7)	756	(59.1)	<0.001	299	(47.8)	242	(53.7)	0.060
Before care enrolment	823	(48.3)	524	(40.9)		326	(52.2)	209	(46.3)	
CD4 count, cells/mm ³ ; (5.3)										
0 to 100	284	(17.6)	190	(15.3)	0.342	284	(46.1)	190	(41.9)	0.279
101 to 200	272	(16.9)	204	(16.5)		270	(43.8)	204	(44.9)	
201 to 350	386	(23.9)	330	(26.7)		33	(5.4)	36	(7.9)	
351 to 500	340	(21.1)	253	(20.4)		14	(2.3)	15	(3.3)	
≥501	332	(20.6)	261	(21.1)		15	(2.4)	9	(2.0)	
WHO clinical stage; (1.8)										
I/II	1448	(86.0)	1075	(84.2)	0.194	392	(62.5)	249	(55.3)	0.029
III	213	(12.7)	175	(13.7)		213	(34.0)	175	(38.9)	
IV	22	(1.3)	26	(2.0)		22	(3.5)	26	(5.8)	
BMI, kg/m ² ; (8.5)										
≤18.4	97	(6.3)	76	(6.1)	0.313	70	(12.3)	57	(13.2)	0.672
18.5 to <25	793	(51.7)	675	(54.6)		345	(60.5)	250	(57.7)	
≥25	644	(42.0)	486	(39.3)		155	(27.2)	126	(29.1)	

Laboratory result; (16.7)										
Normal	1061	(72.5)	775	(74.0)	0.426	339	(63.5)	257	(64.7)	0.694
Abnormal	402	(27.5)	273	(26.0)		195	(36.5)	140	(35.3)	
Tuberculosis; (1.6)										
No	1612	(94.9)	1202	(94.9)	0.991	553	(88.2)	396	(88.2)	0.999
Yes	87	(5.1)	65	(5.1)		74	(11.8)	53	(11.8)	
Phone availability; (4.8)										
No	167	(10.1)	94	(7.7)	0.027	69	(11.3)	27	(6.2)	0.005
Yes	1482	(89.9)	1124	(92.3)		541	(88.7)	410	(93.8)	

Main definitions of baseline variables: A TB case was defined as a patient receiving TB treatment at the time of HIV care enrolment. Calendar time was divided into time period-1 (20 October 2014 to 31 October 2015) and time period-2 (01 November 2015 to 31 March 2016), corresponding to the WHO 2010 and WHO 2013 guidelines implementation periods under SOC. An abnormal baseline laboratory test result was defined as any of haemoglobin <10 g/dL, creatinine >121 µmol/L or aspartate aminotransferase (AST) >42 units/L. Same-day HIV diagnosis was defined as an HIV-positive diagnosis on the day of facility-based HIV care enrolment. Patients with recorded phone numbers were considered to have access to a phone. BMI, body mass index; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care.

^aAdvanced HIV disease was defined as patients presenting with CD4 <200 cells/mm³ and/or WHO III/IV staging;

^bsecondary healthcare level comprised ART outpatient departments in one health centre (with inpatient capacity) in Treat-All and one hospital in SOC.

Table 2: Predictors of ART initiation for all patients enrolled into HIV care under Treat-All and standard of care (SOC).

	Treat-All (n = 1726)				SOC (n = 1287)			
	HR	95% CI	aHR	95% CI	HR	95% CI	aHR	95% CI
Implementation period								
Period-1	1		1		1		1	
Period-2	1.25	(1.11 to 1.40)	1.22	(1.08 to 1.38)	1.28	(1.12 to 1.47)	1.28	(1.11 to 1.47)
Facility								
PHC	1		1		1		1	
SHC ^a	0.66	(0.60 to 0.73)	0.64	(0.58 to 0.72)	1.63	(1.44 to 1.84)	1.39	(1.21 to 1.59)
Gender and pregnancy status								
Non-pregnant women	1		1		1		1	
Men	0.92	(0.82 to 1.04)	0.93	(0.81 to 1.07)	1.13	(0.99 to 1.29)	1.04	(0.90 to 1.22)
Pregnant women	1.88	(1.65 to 2.13)	1.96	(1.70 to 2.26)	3.38	(2.86 to 3.99)	3.50	(2.87 to 4.25)
Age at HIV care enrolment, years								
16 to 24	1		1		1		1	
25 to 49	0.90	(0.80 to 1.01)	1.03	(0.91 to 1.18)	1.04	(0.90 to 1.19)	0.97	(0.83 to 1.14)
≥50	0.78	(0.63 to 0.96)	1.05	(0.82 to 1.34)	0.93	(0.72 to 1.20)	0.99	(0.75 to 1.30)
Marital status								
Married	1		1		1		1	
Not married	1.01	(0.91 to 1.13)	1.01	(0.89 to 1.14)	1.05	(0.92 to 1.18)	1.07	(0.93 to 1.23)
Education								
None	1		1		1		1	
Primary	1.35	(1.01 to 1.79)	1.32	(0.98 to 1.77)	0.99	(0.78 to 1.26)	0.93	(0.72 to 1.20)
Secondary	1.57	(1.20 to 2.04)	1.48	(1.12 to 1.95)	1.05	(0.84 to 1.32)	0.85	(0.67 to 1.09)
Tertiary	1.56	(0.97 to 2.50)	1.50	(0.89 to 2.54)	1.46	(0.84 to 2.52)	1.01	(0.58 to 1.74)
HIV diagnosis								
Same day as care enrolment	1		1		1		1	
Before care enrolment	1.05	(0.95 to 1.16)	1.22	(1.10 to 1.36)	1.24	(1.09 to 1.39)	1.28	(1.12 to 1.45)
CD4 count, cells/mm ³								
0 to 100	0.78	(0.66 to 0.93)	0.90	(0.74 to 1.10)	1.41	(1.17 to 1.71)	1.42	(1.14 to 1.77)
101 to 200	0.87	(0.74 to 1.03)	0.85	(0.72 to 1.01)	1.17	(0.97 to 1.41)	1.12	(0.92 to 1.36)
201 to 350	1		1		1		1	
351 to 500	0.86	(0.74 to 1.02)	0.84	(0.72 to 1.00)	0.66	(0.55 to 0.80)	0.67	(0.56 to 0.81)
≥501	0.91	(0.76 to 1.08)	0.86	(0.71 to 1.03)	0.49	(0.41 to 0.59)	0.48	(0.40 to 0.59)
WHO clinical stage								
I/II	1		1		1		1	
III	0.76	(0.65 to 0.90)	0.87	(0.72 to 1.07)	1.41	(1.19 to 1.68)	1.04	(0.84 to 1.28)
IV	0.61	(0.39 to 0.97)	0.77	(0.48 to 1.24)	1.48	(0.99 to 2.22)	0.99	(0.63 to 1.55)
BMI, kg/m ²								
≤18.4	1		1		1		1	
18.5 to <25	1.06	(0.84 to 1.34)	0.88	(0.68 to 1.14)	0.73	(0.57 to 0.94)	0.85	(0.64 to 1.13)
≥25	1.25	(0.98 to 1.61)	0.86	(0.64 to 1.15)	0.81	(0.62 to 1.05)	0.89	(0.67 to 1.20)
Laboratory result								

Normal	1		1		1		1	
Abnormal	1.03	(0.86 to 1.24)	1.13	(0.93 to 1.37)	1.28	(1.06 to 1.55)	1.13	(0.91 to 1.40)
Tuberculosis								
No	1		1		1		1	
Yes	0.79	(0.63 to 0.98)	0.86	(0.56 to 1.34)	1.25	(0.97 to 1.61)	1.06	(0.74 to 1.51)
Phone availability								
No	1		1		1		1	
Yes	1.23	(1.03 to 1.47)	1.07	(0.89 to 1.29)	1.39	(1.07 to 1.61)	1.20	(0.92 to 1.58)

The flexible parametric models (Royston–Parmar models) for Treat-All and SOC had each five internal knots in addition to one internal knot for the time-varying covariate tuberculosis. All variables tested in univariate analysis were included in multivariate analysis. aHR, adjusted hazard ratio; BMI, body mass index; HR, hazard ratio; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care.

^aSecondary healthcare level comprised ART outpatient departments in one health centre with inpatient capacity in Treat-All and one hospital in SOC.

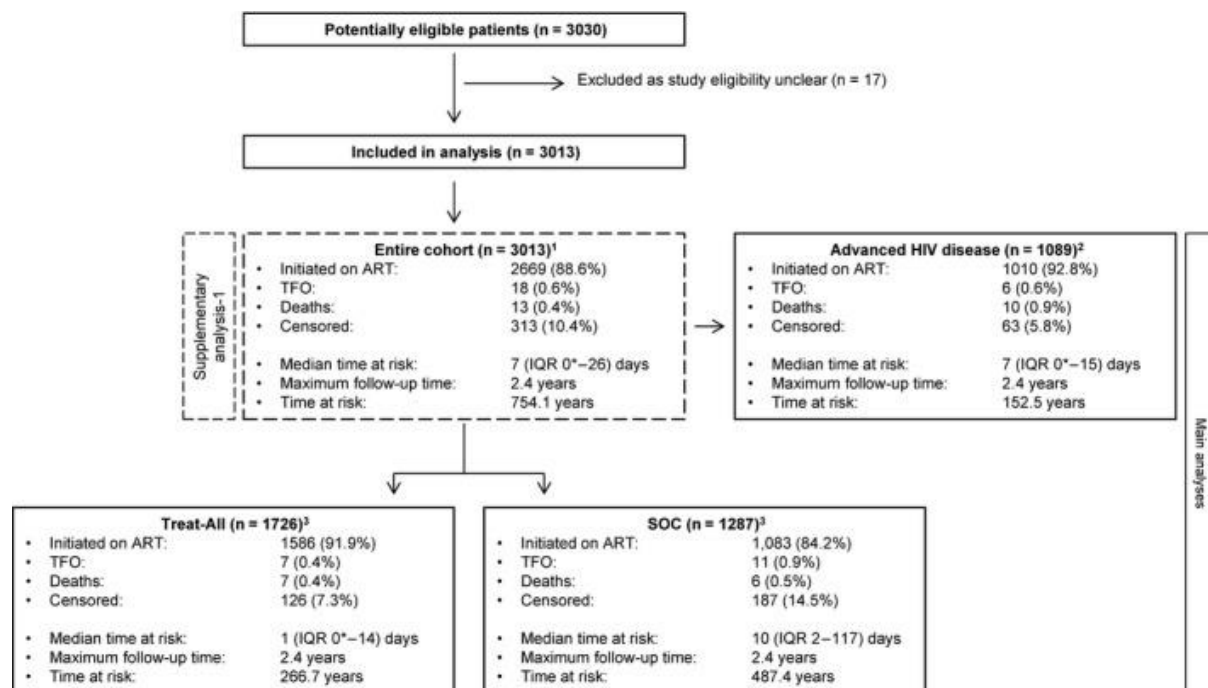
Table 3: Predictors of ART initiation for patients with advanced HIV disease.

	Univariate (n = 1089)		Multivariate (n = 1089)	
	HR	95% CI	aHR	95% CI
Health zone				
SOC	1		1	
Treat-all	1.23	(1.08 to 1.39)	1.75	(1.47 to 2.08)
Implementation period				
Period-1	1		1	
Period-2	1.28	(1.11 to 1.48)	1.35	(1.17 to 1.57)
Facility				
PHC	1		1	
SHC ^a	0.86	(0.76 to 0.98)	0.86	(0.75 to 0.98)
Gender and pregnancy status				
Non-pregnant women	1		1	
Men	1.02	(0.89 to 1.16)	1.04	(0.90 to 1.21)
Pregnant women	2.02	(1.62 to 2.50)	1.90	(1.50 to 2.41)
Age at HIV care enrolment, years				
16 to 24	1		1	
25 to 49	0.96	(0.78 to 1.17)	1.02	(0.82 to 1.27)
≥50	0.89	(0.68 to 1.17)	1.01	(0.75 to 1.36)
Marital status				
Married	1		1	
Not married	0.98	(0.86 to 1.12)	0.97	(0.85 to 1.12)
Education				
None	1		1	
Primary	1.00	(0.74 to 1.36)	0.90	(0.66 to 1.22)
Secondary	1.11	(0.84 to 1.46)	0.96	(0.71 to 1.28)
Tertiary	1.27	(0.68 to 2.39)	0.93	(0.50 to 1.74)
Time of HIV diagnosis, days				
Same day	1		1	
Before	1.19	(1.05 to 1.35)	1.31	(1.15 to 1.49)
CD4 count, cells/mm³				
0 to 100	1.28	(0.97 to 1.69)	1.23	(0.89 to 1.70)
101 to 200	1.27	(0.96 to 1.68)	1.11	(0.79 to 1.57)
201 to 350	1		1	
351 to 500	0.94	(0.58 to 1.51)	0.91	(0.55 to 1.50)
≥501	0.95	(0.56 to 1.61)	0.88	(0.49 to 1.57)
WHO clinical stage				
I/II	1		1	
III	0.85	(0.75 to 0.97)	0.96	(0.81 to 1.14)
IV	0.76	(0.56 to 1.04)	0.83	(0.60 to 1.16)
BMI, kg/m²				
≤18.4	1		1	
18.5 to <25	1.03	(0.84 to 1.26)	1.01	(0.81 to 1.25)

≥25	1.14	(0.90 to 1.43)	1.03	(0.79 to 1.34)
Laboratory result				
Normal	1		1	
Abnormal	1.01	(0.86 to 1.20)	1.05	(0.88 to 1.25)
Tuberculosis				
No	1		1	
Yes	0.90	(0.74 to 1.08)	0.65	(0.49 to 0.86)
Phone availability				
No	1		1	
Yes	1.24	(0.98 to 1.56)	1.18	(0.91 to 1.53)

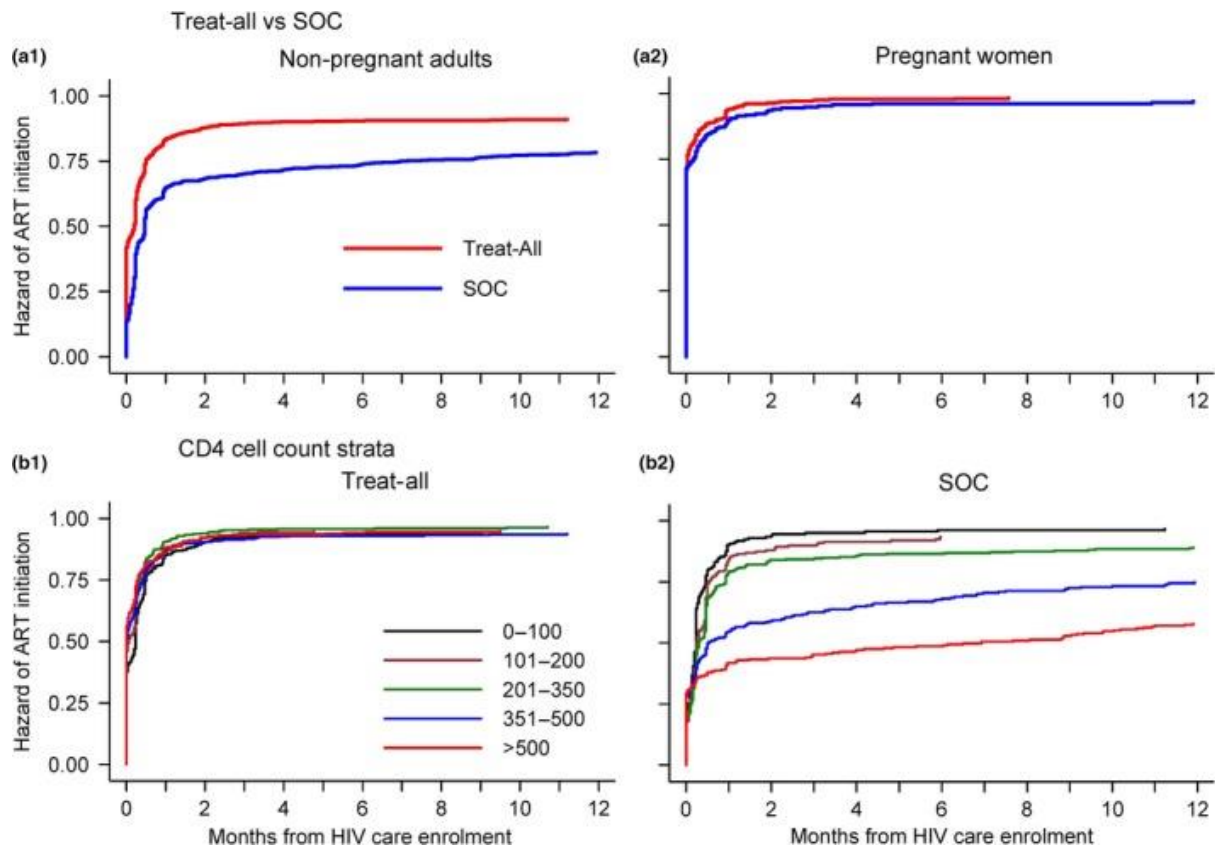
The flexible parametric model (Royston–Parmar models) had four internal knots, and three internal knots for the time-varying covariates health zone and TB. All variables tested in univariate analysis were also included in multivariate analysis. aHR, adjusted hazard ratio; BMI, body mass index; HR, hazard ratio; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care.

^aSecondary healthcare level comprised ART outpatient departments in one health centre with inpatient capacity in Treat-All and one hospital in SOC.



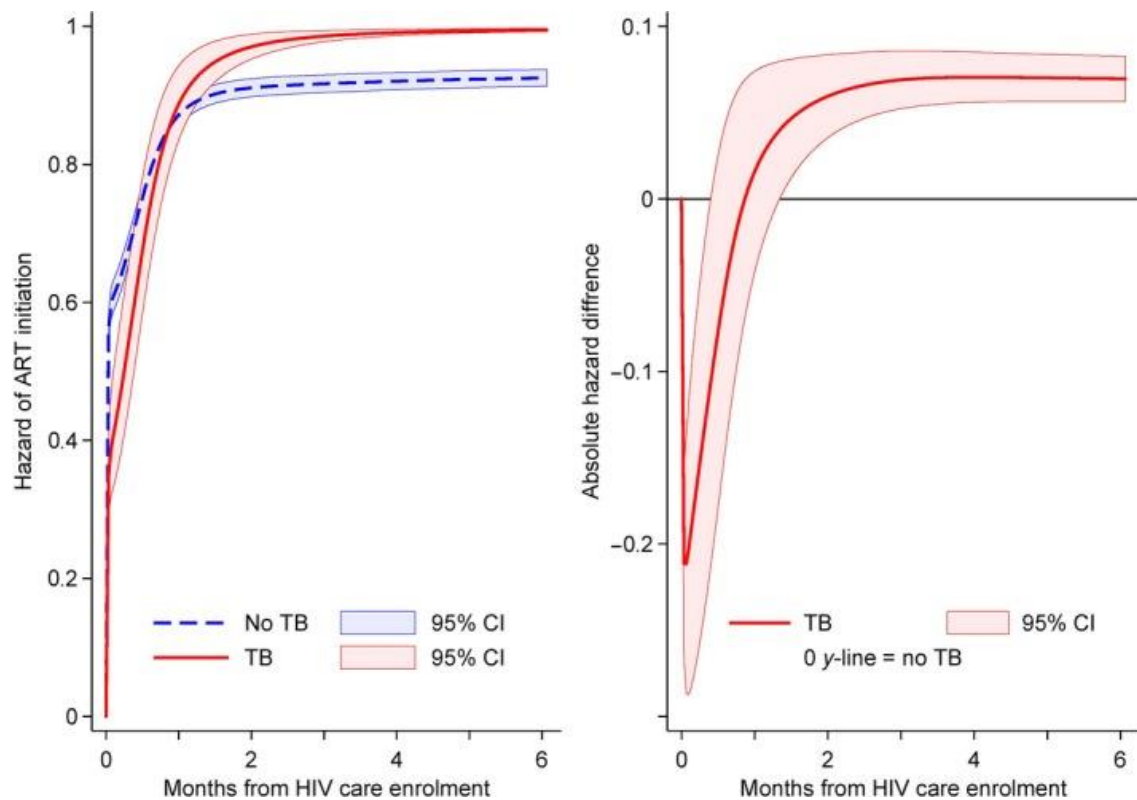
Total follow-up time was 2.4 years in all analyses. *Zero days indicates same-day ART initiation. ¹The analysis directly compared Treat-All with SOC irrespective of CD4 and WHO clinical staging criteria. ²The analysis directly compared Treat-All with SOC restricted to patients with advanced HIV disease (CD<200 cells/mm³ and/or WHO III/IV). ³The Treat-All and SOC interventions were analysed separately. ART, antiretroviral therapy; n, number; IQR, interquartile range; SOC, standard of care; TFO, transferred out.

Figure 1: Study flow chart of main analyses.



SOC, standard of care. As most ART initiations occur within 12 months, the plotted curves are graphed only for this period.

Figure 2: Crude Kaplan–Meier estimates of time to ART initiation since HIV care enrolment for (a) Treat-All and SOC by pregnancy status and (b) CD4 cell strata by intervention.



After fitting the covariate-adjusted flexible parametric survival model for Treat-All (see Table 2), we estimated the standardized failure curves for patients with and without TB under Treat-All and the contrasts using the post estimation Stata command `stpm2_standsurv`.^{216,217} CI, confidence interval.

Figure 3: Cumulative hazard of ART initiation and absolute difference in hazard of ART initiation by TB status under Treat-All.

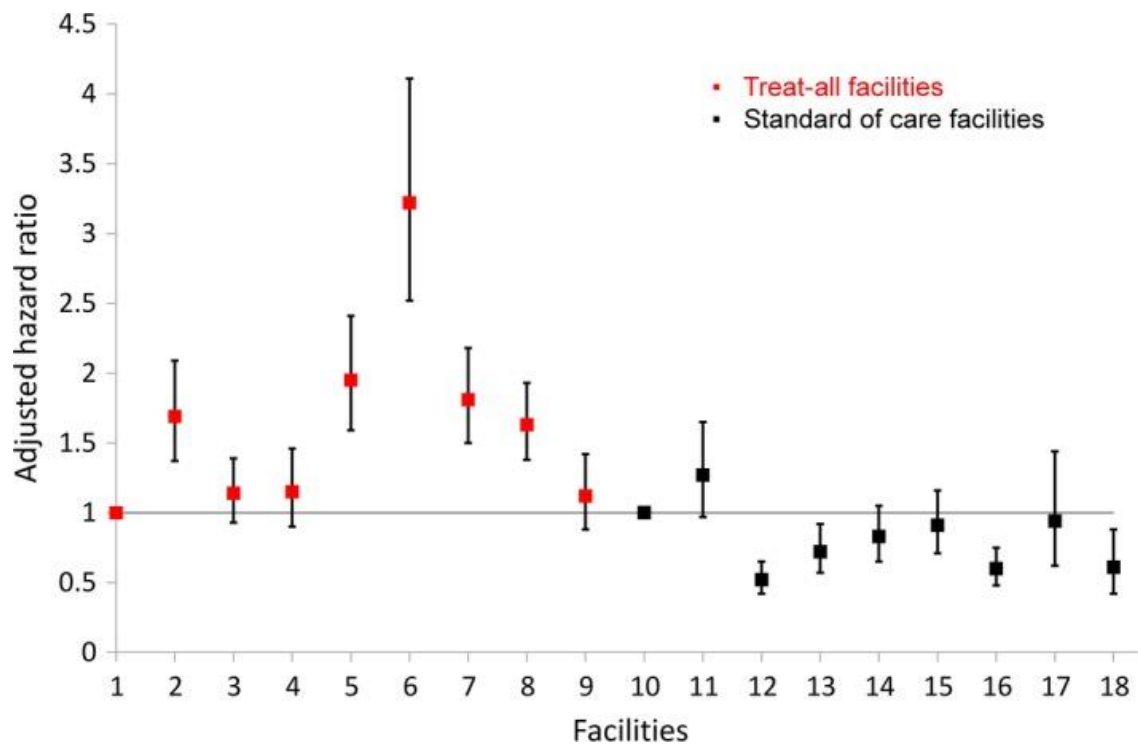
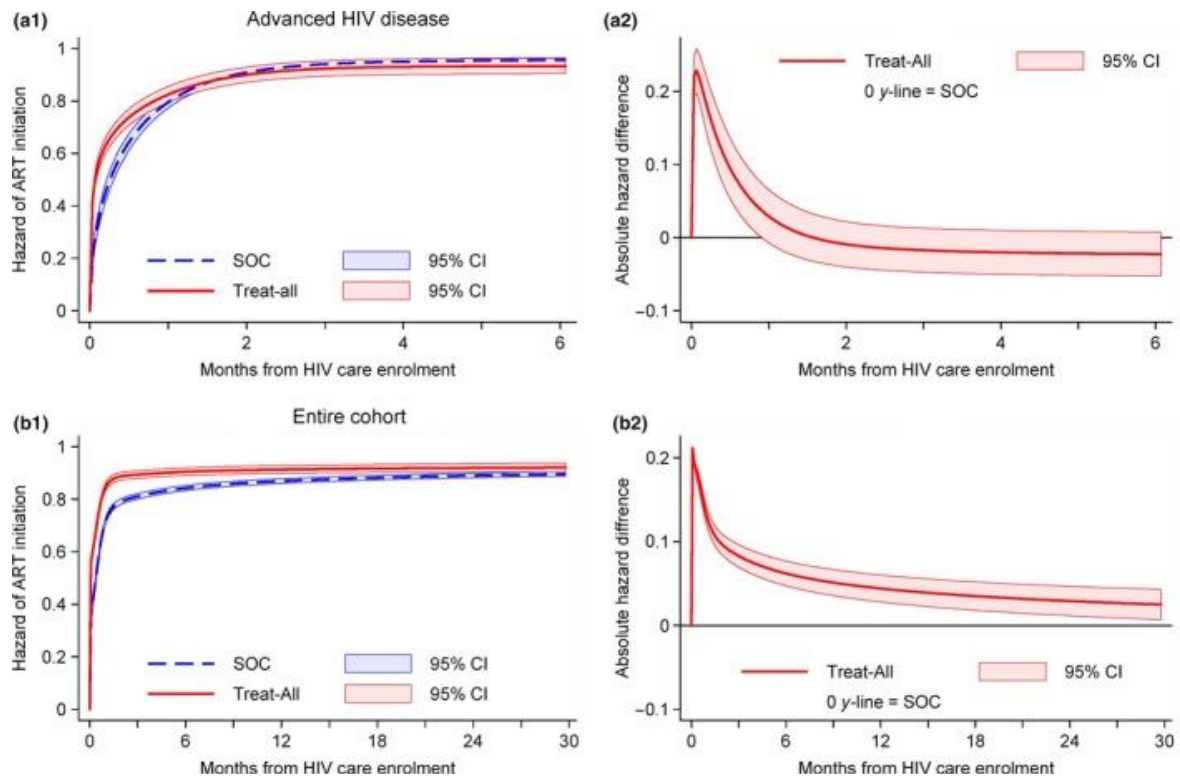
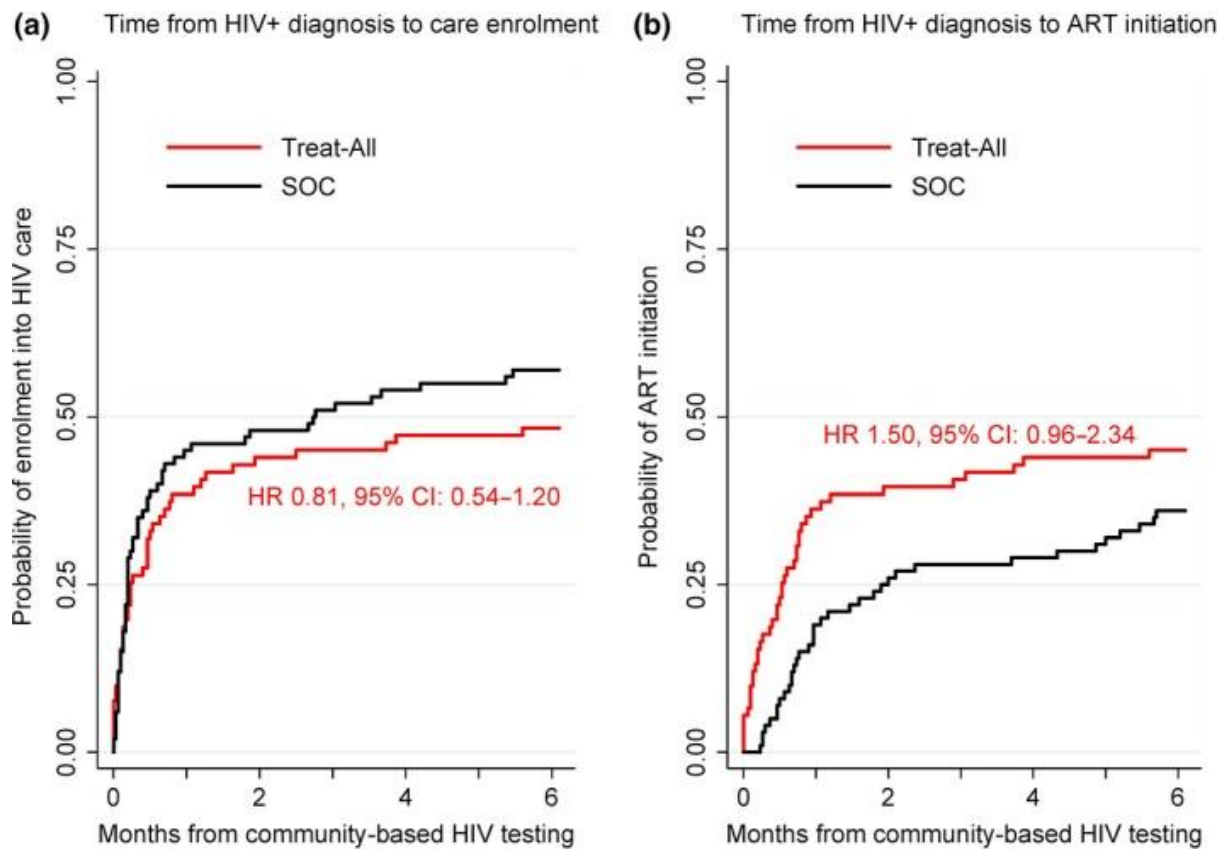


Figure 4: Variations in adjusted hazard ratios of ART initiation comparing primary care facilities with the secondary care facility under Treat-All (facility 1) and under standard of care (facility 10).



After fitting the covariate-adjusted flexible parametric survival models for patients with advanced HIV disease (see Table 3) and for the entire cohort (see Table S2), we estimated the standardized failure curves for Treat-All and SOC and the contrasts (Treat-All vs. SOC) using the post estimation Stata command `stpm2_standsurv`.^{216,217} CI, confidence interval; SOC, standard of care.

Figure 5: Cumulative hazard of ART initiation and absolute difference in hazard of ART initiation by intervention for patients with advanced HIV disease (a1-2) and for the entire cohort (b1-2).



ART, antiretroviral therapy; CI, confidence interval Hr, crude hazard ratio comparing outcomes under treat-All vs SOC; SOC, standard of care.

Figure 6: Time from community-based HIV-positive diagnosis under Treat-All and standard of care (SOC) (a) to HIV care enrolment and (b) to antiretroviral therapy initiation.

SUPPORTING INFORMATION

Multiple imputation diagnostic

Table S1. Covariates with missing values

Additional results

Table S2. Multivariate comparison of ART initiation between Treat-All and SOC for the entire cohort of patients enrolled into facility-based HIV care

Figure S1. Trace plots of covariates with missing values.

MULTIPLE IMPUTATION DIAGNOSTIC

As implemented in Stata version 14.1 (College Station, Texas), multiple imputation by chained equation was used to impute missing values of covariates. Table S1 shows the absolute number and proportion of missing values by covariate.

Table S1: Covariates with missing values.

	Missing values ¹	
	Number	Percentage
CD4 count	161	5.3%
Body mass index	255	8.5%
WHO clinical stage	54	1.8%
Education	501	16.6%
Time of HIV diagnosis	29	1.0%
Gender and pregnancy status	41	1.4%
Marital status	80	2.7%
Laboratory result	502	16.7%
Phone availability	146	4.8%
Tuberculosis	47	1.6%

¹The total number of observations (denominator) was 3013.

A total of 20 imputed datasets was created. Imputation diagnostic was performed comparing the distributions of the observed, imputed and completed values. In addition, trace plots were inspected to assess whether imputation for covariates reached convergence. Imputation diagnostics were satisfied and Figure S1 presents the trace plot.

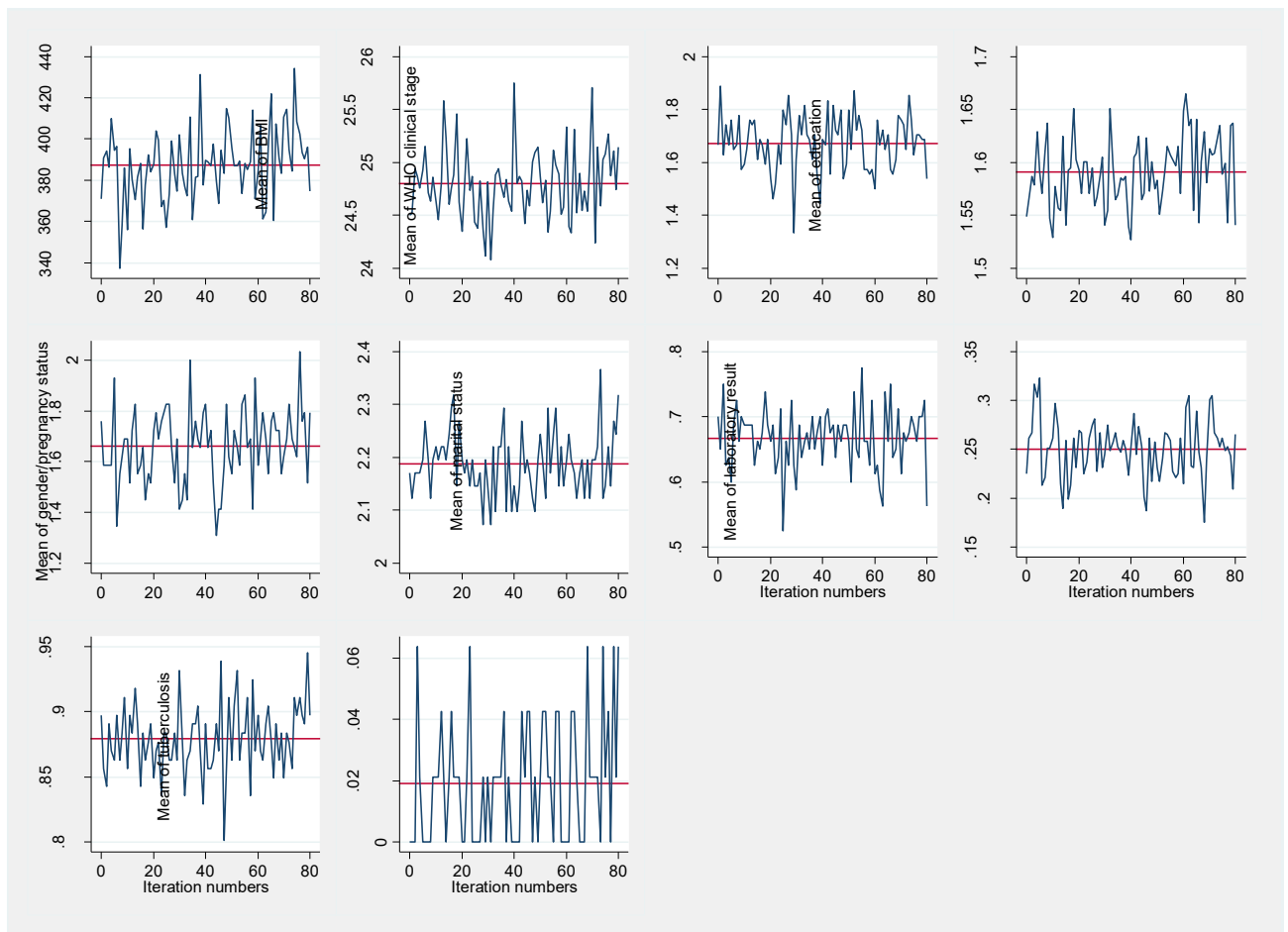


Figure S1: Trace plots of covariates with missing values.

ADDITIONAL RESULTS

Table S2: Multivariate comparison of ART initiation between Treat-All and SOC for the entire cohort of patients enrolled into facility-based HIV care.

	Univariate (n= 3013)		Multivariate (n= 3013)	
	HR	95% CI	aHR	95% CI
Health zone				
SOC	1		1	
Treat-All	1.73	(1.60 to 1.87)	1.99	(1.81 to 2.19)
Implementation period				
Period-1	1		1	
Period-2	1.21	(1.11 to 1.32)	1.26	(1.16 to 1.38)
Facility				
PHC	1		1	
SHC ¹	1.01	(0.93 to 1.09)	0.90	(0.82 to 0.97)
Gender and pregnancy status				
Non-pregnant women	1		1	
Men	0.99	(0.91 to 1.09)	0.96	(0.87 to 1.06)
Pregnant women	2.47	(2.23 to 2.73)	2.46	(2.21 to 2.75)
Age at HIV care enrolment, years				
16 to 24	1		1	
25 to 49	0.97	(0.89 to 1.06)	1.02	(0.92 to 1.13)
≥50	0.85	(0.72 to 1.00)	1.01	(0.84 to 1.20)
Marital status				
Married	1		1	
Not married	1.10	(1.01 to 1.19)	1.02	(0.93 to 1.11)
Education				
None	1		1	
Primary	1.15	(0.95 to 1.38)	1.06	(0.87 to 1.31)
Secondary	1.35	(1.14 to 1.61)	1.12	(0.93 to 1.35)
Tertiary	1.53	(1.07 to 2.19)	1.14	(0.79 to 1.64)
Time of HIV diagnosis, days				
Same day	1		1	
Before	1.16	(1.08 to 1.26)	1.25	(1.15 to 1.35)
CD4 count, cells/mm ³				
0 to 100	1.02	(0.90 to 1.15)	1.09	(0.94 to 1.27)
101 to 200	1.01	(0.89 to 1.15)	0.99	(0.86 to 1.13)
201 to 350	1		1	
351 to 500	0.80	(0.71 to 0.90)	0.76	(0.67 to 0.86)
≥501	0.71	(0.63 to 0.80)	0.66	(0.58 to 0.75)
WHO clinical stage				
I/II	1		1	
III	1.01	(0.90 to 1.13)	1.01	(0.87 to 1.16)

IV	0.92	(0.68 to 1.26)	0.94	(0.68 to 1.31)
BMI, kg/m ²				
≤18.4	1		1	
18.5 to <25	0.90	(0.76 to 1.07)	0.91	(0.76 to 1.09)
≥25	1.05	(0.88 to 1.25)	0.94	(0.77 to 1.16)
Laboratory result ⁴				
Normal	1		1	
Abnormal	1.15	(1.02 to 1.31)	1.11	(0.97 to 1.27)
Tuberculosis				
No	1		1	
Yes	0.97	(0.82 to 1.15)	0.88	(0.68 to 1.15)
Phone availability				
No	1		1	
Yes	1.21	(1.03 to 1.42)	1.19	(1.00 to 1.41)

aHR, adjusted hazard ratio; ART, antiretroviral therapy; BMI, body mass index; HR, hazard ratio; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care.

¹Secondary healthcare level comprised ART outpatient departments in one health centre with inpatient capacity in Treat-All and one hospital in SOC.

The flexible parametric model (Royston–Parmar models) had five internal knots, and one internal knot for the time-varying covariates health zone and TB.

All variables tested in univariate analysis were also included in multivariate analysis.

RESULTS FOR OBJECTIVE 3

HIV programmatic outcomes following implementation of the ‘Treat-All’ policy in a public sector setting in Eswatini: a prospective cohort study

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This paper is a word-for-word copy of the version in PubMed Central® (PMC), to which consistent formatting of references, figures, tables, appendices, and supplementary material has been applied.

Paper overview

This study uses data from a cohort of patients initiated on first-line ART in two health zones in the Shiselweni region in Eswatini. ART initiation was practised at the time of HIV diagnosis and irrespective of immunological criteria (Treat-All) in one health zone and standard of care according to the CD4 350 and 500 cells/mm³ treatment eligibility thresholds in the neighbouring health zone. This study 1) examines the time from facility-based ART initiation to all-cause attrition and to the composite unfavourable treatment outcome (attrition, viral failure) in both health zones, and 2) assesses whether patients with advanced HIV disease were de-prioritized under Treat-All.

Significance of the paper

The 2015 WHO guidelines recommend immediate ART and emphasize that patients with advanced HIV disease should be prioritized. In the context of poorly performing PMTCTB+ programmes, concerns were raised that Treat-All may lead to inferior programmatic and patient-level outcomes, specifically for PLHIV with higher baseline CD4 cell counts >350 and >500 cells/mm³. Another concern is that overburdened health facilities may not be able to maintain quality of care in rapidly expanding ART cohorts, leading to higher ART attrition and to the de-prioritization of patients with advanced HIV disease. As Treat-All has been scaled up recently, there is still a general lack of mid-term and long-term treatment outcomes with regards to retention on ART as well as viral suppression

and viral failure. Experiences from routine settings on mid-term treatment outcomes of Treat-All are scarce but needed to inform the rapid roll-out of Treat-All in RLS.

Candidate`s contributions

The candidate in collaboration with KJ and RT designed the study. The candidate established the cohort and was involved in data acquisition. The candidate in collaboration with MS, AB, and IC established the analysis plan. The candidate acquired and processed all data, performed all analyses, wrote the first draft of the manuscript, integrated comments from co-authors, and submitted the manuscript for peer review.

ABSTRACT

Introduction

The Treat-All policy – antiretroviral therapy (ART) initiation irrespective of CD4 cell criteria – increases access to treatment. Many ART programmes, however, reported increasing attrition and viral failure during treatment expansion, questioning the programmatic feasibility of Treat-All in resource-limited settings. We aimed to describe and compare programmatic outcomes between Treat-All and standard of care (SOC) in the public sectors of Eswatini.

Methods

This is a prospective cohort study of ≥ 16 -year-old HIV-positive patients initiated on first-line ART under Treat-All and SOC in 18 health facilities of the Shiselweni region, from October 2014 to March 2016. SOC followed the CD4 350 and 500 cells/mm³ treatment eligibility thresholds. Kaplan-Meier estimates were used to describe crude programmatic outcomes. Multivariate flexible parametric survival models were built to assess associations of time from ART initiation with the composite unfavourable outcome of all-cause attrition and viral failure.

Results

Of the 3170 patients, 1888 (59.6%) initiated ART under Treat-All at a median CD4 cell count of 329 (IQR 168 to 488) cells/mm³ compared with 292 (IQR 161 to 430) ($p < 0.001$) under SOC. Although crude programme retention at 36 months tended to be lower under Treat-All (71%) than SOC (75%) ($p = 0.002$), it was similar in covariate-adjusted analysis (adjusted hazard ratio [aHR] 1.06, 95% CI 0.91 to 1.23). The hazard of viral suppression was higher for Treat-All (aHR 1.12, 95% CI 1.01 to 1.23), while the hazard of viral failure was comparable (Treat-All: aHR 0.89, 95% CI 0.53 to 1.49). Among patients with advanced HIV disease ($n = 1080$), those under Treat-All (aHR 1.13, 95% CI 0.88 to 1.44) had a similar risk to SOC of a composite unfavourable outcome. Factors increasing the risk of the composite unfavourable outcome under both interventions were aged 16 to 24 years, being unmarried, anaemia, ART initiation on the same day as HIV care enrolment and $CD4 \leq 100$ cells/mm³. Under Treat-All only, the risk of the unfavourable outcome was higher for pregnant women, WHO III/IV clinical stage and elevated creatinine.

Conclusions

Compared to SOC, Treat-All resulted in comparable retention, improved viral suppression and comparable composite outcomes of retention without viral failure.

INTRODUCTION

The World Health Organization (WHO) recommends antiretroviral therapy (ART) initiation at the time of HIV diagnosis irrespective of clinical and immunological criteria, aiming at improving patient-level outcomes and reducing HIV transmission.¹⁶ High acceptability of this Treat-All policy led to 93% adoption and 84% implementation coverage in low- and middle-income countries in July 2019,²²⁶ and facility-site level implementation started in southern Africa as early as 2016.²²⁷ With an estimated 67% ART coverage in eastern and southern Africa in 2018, an additional three million are required to access treatment with the introduction of Treat-All.²²⁸

HIV programmes need to maximize retention on and adherence to ART during treatment expansion to take advantage of the clinical, programmatic and public health benefits of Treat-All and achieve the second and third 90s of the UNAIDS 90-90-90 targets.^{5,229} However, challenges in ART programming may be exacerbated with Treat-All, questioning the feasibility of universal ART in resource-limited settings (RLS).^{31–33,35,39–43} Expanding treatment in overburdened health facilities may overextend health systems and decrease the quality of care, treatment follow-up and record-keeping.^{104,107,109} High rates of loss to follow-up (LTFU), all-cause attrition and viral failure have been reported from rapidly growing ART cohorts,^{102–104,107–110} and previous guideline changes to increase the treatment eligibility threshold yielded mixed findings.^{230,231} Patients with high CD4 cell counts on ART – a group that will increase with Treat-All – have a higher risk of unstructured treatment interruptions, missing clinical appointments and LTFU, leading to lower long-term retention.^{68,102,107,112,232} Also, patients should not be de-prioritized when presenting late to HIV treatment,¹⁶ a possible challenge for expanding treatment programmes which may prioritize ART initiations over quality of follow-up care.

The impact of changing ART eligibility criteria in RLS is poorly understood because of the lack of recent programme data,¹⁷⁰ the gap between supporting health policies and efficient operationalization^{34,57} and inconclusive treatment outcome data from ongoing Treat-All trials.^{233–236} Eswatini (formerly Swaziland) is one of the few countries that piloted the Treat-All policy before it became a WHO recommendation in 2016.¹⁶ While Treat-All has increased timely ART initiation in routine settings,^{237–239} studies on longer-term outcomes are scarce. To inform scale-up of Treat-All in RLS, we aimed to assess varying patterns of associations with treatment outcomes under Treat-All and under the concurrent national standard of care (SOC) at the time, and to compare programmatic outcomes between both interventions.

METHODS

Study design

This is a prospective cohort study of ≥ 16 -year-old HIV-positive patients initiated on first-line ART under the Treat-All programmatic approach and under SOC in 18 public sector health facilities of the Shiselweni region (Eswatini), from 20 October 2014 to 31 March 2016.

Study setting

The setting has been described previously.²¹⁵ The predominantly rural Shiselweni region has a population of $\sim 210,000$ ¹⁷⁷ and HIV prevalence is 31% in 18- to 49-year-olds.^{173,181} The study was conducted in two neighbouring health zones, each comprising eight HIV/TB care integrated primary care facilities and one HIV/TB care collocated secondary care outpatient department. The Treat-All health zone offered prompt facility-based ART initiation irrespective of CD4 and clinical criteria for all newly diagnosed patients and those already enrolled in pre-ART care. The neighbouring SOC health zone followed national treatment guidelines with ART initiation at $CD4 \leq 350$ (October 2014 to October 2015) and ≤ 500 cell/mm³ (November 2015 onwards), WHO III/IV clinical staging and the prevention of mother-to-child transmission programmatic approach option B+ (PMTCTB+).

Trained lay counsellors conducted HIV testing, and pre-treatment and treatment adherence counselling. ART initiation and follow-up care were performed by nurses in primary care clinics and supported by onsite medical doctors in secondary care outpatient departments. Patients usually had a baseline CD4 cell count and laboratory test (haemoglobin, alanine aminotransferase (ALT), creatinine). The CD4 result was not a requirement for ART initiation under Treat-All. Routine viral load (VL) monitoring was available (using the Biocentric platform)^{140,183} with VL testing recommended at six and twelve months after ART initiation, and annually thereafter.¹⁴⁰ Enhanced adherence counselling was provided for patients with a $VL \geq 1000$ copies/mL, with treatment switching in case of viral failure (two consecutive VLs ≥ 1000 copies/mL). Telephonic and physical defaulter tracing was recommended for patients missing clinical appointments.

Analyses, outcomes and definitions

Several analyses were conducted (Figure 1). First, baseline factors were described separately for both interventions. Laboratory measures were recorded at the time of ART initiation and a TB case was defined as a patient receiving TB treatment between six months before and three months after ART initiation. Calendar time was divided into time period-1 and time period-2, corresponding to the WHO 2010 (October 2014 to October 2015) and WHO 2013 (November 2015 onwards) treatment guideline implementation periods followed under SOC. Same-day ART initiation was defined as patients starting ART on the same day as HIV care enrolment (the date of opening a patient file at the health facility).

Second, we describe crude and covariate adjusted programmatic indicators. Retention was defined as patients in ART care at different time points (without the outcome of death or LTFU). We chose this

end point because the vital status was not actively ascertained in both interventions. LTFU was defined as six months without a clinic visit measured from the last clinic visit. Follow-up time was censored at database closure (31 October 2017) or date of transfer out of the facility. Then we describe VL testing uptake (the probability of receiving at least one VL test) and viral suppression, defined as the proportion of VLs < 1000 copies/mL among patients with a first VL measurement recorded. Finally, viral failure was compared, defined as two consecutive VLs $\geq$ 1000 copies/mL measured at least five months after ART initiation and performed $\geq$ 1.5 months apart or treatment switching to a protease inhibitor based regimen with two new drugs in the absence of documented viral failure. All viral load outcomes were measured from five months after ART initiation.

Third, Treat-All aims to retain patients on virally suppressed ART to improve patient level outcomes and reduce transmission of HIV. Accordingly, we established a composite primary endpoint of death, LTFU and viral failure. To assess whether the unfavourable outcome was more likely to occur in the Treat-All zone, we compared the interventions directly, first for the entire cohort and then restricted to patients presenting with advanced HIV disease defined as CD4 < 200 cells/mm³ and/or WHO III/IV clinical staging.

Finally, we conducted separate analyses of the composite primary endpoint for both models of care to assess possible varying patterns of associations with Treat-All and SOC during the implementation of different treatment guidelines.

All data were collected by trained data clerks from individual-level clinic records and paper registers, and entered into EpiData software. VL and TB data were complemented with data from separate electronic databases used for routine programme monitoring.

Statistics

Baseline characteristics and crude programmatic outcomes were described with frequencies and proportions, and compared using the Pearson's chi-squared test for categorical variables and Wilcoxon's rank-sum test for continuous variables. Kaplan-Meier estimates were used to describe retention, VL testing uptake and viral failure.

Variables for inclusion in multivariate analyses were selected a priori based on clinical relevance and literature review. We used multiple imputation by chained equations¹⁹⁵ to impute missing covariate data using 20 datasets (Table S1). Multiple imputation diagnostics were satisfied according to trace plots and Kernel density plots (Figure S1 and S2). Covariate adjusted parametric survival models (Royston-Parmar models)¹⁹⁶ were built to describe associations with time to the composite outcome. We used Akaike's information criteria to determine the number and location of internal knots for the baseline spline function. Covariates violating the proportional hazards assumption (assessed with

Schoenfeld residual statistics) were included in the models as time-varying effects. All analyses were performed with Stata 14.1 (StataCorp, College Station, Texas, USA).

Ethics

This study was approved by the Scientific and Ethics Committee of Eswatini, the Research Ethics Committees of MSF and the University of Cape Town, South Africa. Informed written consent was obtained before ART initiation from patients in Treat-All who were ineligible for ART according to the national SOC.

RESULTS

Baseline characteristics

Treat-All and SOC

Figure 1 shows the study flow. Thirty-five patients were removed from the analysis because study eligibility was unclear. Of the remaining 3170 patients (Table 1a), 1888 (59.6%) initiated treatment under Treat-All. Baseline factors comparable between health zones were attendance at primary care level (64.5%), being pregnant (22.7%), median age (31 years, interquartile range (IQR) 25 to 38), clinical factors (body mass index (BMI), haemoglobin, ALT, creatinine) and TB co-infection (7.0%). Under Treat-All, patients were more likely to receive tenofovir (TDF) (98.7% vs. 92.6%) and efavirenz (EFV) (98.9% vs. 92.4%) based ART regimens, start treatment on the same day as HIV diagnosis (22.8% vs. 13.9%) and HIV care enrolment (44.4% vs. 24.3%), have secondary education (67.7% vs. 57.7%) and not have access to a phone (11.4% vs. 7.9%). Overall, patients had a higher median CD4 cell count under Treat-All (329, IQR 168 to 488, vs. 292, 161 to 430; $p < 0.001$). The difference was highest for non-pregnant adults in period-1 when SOC applied the $CD4 \leq 350$ treatment eligibility threshold (334, IQR 156 to 494, vs. 260.5, IQR 124 to 362; $p < 0.001$).

Advanced HIV disease

Overall, 1074/3170 (33.9%) patients presented with advanced HIV disease, of whom 620 (57.8%) were under Treat-All. Distribution of baseline factors is presented in Table 1b. Of the patients with available CD4 cell count and WHO clinical staging data, 642/1060 (60.6%) presented with both CD4 cell count ≤ 200 cells/mm³ and WHO clinical stage I/II (Table S2).

Programmatic outcomes

The frequency of the outcomes is presented in Figure 1.

Retention

Treat-all

Under Treat-All, pregnant women (vs. men, non-pregnant women) ($p < 0.001$), younger patients (16 to 24 years) ($p < 0.001$) and those with low CD4 cell count (≤ 100 cells/mm³) ($p = 0.005$) tended to have had lower retention (Figure 2a-c, Table S3). Additional Kaplan-Meier graphs of retention under Treat-All are in Figure S3.

Treat-all versus SOC

Comparing both health zones, crude 6- and 36-month retention were 84% and 71% under Treat-All compared with 89% and 75% under SOC ($p = 0.005$) (Figure 2d). Retention tended to be lower for pregnant women than non-pregnant adults under both interventions (Table 2). Overall, 6% and 3% of patients under Treat-All and SOC never came for a follow-up visit after initiation of ART. In covariate-adjusted analysis, the hazard of attrition was similar for Treat-all (adjusted hazard ratio (aHR) 1.06, 95% CI 0.91 to 1.23) compared with SOC (*model not shown*) (Figure 3).

Viral outcomes

Among patients retained in care for ≥ 5 months (Treat-All: $n = 1587$, SOC: $n = 1127$), time to first VL test was similarly low and delayed in both health zones at 6 (Treat-All: 19%, SOC: 15%) and 36 months (Treat-All: 89%, SOC: 86%) ($p = 0.555$) (Figure 2e), with 90% and 87% respectively being virally suppressed ($p = 0.012$). In multivariate analysis, the hazard of viral suppression was higher for Treat-all (aHR 1.12, 95% CI 1.01 to 1.23) than SOC (*model not shown*) (Figure 3). Assuming that patients without a VL test result and retained in care ≥ 5 months had an elevated VL, viral suppression decreased to 76% under Treat-All and 72% under SOC ($p = 0.019$). The cumulative 3-year hazard of viral failure was 4% under Treat-All and 3% under SOC ($p = 0.690$) (Figure 2f) and remained comparable in covariate-adjusted analysis (Treat-All: aHR 0.89, 95% CI 0.53 to 1.49) (*model not shown*) (Figure 3).

Composite unfavourable outcome (death, LTFU and viral failure)

Comparing Treat-All and SOC in one covariate-adjusted model, the hazard of the unfavourable outcome was similar for the entire cohort (Treat-All: aHR 1.04, 95% CI 0.90 to 1.20) (Table S4) and for patients with advanced HIV disease (Treat-All: aHR 1.13, 95% CI 0.88 to 1.44) (Table 3, Figure 3).

In both analyses, the hazard was higher for BMI < 18.5 kg/m², haemoglobin ≤ 9 g/dL, creatinine ≥ 121 μ mol/L and being unmarried. The hazard was higher for the entire cohort only for the CD4 strata ≤ 200 cells/mm³ (vs. CD4 201 to 350), WHO clinical stage III/IV (vs. WHO stage I), age 16 to 24 years (vs. 25 to 49 years) and shorter time since HIV care enrolment. The hazard of the

unfavourable outcome varied over time for TB, with lower hazard during the first nine months after ART initiation and similar hazard thereafter (Figure S4).

Predictors of the composite unfavourable outcome (Treat-All vs. SOC)

A breakdown of crude outcomes is shown in Figure 1 and predictors in Table 4. In both health zones, the hazard of the unfavourable outcome was higher for young adults aged 16 to 24 years (vs. 25 to 49 years), unmarried patients, haemoglobin ≤ 9 g/dL, ART initiation on the same day or within three months of HIV care enrolment (vs. ART initiation after three months) and CD4 cell count ≤ 100 cells/mm³. The effect of same-day ART initiation varied over time under Treat-All, with higher hazards during the first 1.1 years after ART initiation while the difference in hazard ceased thereafter (Figure 4a,c). The effect of baseline CD4 varied over time under SOC, with the highest hazard during the first year of treatment for CD4 ≤ 100 cells/mm³ (vs. CD4 201 to 350) (Figure 4b,d). Although the hazard difference decreased thereafter, it remained higher for almost the entire observation period. Other factors did not show any strong associations.

Under SOC only, the hazard was higher for low BMI < 18.5 kg/m² (aHR 2.21, 95% CI 1.52 to 3.21) and lower for the later implementation period (aHR 0.71, 95% CI 0.54 to 0.92). Under Treat-All only, the hazard was higher for pregnant women (aHR 1.37, 95% CI 1.10 to 1.71), WHO staging III/IV (aHR 1.41, 95% CI 1.05 to 1.90) (vs. WHO stage I) and elevated creatinine ≥ 121 μ mol/L (aHR 1.73, 95% CI 1.00 to 2.99).

In supplementary analysis, including health facility as a co-variate instead of primary versus secondary care level, two primary care facilities under Treat-All and one primary care facility under SOC showed an increased hazard of an unfavourable outcome when compared with the secondary care facility at each health zone (Figure S5).

DISCUSSION

This study assessed programmatic and patient outcomes of universal ART provision (Treat-All) in a predominantly rural public sector setting in Eswatini. Compared to SOC, Treat-All resulted in comparable retention, improved viral suppression and comparable composite outcomes of retention without viral failure, after adjusting for differences between patients accessing each service. Although crudely a higher proportion of patients were lost to care under Treat-All, this service also enrolled more patients with higher CD4 counts,²³⁸ suggesting improved coverage of the overall HIV population.

Explanation of findings

Similarly to other settings,²⁴⁰ low CD4 cell count was associated with an adverse outcome. The association was more pronounced for patients presenting with advanced HIV disease, and the effect of CD4 cell count varied with time under SOC, with higher hazard early during treatment. Notably, under Treat-All, outcomes for patients with high CD4 cell counts were similar to those for patients with 201 to 350 cells/mm³, a pattern confirmed by two other Treat-All trials^{233,234} but in contrast to findings from the Western Cape, South Africa, where attrition was increased for CD4 >500 cells/mm³.²³⁵

Overall, the median CD4 cell count at ART initiation was only slightly higher under Treat-All (37 cells/mm³), possibly explained by concurrent expansion of treatment eligibility criteria under SOC during the study period. Pregnant and lactating women were already eligible for prompt ART (PMTCTB+) under SOC and treatment eligibility for non-pregnant adults was expanded from ≤ 350 to ≤ 500 cell/mm³. Restricting analysis to non-pregnant adults under period-1 (WHO 2010 treatment guideline implementation), the difference in median CD4 cell count increased to 73.5 cells/mm³.

ART initiation on the same day as HIV care enrolment was associated with an adverse outcome, possibly stronger during the first year of treatment. Data on same-day ART initiation remain conflicting, with randomized controlled trials showing benefits and observational studies indicating no benefit or increased risk of unfavourable treatment outcomes.^{210,240–243} A reason could be that observational studies may not be able to sufficiently adjust for time-dependent confounding. For instance, patients with higher CD4 cell count may be less likely to initiate ART the same day and more likely to have a favourable outcome while immunocompromised patients may be more likely to start treatment on the same day and to have an unfavourable outcome. Patients initiating ART are a subset of those diagnosed, linked and enrolled into care, thus our findings not comparable with studies with follow-up starting at the time of HIV diagnosis. Further studies are needed to understand same-day ART and its impact on HIV programmes implementing Treat-All, specifically because many RLS already apply rapid treatment initiation.²²⁷ Nevertheless, attention is needed to identify patients not ready for same-day ART and to provide adequate adherence support after same-day ART initiation.²⁰⁹

Men and non-pregnant women had the same risk of an unfavourable outcome. Although men in general show worse HIV care outcomes,^{162,240,244} findings from Eswatini remain inconsistent, with increased and similar risk for men.^{106,199,224} Adverse treatment outcomes were high for pregnant women under Treat-All, which is in line with findings from PMTCT B+ and general ART programmes.^{101,240,241} Specific interventions supporting pregnant women under Treat-All may be needed to achieve the full benefits of universal ART expansion for this group.

Similar to other studies,^{239,241,245–247} younger age, being unmarried and clinical factors (BMI, haemoglobin, creatinine) increased the risk of adverse outcomes in both health zones and irrespective

of disease progression. In contrast to another setting,²⁴⁵ the level of education did not show associations. While this setting showed significant variations for ART initiation across facilities,²³⁸ the variations with respect to programmatic outcomes were minor.

The later WHO 2013 guideline implementation period (time period-2) showed a lower risk of an unfavourable outcome under SOC. Temporal trends have also been reported from other settings.^{102–104,107–110} In our case, quality of follow-up care may be one explanation. This time period coincided with the expansion of differentiated community-centred ART care models for patients stable on ART and was more pronounced under SOC, which may have supported long-term adherence and decongested busy facilities.²⁴⁸

WHO emphasizes that patients in greatest need of ART should not be de-prioritized during treatment scale-up.¹⁶ Although about one third of patients in both health zones presented with advanced HIV disease and had an increased likelihood of adverse outcome if CD4 was ≤ 100 cells/mm³, covariate-adjusted analysis indicated that the risk was similar under Treat-All and SOC. In addition, TB co-infection emerged as a protective factor during early treatment. As per national guideline recommendations, co-infected patients may have received more attention by health workers given their high risk of mortality, resulting in less loss to care. Although median CD4 cell count increased during ART programme expansion internationally,²⁴⁹ the challenge of advanced HIV disease is likely to persist.²⁵⁰ Scale-up of optimized packages of care for patients with advanced HIV (e.g. better diagnostics and effective prophylactic treatment) is essential to further reduce mortality and morbidity.^{250,251} Our findings are encouraging in that patients with advanced HIV disease were probably not de-prioritized under Treat-All compared with SOC.

Findings in context

Overall retention was comparable to ART programmes in low- and middle-income countries¹⁰⁰ and two Treat-All trials in Southern Africa.^{234,235} However, point estimates of retention tended to be lower than under SOC, than previous retention estimates from this setting before the introduction of Treat-All²¹⁵ and than in a streamlined combination intervention trial in Eastern Africa.²³³ Similarly to another Treat-All trial in South Africa,²³⁴ 6% of patients never returned for a clinic visit after ART initiation (vs. 3% under SOC). A broad range of supportive interventions may improve retention (e.g. community-based adherence support, health technology interventions),^{113–115,252} potentially also under Treat-All.⁶⁸

While VL testing uptake was low and delayed in both health zones, crude viral suppression tended to be slightly higher under Treat-All and comparable to other settings.²⁵³ Overall, viral failure seemed lower than in other ART programmes,^{254,255} possibly explained by variability of definitions,

underestimation of true viral failure because of suboptimal VL testing coverage and record keeping, and high viral re-suppression rates (~60%) in patients with single elevated VLs.^{140,184}

Limitations and strengths

First, our estimates of ART retention are conservative. Previous studies showed that transient treatment interruptions and movements between clinics are common and many patients recorded with LTFU are retained.^{112,256,257} Because of limitation in routine monitoring and limited tracking of patients lost to follow-up, this study was not able to adjust for silent transfer between treatment sites and silent return to care. In addition, ART retention in clinic was measured rather than retention in care or national-level retention, likely biasing estimation of retention downwards.^{258,259} We also did not report on overall HIV care retention of patients entering care as done in other routine Treat-All settings,²³⁹ thus possibly not detecting a higher care retention benefit of Treat-All when compared with SOC. Finally, not accounting for transient treatment interruptions possibly introduced a spurious trend of increased LTFU in our cohort, which had a relatively short follow-up time (analysis bias) compared with other cohorts.¹⁶⁸ Second, given the observational study design and comparison of two different health zones, we may not have been able to adjust for all unobserved variables (e.g. exposure to differentiated service delivery model for patients stable on ART). Third, assessing ART coverage and population-level viral suppression due to Treat-All was beyond the scope of this analysis. Nevertheless, ART initiation rates measured from the time of facility-based HIV care enrolment was higher under Treat-All (91%) than SOC (74%; $p < 0.001$) in this setting.²³⁸ This possible additional ART coverage under Treat-All may have an increased overall effect on viral suppression of the entire population living with HIV despite lower retention in crude analysis. In addition, ART has been progressively expanded in this setting since 2006,²¹⁵ achieving 82.7% population-level ART coverage and 79.1% population-level VL suppression among people living with HIV in 2016/17.¹⁸⁸

Despite the wide-scale adoption of Treat-All in RLS,^{229,260} studies accounting for this policy change under routine conditions are lacking. This study began two years before publication of the WHO Treat-All guidelines, and thus has the potential to inform implementation of this policy in similar rural settings. We adjusted for a wide range of covariates, which likely enabled us to show a comprehensive picture of Treat-All. In addition, we encountered risk factors that have not been widely described previously (e.g. same-day ART initiation) but that may affect programmatic outcomes of large HIV programmes. Finally, we assessed the programmatic impact of treatment expansion on patients with advanced HIV disease.

CONCLUSIONS

Compared to SOC, Treat-All resulted in comparable retention, improved viral suppression and comparable composite outcomes of retention without viral failure. Patients with advanced HIV disease were possibly not de-prioritized and predictors of unfavourable outcomes were comparable between Treat-All and SOC. This study contributes to evidence that treatment expansion through the Treat-All programmatic approach may be feasible in RLS without increasing unfavourable outcomes, and as such is likely to have public health benefits.

Table 1. Baseline characteristics of patients initiating first-line ART under Treat-All and standard of care (SOC) (entire treatment cohort and patients with advanced HIV disease)

(Missing values for entire cohort)	(a) Entire cohort (n = 3170)			(b) Advanced HIV disease (n = 1074) ^a		
	Treat-All	SOC (n = 1282)	<i>p</i>	Treat-All	SOC (n = 454)	<i>p</i>
	(n = 1888) (n, %)	(n, %)	value	(n = 620) (n, %)	(n, %)	value
Implementation period ^b						
Period-1	1397 (74.0)	851 (66.4)	<0.001	428 (69.0)	317 (69.8)	0.781
Period-2	491 (26.0)	431 (33.6)		192 (31.0)	137 (30.2)	
Facility						
PHC	1215 (64.4)	830 (64.7)	0.822	394 (63.5)	249 (54.8)	0.004
SHC ^c	673 (35.6)	452 (35.3)		226 (36.5)	205 (45.2)	
Time since HIV diagnosis (0.5%) ^d						
≥90 days	572 (30.5)	499 (39.1)	<0.001	119 (19.3)	114 (25.2)	<0.001
1 to 89 days	877 (46.7)	601 (47.1)		376 (61.0)	305 (67.3)	
Same day	429 (22.8)	177 (13.9)		121 (19.6)	34 (7.5)	
Time since HIV care enrolment ^e						
≥90 days	308 (16.3)	325 (25.4)	<0.001	36 (5.8)	44 (9.7)	<0.001
1 to 89 days	741 (39.2)	646 (50.4)		321 (51.8)	331 (72.9)	
Same day	839 (44.4)	311 (24.3)		263 (42.4)	79 (17.4)	
Sex						
Men	510 (27.0)	400 (31.2)	0.011	262 (42.3)	221 (48.7)	0.037
Women	1378 (73.0)	882 (68.8)		358 (57.7)	233 (51.3)	
Pregnancy (0.5%)						
No	1443 (76.8)	996 (78.2)	0.349	540 (87.5)	421 (92.7)	0.006
Yes	437 (23.2)	278 (21.8)		77 (12.5)	33 (7.3)	
Age at HIV care enrolment, years						
16 to 24	416 (22.0)	292 (22.8)	0.877	71 (11.5)	43 (9.5)	0.391
25 to 49	1317 (69.8)	884 (69.0)		486 (78.4)	356 (78.4)	
≥50	155 (8.2)	106 (8.3)		63 (10.2)	55 (12.1)	
Marital status (1.4%)						
Married	638 (34.5)	594 (46.6)	<0.001	240 (39.6)	227 (50.1)	0.001
Not married	1212 (65.5)	681 (53.4)		366 (60.4)	226 (49.9)	
Education (14.4%)						
None	75 (4.8)	101 (8.9)	<0.001	34 (6.6)	44 (11.0)	0.105
Primary	410 (26.0)	359 (31.6)		145 (28.0)	114 (28.5)	
Secondary	1068 (67.7)	656 (57.7)		330 (63.7)	236 (59.0)	
Tertiary	25 (1.6)	21 (1.8)		9 (1.7)	6 (1.5)	
CD4 count, cells/mm ³ (3.0%)						
0 to 100	277 (15.1)	192 (15.4)	<0.001	277 (45.3)	192 (42.3)	0.295
101 to 200	274 (15.0)	200 (16.1)		272 (44.4)	200 (44.1)	
201 to 350	424 (23.2)	387 (31.1)		31 (5.1)	37 (8.1)	
351 to 500	420 (23.0)	273 (21.9)		15 (2.5)	14 (3.1)	
≥501	434 (23.7)	194 (15.6)		17 (2.8)	11 (2.4)	
WHO clinical stage (0.5%)						

I	1282 (68.3)	904 (70.7)		255 (41.3)	182 (40.4)	
II	365 (19.5)	177 (13.8)	<0.001	133 (21.6)	72 (16.0)	0.028
III/IV	229 (12.2)	197 (15.4)		229 (37.1)	197 (43.7)	
Tuberculosis						
No	1763 (93.4)	1186 (92.5)		520 (83.9)	384 (84.6)	
Yes	125 (6.6)	96 (7.5)	0.347	100 (16.1)	70 (15.4)	0.753
BMI, kg/m ² (6.3%)						
<18.5	105 (6.1)	81 (6.5)		70 (12.3)	60 (13.8)	
18.5 to 24.9	869 (50.1)	670 (53.6)	0.113	343 (60.3)	254 (58.3)	0.739
≥25	759 (43.8)	500 (40.0)		156 (27.4)	122 (28.0)	
Haemoglobin, g/dL (22.6%)						
≤9	262 (18.1)	156 (15.6)		122 (25.8)	89 (24.5)	
≥10	1187 (81.9)	847 (84.4)	0.102	350 (74.2)	275 (75.5)	0.645
ALT, U/L (30.1%)						
≤42	1289 (87.4)	639 (86.2)		393 (82.0)	213 (81.8)	
≥43	186 (12.6)	102 (13.8)	0.446	86 (18.0)	48 (18.4)	0.883
Creatinine, μmol/L (20.6%)						
≤120	1532 (97.7)	926 (97.7)		484 (95.5)	315 (94.6)	
≥121	36 (2.3)	22 (2.3)	0.968	23 (4.5)	18 (5.4)	0.568
NRTI						
TDF	1864 (98.7)	1187 (92.6)		610 (98.4)	410 (90.3)	
AZT	20 (1.1)	83 (6.5)	<0.001	8 (1.3)	34 (7.5)	<0.001
ABC	4 (0.2)	12 (0.9)		2 (0.3)	10 (2.2)	
NNRTI						
EFV	1868 (98.9)	1184 (92.4)		614 (99.0)	417 (91.9)	
NVP	20 (1.1)	98 (7.6)	<0.001	6 (1.0)	37 (8.1)	<0.001
Phone availability (1.0%)						
No	213 (11.4)	100 (7.9)		76 (12.3)	28 (6.2)	
Yes	1652 (88.6)	1172 (92.1)	0.001	541 (87.7)	423 (93.8)	0.001

ABC, abacavir; ALT, alanine aminotransferase; AZT, zidovudine; BMI, body mass index; EFV, efavirenz; IQR, interquartile range; n, number; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

^a Advanced HIV disease was defined as patients presenting with CD4 < 200 cells/mm³ and/or WHO III/IV staging;

^b period-1 is the WHO 2010 (from October 2014 to October 2015) and period-2 is the WHO 2013 (from November 2015 onwards) ART initiation guideline implementation period as followed under standard of care;

^c secondary healthcare: ART outpatient departments in one health centre (with inpatient capacity) in Treat-All and ART outpatient departments in one hospital in standard of care;

^d this is the time from HIV diagnosis to ART initiation;

^e this is the time from facility-based HIV care enrolment to ART initiation

Table 2. Kaplan–Meier estimates of retention on antiretroviral therapy, overall and for pregnant and non-pregnant adults (percentage and 95% confidence interval)

	Entire cohort (n = 3170)		Advanced HIV disease (n = 1074)	
	Treat-All (n = 1888)	SOC (n = 1282)	Treat-All (n = 620)	SOC (n = 454)
Retention, entire cohort				
1 day ^a	94 (93 to 95)	97 (95 to 97)	95 (93 to 96)	95 (93 to 97)
6 months	84 (82 to 85)	89 (87 to 90)	81 (78 to 84)	86 (82 to 89)
12 months	78 (76 to 80)	83 (81 to 85)	76 (73 to 80)	81 (77 to 84)
24 months	72 (70 to 74)	77 (75 to 79)	70 (66 to 73)	74 (70 to 78)
36 months	71 (69 to 73)	75 (73 to 78)	68 (64 to 71)	72 (68 to 76)
Retention, non-pregnant adults				
1 day ^a	95 (94 to 96)	97 (96 to 98)	96 (94 to 97)	95 (92 to 97)
6 months	86 (84 to 88)	90 (88 to 92)	82 (78 to 85)	86 (82 to 89)
12 months	81 (79 to 83)	85 (83 to 87)	76 (72 to 80)	81 (77 to 84)
24 months	75 (73 to 77)	79 (77 to 82)	70 (66 to 74)	75 (70 to 79)
36 months	74 (72 to 76)	78 (75 to 80)	68 (64 to 72)	72 (67 to 76)
Retention, pregnant women				
1 day ^a	90 (87 to 93)	94 (90 to 96)	87 (77 to 93)	97 (80 to 100)
6 months	77 (73 to 81)	84 (79 to 88)	79 (68 to 87)	85 (67 to 93)
12 months	70 (65 to 74)	77 (71 to 81)	78 (67 to 86)	75 (56 to 87)
24 months	62 (57 to 66)	70 (64 to 75)	69 (57 to 78)	72 (53 to 84)
36 months	61 (56 to 65)	67 (61 to 73)	65 (53 to 75)	72 (53 to 84)

SOC, standard of care.

^a *These patients never came back for a clinic visit after ART initiation.*

Table 3. Predictors of the unfavourable outcome for patients with advanced HIV disease (Treat-All and SOC combined) initiated on first-line ART (n = 1080)

	Univariate analysis HR (95% CI)	Multivariate analysis ^a aHR (95% CI)
Health zone		
SOC	1	1
Treat-All	1.15 (0.93 to 1.43)	1.13 (0.88 to 1.44)
Implementation period^b		
Period-1	1	1
Period-2	0.87 (0.68 to 1.10)	0.83 (0.64 to 1.07)
Facility		
PHC	1	1
SHC ^c	0.88 (0.71 to 1.10)	0.84 (0.65 to 1.07)
Time since HIV diagnosis^d		
≥90 days	1	1
1 to 89 days	0.80 (0.63 to 1.04)	0.86 (0.62 to 1.18)
Same day	0.94 (0.67 to 1.33)	0.65 (0.42 to 1.00)
Time since HIV care enrolment^e		
≥90 days	1	1
1 to 89 days	0.73 (0.50 to 1.07)	0.84 (0.53 to 1.36)
Same day	1.00 (0.67 to 1.48)	1.21 (0.75 to 1.96)
Sex		
Men	1	1
Women	1.29 (1.04 to 1.60)	1.17 (0.91 to 1.51)
Pregnancy		
No	1	1
Yes	1.07 (0.76 to 1.51)	1.03 (0.69 to 1.53)
Age at HIV care enrolment, years		
16 to 24	1.46 (1.08 to 1.99)	1.22 (0.87 to 1.72)
25 to 49	1	1
≥50	0.91 (0.64 to 1.31)	1.08 (0.74 to 1.59)
Marital status		
Married	1	1
Not married	1.76 (1.40 to 2.21)	1.53 (1.19 to 1.97)
Education		
None	1	1
Primary	1.11 (0.71 to 1.73)	1.08 (0.68 to 1.71)
Secondary	0.99 (0.65 to 1.51)	0.97 (0.62 to 1.51)
Tertiary	1.16 (0.46 to 2.91)	1.10 (0.41 to 2.91)
CD4 count, cells/mm³		
0 to 100	1.39 (0.85 to 2.26)	1.59 (0.94 to 2.68)
101 to 200	1.05 (0.64 to 1.72)	1.35 (0.78 to 2.33)
201 to 350	1	1
≥351	0.98 (0.50 to 1.93)	1.05 (0.52 to 2.12)

WHO clinical stage		
I	1	1
II	1.10 (0.82 to 1.48)	1.03 (0.75 to 1.41)
III/IV	1.20 (0.94 to 1.51)	1.22 (0.91 to 1.66)
Tuberculosis		
No	1	1
Yes	0.94 (0.71 to 1.26)	0.76 (0.56 to 1.04)
BMI, kg/m ²		
<18.5	1.87 (1.42 to 2.47)	1.89 (1.40 to 2.54)
18.5 to 24.9	1	1
≥25	0.87 (0.67 to 1.14)	0.94 (0.70 to 1.26)
Haemoglobin, g/dL		
≤9	1.63 (1.28 to 2.08)	1.43 (1.09 to 1.87)
≥10	1	1
ALT, U/L		
≤42	1	1
≥43	1.24 (1.01 to 1.54)	1.03 (0.80 to 1.33)
Creatinine, μmol/L		
≤120	1	1
≥121	1.67 (1.33 to 2.09)	1.77 (1.35 to 2.32)
NRTI		
TDF	1	1
AZT	1.29 (0.78 to 2.12)	1.03 (0.47 to 2.26)
ABC	1.12 (0.42 to 3.01)	0.95 (0.34 to 2.67)
NNRTI		
EFV	1	1
NVP	1.25 (0.76 to 2.07)	1.42 (0.65 to 3.13)
Phone availability		
No	1	1
Yes	0.80 (0.57 to 1.12)	1.10 (0.76 to 1.60)

ABC, abacavir; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AZT, zidovudine; BMI, body mass index; CI, confidence interval; EFV, efavirenz; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

^a The proportional hazard assumption was satisfied. The flexible parametric model had three internal knots;

^b period-1 is the WHO 2010 (from October 2014 to October 2015) and period-2 is the WHO 2013 (from November 2015 onwards) ART initiation guideline implementation period as followed under standard of care;

^c secondary healthcare: ART outpatient departments in one health centre (with inpatient capacity) in Treat-All and ART outpatient departments in one hospital in standard of care;

^d this is the time from HIV diagnosis to ART initiation;

^e this is the time from facility-based HIV care enrolment to ART initiation.

Table 4. Predictors of the unfavourable outcome for patients initiated on first-line ART under Treat-All and standard of care

	Treat-All (n = 1888)		SOC (n = 1282)	
	Univariate analysis	Multivariate analysis ^a	Univariate analysis	Multivariate analysis ^b
	HR (95% CI)	aHR (95% CI)	HR (95% CI)	aHR (95% CI)
Implementation period ^c				
Period-1	1	1	1	1
Period-2	1.34 (1.12 to 1.62)	1.12 (0.92 to 1.36)	0.70 (0.55 to 0.91)	0.71 (0.54 to 0.92)
Facility				
PHC	1	1	1	1
SHC ^d	0.93 (0.78 to 1.11)	0.87 (0.72 to 1.05)	1.01 (0.81 to 1.28)	0.94 (0.72 to 1.23)
Time since HIV diagnosis ^a				
≥90 days	1	1	1	1
1 to 89 days	1.51 (1.22 to 1.85)	1.12 (0.86 to 1.46)	1.72 (1.33 to 2.23)	1.05 (0.74 to 1.48)
Same day	1.76 (1.39 to 2.23)	0.98 (0.73 to 1.30)	2.52 (1.83 to 3.46)	0.92 (0.59 to 1.44)
Time since HIV care enrolment ^e				
≥90 days	1	1	1	1
1 to 89 days	1.99 (1.47 to 2.69)	1.53 (1.02 to 2.30)	2.29 (1.62 to 3.24)	2.07 (1.30 to 3.31)
Same day	2.62 (1.95 to 3.52)	2.08 (1.42 to 3.06)	3.71 (2.59 to 5.32)	3.11 (1.91 to 5.05)
Sex				
Men	1	1	1	1
Women	1.25 (1.03 to 1.52)	1.14 (0.90 to 1.45)	1.18 (0.92 to 1.50)	1.03 (0.76 to 1.39)
Pregnancy				
No	1	1	1	1
Yes	1.62 (1.36 to 1.94)	1.37 (1.10 to 1.71)	1.51 (1.19 to 1.93)	1.21 (0.88 to 1.68)
Age at HIV care enrolment, years				
16 to 24	1.62 (1.35 to 1.95)	1.32 (1.08 to 1.63)	1.83 (1.45 to 2.32)	1.48 (1.11 to 1.98)
25 to 49	1	1	1	1
≥50	0.81 (0.58 to 1.14)	1.04 (0.72 to 1.50)	0.88 (0.56 to 1.39)	1.02 (0.64 to 1.64)
Marital status				
Married	1	1	1	1
Not married	1.70 (1.40 to 2.06)	1.48 (1.20 to 1.81)	1.62 (1.29 to 2.03)	1.39 (1.09 to 1.78)
Education				
None	1	1	1	1
Primary	1.03 (0.62 to 1.70)	1.05 (0.62 to 1.77)	1.05 (0.68 to 1.64)	1.01 (0.64 to 1.60)
Secondary	1.30 (0.80 to 2.10)	1.15 (0.68 to 1.94)	0.99 (0.65 to 1.52)	0.87 (0.56 to 1.37)
Tertiary	1.54 (0.70 to 3.40)	1.23 (0.53 to 2.83)	1.81 (0.82 to 4.00)	2.15 (0.92 to 5.04)
CD4 count, cells/mm ³				
0 to 100	1.48 (1.14 to 1.93)	1.48 (1.10 to 1.98)	1.93 (1.39 to 2.69)	1.75 (1.19 to 2.55)
101 to 200	1.15 (0.87 to 1.53)	1.19 (0.89 to 1.59)	1.43 (1.01 to 2.03)	1.36 (0.94 to 1.99)
201 to 350	1	1	1	1
351 to 500	1.05 (0.81 to 1.35)	1.16 (0.89 to 1.50)	1.18 (0.84 to 1.66)	1.37 (0.95 to 1.97)
≥501	1.04 (0.81 to 1.34)	1.18 (0.91 to 1.53)	1.44 (1.01 to 2.05)	1.31 (0.87 to 1.96)
WHO clinical stage				

I	1	1	1	1
II	0.86 (0.69 to 1.08)	0.96 (0.75 to 1.22)	1.30 (0.96 to 1.76)	1.16 (0.84 to 1.59)
III/IV	1.34 (1.07 to 1.70)	1.41 (1.05 to 1.90)	1.39 (1.04 to 1.85)	1.07 (0.74 to 1.54)
Tuberculosis				
No	1	1	1	1
Yes	0.91 (0.65 to 1.28)	0.72 (0.49 to 1.04)	1.01 (0.67 to 1.52)	0.68 (0.43 to 1.08)
BMI, kg/m ²				
<18.5	1.34 (0.98 to 1.85)	1.31 (0.93 to 1.84)	2.42 (1.72 to 3.41)	2.21 (1.52 to 3.21)
18.5 to 24.9	1	1	1	1
≥25	0.84 (0.70 to 1.01)	0.87 (0.72 to 1.07)	0.91 (0.72 to 1.16)	0.89 (0.68 to 1.16)
Haemoglobin, g/dL				
≤9	1.65 (1.34 to 2.03)	1.32 (1.06 to 1.65)	1.81 (1.38 to 2.39)	1.39 (1.02 to 1.90)
≥10	1	1	1	1
ALT, U/L				
≤42	1	1	1	1
≥43	0.84 (0.62 to 1.13)	0.86 (0.63 to 1.17)	0.78 (0.51 to 1.20)	0.81 (0.51 to 1.30)
Creatinine, μmol/L				
≤120	1	1	1	1
≥121	1.65 (0.99 to 2.75)	1.73 (1.00 to 2.99)	1.67 (0.81 to 3.42)	1.95 (0.91 to 4.17)
NRTI				
TDF	1	1	1	1
AZT	0.64 (0.24 to 1.71)	0.67 (0.17 to 2.66)	1.24 (0.82 to 1.86)	1.23 (0.64 to 2.38)
ABC	3.10 (1.00 to 9.65)	2.96 (0.89 to 9.91)	1.34 (0.50 to 3.60)	1.06 (0.38 to 2.96)
NNRTI				
EFV	1	1	1	1
NVP	0.63 (0.23 to 1.68)	0.66 (0.17 to 2.58)	1.12 (0.75 to 1.66)	1.13 (0.61 to 2.11)
Phone availability				
No	1	1	1	1
Yes	0.89 (0.69 to 1.15)	0.80 (0.61 to 1.06)	1.06 (0.69 to 1.62)	1.09 (0.70 to 1.70)

ABC, abacavir; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AZT, zidovudine; BMI, body mass index; CI, confidence interval; EFV, efavirenz; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

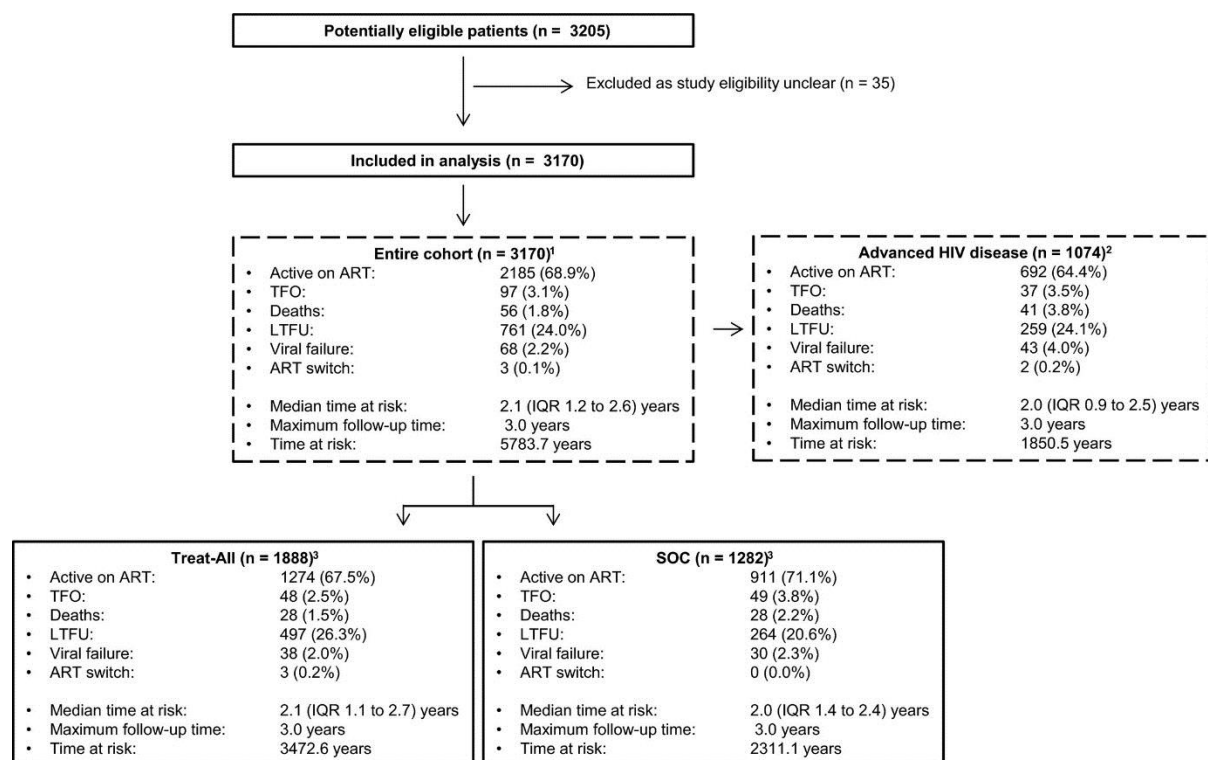
^a This is the time from HIV diagnosis to ART initiation;

^b specifications of the flexible parametric models: Treat-All: three main internal knots and two internal knots for the time-varying covariate (time since HIV care enrolment). SOC: three main internal knots and one internal knot for the time-varying covariate (CD4 cell count);

^c period-1 is the WHO 2010 (from October 2014 to October 2015) and period-2 is the WHO 2013 (from November 2015 onwards) ART initiation guideline implementation period as followed under standard of care;

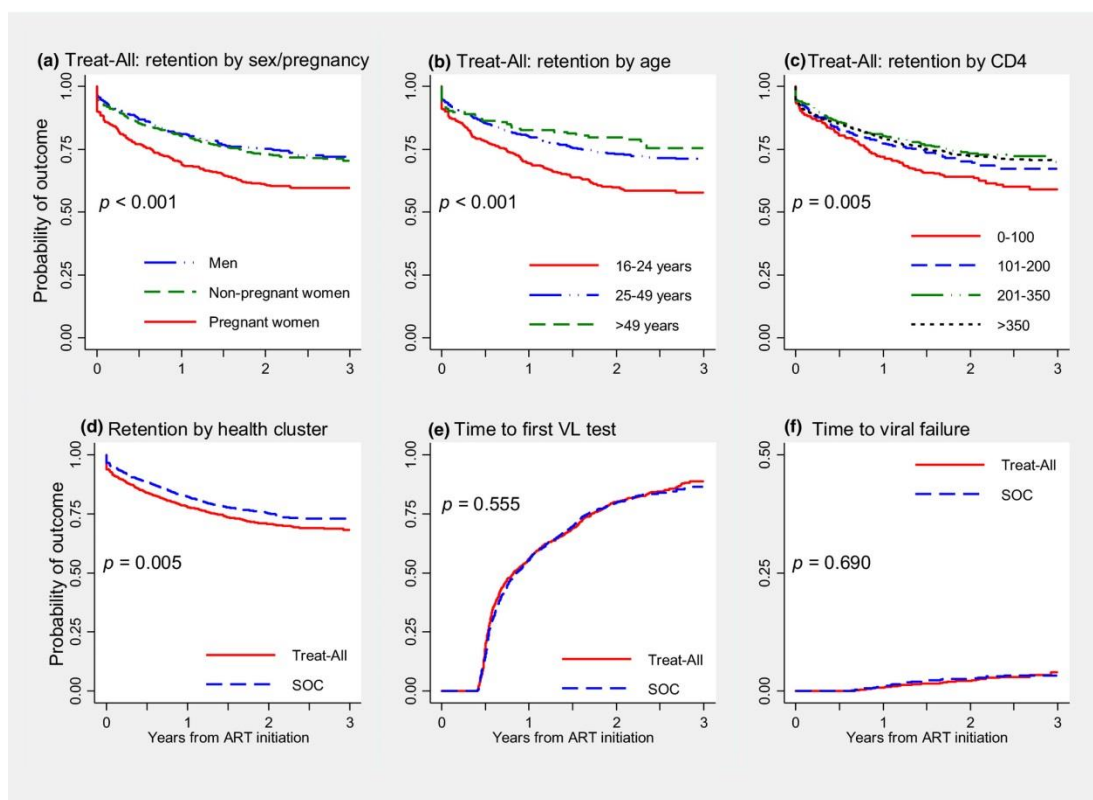
^d secondary healthcare: ART outpatient departments in one health centre (with inpatient capacity) in Treat-All and ART outpatient departments in one hospital in standard of care;

^e this is the time from facility-based HIV care enrolment to ART initiation.



¹The analysis directly compares Treat-All with SOC irrespective of CD4 and WHO clinical staging criteria. ²The analysis directly compares Treat-All with SOC restricted to patients with advanced HIV disease (CD<200 cells/mm³ and/or WHO III/IV). ³The treat-All and SOC interventions were analysed separately. ART, antiretroviral therapy; n, number; IQR, interquartile range; LTFU, loss to follow-up; SOC, standard of care; TFO, transferred out.

Figure 1: Study flow and analyses performed.



Viral load (VL) uptake and viral failure analyses: Observation time started five months after ART initiation for patients without unfavourable outcome until five months after ART initiation. Patients were right censored in case of loss to care, deaths, transfer out or without a VL test at the end of the observation period. ART, antiretroviral therapy; SOC, standard of care; VL, viral load.

Figure 2: Kaplan-Meier plots of retention on antiretroviral therapy for different baseline characteristics under Treat-All (a-c), for Treat-All versus SOC (entire cohort) (d), and for time to first viral test uptake (e) and time to viral failure (f).

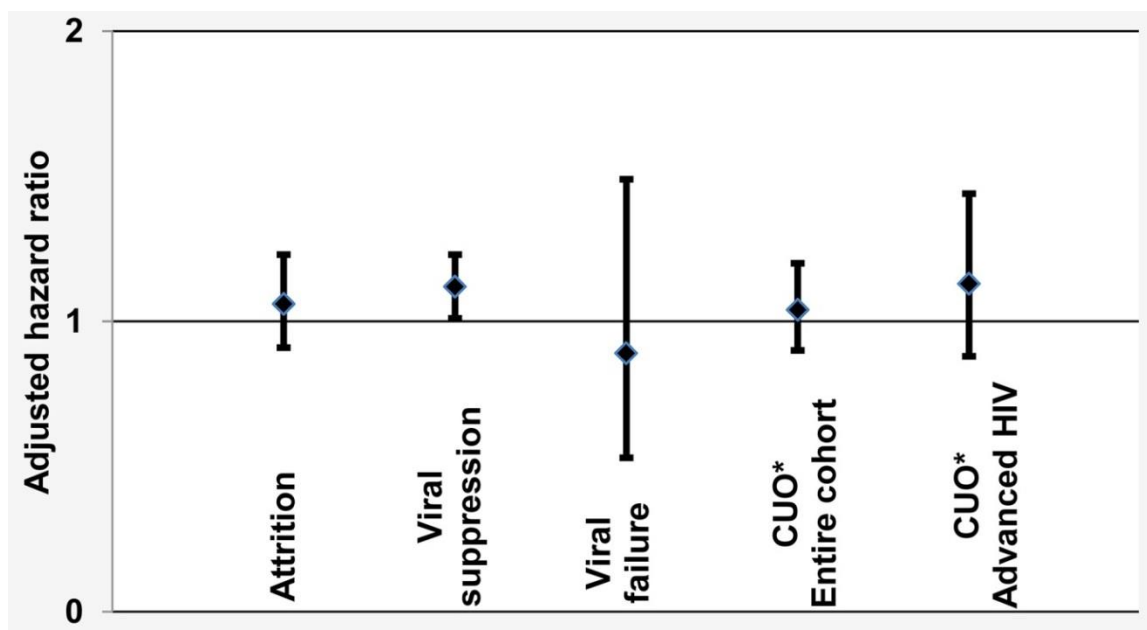
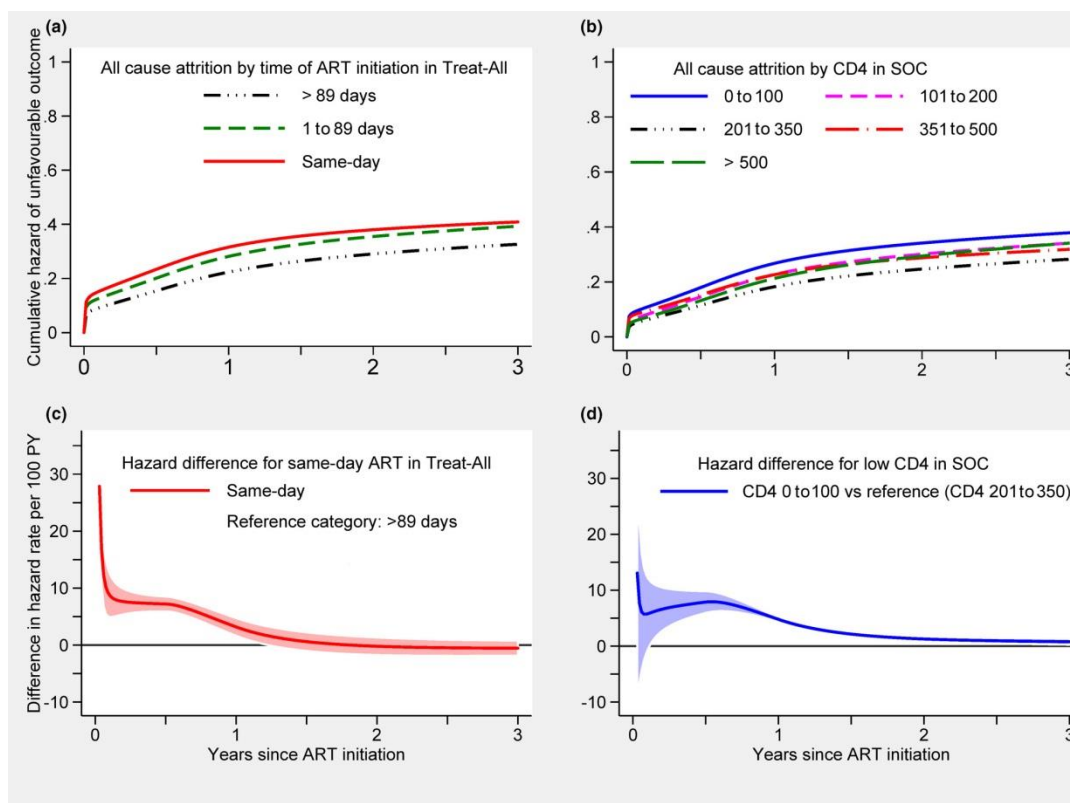


Figure 3: Summary of covariate adjusted hazard ratios of different programmatic outcomes under Treat-All when compared with standard of care (zero line). CUO, composite unfavourable outcome.



ART, antiretroviral therapy; PY, person years; SOC, standard of care.

Figure 4: Cumulative hazard and absolute difference in hazard of an unfavourable outcome by time since HIV care enrolment under Treat-All (a,c) and by CD4 cell strata under standard of care (b,d) for all patients.

SUPPORTING INFORMATION

Missing values and imputation diagnostics

Table S1. Complete and missing values for covariate and imputation procedures.

Figure S1. Trace plots of imputed data for all covariates with missing values.

Figure S2. Kernel density plots for imputed haemoglobin for all imputed datasets as an example using the *middiagplots* command in Stata.

Additional results

Table S2. Distribution of CD4 cell count and WHO clinical staging for patients with advanced IV disease under Treat-All and SOC (n = 1060).

Table S3. Kaplan-Meier estimates of retention under Treat-All for selected variables.

Table S4. Predictors of the unfavourable outcome for the entire cohort (Treat-All and SOC combined) initiated on first-line ART (n = 3170).

Figure S3. Kaplan-Meier graphs of retention under Treat-All for selected variables.

Figure S4. Absolute difference in hazard of an unfavourable outcome by TB status for the entire cohort (Treat-All and SOC combined).

Figure S5. Variations in adjusted hazard ratios of the composite unfavourable outcome comparing primary care facilities with the secondary care facility under Treat-All (facility 1) and under standard of care (facility 10).

MISSING VALUES AND IMPUTATION DIAGNOSTICS

Table S1. Complete and missing values for covariate and imputation procedures.

	Complete observations (n)	Missing values (%)
Time since HIV diagnosis	3155	0.5%
Pregnancy	3154	0.5%
Marital status	3125	1.4%
Education	2715	14.4%
CD4 count	3075	3.0%
WHO clinical stage	3154	0.5%
BMI	2971	6.3%
Haemoglobin	2452	22.6%
ALT	2216	30.1%
Creatinine	2516	20.6%
Phone availability	3137	1.0%

ALT, alanine aminotransferase; BMI, body mass index; WHO, World Health Organization.

Missing values were assumed to be missing at random. Multivariate imputation by chained equations was used, as implemented in Stata 14.1., to impute missing values in 20 datasets, using predictive mean matching for continuous variables, ordered logistic regression for ordinal variables, multinomial logistic regression for nominal variables and logistic regression for binary variables.²⁶¹ Imputation diagnostic was performed after imputation by plotting trace plots and mdiagplots.²⁶²

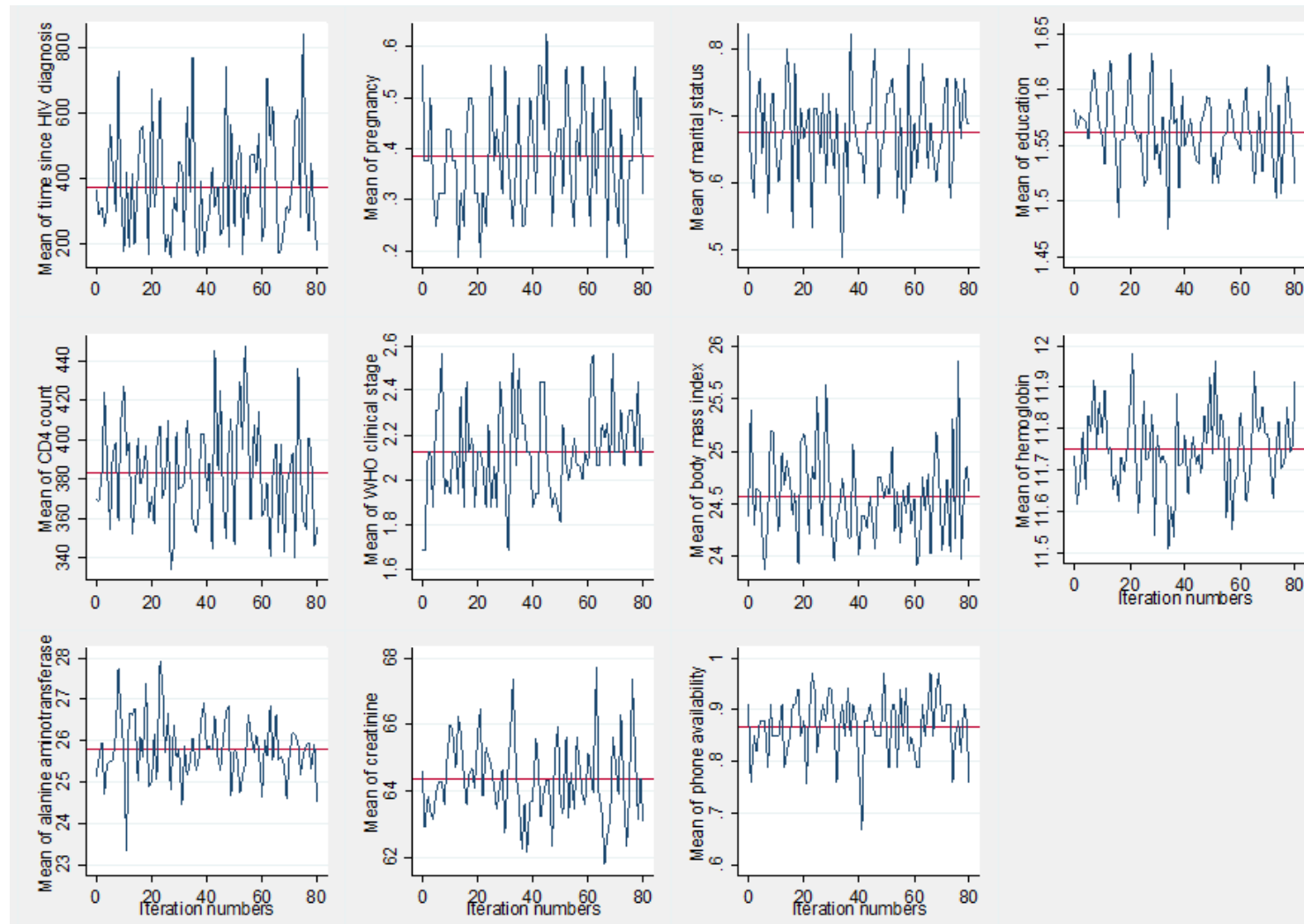


Figure S1. Trace plots of imputed data for all covariates with missing values.

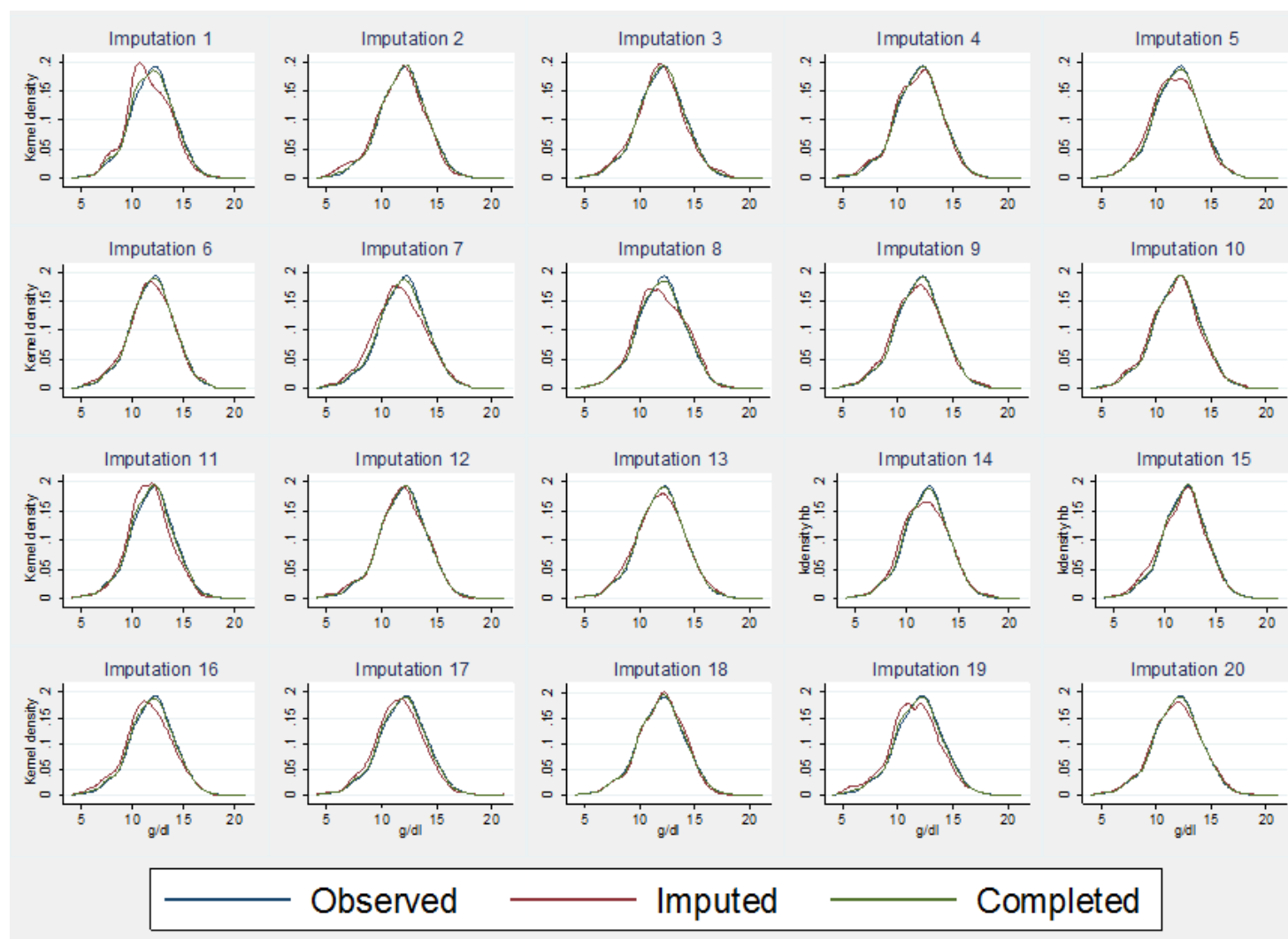


Figure S2. Kernel density plots for imputed haemoglobin for all imputed datasets as an example using the `midplots` command in Stata.

ADDITIONAL RESULTS

Table S2: Distribution of CD4 cell count and WHO clinical staging for patients with advanced HIV disease under Treat-All and SOC (n=1060).

		CD4 cell count in cells/mm3				
		0–100	101–200	201–350	351–500	≥501
WHO	I	152 (32.7)	285 (60.6)	0 (0)	0 (0)	0 (0)
clinical	II	113 (24.3)	92 (19.6)	0 (0)	0 (0)	0 (0)
staging	III/IV	200 (43.0)	93 (19.8)	68 (100)	29 (100)	28 (100)

Advanced HIV disease is defined as CD4 <200 cells/mm3 and/or WHO III/IV clinical staging.

Patients with missing CD4 cell count and/or WHO clinical staging are not presented in the table (n=14).

Table S3: Kaplan–Meier estimates of retention under Treat-All for selected variables.

	6 months	12 months	24 months	36 months
Sex-pregnancy status				
Men	87 (84 to 90)	81 (77 to 84)	75 (71 to 79)	72 (68 to 76)
Non-pregnant women	85 (83 to 87)	80 (78 to 83)	73 (70 to 76)	70 (67 to 74)
Pregnant women	77 (73 to 81)	69 (64 to 73)	61 (56 to 65)	60 (55 to 64)
Age at HIV care enrolment, years				
16–24	78 (74 to 82)	69 (65 to 73)	60 (55 to 64)	58 (53 to 63)
25–49	85 (83 to 87)	80 (78 to 82)	73 (71 to 75)	71 (68 to 73)
≥50	86 (80 to 91)	82 (76 to 88)	80 (73 to 85)	76 (68 to 82)
CD4 count, cells/mm ³				
0–100	80 (75 to 85)	72 (66 to 77)	64 (58 to 70)	59 (52 to 65)
101–200	83 (78 to 87)	77 (72 to 82)	70 (64 to 75)	67 (61 to 73)
201–350	86 (82 to 89)	80 (76 to 84)	73 (69 to 77)	70 (63 to 76)
≥351	85 (83 to 87)	79 (76 to 82)	72 (69 to 75)	71 (68 to 74)

Table S4: Predictors of the unfavourable outcome for the entire cohort (Treat-All and SOC combined) initiated on first-line ART (n = 3170).

	Univariate analysis		Multivariate analysis ⁵	
	HR	95% CI	aHR	95% CI
Health zone				
SOC	1		1	
Treat-All	1.21	(1.06 to 1.39)	1.04	(0.90 to 1.20)
Implementation period¹				
Period-1	1		1	
Period-2	1.02	(0.88 to 1.18)	0.93	(0.80 to 1.08)
Facility				
PHC	1		1	
SHC ²	0.96	(0.84 to 1.10)	0.88	(0.76 to 1.03)
Time since HIV diagnosis³				
≥90 days	1		1	
1–89 days	1.60	(1.36 to 1.88)	1.10	(0.89 to 1.35)
Same day	2.03	(1.68 to 2.45)	0.95	(0.75 to 1.21)
Time since HIV care enrolment⁴				
≥90 days	1		1	
1–89 days	2.13	(1.69 to 2.67)	1.74	(1.29 to 2.33)
Same day	3.03	(2.42 to 3.80)	2.38	(1.79 to 3.17)
Sex				
Men	1		1	
Women	1.24	(1.06 to 1.44)	1.10	(0.91 to 1.32)
Pregnancy				
No	1		1	
Yes	1.59	(1.37 to 1.83)	1.33	(1.12 to 1.59)
Age at HIV care enrolment, years				
16–24	1.69	(1.46 to 1.96)	1.36	(1.15 to 1.61)
25–49	1		1	
≥50	0.84	(0.64 to 1.10)	0.99	(0.75 to 1.32)
Marital status				
Married	1		1	
Not married	1.69	(1.46 to 1.96)	1.44	(1.23 to 1.68)
Education				
None	1		1	
Primary	1.04	(0.75 to 1.45)	1.00	(0.71 to 1.41)
Secondary	1.19	(0.87 to 1.63)	1.00	(0.71 to 1.40)
Tertiary	1.65	(0.95 to 2.87)	1.47	(0.83 to 2.63)
CD4 count, cells/mm³				
0–100	1.67	(1.36 to 2.05)	1.57	(1.25 to 1.98)
101–200	1.27	(1.02 to 1.59)	1.27	(1.01 to 1.59)
201–350	1		1	
351–500	1.12	(0.92 to 1.38)	1.21	(0.98 to 1.48)

≥501	1.21	(0.98 to 1.48)	1.22	(0.99 to 1.52)
WHO clinical stage				
I	1		1	
II	1.00	(0.84 to 1.20)	1.02	(0.84 to 1.23)
III/IV	1.35	(1.12 to 1.61)	1.28	(1.02 to 1.61)
Tuberculosis				
No	1		1	
Yes	0.94	(0.73 to 1.22)	0.62	(0.45 to 0.84)
BMI, kg/m ²				
<18.5	1.71	(1.36 to 2.15)	1.63	(1.27 to 2.09)
18.5–24.9	1		1	
≥25	0.87	(0.76 to 1.01)	0.89	(0.76 to 1.04)
Haemoglobin, g/dL				
≤9	1.72	(1.46 to 2.03)	1.34	(1.12 to 1.61)
≥10	1		1	
ALT, U/L				
≤42	1		1	
≥43	0.81	(0.64 to 1.03)	0.85	(0.66 to 1.10)
Creatinine, μmol/L				
≤120	1		1	
≥121	1.65	(1.08 to 2.52)	1.62	(1.04 to 2.52)
NRTI				
TDF	1		1	
AZT	1.01	(0.70 to 1.46)	1.08	(0.61 to 1.92)
ABC	1.63	(0.78 to 3.44)	1.52	(0.70 to 3.26)
NNRTI				
EFV	1		1	
NVP	0.93	(0.65 to 1.33)	1.04	(0.60 to 1.80)
Phone availability				
No	1		1	
Yes	0.92	(0.74 to 1.14)	0.88	(0.70 to 1.10)

ABC, abacavir; aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AZT, zidovudine; BMI, body mass index; CI, confidence interval; EFV, efavirenz; HR, hazard ratio; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PHC, primary healthcare level; SHC, secondary healthcare level; SOC, standard of care; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

¹ Period-1 is the WHO 2010 (from October 2014 to October 2015) and period-2 is the WHO 2013 (from November 2015 onwards) ART initiation guideline implementation period as followed under standard of care.

² Secondary healthcare: ART outpatient departments in one health centre (with inpatient capacity) in Treat-All and ART outpatient departments in one hospital in standard of care.

³ This is the time from HIV diagnosis to ART initiation.

⁴ This is the time from facility-based HIV care enrolment to ART initiation.⁵ The flexible parametric model had four internal knots and one internal knot for the time-varying covariate (TB case).

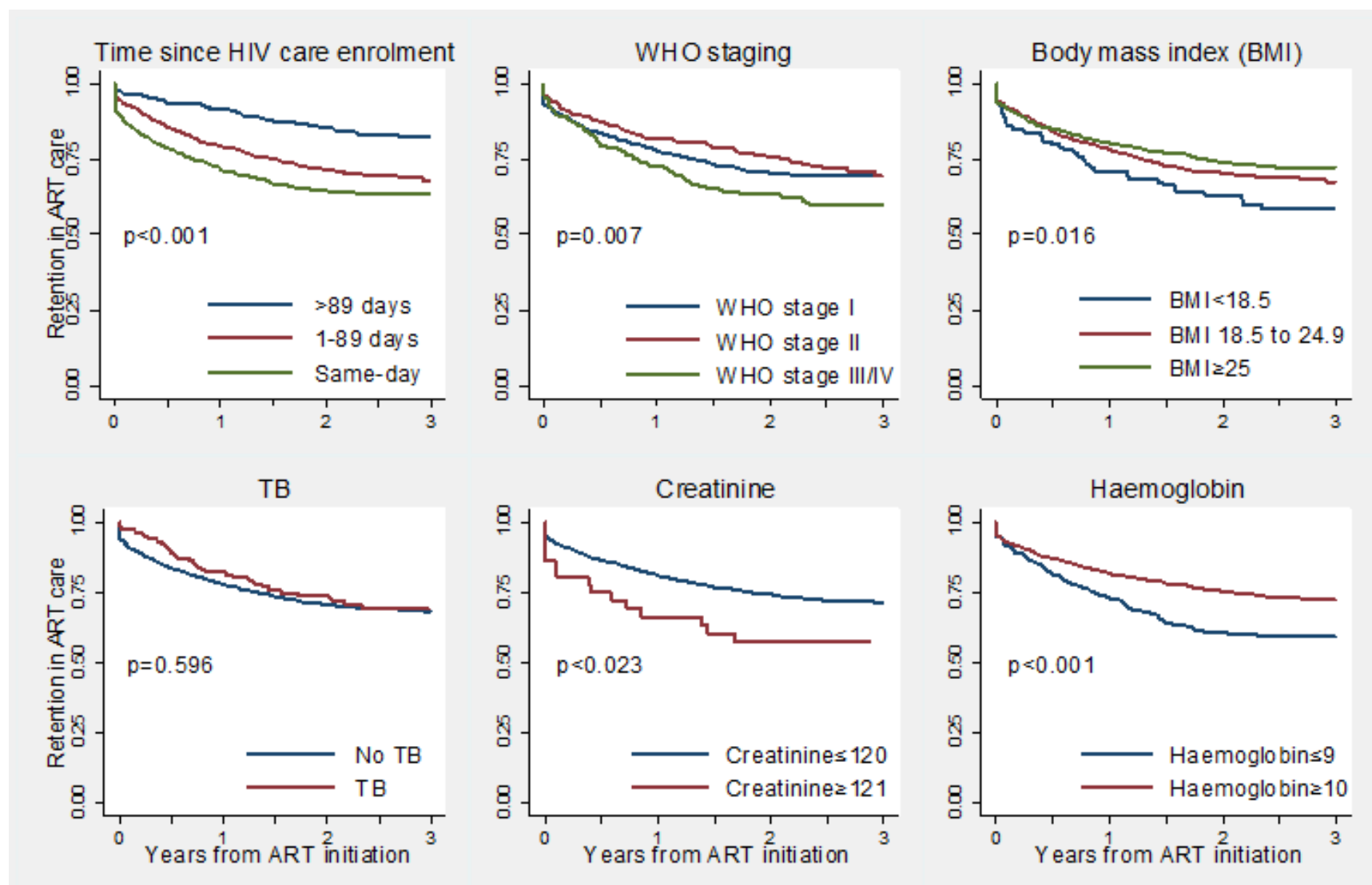
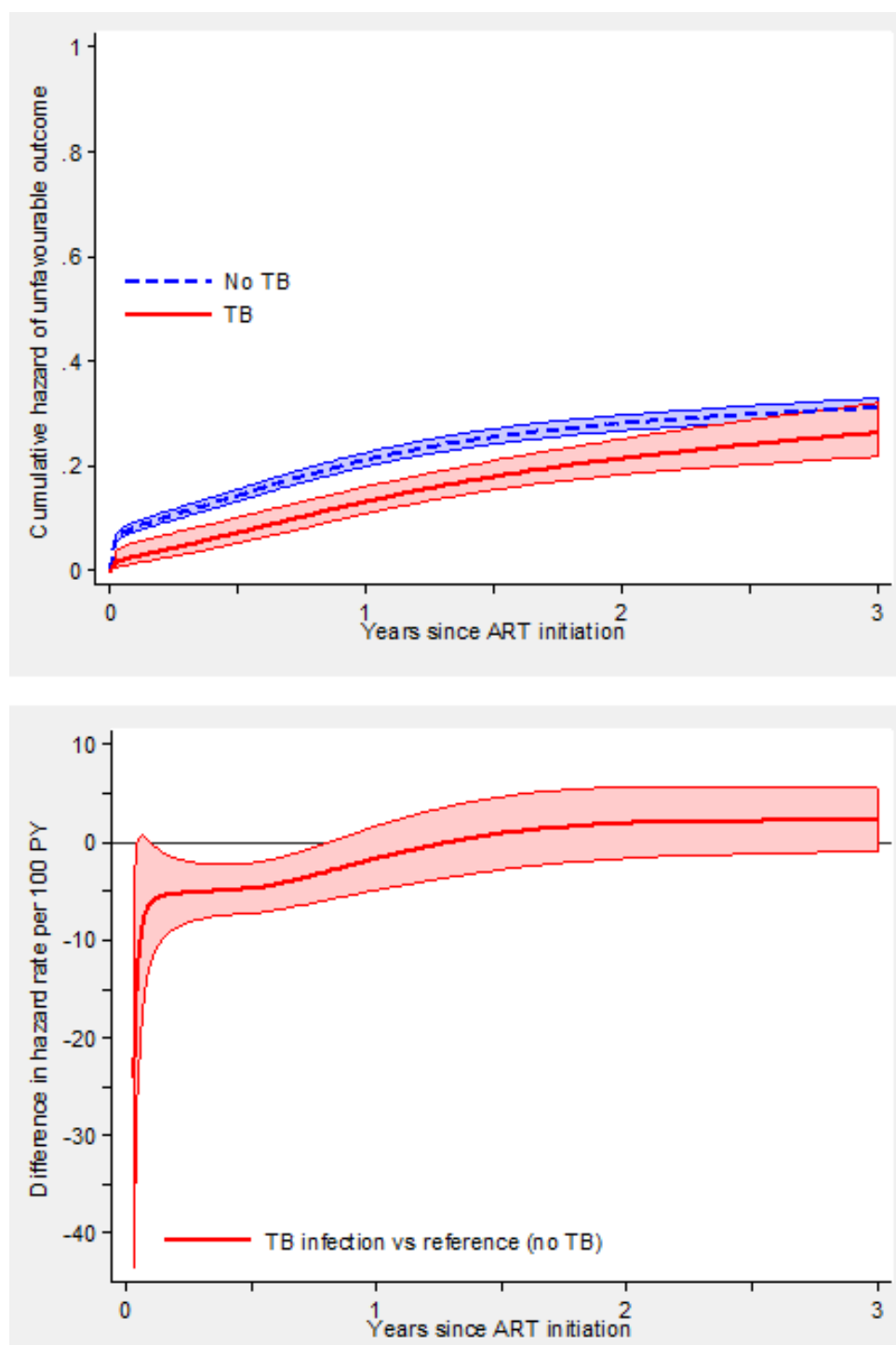


Figure S3. Kaplan–Meier graphs of retention under Treat-All for selected variables.



ART, antiretroviral therapy; PY, person years.

The effect of baseline TB varied over time, with lower hazard of an unfavourable outcome during the first 8 months of TB treatment and similar hazard thereafter.

Figure S4. Absolute difference in hazard of an unfavourable outcome by TB status for the entire cohort (Treat-All and SOC combined).

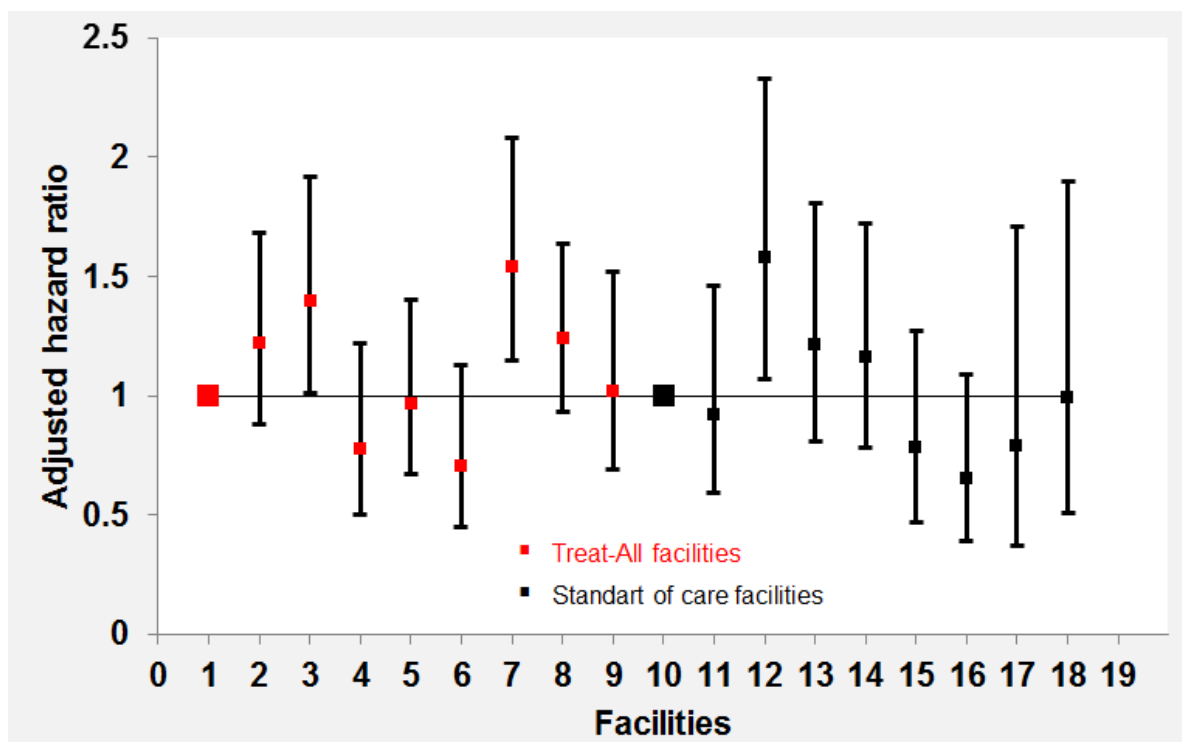


Figure S5: Variations in adjusted hazard ratios of the composite unfavourable outcome comparing primary care facilities with the secondary care facility under Treat-All (facility 1) and under standard of care (facility 10).

RESULTS FOR OBJECTIVE 4

The impact of same-day antiretroviral therapy initiation under the WHO Treat-All policy

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Paper overview

This study uses data from a prospective cohort of patients offered and initiated on first-line ART under the Treat-All approach in Nhlanguano health zones in the Shiselweni region in Eswatini, as described under Result-2 and Result-3. From the causal perspective, this study compares treatment outcomes between patients who initiated ART on the same day as facility-based HIV care enrolment and those with ART initiation between 1 to 14 days thereafter. It also describes predictors of same-day ART initiation in this public sector setting.

Significance of the paper

At the time of the inception of this study, it was unclear how much more quickly ART should be initiated under the Treat-All approach. Thereafter, WHO provided guidance on rapid ART initiation within 7 days of HIV diagnosis with the possibility of same-day ART initiation for patients ready to start therapy immediately after HIV diagnosis. Because this setting had been applying the Treat-All approach several years before it was recommended by WHO, it provided a unique opportunity to understand how same-day ART initiation is practised under Treat-All and the effect on treatment outcomes. This study has the potential to detect benefits and risks of same-day ART initiation in the context of rapid scale-up of Treat-All, thus informing ongoing roll-out of this policy in RLS. Notably, while the previous cohort analysis of Result-3 already suggested a possible time-varying association

of same-day ART with the composite unfavourable treatment outcome, this paper investigates the effect of same-day ART from the causal perspective.

Candidate`s contributions

The candidate in collaboration with MS and AB designed the analysis plan. The candidate established the cohort and was involved in data acquisition. The candidate acquired and processed all data, performed all analyses apart of TMLE (performed by MS). The candidate wrote the first draft of the manuscript, integrated comments from co-authors, and submitted the manuscript for peer review.

ABSTRACT

Rapid initiation of antiretroviral therapy (ART) is recommended for people living with HIV, with the option to start treatment on the day of diagnosis (same-day-ART). However, the effect of same-day-ART remains unknown in realistic public sector settings. We established a cohort of ≥ 16 -year-old patients who initiated first-line ART under Treat-All in Nhlanguano (Eswatini) between 2014-2016, either on the day of HIV care enrolment (same-day-ART) or 1-14 days thereafter (early-ART). Directed acyclic graphs, flexible parametric survival analysis and targeted maximum likelihood estimation (TMLE) were used to estimate the effect of same-day-ART initiation on the composite unfavourable treatment outcome (loss to follow-up; death; viral failure). Of 1328 patients, 839 (63.2%) initiated same-day ART. The adjusted hazard ratio of the unfavourable outcome was increased by 1.48 (95% CI:1.16-1.89) for same-day-ART compared with early-ART. TMLE suggested that after 1 year, 28.9% of patients would experience the unfavourable outcome under same-day-ART compared with 21.2% under early-ART (difference: 7.7%; 1.3-14.1%). This estimate was driven by loss to follow-up and varied over time, with a higher hazard during the first year after HIV care enrolment and a similar hazard thereafter. We found an increased risk with same-day-ART. A limitation was possible silent transfers that were not captured.

BACKGROUND

The World Health Organization policy for Treat-All recommends lifelong antiretroviral therapy (ART) for all people living with HIV at the time of diagnosis, irrespective of immunological criteria.¹⁶ Despite high uptake of this policy in Africa,²²⁶ of 20.6 million people living with HIV in Eastern and Southern Africa, treatment coverage (67%) and viral suppression (58%) remained below The Joint United Nations Programme on HIV/AIDS targets in 2018, with an additional 3.0 million people living with HIV needing to access treatment and achieve viral suppression.^{5,228}

Accelerated ART initiation has been proposed to overcome some of these gaps.^{263,264} A systematic review found that ART initiation on the same day as HIV diagnosis or the day of treatment eligibility improved treatment uptake, HIV care retention and viral suppression.²¹⁰ Based on this evidence, the World Health Organization released guidelines in 2017 recommending ART initiation within 7 days of HIV diagnosis (rapid ART), with the possibility of initiating treatment on the same day as HIV diagnosis (same-day ART) for patients ready to start.²⁰⁹

As HIV programmes allow for accelerated ART initiation under Treat-All and most treatment initiations already occur quickly, within 14–30 days after HIV diagnosis or care enrolment,^{227,237–239,265} the question increasingly shifts to how much faster ART can be initiated in routine resource-limited settings. This question has also been raised recently in public HIV treatment programmes in high-income countries.²⁶⁶ Concerns were specifically raised about the feasibility of same-day ART initiation in realistic public sector settings because of lack of real-world evidence and practical limitations. Firstly, evidence of the benefits of accelerated ART mainly originated from randomized trials.²¹⁰ These trials often applied additional procedures not routinely available in resource-limited settings (e.g. accelerated counselling protocols, treatment readiness survey), used treatment eligibility criteria in use before Treat-All, restricted ART interventions to specific patient groups (e.g. non-pregnant adults) or few facilities, or applied different definitions of same-day ART.^{69,141,210,243} In contrast, benefits of same-day ART initiation remained uncertain in observational studies.²¹⁰ Secondly, real-world effectiveness may be compromised because of pre-existing constraints in the public sector, such as resource limitation (e.g. human resources), overburdened health facilities and suboptimal quality of care.^{57,104,107,109}

Treat-All has been implemented in a public sector setting in southern Eswatini (formerly Swaziland) since 2014, with same-day ART initiation increasingly practised.²³⁸ Therefore, this setting provides a unique opportunity to better understand how much faster ART should be started in a context where it is already started quickly. We aimed to answer the following questions: 1) how is same-day ART being implemented in a public sector programme applying the Treat-All approach, and 2) what is the effect of same-day ART initiation compared with early ART initiation (1–14 days after HIV care enrolment) on treatment outcomes for patients starting treatment quickly.

METHODS

Setting

Details of the study setting were described elsewhere.^{215,238} In brief, Eswatini has an HIV prevalence of 32% among adults aged 18–49 years, and annual tuberculosis incidence was 308 cases per 100,000 population with 75% HIV co-infection in 2017.^{173,267} Treat-All was piloted in eight primary and one secondary care public sector facilities in the predominantly rural Nhlanguano health zone of the Shiselweni region. Other facilities of the region were excluded from this study as they applied the CD4 350 and 500 cells/mm³ treatment eligibility thresholds as recommended by national treatment guidelines.²³⁸ ART initiation was possible in the absence of baseline CD4 cell counts and biochemistry results.²¹⁸ ART initiation on the day of facility-based HIV care enrolment was policy for pregnant/lactating women and encouraged for other patients in the absence of (presumptive) opportunistic infections.^{185,218} Without specific standard operating procedures in place for same-day ART initiation under Treat-All at that time, the clinician decided on the timing of ART initiation after clinical and psychological readiness assessment, the patient's perceived readiness as well as other clinical considerations. As HIV care registration and ART initiation were performed by facility-based clinicians, same-day ART initiation (on the day of HIV diagnosis) was in practice infeasible for HIV-positive patients transferred in from non-HIV care facilities and community HIV testing sites. Led by lay counsellors, one group-counselling session and at least one individual-counselling session were recommended, and both could happen on the same day as HIV diagnosis, care enrolment and ART initiation. Adherence counselling support continued thereafter as per patients' needs. Routine follow-up visits were scheduled at 2, 4 and 12 weeks after ART initiation and 3-monthly thereafter. Routine viral load monitoring was performed 6 and 12 months after ART initiation and annually thereafter. Patients with viral loads >1000 copies/mL received enhanced adherence counselling over 3 months and were switched to second-line ART in case of viral failure (two consecutive viral load measurements >1000 copies/mL).¹⁴⁰ Patients who missed their clinical appointment for medication refills received phonic defaulter tracing with the possibility of home visits.

Study design

This is a nested, retrospectively established cohort of adults ≥ 16 years old initiating standard first-line ART under the Treat-All programmatic approach in Nhlanguano health zone either on the day of facility-based HIV care enrolment (same-day ART) or 1–14 days after HIV care enrolment (early ART), between 10 October 2014 and 31 March 2016. A standard first-line treatment regimen contained lamivudine, and tenofovir or zidovudine, and efavirenz or nevirapine. A patient was considered enrolled into HIV care and initiated on ART if a paper and/or electronic patient record was created. In this setting, we considered early ART as a relevant comparison group to same-day ART because this was the national policy at the time of the study.

Analyses and main definitions

Analyses were performed with Stata 14.1 and R. Firstly, baseline characteristics were described with frequency statistics and proportions. The Pearson's chi-squared and Mann-Whitney U test were used to compare differences in categorical and continuous variables. We used multiple imputation by chained equations¹⁹⁵ to deal with missing values of the measured pre-treatment variables (see Web Table 1).

Secondly, we assessed predictors of same-day ART initiation compared with early ART by using multivariable Poisson regression models including all variables measured before treatment initiation (listed in Table 1 and Figure 1).

Thirdly, we emulated a Target Trial^{268–270} of HIV-infected patients aged ≥ 16 years already initiated on ART within 14 days of facility-based HIV care enrolment to estimate the causal effect²⁷¹ of same-day ART (vs early ART) on the composite unfavourable treatment outcome of death, loss to follow-up (LTFU), viral failure and treatment switching to a second-line ART in the absence of documented viral failure. Time zero was the date of ART initiation because some captured outcomes (viral failure, treatment switch) could only have happened after ART initiation and the outcomes of death and LTFU before ART initiation were not well defined (e.g. pre-treatment visits were not recorded after care enrolment, which may lead to possible misclassification of deaths as LTFU). Therefore, our target population excluded patients starting treatment >14 days after care enrolment and patients never starting treatment for any reason (including deaths within 14 days of care enrolment).

Viral failure was defined as two consecutive viral load measurements >1000 copies/mL measured at least 5 months after ART initiation and 1.5 months apart. The composite endpoint was chosen to reflect the goals of Treat-All and The Joint United Nations Programme on HIV/AIDS 90-90-90 cascade targets of keeping patients on effective (virally suppressed) ART and reduce transmission of HIV. Minimum follow-up time before database closure was 7 months. Patients were censored at the last clinic visit date when a transfer out was recorded by the clinician and at database closure (31 October 2017). LTFU was defined as no-show to the facility for ≥ 6 months measured at the last clinic visit. Lacking local evidence, no assumptions were made about possible reasons of LTFU such as undocumented deaths, silent transfer out, unstructured treatment interruptions and actual disengagement from care.^{256,257,272}

We summarized our assumptions about the data-generating process in a directed acyclic graph (Figure 1); see Web Appendix 1 for a detailed explanation. Briefly, treatment assignment is based on various factors, including pregnancy, clinician's preference in each facility, temporal trends, the patient's perceived readiness and the impact of counselling, and clinical assessment including CD4 count and co-morbidities. Timing of treatment initiation may affect the composite outcome in different ways: firstly, biologically, if treatment delay would affect viral suppression and thus the development of co-

morbidities and negative outcomes; secondly, earlier treatment may have a psychological impact on patients. If they do not feel ready for ART and are possibly coerced into treatment, adherence to therapy may be suboptimal and treatment may be interrupted. The directed acyclic graph shows that inclusion of all visualized pre-treatment variables, and exclusion of all post-treatment variables (e.g. suppression during follow-up, ART regimen), is sufficient to identify the desired total causal effect (because all back-door paths are blocked and no mediators are being conditioned on).²⁷³ However, as treatment readiness and counselling, as well as some baseline co-morbidities (e.g. cryptococcal meningitis), are unmeasured, some remaining unmeasured confounding may persist in our analysis.

Based on the above assumptions, we included all measured pre-treatment variables in an adjusted flexible parametric survival analysis (Royston-Parmar models)^{196,197} to estimate the effect of same-day ART initiation on the hazard of the unfavourable outcome. We visualized the results of this model using averaged failure and hazard difference curves to compare the time to the composite unfavourable outcome between same-day and early ART.^{196,197} We allowed the effect of same-day ART to vary with respect to time.

Then, we used targeted maximum likelihood estimation (TMLE)^{274,275} to estimate the probability of experiencing the unfavourable outcome 12 months, 18 months and 24 months after ART initiation under same-day and early ART, and under no censoring, using all measured pre-treatment variables. TMLE requires estimation of the expected outcome, treatment assignment and censoring processes, given the measured covariates. We facilitated this step using extensive super learning to avoid model mis-specification (see Web Table 2 and 3).^{276,277}

Several supplementary analyses were performed. We compared same-day ART with rapid ART initiation defined as ART initiation 1–7 days after HIV care enrolment (rather than early ART) as per World Health Organization recommendations. Then, the composite unfavourable outcome was decomposed to all-cause attrition (death and LTFU combined). Finally, time zero was defined as the date of HIV care enrolment (instead of ART initiation).

Ethics

This retrospective analysis was nested within a prospective cohort study assessing the feasibility of Treat-All²³⁸ and was approved by the Médecins Sans Frontières ethics review board, the Eswatini National Health Research Review Board and the Human Research Ethics Committee of the University of Cape Town.

RESULTS

Figure 2 shows the study flow chart. Of 1899 patients initiating ART, 1341 (70.6%) started treatment within 14 days after facility-based HIV care enrolment. Thirteen (1.0%) patients were removed from

the analysis, as study eligibility remained unclear. Of 1328 patients remaining, 839 (63.2%) started ART on the same day as HIV care enrolment.

Predictors of same-day ART initiation

Table 1 shows baseline characteristics of patients starting ART same-day and early. In multivariable analysis (Table 1), the risk of same-day ART initiation was higher for 6 of 8 primary care clinics (vs secondary care clinic) with adjusted risk ratios (aRR) ranging from 1.45 to 2.31, patients diagnosed ≥ 90 days before facility-based HIV care enrolment (aRR 1.38; 1.01–1.88) (vs diagnosed on the same day as HIV care enrolment), and pregnant women (aRR 1.37; 1.15–1.62) (vs non-pregnant women).

Same-day ART initiation

Descriptive analyses

Crude decomposed outcomes and censoring due to transfer out are presented in Figure 2, and Figure 3. The crude cumulative hazard of remaining on effective first-line ART (not experiencing the composite unfavourable outcome) was lower for same-day ART (vs early ART) during the first 2 years after ART initiation but comparable at 3 years (see Web Figure 1). For same-day ART, it was 72% (95% confidence interval [CI]: 68–74%) (vs early ART: 81%; 77–84%) at 1 year and 62% (59–66%) (vs early ART: 69%; 63–73%) at 3 years. The likelihood of experiencing the unfavourable outcome was high immediately after ART initiation, with 3.7% (95% CI: 2.3–5.8%) and 8.7% (95% CI: 7.0–10.8%) of patients under early and same-day ART never returning to care.

Relative impact of same-day ART on the unfavourable outcome

Multiple imputation of missing values was successful, with good convergence of the imputation algorithm and good other diagnostics (see Web Figure 2 and 3).

The hazard of the unfavourable treatment outcome was increased for same day-ART by 39% in univariate analysis (crude hazard ratio [cHR] 1.39; 95% CI: 1.14–1.70) and by 48% in multivariable analysis (adjusted hazard ratio [aHR] 1.48; 95% CI: 1.16–1.89) (Figure 4a) (see Web Table 4 for the full model). The estimates varied over time, with a higher hazard during the first year after ART initiation and a similar hazard thereafter (Figure 4b).

Absolute difference in unfavourable outcomes comparing same-day ART with early ART

Using TMLE, we estimated that 28.9% (95% CI: 25.4–32.3%) of patients would have experienced an unfavourable outcome after 12 months if they had received same-day ART compared with 21.2% (15.8–26.6%) if they had received early ART, which corresponds to a difference of 7.7% (1.3–14.1%) and an risk ratio of 1.36 (1.03–1.81) (see Table 2). Differences between the two treatment strategies were also observed for 2 and 3 years of follow-up, though less pronounced than in the first year (see

Table 2). Diagnostics of the TMLE approach were satisfactory, with no truncation of estimated probabilities of treatment assignment, small maximum clever covariates and a broad selection of learning algorithms (see Web Table 2 and 3).

Supplementary analyses

Table 3 presents crude and adjusted hazard ratios for different assumptions. Changing time zero to the date of care enrolment, changing the unfavourable composite outcome to all-cause attrition and comparing same-day ART with rapid ART did not change findings overall, with adjusted hazard ratios ranging from 1.43 to 1.83.

DISCUSSION

This is to our knowledge the first study evaluating faster ART initiation in a routine programmatic HIV-care setting applying the Treat-All policy. In patients starting treatment quickly, initiating ART on the day of facility-based HIV care enrolment had inferior treatment outcomes compared with patients starting treatment 1–14 days thereafter or starting treatment within 1–7 days. The estimated effect was accrued during the first year of therapy.

Interpretation of findings

Predictors of same-day ART

The main predictors of same-day ART initiation were related to policy and facility factors. Pregnant women were associated with increased same-day ART initiation, coinciding with the same-day ART policy under the prevention of mother-to-child transmission Option B+ approach. Facility-level factors also played a role, with almost all primary care facilities providing more same-day ART than the secondary care facility. This may be because primary care facilities had point-of-care biochemistry, haemoglobin and CD4 testing available, thus making baseline results available on the same day for treatment decisions, as opposed to the secondary care facility where results often became available a few days later. Clinicians may have felt more comfortable initiating ART with CD4 cell count and biochemistry known. In addition, the one-stop-shop primary care clinics provided all HIV services at the same location whereas HIV testing and care registration were co-located in the secondary care facility. This required patients diagnosed with HIV in the outpatient department to transfer to the HIV department, thus possibly delaying care registration and ART initiation. More patients may also have had unmeasured co-morbidities at the secondary care facility, necessitating delaying ART initiation.

Patients who knew their HIV-positive status for ≥ 90 days were more likely to initiate ART on the same day. Firstly, patients may have been transferred in from community HIV testing sites and other

facilities. Given more time between testing and care enrolment, they may have come to terms with life-long therapy and therefore been ready to start same-day treatment. Secondly, treatment interruptions are frequent in routine settings,¹¹² and these patients may have been treatment interrupters re-initiating ART without disclosing prior treatment.

Lastly, clinical factors as well as social factors such as level of education and marital status appeared not to play a major role in quicker ART initiation. This may indicate that same-day ART initiation was driven by facility and health policy factors as indicated in our analysis rather than by clinical presentation of the patient, clinicians' considerations, or patients' preferences.

Same-day ART

Same-day ART initiation had a higher hazard of the unfavourable treatment outcome than early and rapid ART. Our estimated effect was time-varying, with increased hazard during the first year of treatment and similar hazards thereafter.

We provide several explanations. Firstly, same-day ART may not address patients' concerns about expedited ART initiation, and not give enough time to conceptualize lifelong therapy.^{80,278–282} This may have contributed to immediate disengagement from care after treatment initiation, with 9% of patients under same-day ART never returning for a follow-up visit.

Secondly, estimates may be affected by unmeasured confounding. Treatment readiness may predict assignment to the intervention and is also likely associated with the outcome (through the factor of adherence). In addition, we could not measure all possible baseline and time-updated co-morbidities that may predict the intervention and the outcome. For instance, cryptococcal meningitis may have been unevenly distributed in the groups and affect early death and loss to care differently.

Thirdly, the clinical tools used to assess treatment readiness may have been inappropriate to identify patients ready for same-day ART, as the very same tools were used before same-day ART initiation was an option. Contextualized screening tools for expedited ART initiation adapted to different populations (e.g. pregnant women) and settings may be needed to reliably assess patients' readiness for same-day treatment. For instance, one randomized trial used a treatment readiness survey to identify patients not ready for same-day ART initiation and excluded them from expedited treatment.¹⁴¹ In addition, training related to expedited counselling protocols and same-day ART for health workers during the early implementation period was lacking, possibly leaving health workers poorly equipped for effective implementation of same-day ART at scale. Lastly, counselling support after same-day ART initiation may have been de-prioritized in this busy public sector setting with competing activities, thus providing insufficient adherence support early during treatment.

Findings in context

The definition of same-day ART differs across studies. Definitions include treatment initiation on the day of HIV diagnosis, day of treatment eligibility, day of HIV care enrolment, or a combination of them.^{69,141,224,241–243} The same-day ART intervention group often consisted of patients initiating treatment days after the offer of same-day treatment,^{69,242,243} so that studies evaluated the intention to initiate same-day treatment rather than actual same-day treatment initiation.^{69,141,243} The offer of same-day ART was often combined with additional interventions (e.g. point-of-care CD4 and biochemistry testing),²⁸³ and restriction of the patient sample to healthier individuals¹⁴¹ and non-pregnant adults^{69,141,243} may make findings less applicable to routine public sector settings. Streamlining definitions of same-day ART initiation and clarity of what and who is evaluated are warranted.

While same-day ART initiation improves treatment uptake, it may downshift loss to care to the time of treatment.^{69,283} Treatment interruptions were already common in routine HIV programmes before the introduction of the rapid ART policy,^{112,256} and are associated with acquired drug resistance.²⁸⁴ Balancing of patient-level and public health benefits and risks (e.g. unstructured treatment interruptions) is required to make an informed health policy decision.

More emphasis may be needed on a differentiated approach to ART initiation adapted to the patient's needs, with clinical and programmatic (e.g. logistical) constraints taken into consideration, than on choosing between same-day and rapid/early ART initiation as a blanket approach. In fragile health systems, hasty low quality and possibly coerced ART initiation may occur if HIV programmes and funding organizations prioritize achieving targets related to numbers of same-day ART initiations instead of differentiated patient-centred rapid ART initiation.

Importantly, this study did not assess the impact of a policy of same-day ART initiation for all people living with HIV, as this was not feasible in our context (e.g. patients transferred in could not be offered same-day treatment), with the observational study design and available data. Thus, findings are not directly comparable to randomized trials evaluating the offer of same-day treatment to treatment-eligible patients. Our research, however, intends to estimate the risks and benefits of same-day ART initiation for patients with the ability to start treatment early. If there is a causal relationship between same-day ART and unfavourable treatment outcome, then deferral of treatment initiation should be considered for these patients. However, more research into the methods may be required to address questions of frequency, intensity, content and minimum quality of early adherence support in routine public sector settings.

Limitations and strengths

Firstly, this study assessed outcomes of patients successfully initiated on ART soon after facility-based HIV care enrolment. Restriction allowed the establishment of two potentially comparable groups in the context of an observational study design but limits direct comparison with settings where most patients initiate ART 2 weeks after care enrolment. It was beyond the scope of this study

to assess outcomes of patients starting treatment late or never, and they may differ in their characteristics and risks for an adverse outcome. By focusing only on one aspect of faster ART initiation, this study did not address the programmatic advantage of same-day ART in reaching patients otherwise defaulting before treatment. Future studies from the public sector should weigh the benefit of less pre-treatment loss with the risk of higher loss early during treatment.

Secondly, we did not account for loss between the diagnosis of HIV and care enrolment. This may have caused selection bias because only patients successfully linked to facility-based HIV care are considered. Specifically, loss between community-based HIV diagnosis and facility-based enrolment can be high,^{221,243} ranging from 10% to more than half in Eswatini.^{224,238} Intra-facility linkage in this setting may also be sub-optimal as estimated to be between 83% and 92%.^{199,224,238} Therefore, findings should not be generalized to predominantly community settings but rather to settings similar to ours where most HIV diagnosis happens at facility-level.²⁸⁵

Thirdly, patients under same-day ART never returning for refills after treatment initiation could have been silent patient-initiated (undocumented) transfers. The proportion of silent transfers ranges from 5% to 54% in patients documented as LTFU in Africa and is more pronounced in recent and larger treatment cohorts.¹⁵⁹ We did not adjust for it because of a weak physical defaulter tracing intervention in place, and the inability of linking patient records to facilities outside the intervention area. Understanding the magnitude of silent transfer under Treat-All and if it differs between same-day and early ART should be further explored to inform health policy.

Fourthly, we could not adjust for all possible confounding factors identified in the directed acyclic graph (e.g. co-morbidities and treatment readiness), possibly biasing the effect estimate in either direction.

A strength of this study is that we applied different analytical approaches, including state-of-the-art methods (e.g. TMLE), all of which concurred in their main findings. We included a wide range of patients as found in other HIV programmes implementing the Treat-All programmatic approach, so findings may be generalizable to similar settings in rural Sub-Saharan Africa. This study discussed potential shortfalls in programmatic implementation of Treat-All related to contextualized screening tools and training provided, thus drawing attention to the method and quality of implementation.

Conclusions

Facility and health policy factors were the main predictors of same-day ART initiation. Our data also suggest that same-day ART increased the risk of the composite unfavourable outcome including LTFU. However, LTFU may sometimes relate to silent transfer out, thus further research about true health outcomes of patients documented as lost to care is urgently needed.

Table 1: Baseline characteristics of patients initiated on ART under same-day and early ART, and predictors of same-day ART initiation, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Characteristic	% missing values	Baseline characteristics (n=1328)				Predictors of same-day ART (n=1328)				
		Same-day ART (n=839, 63.2%)		Early ART (n=489, 36.8%)		p-value	cRR	(95% CI)	aRR	(95% CI)
Year	0.0					<0.001				
2014		117	13.9	88	18.0		1.00	Referent	1.00	Referent
2015		552	65.8	359	73.4		1.06	0.87, 1.30	1.03	0.83, 1.27
2016		170	20.3	42	8.6		1.41	1.11, 1.78	1.20	0.93, 1.55
Timing of HIV diagnosis ^a	0.5					0.064				
Pre Treat-All		139	16.7	63	12.9		1.00	Referent	1.00	Referent
Treat-All		694	83.3	426	87.1		0.90	0.75, 1.08	1.18	0.85, 1.65
Facility	0.0					<0.001				
SHC		197	23.5	265	54.2		1.00	Referent	1.00	Referent
PHC-1		62	7.4	41	8.4		1.41	1.06, 1.88	1.45	1.07, 1.97
PHC-2		60	7.2	31	6.3		1.55	1.16, 2.06	1.54	1.15, 2.08
PHC-3		35	4.2	33	6.7		1.21	0.84, 1.73	1.20	0.83, 1.72
PHC-4		88	10.5	14	2.9		2.02	1.57, 2.60	1.96	1.51, 2.54
PHC-5		69	8.2	6	1.2		2.16	1.64, 2.84	2.31	1.73, 3.09
PHC-6		130	15.5	25	5.1		1.97	1.58, 2.45	1.80	1.42, 2.28
PHC-7		165	19.7	39	8.0		1.90	1.54, 2.33	1.84	1.47, 2.30
PHC-8		33	3.9	35	7.2		1.14	0.79, 1.65	1.17	0.80, 1.70
Time from HIV diagnosis to care enrolment	0.5					<0.001				
Same-day		426	51.2	237	48.6		1.00	Referent	1.00	Referent
1-89 days		239	28.7	194	39.8		0.86	0.73, 1.01	1.02	0.87, 1.21
≥90 days		167	20.1	57	11.7		1.16	0.97, 1.38	1.38	1.01, 1.88

Sex/pregnancy	0.6				<0.001				
Men		192	23.0	146	30.0	1.00	0.84, 1.19	1.14	0.94, 1.38
Non-pregnant women		350	41.9	266	54.7	1.00	Referent	1.00	Referent
Pregnant women		293	35.1	74	15.2	1.41	1.20, 1.64	1.37	1.15, 1.62
Age at ART initiation, years	0.0				0.042				
16 to 24		220	26.2	104	21.3	1.09	0.93, 1.27	1.03	0.86, 1.22
25 to 49		570	67.9	344	70.3	1.00	Referent	1.00	Referent
≥50		49	5.8	41	8.4	0.87	0.65, 1.17	1.01	0.75, 1.37
Marital status	2.0				0.318				
Married		252	30.8	162	33.5	1.00	Referent	1.00	Referent
Not married		566	69.2	322	66.5	1.05	0.91, 1.22	1.04	0.89, 1.21
Education	16.0				0.037				
None		23	3.2	19	4.7	1.00	Referent	1.00	Referent
Primary		153	21.4	111	27.6	1.03	0.68, 1.55	1.02	0.67, 1.56
Secondary		523	73.2	267	66.4	1.19	0.80, 1.76	1.12	0.74, 1.69
Tertiary		15	2.1	5	1.2	1.36	0.74, 2.50	1.23	0.66, 2.30
CD4 count b, cells/mm ³	3.9				<0.001				
0 to 100		107	13.4	103	21.6	0.78	0.62, 0.98	0.87	0.68, 1.11
101 to 200		125	15.6	87	18.2	0.91	0.73, 1.13	0.92	0.73, 1.15
201 to 350		206	25.8	111	23.3	1.00	Referent	1.00	Referent
351 to 500		174	21.8	94	19.7	1.00	0.82, 1.22	0.99	0.81, 1.21
≥501		187	23.4	82	17.2	1.07	0.88, 1.30	1.05	0.86, 1.29
WHO clinical stage ^b	0.8				<0.001				
I/II		642	77.2	281	57.9	1.00	Referent	1.00	Referent
III		114	13.7	119	24.5	0.71	0.58, 0.86	0.91	0.74, 1.13
IV		76	9.1	85	17.5	0.68	0.54, 0.86	0.93	0.70, 1.22
Tuberculosis ^{b,c}	0.0				<0.001				
No		808	96.3	449	91.8	1.00	Referent	1.00	Referent

Yes	31	3.7	40	8.2	0.68	0.47, 0.97	0.83	0.56, 1.21
BMI ^{b,d} , kg/m ²	8.8				<0.001			
<18.5	34	4.6	38	8.1	0.85	0.61, 1.18	1.01	0.72, 1.43
18.5 to 24.9	345	46.5	268	57.1	1.00	Referent	1.00	Referent
≥25	363	48.9	163	34.8	1.20	1.04, 1.38	1.10	0.94, 1.28
Haemoglobin ^b , g/dL	24.1				0.063			
≤9	132	21.9	69	17.1	1.12	0.95, 1.32	1.13	0.95, 1.35
≥10	472	78.1	335	82.9	1.00	Referent	1.00	Referent
ALT ^b , U/L	22.5				0.124			
≤42	561	89.8	350	86.6	1.00	Referent	1.00	Referent
≥43	64	10.2	54	13.4	0.90	0.71, 1.13	0.99	0.78, 1.27
Creatinine ^b , µmol/L	17.5				0.113			
≤120	654	98.1	414	96.5	1.00	Referent	1.00	Referent
≥121	13	1.9	15	3.5	0.78	0.47, 1.29	0.79	0.47, 1.33
Phone availability	1.3				0.121			
No	70	8.5	54	11.1	1.00	Referent	1.00	Referent
Yes	754	91.5	433	88.9	1.13	0.88, 1.44	1.03	0.80, 1.34

ALT, alanine transaminase; aRR, adjusted risk ratio; ART, antiretroviral therapy; BMI, body mass index; cRR, crude risk ratio; n, number; PHC, primary health care facility; SHC, secondary health care facility; WHO, World Health Organization.

Footnote:

^aThe covariate HIV diagnosis describes whether HIV-positive diagnosis was established before or during the roll-out of the Treat-All policy.

^bBaseline clinical and laboratory data were obtained at the time of ART initiation and categorized into normal and pathological.

^cA baseline TB case was any incident TB case from 6 months before to 1.5 months after ART initiation.

^dBMI = Weight (kg) / Height (m)

Table 2: Estimated effect of same-day ART initiation on the unfavourable outcome using targeted maximum likelihood estimation (TMLE), Same-day antiretroviral therapy under Treat-All, 2014–2016

Time since ART	Point estimate	95% CI
1) Flexible parametric survival model		
Adjusted hazard ratio (aHR)	1.48	1.16, 1.89
2) Targeted maximum likelihood estimation (TMLE)		
<i>Average treatment effect (ATE)</i>		
12 months	0.08	0.01, 0.14
18 months	0.07	0.00, 0.14
24 months	0.06	-0.06, 0.18
<i>Marginal Odds Ratio (MOR)</i>		
12 months	1.36	1.03, 1.81
18 months	1.27	1.00, 1.61
24 months	1.19	0.83, 1.70
<i>Probability of the Unfavorable Outcome</i>		
Same-day ART ^a		
12 months	0.29	0.25, 0.32
18 months	0.35	0.31, 0.38
24 months	0.37	0.28, 0.45
Delayed ART ^b		
12 months	0.21	0.16, 0.27
18 months	0.27	0.22, 0.33
24 months	0.31	0.23, 0.39

ART, antiretroviral therapy; CI, confidence interval; ATE, average treatment effect.

Footnote:

^aThis is the probability of the unfavourable treatment outcome if everybody in the cohort had received same-day ART.

^bThis is the probability of the unfavourable treatment outcome if everybody in the cohort had received delayed ART.

Table 3: Estimates of combination of supplementary analyses with different assumptions, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Outcomes	cHR	(95% CI)	aHR	(95% CI)
A) Time Zero: Date of ART Initiation				
Same-day vs early ART				
Unfavourable outcome ^a	1.39	1.14, 1.70	1.48	1.16, 1.89
All-cause attrition ^b	1.39	1.13, 1.71	1.47	1.14, 1.88
Same-day vs rapid ART^c				
Unfavourable outcome ^a	1.38	1.08, 1.76	1.44	1.08, 1.92
All-cause attrition ^b	1.35	1.05, 1.72	1.43	1.07, 1.92
B) Time Zero: Date of HIV Care Enrolment				
Same-day vs early ART				
Unfavourable outcome ^a	1.41	1.15, 1.73	1.83	1.41, 2.38
All-cause attrition ^b	1.40	1.14, 1.73	1.67	1.30, 2.16
Same-day vs rapid ART^c				
Unfavourable outcome ^a	1.40	1.10, 1.78	1.81	1.33, 2.47
All-cause attrition ^b	1.36	1.06, 1.74	1.80	1.31, 2.47

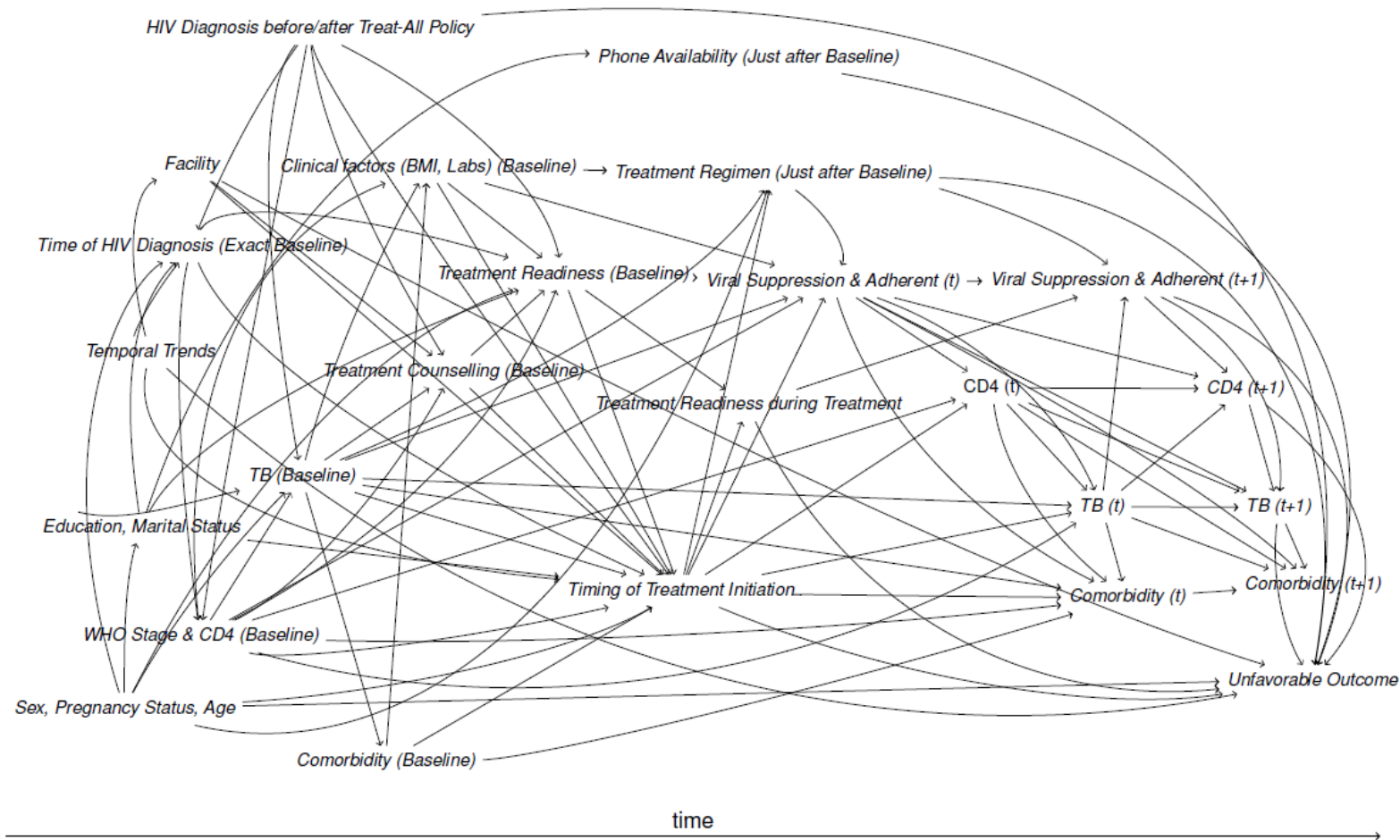
aHR, adjusted hazard ratio; cHR, crude hazard ratio; CI, confidence interval.

Footnote:

^aThis is the composite unfavourable treatment outcome of death, loss to follow-up, viral failure and treatment switching to a second-line ART in the absence of viral failure.

^bAll-cause attrition comprised the outcomes of death and loss to follow-up.

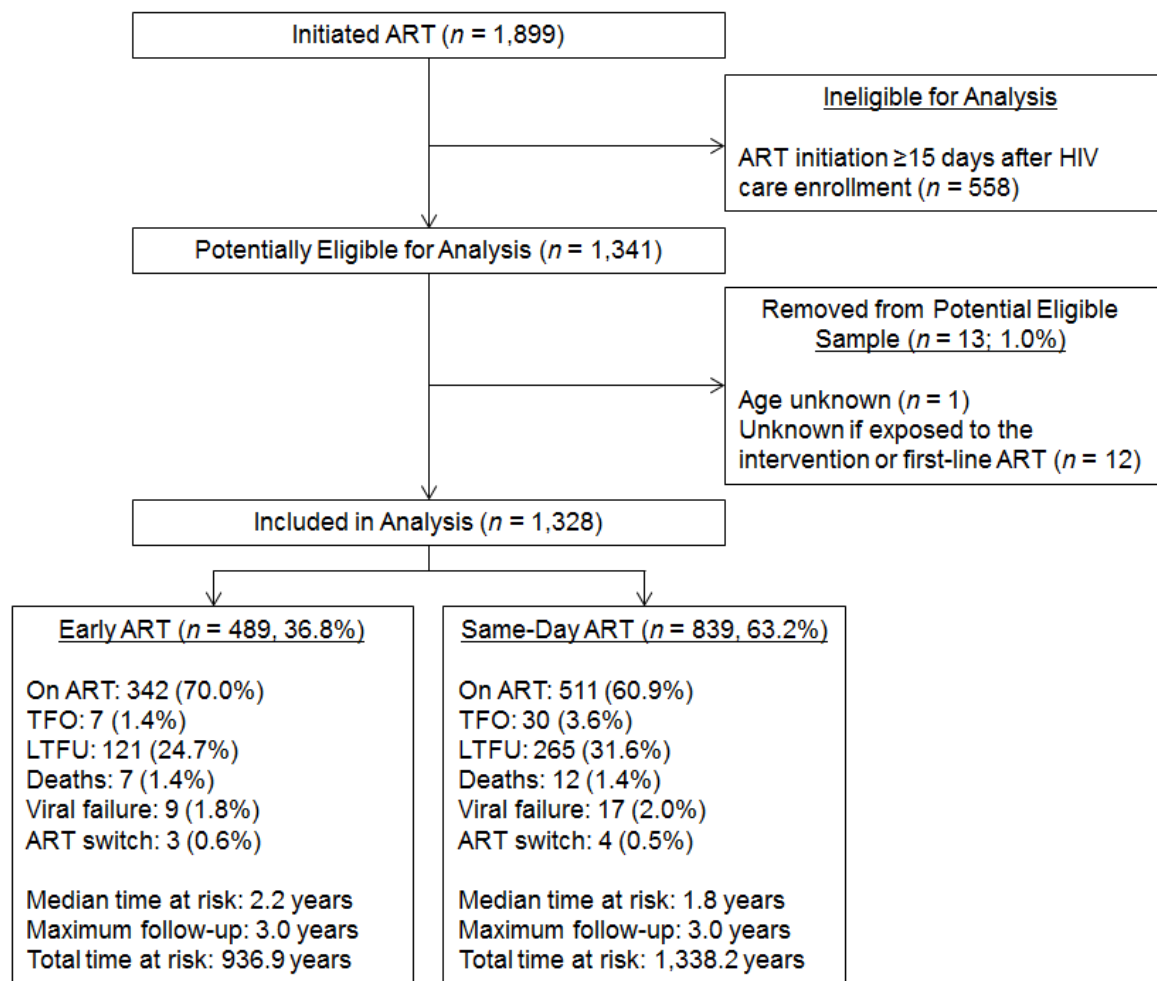
^cA total of 1133 patients initiating ART within 7 days, with 294 (25.9%) within 1–7 days and 839 (74.1%) same-day.



BMI, body mass index; CD4, CD4 cell count; t, time; TB, tuberculosis; WHO, World Health Organization.

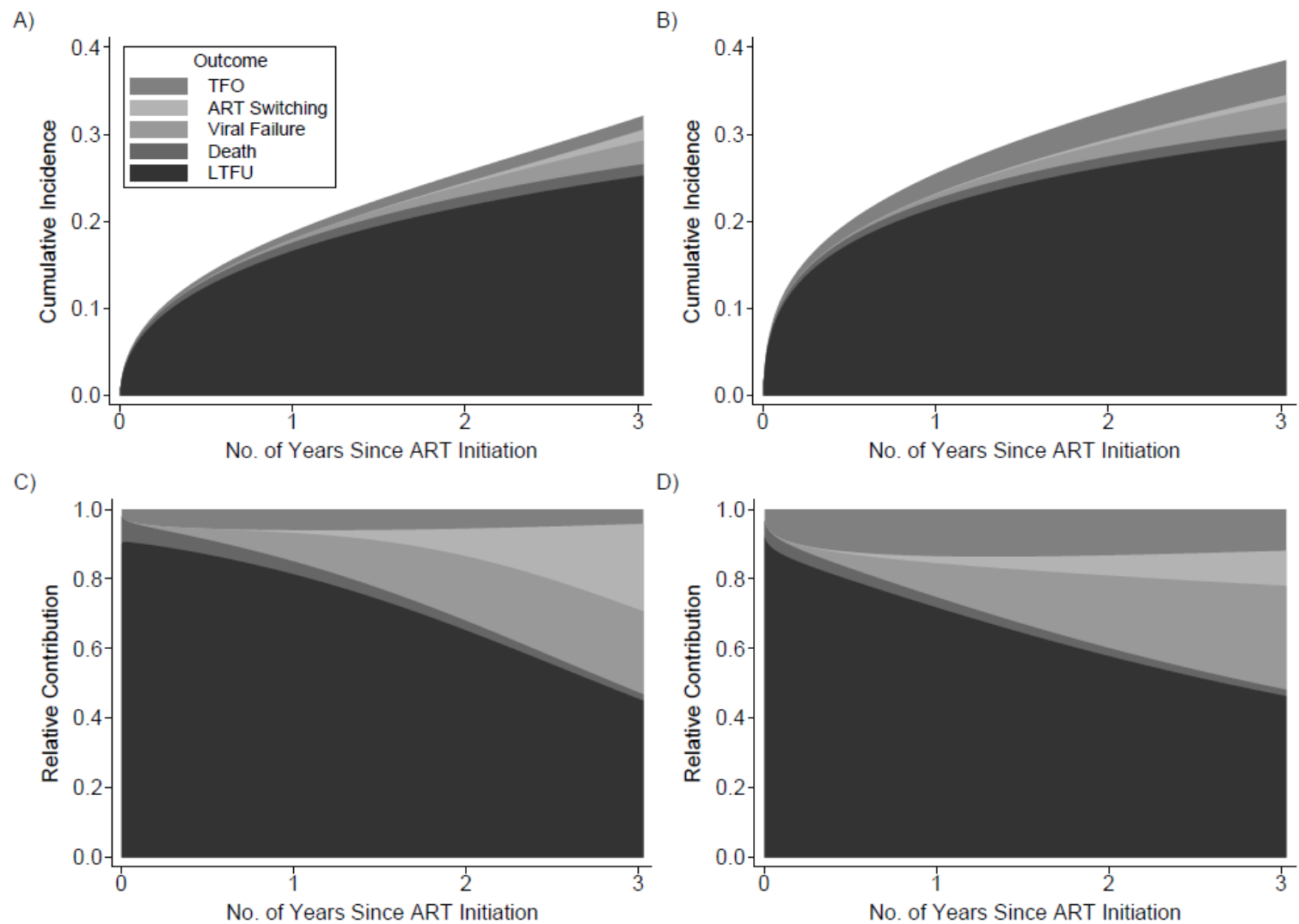
Figure 1: Directed acyclic graph (DAG) showing structural assumptions about the data-generating process, Same-day antiretroviral therapy under Treat-All, 2014–2016.

BMI, body mass index; CD4, CD4 cell count; t, time; TB, tuberculosis; WHO, World Health Organization.



ART, antiretroviral therapy; LTFU, loss to follow-up; n, number; TFO, transfer out.

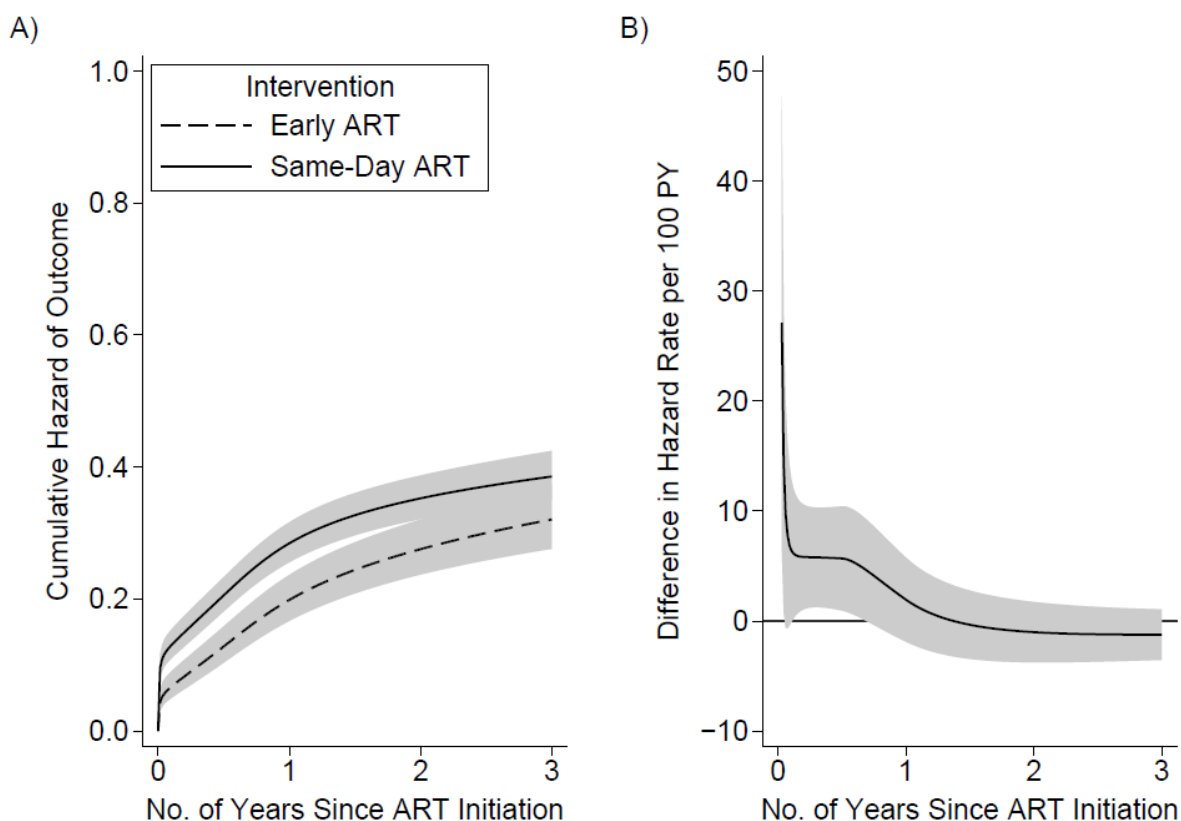
Figure 2: Study flow chart, Same-day antiretroviral therapy under Treat-All, 2014–2016.



ART, antiretroviral therapy.

We used the competing risks post-estimation command `stpm2cif` in Stata²⁸⁶ to estimate the cumulative incidence function for different causes of the outcome (early ART: Panel A; same-day ART: Panel B), and the relative contribution to the overall hazard for different causes of the outcome (early ART: Panel C; same-day ART: Panel D). The curves are based on a flexible parametric survival model (Royston-Parmar models)^{196,197} using restricted cubic splines. For both interventions, the relative cause-specific contribution of LTFU decreased from approximately 90% at the time of ART initiation to less than half at the end of the observation period (early ART: Panel C; same-day ART: Panel C). The cumulative incidence of LTFU was lower for early ART (Panel A) after treatment initiation, but its relative contribution to the outcomes was more pronounced during the first 2 years since treatment initiation when compared with same-day ART (Panel B). Death was rare and similar between both interventions while cumulative transfer out was higher for same-day ART. For both interventions, the relative contribution of viral failure and ART switching to the overall hazard increased rapidly after 6 months since ART initiation (early ART: Panel C; same-day ART: Panel D).

Figure 3: Stacked cause-specific cumulative incidence functions (early ART: Panel A; same-day ART: Panel B), and stacked cause-specific relative contribution to the overall hazard (early ART: Panel C; same-day ART: Panel D) of the outcomes of loss to follow-up (LTFU), death, viral failure, treatment switching and censoring due to transfer out (TFO) for early vs same-day antiretroviral therapy (ART), Same-day antiretroviral therapy under Treat-All, 2014–2016.



ART, antiretroviral therapy; PY, person years.

The adjusted hazard ratio for same-day ART was 1.48 (95% Confidence Interval: 1.16, 1.89) and varied over time with higher hazard of the unfavourable outcome during the first year of ART. The line at 0 in Panel B indicates the reference group (Early-ART).

Figure 4: Averaged cumulative hazard (Panel A) and averaged difference in hazard rate (Panel B) of the unfavourable outcome for time from ART initiation to unfavourable outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

SUPPORTING INFORMATION

Web Appendix 1: Some explanation of the developed directed acyclic graph (DAG)

Web Table 1: Pre-treatment variables with missing values, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Table 2: Details and diagnostics^a for the TMLE analysis, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Table 3: Details and diagnostics^a for the TMLE analysis, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Table 4: Univariate and multivariate analysis of time to unfavourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Table 5: Point estimates of the cumulative hazard of favourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Figure 1: Cumulative hazard of favourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Figure 2: Trace plots of imputed data for all covariates with missing values, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Figure 3: Kernel density plots for imputed CD4 cell count and haemoglobin for all imputed datasets as an example using the *middiagplots* command in Stata, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Web Appendix 1: Some explanation of the developed directed acyclic graph (DAG).

Treatment assignment, such as the decision to initiate ART on the same day, was based on the following considerations. Firstly, ART initiation on the day of facility-based HIV care enrolment was policy for pregnant/lactating women and encouraged for other patients in the absence of (presumptive) opportunistic infections. Secondly, same-day ART was practised at the clinician's discretion based on the clinical and psychological pre-treatment assessment and depended on the patient's self-perceived readiness, where the clinician's advice may vary by facility. Thirdly, baseline CD4 cell count may also predict timing of ART initiation (e.g. patients with low CD4 count and no symptoms suggestive of opportunistic infection may initiate ART on the same day, patients with low CD4 cell count and symptoms suggestive of opportunistic infection may delay ART initiation and patients with high CD4 count may initiate immediately or delay). Fourthly, treatment readiness of the patient with regards to psychological preparedness (and not clinical readiness) at baseline could be a main factor predicting same-day ART initiation, as clinicians would not enforce same-day ART if the patient communicated not being ready for it. Fifthly, a patient's marital status may also affect the decision to start treatment on the same day; married patients may favour deferring the decision on when to start treatment, as they may first wish to consult with their partner. However, higher education level may accelerate initiation, as knowledge of HIV and the benefit of treatment may be increased. Sixthly, the decision to start on the same day may relate to calendar year, as practising clinicians may change advice with increasing experience. Lastly, the time from HIV diagnosis to care enrolment may influence same-day ART, with patients knowing their HIV status for longer possibly being more ready to start treatment immediately. For these reasons, we considered sex, pregnancy status, age, co-morbidities at enrolment, laboratory values at enrolment, education, marital status, temporal trends (calendar year), time of HIV diagnosis, facility, treatment counselling and treatment readiness to be relevant to deciding on the timing of treatment assignment. Consequently, these variables lie on back-door paths from treatment to the outcome.²⁷³

There are two ways through which timing of ART initiation could affect the composite outcome. The first way is biologically, if treatment delay would affect viral suppression and thus the development of co-morbidities and negative outcomes. Secondly, earlier treatment may have a psychological impact on patients, who, if they did not feel ready for ART and were pushed into treatment, could stop being adherent to their treatment or even be lost to the programme.

Note that all post-treatment variables, which are visualized in the DAG, are mediators on the path from the intervention to the outcome and should thus not be conditioned upon.²⁷³ However, those variables that determine treatment assignment, as described above, are crucial to block back-door paths from the intervention to the outcome. While we have measured most of these variables,

treatment readiness and counselling are unmeasured, as are some baseline comorbidities; this suggests the possibility of some unmeasured confounding.

Web Table 1: Pre-treatment variables with missing values, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Variable	Complete observations	Incomplete observations	
		n	%
CD4 count	1276	52	4.1
Body-mass-index	1207	121	10.0
Haemoglobin	1008	320	31.7
ALT	1029	299	29.1
Creatinine	1096	232	21.2
Time from HIV diagnosis to care enrolment	1320	8	0.6
WHO clinical stage	1317	11	0.8
Education	1116	212	19.0
Pregnancy status	1321	7	0.5
Timing of HIV diagnosis	1322	6	0.5
Marital status	1302	26	2.0
Phone availability	1311	17	1.3

ALT, alanine transaminase; n, number; %, percentage.

Footnote: Twelve pre-treatment variables had missing values ranging from 0.5% to 31.7%. The imputation model included all pre-treatment variables as listed in Table 1, viral load follow-up test results and the intervention exposure.

Web Table 2: Details and diagnostics^a for the TMLE analysis, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Diagnostics for the product of the estimated probabilities of treatment assignment and censoring; as well as the clever covariate (CC) summary based on the inverse of this product. Ideally, no observations are truncated (i.e. 0% of probabilities are <0.01), the maximum clever covariate is not too high (say <10 or <20), and the mean clever covariate is about 1.

	12 months		24 months		36 months	
	Same day	Early	Same day	Early	Same day	Early
Number uncensored and followed treatment	814	483	810	482	570	395
% truncated	0%	0%	0%	0%	0%	0%
Mean CC	0.89	0.75	0.89	0.75	0.72	0.66
Max. CC	3.86	9.76	4.09	12.25	4.91	8.69

^aThe diagnostics were based on a TMLE analysis using the R-package *ltmle*,^{2/5} with 10-fold cross validation, a squared loss function (for cross validation), and a truncation level of 0.01, meaning that estimated treatment assignment and censoring probabilities (needed for the targeted update step) would have been truncated if they were lower than 0.01 (although this did not occur). Results averaged over the 10 imputed datasets are reported.

Web Table 3: Details and diagnosticsa for the TMLE analysis, Same-day antiretroviral therapy under Treat-All, 2014–2016.

Choice of learners: We have used super learning to estimate the i) expected outcome, ii) treatment assignment and iii) censoring processes, given the measured covariates.^{287,288} The learners and screening algorithms used are listed below, together with their average weight in the final prediction algorithm. All learners are from the package super learner (and are described in the respective help file), except “SL.lae” which is from the package MAMI²⁸⁹ and implements Lasso Averaging Estimation.²⁹⁰ The screening algorithms used are hand-written: screening 5 variables with LASSO²⁹¹ (“lasso”), categorizing variables according to quintiles and using bivariate associations with Cramer’s V ²⁹² to select the 4 strongest associations (“cramer”) and using Lasso screening where the number of selected variables is chosen by generalized cross validation,²⁹³ but where “SL.cramer” is used in case this strategy fails (due to numerical reasons); (“lasso2”).

	Model	12 months			24 months			36 months		
		Outc.	Treat.	Cens.	Outc.	Treat.	Cens.	Outc.	Treat.	Cens.
Learner	Screening									
SL.mean	--	0.215	0.000	0.000	0.252	0.000	0.000	0.076	0.000	0.000
SL.glm	--	0.051	0.216	0.000	0.000	0.212	0.000	0.020	0.205	0.283
SL.bayesglm	--	0.113	0.000	0.000	0.080	0.000	0.000	0.265	0.000	0.003
SL.stepAIC	--	0.061	0.509	0.021	0.078	0.484	0.019	0.072	0.504	0.031
SL.gam	--	0.000	0.000	0.002	0.000	0.000	0.019	0.002	0.000	0.072
SL.knn	--		0.000	0.075		0.000	0.075		0.000	0.007
SL.lae	--	0.000	0.000	0.000	0.012	0.000	0.026	0.028	0.000	0.000
SL.randomForest	--	0.160	0.191	0.205	0.082	0.193	0.196	0.152	0.173	0.083
SL.nnet	--	0.014	0.000	0.608	0.041	0.001	0.427	0.143	0.000	0.000
SL.bayesglm	Cramer	0.000	0.000	0.000	0.019	0.000	0.007	0.000	0.000	0.024
SL.gam	Cramer	0.000	0.000	0.000	0.014	0.000	0.005	0.029	0.000	0.225
SL.step.interaction	Cramer	0.033	0.000	0.009	0.000	0.000	0.000	0.029	0.000	0.000
SL.bayesglm	Lasso	0.000	0.000	0.000	0.000	0.000	0.075	0.028	0.000	0.000
SL.gam	Lasso	0.000	0.000	0.000	0.000	0.000	0.058	0.000	0.000	0.018
SL.step.interaction	Lasso	0.000	0.000	0.076	0.000	0.000	0.068	0.030	0.000	0.047
SL.bayesglm	Lasso2	0.200	0.000	0.000	0.261	0.000	0.000	0.000	0.000	0.000
SL.gam	Lasso2	0.109	0.000	0.000	0.138	0.000	0.000	0.000	0.021	0.087
SL.step.interaction	Lasso2	0.026	0.084	0.000	0.000	0.110	0.000	0.025	0.097	0.031
SL.earth	Cramer	0.016	0.000	0.000	0.019	0.000	0.017	0.008	0.000	0.042
SL.earth	Lasso	0.000	0.000	0.003	0.003	0.000	0.006	0.093	0.000	0.048

^aThe diagnostics were based on a TMLE analysis using the R-package ltmle,²⁷⁵ with 10-fold cross validation, a squared loss function (for cross validation), and a truncation level of 0.01, meaning that estimated treatment assignment and censoring probabilities (needed for the targeted update step) would have been truncated if they were lower than 0.01 (although this did not occur). Results averaged over the 10 imputed datasets are reported.

Web Table 4: Univariate and multivariate analysis of time to unfavourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

(% missing values)	Univariate analysis (n=1328)		Multivariate analysis (n=1328) ¹	
	cHR	95% CI	aHR	95% CI
Intervention, (0%)				
Early ART	1		1	
Same-day ART	1.39	1.14, 1.70	1.48	1.16, 1.89
Year, (0%)				
2014	1		1	
2015	1.10	0.84, 1.43	1.12	0.84, 1.48
2016	1.27	0.91, 1.77	1.21	0.84, 1.75
Timing of HIV diagnosis, (0.5%)				
Pre Treat-All	1		1	
Treat-All	1.09	0.83, 1.41	0.76	0.47, 1.22
Facility, (0%)				
SHC	1		1	
PHC-1	1.25	0.88, 1.78	1.17	0.80, 1.72
PHC-2	1.32	0.92, 1.91	1.37	0.93, 2.01
PHC-3	0.65	0.38, 1.10	0.65	0.38, 1.13
PHC-4	0.89	0.60, 1.33	0.80	0.53, 1.23
PHC-5	0.68	0.41, 1.12	0.64	0.37, 1.09
PHC-6	1.40	1.04, 1.89	1.41	1.01, 1.97
PHC-7	1.21	0.92, 1.61	1.17	0.85, 1.61
PHC-8	1.02	0.65, 1.60	1.04	0.65, 1.64
Time from HIV diagnosis to care enrolment, (0.5%)				
Same-day	1		1	
1–89 days	0.92	0.75, 1.14	1.00	0.80, 1.26
≥90 days	0.89	0.68, 1.17	0.73	0.46, 1.15
Sex/pregnancy, (0.6%)				
Men	0.91	0.71, 1.16	0.92	0.70, 1.22
Non-pregnant women	1		1	
Pregnant women	1.30	1.05, 1.62	1.20	0.94, 1.54
Age at ART initiation, years, (0%)				
16 to 24	1.44	1.17, 1.77	1.30	1.02, 1.65
25 to 49	1		1	
≥50	0.76	0.49, 1.18	0.88	0.56, 1.39
Marital status, (2.0%)				
Married	1		1	
Not married	1.40	1.13, 1.74	1.28	1.02, 1.61
Education, (16.0%)				

None	1		1	
Primary	0.89	0.51, 1.56	0.91	0.51, 1.63
Secondary	1.09	0.64, 1.86	0.99	0.55, 1.78
Tertiary	1.04	0.41, 2.61	0.91	0.35, 2.40
CD4 count, cells/mm ³ , (3.9%)				
0 to 100	1.31	0.97, 1.78	1.33	0.95, 1.86
101 to 200	0.95	0.68, 1.32	0.97	0.69, 1.37
201 to 350	1		1	
351 to 500	1.26	0.94, 1.69	1.26	0.94, 1.69
≥501	1.25	0.93, 1.67	1.25	0.92, 1.68
WHO clinical stage, (0.8%)				
I/II	1		1	
III	0.85	0.65, 1.10	1.02	0.77, 1.36
IV	1.22	0.93, 1.60	1.54	1.09, 2.18
Tuberculosis, (0%)				
No	1		1	
Yes	0.78	0.50, 1.23	0.75	0.46, 1.21
BMI, kg/m ² , (8.8%)				
<18.5	1.29	0.87, 1.93	1.23	0.81, 1.88
18.5 to 24.9	1		1	
≥25	0.93	0.75, 1.16	0.90	0.71, 1.15
Haemoglobin, g/dL, (24.1%)				
≤9	1.35	1.05, 1.73	1.21	0.93, 1.58
≥10	1		1	
ALT, U/L, (22.5%)				
≤42	1		1	
≥43	0.88	0.62, 1.24	0.91	0.63, 1.30
Creatinine, μmol/L, 17.5%)				
≤120	1		1	
≥121	1.74	1.02, 2.98	1.96	1.13, 3.38
Phone availability, (1.3%)				
No	1		1	
Yes	0.84	0.61, 1.14	0.73	0.52, 1.02

ALT, alanine transaminase; aHR, adjusted hazard ratio; cHR, crude hazard ration; ART, antiretroviral therapy; BMI, body mass index; n, number; PHC, primary health care facility; SHC, secondary health care facility; WHO, World Health Organization.

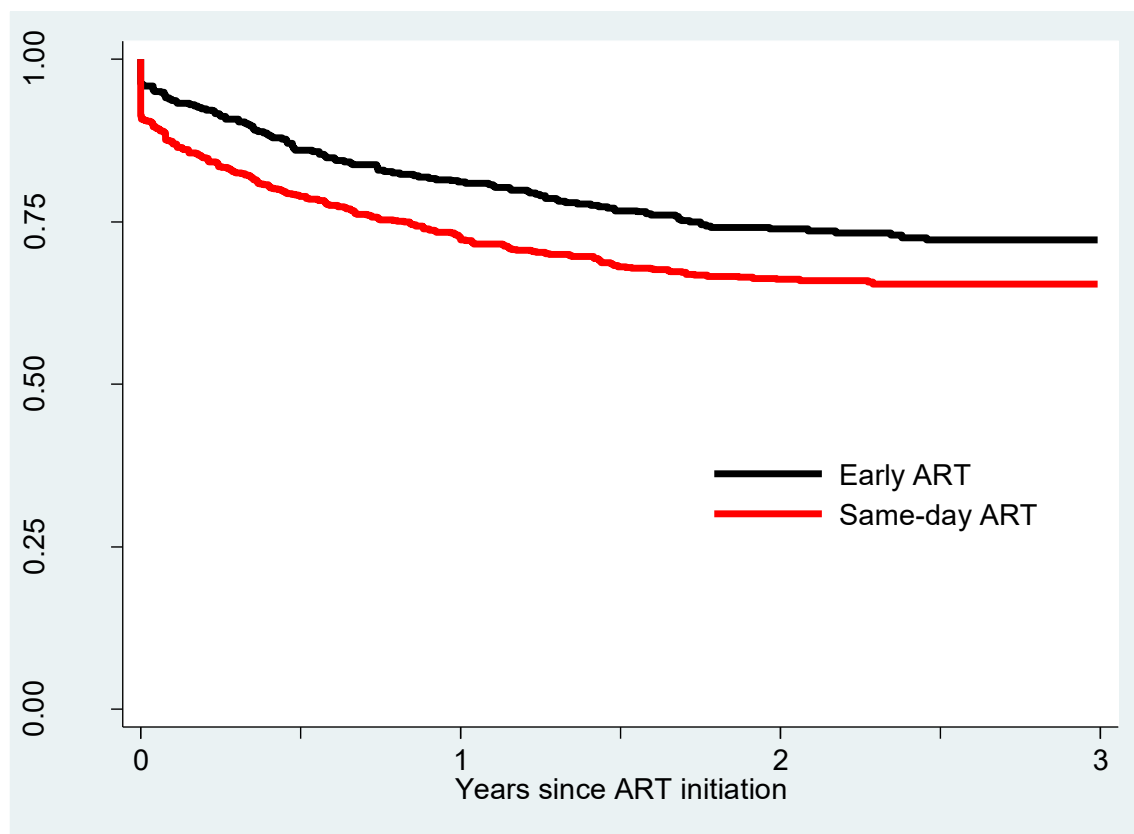
Footnote: A standard first-line treatment regimen contained 3TC, TDF or AZT, and EFV or NVP. A baseline TB case was any incident TB case between 6 months before and 1.5 months after ART initiation. Baseline clinical and laboratory data were obtained at the time of ART initiation and categorized into normal and pathological. The covariate HIV diagnosis describes whether HIV-positive diagnosis was established before or during the roll-out of the Treat-All policy.

¹Model specifications: The flexible parametric survival model had 3 internal knots (4 degrees of freedom) and 1 internal knot (2 degrees of freedom) for the time-varying covariate intervention exposure.

Web Table 5: Point estimates of the cumulative hazard of favourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.

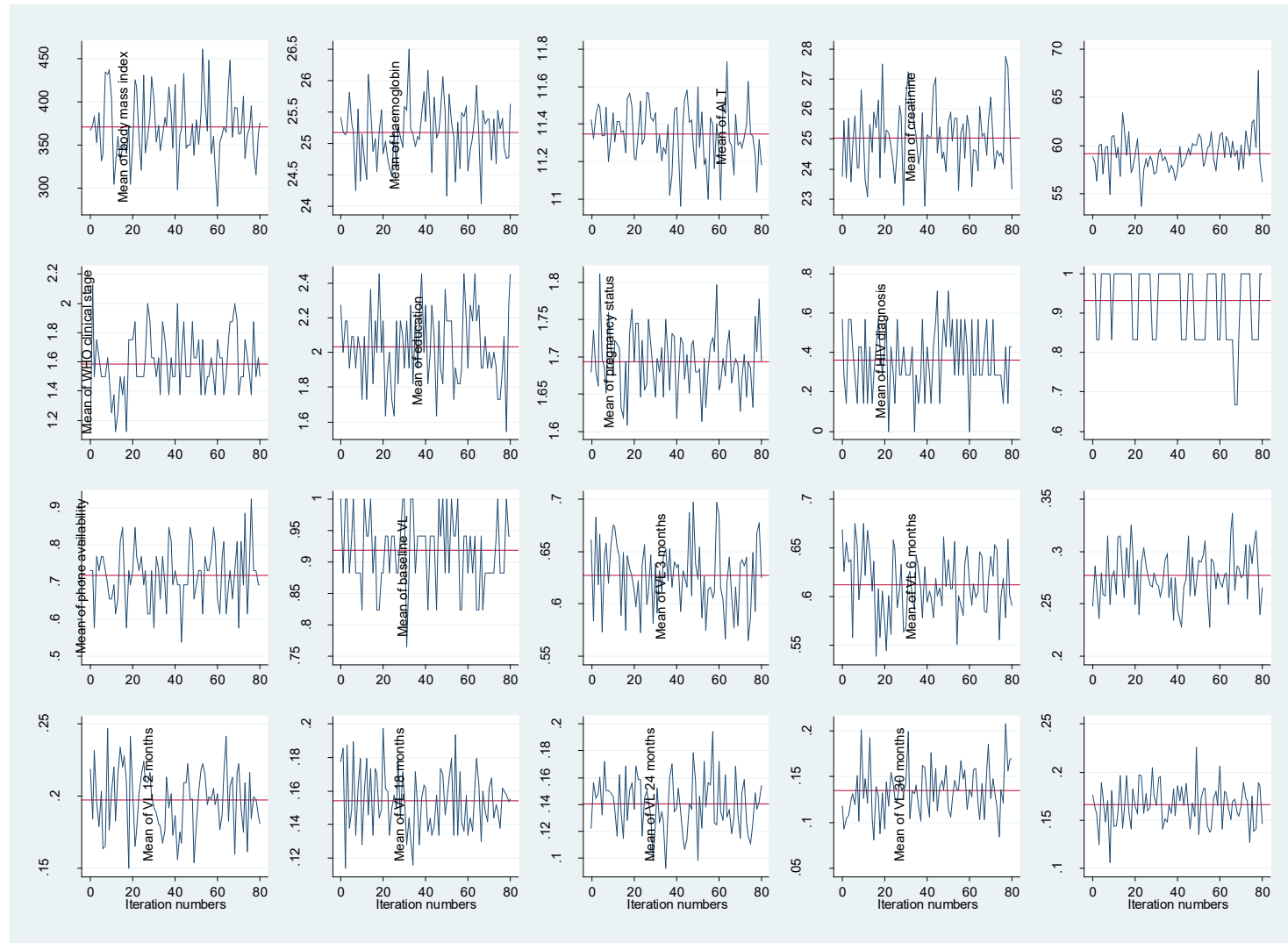
Time since ART	Early ART		Same-day ART	
	%	95% CI	%	95% CI
1 day*	96	94, 98	91	89, 93
3 months	91	88, 93	84	81, 86
6 months	86	83, 89	79	76, 81
1 year	81	77, 84	72	68, 74
2 years	73	69, 77	64	61, 68
3 years	69	63, 73	62	59, 66

* These are patients who initiated ART but never returned for a follow-up visit.
ART, antiretroviral therapy.



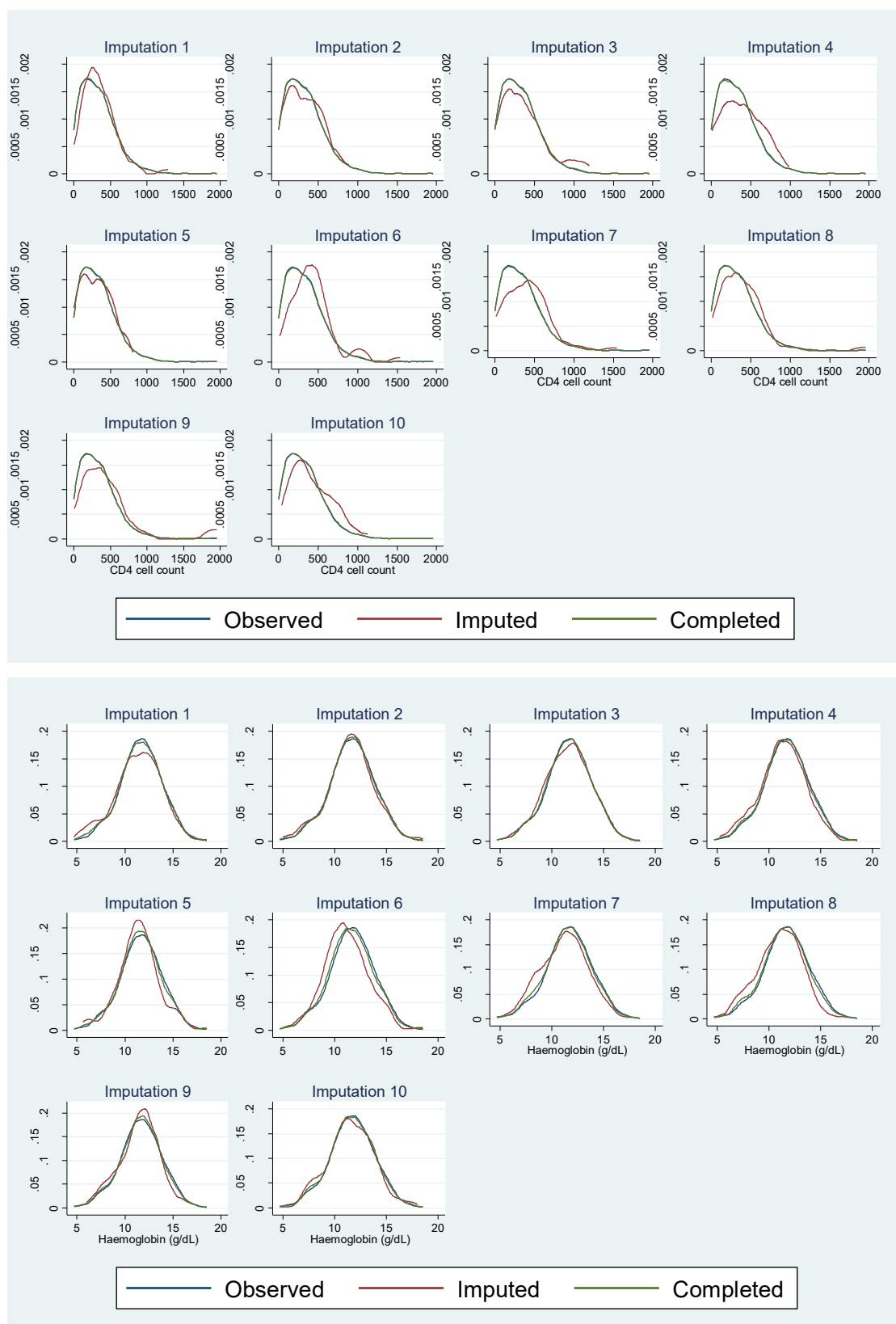
ART, antiretroviral therapy.

Web Figure 1: Cumulative hazard of favourable treatment outcome for patients initiating same-day ART vs early ART, Same-day antiretroviral therapy under Treat-All, 2014–2016.



ALT, alanine transaminase; VL, viral load.

Web Figure 2: Trace plots of imputed data for all covariates with missing values, Same-day antiretroviral therapy under Treat-All, 2014–2016.



Web Figure 3: Kernel density plots for imputed CD4 cell count and haemoglobin for all imputed datasets as an example using the `middiagplots` command in Stata, Same-day antiretroviral therapy under Treat-All, 2014–2016.

RESULTS FOR OBJECTIVE 5

Decreased risk of HIV-associated TB during antiretroviral therapy expansion in rural Eswatini from 2009 to 2016: a cohort and population-based analysis

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Paper overview

This study uses data from a cohort of patients initiated on TB treatment in the Shiselweni region in Eswatini from 2009 to 2016. The analyses describe 1) trends in HIV-associated TB notifications at cohort and population levels, 2) patient-level predictors of HIV-associated TB, and 3) ART coverage trends during declining TB.

Significance of the paper

This manuscript addresses temporal trends in HIV-associated TB. Most previous studies used aggregated TB and ART data, lacked context-specific HIV prevalence estimates, and did not disaggregate data by demographic factors (gender, age) or HIV status. In addition, a modelling study predicted TB rebound if HIV incidence reduction is delayed and immunovirological outcomes cannot be achieved and maintained during the scale-up of ART. Studies from urban areas indicated, despite a decline in TB cases, that high TB notification rates were maintained. There is a lack of understanding of temporal trends of HIV-associated TB at the patient level and of TB case notifications at the population level, and signs of possible TB rebound from high HIV prevalence settings that have successively expanded access to ART, including the introduction of Treat-All.

Candidate's contributions

The candidate supported the TB programme implementation and established the database for monitoring the implementation of drug-sensitive TB. The candidate (with advice from MS and AB) designed and planned the research. The candidate combined the different databases (drug-sensitive and drug-resistant TB), processed all data, performed all analyses, wrote the first draft of the manuscript, integrated comments from co-authors, and submitted the manuscript for peer review.

ABSTRACT

Objectives

This paper assesses patient- and population-level trends in TB notifications during rapid expansion of antiretroviral therapy in Eswatini which has an extremely high incidence of both TB and HIV.

Methods

Patient- and population-level predictors and rates of HIV-associated TB were examined in the Shiselweni region in Eswatini from 2009 to 2016. Annual population-level denominators obtained from projected census data and prevalence estimates obtained from population-based surveys were combined with individual-level TB treatment data. Patient- and population-level predictors of HIV-associated TB were assessed with multivariate logistic and multivariate negative binomial regression models.

Results

Of 11 328 TB cases, 71.4% were HIV co-infected and 51.8% were women. TB notifications decreased fivefold between 2009 and 2016, from 1341 to 269 cases per 100 000 person-years. The decline was sixfold in PLHIV vs. threefold in the HIV-negative population. Main patient-level predictors of HIV-associated TB were recurrent TB treatment (adjusted odds ratio [aOR] 1.40, 95% confidence interval [CI]: 1.19–1.65), negative (aOR 1.31, 1.15–1.49) and missing (aOR 1.30, 1.11–1.53) bacteriological status and diagnosis at secondary healthcare level (aOR 1.18, 1.06–1.33). Compared with 2009, the probability of TB decreased for all years from 2011 (aOR 0.69, 0.58–0.83) to 2016 (aOR 0.54, 0.43–0.69). The most pronounced population-level predictor of TB was HIV-positive status (adjusted incidence risk ratio 19.47, 14.89–25.46).

Conclusions

This high HIV-TB prevalence setting experienced a rapid decline in TB notifications, most pronounced in PLHIV. Achievements in HIV-TB programming were likely contributing factors.

INTRODUCTION

HIV is driving the TB epidemic in high HIV prevalence settings,^{143,144} with sub-Saharan Africa having the highest HIV prevalence and TB incidence globally.^{37,191} TB has emerged as the main opportunistic infection in people living with HIV (PLHIV), with HIV co-infection rates exceeding 50% in many southern African countries.¹⁹¹

Several patient-level factors predict HIV-associated TB including older age, male sex and advanced HIV disease.¹⁴⁷ Despite the protective effect of antiretroviral therapy (ART) against active TB disease across all baseline CD4 cell count strata, possibly stronger for lower CD4 count levels,^{21,294} PLHIV receiving ART remain at higher risk of TB than the HIV-negative population.^{151,152,294} At the population-level, ecological studies suggested a decline in annual TB notifications with expansion of HIV treatment eligibility criteria and increased ART coverage,^{143,146,295} most pronounced in new and smear-negative TB cases.^{143,146,153} Although modelling studies overall support these findings, the long-term impact of ART scale-up on TB reduction remains inconclusive.^{22,54,55} In some settings, the decline in TB occurred before or at the beginning of ART expansion,^{143,146} suggesting other factors contributing to TB control.^{142,145–147} For instance: (1) increased TB programme coverage, diagnosis and effective treatment is believed to reduce TB prevalence and mortality; (2) ART expansion is likely to drive the decline in incident TB in PLHIV; and (3) both interventions combined in high HIV-TB prevalence settings may have a synergistic effect.⁵⁴ Other factors are level of care and HIV prevalence at district level.^{147,150}

Eswatini (former Swaziland) – the country with the highest HIV prevalence (32% in 18- to 49-year-olds) in the world¹⁷³ – experienced significant changes in the TB epidemic. In 2012 it had the highest annual TB incidence (1350/100 000 population) globally and 77% of TB patients were HIV co-infected.²⁹⁶ Since then, estimated incidence rapidly declined to 398 cases per 100 000 population in 2016,¹⁹¹ coinciding with changes in TB programme interventions¹⁴² and unprecedented ART expansion. This is the first study from Eswatini examining both patient- and population-level predictors and trends of HIV-associated TB during progressive expansion of HIV-TB care over a period of 8 years.

METHODS

Context

The predominantly rural Shiselweni region in southern Eswatini had a population of approximately 209 000 in 2009.¹⁷⁷ The peak of the TB epidemic in Eswatini was during 2009–2010, and in 2009, the Shiselweni region had the highest reported case notification rate (1293/100 000 population) in the country (see Appendix S1, Figures S1-S2).²⁹⁷ The Ministry of Health supported by Médecins Sans

Frontières (MSF) provided free ambulatory HIV and TB care (diagnosis, treatment initiation and treatment follow-up) at three secondary health facilities and integrated it into 22 nurse-led mobile doctor-supported primary care clinics from 2009 to 2010. A description of changes in TB programming can be found elsewhere.^{142,298} In summary, the Stop-TB strategy was adopted in 2009 and comprised intensified TB screening, introduction of infection control measures and provision of isoniazid preventive therapy (in 2012). TB diagnosis was based on sputum smear-microscopy, which was increasingly replaced by Xpert MTB/RIF from late 2011. Due to high HIV co-infection rates, empiric TB therapy was encouraged following World Health Organisation (WHO) recommendations.²⁹⁹ HIV co-infected TB patients were eligible for ART irrespective of CD4 cell count, and the ART eligibility threshold for non-TB patients was expanded from 200 to 350 cells/mm³ in 2010 and to 500 cells/mm³ in 2015. One of the three health clusters introduced prompt ART initiation irrespective of immunologic criteria, in January 2013 under the prevention of mother-to-child transmission (PMTCT) option B+ approach^{185,186} and in October 2014 for all PLHIV (the WHO treat-all approach).

Study design, data management and definitions

We analysed patient-level (retrospective cohort analysis) and population-level (ecological analysis) temporal trends and predictors of TB notifications in the Shiselweni region from January 2009 to December 2016. A TB notification case was defined as a patient starting treatment for drug-sensitive or resistant TB. Patient-level data were routinely abstracted from health facility records and entered into electronic TB treatment databases used for routine programme monitoring. Patients transferred in from another facility or outside the region were removed from analyses. Patients restarting TB therapy after treatment interruption or transitioning from first- to second-line TB drug treatment (e.g. treatment failure) were counted once at the time of starting the first TB treatment course. The number of patients active on ART was obtained from the national electronic ART treatment database.

The electronic TB treatment register was maintained by MSF and the electronic ART database by the Ministry of Health with support for data entry by trained MSF data clerks at regional level. Data quality checks and data cleaning were routinely performed as well as data workshops addressing data completeness and reliability. Although these databases were not formally validated against other databases (e.g. laboratory data), the data obtained from the electronic TB database and from paper TB treatment registers were found to be consistent during data reviews.

Statistics

Cohort analysis

Baseline data were compared using the Pearson's chi-squared test. Multiple imputation by chained equations was used to handle missing data (see Appendix S2).¹⁹⁵ A multivariate logistic regression

model with 10 imputed datasets was used to describe predictors of HIV-associated TB. Variables for inclusion were determined a priori based on knowledge from previous studies.

Ecological analysis

First, TB notification rates were calculated separately in each imputed dataset and then averaged across the 10 imputed datasets to create one dataset with complete observations to describe crude and standardised annual rates of TB notifications per 100 000 person-years. Numerators of number of TB cases stratified by sex, age and HIV status were divided by the corresponding mid-year projected regional population estimates (denominators) of the 2007 Eswatini population and housing census.^{177,189} To obtain stratified denominators of PLHIV, sex- and age-stratified population data were multiplied by the corresponding regional HIV prevalence estimates. Because regional stratified HIV prevalence estimates were not available from a single source, we used the 2011 Swaziland HIV Incidence Measurement Survey (SHIMS) estimates^{173,181} for the 20- to 49-year-olds, the 2006–2007 Demographic and Health Survey (DHS) estimates¹⁸⁹ for the ≤ 14 - and ≥ 50 -year-olds, and averaged SHIMS and DHS prevalence estimates for the 15- to 19-year-olds. Finally, the stratified mid-year numbers of patients active on ART were divided by the corresponding stratified population estimates of PLHIV to obtain sex- and age-stratified ART coverage estimates.

Second, because the outcome was number of TB cases and data showed overdispersion, we built negative binomial regression models to obtain population-level adjusted incidence risk ratios (aIRR). Model-1 considered the entire study period adjusted for the population-level covariates sex, age and HIV status. Model-2 combined HIV status and ART status into one covariate with three categories (HIV-negative case, PLHIV on ART, PLHIV without ART), but was restricted to the years from 2009 to 2014 as reliable stratified ART coverage estimates were not available for the time period thereafter.

Finally, we plotted trends in TB notifications and ART coverage between 2008 and 2016. To complement missing information, the national TB programme annual report²⁹⁷ provided the 2008 regional TB notification estimate, and the first and second Swaziland HIV Incidence Measurement Surveys^{173,181,188} provided the regional 2011 and regional 2016 ART coverage estimates overall and separately for men and women.

Analyses were performed with Stata/SE 14.1 (College Station, Texas, USA).

Ethics

This analysis was approved by the Eswatini National Health Research Review Board and the University of Cape Town Ethics committee. This research fulfilled the exemption criteria set by the MSF Ethics Review Board (ERB) for posteriori analyses of routinely collected clinical data and thus

did not require MSF ERB review. It was conducted with permission from Micaela Serafini (Medical Director, Operational Centre Geneva, MSF).

RESULTS

Of 11 328 TB treatment notifications in Shiselweni, the annual number declined from 2800 to 566 between 2009 and 2016 and in all age groups irrespective of HIV status (Table 1a, Figure 1). From 2009 to 2010, most cases (96.4% and 70.8%) started TB treatment at secondary care facilities and approximately half of them at primary care clinics the years thereafter (see Appendix S3, Figure S5a). The proportion of patients with unknown HIV status decreased from 10.6% in 2009 to 1.4% in 2016 (Figure S5b).

Trends in HIV-associated TB notifications (cohort level)

Of 8083 HIV co-infected TB cases, the annual number declined from 2056 to 388 between 2009 and 2016 (Table 1b, Figure 1). The median age was 32 (interquartile range [IQR] 26–41) years, 86.2% had pulmonary TB, and 86.4% were new treatment cases without significant variations over time. The male-to-female ratio increased from 0.82 to 1.22 between 2008 and 2016, corresponding to 45.0% and 54.9% males, respectively. During the phase-out of smear-microscopy testing and phase-in of Xpert testing in 2012 (see Appendix S3, Figure S6), bacteriologically confirmed TB increased from 35.0% in 2009 to 81.7% in 2016 while proportionally fewer had missing bacteriologic (14.7% vs. 6.2) status, respectively (Figure S5c). In 2009, 0.6% of patients started a second-line TB drug treatment regimen compared with 7.7% in 2016 (Figure S5d). The proportion of patients diagnosed as HIV-positive ≥ 91 days before starting TB treatment increased from 31.7% to 43.8% between 2009 and 2016. Regarding the timing of cotrimoxazole prophylaxis and ART initiation in relation to TB treatment and considering the same time period, the proportion of patients receiving cotrimoxazole prophylaxis ≥ 91 days before starting TB treatment increased from 11.9% to 34.8%, and the proportion of patients receiving ART before TB treatment increased from 13.5% to 35.6%, respectively (Figure S5e,f). Of note, 59.0% of patients had missing ART status in 2009 vs. 9.8% in 2016.

Patient-level predictors of HIV-associated TB

All TB notification data ($n = 11\,328$; 10 imputed datasets) were used in multivariate logistic regression analysis (Table 2). The multiple imputation diagnostic was satisfied (see Appendix S2, Figure S3–S4). The probability of being an HIV-positive TB treatment case fell in all years from 2011 (adjusted odds ratio [aOR] 0.69, 95% confidence interval [CI]: 0.58–0.83) to 2016 (aOR 0.54, 0.43–0.69) (vs. 2009), in the age groups ≤ 29 and ≥ 40 years old (vs. 35–39 years) and in males (aOR 0.65, 0.59–0.72). The probability was higher for secondary healthcare level (aOR 1.18, 1.06–1.33),

recurrent TB (aOR 1.40, 1.19–1.65) and negative (aOR 1.31, 1.15–1.49) or missing (aOR 1.30, 1.11–1.53) bacteriologic status. No differences were detected for TB site and treatment regimen.

Population-level trends in TB notification

Population-level adjusted TB notification rates per 100 000 person-years are presented in Appendix S3, Table S1–S2. The overall TB notification rate decreased fivefold between 2009 and 2016, from 1341 to 269 per 100 000 person-years (Figure 1a,b). The decline was more pronounced in females (sixfold) than males (4.2-fold) and more pronounced in PLHIV (sixfold) than in the HIV-negative population (threefold). The decline was 7.2- and 4.9-fold for HIV-positive females and males vs. 3.6- and 2.7-fold for HIV-negative females and males, respectively (Figure 1c,d).

Figure a–d shows that TB notifications declined in all age groups and irrespective of HIV status. TB notifications were highest in middle-aged females, while they also remained high for older males. For the HIV-negative population, TB notifications steadily increased with age while a U-shaped pattern was seen for HIV-positive cases in the early years, with higher notification rates in the younger and older age groups. Although PLHIV sustained higher notification rates for all ages, the age pattern of the combined year 2015–2016 was similar to the HIV-negative population with notification rates steadily increasing with age.

Population-level predictors of TB

In both models, men had an approximately 1.8-fold increased risk of TB. Compared with 35- to 39-year-olds, younger age (≤ 19 years) decreased the risk of TB while older age (≥ 55 years) increased it. In Model-1 (see Appendix S3, Table S3), an HIV-positive status (irrespective of ART) increased the risk of TB by 19.5 times (adjusted incidence risk ratio [aIRR] 19.47, 95% CI: 14.89–25.46). In Model-2 (see Appendix S3, Table S4), the risk was 5.3 times higher in PLHIV on ART (aIRR 5.30, 3.94–7.12) and 12.3 times higher in PLHIV not on ART (aIRR 12.26, 9.07–16.56).

In both models, calendar year interacted with HIV/ART status. Comparing 2016 with 2009 in Model-1, the effect of calendar year on declining TB was higher in PLHIV (aIRR 0.13, 95% CI: 0.10–0.17) than in HIV-negative people (aIRR 0.32, 0.24–0.44) (Figure 3a). In Model-2, the year 2016 (vs. 2009) had the most pronounced protective effect for PLHIV not on ART (aIRR 0.15, 0.10–0.20), followed by HIV-negative people (aIRR 0.27, 0.20–0.37) and by PLHIV on ART (aIRR 0.50, 0.36–0.70), while the effect of calendar year was similar for the years 2010 to 2012 (Figure 3b).

ART coverage trends and declining TB from 2008 to 2016

The TB notification rate was 1078 cases per 100 000 population in 2008,²⁹⁷ and the peak was in 2009 (Figure 4). ART coverage increased from 22.0% ($n = 7766$) in 2009, to 55.7% ($n = 20\,139$) in 2014 (study data), and to 82.7% in 2016.¹⁸⁸ ART coverage was similar for both gender in 2011 (men:

36.7%; women: 35.6%),^{173,181} but point estimates tended to be higher for women in 2016 (men: 79.1%; women: 84.1%).¹⁸⁸ During the first year of TB decline in 2010, ART coverage was between 22.0% and 29.9%. When the pace of TB decline reduced in 2014, ART coverage was between 50.8% and 55.7%.

DISCUSSION

We describe patient- and population-level predictors and trends of HIV-associated TB from a high HIV-TB prevalence setting in rural Eswatini. The absolute numbers of TB cases as well as the incidence decreased rapidly over a period of 8 years for both sexes and all age groups and was most pronounced in PLHIV, coinciding with an almost fourfold increase in ART coverage, but was also seen in HIV-uninfected patients.

Findings in context

TB notifications reached unprecedented levels in 2009, with similar trends seen in the other three regions of Eswatini.²⁹⁷ When the trend reversed in 2010, ART coverage was between 22% and 30% vs. 15–20% and 30–40% in peri-urban and urban high HIV prevalence settings in South Africa.^{145,150} When the pace of decline slowed down in 2014, ART coverage was between 51% and 56%. A modelling study suggested that ART programmes are needed to sustain high levels of ART adherence and good immunologic response to avert TB rebound.²² TB rebound was not detected in this setting, with viral load suppression rates in ART patients being $\geq 84\%$.^{134,186}

Calendar year interacted with HIV and ART status. The protective effect of the most recent calendar year (vs. the baseline year) was most pronounced for PLHIV without ART, followed by HIV-negative people and PLHIV on ART. First, this was possibly due to different patterns in population-level trends of median CD4 cell counts. Previous treatment guidelines restricted ART initiation to patients with low CD4 cell counts,^{12,14} possibly resulting in a higher population-level median CD4 count for PLHIV not on ART. An increased risk of TB has been documented for PLHIV with low CD4 cell counts and during the first 4 months after ART initiation (unmasking of subclinical TB)^{300,301} In addition, ART patients may have spent a long time at low CD4 cell counts³⁰⁰ and the effect of immune dysfunction persists despite treatment.²⁹⁴ In this setting, the overall infectious pool was largely reduced by fewer PLHIV being co-infected with TB, which is expected to reduce infectious contacts for the HIV-negative population, explaining the decline in HIV-negative TB. Second, the temporal decline in TB may be due to the synergistic effect of TB and HIV programmatic achievements⁵⁴ possibly affecting the HIV-negative population and PLHIV differently. For instance, national TB data suggested increased ART initiation and cotrimoxazole prophylaxis and reduced adverse TB treatment outcomes in co-infected TB patients.²⁹⁸ The introduction of isoniazid preventive therapy for PLHIV in 2012 may also have contributed to a decline in TB cases in PLHIV in later

years, although its predicted population-level impact in hyperendemic settings is likely smaller than in intermediate TB incidence contexts.^{302,303} In addition, a recent modelling study concluded that ART expansion and high ART coverage are the most important factor in southern and eastern Africa to decrease TB in the HIV-positive population and to a lesser extent in the HIV-negative population, while improvements in TB case detection, TB treatment success and isoniazid preventive therapy play no or only a minor role.³⁰⁴ In fact, the decline in active TB disease coincided with an unprecedented population-level impact of the HIV programme in the study area. In 2016, 91.3% of PLHIV were aware of their HIV-positive status, 82.7% of PLHIV accessed ART and 79.1% of PLHIV were virally suppressed.¹⁸⁸

Although PLHIV sustained an increased risk of active TB disease in this study, TB as an entry point into HIV care became less significant in recent years. The number of HIV co-infected TB cases decreased and proportionally more PLHIV already knew their HIV-positive status, received cotrimoxazole and were on ART for more than 3 months when starting TB therapy.

This study suggests that national guidelines for the diagnosis and management of TB in HIV co-infected patients were translated into routine practice. HIV-associated TB was more likely in bacteriologically negative, extra-pulmonary and recurrent TB cases. First, patients with advanced HIV disease are more likely to have atypical disease presentation, recurrent TB episodes and bacteriologically negative TB.^{294,305–307} To avoid underdiagnoses and treatment delays for smear-negative TB cases, clinicians followed diagnostic algorithms designed for resource-poor, high HIV-TB prevalence settings, allowing ambulatory empiric therapy based on clinical suspicion.²⁹⁹ Second, the proportion of patients with missing or negative bacteriologic status decreased over time. This was likely due to the replacement of smear-microscopy with the Xpert MTB/RIF assay, which is a more sensitive tool in detecting TB, specifically among HIV co-infected patients.³⁰⁸ Yet despite Xpert, empiric therapy continued to play a role (18% in 2016), likely due to extra-pulmonary TB and programmatic factors, as was also reported from other settings.^{309–311} Third, diagnosis in secondary-level health care was also associated with HIV-associated TB, probably because sicker patients with HIV co-infection were more likely to access and health workers to refer complicated cases (e.g. bacteriologically negative TB) to higher healthcare levels.

We noticed sex disparities. Despite an increase in the male-to-female ratio to 1.2, it remained significantly lower than the ratio of 1.7 globally.³¹² In addition, the probability of HIV-associated TB was reduced in men at patient-level but increased at population-level. Sex disparities may be caused by an interplay of sex-specific differences in HIV burden, access to TB services and biologic factors.^{149,313} For instance, while higher HIV prevalence in women^{173,188} likely disproportionately increased their vulnerability to TB disease at population-level prior ART expansion, women appeared to benefit more from HIV service expansion through earlier initiation of ART, better treatment

outcomes and higher ART coverage.^{188,215} A similar trend was reported from neighbouring KwaZulu-Natal (South Africa) where women had a more pronounced decline in HIV/TB related deaths during the rapid roll out of ART.³¹⁴ Notably, during our entire study period the male-to-female ratio remained lower than in low HIV prevalence settings, indicating persistent high risk of TB disease in HIV-positive women despite high ART coverage.

Finally, the mid-year ages (35–39 years old) were also predictive of HIV-associated TB. This all reflects the state of the HIV epidemic, with females and middle-aged adults having the highest HIV burden.^{173,181}

Considerations for the future

HIV-associated TB and the slow global decline of TB may jeopardise achievement of the ambitious targets of the End TB strategy.^{312,315} HIV and TB programmes should continue to target populations at increased risk of TB disease and those with the most unfavourable treatment outcomes (e.g. PLHIV, children^{316–319}). Despite this unprecedented success, the estimated TB incidence in Eswatini remained one of the highest in the world in 2016.¹⁹¹ In this context, the impact of further ART expansion on the TB burden remains uncertain, given a slowing of the downward trends in TB notifications at the already high ART coverage achieved. There is the need of continued focus on health system factors. We believe that decentralisation of HIV and TB services were most important to improve timely access to diagnosis and treatment in our setting. Quality of care also likely improved over time as suggested by our data (e.g. increase in bacteriologically confirmed TB cases, improved documentation) as well as TB treatment success rates.³²⁰ Although ART will likely remain the corner stone for controlling the TB epidemic in high HIV prevalence settings,³⁰⁴ combining a wide range of recommended strategies and interventions into routine practice appears crucial:^{315,321} (i) decreasing the pool of transmittable TB through earlier detection by increased index case tracing and the use of sensitive (e.g. Xpert MTB/RIF Ultra) and point-of-care tests (urine lipoarabinomannan assay);^{322–325} (ii) reducing delays between TB detection and treatment by strengthened decentralised and integrated HIV-TB service;^{321,326} (iii) improving TB treatment outcomes with more effective and more tolerable TB treatment regimens; (iv) combining TB and HIV interventions and ART initiation at high CD4 cell counts;³⁰⁰ and (v) provision of extended isoniazid or other TB preventive treatment for PLHIV.

Limitations and strengths

First, this study likely underestimated TB incidence because TB treatment case notifications do not account for undiagnosed TB¹⁵⁸ or for pre-treatment loss between diagnosis and treatment initiation, which can be as high as 38%.³²⁷ For instance, our electronic TB register was not linked to the presumptive TB register and the laboratory database, thus possibly missing Xpert and smear positive TB cases that have never been notified about their disease or being lost administratively before registration as a TB treatment case. Suboptimal completeness and reliability of routine TB

surveillance data have also been reported from South Africa.³²⁸ On the other hand, the introduction of Xpert may have increased TB detection in culture-positive cases,³²⁹ and some patients receiving empiric treatment may not be real TB cases,³³⁰ possibly increasing estimates. Second, the ecological study design cannot assess a possible causal relationship between ART scale-up and population-level decline in TB cases. We could also not account for other external factors such as changes in HIV-TB programming and migration patterns. Specifically we could not adjust for the expansion of isoniazid preventive therapy since 2012 as data were incomplete and inconsistent. Not adjusting for it, however, could result in overestimation of the population-level effect of ART on TB notifications in PLHIV. Finally, this analysis was restricted to the Shiselweni region of Eswatini as patient-level data from other regions were not available.

A strength of this study was the use of stratified patient-level data over 8 years in a predominantly rural setting. Previous studies were conducted in urban settings^{145,147,150} and used aggregated national level data.^{142,143,146} Few studies have reported from rural settings,¹⁵³ and some of those using patient-level data^{145,147,150} reported from the years before ART expansion beyond the 350 cells/mm³ threshold.¹⁴⁵ Finally, we analysed both patient- and population-level trends and predictors of active TB disease and could provide a comprehensive picture of trends in the TB epidemic in this resource-poor setting.

CONCLUSIONS

This rural, high HIV-TB prevalence setting experienced a rapid decline in TB notifications that was most pronounced in the HIV-infected population but also saw declines in the HIV-uninfected population. ART expansion and changes in HIV-TB programming were likely important contributing factors. However, the TB epidemic is far from over, calling for concerted international efforts to continue ART expansion and to accelerate implementation of improved TB prevention and treatment interventions.

Table 1: Temporal trends in TB notifications, overall (a) and for HIV-associated TB cases (b).

	2009	2010	2011	2012	2013	2014	2015	2016	Total
(a)									
TB notifications, overall	2800	2333	1745	1316	963	914	691	566	11 328
Healthcare level									
Primary	101 (3.6)	681 (29.2)	921 (52.8)	669 (50.8)	485 (50.4)	462 (50.5)	354 (51.2)	296 (52.3)	3969 (35.0)
Secondary	2699 (96.4)	1652 (70.8)	824 (47.2)	647 (49.2)	478 (49.6)	452 (49.5)	337 (48.8)	270 (47.7)	7359 (65.0)
HIV status									
Negative	446 (15.9)	452 (19.4)	436 (25.0)	342 (26.0)	262 (27.2)	265 (29.0)	218 (31.5)	170 (30.0)	2591 (22.9)
Positive	2056 (73.4)	1660 (71.2)	1235 (70.8)	945 (71.8)	690 (71.7)	643 (70.4)	466 (67.4)	388 (68.6)	8083 (71.4)
Missing	298 (10.6)	221 (9.5)	74 (4.2)	29 (2.2)	11 (1.1)	6 (0.7)	7 (1.0)	8 (1.4)	654 (5.8)
(b)									
HIV-associated TB notifications	2056	1660	1235	945	690	643	466	388	8083
Age, years (IQR) (n missing = 30)	32 (26–40)	31 (24–41)	33 (26–42)	32.5 (26–42)	34 (28–43)	33 (28–40)	33 (28–41)	34 (28–40)	32 (26–41)
Sex									
Females	1130 (55.0)	915 (55.1)	645 (52.2)	474 (50.2)	323 (46.8)	300 (46.7)	222 (47.6)	175 (45.1)	4184 (51.8)
Males	926 (45.0)	745 (44.9)	590 (47.8)	471 (49.8)	367 (53.2)	343 (53.3)	244 (52.4)	213 (54.9)	3899 (48.2)
Male/female ratio	0.82	0.81	0.91	0.99	1.14	1.14	1.10	1.22	0.93
TB site									
Pulmonary	1745 (84.9)	1459 (87.9)	1098 (88.9)	824 (87.2)	578 (83.8)	521 (81.0)	410 (88.0)	334 (86.1)	6969 (86.2)
Extra-pulmonary	303 (14.7)	194 (11.7)	134 (10.9)	119 (12.6)	106 (15.4)	120 (18.7)	55 (11.8)	53 (13.7)	1084 (13.4)
Missing	8 (0.4)	7 (0.4)	3 (0.2)	2 (0.2)	6 (0.9)	2 (0.3)	1 (0.2)	1 (0.3)	30 (0.4)
TB classification									
New case	1709 (83.1)	1377 (83.0)	1076 (87.1)	861 (91.1)	626 (90.7)	577 (89.7)	407 (87.3)	347 (89.4)	6980 (86.4)
Recurrent case	334 (16.2)	275 (16.6)	151 (12.2)	80 (8.5)	64 (9.3)	63 (9.8)	57 (12.2)	41 (10.6)	1065 (13.2)
Missing	13 (0.6)	8 (0.5)	8 (0.6)	4 (0.4)	0 (0.0)	3 (0.5)	2 (0.4)	0 (0.0)	38 (0.5)
TB treatment type									
First line	2043 (99.4)	1641 (98.9)	1201 (97.2)	890 (94.2)	650 (94.2)	601 (93.5)	420 (90.1)	358 (92.3)	7804 (96.5)
Second line*	13 (0.6)	19 (1.1)	34 (2.8)	55 (5.8)	40 (5.8)	42 (6.5)	46 (9.9)	30 (7.7)	279

									(3.5)
Bacteriologic status									
Positive	720 (35.0)	475 (28.6)	385 (31.2)	449 (47.5)	413 (59.9)	407 (63.3)	368 (79.0)	317 (81.7)	3534 (43.7)
Negative	1033 (50.2)	753 (45.4)	571 (46.2)	355 (37.6)	176 (25.5)	125 (19.4)	56 (12.0)	47 (12.1)	3116 (38.6)
Missing	303 (14.7)	432 (26.0)	279 (22.6)	141 (14.9)	101 (14.6)	111 (17.3)	42 (9.0)	24 (6.2)	1433 (17.7)
Time of HIV diagnosis, days									
≥91 days before TB treatment	651 (31.7)	523 (31.5)	339 (27.4)	322 (34.1)	244 (35.4)	258 (40.1)	198 (42.5)	170 (43.8)	2705 (33.5)
90–1 days before TB treatment	827 (40.2)	591 (35.6)	489 (39.6)	369 (39.0)	291 (42.2)	257 (40.0)	175 (37.6)	139 (35.8)	3138 (38.8)
During TB treatment	535 (26.0)	462 (27.8)	336 (27.2)	207 (21.9)	115 (16.7)	100 (15.6)	60 (12.9)	59 (15.2)	1874 (23.2)
Missing [†]	43 (2.1)	84 (5.1)	71 (5.7)	47 (5.0)	40 (5.8)	28 (4.4)	33 (7.1)	20 (5.2)	366 (4.5)
Time of ART initiation, days									
≥91 days before TB treatment	277 (13.5)	268 (16.1)	203 (16.4)	195 (20.6)	173 (25.1)	166 (25.8)	147 (31.5)	138 (35.6)	1567 (19.4)
90–1 days before TB treatment	236 (11.5)	160 (9.6)	167 (13.5)	124 (13.1)	119 (17.2)	100 (15.6)	60 (12.9)	63 (16.2)	1029 (12.7)
During TB treatment	330 (16.1)	470 (28.3)	484 (39.2)	450 (47.6)	264 (38.3)	285 (44.3)	186 (39.9)	149 (38.4)	2618 (32.4)
Missing	1213 (59.0)	762 (45.9)	381 (30.9)	176 (18.6)	134 (19.4)	92 (14.3)	73 (15.7)	38 (9.8)	2869 (35.5)
Time of cotrimoxazole initiation, days									
≥91 days before TB treatment	244 (11.9)	225 (13.6)	166 (13.4)	198 (21.0)	163 (23.6)	179 (27.8)	122 (26.2)	135 (34.8)	1432 (17.7)
90–1 days before TB treatment	350 (17.0)	293 (17.7)	301 (24.4)	276 (29.2)	245 (35.5)	215 (33.4)	136 (29.2)	125 (32.2)	1941 (24.0)
During TB treatment	1224 (59.5)	837 (50.4)	525 (42.5)	277 (29.3)	146 (21.2)	135 (21.0)	93 (20.0)	85 (21.9)	3322 (41.1)
Missing	238 (11.6)	305 (18.4)	243 (19.7)	194 (20.5)	136 (19.7)	114 (17.7)	115 (24.7)	43 (11.1)	1388 (17.2)

ART, antiretroviral therapy; IQR, interquartile range.

*Second line TB treatment cases were patients who received a treatment regimen for mono-resistance, poly-resistance, multidrug resistance or extensive drug resistance TB.

[†]These patients had a confirmed HIV-positive status but the date of diagnosis was unknown.

Table 2: Baseline characteristics and uni- and multivariate associations with HIV among all patients with TB.

	Baseline characteristics of TB cases (n = 10 674) [†]			Predictors of HIV-associated TB (n = 11 328) [§]			
	HIV-negative	HIV-positive		OR	95% CI	aOR	95% CI
Total number (missing = 654) [†]	2591	8083					
Calendar year							
2009	446 (17.2)	2056 (25.4)	<0.001	1		1	
2010	452 (17.4)	1660 (20.5)		0.82	(0.70–0.94)	0.92	(0.78–1.09)
2011	436 (16.8)	1235 (15.3)		0.64	(0.55–0.74)	0.69	(0.58–0.83)
2012	342 (13.2)	945 (11.7)		0.62	(0.52–0.72)	0.71	(0.59–0.86)
2013	262 (10.1)	690 (8.5)		0.60	(0.50–0.72)	0.70	(0.57–0.86)
2014	265 (10.2)	643 (8.0)		0.55	(0.46–0.66)	0.53	(0.43–0.65)
2015	218 (8.4)	466 (5.8)		0.49	(0.40–0.59)	0.53	(0.42–0.66)
2016	170 (6.6)	388 (4.8)		0.52	(0.43–0.64)	0.54	(0.43–0.69)
Healthcare level							
Primary	1148 (44.3)	2698 (33.4)	<0.001	1		1	
Secondary	1443 (55.7)	5385 (66.6)		1.57	(1.43–1.71)	1.18	(1.06–1.33)
Sex							
Females	1060 (40.9)	4184 (51.8)	<0.001	1		1	
Males	1531 (59.1)	3899 (48.2)		0.65	(0.60–0.71)	0.65	(0.59–0.72)
Age, years (missing = 30)							
0–4	260 (3.2)	481 (4.5)	<0.001	0.11	(0.08–0.14)	0.08	(0.06–0.11)
5–9	226 (2.8)	327 (3.1)		0.20	(0.14–0.27)	0.16	(0.11–0.22)
10–14	213 (2.6)	305 (2.9)		0.21	(0.15–0.28)	0.17	(0.12–0.23)
15–19	173 (2.1)	407 (3.8)		0.07	(0.05–0.09)	0.06	(0.05–0.08)
20–24	720 (8.9)	1022 (9.6)		0.21	(0.17–0.27)	0.19	(0.15–0.24)
25–29	1460 (18.1)	1701 (16.0)		0.54	(0.42–0.69)	0.49	(0.38–0.63)
30–34	1538 (19.1)	1696 (16.0)		0.86	(0.66–1.12)	0.85	(0.65–1.11)
35–39	1166 (14.5)	1268 (11.9)		1		1	
40–45	771 (9.6)	887 (8.3)		0.59	(0.45–0.78)	0.56	(0.43–0.75)
45–49	512 (6.4)	629 (5.9)		0.39	(0.30–0.52)	0.38	(0.29–0.51)
50–54	385 (4.8)	517 (4.9)		0.26	(0.20–0.35)	0.26	(0.20–0.35)
55–59	251 (3.1)	398 (3.7)		0.15	(0.12–0.21)	0.15	(0.11–0.21)
≥60	378 (4.7)	986 (9.3)		0.06	(0.04–0.07)	0.05	(0.04–0.06)
TB site (missing = 30)							
Pulmonary	2285 (88.4)	6969 (86.5)	0.013	1		1	
Extra-pulmonary*	299 (11.6)	1084 (13.5)		1.19	(1.04–1.36)	1.06	(0.91–1.24)
TB classification (missing = 38)							
New case	2345 (90.9)	6980 (86.8)	<0.001	1		1	
Recurrent case	234 (9.1)	1065 (13.2)		1.50	(1.30–1.74)	1.40	(1.19–1.65)
Bacteriologic status							
Positive	1197 (46.2)	3534 (43.7)	<0.001	1		1	
Negative	840 (32.4)	3116 (38.6)		1.25	(1.13–1.39)	1.31	(1.15–1.49)

Missing	554 (21.4)	1433 (17.7)	0.85	(0.75–0.95)	1.30	(1.11–1.53)
TB treatment type						
First line	2516 (97.1)	7804 (96.5)	0.168	1	1	
Second line [‡]	75 (2.9)	279 (3.5)	1.21	(0.93–1.56)	1.16	(0.86–1.56)

OR, odds ratio from univariate analysis; aOR, adjusted odds ratio from multivariate analysis; CI, confidence interval.

*Patients diagnosed with both pulmonary and extra-pulmonary TB are counted under extra-pulmonary TB.

[†]Among all patients ($n = 11\,328$), 654 (5.8%) had missing HIV status and were not included in description of baseline characteristics.

[‡]Second line TB treatment cases were patients who received a treatment regimen for mono-resistance, poly-resistance, multidrug resistance or extensive drug resistance TB.

[§]Missing values of HIV status, age, TB site and TB classification were imputed into 10 datasets. Thus all observations ($n = 11\,328$) were used in multivariate logistic regression analysis.

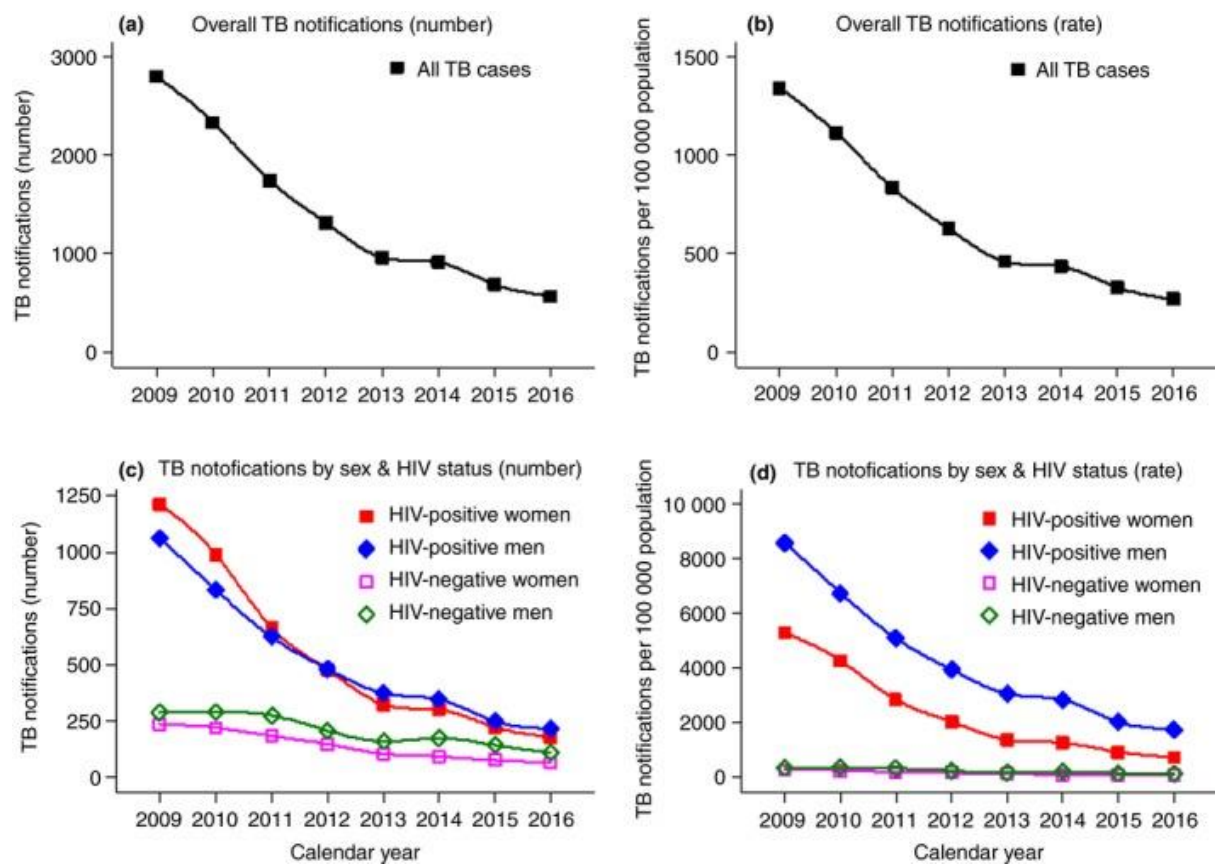


Figure 1: Temporal trends in TB notifications (absolute numbers vs. rates), overall and stratified by sex and HIV status.

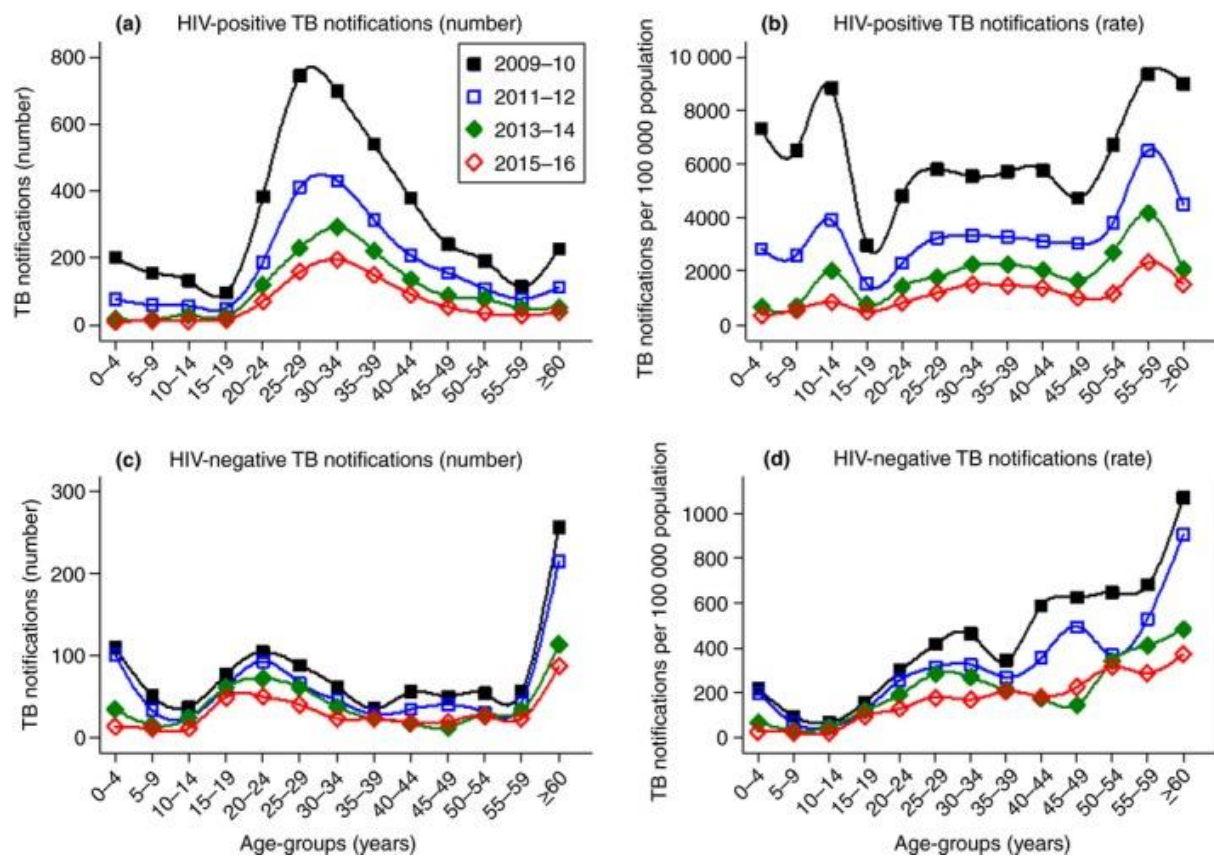
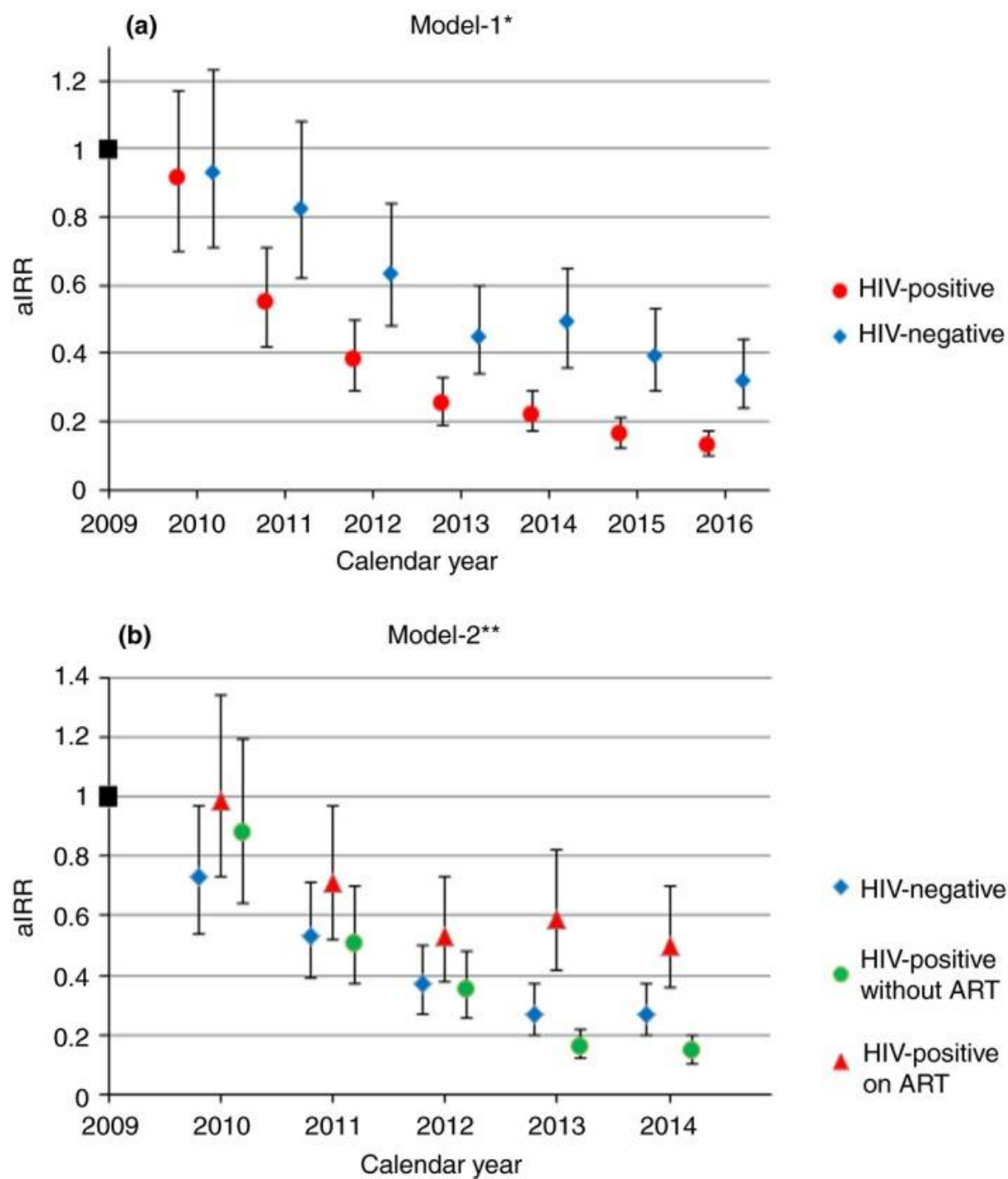
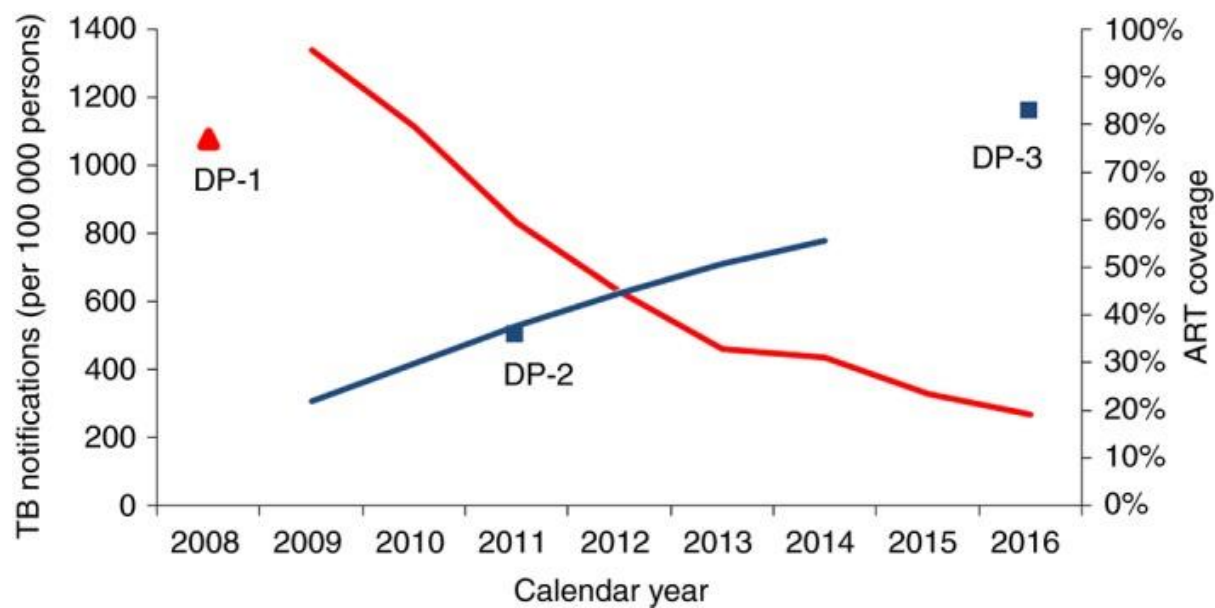


Figure 2: Age-stratified temporal trends in TB notifications (absolute numbers vs. rates) for HIV-positive and HIV-negative cases.



*Model-1 considered the entire study period adjusted for the population-level covariates sex, age and HIV status. **Model-2 combined HIV status and ART status into one covariate with three categories (HIV-negative case, PLHIV on ART, PLHIV without ART), but was restricted to the years from 2009 to 2014 as reliable stratified ART coverage estimates were not available for the time period thereafter.

Figure 3: The effect of calendar year on TB notifications in Model-1 (a) and Model-2 (b). aIRR, adjusted incidence risk ratio.



This graph combines estimates from the study (blue and red lines) and data points obtained from the annual TB report for TB notifications in 2008²⁹⁷ and from the Swaziland HIV Incidence Measurement Surveys for ART coverage in 2011^{173,181} and 2016.¹⁸⁸ Blue line: ART coverage for all age groups combined. Red line: TB notification rates for all age groups combined irrespective of HIV status. DP-1, data point 1: TB notification per 100 000 population in 2008.²⁹⁷ DP-2, data point 2: ART coverage in ≥ 18 to 49-year-olds in 2011.^{173,181} DP-3, data point 3: ART coverage in ≥ 15 -year-olds in 2016.¹⁸⁸

Figure 4: Temporal trends in TB notifications and ART coverage from 2008 to 2016.

SUPPORTING INFORMATION

Appendix S1. TB case notifications in the wider context of Eswatini.

Figure S1. Annual absolute number of TB notifications in Eswatini from 1995 to 2016.

Figure S2. Annual TB notification rates (per 100 000 population) in the four regions of Eswatini from 2008 to 2012.

Appendix S2. Multiple imputation diagnostic.

Figure S3. Diagnostic plot for the convergence of the mean of imputed variables.

Figure S4. Diagnostic plots comparing the distributions of the observed, imputed, and completed values.

Appendix S3. Additional results.

Figure S5. Temporal trends in baseline characteristics of patients starting TB treatment in the Shiselweni region, Eswatini.

Figure S6. The phase-out of TB smear testing (a) and the phase-in of the Xpert MTB/RIF assay (b) for the diagnosis of TB in the Shiselweni region, Eswatini.

Table S1. Total number of TB notifications overall and stratified by sex and HIV status notification rates (per 100 000 population), and relative and absolute decline from 2009 to 2016.

Table S2. Age-specific total number of TB notifications, overall and stratified by HIV status, and notification rates (per 100 000 population) from 2009 to 2016.

Table S3. Population-level adjusted risk of TB notification from 2009 to 2014 (Model-1*).

Table S4. Population-level adjusted risk of TB notification from 2009 to 2014, taking ART coverage for sex and age group into account (Model-2*).

APPENDIX S1: TB CASE NOTIFICATIONS IN THE WIDER CONTEXT OF ESWATINI

The analysis period for this study started in 2009. To put the burden of TB in the wider context, the next figures present the overall TB notifications reported in Eswatini and the TB notifications from the 4 regions of Eswatini. In Eswatini, the number of TB cases increased from 1995 (n = 2058), reaching its peak in 2010 (n = 11,057), and declined thereafter (Figure S1). The highest estimated TB incidence was reported from the Shiselweni region (1293 cases per 100,000 population) in 2009 (Figure S2). All regions saw a decline in TB incidence starting between 2008 and 2011.

Figure S1 and S2 were reproduced from routine national monitoring and evaluation data obtained from the 2012 and 2017 TB program annual reports ^{297,331}, with permission from the Eswatini National TB Control Programme.

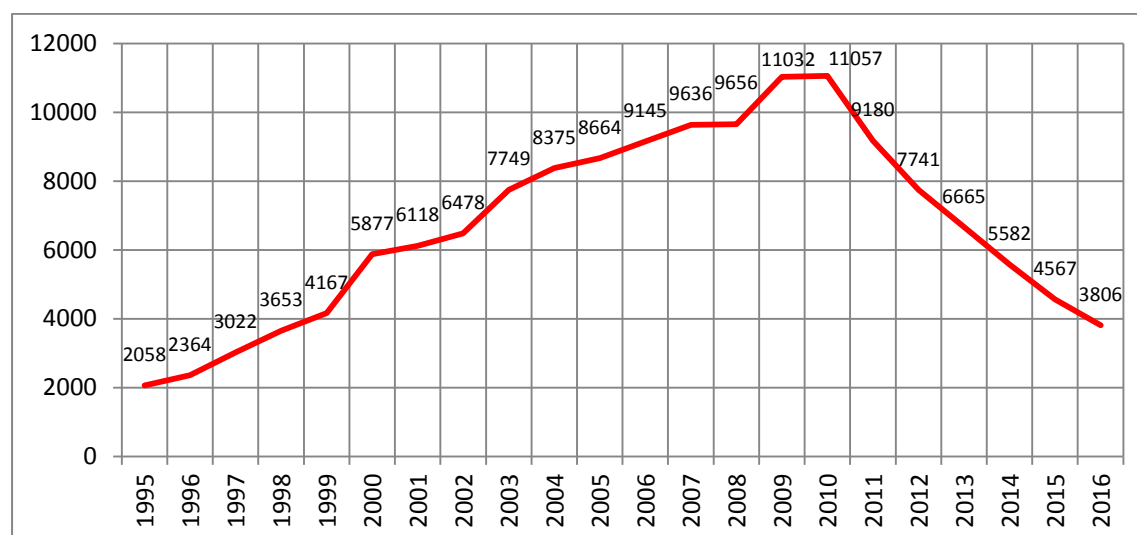


Figure S1: Annual absolute number of TB notifications in Eswatini from 1995 to 2016.

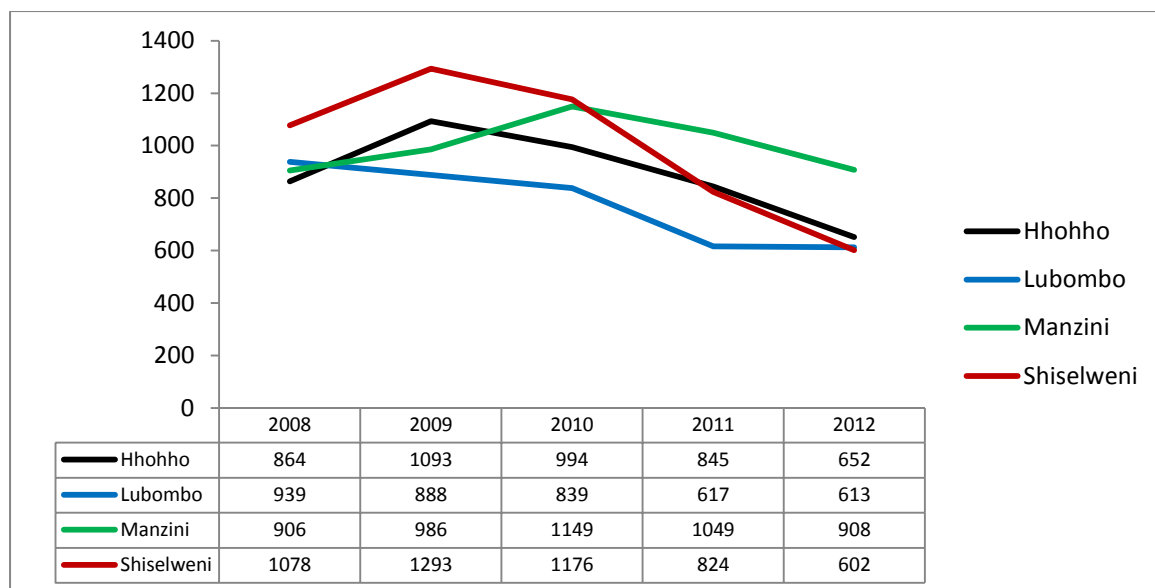


Figure S2: Annual TB notification rates (per 100,000 population) in the 4 regions of Eswatini from 2008 to 2012.

APPENDIX S2: MULTIPLE IMPUTATION DIAGNOSTIC

We used multiple imputation by chained equations to handle missing data. Missing values of HIV status, age, TB site, and TB classification were imputed as implemented in Stata version 14.1 (College Station, Texas). Among all patients ($n = 11,328$), 41 (0.4%) had missing TB site status, 56 (0.5%) missing TB classification status, 56 (0.5%) missing age, and 654 (5.8%) missing HIV status. Convergence of the imputation algorithm was reviewed by plotting the mean of the imputed values against the cycle number (Figure S3). Observed, imputed, and completed distributions of categorical variables were graphically displayed for each imputation (Figure S4).

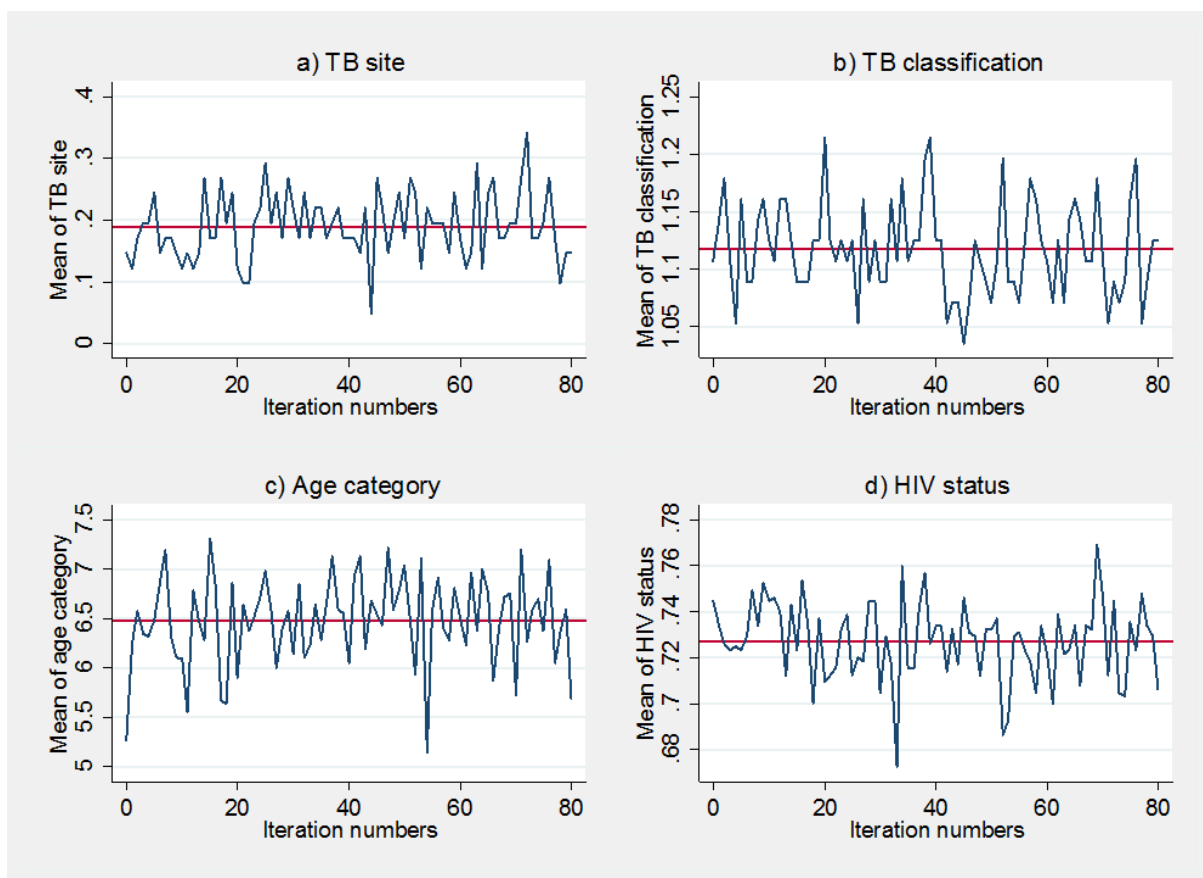
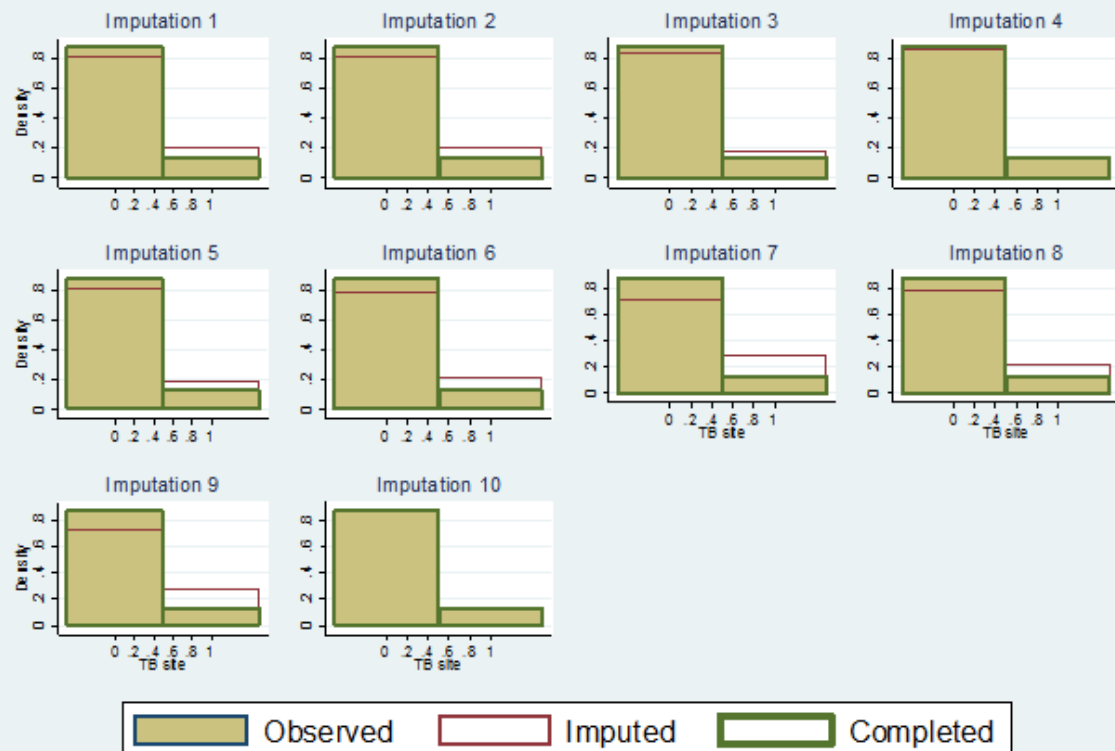
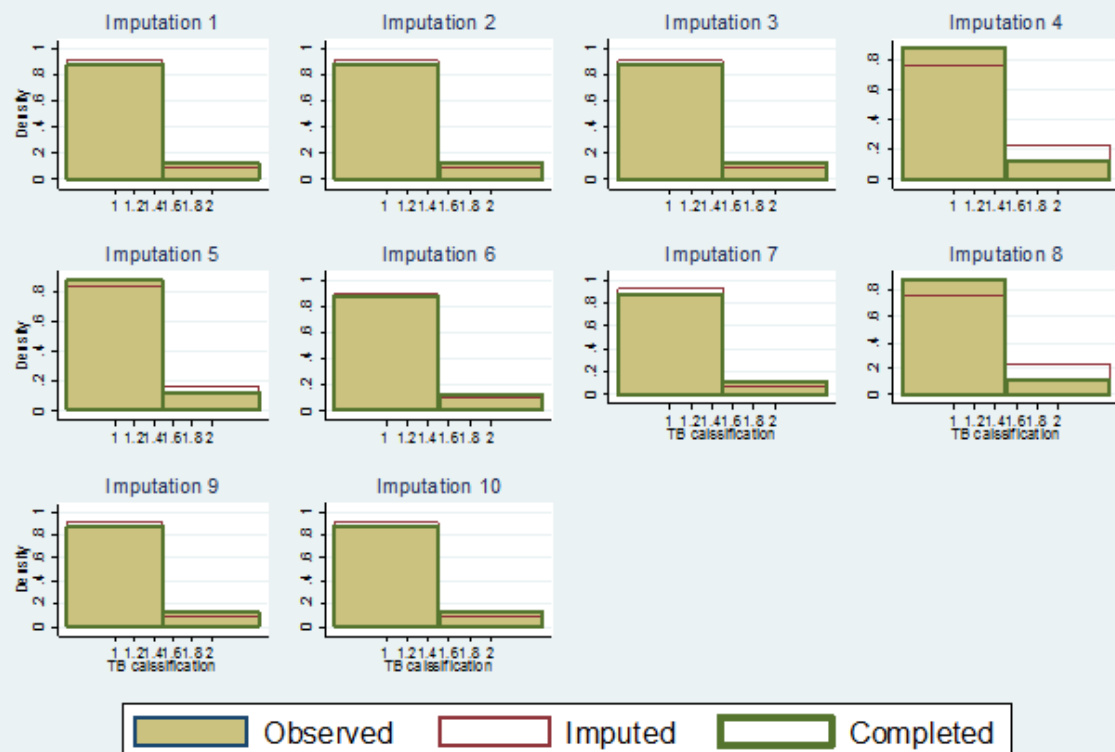


Figure S3 a-d: Diagnostic plot for the convergence of the mean of imputed variables

a) TB site



b) TB classification



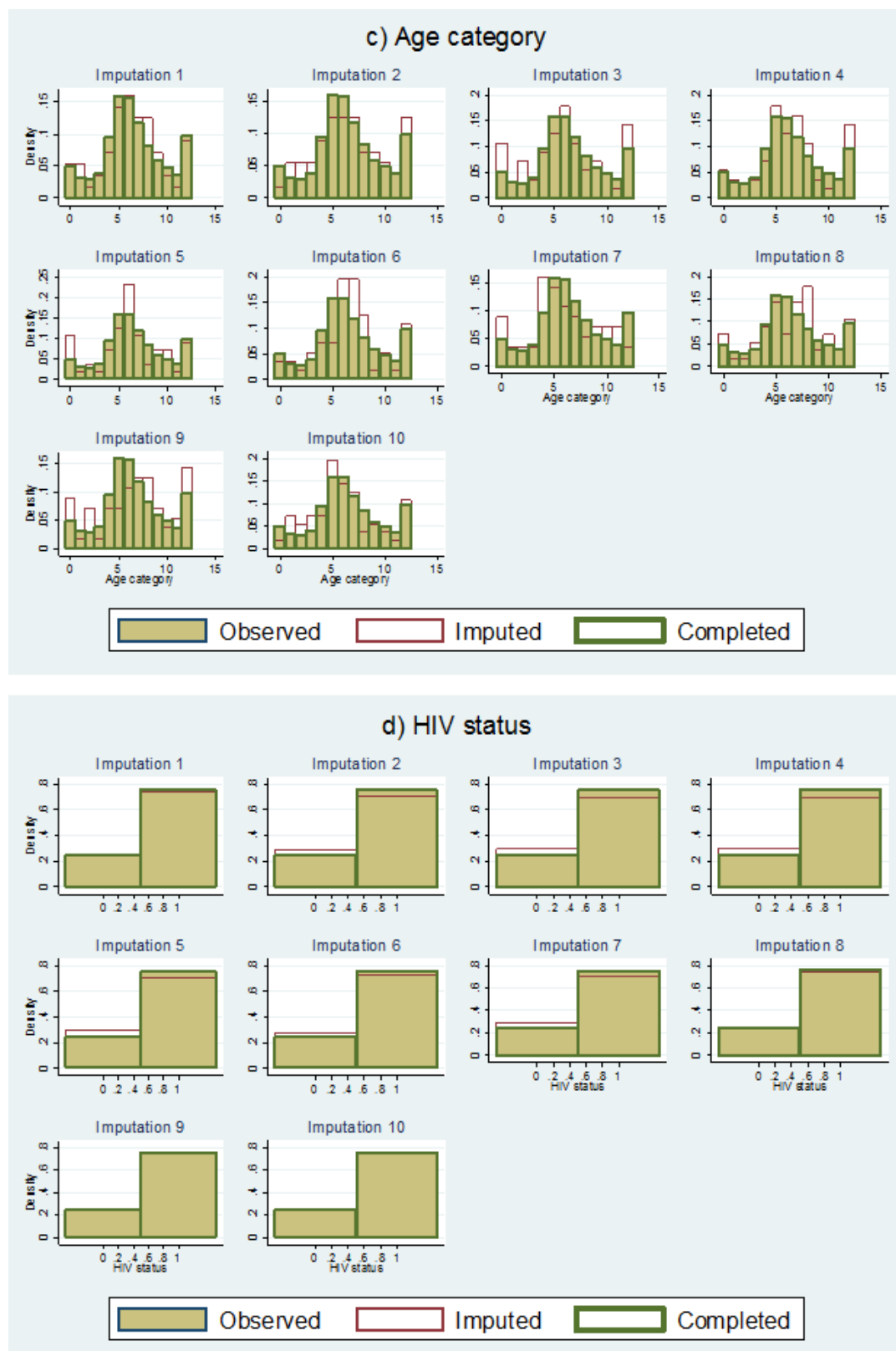


Figure S4 a-d: Diagnostic plots comparing the distributions of the observed, imputed, and completed values.

APPENDIX S3: ADDITIONAL RESULTS

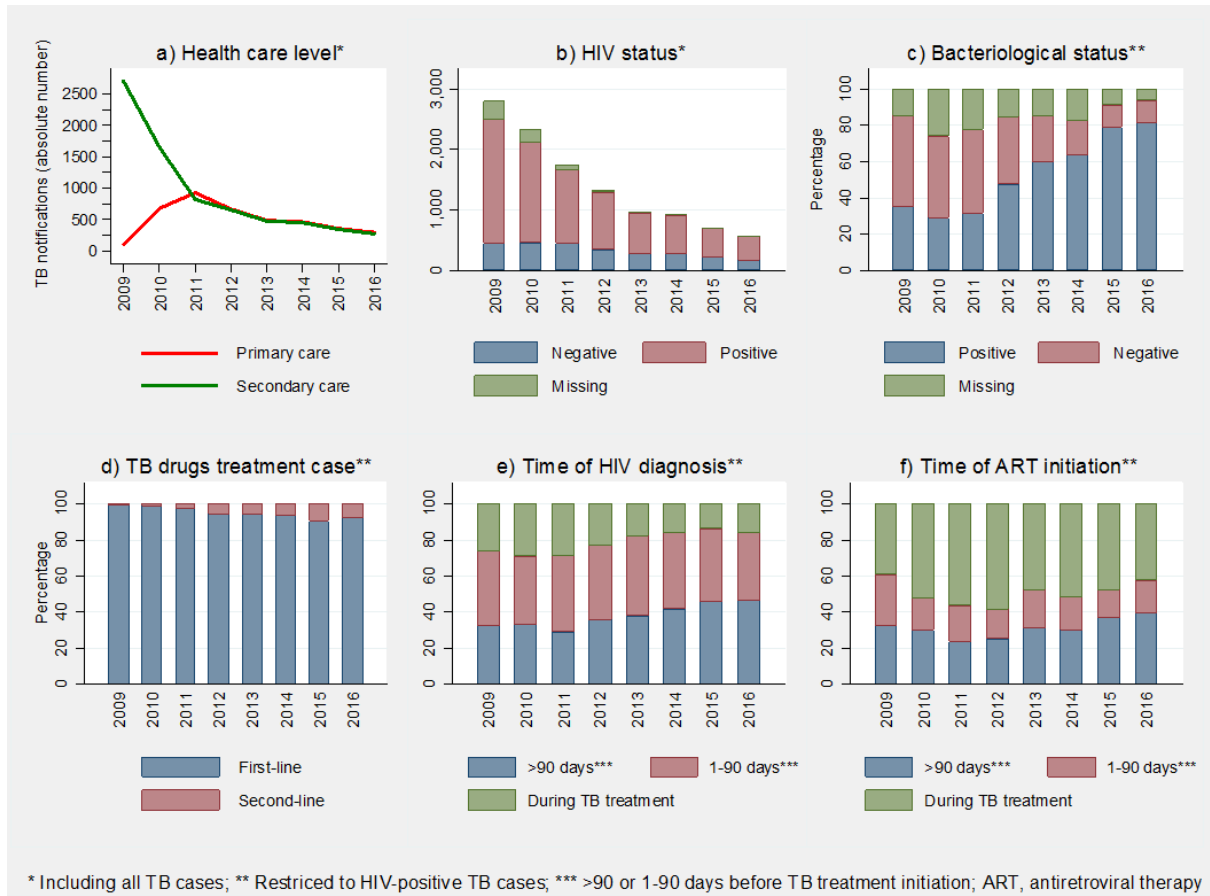
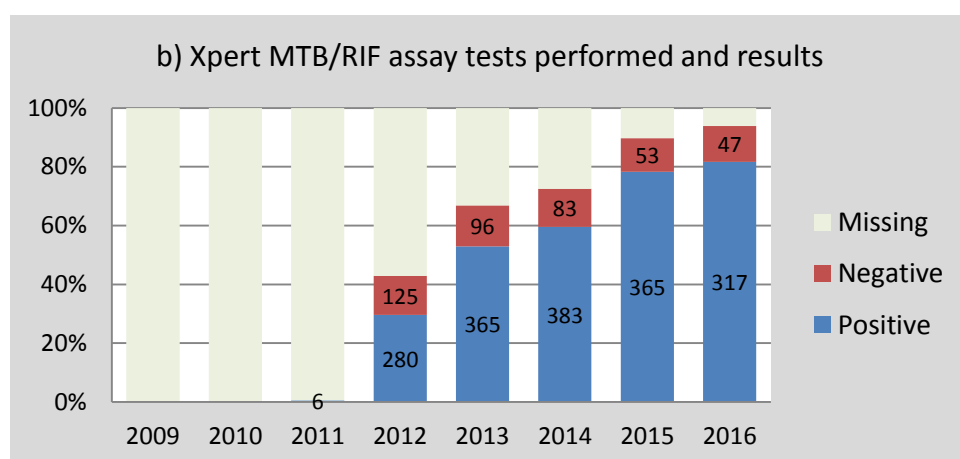
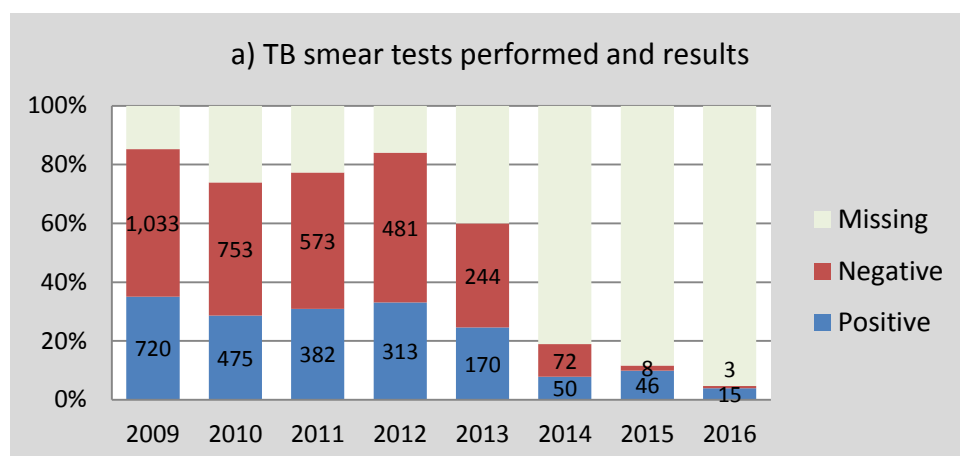


Figure S5 a-f: Temporal trends in baseline characteristics of patients starting TB treatment in the Shiselweni region, Eswatini.



All data were obtained from TB treatment registers.

The category “missing” indicates that test results were not recorded in the TB treatment register, because either the test was not performed or the results were not recorded.

The figure shows the transitioning from TB diagnostic based on smear microscopy testing to Xpert MTB/RIF testing since late 2011. The use of TB smear was most pronounced in the early years of the study period (2009–2011), the transition period was from 2012 to 2013, and the predominant use of the Xpert MTP/RIF assay was from 2014 to 2016.

Figure S6 a-b: The phase-out of TB smear testing (a) and the phase-in of the Xpert MTB/RIF assay (b) for the diagnosis of TB in the Shiselweni region, Eswatini.

Table S1: Total number of TB notifications overall and stratified by sex and HIV status notification rates (per 100,000 population), and relative and absolute decline from 2009 to 2016.

Calendar year	Total		Females		Males		HIV-negative		HIV-positive		HIV-negative females		HIV-negative males		HIV-positive females		HIV-positive males	
	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence
2009	2800	1341	1450	1297	1350	1391	524	302	2276	6439	236	266	288	340	1214	5293	1062	8558
2010	2333	1116	1210	1083	1123	1155	511	295	1822	5135	221	249	290	342	989	4273	833	6754
2011	1745	834	847	758	898	922	458	264	1287	3613	183	207	275	323	664	2843	623	5076
2012	1316	629	627	561	689	706	355	204	961	2686	148	168	207	242	479	2034	482	3941
2013	963	460	429	384	534	546	265	153	698	1941	105	119	160	187	324	1365	374	3063
2014	914	436	394	353	520	531	266	153	648	1792	92	105	174	203	302	1262	346	2833
2015	691	329	299	268	392	399	219	126	472	1298	76	87	143	166	223	924	249	2035
2016	566	269	242	217	324	329	173	100	393	1074	64	73	109	127	178	732	215	1751
Decrease ¹ (n)	2234	1072	1208	1080	1026	1062	351	202	1883	5365	172	193	179	213	1036	4561	847	6807
Decrease ¹ (relative)	4.9	5.0	6.0	6.0	4.2	4.2	3.0	3.0	5.8	6.0	3.7	3.6	2.6	2.7	6.8	7.2	4.9	4.9

1Absolute and relative (fold) decrease in TB notifications between 2009 and 2016.

n, number; incidence, number of TB notifications per 100,000 population.

Table S2: Age-specific total number of TB notifications, overall and stratified by HIV status, and notification rates (per 100,000 population) from 2009 to 2016.

Year	Age group, years	All TB cases		HIV-positive		HIV-negative	
		n	Incidence	n	Incidence	n	Incidence
2009	0–4	153	570	107	7726	46	181
	5–9	105	371	85	7149	20	74
	10–14	72	254	56	7568	16	58
	15–19	83	316	40	2494	43	175
	20–24	258	1209	204	5144	54	311
	25–29	477	2806	433	6757	44	415
	30–34	440	3413	409	6578	31	465
	35–39	342	3473	326	6889	16	313
	40–44	242	3060	211	6466	31	667
	45–49	152	2329	123	4852	29	726
	50–54	134	2426	106	7402	28	684
	55–59	88	1861	57	9360	31	752
	≥60	254	1908	119	9415	135	1121
2010	0–4	158	599	94	6912	64	256
	5–9	101	358	70	5892	31	115
	10–14	95	336	74	10,054	21	76
	15–19	90	338	56	3455	34	136
	20–24	230	1061	180	4492	50	283
	25–29	355	2100	311	4875	44	418
	30–34	320	2437	289	4551	31	457
	35–39	232	2353	213	4501	19	371
	40–44	191	2394	167	5090	24	511
	45–49	138	2108	117	4606	21	524
	50–54	111	2018	86	6031	25	613
	55–59	82	1743	57	9421	25	610
	≥60	230	1738	108	8592	122	1019
2011	0–4	108	413	47	3489	61	246
	5–9	56	200	35	2976	21	78
	10–14	50	178	37	5055	13	48
	15–19	60	223	26	1591	34	134
	20–24	154	698	105	2588	49	272
	25–29	283	1679	244	3839	39	372
	30–34	257	1930	230	3565	27	393
	35–39	201	2028	186	3913	15	291
	40–44	138	1714	117	3545	21	442
	45–49	116	1765	98	3851	18	447
	50–54	73	1328	54	3792	19	467
	55–59	74	1583	47	7833	27	662

	≥60	175	1330	61	4880	114	958
2012	0-4	69	261	30	2203	39	156
	5-9	37	137	25	2193	12	46
	10-14	32	114	20	2751	12	44
	15-19	51	188	24	1461	27	106
	20-24	127	564	83	2020	44	239
	25-29	194	1150	167	2629	27	257
	30-34	219	1634	201	3088	18	261
	35-39	141	1406	128	2664	13	249
	40-44	103	1269	90	2715	13	271
	45-49	79	1196	57	2232	22	543
	50-54	65	1181	54	3792	11	270
	55-59	47	1011	31	5210	16	395
	≥60	152	1161	51	4100	101	852
2013	0-4	23	87	9	662	14	56
	5-9	16	60	6	538	10	39
	10-14	34	122	18	2483	16	59
	15-19	44	161	12	729	32	125
	20-24	92	401	66	1585	26	139
	25-29	134	789	104	1630	30	283
	30-34	156	1164	142	2177	14	204
	35-39	117	1146	109	2230	8	150
	40-44	79	967	76	2284	3	62
	45-49	55	827	51	1986	4	98
	50-54	56	1014	42	2939	14	342
	55-59	47	1018	28	4746	19	472
	≥60	110	844	35	2827	75	636
2014	0-4	29	110	9	664	20	80
	5-9	14	54	9	824	5	20
	10-14	19	68	11	1521	8	29
	15-19	42	154	13	793	29	113
	20-24	99	424	53	1257	46	241
	25-29	155	900	124	1922	31	288
	30-34	172	1288	149	2290	23	336
	35-39	128	1227	113	2263	15	276
	40-44	74	902	60	1802	14	287
	45-49	43	640	35	1352	8	194
	50-54	49	884	35	2442	14	340
	55-59	35	762	21	3590	14	349
	≥60	55	424	16	1297	39	332
2015	0-4	17	65	6	445	11	44
	5-9	8	31	5	467	3	12
	10-14	10	36	8	1111	2	7
	15-19	41	151	8	491	33	129

	20–24	67	283	38	890	29	149
	25–29	113	644	91	1388	22	200
	30–34	121	910	107	1651	14	205
	35–39	87	816	73	1432	14	252
	40–44	59	717	51	1530	8	163
	45–49	40	588	34	1300	6	143
	50–54	32	575	19	1321	13	315
	55–59	27	590	12	2062	15	375
	≥60	69	533	20	1627	49	418
2016	0–4	5	19	3	224	2	8
	5–9	14	56	7	660	7	29
	10–14	13	47	4	563	9	34
	15–19	24	89	8	495	16	63
	20–24	53	221	32	743	21	107
	25–29	85	474	67	1004	18	160
	30–34	97	731	88	1361	9	132
	35–39	86	794	77	1486	9	159
	40–44	51	615	41	1222	10	202
	45–49	32	465	19	720	13	307
	50–54	28	500	15	1039	13	313
	55–59	23	502	15	2582	8	200
	≥60	55	427	17	1388	38	326

n, number; incidence, number of TB notifications per 100,000 population.

Table S3. Population-level adjusted risk of TB notification from 2009 to 2014 (Model-1*).

	aIRR	95% CI
Sex		
Female	1	
Male	1.82	(1.64–2.01)
Age category		
0–4	0.54	(0.42–0.70)
5–9	0.39	(0.30–0.51)
10–14	0.52	(0.40–0.69)
15–19	0.51	(0.39–0.66)
20–24	0.82	(0.64–1.05)
25–29	1.01	(0.79–1.29)
30–34	1.10	(0.86–1.41)
35–39	1	
40–44	1.06	(0.82–1.37)
45–49	1.00	(0.77–1.31)
50–54	1.26	(0.97–1.64)
55–59	1.66	(1.28–2.16)
≥60	1.83	(1.43–2.34)
HIV status		
Negative	1	
Positive	19.47	(14.89–25.46)
Effect of calendar year if HIV negative		
2009	1	
2010	0.93	(0.71–1.23)
2011	0.82	(0.62–1.08)
2012	0.63	(0.48–0.84)
2013	0.45	(0.34–0.60)
2014	0.49	(0.36–0.65)
2015	0.39	(0.29–0.53)
2016	0.32	(0.24–0.44)
Effect of calendar year if HIV-positive		
2009	1	
2010	0.91	(0.70–1.17)
2011	0.55	(0.42–0.71)
2012	0.38	(0.29–0.50)
2013	0.25	(0.19–0.33)
2014	0.22	(0.17–0.29)
2015	0.16	(0.12–0.21)
2016	0.13	(0.10–0.17)

aIRR, adjusted incidence risk ratio; CI, confidence interval.

**Model-1 considered the entire study period adjusted for the population-level covariates sex, age and HIV status.*

Table S4. Population-level adjusted risk of TB notification from 2009 to 2014, taking ART coverage for sex and age group into account (Model-2*).

	aIRR	95% CI
Sex		
Female	1	
Male	1.77	(1.59–1.97)
Age category		
0–4	0.57	(0.43–0.74)
5–9	0.43	(0.32–0.57)
10–14	0.69	(0.52–0.92)
15–19	0.47	(0.35–0.62)
20–24	0.88	(0.68–1.14)
25–29	1.04	(0.81–1.33)
30–34	1.13	(0.88–1.45)
35–39	1	
40–44	0.99	(0.77–1.28)
45–49	0.90	(0.70–1.17)
50–54	1.20	(0.92–1.56)
55–59	1.90	(1.42–2.53)
≥60	1.37	(1.06–1.77)
HIV & ART status		
HIV-negative	1	
HIV-positive on ART	5.30	(3.94–7.12)
HIV-positive without ART	12.26	(9.07–16.56)
Effect of calendar year if HIV-negative		
2009	1	
2010	0.73	(0.54–0.97)
2011	0.53	(0.39–0.71)
2012	0.37	(0.27–0.50)
2013	0.27	(0.20–0.37)
2014	0.27	(0.20–0.37)
Effect of calendar year if HIV-positive on ART		
2009	1	
2010	0.99	(0.73–1.34)
2011	0.71	(0.52–0.97)
2012	0.53	(0.38–0.73)
2013	0.59	(0.42–0.82)
2014	0.50	(0.36–0.70)
Effect of calendar year if HIV-positive without ART		
2009	1	
2010	0.88	(0.64–1.19)
2011	0.51	(0.37–0.70)
2012	0.35	(0.26–0.48)
2013	0.16	(0.12–0.22)

2014	0.15	(0.10–0.20)
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aIRR, adjusted incidence risk ratio; CI, confidence interval.

***Model-2 combined HIV status and ART status into one covariate with three categories (HIV-negative case, PLHIV on ART, PLHIV without ART), but was restricted to the years from 2009 to 2014 as reliable stratified ART coverage estimates were not available for the time period thereafter.*

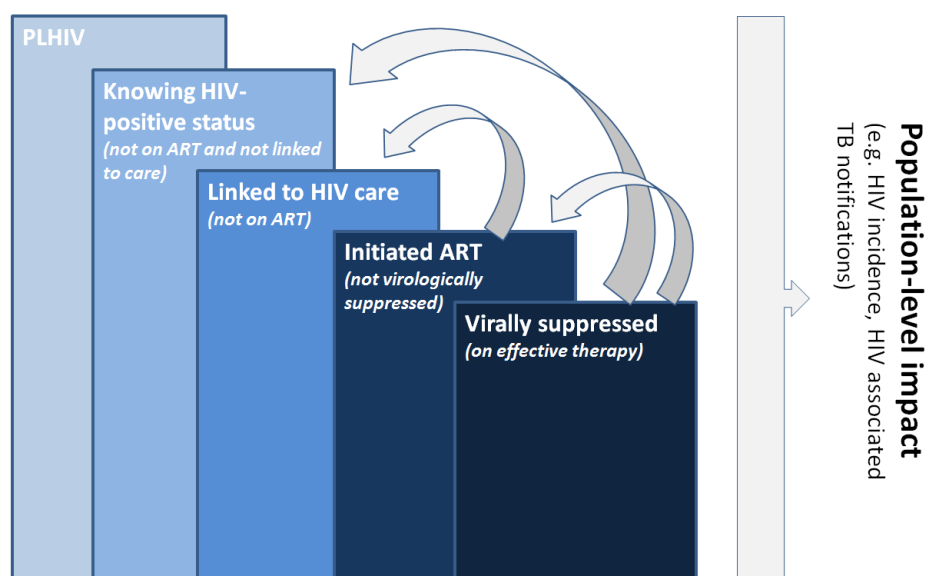
Chapter III: Discussion

Findings of the thesis have been discussed in detail in Chapter II under each paper. This section discusses these findings in the wider context and considers new evidence since the inception of this research project. In addition, this section also discusses in more detail the viral load cascade, HIV drug resistance, and the potential population-level impact of ART scale-up as these outcomes were not evaluated in the studies presented in Chapter II.

Prior to the inception of this research project, little was known about the feasibility of Treat-All in realistic public sector settings. This thesis has demonstrated that ART expansion is feasible in the public sector of this predominantly rural, high HIV and TB prevalence setting in southern Eswatini. Before Treat-All, programmatic outcomes improved with ART expansion, with 12-month retention on therapy (86%) and ART coverage (57% in all PLHIV) being reasonably high in 2014. Thereafter, the Treat-All approach achieved overall higher rates of ART initiation (91% at 3 months) with favourable rates of ART retention (12 months: 81% for non-pregnant adults) and the risk of the composite unfavourable treatment outcome (attrition and viral failure) similar between Treat-All and SOC (aHR 1.04, 95% CI 0.90 to 1.20). For patients presenting with advanced HIV disease under Treat-All versus SOC, ART initiation was quicker (aHR 1.75, 95% CI 1.47 to 2.08) and the risk of an unfavourable treatment outcome was similar (aHR 1.13, 95% CI 0.88 to 1.44). Findings, however, suggest that caution is needed with same-day ART initiation, as the unfavourable treatment outcome increased compared with ART initiation between 1 and 14 days after facility-based HIV care enrolment. At the population level, ART expansion may have contributed to a reduction in notifications of TB disease, most pronounced in PLHIV (sixfold decline vs three fold decline in HIV-negative people). There was no evidence of TB rebound.

INTERPRETATION OF FINDINGS

The discussion in this section situates the thesis findings within the context of optimising the HIV care cascade (see Figure 2): from HIV diagnosis to care enrolment, to ART initiation, and to treatment outcomes including viral suppression and HIV drug resistance. There is also a specific focus on patients with advanced HIV disease. The section concludes with considerations on the population-level impact of ART expansion on TB notifications, population-level HIV care outcomes (e.g. ART coverage) and HIV incidence.



PLHIV, people living with HIV.

This HIV care cascade displays the main steps from being a person living with HIV (and not knowing about the HIV-positive status) to viral suppression. All these steps are interlinked, and patients can move between the different steps. These steps should not be seen separately from each other as they are interlinked. The performance of the HIV programme or an intervention at each of the steps may also determine the population-level impact of that intervention.

Figure 2: The HIV care cascade and population-level impact.

Importantly, the effectiveness of universal ART can be analysed, described and discussed in different ways. For instance, studies that start analysis at a specific point along the HIV care cascade and assess health outcomes at the individual level may miss the population-level benefit of the very same intervention, specifically if the intervention (e.g. Treat-All approach) affects several steps along the cascade. While a study on health outcomes of patients who initiated ART may increase understanding of barriers and facilitators to maintaining successful therapy under Treat-All, the very same study cannot demonstrate the possible benefit of Treat-All on the steps before the start of treatment including HIV testing, linkage, and prompt ART initiation. It may also ignore that some outcomes are not final. For instance, patients recorded as lost to ART may temporarily enter the HIV care

continuum at an earlier point, but re-engage in HIV care and re-initiate ART at a later time. In addition, focus on the patient level (e.g. worsened treatment outcomes for some patients under Treat-All) may hide other benefits such as more patients accessing ART under Treat-All. Therefore, although the discussion follows a linear approach, points raised under each step of the cascade should not be considered in isolation and separate from other steps along the cascade, but interlinked with each other at the individual and population level.

Linkage to HIV care under Treat-All

In this research project, the evaluation of linkage from community-based HTS to facility-based HIV care enrolment and ART initiation was limited because of inadequate data availability. Overall, linkage to care was suboptimal under Treat-All (48% at 6 months), but comparable with SOC (57%, $p=0.286$; see Result-2). Linkage under Treat-All was higher than it was before in this setting (34%)⁷⁹ and in Eswatini (24% at 12 months).⁷⁸ It was similar to Treat-All trial settings in South Africa (TasP, PopART),^{221,332} but inferior to Treat-All trial settings outside of South Africa (SEARCH, PopART, BCPP)^{332–334} (Table 4).

Suboptimal performance at early stages of the HIV care cascade may negatively impact consecutive steps and outcomes downstream of the HIV care continuum, specifically when most HIV diagnosis occur at the community level. For instance, low linkage was presumed to be a main reason in the TasP trial for not achieving population-level HIV incidence reduction under Treat-All despite successful expansion of community HTS, high ART uptake after facility-based care enrolment, and favourable ART outcomes.²²³ In contrast, in this setting, most HIV diagnoses were performed at the facility level (~80%),²²⁵ so pre-facility leakages possibly had less impact than latter stages of the care continuum, specifically as knowledge of HIV-positive status in PLHIV was already high (91%).¹⁸⁸ However, intra-facility linkage from HIV testing to care enrolment – although not assessed in this thesis – could be a gap requiring more attention as it was already sub-optimal in sub-Saharan Africa and Eswatini before the introduction of Treat-All.^{73,199}

This thesis does not report on factors affecting timely linkage to HIV care enrolment and ART initiation. Treat-All trials showed that successful linkages from community-based HTS were associated with a wide range of factors including programmatic (e.g. HTS strategy), facility (e.g. clinic opening hours, overcrowded clinics), socio-demographic (e.g. age), economic (e.g. wealth), patient (e.g. self-stigma, not feeling ready), behavioural (e.g. sexual, HIV-related), and access (e.g. long travel distance to the clinic) determinants.^{219,332–334} Notably, evidence of interventions improving linkage to care under Treat-All remains scarce. For instance, a recent systematic review evaluated linkage to care interventions implemented in the era of ART expansion after 2014.³³⁵ Linkage was increased for interventions providing counselling support and targeting supply-side constraints by removing policy and structural barriers for ease of access to ART (e.g. same-day ART initiation,

reducing counselling sessions, changes in appointment scheduling).³³⁵ In contrast, individual-level behavioural interventions, combination interventions, and financial incentives did not effectively increase linkages or showed mixed results.³³⁵ Higher linkage to care rates under SEARCH, BCPP, and PopART (outside of South Africa) suggest that combination linkage to care interventions and streamlined care may reduce pre-treatment leakages under universal ART (Table 4).^{332–334}

Table 4: Linkage to HIV care, ART initiation, and ART outcomes of main Treat-All trials, and of Nhlanguano health zone following the Treat-All approach.

Study	Linkage to HIV care (since community-based HTS)			ART initiation (since HIV care enrolment)	Retention on ART (since ART initiation)
	3 months	6 months	12 months	3 months	
TasP ²²¹	37.1%	47.6%	62.6%	91.0% (CD4≤350) 87.3% (CD4>350)	84.4% (12 months after first clinic visit)
SEARCH ^{233,334}	61.3%	NA	73.4%	NA	92% (48 weeks)
PopART ^{235,332}	45%*	57%*	71%*	90%**	82.7% (6 months)***
	36%**	47%**	66%**	81%**	76.8% (12 months)***
BCPP ^{333,336}	82%	NA	84%	87% (at 1 months)	93% (6 months)
Nhlanguano health zone	NA	48%	NA	91%	84% (6 months); 78% (12 months); 71% (36 months)

NA, not available.

* PopART in Zambia; ** PopART in South Africa; *** 3 PopART primary care clinics in South Africa (attrition was reported, therefore transformed into retention estimates for this table)

ART initiation under Treat-All

This research project, supported by external evidence, demonstrated an overall benefit of Treat-All on ART uptake.

First, ART expansion prior to Treat-All had already resulted in increased rates of ART initiation and retention in care.²³⁰ Then, in this setting, ART initiation measured from the time of facility-based care enrolment was higher under Treat-All (91% at 3 months; see Result- 2) than SOC. High rates of ART initiation were also reported from Treat-All trials (Table 4)^{221,332} and from several routine universal ART settings in Sub-Saharan Africa with overall higher and more rapid treatment initiations under Treat-All.^{237,239}

Second, prior to Treat-All, treatment eligible patients with high CD4 count were less likely to start ART.^{87–89,337} In this setting, levels of ART initiation appeared to be similar across CD4 strata under Treat-All but with a significant gradient under SOC, where patients with CD4 count above 350 cells/mm³ were less likely to start treatment (see Result-2). Other trial and routine Treat-All settings also reported high treatment uptake in patients with higher CD4 counts,^{221,237,239} indicating that the policy change towards Treat-All may have facilitated access to ART for less immunosuppressed and healthier patients.

Third, Result-2 demonstrated that predictors of ART initiation were overall similar between Treat-All and SOC. The main exceptions were the aforementioned different patterns in CD4 count as well as differences across facilities. Thus, unmeasured facility-level factors may have played a role in successful ART expansion.

Fourth, this research project demonstrated that a high proportion of patients started ART on the day of facility-based HIV care enrolment (e.g. 42% in non-pregnant adults, 71% in pregnant women; see Result-2). Despite different definitions applied for same-day ART initiation, high and increasing rates have also been documented from other routine Treat-All settings.^{338,339} Result-4 demonstrated that predictors of same-day ART initiation (vs 1 to 14 days since care enrolment) ranged from programmatic factors to clinical determinants. Notably, no other studies were identified describing the determinants of patients initiating ART within 14 days after care enrolment.

Finally, despite demonstrated programmatic feasibility of treatment initiation under Treat-All, qualitative studies have highlighted potential access barriers to universal ART. Barriers included patient level (e.g. feeling healthy, acceptance of HIV-positive status) and facility level factors (e.g. limited privacy, long waiting hours, administrative barriers).^{281,340–344} On the other hand, overall patient satisfaction was sustained during the roll-out of Treat-All in northern Eswatini.³⁴⁵

ART outcomes under Treat-All

Before the roll-out of Treat-All, fragile health systems were anticipated to lack the ability to expand ART without decreasing the quality of HIV care, and asymptomatic patients with high CD4 counts were assumed to be more likely to disengage from treatment.

Lessons learnt from ART care expansion prior to Treat-All can inform further treatment expansion. At the inception of this research project, however, long-term ART outcome data from more recent treatment cohorts were lacking.¹⁷⁰ Notably, scarcity of comprehensive ART programme evaluations immediate prior to the introduction of Treat-All have persisted. Result-1 described the evolution of the ART care programme before the introduction of Treat-All in southern Eswatini and found that short-term and long-term retention on ART increased with programme expansion. Crude 6-month and 12-month retention rates were 88% and 86% before Treat-All and comparable to estimates (6-months: 92%; 12-months: 86%) from an HIV programme evaluation in Zimbabwe before universal ART expansion.³⁴⁶ Similarly to Result-1, the same study showed higher crude retention on ART for the later combined years 2012 to 2015 than the earlier years 2007 to 2010.³⁴⁶ Based on these findings, ART retention could be anticipated to be maintained at similar levels or increase with the introduction of Treat-All.

Result-3 reported medium-term programmatic ART outcomes under Treat-All, while other recently published Treat-All studies reported mainly short-term outcomes. A routine setting in Malawi showed higher crude 12-month ART retention under Treat-All (83.0%, 95% CI 81% to 85%) than in our setting (78%, 95% CI 76% to 80%) and demonstrated an increase in retention after the introduction of Treat-All.³⁴⁷ Similarly to Result-3, retention was lower for young adults and pregnant/lactating women.³⁴⁷ In contrast, a routine setting in Nigeria had high rates of LTFU at 12 months (34%) after ART initiation.³⁴⁸ Similarly, high 6-month (17.3%) and 12-month (23.2%) attrition from ART were reported from three Treat-All trial primary care facilities in South Africa (PopART).²³⁵ The SEARCH trial, however, achieved 95.5% retention at 1 year after linkage to care, and 92% at 48 weeks after ART initiation.^{68,233} Comparing retention estimates before and after the introduction of Treat-All, an increase in HIV care retention (measured from the time of care enrolment) was seen in Rwanda.²³⁹

In this research project (Result-3), crude 12-month all-cause attrition appeared higher under Treat-All (78%) than under SOC (83%) and before its introduction in this setting (86%; see Result-1). Several explanations exist. First, not accounting for treatment interruptions during analysis can result in a spurious trend of increased attrition for more recent treatment cohorts with shorter follow-up time.¹⁶⁸ Second, the research design was not conceptualized to compare outcomes before and after the introduction of Treat-All. Third, differences in the populations compared may affect crude estimates. In covariate adjusted analyses (Result-3), however, the hazard of the composite unfavourable treatment outcome (death, LTFU, viral failure, treatment switching) (aHR 1.04, 95% CI 0.90 to 1.20)

and of all-cause attrition (death, LTFU) (aHR 1.06, 95% CI 0.91 to 1.23) were similar between Treat-All and SOC.

Findings with regards to CD4 count remained heterogeneous. In this setting (see Result-3, supplementary material), the risk of the composite unfavourable treatment outcome was similar for high CD4 count ($CD4 >350$ to 500 and $CD4 \geq 501$ cells/mm³) when compared with CD4 count 201 to 350 cells/mm³. The SEARCH trial also demonstrated similar risk of HIV care attrition for patients presenting with CD4 350 to 500 versus above 500 cells/mm³.²³³ In contrast, attrition on ART was increased for patients presenting with CD4 count above 500 cells/mm³ in PopART primary care clinics in South Africa,²³⁵ and in a routine setting in Nigeria a CD4 count above 350 increased the risk of LTFU.³⁴⁸

Result-3 showed that factors increasing the risk of the unfavourable composite outcome were similar between Treat-All and SOC and included younger age and pregnant/lactating women. These risk factors were also identified in other Treat-All trial settings as well as in routine public sector settings before the introduction of Treat-All.^{107,239,347,348} In summary, it appears that Treat-All may not significantly alter associations with unfavourable treatment outcomes when compared with SOC. Therefore, interventions implemented prior to Treat-All to improve outcomes for specific populations (e.g. young people) may remain effective and relevant in the context of universal ART. Notably, no other studies were identified comparing associations directly between Treat-All and SOC.

Lastly, Result-3 indicated that the risk of the composite unfavourable treatment outcome was increased for patients starting ART on the day of facility-based HIV care enrolment under Treat-All (aHR 2.08, 95% CI 1.42 to 3.06). In contrast, randomized controlled trials implemented before the roll-out of the Treat-All policy showed an overall benefit of same-day ART initiation, while observational studies indicated higher rates of attrition.²¹⁰ Notably, a recent observational study from two South African districts applying the Treat-All policy demonstrated that same-day ART initiation (on the day of HIV diagnosis) also increased loss to ART care.³³⁹ In this research project, Result-4 applied a causal framework to describe the absolute and relative risk of an unfavourable treatment outcome under same-day ART initiation compared with treatment initiation within 1 to 14 days. Findings suggested that same-day ART initiation increased the risk of the composite outcome of death, LTFU, and viral failure (aHR 1.48, 95% CI: 1.16 to 1.89) as well as for the disaggregated outcome of all-cause attrition. These findings caution against the implementation of same-day ART initiation for every patient. A differentiated and patient-centred approach may be required. Simple to use clinical screening algorithms may have the ability to identify patients ready for same-day ART, leading to increased treatment uptake, although the challenge of sub-optimal retention on ART is likely to persist.³⁴⁹ Nevertheless, it should be noted that the downsides to same-day ART might be offset by higher ART initiations and less pre-ART attrition, which could not be explored in this study.

Lastly, it needs to be acknowledged that the methods applied in obtaining the effect estimate of same-day ART initiation had some weaknesses that should be considered when interpreting findings in the wider context. These methodological limitations are further discussed in the next section (Additional methodological considerations).

Viral load cascade and HIV drug resistance

Adherence to ART results in viral suppression in the absence of acquired and pre-treatment resistance, and achieving viral suppression results is favourable for individual-level health and programmatic-level outcomes. Notably, 84% of patients on ART in the Shiselweni region already had an undetectable VL (<100 copies/mL) prior to the introduction of Treat-All.¹³⁴ Result-3 showed that 90% of patients with a VL test result were virally suppressed (VL <1,000 copies/mL) under Treat-All. In addition, time to viral suppression was improved (aHR 1.12, 95% CI 1.01 to 1.23) for patients on ART when compared with SOC, and the risk of viral failure (aHR 0.89, 95% CI 0.53 to 1.49) was similar. Overall, viral suppression was comparable to other Treat-All trial settings,^{223,233} but higher than in a routine Treat-All setting in Nigeria reporting low level of VL suppression and VL testing coverage.³⁴⁸ This research project did not describe in more detail the VL care cascade under Treat-All. However, VL cascade findings from the Shiselweni region are available for the time immediately before Treat-All. It was reported that 58.9% of adults with an elevated VL above 1,000 copies/mL achieved viral re-suppression,¹⁸⁴ which is overall in line with a recently published WHO review estimating re-suppression rates of 50.4% in adults.³⁵⁰ However, only 43.2% of patients with viral failure (two consecutive VLs >1,000 copies/mL) switched to a different treatment regimen (vs 53.4% internationally),³⁵⁰ even though 92.4% of failing patients on first-line ART had resistance patterns requiring switching.¹⁸⁴ Without access to routine HIV drug resistance testing, the differentiation of reasons for VL elevations for clinical management (e.g. suboptimal adherence vs drug resistance) as well as quality improvements along the VL cascade (e.g. timely treatment switching, VL cascade analyses) appear to be crucial to achieve and sustain patient-level and programmatic-level benefits during treatment expansion.³⁵⁰ Challenges reported in the implementation of routine VL monitoring prior to Treat-All are likely to continue with treatment expansion,³⁵¹ necessitating continued focus on the leaky VL cascade.

Suboptimal performance along the VL care continuum has public health implications. In 2016, 51.8% and 79.0% of patients with unsuppressed VLs already had drug resistance at 12 and 48 months, respectively, after ART initiation in Eswatini, but resistance levels were lower than in most other countries surveyed.³⁵² Most resistance detected while on ART is acquired during therapy, so patients on failing treatment regimens may be a source of transmission of drug-resistant strains and contributor to elevated pre-treatment resistance in people newly infected with HIV. The contribution of transmission of resistant strains by patients on ART is likely to increase with Treat-All, as the number of patient failing ART increases and the number of PLHIV not on ART decreases. Although low

levels of HIV drug resistance were reported from the BCCP Treat-All trial in Botswana (1.5% and 2.9% NRTI and NNRTI resistance in treatment-naïve patients),³⁵³ WHO reported that pre-treatment resistance to NNRTI was >10% in 12 out of 18 surveyed countries between 2014 and 2018, while pre-treatment resistance to tenofovir and lamivudine was less than 4.5% and 5.7%.³⁵² In Eswatini in 2016 (the year of scale-up of Treat-All), an estimated 10.5% and 1.0% of adults had pre-treatment resistance to NNRTI and NRTI drugs, with highest levels detected in patients previously exposed to antiretroviral medications (NRTI: 2.8%; NNRTI: 16.1%)³⁵² Optimization of ART regimens under the Treat-All approach will remain crucial to maintain favourable patient-level and programmatic outcomes, as well as to reduce the public health risk of increased transmission of HIV drug-resistant strains. During the implementation of Treat-All in Nhlanguano health zone, the predominant ART regimen was TDF/3TC/EFV (see Result-3). Responding to changing patterns in HIV drug resistance, the Eswatini national ART guidelines have been revised and dolutegravir-based first-line treatment regimens have been phased in since 2019, thus supporting the effective implementation of Treat-All.

Advanced HIV disease

Prior to Treat-All, the prevalence of advanced HIV disease ($CD4 < 200 \text{ cells/mm}^3$) at ART initiation decreased in RLS between 2004 and 2017,^{249,354} with a decline in Eswatini from 72% in 2004 to 54% in 2010.²⁴⁹ At the population level, three cross-sectional surveys conducted in MSF-supported HIV programmes (Kenya, Malawi, South Africa) prior to Treat-All (2012 to 2013) found that overall 10% of PLHIV lived with advanced HIV disease, with 37% of them being unaware of their HIV-positive status.³⁵⁵

Advanced HIV disease is likely to remain a challenge under universal ART. In Eswatini, after treatment eligibility expansion including the phase-in of Treat-All, an estimated 7.6% of adults (>15 years) presented with $CD4 < 200 \text{ cells/mm}^3$ at the community level and 2.2% with severe immunosuppression ($CD4 < 100$).¹⁸⁸ Similar estimates were found in the Shiselweni region, where Treat-All was introduced earlier than in the rest of the country.¹⁸⁸ In this research project, 35% and 30% of patients had a $CD4 \leq 200 \text{ cells/mm}^3$ at the time of facility-based HIV care enrolment (see Result-2) and ART initiation (see Result-3), similar to a RLS in South Africa reporting 35% to 40% at the time of ART initiation under Treat-All in 2017.³⁵⁴

WHO recommends prioritization of patients presenting with advanced clinical disease stage III/IV and/or $CD4 \leq 350 \text{ cells/mm}^3$, as these patients are in greatest need of timely treatment.¹⁶ During treatment eligibility expansion from $CD4$ count threshold 200 to 350 cells/mm^3 in South Africa between 2010 to 2012, the sickest patients ($CD4 \leq 200$) maintained similar ART initiation rates to before eligibility criteria expansion, while the number of ART initiations increased in newly treatment eligible patients ($CD4 201$ to 350).³⁵⁶ These findings are of importance as concerns were raised before

Treat-All that patients with advanced immunosuppression may not receive sufficient quality care during ART expansion.

In a routine Treat-All setting in Nigeria, patients on ART and with CD4 <200 cells/mm³ were not more likely to become LTFU, although losses were more likely for patients presenting at higher WHO clinical stages.³⁴⁸ In Rwanda, patients with CD4 below 200 cells/mm³ had similar outcomes in terms of ART initiation and 6-month retention to patients presenting with CD4 above 500 cells/mm³ and/ or WHO clinical stage III/IV (vs clinical stage I/II).²³⁹ This research project demonstrated that patients with low CD4 counts had overall worse treatment outcomes than patients with CD4 201 to 350 (see Result-3). However, when compared with SOC, patients with advanced HIV disease under Treat-All were more likely to initiate ART, specifically during the first month after care enrolment (aHR 1.75, 95% CI 1.47 to 2.08; see Result-2) and achieved similar treatment outcomes (aHR 1.13, 95% CI 0.88 to 1.44; see Result-3).

In conclusion, despite the likely persistence of the challenge of advanced HIV disease during ART expansion, there is no indication that patients with advanced HIV disease are de-prioritized under Treat-All with respect to ART initiation and follow-up care.

Population-level impact

TB notifications

This research project evaluated the potential impact of treatment expansion on TB notifications at the individual and population levels. Findings suggested that ART expansion reduced TB notifications overall, being most pronounced in PLHIV. In this study setting, population-level ART coverage was 82.7% at the end of the observation period¹⁸⁸ compared with approximately 7% in 2006 (see Result-1). A recent study evaluating trends in TB notifications in 23 countries in sub-Saharan Africa prior to Treat-All from 2010 to 2015 confirmed these conclusions and also described a higher decline in TB notifications for countries with higher ART coverage.³⁵⁷

An important side finding was temporal trends in sex disparities in TB notifications during ART expansion. A differentiated temporal impact of HIV infection and ART expansion has also been described in recent studies from South Africa and Uganda, with, for instance, higher relative increase in TB notifications in women prior to ART expansion and more pronounced decline thereafter but with overall higher TB notification rates sustained in men.^{358,359}

In the latter years, when Treat-All was introduced in one (Nhlangano) of the three health zones and the WHO 2010 and WHO 2013 treatment eligibility thresholds and PMTCTB+ were applied in the neighbouring health zones and Treat-All phased in the last year of the observation period, TB notifications continued to decline, although the rate of decline was reduced. Notably, Result-5 did not find evidence of TB rebound during ART scale-up, which was anticipated in RLS by a modelling

study if high treatment adherence and immunological response cannot be sustained during treatment expansion.²² First, the observation period into ART scale-up of approximately 8 years was possibly too short to see a TB rebound, which was predicted at approximately 20 years after the start of ART scale-up.²² Second, it may mean that ART was effectively delivered, supported by Result-3 showing high levels of viral suppression at the cohort level (90% under Treat-All) and by the findings of an HIV incidence household survey estimating population-level viral suppression at 79.1% among PLHIV in the Shiselweni region in late 2016.¹⁸⁸

ART coverage, viral suppression, and HIV incidence

The research papers did not assess the population-level impact of Treat-All with regards to HIV incidence and viral suppression. This section discusses findings from other Treat-All settings in Sub-Saharan Africa and evidence from Eswatini regarding the possible impact of ART expansion on population-level HIV outcomes.

Table 5 provides an overview of Treat-All trials reporting on population-level ART coverage and viral suppression for Treat-All and SOC, as well as estimated cumulative HIV incidence reduction. Overall, findings of the Treat-All trials were inconsistent with regards to HIV incidence reduction (see Table 5).³⁶⁰ While the TasP and SEARCH trials failed to demonstrate lower cumulative HIV incidence under Treat-All compared with SOC,^{223,361} the BCCP study achieved a 30% incidence reduction under universal ART.³⁶² The PopART trial did not detect an effect of intervention A (combination HIV care interventions and Treat-All combined), but demonstrated 30% HIV incidence reduction for intervention B (combination HIV care interventions without universal ART) and 19% for intervention A and B combined (in post hoc analysis) versus SOC.³⁶³

Suggested reasons for inconsistent findings included unmeasured imbalance in characteristics of intervention and control communities, heterogeneity and clusters of HIV transmission, and unaccounted migration.³⁶⁰ Other study specific explanations exist. For instance, low rates of linkage from community-based HTS to HIV care enrolment in both arms of the TasP trial impacted latter steps in the HIV care continuum, resulting in a low increase in ART coverage and population-level viral suppression at study-end.^{223,364} In the SEARCH trial, SOC already had high levels of HIV testing and expanded treatment eligibility criteria at the beginning of the study, which was associated with a rapid increase in population-level viral suppression, making detection of a difference with Treat-All less likely.³⁶¹ As access and uptake of HIV treatment had already increased in many settings before the introduction of universal ART, the additional benefit of ART expansion (e.g. treatment eligibility expansion from 500 cells/mm³ to Treat-All) may have been less obvious and thus more difficult to detect. In addition, these trials suffered from reduction in statistical power during study implementation because SOC adopted expanded WHO treatment eligibility criteria.³⁶⁰ Notably, there was also a discrepancy between population-level viral suppression and HIV incidence reduction in

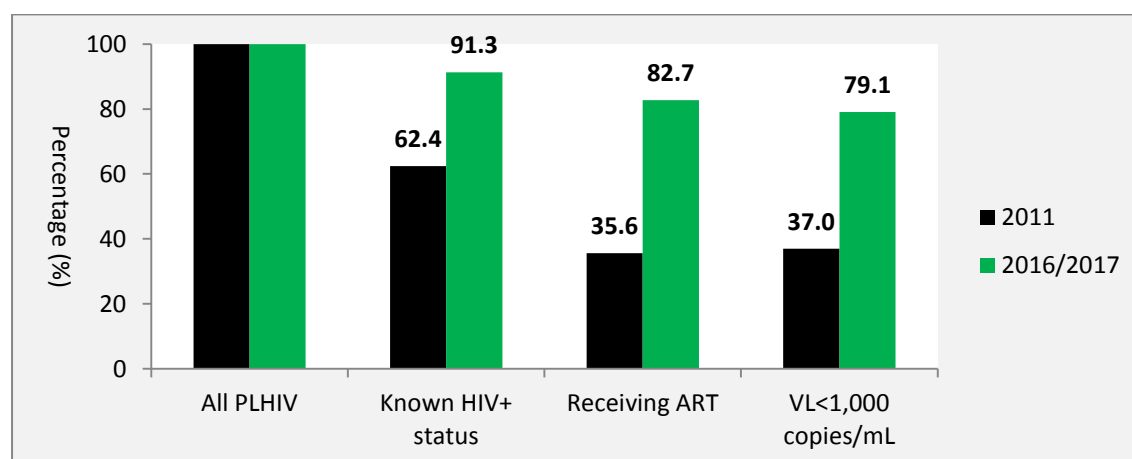
one of the studies. While higher population-level viral suppression is considered a proxy for higher HIV incidence reduction, this effect has not been seen in the PopART trial, with intervention arm A with higher viral suppression not showing an HIV incidence reduction but intervention arm B with lower viral suppression showing a significant incidence reduction compared with SOC.^{360,363} Notably, the trials were implemented in different contexts (e.g. differences in HIV prevalence and baseline ART coverage), had different intervention focus, and delivered a wide range of heterogeneous combination interventions, limiting direct comparison.³⁶⁵ For instance, the BCCP trial focused on combination prevention, while the SEARCH trial focused on streamlined combination interventions integrated into a community-based multi-disease campaign, and the TasP trial did not add linkage intervention.^{223,360–362}

Table 5: Treat-All trials assessing the impact of Treat-All on population-level ART coverage, viral suppression, and HIV incidence.

Study	ART coverage		Population-level VL suppression			HIV incidence		Study implementation years, and definition of viral suppression
	Baseline	Study end	Baseline	Study end	Adjusted relative risk difference	HIV incidence per 100 person-years	Adjusted relative risk difference	
TasP ^{223,364}								
SOC	33.7%	52.8%	26.0%	44.6%	Reference	2.27	Reference	- CY: 2012 to 2016
Intervention	29.6%	53.4%	23.5%	46.2%	p= 0.514	2.11	1.01 (0.87 – 1.17)	- VS: <400
SEARCH ^{361,366}								
SOC	NA	NA	42%	68%	Reference	0.27	Reference	- CY: 2013 to 2017
Intervention	50%	87%	42%	79%	1.15 (1.11 – 1.20)	0.25	0.95 (0.77 – 1.17)	- VS: <500
PopART ³⁶³								
SOC	35%	NA	54%	60.2%	Reference	1.6	Reference	- CY: 2013 to 2018
Intervention A	33%	81%	56%	71.9%	1.16 (0.99 – 1.36)	1.5	0.93 (0.74 – 1.18)	- VS: <400
Intervention B	41%	80%	57%	67.5%	1.08 (0.92 – 1.27)	1.1	0.70 (0.55 – 0.88)	
Intervention A + B	NA	NA	NA	NA	NA	NA	0.81 (0.66 – 0.99)	
BCPP ³⁶²								
SOC	NA	NA	75%	83%	Reference	0.92	Reference	- CY: 2013 to 2018
Intervention	NA	NA	70%	88%	1.12 (1.09 – 1.16)	0.59	0.70 (0.50 – 0.98)	- VS: <400

CY, calendar years when study was conducted; NA, not available/ reported; VS, definition of viral suppression in copies/mm³.

In Eswatini, the first national population survey on HIV prevalence and incidence was conducted in 2011 (SHIMS-1),¹⁷³ followed by a second national survey with similar methods applied in 2016/2017 (SHIMS-2).¹⁸⁸ Separate estimates of coverage were available for the Shiselweni region but not for HIV incidence. The data collection in the Shiselweni region for SHIMS-2 was completed in the last quarter of 2016. Importantly, as coverage estimates were not available separately for Treat-All (Nhlangano health zone) and SOC (Hlathikulu health zone), a change in coverage estimates rather reflects the impact of HIV care expansion in the entire region than Treat-All solely. Figure 3 shows trends in population-level outcomes among PLHIV in the Shiselweni region over a period of 5 years. From 2013 to late 2016, awareness of HIV status increased by 29%, ART coverage increased by 47% points, and viral suppression by 42% points.^{173,180,180,181,188} The UNAIDS 90-90-90 population-level cascade targets of $\geq 90\%$ awareness of HIV-positive status, $\geq 81\%$ ART coverage, and $\geq 73\%$ viral suppression among all PLHIV was achieved at the latest in 2016 (Figure 3). These coverage estimates were higher than in the PopART and TasP trials, similar to SEARCH, and lower than in BCCP.

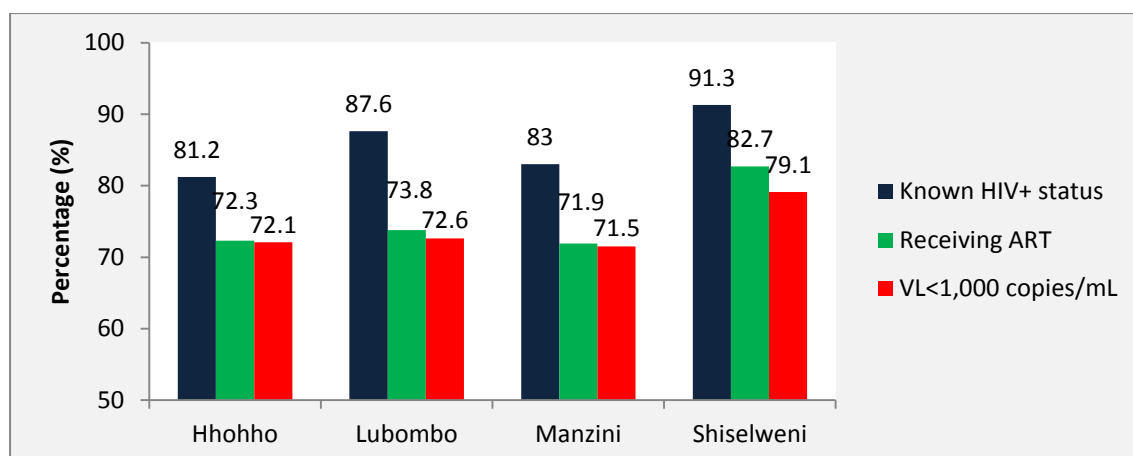


HIV+, HIV-positive; PLHIV, people living with HIV; VL, viral load.

The 2011 and 2016/2017 estimates were obtained from the first (SHIMS-1)^{173,180,181} and second (SHIMS-2)¹⁸⁸ Swaziland HIV Incidence Measurements Surveys. The denominator for all estimates is the total number of PLHIV.

Figure 3: Temporal trends in population-level outcomes along the HIV care continuum for PLHIV in the Shiselweni region.

Notably, the population-level impact was more pronounced in the Shiselweni region than in the rest of the country. While ART coverage and viral suppression were similar across all regions of Eswatini in 2011, they were higher in Shiselweni in 2016/2017 (Figure 4).^{173,180,180,181,188} Possible reasons include faster HIV care programme expansion with PMTCTB+ and Treat-All phased in a few years before roll-out in other parts of the country, earlier (from 2012) routine VL monitoring with enhanced adherence support interventions implemented at scale earlier, a higher level of decentralization of HIV care, and earlier and more rapid scale-up of differentiated care models for patients stable on ART.²⁴⁸



HIV+, HIV-positive; PLHIV, people living with HIV; VL, viral load.

These are 2016/2017 estimates for the four different regions and were obtained from the second (SHIMS-2)¹⁸⁸ Swaziland HIV Incidence Measurements Survey. The denominator for all estimates is the total number of PLHIV.

Figure 4: Population-level outcomes along the HIV care continuum in the four regions of Eswatini in 2016/2017.

Other factors than Treat-All likely contributed to achieving population-level impact and the UNAIDS 90-90-90 cascade targets. This has also been suggested by Treat-All trials which, in addition to the introduction of Treat-All, used a wide variety of combination interventions to improve quality care along the HIV care continuum.^{223,361,363,366} Unlike most Treat-All trials,^{223,361,363,366} combination interventions were already in place in this setting prior to the roll-out of Treat-All and no additional medical study staff were added. This suggests that population-level impact can potentially be achieved by building on programmatic gains made during treatment expansion prior to Treat-All.

ADDITIONAL METHODOLOGICAL CONSIDERATIONS

This section does not provide a comprehensive review of all possible methodological issues that researchers are faced with when conducting research. However, it aims to highlight a few important methodological issues that have not been discussed in Chapter I and II but require consideration in the interpretation of findings of this research project.

Study designs

This research project used different study designs in the context of public health research conducted under real-world conditions. The choice of study designs comes with the trade-off between pros and cons of each chosen approach. These trade-offs include considerations about feasibility to execute the research project amid practical real-world limitations in its implementation (e.g. ethical considerations, funding, timeframe), and the strengths and weaknesses of specific study design to answer one or more research questions of interest.^{367,368} Generally speaking, different forms of randomized controlled trials are prospective with the researcher assigning exposure to an intervention.³⁶⁹ These trials come with increased internal validity and are able to specifically answer questions of efficacy with regards to an intervention, but their external validity may be compromised and their execution may not always be feasible in routine programme settings.³⁶⁷ In contrast, observations study designs – such as prospective and retrospective cohorts, cross-sectional studies, ecological studies – are regarded inferior to randomized trials with regards to internal validity, while external validity may be increased and its execution in RLS more feasible.³⁷⁰ As cohort studies overall resemble experimental studies though lacking random assignment, they are considered to have greater validity to other observational study designs such as cross-sectional surveys and ecological studies.^{367,369}

This research project used a combination of observational study designs to mainly answer programmatic questions related to feasibility and impact of interventions implemented in a real-world public sector setting. It was beyond the scope and practically not feasible to consider more resource intensive study approaches such as randomized trials.

Cohort study design

The longitudinal observational study design was used as the main study design in this research. Result-2, Result-3 and part of Result-4 were prospective cohort studies as the cohorts and data collection plan were defined before the execution of the research, and patients needed to consent to be enrolled into the cohorts. A well-planned prospective data collection can increase the reliability (e.g. consistency, stability, dependability) and validity (e.g. true and accurate) of data collected, specifically with data quality control measures in place,³⁶⁸ as in this research project.

In contrast, Result-1 and parts of Result-5 relied on the retrospective cohort study design. The cohort was defined retrospectively after the HIV and TB programme activities had been implemented for years. Although data collection was prospective in nature for routine programme monitoring and therefore is still a forward-direction study, the study design was retrospective as the treatment outcome has already happened at the time of inception of the research and the cohort was established retrospectively.³⁷¹ The retrospective cohort study designs in this thesis should be considered inferior to the prospective cohort design because of possible more challenges to data reliability and validity.

Ecological study design

This thesis also used an ecological study design for parts of Result-5. The ecological study is observational in nature and uses aggregated data of groups, thus lacking the ability to assess causal relationships or perform other hypothesis testing.^{372,373} Even in the absence of confounding, causal inferences cannot be made due to aggregation bias, which is also referred to as ecological fallacy where group-level associations differ from individual-level association between exposure and outcome.³⁷² For instance, Result-5 estimated and described trends in annual incidence of TB notifications overall and for different population groups such as by HIV-status and sex. While findings indicated that TB notifications decreased over time and were most pronounced in PLHIV, it cannot be inferred that this observation also applies at individual-level. On the other hand, it has been suggested that the population-level context of individual characteristics can be a stronger determinant of the outcome at population-level than individual-level risk factors.³⁷³ Notably, Result-5 also used regression analysis of these population-level data as it is also recommended in order to better control for confounding.³⁷³ A main advantage of the ecological study design was that it allowed describing temporal changes in TB disease notifications for different populations, thus enabling hypotheses regarding the possible causes of this trend (e.g. increase in ART coverage). Importantly, although temporal changes in the diagnosis of diseases (e.g. introduction of new diagnostic tools such as Xpert testing in Result-5) may bias estimated temporal trends in disease prevalence or incidence, it has been argued that nevertheless the true magnitude of disease may often be estimated with reasonable certainty.³⁷³

Retrospective quasi-experimental study design

Result-4 applied a quasi-experimental study design to assess the real-world effect of same-day ART initiation under Treat-All. This was in the context of the then new WHO recommendations to initiate HIV treatment more quickly (within 7 days) and the then national recommendations to initiate ART within 14 days.^{209,218} The question of efficacy emerged during the introduction of Treat-All in Nhlanguano health zone. Informed by routine M&E data, clinicians and programme implementers raised concerns that same-day ART initiation may decrease retention on ART. Thus, a post-hoc analysis of already available data from the prospective Treat-All cohort was initiated in order to detect

potential risks of same-day ART among patients who already initiated treatment quite fast (within 14 days).

As highlighted before, evidence from randomized clinical trials is regarded superior to observational studies, specifically for the investigation of treatment and interventions effects.³⁷⁰ Nevertheless, observational studies can go beyond pure descriptive analysis and estimate treatment effects. Although these effects may appear more pronounced in observational studies than randomized trials and possibly be attributable to confounding, it is argued that well-conducted observational studies may generate unbiased estimates of this effect.^{370,374} Some authors suggested that differences in treatment effects may not be a result of confounding but because of differences between data analysis, study designs and study procedures other than randomization, and populations.^{269,375,376} It has also been argued that the usefulness of treatment effects detected in clinical trials also depends on the ability to adjust to a different real-world target population, and both randomized trials and observational studies may have a role to play to fully understand the effect of an intervention in the real world.³⁷⁷ Given these challenges, different epidemiological, conceptual and statistical approaches have been proposed and combined to address causal inference from observational data, including emulating a target trial, using causal diagrams, targeted maximum likelihood estimation and machine learning algorithms.^{268–270,273–277} Result-4 applied these suggested approaches to reduce the risk of bias when estimating the effect of same-day ART initiation from prospective cohort data. Notably, the research question of Result-4 has been informed by the potential problem identified during programme implementation, and the availability or lack of data. The research question may have been slightly different if it would have been possible to plan the research in advance. Therefore, it is acknowledged that the research question applied in Result-4 may not satisfy all information needs related to same-day ART initiation but is rather a trade-off between what was possible and reasonable given the available study design, data and context. As the overall focus of this thesis is on the programmatic feasibility of Treat-All, it did not aim to generate a purely methodological paper that provides a comparison of different analyses in the context of causal modelling and discuss all possible opportunities and pitfalls related to it. Further studies applying different research questions, assumptions and designs may be warranted to fully understand the effect of same-day ART initiation in resource-poor public sectors settings.

Statistical analyses

The main statistical method used was survival analysis. Kaplan Meier curves were used to graphically display crude cumulative failure events, and multivariable flexible parametric survival models (Royston–Parmar models)^{196,197} were built to describe associations between baseline factors and the outcome events.

Censoring in survival analysis

First, this research project overall applied a pragmatic approach to define the outcome of interest with several adverse patient-level outcomes being combined into a composite outcome. For instance, Result-1 assessed the time to all-cause ART attrition defined as the composite outcome of death and LTFU. Result-3 combined the outcome of all-cause attrition with viral failure, and Result-4 combined the outcomes all-cause attrition, viral failure and second-line HIV treatment-switching. However, it is common in survival analysis that not all patients experience the outcome of interest during the study observational period. Therefore, the statistical approach when dealing with survival data needs to address censoring that occurs in the case of incomplete information about survival time.^{378,379} Several common statistical approaches – all of which come with their own assumptions and pitfalls – have been proposed to deal with censored data:³⁷⁸ Complete-data analysis that uses only complete uncensored data; imputation approaches of censored data; dichotomized data analysis at a fixed period of time; or – as in this research project applied – likelihood-based approaches in survival analysis that uses all available information but requires assumptions about the censoring process.

This thesis widely applied survival analyses and had right-censored data, with the observation period of an individual ending before the event of interest occurred.^{378,379} Censoring should be non-informative in order not to result in biased results due to over- or under-estimation of event-free survival time.^{378,379} In this research project, the main reason for censoring was administrative end-of-study censoring. It occurs for individuals without experiencing the outcome of interest at study completion (e.g. at database closure) and is often regarded as non-informative and therefore unproblematic.^{378,379} The statistical methods assumed end-of-study censoring to be non-informative as time of study entry (e.g. Result-2: facility-based HIV care registration, Result-3: ART initiation) was likely independent of survival time (e.g. Result-2: time to ART initiation; Result-3: time to composite unfavourable outcome of LTFU, death and viral failure). The other right-censoring event was at the time of transfer out of the study site that could occur any time before study completion. TFO-censoring may have introduced informative-censoring. Patients transferred out could have been more likely to experience death (that was part of the composite unfavourable health outcome in Result-1, Result-3 and Result-4) if TFO would have occurred because of clinical necessity due to occurrence of opportunistic infections that are known to be associated with increased mortality (e.g. TB, cryptococcal meningitis). On the other hand, TFO could also have been associated with decreased LTFU (that was part of the composite unfavourable outcome of Result-1, Result-3 and Result-4) if stable and treatment experienced patients were transferred to sites offering differentiated ART care (e.g. treatment clubs, community ART groups) that has shown to improve and sustain treatment adherence and higher levels of care retention.^{116–118} Lacking local data about the reasons of and the underlying process of TFO, no further assumptions were made and TFO was considered as non-informative censoring, possibly resulting in biased estimates if the assumptions did not hold true. Although methodological papers suggest different approaches to handle this challenge (e.g. full case

analysis, competing risk analysis, estimation of bias indexes),^{380–382} they come with their own challenges and it was beyond the scope of this thesis to address all these issues in depth. These issues, however, could be addressed in research papers with focus on methodological issues.

Another main challenge in survival analysis is censoring due to LTFU. Loss-to-follow-up censoring occurs when patients exit the study in an unplanned manner before study completion and free of the outcome of interest.^{378,379} This type of censoring has shown to be often informative and assumptions about the censoring mechanism should be made.³⁷⁸ This is specifically an issue in HIV research. It has been widely described that patient lost to ART care have several outcomes (e.g. actual LTFU, undocumented deaths, silent TFO, treatment interruptions) whose magnitude and distribution may vary by different study sites, size of the treatment cohorts, availability of defaulter tracing interventions, and different calendar time periods.^{112,159–161} In this research project, the outcome of LTFU was not censored but was part of the composite unfavourable programmatic outcome. Thus, the problem of informative censoring did not occur. On the other hand, it was impossible to give more details of the actual outcomes of patients lost to the programme as defaulter tracing interventions were not in place or insufficient.

Model specifications

This research project used mainly flexible parametric survival models (Royston–Parmar models) that allows for greater flexibility with the shapes of the survival distribution being modelled.^{196,197} A challenge, however, is to find the right statistical model specification.

First, a key assumption in survival analysis is that the proportional hazards assumption is not violated. In case of violation – as it also happened several times in this research project –, the Royston–Parmar models allows quite easily to model time-varying covariates by letting the variable in question interact with follow-up time by using the spline functions.^{196,197} This approach allowed not only to get an overall summary estimate of a time-varying effect (e.g. adjusted hazard ratio) as computed in the regression model, but also to display graphically how the magnitude of model parameters changes with follow-up time (e.g. hazard rate, hazard rate difference).¹⁹⁶ However, challenges emerge with the presence of more than one covariate interacting with time, as the interaction with time of one covariate may depend on the value of another covariate factor.¹⁹⁶

Second, several additional issues need be considered in obtaining the final model specification. Royston–Parmar models require defining the spline function and complexity determined by the number and position of knots for the restricted cubic spline function.¹⁹⁶ There is no gold-standard approach to determine the final spline model and informal (e.g. inspecting the appearance of fitted functions graphically) and formal approaches (e.g. AIC and BIC values) have been proposed.¹⁹⁶ These approaches, however, come with their own challenges.¹⁹⁶ For instance, if the number and position of knots is assessed with AIC and BIC criteria, a model with the lowest AIC and BIC values may be

preferred. However, there may be situation when the AIC values decrease while the BIC values increase. In addition, for instance, if the difference in AIC values between different models is minor, a more parsimonious model with slightly higher AIC but less knots may be preferable.¹⁹⁶ This research project used a combination of formal and informal approaches to assess the number and position of knots. As more experience was gained during this research project on how to find the final model, there were slight variations in the approaches applied for the different Results. Various sensitivity analyses could address these challenges encountered with the modelling of (multiple) time-varying effects and model specifications. Yet, it was beyond the scope of this research project to investigate methodological issues in depths, thus sensitivity analyses were kept to a reasonable minimum.

Finally, other model specification issues such as determining the number of covariates included in the model or the use of continues vs categorical variables need consideration. Overall, continues variables (e.g. age, CD4 cell count) were categorized in order to increase comparability with other studies in the field as they also tend to categorize covariate factors. The selection of variables for inclusion in the statistical model was mainly based on DAG for most of the analyses.

Missing data

Missing values of explanatory variables is an issue in many observational studies. Different ad hoc approaches that address missingness in epidemiological and clinical research are often based on strong assumptions and include complete-case analysis, missing indicator method, single value imputation, and sensitivity analyses assuming best-case and worst-case scenarios.³⁸³ In most situations, these approaches are considered statistically not valid as they have a high likelihood to lead to bias.³⁸⁴ In contrast, this research project applied multiple imputation to address missingness. Multiple imputation has been widely suggested as a standard advanced approach to deal with missing data.^{195,383,384} It is generally based on the assumption that values are missing ad random (MAR) with missing values being imputed based on the predictive distribution of observed values, with multiple datasets created that are then averaged together following Rubin`s rules to address uncertainty and account for variability in estimations.³⁸⁴ Multiple imputation was used throughout this research project because missing data was ubiquitous. Recommendations on how to perform multiple imputation were followed and included:^{195,384} multiple imputation by chained equations for imputation of continuous and binary variables as well as ordered categorical and unordered categorical variables; addressing non-normally distributed continuous data (e.g. CD4 cell count) with recommended imputation techniques such as predictive mean matching; using all model-specific covariates and the outcome variable in the imputation procedures as well as factors related to survival (e.g. survival time) in case of survival time data; if available, the inclusion of non-model-specific predictor variables of the incomplete variables. There is no consistent guidance in the literature on how many imputations to choose with standard recommendations suggesting that small numbers of imputed data sets (e.g. 3 to 5) may be sufficient while some authors recommend that the number of imputed

datasets should be similar to the percentage of missing values of incomplete variables.¹⁹⁵ With most datasets containing at least 10% to 20% of missing values and some clinical variables reaching more than 50% missingness, this research project applied a balanced approach with either 10 or 20 imputed data sets created. Finally, imputation diagnostics were performed as implemented in Stata14, such as graphical checks to explore and compare the observed, imputed and complete distributions of imputed variables for each imputation as well as graphical checks to test the convergence of each imputed variable using trace plots.^{262,385,386}

Although some of the details of the multiple imputation procedures and underlying assumptions of missingness and magnitude of missingness were provided, the research project did not report on all possible details. This is a potential weakness and was first due to the practical constraints of length of publications, and second it was beyond the scope of this analyses presented as it may distract the reader from the overall aim of this research, and methodological papers may be better positioned to provide all these details. As such, this research did also not provide further sensitivity analyses such as comparing estimates obtained from the imputation-based models with estimates from full-case-based models. Limitations of reporting on the multiple imputation procedures, assumptions of missingness and sensitivity analyses are common in the research literature.³⁸⁴ Future research and guidance may be need to find the right balance between too much and too little reporting on multiple imputation methods.

External validity

Bias can occur in all steps of a research project from planning, to execution, analysis and dissemination. Some of these biases have already been discussed in Chapter II through the research results. In addition, in the context of this research project, attention is required to possible partner selection bias that is also known under the terminology of implementer bias or NGO effect.³⁸⁷⁻³⁸⁹ Understanding the effectiveness of any intervention requires the generalization of context specific findings to different settings. Clinical and public health interventions in RLS are likely facing a wide range of implementation-related challenges. Governments may not always have the resources and ability to effectively address these barriers while implementing partners such as international NGOs may have the resources to overcome them. Evidence from other research fields (e.g. technology promotion, education and economic research) suggests that the heterogeneity across implementers results in differences in implementation and that NGO-supported projects may increase intervention effectiveness.³⁸⁷⁻³⁸⁹ The actual root cause of this effect may be multifaceted including additional funding provided by NGOs, better reputation and therefore trust of the population which may increase uptake and use of an interventions, as well as less bureaucratic barriers and political opposition.^{387,389} This NGO effect raises question if governments and the public sector can successfully expand interventions when lacking this form of support.³⁸⁷ Although the setting and procedures used in this

research project resembled real-world conditions of a public sector setting, Treat-All was introduced jointly between the MOH and MSF. This collaboration and the additional resources coming with it could be a threat to external validity by possibly reducing generalizability across other public sector settings lacking this kind of support.

On the other hand, external support to government-led HIV interventions appears common in Sub-Saharan Africa. Although the Shiselweni region of Eswatini that was supported by MSF showed better outcomes along the UNAIDS 90-90-90 population-level indicators than other regions (see Figure 4) and thus possibly suggesting implementer bias, the other regions of the country also received external support during the entire duration of this research project, namely through contracted implementing partners of PEPFAR. This may suggest that the expansion of the Treat-All approach to other parts of the country may be feasible amid available external funding and external implementation support. Importantly, this external support is not specific to Eswatini. For instance, the US government has contributed to funding of the international HIV response in more than 50 countries and invested about US\$85 billion dollars between 2003 and 2020.³⁹⁰ This may have contributed to the positive correlation between US government funding through PEPFAR and HIV incidence reduction in Sub-Saharan countries, as well as a higher reduction in all-cause mortality in PEPFAR priority countries vs non-priority countries.^{391,392} Another important external government support is the Global Fund with about US\$4 billion dollars provided each year for the fight against HIV, TB and malaria.³⁹³ In addition and related to ART expansion, all the well-known Treat-All trials in Sub-Saharan Africa were not solely conducted by local health authorities but additional support was received by research implementation partners and organizations.³⁶⁰ In conclusion, while it is likely that some implementer bias exists in this research project due to the collaboration between MSF and the MOH, it may not significantly reduce generalizability to settings where collaborative implementation of HIV and TB activities and additional funding is already the norm.

LIMITATIONS AND STRENGTHS

Limitations and strengths specific to the individual studies are discussed in each paper. This section summarizes cross-cutting issues affecting the entire thesis.

Limitations

The analysis of the Treat-All data and comparison with SOC can be done in different ways. For instance, Result-3 focused on all-cause attrition measured from the time of ART initiation. Another approach could have been to start analysing attrition from an earlier time point of the HIV care cascade, namely from the time of facility-based HIV care registration. In addition, it was also problematic to compare the Treat-All and SOC interventions with regards to associations of CD4 cell count and the outcomes of Result-2 (time to ART initiation) and Result-3 (time to composite unfavourable outcome) because patients with higher CD4 cell count under Treat-All would not be eligible for treatment under SOC. This research project mainly described associations between CD4 cell count and the outcomes separately for Treat-All and SOC, but other researchers may have considered a different approach. All these choices on how to analyse and present these data come with pros and cons. For this research project, decisions were made based on how other similar studies analysed similar data in order to ensure that findings can be compared, or what approach was found most appropriate in order to answer a specific research question. It is acknowledged that other analytic approaches could also have answered similar important research questions.

This research project could not fully cover the entire impact of changing treatment eligibility criteria. During the implementation of Treat-All, ART eligibility criteria under SOC were successively expanded from the CD4 count eligibility threshold of 350 to 500 cells/mm³ and PMTCTB+ was already practised under SOC. The challenge of expanding treatment eligibility during study implementation was also encountered in Treat-All trials.³⁶⁰ In addition, it is possible that patients ineligible for ART under SOC also initiated treatment. Thus, this observational research was more closely aligned with putative intention-to-treat comparison rather than a per-protocol comparison.

Analyses did not distinguish between mortality and actual LTFU from HIV care. Because of low recorded mortality and high LTFU indicating a misclassification of outcomes, both endpoints were combined into the composite outcome of all-cause attrition. The suboptimal ascertainment of HIV care outcomes (e.g. no routinely implemented physical defaulter tracing, no access to mortality registers) possibly resulted in an underestimation of mortality. Nevertheless, an overall temporal decline in mortality has been reported in patients lost to ART care in Africa, while the rate of treatment interruptions and undocumented transfer out of clinic increased.²⁵⁷

In addition, analyses used a retrospective definition of LTFU from HIV care, considering patients to be retained in care as long as they were in care at database closure and irrespective of treatment interruptions before. None of the analyses adjusted for treatment interruptions nor applied a prospective definition of LTFU with patients considered LTFU from the first time it is recorded and irrespective if they reengage in care later. All analyses assumed a linear continuum and cascade of HIV care that is unidirectional with one starting point (e.g. at HIV care registration in Result-2; at ART initiation in Result-1 and Result-3) and end point. This approach oversimplifies the complex treatment experience of patients in real-world settings. More cyclical HIV care cascades have recently been proposed to better document the dynamic treatment cycle of (multiple) disengagement from care and resumption of care.³⁹⁴

Viral failure – defined as two consecutive VLs above 1,000 copies/mL – was part of the composite outcomes of Result-3 (death, LTFU and viral failure) and Result-4 (death, LTFU, viral failure and treatment switching). However, different settings and studies apply different threshold levels to define viral failure (e.g. ≤ 400 copies/mL in the RapIT trial⁶⁹), and not all VL assays or specimens types (e.g. plasma specimens vs dried blood spot testing) have the same lower limit of viral detection. Although WHO has recommended the threshold of 1,000 copies/mL to define viral failure during the implementation of this research project,¹⁶ the most recent WHO guidance allows for more rapid treatment switching such as after the second detectable VL at the lower threshold levels of >50 to 1,000 copies/mL.³⁹⁵ These differences across settings and the changes in definition of viral failure should be taken into consideration when comparing findings of this thesis with other studies.

Only a limited aspect of feasibility was addressed in this research project, with focus on patient-level outcomes, programmatic-level outcomes, and TB population-level impact. Feasibility in the broader context of the health care system requires additional analyses such as evaluation of the cost-effectiveness of Treat-All. In addition, the acceptability of Treat-All by the community, PLHIV, and health workers was not assessed. However, acceptance of Treat-All may impact treatment engagement (e.g. linkage to care, ART uptake) and long-term engagement in HIV care. Although insights from qualitative research were used in the manuscripts to explain some findings of this research project, a comprehensive review of qualitative literature related to Treat-All was beyond the scope of this research project.

As the studies in this research project were observational, this thesis cannot establish a causal relationship between Treat-All and outcomes. Other routine interventions and unmeasured temporal trends may have had a differential effect on outcomes under Treat-All and SOC. For instance, differentiated models of care for patients stable on ART were introduced in the intervention arm and SOC during the study period,²⁴⁸ possible decongesting facilities, improving long-term adherence, and affecting quality of care over time. Other interventions that were scaled up and strengthened were TB

preventive therapy for PLHIV, improved diagnosis of opportunistic infections (e.g. introduction of the point-of-care urine lipoarabinomannan and cryptococcal antigen assays), as well as strengthening of the VL cascade.

This thesis did not address acute HIV infection (AHI) – that is, the time period immediately after HIV infection. In a secondary care facility in this setting, approximately 2.3% of symptomatic patients presenting with fever, sore throat, and symptoms of sexually transmitted infection had AHI.³⁹⁶ AHI may disproportionately contribute to life-time HIV transmission events in PLHIV, ranging between 10% and 50%.³⁹⁷ As the diagnosis and treatment of AHI are challenging in RLS (e.g. short duration of AHI, nonspecific symptoms, costly tests to detect AHI),^{397,398} routine implementation studies are scarce in Sub-Saharan Africa.^{399–401} However, routine AHI screening is estimated to increase the yield of HIV-positive diagnoses by 1% to 10%,⁴⁰² and immediate ART initiation during AHI is likely to reduce HIV transmission and benefit the patient's health.^{403–406}

Although not uncommon in health research, a weakness of this research project was that some health research related terms were used inconsistently and interchangeable across the 5 research results. Although it may not negatively impact the quality of research, it has potential to raise confusion and misunderstanding in health research communication, specifically when researchers, implementers, target audience and community have a different understanding of these terms. First, the term feasibility should have been better defined during the inception of this research project. Notably, the term feasibility and feasibility study is widely used and it can refer to studies that are performed in preparation of randomized controlled trials that assess efficacy of interventions, or studies conducted in the field of implementation research that evaluate successful implementation of an intervention.^{407,408} Similar lack of clarity exists between the terms implementation effectiveness and treatment effectiveness, intervention failure and implementation failure, or the differences between clinical treatment outcomes and implementation outcomes.⁴⁰⁸ For some terms, the meaning may be overlapping and they may be used interchangeably by researchers.^{407,408} Adding to this confusion, this research project reported results from patient-level outcomes, population-level outcomes and discussed programmatic outcomes. Second, similar inconsistency in terminology is with respect to the term of efficacy (or effect respectively) and effectiveness with differences in meaning in real (non-technical) language, field of research, and by target audience.^{409,410} Complicating the situation, the difference between efficacy and effectiveness trials may not be binary but rather a continuum.⁴¹⁰ While a few authors even suggest to redefine these terms in the field of public health and medicine,⁴⁰⁹ many others advocate for a more consistent use in medical communication. Their inconsistent use may negatively affect consistent interpretation of results from studies, resulting in differences in recommendations in medical guidelines.⁴¹¹ This research project considered the term effectiveness with regards to the ability of the intervention (e.g. Treat-All and ART expansion) to achieve its desired effect under real-world conditions, either at patient-level, programmatic-level or population-

level. No further distinctions were made. The term efficacy is considered for the ability of an intervention to achieve its objective under controlled circumstances, either through experimental study designs based on randomization or quasi-experimental methods applied to observational studies and data (e.g. part of Result-4). Not all researchers in the field of medicine and public health may agree with these definitions and distinction. Last, the terminology of multivariate and multivariable were used interchangeably, a common practice in the medical literature.⁴¹² Some authors – specifically in the field of public health – propose a more accurate distinction, and consider the term multivariable for statistical methods that have one outcome variable and two or more independent variables, and the term multivariate to statistical models with two or more outcomes and multiple independent variables.^{413,414}

Strengths

Treat-All was introduced in a routine public sector setting – overall comparable to other predominantly rural, and high HIV and TB burden contexts – several years before WHO recommended universal ART. Lessons learnt from this project, therefore, have the potential to inform ongoing implementation of Treat-All in similar RLS, specifically in relation to longer term treatment outcomes and same-day ART initiation.

This research project used both HIV care and TB care data. Combined analyses allowed for better insights into care expansion in this high HIV and TB prevalence context, and triangulation of findings. For instance, Result-2 highlighted the time-varying effect of TB co-infection on ART initiation under Treat-All, and Result-5 demonstrated a stronger temporal decline in TB notifications for patients co-infected with HIV.

Findings of this research project were contextualized through findings from other local HIV and TB research, helping inform conclusions. For instance, Result-1 and Result-5 used ART coverage estimates obtained from this research project as well as those obtained by the Swaziland HIV incidence measurement surveys. This helped in understanding the overall population-level programmatic impact of ART expansion with regards to the UNAIDS 90-90-90 cascade targets which were not directly evaluated in this thesis.

Finally, this research project applied analytic approaches that improved the robustness of findings as well as increased programmatic understanding. First, multiple imputation was used to account for missing data in covariate – adjusted analyses. In contrast to complete case analysis, this approach, under the assumption that data are missing at random, can increase precision and reduce bias. Second, flexible parametric survival methods (Royston-Parmar model) allowed adjustment for and better description of time-varying effects. From the programmatic point of view, this approach helped to visualize when the time-varying effect of a covariate or an intervention is greatest and could possibly

be intervened on. For instance, Result-3 and Result-4 demonstrated that the unfavourable treatment outcome was most pronounced during the first months after ART initiation for same-day treatment initiation, suggesting that interventions aiming at improving outcomes for same-day ART should be deployed during this time period. Third, Result-4 used targeted maximum likelihood estimation (TMLE)^{274,275} – a state of the art analytic approach – to estimate the causal effect of same-day ART initiation on unfavourable treatment outcomes. Obtaining estimates in the causal framework from routine settings enables HIV and TB programmes to be informed on public health interventions in a more timely and realistic way when randomized trials would be time-consuming or unfeasible (e.g. resource intensive, unethical) or would lack generalizability if conducted in an unrealistic and artificial research context.

RECOMMENDATIONS

The following recommendations are made based on evidence from this research project, as well as informed by evolving literature and HIV/TB programmatic guidance by WHO.

Pay attention to vulnerable patients

This research project showed that specific groups of patients were at increased risk of an unfavourable outcome. For instance, young people were less likely to initiate treatment, and both young people and pregnant/lactating women had inferior treatment outcomes. These populations already had suboptimal outcomes before the introduction of Treat-All. Targeted interventions known to effectively address their specific needs and improve their health outcomes should continue and be strengthened during expansion of Treat-All. Notably, the high proportion of young people among the general population in Sub-Saharan Africa makes youth-centred interventions increasingly important.

Implement quality VL follow-up care

This research project, as well as other Treat-All trials, did not describe the entire VL cascade for patients on ART, from the time of viral elevation, to viral re-suppression, to treatment switching, and to viral re-suppression after switching. Even in well performing ART programmes with the vast majority of patients presenting with suppressed VL during ART, the number of patients with viral elevation is likely to increase with the roll-out of Treat-All. Therefore, settings expanding ART should introduce and strengthen routine VL cascade analysis to monitor the treatment response and trigger timely clinical decision making. Findings from VL cascade analysis can inform HIV programmes of gaps at the end of the UNAIDS 90-90-90 cascade and trigger health policy and programmatic action.

In addition, HIV programmes should introduce routine surveillance for the monitoring of pre-treatment drug resistance.^{352,415} This routine surveillance should inform optimization of first-line ART regimens,^{352,415} which is crucial to sustain effective ART and to achieve favourable viral outcomes during Treat-All as well as for reduction of transmission in the context of treatment as prevention and expansion of HIV pre-exposure prophylaxis in RLS.

Strengthen care for patients presenting with advanced HIV disease

This thesis demonstrated that even though patients with advanced HIV disease were not disadvantaged under Treat-All, a substantial proportion of patients continue to present for the first time with advanced disease. Several recommendations should be considered to address the continued challenge of advanced HIV disease under Treat-All. First, innovative HIV testing approaches are needed to engage patients with advanced HIV disease who are unaware of their HIV status earlier, as well as those who are aware but not yet on treatment, defaulted from treatment, or on ineffective (virally unsuppressed) therapy.⁴¹⁶ Second, the availability of better diagnostics for the diagnosis of

asymptomatic and symptomatic opportunistic infections should be accelerated. For instance, POC diagnostics for TB (e.g. urine lipoarabinomannan assay)^{324,325} and cryptococcal (e.g. lateral flow cryptococcal antigen assays)^{417,418} infection and disease can be used in decentralized settings, as well as innovative laboratory approaches intended to increase screening coverage (e.g. reflex CrAg screening).^{417,419} In addition, more sensitive tests with short test to result turn-around time should be introduced, such as the Xpert MTB/RIF Ultra.^{322,323} Third, newly available and effective treatment regimens should be quickly utilized for the treatment of HIV and opportunistic infections. For instance, a study from South Africa demonstrated that the phase-out of stavudine and the introduction of tenofovir and of fixed dose combination decreased mortality in patients with CD4 counts <200 cells/mm^{3,354} With respect to opportunistic infections, flucytosine-based treatment regimens for the treatment of HIV-associated cryptococcal meningitis are effective and recommended by WHO,^{418,420} but are not widely available in RLS⁴²¹ including in Eswatini in 2019. This is of concern as currently used treatment regimens with amphotericin and fluconazole sustain high mortality rates of 44% in RLS.⁴²² Similarly, the implementation of shorter, more tolerable, and fully-oral treatment regimens for the treatment of multidrug- and rifampicin-resistant TB, as recommended by WHO,^{423,424} should be accelerated to reduce TB-associated mortality in PLHIV. Finally, preventive therapy of opportunistic infections, such as cotrimoxazol preventive therapy, may need to be strengthened in expanding HIV programmes in RLS.³⁵⁴

Expand interventions for TB control

Result-5 showed that the pace of decline in TB notifications decreased during ART expansion, suggesting reduced impact of further ART expansion on TB notifications when treatment coverage is already high. Strengthening of known interventions and the introduction of new interventions other than solely ART expansion appear to be important to sustain a decline in the burden of TB in high HIV prevalence settings. First, the accelerated introduction of TB preventive therapy is recommended to prevent progression from TB infection to active TB disease specifically in people infected with HIV, with different regimens available such as 6-month daily isoniazid, 3-month daily isoniazid and rifampicin (3HR), or 3-month weekly isoniazid and rifapentine (3HP).^{425,426} Second, intensified case finding and the use of efficient and near-patient diagnostic tools (e.g. lateral flow urine lipoarabinomannan assay, Xpert MTB/RIF Ultra)^{322,323,427} for timely and sensitive diagnosis of TB disease at all health care levels remain crucial to prevent spread of undiagnosed TB. Finally, improving TB treatment outcomes will remain a cornerstone for effective control. Interventions proposed are strengthening of HIV and TB service integration (e.g. timely ART initiation) and the introduction of more effective and less toxic TB treatment regimens.^{16,315}

Establish contextualized screening algorithms for same-day ART initiation

Expanding the same-day ART policy can increase timely treatment initiation. Accelerated implementation without assessing treatment readiness, however, may result in harm. Despite the

possible programmatic net gain, with more patients accessing ART, higher risk of acquired HIV drug resistance because of increased early loss to care after ART initiation may pose a public health risk. Contextualized screening algorithms need to be established and evaluated for effective identification of patients not ready for same-day ART. HIV programmes also need to take care that these algorithms are consistently used by health workers.

Consider integrating AHI care into HIV programmes in RLS

HIV programmes in high HIV incidence settings should consider the diagnosis and treatment of AHI for further reduction of HIV transmission under Treat-All. Because of multiple operational challenges to diagnosing AHI in RLS, implementation research may be required to inform health policy and operationalization.

Continue to use observational data from routine setting

Even with the completion of the Treat-All trials, observational data are likely to continue playing an important role in understanding public health interventions. For instance, first, large well-planned and funded Treat-All trials may not be generalizable to many other settings that continue to expand ART. The political and health context in which the Treat-All trials were conducted in Southern Africa (e.g. politically stable, high HIV prevalence setting) is very different from settings facing political unrest, violent conflicts, or other prevalent diseases and public health emergencies that intersect with the HIV epidemic (e.g. malaria, Ebola, collapsing health sector). Second, observational data will remain to play an important role in settings where the execution of more controlled studies would be difficult or impossible (e.g. lack of research funding and capacity, humanitarian conflict). Third, the health context in the past may be different from the context today and tomorrow. This research project and the Treat-All trials were completed before the outbreak of the COVID-19 pandemic. As, the COVID-19 pandemic likely has adverse consequences on continued ART scale-up and quality ART care, observational data – that are often already widely available – could more quickly provide answers to important emerging questions (e.g. interruptions of ART services and their impact on health outcomes for PLHIV). In contrast, prospectively planned randomized trials need timely planning, sufficient funding and research capacity, thus may delay answering these questions in a timely manner.

CONCLUSIONS

This thesis investigated the feasibility of universal ART expansion irrespective of immunological treatment eligibility initiation criteria in a predominantly rural and resource-poor public sector setting. Findings showed that programmatic ART care outcomes improved during ART expansion and the HIV programme achieved high ART coverage among PLHIV prior to the introduction of Treat-All. Thereafter, in the same setting, the roll-out of the Treat-All approach appeared feasible. Treat-All achieved higher and faster ART initiation rates from the time of facility-based HIV care enrolment when compared with SOC, as well as similar ART outcomes with regards to attrition and viral failure. At the same time, linkage to care from community-based HTS did not worsen but showed potential for higher ART initiation, and patients presenting with advanced HIV disease were not de-prioritized under Treat-All. However, treatment outcomes of patients initiated on ART on the same day as HIV care enrolment appeared inferior when compared with those in patients initiated within 1 to 14 days after care enrolment. Finally, this thesis demonstrated a potential population-level impact on TB notifications during successive expansion of ART. TB notifications declined overall, particularly in HIV-infected patients, without signs of TB rebound. Findings of this research project are likely applicable to similar public sector settings in sub-Saharan Africa and can inform international expansion of the Treat-All approach.

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