The use of epidemiological and health economic modelling in shaping policy of HIV prevention and treatment services

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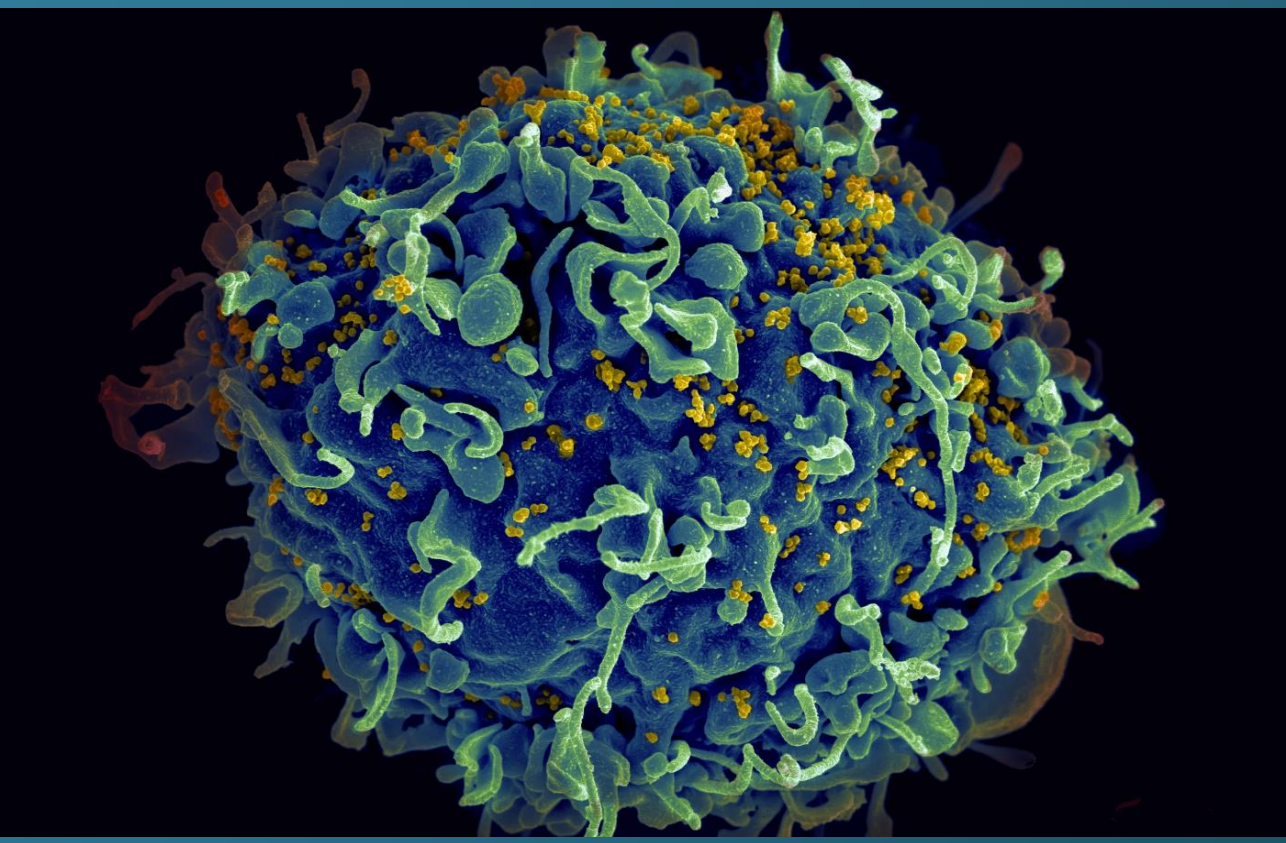

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Contents

Abbreviations

3TC	lamivudine
ABYM	adolescent boys and young men
AGYW	adolescent girls and young women
aHR	adjusted hazard ratio
AIDS	acquired immunodeficiency syndrome
aIRR	adjusted incidence risk ratio
ALT	alanine aminotransferase
ANC	antenatal care
aOR	adjusted odds ratio
ART	antiretroviral treatment
ARV	antiretroviral
BL	baseline
CAB-LA	long-acting injectable cabotegravir
CET	cost-effectiveness threshold
CHW	community health worker
CI	confidence interval
COVID-19	Coronavirus disease
DALYs	disability-adjusted life-years
DRV	darunavir
DSD	differentiated service delivery
DTG	dolutegravir
EFV	efavirenz
EIMC	early infant male circumcision
FDA	Food and Drug Administration
FM	feasible maximum
FSW	female sex workers
FTC	emtricitabine
GDP	gross domestic product
GF	Global Fund
HBsAg	Hepatitis B surface antigen
HCT	HIV counselling and testing
HIV	human immunodeficiency virus
HIVST	HIV self-test
HPTN	HIV Prevention Trials Network
HR	hazard ratio

HTS	HIV testing services
ICER	incremental cost-effectiveness ratio
iDSI	International Decision Support Initiative
IEC	information, education and communication
INSTI	integrase strand transfer inhibitor
IQR	interquartile range
LMIC	low- and middle-income countries
LTFU	lost to follow-up
LYS	life years saved
MMC	medical male circumcision
MMD	multi-month dispensation
MPC	master procurement catalogue
MSM	men who have sex with men
NDOH	National Department of Health
NMB	net monetary benefit
NNT	number needed to treat
OR	odds ratio
PCR	polymerase chain reaction
PEP	post-exposure prophylaxis
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PHC	primary healthcare
PLHIV	people living with HIV
PMTCT	prevention of mother-to-child transmission
PrEP	pre-exposure prophylaxis
PSA	probabilistic sensitivity analysis
RAL	raltegravir
RR	risk ratio
SEP	single exit price
SMS	short message service
SSA	sub-Saharan African
STAR	Self-Testing AfRica
STI	sexually transmitted infection
TAF	tenofovir alafenamide
TAPS	Treatment And Prevention for FSW in South Africa
TasP	treatment as prevention
TDF	tenofovir disoproxil fumarate
TDF/FTC	tenofovir disoproxil fumarate/emtricitabine

TLD	first-line ART consisting of TDF, 3TC, and DTG
TWG	technical working group
USD	United States Dollar
UTT	universal test and treat
VL	viral load
WBOT	ward-based outreach team
WHO	World Health Organization
YM	young men
YW	young women
ZAR	South African Rand

Chapter 1
General introduction and thesis outline

HIV

An estimated 38.4 million people were living with the human immunodeficiency virus (HIV) globally in 2021, of which 25.6 million (66.7%) were in sub-Saharan Africa (SSA) (1). South Africa alone accounts for an approximate 7.5 million people living with HIV (PLHIV), while Zambia has 1.3 million PLHIV (2,3). In 2021, an estimated 51,000 and 19,000 AIDS-related deaths occurred in South Africa and Zambia, respectively (2,3). As of 2019, HIV was the leading cause of death in low- and middle-income countries (LMIC) (4).

Governments from both South Africa and Zambia are committed to meeting the UNAIDS fast-track targets by 2025 (5). These targets aim to have, by 2025, 95% of PLHIV diagnosed, 90% of PLHIV on antiretroviral treatment (ART) and 86% of PLHIV virally suppressed. Zambia is very close to achieving these goals with 91%-90%-87% (3) for the respective target goals. With a much higher burden of HIV compared to Zambia, South Africa is lagging behind with 94%-74%-67% for the respective targets (2). Another target, that is often cited as a target to reach by scaling up prevention and treatment interventions, is the "virtual elimination threshold", which was shown through modelling would eliminate HIV if a population-level HIV incidence could be maintained below 0.1% annually (6). As of 2021, Zambia was estimated to have an annual HIV incidence of 0.4% (3) and South Africa, 0.69% (2).

HIV prevention and treatment

Several strategies exist for the prevention of HIV transmission. Before biomedical interventions were available, we had to solely rely on condoms and behavioural interventions. Condoms have shown to be approximately 70% effective in preventing transmission between heterosexual couples and men who have sex with men (MSM) (7,8). However, consistent condom use in sub-Saharan Africa is low, ranging between 30%-80%, and the use of condoms is reliant on male partners agreeing to it, while women are find it hard to negotiate the use of condoms (9–14). Behavioural interventions have also proven to be not as effective in preventing HIV infection as was hoped (15,16).

Treatment and treatment as prevention

HIV treatment as prevention (TasP) is the process whereby an HIV-infected person takes antiretroviral HIV treatment, consistently, which causes the HIV viral load to be suppressed to undetectable levels in the blood and other cells – this prevents onward transmission to HIV-negative individuals. In several studies, TasP has been shown to be highly effective (93%-96%) in preventing HIV infection in different population groups and across different countries (17–20).

Since 2013, the first-line regimen for HIV treatment has been tenofovir disoproxil fumarate (TDF) combined with efavirenz (EFV), and with either lamivudine (3TC) or emtricitabine (FTC). In 2013, a second-generation HIV drug under the integrase strand transfer inhibitor (INSTI) class, called dolutegravir (DTG), was first approved for use by the United States Food and Drug Administration, and subsequently approved and rolled out in a number of countries. In comparison to the first-line EFV-containing regimen, which had a low resistance barrier with an estimated 5-8% of patients developing resistance (21), the advantage of DTG is it has been shown to have a lower resistance barrier, better tolerability and less side-effects than other drugs in the INSTI class and EFV (22–27).

Of the 7.5 million and 1.3 million PLHIV in South Africa and Zambia, respectively, an estimated 5.5 million and 1.2 million are on HIV treatment (2,3). At 73% ART coverage, South Africa in particular falls short of the UNAIDS' 95% target of PLHIV on ART by 2025 (5); however, Zambia gets closer with 92%. A key driver in achieving 95% ART coverage is retention in care. A differentiated service delivery (DSD) model is an alternative method of providing a service to a patient in public care. DSD models for HIV treatment can differ from conventional care by the cadre of provider, location of service delivery, frequency of interactions with the healthcare system, and/or types of services offered. These changes can help remove barriers to care, making it easier for patients to access HIV treatment, and support long-term retention to care (28). Retention in care in DSD models has been shown to be within 5% of that for conventional care (29).

Routine HIV testing is regarded as a prevention strategy for two reasons: 1) it intercepts undiagnosed PLHIV, who may potentially transmit the virus

unknowingly, and once diagnosed, they are initiated on ART to suppress the virus; 2) if diagnosed PLHIV initiate ART, this will contribute to the treatment as prevention strategy as their viral load becomes undetectable and therefore cannot infect others. In addition, by identifying PLHIV who are unaware of their HIV status early, linking them to ART will prevent their otherwise inevitable death from AIDS. For these reasons, optimising HIV testing is regarded as a critical step towards filling the gap in getting closer to HIV elimination.

In recent years, HIV self-testing (HIVST) technology has been developed and has given people the opportunity to diagnose their HIV status themselves in the privacy of their own homes, by allowing them to collect their own specimen for testing (oral fluid or blood), and performing the test using a rapid diagnostic test included in the self-test kit (30). By having a private testing strategy, those who want to test for HIV can avoid common socio-structural barriers that is associated with conventional HIV testing at a public health facility, and the potential stigma with accessing testing for HIV. HIV self-testing has been shown to be feasible, acceptable and effective at increasing testing uptake in sub-Saharan Africa (31–33).

Pre-exposure prophylaxis

Biomedical interventions have been successfully trialled and implemented in recent years. Oral pre-exposure prophylaxis (PrEP), specifically the combination drug tenofovir/emtricitabine (TDF/FTC), currently used in first-line HIV treatment, has been shown to be 65%-85% effective in preventing HIV acquisition in a number of populations, including in sub-Saharan Africa (34,35). People who deem themselves at risk of HIV acquisition take oral PrEP daily while HIV negative, to prevent infection with HIV once exposed. However, effectiveness is closely linked to adherence and persistence use (35). One of the newer developments in biomedical interventions that can potentially overcome the adherence issue in the short-term is long-acting injectable cabotegravir (CAB-LA). CAB-LA is a 2-monthly injection, and has been shown in trials to be one of the most effective HIV prevention technologies to date; compared to oral TDF/FTC, CAB-LA had effectiveness estimates 66% [95% confidence interval (CI) 38%-82%] in MSM and transgender women, and 89% [95%CI 68%-96%] in young women (36–38). In 2022, the World Health Organization (WHO) recommended CAB-LA for

use as PrEP in populations at substantial risk of HIV acquisition (39), and since then a number of countries have approved use, including South Africa, Uganda and Zimbabwe (40–42).

South Africa's National Strategic Plan for HIV, TB and STIs over 2017-2022 (43) has set the goal to reduce new HIV infections to less than 100,000 by 2022 through combination prevention interventions. As of 2021, the number of new HIV infections in South Africa was estimated to be 210,000 (2). Since 2016, oral PrEP was being made available through demonstration projects and implementation studies. In 2020, the National Department of Health (NDOH) committed to rolling oral PrEP out to every primary healthcare clinic in South Africa. However, both the large-scale roll-out of PrEP, and as a result the uptake, was negatively impacted after the emergence of the COVID-19 pandemic in March 2020, as subsequent lockdowns were instituted country-wide, and along with this, a reluctance of people accessing services at health facilities (44).

Epidemiological modelling

Mathematical modelling of infectious diseases, or epidemiological modelling, is useful in simulating populations and projecting future outcomes, as well as evaluating the impacts of specific health interventions. The complex underlying modelling structure(s) can produce results that can be used to inform planning of public health of interventions, and their implementation. There are several epidemiological models that have been used in this thesis, with the main one being Thembisa for South Africa. Other models used in work in Chapter 7 in this thesis are EMOD-HIV, Optima HIV, and HIV Synthesis, with a brief description of each below.

Thembisa is a deterministic compartmental HIV transmission model that has been developed specifically to model the HIV epidemic in South Africa at a national and provincial level (45). It is in use by both the South African Government and UNAIDS to produce estimates for the country. The national population in the model is stratified by age, sex, sexual behaviour, marital status, HIV testing history, male circumcision status, HIV status, ART status, and outputs are produced annually over time from 1985. It can model a number of HIV interventions for both prevention and treatment, including PrEP (oral PrEP or CAB-LA), condoms, conventional HIV testing, HIV self-

testing, and initiation on ART (45). Thembisa is well-calibrated to several data sources in South Africa, including data on HIV prevalence from nationally representative household surveys (10,46–49), HIV testing (50), ART uptake (10,48) and all-cause mortality data (51).

EMOD-HIV is an individual-based network HIV transmission model calibrated to the South Africa HIV epidemic (52,53). In contrast to a compartmental type model, which means the population is divided into compartments, EMOD-HIV is an agent-based model, meaning that it simulates individuals instead of groups. This method of modelling allows the model to include demographic variables and HIV transmission dynamics at a finer scale, while allowing for complex contact network between individuals.

Optima HIV is a compartmental HIV transmission model calibrated to epidemic trends in more than 20 countries (54). The model is disaggregated by sex, age (in 5-year age groups) and sub-population (female sex workers, clients of sex workers, MSM and general population), HIV status, and ART status.

HIV Synthesis is an individual-based HIV model and simulates population of adults living in SSA countries from 1989, tracking risk of HIV acquisition every 3 months (55,56). The model also includes age, sex, HIV testing, male circumcision, sexually transmitted infections, oral PrEP and ART. The model generates setting scenarios generated through simulation by randomly varying parameters, including the rate of HIV testing, ART adherence, ART interruption and treatment failure, within plausible bounds in the SSA region.

Cost and outcomes analyses

In health economics, cost and outcomes analyses cover a broad set of methodology that is used to simultaneously evaluate both outcomes and cost of new or existing health interventions in order to help inform policy on its implementation. When comparing more than one intervention at a time, there is usually a standard-of-care, or baseline scenario, to which the new interventions are compared against, in order to assess whether they will be worth implementing. Different types of methodology exist under cost and outcomes analysis, each with their own set of defined outcomes and policy questions. There are two main types that were used in this thesis: 1) cost-effectiveness analysis, and 2) budget impact analysis. A cost-effectiveness

analysis aims to answer the question: “which health intervention yields a given level of effectiveness for the lowest cost (or the highest impact under a given cost)?”. The main output from a cost-effectiveness analysis is an incremental cost-effectiveness ratio (ICER)- a direct comparison to the baseline scenario or standard-of-care intervention, estimating the incremental impact acquired from implementing a particular intervention. This outcome is expressed as a cost for one unit of a natural outcome, e.g. “cost per life year saved” or “cost per HIV infection averted”. A budget impact analysis is more focused on the total cost of implementing one or more interventions and its main aim is to inform policy-makers and other stakeholders on how much these would cost compared to the available budget.

Adapted fractional factorial design

Often cost-effectiveness analyses are straightforward in design with at most, a handful of interventions, under comparison. However, in this thesis we applied a particular methodology to the cost-effectiveness analysis, namely an adapted form of the fractional factorial design, to optimize the distribution of HIV testing modalities (Chapter 3). Fractional factorial design is a statistical experimental design which comprises of a subset of a full factorial design, where the individual experimental runs are carefully selected based on a set of criteria which ensures only non-redundant runs are implemented, in the case of this thesis – only the experimental model runs which were plausible.

Research Aims

The overall aim of this thesis is, through the use of health economic and epidemiological modelling methods, understand how to cost-effectively maximize impact of our HIV programmes in order to guide national and international health policy. Broadly, I will achieve the following through my work:

- Informing policy-makers on the most optimal strategy of targeting HIV prevention methods, specifically oral PrEP and HIV self-testing; informing national and international price negotiations by estimating the optimal price for the latest available HIV prevention method, CAB-LA.
- Re-evaluate existing HIV treatment interventions and their current policies, including the latest ART regimen and interventions used to improved patient retention, across SSA countries, estimating their impact and cost-effectiveness in a way that is useful for policy-makers.
- Designing the optimal package of interventions by applying health economics and epidemiological modelling methods to both HIV prevention and treatment interventions for South Africa with the aim of reaching HIV elimination.

Outline of thesis

Part 1 of this thesis focuses on research for HIV prevention interventions that can help inform policy on targeting of high-risk populations for oral PrEP use (**Chapter 2**) and how to optimize HIV self-testing in a way that will outperform current policy on distribution of this intervention (**Chapter 3**). Lastly, **Chapter 4** estimates a price threshold for a new PrEP technology, work which can and will be used by policy-makers in price negotiations for pharmaceutical manufacturers, in order to make it affordable for a large-scale roll-out to ensure a meaningful impact.

Part 2 of this thesis is focussed on research for HIV treatment interventions. **Chapter 5** examines the cost-effectiveness of a new HIV treatment, helping to inform current HIV treatment policy, and illustrates how trial-based data can be adapted in a modelling framework in order to make it relevant for

national-level epidemiological and cost-modelling. **Chapter 6** evaluates the current policy of differentiated service delivery (DSD) models for HIV treatment in Zambia, which require a minimum duration on ART before a patient is considered eligible. **Chapter 7** makes use of modelling to help inform low- and middle-income countries on what the upper bound costs should be for HIV treatment retention interventions.

Lastly, Part 3 combines HIV prevention and treatment interventions in work that aims to optimise all HIV interventions for the South African government, with a special focus on a retention intervention as a means of informing policy on the way forward to achieving HIV elimination (**Chapter 8**).

Part 1:
Interventions for HIV prevention

Chapter 2

The impact of self-selection based on HIV risk on the cost-effectiveness of pre-exposure prophylaxis in South Africa

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AIDS 34, 883–891

Abstract

Objectives

We explored the impact and cost-effectiveness of pre-exposure prophylaxis (PrEP) provision to different populations in South Africa, with and without effective self-selection by individuals at highest risk of contracting HIV (through concurrent partnerships and/or commercial sex).

Design and methods

We used a previously-developed HIV transmission model to analyse the epidemiological impact of PrEP provision to adolescents, young adults, pregnant women, female sex workers (FSWs) and men who have sex with men (MSM), and data from South African PrEP programmes to estimate the cost and cost-effectiveness of PrEP (cost in 2019 USD per HIV infection averted over 20 years, 2019-38). PrEP uptake followed data from early implementation sites, scaled-up linearly over 3 years, with target coverage set to 18% for adolescents, young adults and pregnant women, 30% for FSW and 54% for MSM.

Results

The annual cost of PrEP provision ranges between $75-$134 per person. PrEP provision adolescents and young adults, regardless of risk behaviour, will each avert 3.2%-4.8% of HIV infections over 20 years; provision to high-risk individuals only has similar impact at lower total cost. The incremental cost per HIV infection averted is lower in high-risk vs. all-risk sub-populations within female adolescents ($507 vs. $4,537), male adolescents ($2,108 vs. $5,637), young women ($1,592 vs. $10,323) and young men ($2,605 vs. $7,715), becoming cost saving within 20 years for high-risk adolescents, young women, MSM and FSWs.

Conclusions

PrEP is an expensive prevention intervention, but uptake by those at highest risk of HIV infection will make it more cost-effective, and cost-saving after 14-18 years.

Introduction

In September 2015, the World Health Organization (WHO) released updated antiretroviral treatment guidelines which included recommendations that pre-exposure prophylaxis (PrEP) be made available to people at substantial risk of acquiring HIV (57,58). "Substantial risk of acquiring HIV" was purposefully not defined in the guidelines, although an acceptable threshold for high risk was given as an annual HIV incidence of greater than 3% in a particular sub-population (57). PrEP has been shown to be effective in preventing HIV infection through sexual transmission in different population groups, when used consistently (34,35,59–64).

While previous studies focusing on Sub-Saharan Africa have concluded that overall PrEP provision is cost-effective in a number of countries, in relation to a threshold of 3 times gross domestic product per capita (65–75), few have looked at how HIV, cost and cost-effectiveness are impacted when targeting PrEP to high-risk sub-populations relative to the general population (66,69,72,74,75). None of these studies have included the detailed costs of PrEP provision based on observations of routine care.

Additionally, a recently published review of modelled economic analyses of PrEP provision by Case et al found that there was limited modelling of PrEP for men at high risk of HIV, and modelling of PrEP provision for female adolescents and young women did not incorporate uptake and adherence observed in current implementation projects (76). Case et al identified that most modelling studies assumed that existing human resources would suffice to cover an increase in PrEP demand, and many excluded the cost of outreach and engagement, as well as the additional benefit of linkages of PrEP programmes to HIV testing and treatment.

The 2016 South African HIV Investment Case (77) estimated that PrEP provision was one of the least cost-effective interventions to implement and should only be implemented after scaling up more cost-effective interventions such as condom provision, medical male circumcision (MMC), universal test and treat (UTT), HIV counselling and testing of different population groups, and a number of social and behaviour change mass media campaigns. However, the Investment Case did not consider a higher adoption by individuals at higher HIV risk and was based on preliminary cost estimates

that have since been updated based on data from early implementation sites, where delivery is part of other public health services.

PrEP roll-out in South Africa commenced in June 2016 with the launch of a FSW-targeted prevention campaign. More recently, PrEP has also become available to MSM, university students and young women, financed by international donors and by the government's conditional grant for HIV/AIDS (77). To guide local PrEP guidelines (78) and planning of further PrEP scale-up under the conditional grant, we were tasked by the South African National Department of Health's (NDOH) PrEP technical working group (TWG) to estimate the average and total cost of PrEP provision to different populations, and to generate evidence on which distribution strategy would be most cost-effective and whether higher PrEP uptake by high-risk individuals would improve cost-effectiveness.

This study aims to determine the cost-effectiveness of provision of daily oral PrEP in South Africa, a setting with one of the highest HIV prevalence levels in the world, while considering the possibility that those at higher risk of contracting HIV may self-select into the PrEP programme. Our focus on self-selection over supply-side targeting was informed by the TWG's preference that a risk screening tool should not be used to determine whether an individual receives PrEP, to avoid stigmatising PrEP as an intervention reserved for those with higher risk behaviour and to not exclude anybody who perceive themselves to be at HIV risk. Existing risk-scoring tools for HIV often have low sensitivity and/or specificity, leading to misclassification of those at risk of HIV (79–81).

Methods

Epidemiological model

The impact of PrEP on HIV incidence and HIV infections averted was estimated using the Thembisa model (version 4.2) (82,83), a compartmental HIV transmission model of the South African HIV epidemic. The population is stratified by age, sex, sexual experience, marital status, HIV testing history, male circumcision status and sexual behaviour. In addition, the sexually experienced population is divided into two broad sexual risk groups: 'high-risk' (people with a propensity for concurrent partnerships and/or commercial sex) and 'low-risk', with the high-risk group comprising 35% of males and

25% of females. Further details on the sexual behaviour assumptions are described in section 2.2 in the supplementary material.

PrEP is modelled by sub-dividing the sexually-experienced risk groups into individuals who are receiving PrEP or not. PrEP uptake rates vary by age, sex and risk group. Based on a recent meta-analysis, PrEP effectiveness, which accounts for both efficacy and adherence, is assumed to be 65% for non-MSM and 85% for MSM (34,35). The average duration on PrEP is assumed to be 2 years (83). Based on data from open-label PrEP trials, it is assumed PrEP users have a 10% lower rate of condom use than individuals of the same age and sex who are not using PrEP (84,85). Individuals who acquire HIV while on PrEP are assumed to be less likely to transmit HIV than individuals who acquire HIV in the absence of regular HIV testing, as the latter would remain undiagnosed and untreated for longer periods.

Scenarios and target population

We separately modelled the epidemiological impact and the cost effectiveness of PrEP provision to adolescents aged 15-19 years, young adults aged 20-24 years, pregnant women, MSM and FSW of all ages. For the pregnant women, women remain on PrEP from the time of first antenatal visit until cessation of breastfeeding. In HIV-negative women, 87% are assumed to breastfeed, and of those who choose to breastfeed, the median duration of breastfeeding is assumed to be 18 months (86). For adolescents and young adults, we evaluated additional sub-scenarios in which only the high-risk sub-population would adopt PrEP, to simulate scenarios in which individuals can assess their own HIV risk accurately and only those who correctly consider themselves to be at high-risk use PrEP.

For the main analysis, PrEP was assumed to be scaled-up linearly from 2019 onwards. Based on guidance from the NDOH's PrEP TWG and current uptake in demonstration projects, a target coverage of 18% for adolescents, young adults and pregnant women, 30% for FSWs and 54% for MSM by 2021, maintained up until 2038, was assumed. For additional information on model parameterisation and calibration see the Appendix.

Cost and cost-effectiveness analysis

The average cost of PrEP provision was estimated using an ingredient approach, as complete cost data was unavailable due to PrEP being not yet

implemented in the public sector beyond demonstration or early implementation sites. We worked closely with the NDOH's PrEP TWG and with experts from two demonstration projects of PrEP provision in South Africa: the Treatment And Prevention for FSW in South Africa (TAPS) demonstration project of PrEP provision to sex workers, for which data from a comprehensive economic analysis was available (87), and the Health4Men demonstration projects of PrEP provision to MSM. Based on these and on the WHO and South African PrEP guidelines (78), we assumed PrEP would be provided in primary healthcare clinics alongside a package of HIV prevention interventions, including HIV testing and counselling, provision of condoms, screening for symptoms of sexually transmitted infections, laboratory monitoring, and adherence counselling. For a summary of the cost items included see Table S1; a detailed break-down of the costs is available in Table S2.

Costs were analysed from the provider perspective, the South African government, and separated into patient-level and health system-level costs. Patient-level costs included costs associated with provision at the facility, such as cost of staff, HIV testing (at screening, 3-monthly per year and at re-initiation), laboratory monitoring tests, and the PrEP drugs (daily oral PrEP), assuming a generic combination of tenofovir and emtricitabine. We differentiated between costs for the first year (which included an initiation visit) and follow-up years, and calculated costs separately for each population group capturing differences in the HIV and syphilis prevalence, and the need for pregnancy tests.

Health-system costs included staff training, outreach, mobilisation, monitoring and evaluation costs. These costs assumed a service volume of 160 PrEP clients per clinic per year, based on demonstration project experience. Additional building maintenance and utilities were accounted for by inflating the cost per visit by 7%, based on the TAPS cost analysis (87).

Cost inputs for staff and laboratory testing were sourced from the 2019 Government Salary Scales and the 2018 National Health Laboratory Service price list, respectively. Costs for the PrEP regimen and HIV testing consumables were sourced from recent National Department of Health tenders. Costs are presented in 2019 USD, using the January to September 2019 average exchange rate of 1 USD = 14.32 South African Rand (88). To

inform future budgets, both costs and outcomes are presented undiscounted and unadjusted for inflation.

To evaluate the long-term impact of PrEP in different populations we analysed the cost-effectiveness of PrEP as cost per HIV infection averted over a 20-year time period (2019-2038) over a baseline of currently available HIV interventions in the South African public sector HIV programme. This allowed us to ascertain the impact of a reduction in incidence due to PrEP on the need for future ART, in addition to existing prevention interventions at high coverage, such as condom provision, counselling and testing, and medical male circumcision. The calculation of HIV programme costs followed the same approach as the South African HIV Investment Case (77,89), with target populations calculated by Thembisa and per-service costs updated to 2019 prices and salaries. An additional analysis compared the cost effectiveness of PrEP provision with that of scaling up existing HIV interventions, based on an update to the South African HIV Investment Case (77) as shown in Table S5.

Sensitivity analysis and uncertainty analysis

We evaluated the impact of uncertainty around four main model parameters (PrEP effectiveness, reduction in condom use while on PrEP, relative rate of PrEP uptake by those at low risk of HIV, and average cost) by conducting a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. The epidemiological and cost impact of PrEP was recalculated 1,000 times for each population group by randomly drawing parameter values from appropriate probability distributions (Table S2). We report the cost-effectiveness over a 20-year period consisting of the average estimate and a 95% confidence interval using the 2.5th and 97.5th percentiles. The sensitivity of incremental cost and new HIV infections averted to the parameters included in the uncertainty analysis are quantified using partial rank correlation coefficients. One-way sensitivity analyses for PrEP coverage, and average duration on PrEP was performed (Figures S6-S7).

Results

Annual total HIV incidence was projected to decline in all scenarios, including baseline (Figure 1A, 1B), with PrEP reducing HIV incidence marginally over time. Over a 20-year period (2019-2038), PrEP given to 18%

of female adolescents and young men from all risk groups had a larger impact on new HIV infections averted compared to PrEP provision to young women (4.3% and 4.0%, respectively, vs. 3.0%) (Table 1). Providing PrEP to high-risk sub-populations within these populations, also at 18% coverage by 2021 and maintained until 2038, had 80%-95% of the impact of PrEP provision to all risk groups within the same population. The largest impact was from providing PrEP to 54% of MSM, reducing new HIV infections by 4.9%, due to both larger coverage and PrEP effectiveness within this population group. Providing PrEP to 30% of FSW and 18% of pregnant women reduced the number of new HIV infections by 1.4% and 1.7% over the 20-year period, respectively. Though FSW is a high-risk group, the overall impact on reducing new HIV infections is smaller due to the fact that the FSW population is relatively small.

The average cost of PrEP provision per non-pregnant client was $129-$134 for the first year, and $107-$110 for every year thereafter (Table 2). PrEP for pregnant/breastfeeding women cost $75 for coverage during their first year (as PrEP provision was assumed to be part of ANC services) and $110 for every year thereafter. Across initiation and follow-up years, the drug cost only contributed 35% of the cost, while 13-28% was due to laboratory testing (Figure 2). Laboratory costs are higher in the first year due to the higher number of monitoring tests required. Staff costs, not reported separately, made up ~25% of the cost.

The annual cost of the HIV programme was expected to rise in the baseline scenario as a result of covering an increasing population with interventions including ART, costing $34.7 billion over the 20-year period (2019-2038) (Table 1). Introducing PrEP increased the total cost of the HIV programme by 0.1%-0.8% and by 1.2%-2.3% when provided to high-risk sub-populations and all risk groups, respectively. The cost of the HIV programme increased by 1.2% over the 20-year period if 18% of pregnant/ breastfeeding women were provided with PrEP. Successful self-selection by high-risk adolescents of both genders and young women, as well as providing PrEP to FSW and MSM at our assumed target coverages, resulted in declines in the annual cost of the HIV programme, mostly due to the reduced need for ART, but only from 2033 at the earliest (Figure 1E). The annual cost for each scenario for the first 5 years are shown in Table S4.

Table 1. Cost-effectiveness of PrEP provision by population (2019-38)

	Baseline	Female adolescents (15-19)		Young women (20-24)		Pregnant/ breast-feeding women
PrEP coverage by 2021	*0%*	*18%*		*18%*		*18%*
Risk group		*All*	*High-risk*	*All*	*High-risk*	*All*
Number of person years on PrEP [millions]	0.0	7.3	2.0	10.0	2.0	2.8
Total HIV programme cost [billions 2019 USD]	34.68	35.29	34.74	35.63	34.80	34.91
Incremental HIV programme cost [millions 2019 USD] (% change)		608 (1.8%)	61 (0.2%)	949 (2.7%)	121 (0.3%)	227 (0.7%)
Total new HIV infections [millions]	3.81	2.95	2.96	2.99	3.01	3.03
HIV infections averted [thousands] (% change)		134 (4.8%)	121 (4.2%)	92 (3.2%)	76 (2.6%)	53 (1.8%)
ICER [USD/HIV infection averted]		4,537	507	10,323	1,592	4,283

* USD=United States Dollar; ICER=incremental cost-effectiveness ratio; HIV=human immunodeficiency virus; FSW=female sex workers; MSM=men who have sex with men

Table 1. Cost-effectiveness of PrEP provision by population (2019-38) *(continued)*

	FSW	**Male adolescents (15-19)**		**Young men (20-24)**		**MSM**
PrEP coverage by 2021	*30%*		*18%*		*18%*	*54%*
Risk group	*All*	*All*	*High-risk*	*All*	*High-risk*	*All*
Number of person years on PrEP [millions]	0.8	5.7	2.6	10.1	4.0	3.4
Total HIV programme cost [billions 2019 USD]	34.71	35.20	34.87	35.64	34.99	34.89
Incremental HIV programme cost [millions 2019 USD] (% change)	31 (0.1%)	522 (1.5%)	187 (0.5%)	957 (2.8%)	306 (0.9%)	205 (0.6%)
Total new HIV infections [millions]	3.04	2.99	2.99	2.96	2.96	2.93
HIV infections averted [thousands] (% change)	43 (1.4%)	93 (3.2%)	89 (3.1%)	124 (4.4%)	117 (4.1%)	150 (5.4%)
ICER [USD/HIV infection averted]	724	5,637	2,108	7,715	2,605	1,370

* USD=United States Dollar; ICER=incremental cost-effectiveness ratio; HIV=human immunodeficiency virus; FSW=female sex workers; MSM=men who have sex with men

Table 2. PrEP average cost per population group for first and follow-up years on PrEP [2019 USD]

Year of PrEP	Female adolescents (15-19)	Young women (20-24)	Pregnant/ breast-feeding women	FSW	Male adolescents (15-19)	Young men (20-24)	MSM
First year	$132	$132	$75	$134	$130	$130	$129
Follow-up year	$110	$110	$110	$109	$108	$108	$107

* USD=United States Dollar; FSW=female sex workers; MSM=men who have sex with men

Table 3. Results of probabilistic sensitivity analysis; incremental impact on new HIV infections and cost [2019 USD] over 20 years (2019-38)

PrEP target population	Number of new HIV infections averted (95% CI)	% of new HIV infections averted over baseline (95% CI)	Varying PrEP average cost		
			Incremental cost of the HIV programme over baseline [millions] (95% CI)	% increase in cost of the HIV programme over baseline (95% CI)	Incremental cost effectiveness ratio [USD/HIV averted] (95% CI)
Young women	82,044 (58,756; 104,337)	2.7% (1.9%;3.4%)	444 (83;1,054)	1.28% (0.24%; 3.04%)	5,480 (1,074;13,039)
Female adolescents	125,805 (92,345; 154,922)	4.1% (3.0%;5.0%)	275 (5;709)	0.79% (0.02%; 2.04%)	2,230 (45;5,880)
Pregnant/breast-feeding women	53,136 (37,822; 66,029)	1.7% (1.2%;2.1%)	237 (76;427)	0.68% (0.22%; 1.23%)	4,592 (1,355;9,579)
FSW	42,813 (29,141; 54,137)	1.4% (0.9%;1.8%)	34 (-17;93)	0.10% (-0.05%;0.27%)	858 (-347;2,794)
Young men	120,072 (100,649; 136,227)	3.9% (3.3%;4.4%)	571 (183;1,163)	1.65% (0.53%;3.35%)	4,780 (1,519;9,786)
Male adolescents	90,352 (77,165; 101,123)	2.9% (2.5%;3.3%)	324 (98;655)	0.93% (0.28%;1.89%)	3,602 (1,108;7,289)
MSM	149,638 (130,221;158,909)	4.9% (4.2%;5.2%)	219 (26;446)	0.63% (0.07%;1.29%)	1,473 (170;3,145)

Table 3. Results of probabilistic sensitivity analysis; incremental impact on new HIV infections and cost [2019 USD] over 20 years (2019-38) *(continued)*

PrEP target population	Constant PrEP average cost		
	Incremental cost of the HIV programme over baseline [millions] (95% CI)	**% increase in cost of the HIV programme over baseline (95% CI)**	**Incremental cost effectiveness ratio [USD/HIV averted] (95% CI)**
Young women	424 (156;759)	1.22% (0.45%;2.19%)	5,220 (1,849;9,753)
Female adolescents	259 (75;488)	0.75% (0.22%;1.41%)	2,097 (538;4,214)
Pregnant/breast-feeding women	226 (208;248)	0.65% (0.60%;0.72%)	4,375 (3,150;6,558)
FSW	31 (15;49)	0.09% (0.04%;0.14%)	776 (282;1,691)
Young men	544 (334;809)	1.57% (0.96%;2.33%)	4,553 (2,655;6,970)
Male adolescents	308 (200;444)	0.89% (0.58%;1.28%)	3,425 (2,114;5,100)
MSM	205 (194;228)	0.59% (0.56%;0.66%)	1,378 (1,222;1,747)

Figure 1. Impact of PrEP provision to different populations on A) total HIV incidence from 1990, B) total HIV incidence from 2018 onwards, C) new HIV infections averted annually, D) total cost (2019 USD) of the HIV programme and E) incremental cost (2019 USD) to the HIV programme

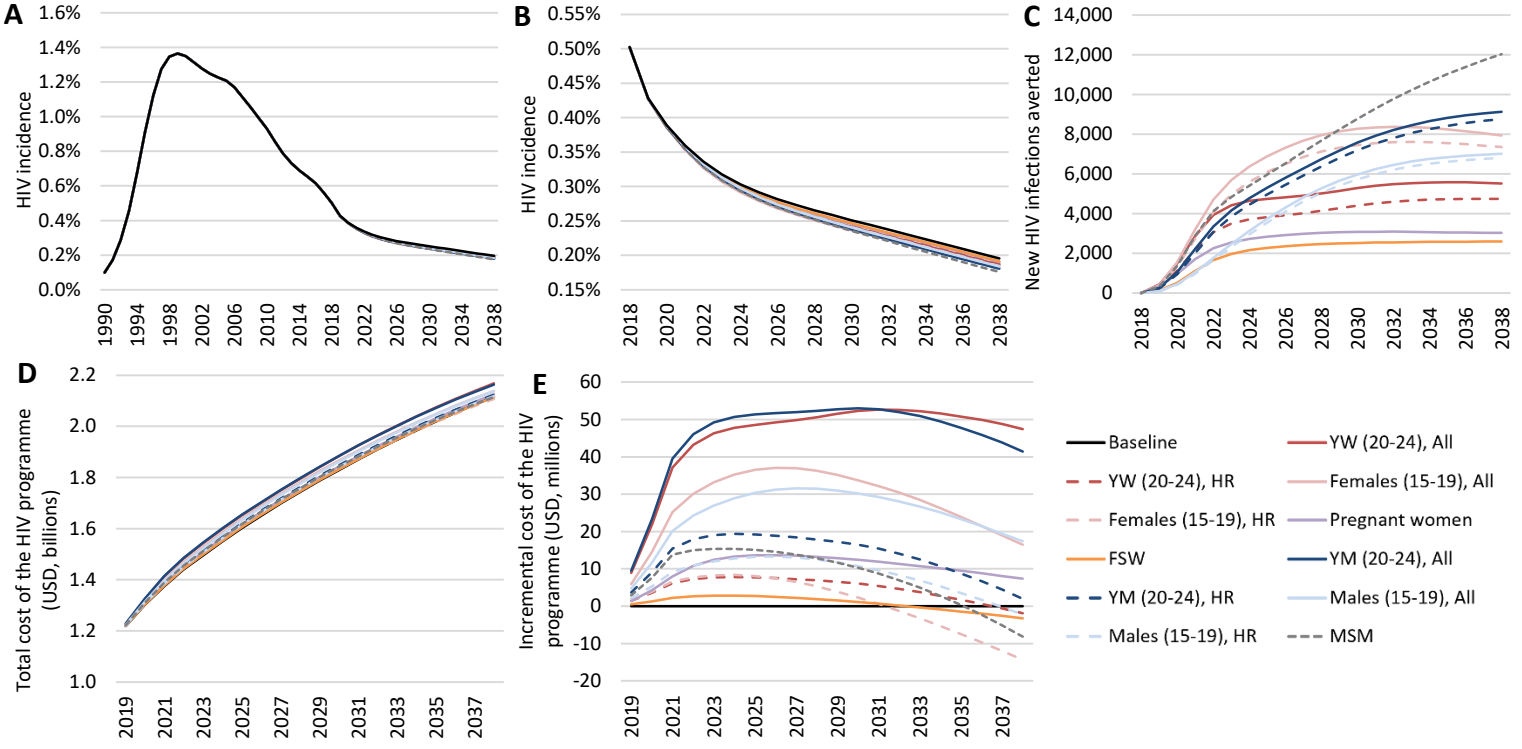
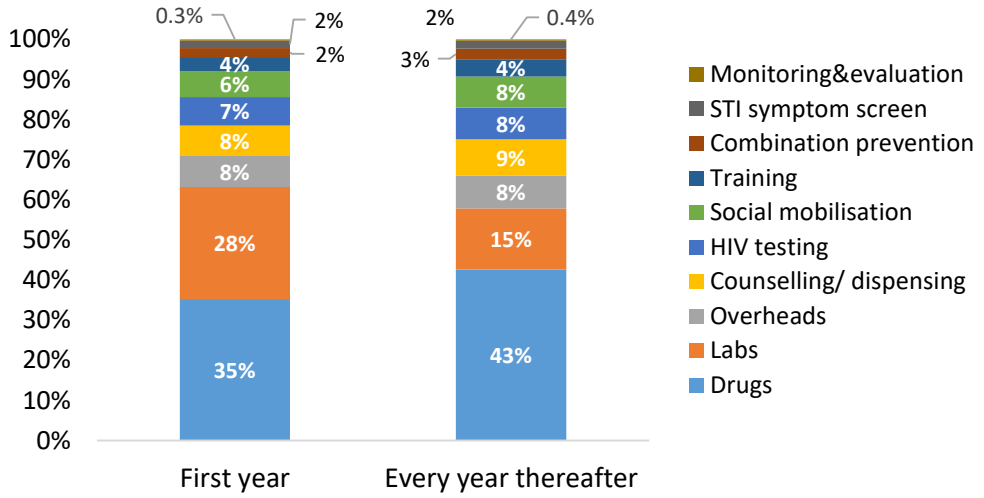


Figure 2. Distribution of PrEP cost between different cost components for the average PrEP average cost across non-pregnant populations A) first year, and B) every year thereafter



The differential impact of PrEP provision to the different population groups on cost and infections averted translated into stark differences in the cost-effectiveness of each scenario. PrEP provision to high-risk groups compared to all risk groups was more cost-effective across all populations: female adolescents ($507 vs. $4,537) and male adolescents ($2,108 vs. $5,637), young women ($1,592 vs. $10,323 per HIV infection averted) and young men ($2,605 vs. $7,715). Providing PrEP to 18% of pregnant women will cost $7,897 per HIV infection averted and providing PrEP to 30% of FSW and 54% of MSM costed $724 and $1,370 per HIV infection averted, respectively (Table 1).

A one-way sensitivity analyses for PrEP coverage shows a linear relationship between coverage and impact, and as a result there is no optimal coverage target (Figure S6). One-way sensitivity analysis of average time on PrEP reaches similar conclusions (Figures S7).

Results from the PSA are shown in scatterplots depicting incremental cost and new HIV infections averted over the 20-year period (Figure S1). The mean and the 95% confidence interval estimates are shown in Table 3. Varying the average cost of PrEP for FSW cost-saving in some scenarios, with around 22% of simulations having a negative incremental cost. Other populations with a potential for cost-savings, though with lower likelihood,

were female adolescents, young women and MSM, with cost savings occurring in 0.3%, 4.1% and 2.0% of simulations, respectively. The annual impact on new HIV infections averted and cost for each population are available in Figures S3-S5.

Besides PrEP average cost, incremental cost was most sensitive to the relative rate of PrEP uptake by those at low risk of HIV (Table S3). New HIV infections averted were sensitive to all parameters we varied, with the exception of PrEP average cost and for PrEP uptake by those at low risk of HIV within pregnant women, FSW and MSM.

Discussion

We found that PrEP is a costly intervention at $129-$134 per user year for non-pregnant users, roughly half the annual cost per patient of ART, and more expensive per unit of service provided than other prevention interventions (for example, condom provision at $0.05/condom and medical male circumcision at $87/procedure) (90). We found that PrEP provision to high-risk groups will have a very similar impact in terms of HIV infections averted but at a much reduced cost compared to providing PrEP to the larger sub-population at the same relative coverage level. Successful self-selection will thus allow for PrEP to be more affordable while still having a substantial impact in the general population.

Our results suggest that it may be more cost-effective to promote PrEP to adolescent girls (ages 15-19) than young women (ages 20-24). This is in part because the Thembisa model assumes a heightened biological risk of HIV transmission in younger girls, associated with the high prevalence of cervical ectopy in puberty (91), and in part because an individual who acquires HIV has more potential to transmit HIV the younger the age at which they become infected (53). Thus the benefits of PrEP in terms of reduced secondary transmission are greater in adolescent girls.

Our analysis echoes what existing PrEP cost-effectiveness studies have shown – that targeting PrEP to high-risk populations is more cost-effective than targeting the general population (67,69,72,74,75). We showed that targeting can make PrEP more cost effective than scaling up existing HIV interventions such as MMC, HCT and UTT, depending on the target population.

Our analysis addresses some of the gaps identified by the PrEP modelling review by Case et al. (76). Our model includes scenarios of PrEP provision for male adolescents and young men at high risk of HIV, and MSM. Our average cost includes additional staff time for all services at each visit, as we do not assume that the increase in PrEP demand can be covered by existing resources, and costs for outreach campaigns and mobilisation. Lastly, modelling the impact of PrEP on the full range of HIV services using Thembisa allowed us to incorporate the additional uptake and benefits of increased HIV testing and subsequent treatment linkage due to PrEP uptake.

Our analysis has a number of limitations. Firstly, there is currently limited data available on the relative uptake of PrEP across different risk groups in routine care, the average duration that people will take PrEP once initiated, and on effective use. In the absence of such data, we assumed PrEP effectiveness for non-MSM populations to be 65%, reflecting the state of current evidence (34,35). Our sensitivity analysis shows that PrEP effectiveness has a large impact on HIV incidence and a smaller but significant impact on incremental cost. Achieving better adherence to PrEP than in the clinical trial setting may be more likely if PrEP efficacy is known to the user. Regardless of the population, a strong focus on adherence, or effective use, will have to be part of any implementation strategy for the benefits from both an epidemiological and economic perspective to unfold.

Secondly, even though the three main cost drivers, drugs, HIV testing, and staff, were costed at high scales and at the lowest cadre levels possible, the estimated cost of PrEP might be an overestimate, and non-essential elements such as demand creation and screening might become less prominent at higher levels of uptake as economies of scale might take hold. In contrast, it might be an underestimate, as additional interventions might have to be added to increase demand if self-selection is not successful.

A general limitation of frequency-dependent models such as Thembisa is that they understate the importance of high-risk groups in sustaining HIV and STI incidence at a population level, when compared with more realistic network models (92). This in turn implies that the cost-effectiveness of PrEP targeted to high-risk groups (especially FSWs and MSM) could be under-estimated. Another limitation is that we lack data on HIV prevalence in high-risk groups other than FSWs and MSM, and this makes it difficult to estimate with confidence the impact of higher PrEP uptake in these groups.

More work needs to be done on geospatial targeting of PrEP, as this will allow more effective targeting of those at highest risk of HIV. McGillen et al found that optimizing prevention interventions, including PrEP, to high-risk populations can have up to an 14% greater impact on reducing incidence compared to without PrEP (93). Preliminary studies have shown that the presence of sexually transmitted infections (STI) is a good surrogate marker for HIV risk, however integrating this into a PrEP programme will increase the cost as additional laboratory testing, and possibly STI treatment, is required. Currently discussions on integrating STI care into the PrEP programme are still underway within the NDOH. It remains to be seen whether self-selection based on individuals' own perception of risk will be successful, and what its effect on overall PrEP effectiveness will be. There has been evidence to show self-selection of those at highest risk of HIV within MSM and FSW populations (87,94,95), however there is uncertainty whether this would be the case in the general population as data on PrEP uptake in these populations are limited.

We found PrEP to be an expensive intervention, especially when compared to existing prevention interventions. However, if self-selection by high-risk groups is successful, it can be rendered much more cost effective and, especially if effectiveness in these populations is higher than current trial data suggest, possibly cost-saving in the long term.

Supplementary Appendix

1. Additional information on the Thembisa model

1.1 Model calibration

The model is calibrated to several HIV data sources, as described elsewhere (83). Of most relevance to the current paper, the model is calibrated to age-specific HIV prevalence data from national household surveys conducted in 2005, 2008, 2012 and 2017, and antenatal surveys conducted between 1997 and 2017. The model is also calibrated to all-cause mortality data, by sex and 5-year age group, over the 1997-2014 period. In calibrating the model to these HIV prevalence and mortality data, we vary the assumptions about sexual behaviour, HIV transmission probabilities per sex act, and rates of HIV disease progression and mortality. In addition, the model is calibrated to 12 HIV prevalence estimates from studies conducted among sex workers over the 1996-2014 period and 9 HIV prevalence estimates from studies conducted among MSM over the 2008-2012 period. In both cases, the model is calibrated to the HIV prevalence data by varying the client-to-sex worker and male-to-male transmission probabilities. Calibration follows a Bayesian approach, with prior distributions being specified for each of the parameters that is varied in the calibration process. Likelihood functions are specified for each data source, assuming that differences between model estimates and survey/recorded death estimates are normally distributed with zero mean. Posterior distributions are simulated numerically, using Incremental Mixture Importance Sampling (96).

1.2 Further information on sexual behaviour assumptions

The sexual behaviour assumptions have been described in detail elsewhere (83). Briefly, age at sexual debut, ranging between 10-30 years, is modelled using log-logistic functions that depend on sex and risk group. 5% of men are assumed to begin sexual activity as bisexual (with 70% of their partners being male). Three types of relationship are modelled: marital/cohabiting, short-term and client-sex worker. Sexually experienced individuals are assumed to enter into marital/cohabiting relationships at rates that depend on their age and sex. In sexually-experienced individuals, short-term non-marital relationships are assumed to form at rates that depend on age, sex, marital status and risk group, with low-risk individuals having substantially lower

numbers of short-term partners than high-risk individuals. Short-term partnership rates are based on previously-estimated levels of non-marital sexual activity in South Africa (97), with the age pattern of non-marital sexual activity being calibrated to achieve consistency with observed age-specific HIV prevalence patterns in antenatal and household HIV prevalence surveys. Assumptions are made about the mixing between high- and low-risk groups (assortativeness), and partner age preferences are calculated by age, sex and type of relationship. Rates of sex worker contact amongst high-risk heterosexual men depend on their age and marital status. Unmarried high-risk women are assumed to enter sex work at a rate sufficient to meet male demand for commercial sex, assuming sex workers have an average of 750 client contacts per annum, and assuming that women remain active as sex workers for an average of 3 years (86). Rates of condom use are assumed to depend on age, sex and relationship type, with rates of condom use being highest at younger ages and in sex worker-client contacts. Condom use is assumed to be higher in HIV-diagnosed individuals than in HIV-positive undiagnosed individuals. In addition, general rates of condom use are assumed to change over time, increasing rapidly in the late 1990s and early 2000s, and then declining slowly. The assumption about higher rates of condom use at younger ages (even after controlling for relationship type) is based on an analysis of self-reported condom use in the 1998 and 2003 Demographic and Health Surveys (86,98). The assumption about rapidly increasing condom use during the late 1990s and early 2000s is supported both by data on numbers of condoms distributed and self-reported data on condom use in national surveys (99,100). The assumed subsequent decline in condom use is based on more recent survey data, which suggest a slight reduction in condom use since 2008 (10).

The high-risk proportions specified (25% for females and 35% for males) are the proportions of individuals assigned to the high-risk group on reaching age 10; although it may seem odd to talk about risk levels in children who are not yet sexually active, it is important to note that we define risk in terms of long-term propensity for concurrent partnerships and commercial sex, not current risk behaviour. Because there is a higher rate of sexual debut in the high-risk group, the fraction of sexually-experienced youth who are defined as high-risk will be higher than the stated 25% and 35% proportions. After age 30 (when all adults are assumed to be sexually experienced), the fraction of

people in the high-risk group is typically less than the 25% and 35% proportions because of higher HIV-related mortality in the high-risk group.

1.3 Further details on the probabilistic sensitivity analysis

Uncertainty regarding the PrEP parameters was combined with uncertainty regarding 37 of the other model parameters. These 37 other parameters related to HIV transmission probabilities, sexual behaviour, HIV testing rates, HIV disease progression and ART mortality, and the uncertainty regarding these parameters was estimated previously using a Bayesian approach, based on fitting the Thembisa model to South African HIV data sources. A sample of 1,000 combinations of these 37 parameters, generated from the posterior distributions determined in the Bayesian analysis, was combined with the sample of 1,000 combinations of the PrEP parameters (83).

2. Additional details of cost analysis

Patient-level costs were aggregated into different visit types (screening and initiation, clinical, pharmacy and re-initiation visits), and the cost per user year was calculated as the cost for each visit type multiplied by the number of times a visit of this type was expected in a year. We based staff time allocations on the experience of the early implementation sites, assuming the lowest level of staff cadre for every activity, such as drugs being dispensed by nurses, and HIV testing and all counselling as well as screening for drug side effects being done by lay healthcare personnel. All HIV testing was however assumed to be done within the facility rather than in the community or the home, using rapid tests. PrEP for pregnant women was costed for the duration of 6 months of their pregnancy, with the assumption that PrEP would be provided through antenatal care (ANC) clinics during this time, with initial HIV and syphilis testing already done in the ANC clinic and no need for pregnancy testing. After giving birth, women were assumed continue receiving PrEP at the same cost as a young woman in follow-up years on PrEP. We followed a two-step approach to estimating costs. First, a list of required ingredients and their quantities per visit type was determined based on the clinical guidelines and the experience in the demonstration projects and early implementation sites. Secondly, we identified the unit cost for each of the ingredients using the most recent public-sector prices from a number of sources.

Supplementary Table 1. Summary of patient-level and health-systems cost items included in the unit cost for PrEP

Patient-level cost items		
Type of visit	**Service**	**Staff requirement**
Screening/ initiation	Readiness assessment	Counsellor
	HIV test[a]	Counsellor
	Hepatitis BsAg test	Professional nurse
	Alanine aminotransferase (ALT) test if HBsAg+	Professional nurse
	Creatinine test	Professional nurse
	Pregnancy urine test (non-pregnant women only)	Professional nurse
	STI symptom screening[b]	Counsellor
	Syphilis test[c]	Professional nurse
	PrEP prescription and dispensing	Professional nurse
	Adherence counselling	Counsellor
Clinical (3 monthly)	HIV test[a]	Counsellor
	Creatinine test (annually after first year)	Professional nurse
	Adherence counselling	Counsellor
	Pregnancy urine test (non-pregnant women only)	Professional nurse
Pharmacy (monthly)	PrEP prescription and dispensing	Professional nurse
Annual testing	Creatinine test (annually after first year)	Professional nurse
	Syphilis test[c]	Professional nurse
Re-initiation	HIV test[a]	Counsellor
	Hepatitis BsAg test	Professional nurse
	Alanine aminotransferase (ALT) test if HBsAg+	Professional nurse
	Pregnancy urine test (non-pregnant women only)	Professional nurse
	STI symptom screening[b]	Professional nurse

Health-systems cost items

- Training (for nurses, counsellors and peer educators)
- Mobilisation and outreach (including outreach campaign events, social media campaigns, and information, education and communication materials)
- Monitoring and evaluation (including clinical stationary)
- Overheads (clerk for booking appointments and drawing client file, building maintenance and utilities)

[a] HIV testing involves a rapid HIV test, a second rapid HIV test if the first is positive, and a confirmatory ELISA if both rapid tests are discordant. HIV testing is conducted at screening, 3-monthly during follow-up, and at re-initiation into the PrEP programme. [b] STI management is not included as it is provided outside of the PrEP programme. We assume that PrEP clients with STI symptoms will be referred for treatment. [c] For MSM and FSW target populations, syphilis testing involves a rapid syphilis test and a confirmatory RPR if the rapid test is positive. For all other target populations, it involves a syphilis RPR only.

Supplementary Table 2. Details of cost items, unit cost, quantities and their sources by visit type for young women

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
Patient-level cost							
Screening and initiation *[frequency of visit: 1 in first year]*							**24.35**
Education/ readiness assessment							
Readiness assessment	Counsellor	0.06	per minute	1	1	Assumption	0.06
STI screen form	Patient form	0.01	per form	2	2	Assumption	0.02
HIV testing services							
1st test [a]	HIV rapid test	0.49	per test	3	1.128	1/(1-HIV prevalence)	0.55
	Counsellor	0.06	per minute	1	16.128	15 minutes incl mark-up for HIV+ people that don't initiate PrEP [bc]	1.03
	Gloves	0.07	per pair	4	1.128	1/(1-HIV prevalence)	0.08
	Cotton wool swabs	0.06	per swab	5	1.128	1/(1-HIV prevalence)	0.07
2nd test (only if 1st positive) [a]	HIV rapid test	0.49	per test	3	0.114	HIV prevalence	0.06
	Counsellor	0.06	per minute	1	1.833	Time adjusted for HIV prevalence bc	0.12
	Gloves	0.07	per pair	4	0.114	HIV prevalence	0.01
	Cotton wool swabs	0.06	per swab	5	0.114	HIV prevalence	0.01
Only in case of discrepant rapid tests	ELISA	4.03	per test	6	0.020	Assumption	0.08
	Counsellor	0.06	per minute	1	0.300	Assumption (15 minutes x discordant probability of 0.02)	0.02
	Gloves	0.07	per pair	4	0.020	Assumption (1 set x discordant probability of 0.02)	0.0014

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
	Needle	0.01	per needle	7	0.020	Assumption (1 set x discordant probability of 0.02)	0.0002
	Cotton wool swabs	0.06	per swab	5	0.020	Assumption (1 set x discordant probability of 0.02)	0.0012
Other monitoring tests *(NB: the cost of creatinine testing is added separately[d])*							
Blood draw and symptom check	Professional nurse	0.30	per minute	1	15	Assumption	4.47
Hepatitis B screening	HBsAg	9.17	per test	8	1	One per person	9.17
If HBsAg is positive	ALT	3.32	per test	6	0.036	Baxter (2013)	0.12
Pregnancy test (women) [a]	Pregnancy test (urine)	0.27	per test	9	1	One per woman	0.27
STI screening							
STI symptom screen	Counsellor	0.06	per minute	1	5	Assumption	0.32
Rapid syphilis test (MSM and FSW only)	Rapid syphilis test	0.60	per test	10	0	Guidelines	0.00
Syphilis RPR (if syphilis rapid positive or instead of rapid test) [a]	RPR titre	2.29	per test	8	1.00	One per person (or depending on syphilis prevalence for FSW, MSM)	2.29
PrEP drugs	PrEP Regimen (TDF+FTC)	3.85	per month	11	1	One per person	3.85
Prescribing & dispensing	Professional nurse	0.30	per minute	1	2	Assumption	0.60
Adherence counselling	Counsellor	0.06	per minute	1	15	[c]	0.96
Condoms	Male condom	0.04	per condom	12	6	Assumption	0.22

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
Lubricant (MSM only) [a]	Lubricant (5ml)	0.03	per sachet	12	0	Assumption	0.00
Syphilis testing (annually, follow-up only) *[frequency of visit: 1 in follow-up year]*							**2.29**
Rapid syphilis test (MSM, FSW only)	Rapid syphilis test	0.60	per test	10	0	Guidelines	0.00
Syphilis RPR (if syphilis rapid positive or instead of rapid test) [a]	RPR titre	2.29	per test	8	1.00	One per person (or depending on syphilis incidence for FSW, MSM)	2.29
Follow-up visit (clinical, 3-monthly) *[frequency of visit: 3 in first year, 4 in follow-up year]*							**7.28**
PrEP drugs	PrEP Regimen (TDF+FTC)	3.85	per month	11	1	One per person	3.85
Adherence counselling	Counsellor	0.06	per minute	1	10	[c]	0.64
Prescribing & dispensing	Professional nurse	0.30	per minute	1	2	Assumption	0.60
HIV testing services							
1st test [a]	HIV rapid test	0.49	per test	3	1	One per person	0.49
	Counsellor	0.06	per minute	1	15	[bc]	0.96
	Gloves	0.07	per pair	4	1	One per person	0.07
	Cotton wool swabs	0.06	per swab	5	1	One per person	0.06
2nd test (only if 1st positive) [a]	HIV rapid test	0.49	per test	3	0.018	HIV incidence	0.01
	Counsellor	0.06	per minute	1	0.294	Time adjusted for HIV incidence [bc]	0.02
	Gloves	0.07	per pair	4	0.018	HIV incidence	0.0013

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
	Cotton wool swabs	0.06	per swab	5	0.018	HIV incidence	0.0011
Only in case of discrepant rapid tests	ELISA	4.03	per test	6	0.02	Assumption	0.08
	Counsellor	0.06	per minute	1	0.3	Assumption (15 minutes x discordant probability of 0.02)	0.02
	Gloves	0.07	per pair	4	0.02	Assumption (1 set x discordant probability of 0.02)	0.0014
	Needle	0.01	per needle	7	0.02	Assumption (1 set x discordant probability of 0.02)	0.0002
	Cotton wool swabs	0.06	per swab	5	0.02	Assumption (1 set x discordant probability of 0.02)	0.0012
Other monitoring tests *(NB: the cost of creatinine testing is added separately[d])*							
Pregnancy test (women) [a]	Pregnancy test (urine)	0.27	per test	9	1	One per woman	0.27
Condoms	Male condom	0.04	per condom	12	6	Assumption	0.22
Lubricant (MSM only) [a]	Lubricant (5ml)	0.03	per sachet	12	0	Assumption	0.00
Follow-up visit (pharmacy, 1-monthly) *[frequency of visit: 8 in first year, 8 in follow-up year]*							**4.67**
Drugs	PrEP Regimen (TDF+FTC)	3.85	per month	11	1	One per person	3.85
Dispensing	Professional nurse	0.30	per minute	1	2	[b]	0.60
Condoms	Male condom	0.04	per condom	12	6	Assumption	0.22
Lubricant (MSM only) [a]	Lubricant (5ml)	0.03	per sachet	12	0	Assumption	0.00
Re-initiation visit (testing only) *[frequency of visit: 1 in first year, 1 in follow-up year]*							**16.21**

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
HIV testing services							
1st test [a]	HIV rapid test	0.49	per test	3	1	One per person	0.49
	Counsellor	0.06	per minute	1	15	[bc]	0.96
	Gloves	0.07	per pair	4	1	One per person	0.07
	Cotton wool swabs	0.06	per swab	5	1	One per person	0.06
2nd test (only if 1st positive) [a]	HIV rapid test	0.49	per test	3	0.018	HIV incidence	0.01
	Counsellor	0.06	per minute	1	0.294	Time adjusted for HIV incidence [bc]	0.02
	Gloves	0.07	per pair	4	0.018	HIV incidence	0.0013
	Cotton wool swabs	0.06	per swab	5	0.018	HIV incidence	0.0011
Only in case of discrepant rapid tests	ELISA	4.03	per test	6	0.02	Assumption	0.08
	Counsellor	0.06	per minute	1	0.3	Assumption (15 minutes x discordant probability of 0.02)	0.02
	Gloves	0.07	per pair	4	0.02	Assumption (1 set x discordant probability of 0.02)	0.0014
	Needle	0.01	per needle	7	0.02	Assumption (1 set x discordant probability of 0.02)	0.0002
	Cotton wool swabs	0.06	per swab	5	0.02	Assumption (1 set x discordant probability of 0.02)	0.0012
	Other monitoring tests *(NB: the cost of creatinine testing is added separately[d])*						
Blood draw and symptom check	Professional nurse	0.30	per minute	1	15	Assumption	4.47
Hepatitis B screening	HBsAg	9.17	per test	8	1	One per person	9.17
If HBsAg is positive	ALT	3.32	per test	6	0.018	Baxter (2013)	0.06

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
Pregnancy test (women)	Pregnancy test (urine)	0.27	per test	9	1	One per woman	0.27
STI screening							
STI symptom screen	Counsellor	0.06	per minute	1	5	Assumption	0.32
Condoms	Male condom	0.04	per condom	12	6	Assumption	0.22
Lubricant (MSM only)	Lubricant (5ml)	0.03	per sachet	12	0	Assumption	0.00

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
Health system costs							
per client year							**16.69**
Training (nurses)							
initial	PrEP training - 1 day	222.74	per person trained	13	0.0125	Assumption (2 day add-on to NIMART training, 160 clients per yr, 1 per year)	2.78
job aids	IEC material	0.18	per person	14	1	Assumption	0.18
Training (counsellors)							
initial	PrEP training - 1 day	222.74	per person trained	13	0.00625	Assumption (1 day add-on to existing training, 160 clients per yr, 1 per year)	1.39
job aids	IEC material	0.18	per person	14	1	Assumption	0.18
Training (peer educators)							
initial	Peer educator/	68.60	per person trained	2	0.00625	Assumption (1 day add-on to existing training, 160 clients per yr, 1 per year)	0.43

	Ingredient	Unit cost (2019 USD)	Cost unit	Cost source	Quantity	Quantity source	Total cost (2019 USD)
	supervisor training						
job aids	IEC material	0.18	per person	14	1	Assumption	0.18
Mobilisation							
Outreach campaign	Outreach campaign event	13.04	per person	15	0.01	Assumption (proportion initiated out of all reached = 1/100)	0.13
IEC materials	IEC material	0.18	per person	14	1	Assumption (1 set per client per year)	0.18
Outreach	Peer educator	192.44	per month	16	0.0424	Assumption (15 mins out of 8 hrs for PrEP/160 clients per year)	8.16
Monitoring and evaluation							
Patient form	Patient form	0.01	per form	2	2	1 x 2-page clinical form per year per person on PrEP	0.02
Paper register (A3 page)	Paper A3 size (Typek)	0.02	per page	17	0.075	1 x A3 per month per clinic	0.0018
Staff time for monthly reporting	Data capturer	0.08	per minute	1	4.5	Assumption (60min per month/site)	0.37
Overheads							-
Building maintenance and utilities	7% mark-up on per visit costs					[b]	
Drawing file	Clerk	0.07	per minute	1	39	Assumption (3 minutes x number of visits per year)	2.68

Acronyms: HIV, Human Immunodeficiency Virus; STI, sexually transmitted infection; PrEP, pre-exposure prophylaxis; ELISA, enzyme-linked immunosorbent assay; HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; RPR, rapid plasma regain; TDF, tenofovir; FSW, female sex worker; pp, per person; IEC, information, education, and communication

[a] Quantities for these ingredients are population-specific and will have different values for young women, female adolescents, FSW, pregnant women, young men, male adolescents and MSM; [b]Source: Gomez GB, 2017. The TAPS Demonstration Project (Treatment And Prevention for female Sex workers), Wits RHI, Johannesburg, South Africa. Unpublished dataset, cited with permission; [c]Source: Data from demonstration projects (personal communication, Kevin

Rebe); [d]Creatinine was costed separately at $2.12 per test (source: South African National Health Laboratory Service price list, 2017) and performed 3 times in the first year or PrEP and annually thereafter.

Unit cost sources

1) South African Government Salary Scale (2019)
2) South Africa, Global Fund proposal (2013)
3) South African National Department of Health, contract RT41-2017
4) National Treasury of South Africa, tender RT76-2016
5) South African National Department of Health, tender HM022015BD
6) South African National Health Laboratory Service price list (2018)
7) South African National Department of Health, contract HM08-2015SYR
8) South African National Health Laboratory Service price list (2017)
9) Kendon Medical Supplies Pty Ltd, quote (19 Aug 2019)
10) Humor Diagnostica Quote (per email, 19 Aug 2019)
11) South African National Department of Health, contract RT71-2019
12) South African National Department of Health, contract RT75-2018
13) Clinton Health Access Initiative (2015)
14) Personal communication, Steve Cohen (2015)
15) RSA Global Fund Grant portfolio budgets 2018, Subject to revision during grant negotiations
16) Provincial DOH CG Business Plans (2017)
17) Makro.co.za (accessed August 2019)

Supplementary Table 3. Incremental cost effectiveness of all HIV interventions included in the South African Investment Case (2019 update)

Intervention	Total New HIV infections (2019-38)	HIV infections averted (2019-38)	Total Cost (2019-38) [2019 USD, billions]	Incremental cost (2019-38) [2019 USD, millions]	Incremental cost effectiveness ratio (USD/ infection averted)
Baseline	3,082,481	-	34.68	-	-
Condom distribution (95%)	2,371,955	710,525	33.61	-1,074	cost-saving
PrEP for 18% female adolescents (15-19), high risk	**2,961,955**	**120,525**	**34.74**	**61**	**507**
FSW HCT (95%)	3,050,669	31,811	34.70	18	560
PrEP for 30% FSW	**3,039,808**	**42,672**	**34.71**	**31**	**724**
MMC (95%)	3,020,264	62,217	34.74	55	889
UTT maximum linkage (95%)	2,793,535	288,945	35.05	371	1,285
PrEP for 54% MSM	**2,932,745**	**149,7s36**	**34.89**	**205**	**1,370**
PrEP for 18% young women (20-24), high risk	**3,006,578**	**75,902**	**34.80**	**121**	**1,592**
PrEP for 18% male adolescents (15-19), high risk	**2,993,629**	**88,851**	**34.87**	**187**	**2,108**
PrEP for 18% young men (20-24), high risk	**2,964,993**	**117,488**	**34.99**	**306**	**2,605**
General population HCT (95%)	2,878,795	203,685	35.26	575	2,822
PrEP for 18% pregnant women	**3,029,561**	**52,920**	**34.91**	**227**	**4,283**
PrEP for 18% female adolescents (15-19), all risk	**2,948,580**	**133,901**	**35.29**	**608**	**4,537**
PrEP for 18% male adolescents (15-19), all risk	**2,989,872**	**92,609**	**35.20**	**522**	**5,637**
PrEP for 18% young men (20-24), all risk	**2,958,461**	**124,020**	**35.64**	**957**	**7,715**
PrEP for 18% young women (20-24), all risk	**2,990,588**	**91,892**	**35.63**	**949**	**10,323**
EIMC (95%)	3,082,289	191	34.88	194	1,013,279

Incremental impacts are relative to baseline. Acronyms: PrEP = pre-exposure prophylaxis, FSW = female sex worker, HCT= HIV Counselling and Testing, MMC = medical male circumcision, MSM = men who have sex with men, UTT = universal test and treat, EIMC = early infant male circumcision

Supplementary Table 4. Probability distributions used for parameters varied in the probabilistic sensitivity analysis

Variable	Population	Distribution	Mean, standard deviation
PrEP unit cost	Young women, female adolescents (first year)	Gamma (12,0.08731)	146, 42
	Young women, female adolescents, pregnant women (follow-up year)	Gamma (12,0.10528)	121, 35
	Pregnant women (first year)	Gamma (12,0.15563)	76, 22
	FSW (first year)	Gamma (12,0.08626)	148, 43
	FSW (follow-up year)	Gamma (12,0.10606)	120, 35
	Young men, male adolescents, MSM (first year)	Gamma (12,0.08893)	144, 41
	Young men, male adolescents, MSM (follow-up year)	Gamma (12,0.10685)	120, 34
PrEP effectiveness	Young women, female adolescents, young men, male adolescents, pregnant women, FSW	Beta (14.14,7.61)	0.65, 0.10
	MSM	Beta (9.99, 1.76)	0.85, 0.10
Reduction in condom use while on PrEP	All populations	Beta (0.80, 7.20)	0.10, 0.10
Relative rate of uptake of PrEP in low risk group vs high risk group	Young women, female adolescents, young men, male adolescents	Beta (1.49, 3.03)	0.33, 0.20

Supplementary Table 5. Budget impact of PrEP provision to individual populations in both 2019 USD and 2019 ZAR (incremental annual cost in years 2018/19 to 2022/23)

Incremental cost of the HIV programme (millions 2019 USD)					
PrEP scenario	**2018/19**	**2019/20**	**2020/21**	**2021/22**	**2022/23**
Young women (20-24), all risk groups	8.95	21.86	37.11	43.23	46.29
Young women (20-24), high risk groups	1.43	3.57	6.21	7.27	7.73
Female adolescents (15-19), all risk groups	5.89	14.59	25.23	30.11	33.17
Female adolescents (15-19), high risk groups	1.53	3.82	6.60	7.75	8.27
Young men (20-24), all risk groups	9.54	23.33	39.53	46.07	49.26
Young men (20-24), high risk groups	3.71	9.10	15.44	17.94	19.04
Male adolescents (15-19), all risk groups	4.70	11.67	20.19	24.25	26.93
Male adolescents (15-19), high risk groups	2.13	5.29	9.14	10.93	12.05
Female sex workers	0.48	1.26	2.25	2.62	2.79
Men who have sex with men	2.88	7.64	13.79	14.98	15.39
Pregnant women	1.39	4.27	8.01	10.84	12.44
Incremental cost on the HIV programme (millions 2019 ZAR)					
PrEP scenario	**2018/19**	**2019/20**	**2020/21**	**2021/22**	**2022/23**
Young women (20-24), all risk groups	128.09	313.03	531.32	618.94	662.80
Young women (20-24), high risk groups	20.43	51.17	88.88	104.06	110.68
Female adolescents (15-19), all risk groups	84.34	208.97	361.32	431.08	474.97
Female adolescents (15-19), high risk groups	21.96	54.65	94.55	110.96	118.48
Young men (20-24), all risk groups	136.56	334.03	566.07	659.59	705.37
Young men (20-24), high risk groups	53.17	130.35	221.14	256.83	272.58
Male adolescents (15-19), all risk groups	67.31	167.08	289.14	347.22	385.59
Male adolescents (15-19), high risk groups	30.50	75.68	130.81	156.46	172.47
Female sex workers	6.90	17.99	32.28	37.56	39.91
Men who have sex with men	41.28	109.45	197.50	214.52	220.37
Pregnant women	19.94	61.08	114.70	155.19	178.06

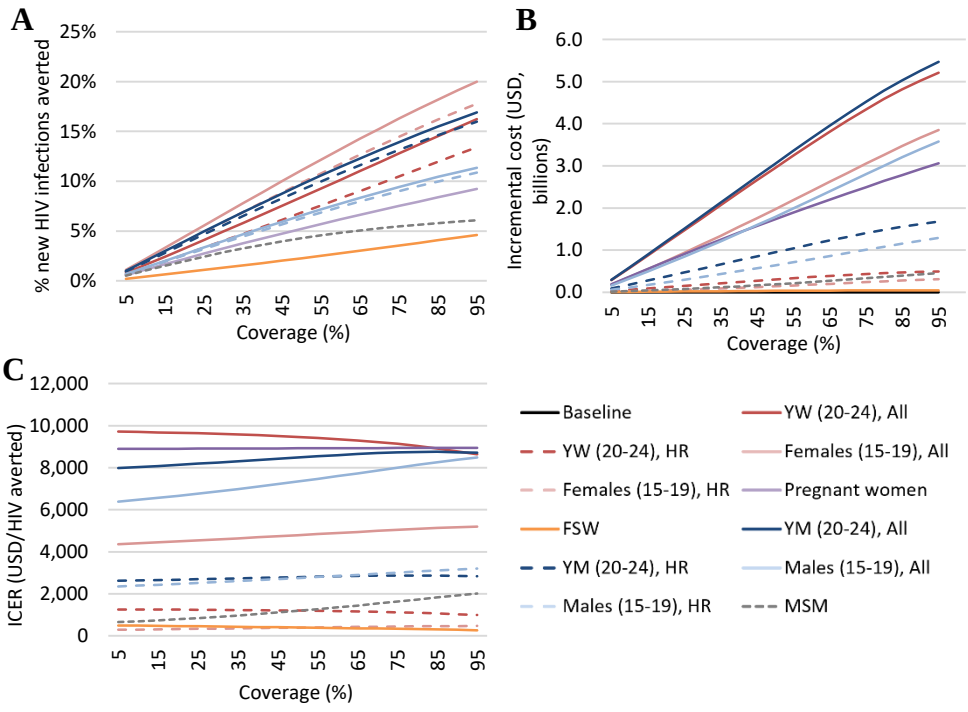
Supplementary Table 6. Partial rank correlation coefficients of results from probabilistic sensitivity analysis, by population

Population	Variable	Incremental cost (2019-38)	New HIV infections averted (2019-38)	ICER/HIV averted (2019-38)
Young women	PrEP unit cost[a]	0.95	-0.02	0.93
	PrEP effectiveness	-0.29	1.00	-0.80
	Reduction in condom use while on PrEP	0.09	-0.87	0.18
	Relative rate of PrEP uptake by those at low risk of HIV	0.96	0.99	0.93
Female adolescents	PrEP unit cost[a]	0.97	-0.03	0.95
	PrEP effectiveness	-0.54	1.00	-0.83
	Reduction in condom use while on PrEP	0.12	-0.93	0.19
	Relative rate of PrEP uptake by those at low risk of HIV	0.96	0.98	0.93
Pregnant/breastfeeding women[b]	PrEP unit cost[a]	1.00	-0.03	0.98
	PrEP effectiveness	-1.00	1.00	-0.93
	Reduction in condom use while on PrEP	0.92	-0.97	0.23
FSW[b]	PrEP unit cost[a]	1.00	-0.03	0.94
	PrEP effectiveness	-1.00	1.00	-0.84
	Reduction in condom use while on PrEP	0.97	-0.97	0.52
Young men	PrEP unit cost[a]	0.98	-0.03	0.98
	PrEP effectiveness	-0.28	1.00	-0.80
	Reduction in condom use while on PrEP	0.10	-0.96	0.23
	Relative rate of PrEP uptake by those at low risk of HIV	0.96	0.97	0.95
Male adolescents	PrEP unit cost[a]	0.99	-0.03	0.98
	PrEP effectiveness	-0.36	1.00	-0.81
	Reduction in condom use while on PrEP	0.10	-0.95	0.19
	Relative rate of PrEP uptake by those at low risk of HIV	0.96	0.98	0.95

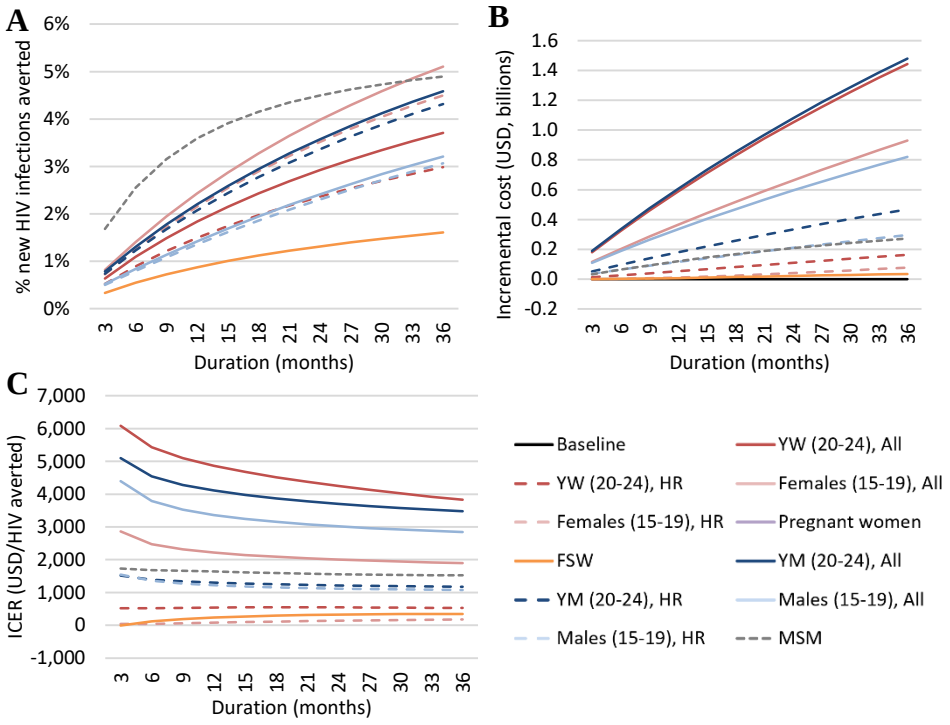
Population	Variable	Incremental cost (2019-38)	New HIV infections averted (2019-38)	ICER/HIV averted (2019-38)
MSM[b]	PrEP unit cost[a]	1.00	-0.03	1.00
	PrEP effectiveness	-1.00	1.00	-0.95
	Reduction in condom use while on PrEP	0.32	-0.41	0.14

[a] average between first and follow-up years; [b] the model does not allow for different rates of uptake in high risk vs low risk MSM and pregnant/breastfeeding women, and in the case of FSWs, all are high risk, hence the partial rank correlations for "relative rate of PrEP uptake by those at low risk of HIV" are therefore omitted.

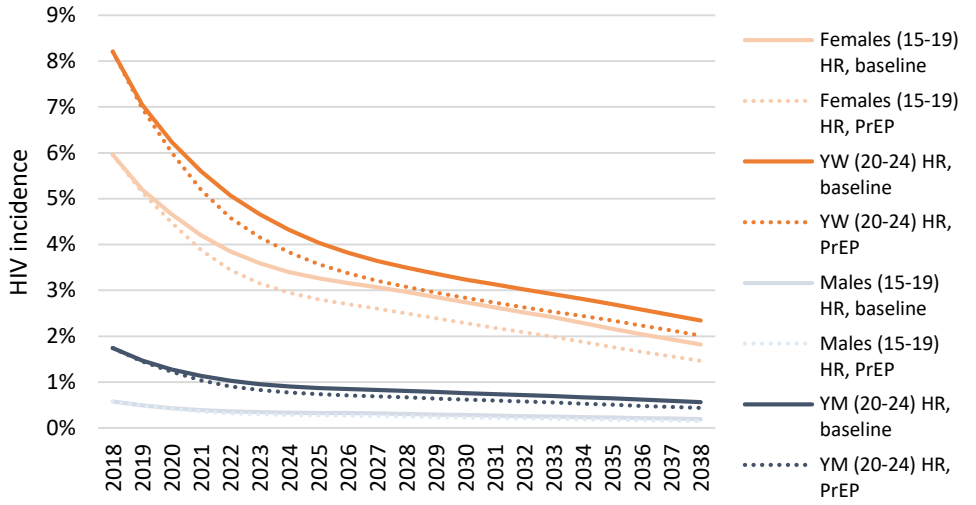
Supplementary Figure 1. Results from a one-way sensitivity analysis varying PrEP coverage for each target population; 20-year impact (2019-38) on (A) % new HIV infections averted over baseline, (B) incremental cost of the HIV programme over baseline and (C) incremental cost-effectiveness ratio of USD/HIV infection averted. The one-way sensitivity analysis of PrEP coverage shows mostly linear relationships between coverage and impact as well as cost effectiveness, with no clear saturation effects. Therefore, we cannot use these analyses to define an optimally cost-effective target coverage



Supplementary Figure 2. Results from a one-way sensitivity analysis varying duration on PrEP for each target population; 20-year impact (2019-38) on (A) % new HIV infections averted over baseline, (B) incremental cost of the HIV programme over baseline and (C) incremental cost-effectiveness ratio of USD/HIV infection averted. Note that duration on PrEP could not be varied for the scenario "PrEP for pregnant women" as this scenario was constrained in the model to use the 2-year duration. The one-way sensitivity analysis of duration on PrEP shows a linear relationship with the impact of PrEP on new HIV infections averted and incremental cost, with no clear saturation effects. Therefore, we cannot use these analyses to define an optimal cost-effective target coverage.

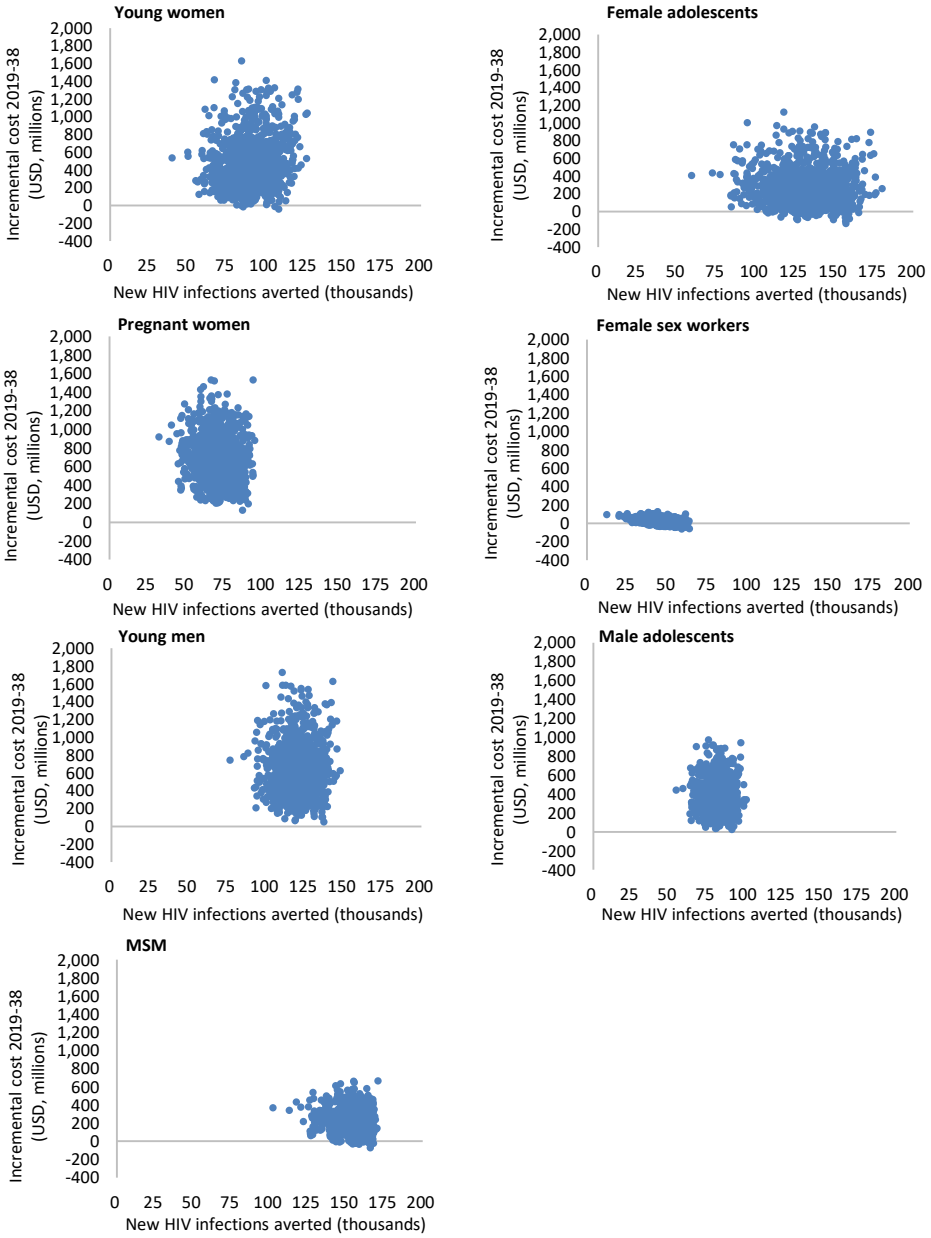


Supplementary Figure 3. HIV incidence rates amongst high-risk groups within adolescents and young adults of both genders, scenarios for baseline (solid lines) and 18% PrEP coverage (dotted lines)

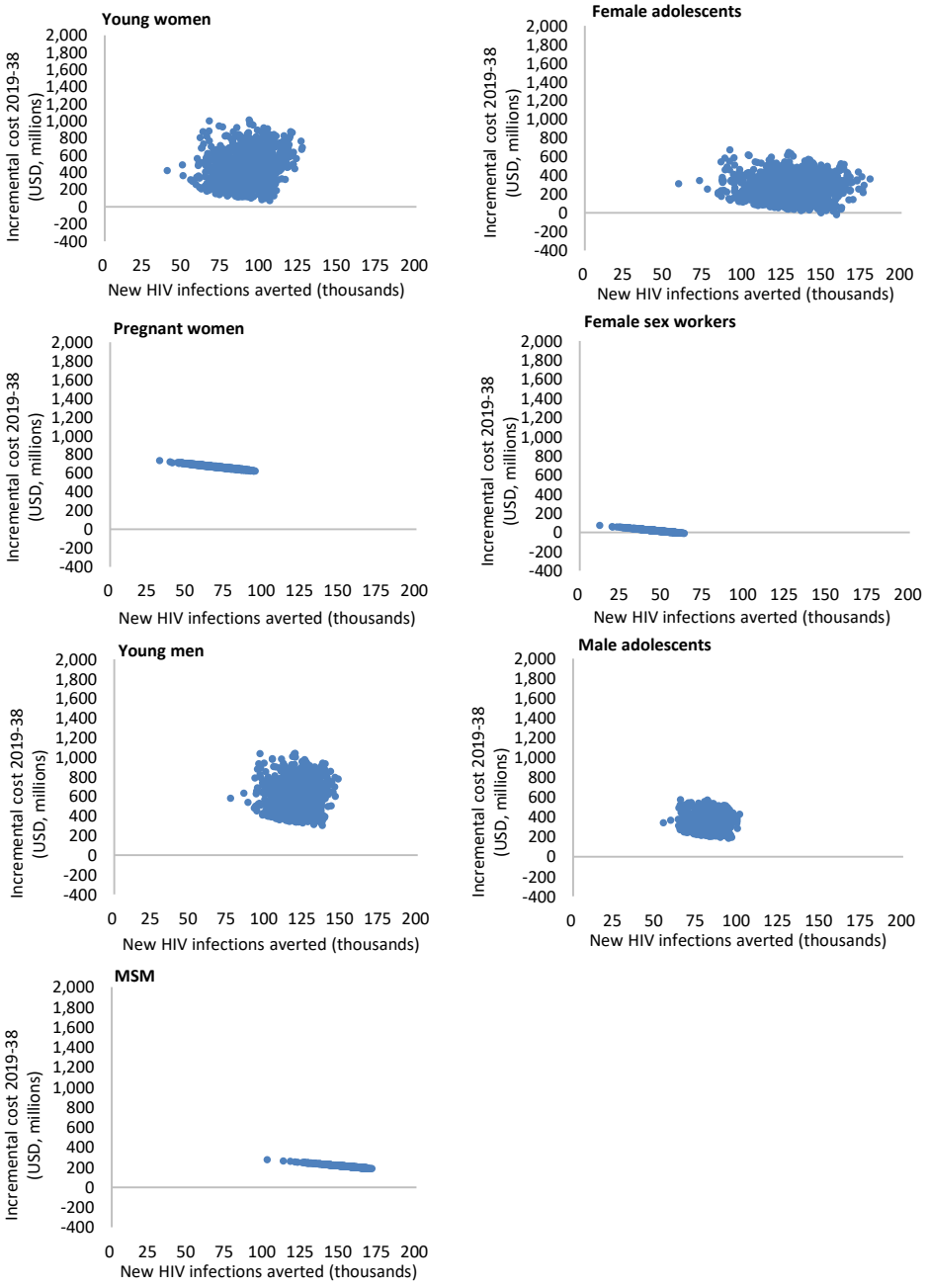


At the baseline scenario, HIV incidence amongst high-risk males aged 15 to 24 is already the below the 3% incidence definition proposed by the World Health Organization for defining populations at substantial risk of HIV (57). For high-risk females aged 15 to 24, current HIV incidence is above 3%, but it is projected to decline under 3% within the next 20 years. If we assume that 18% of high-risk groups will successfully self-select into the PrEP programme, and maintain these coverage levels over time, HIV incidence will be reduced further, and in the case of female adolescents (15-19) and young women (20-24), it will bring the point at which the 3% threshold is breached forward by 5 years.

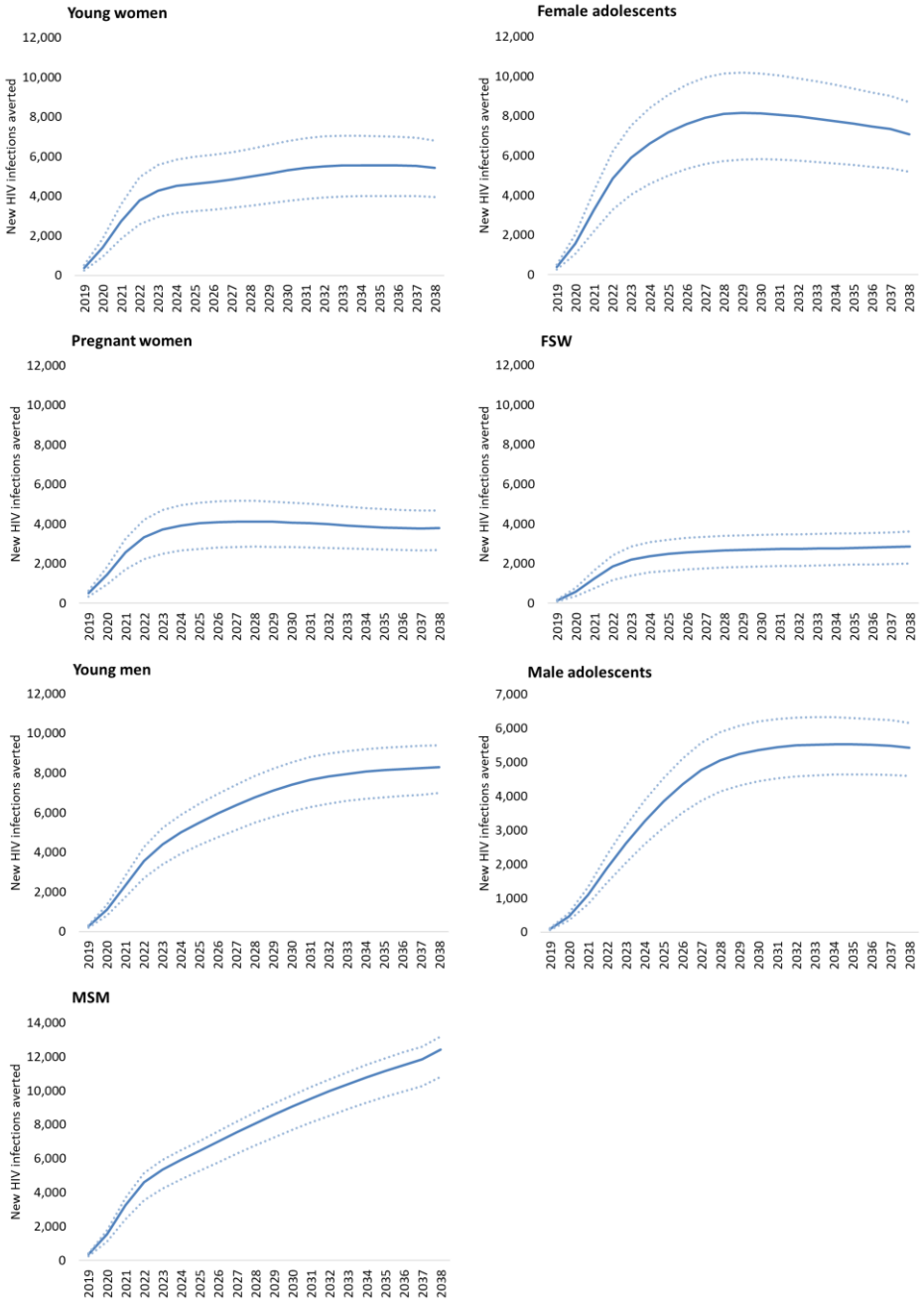
Supplementary Figure 4. Incremental cost [2019 USD] of the HIV programme against new HIV infections averted (2019-38), impact of PrEP over baseline (each dot represents a Monte Carlo simulation from a probabilistic sensitivity analysis)



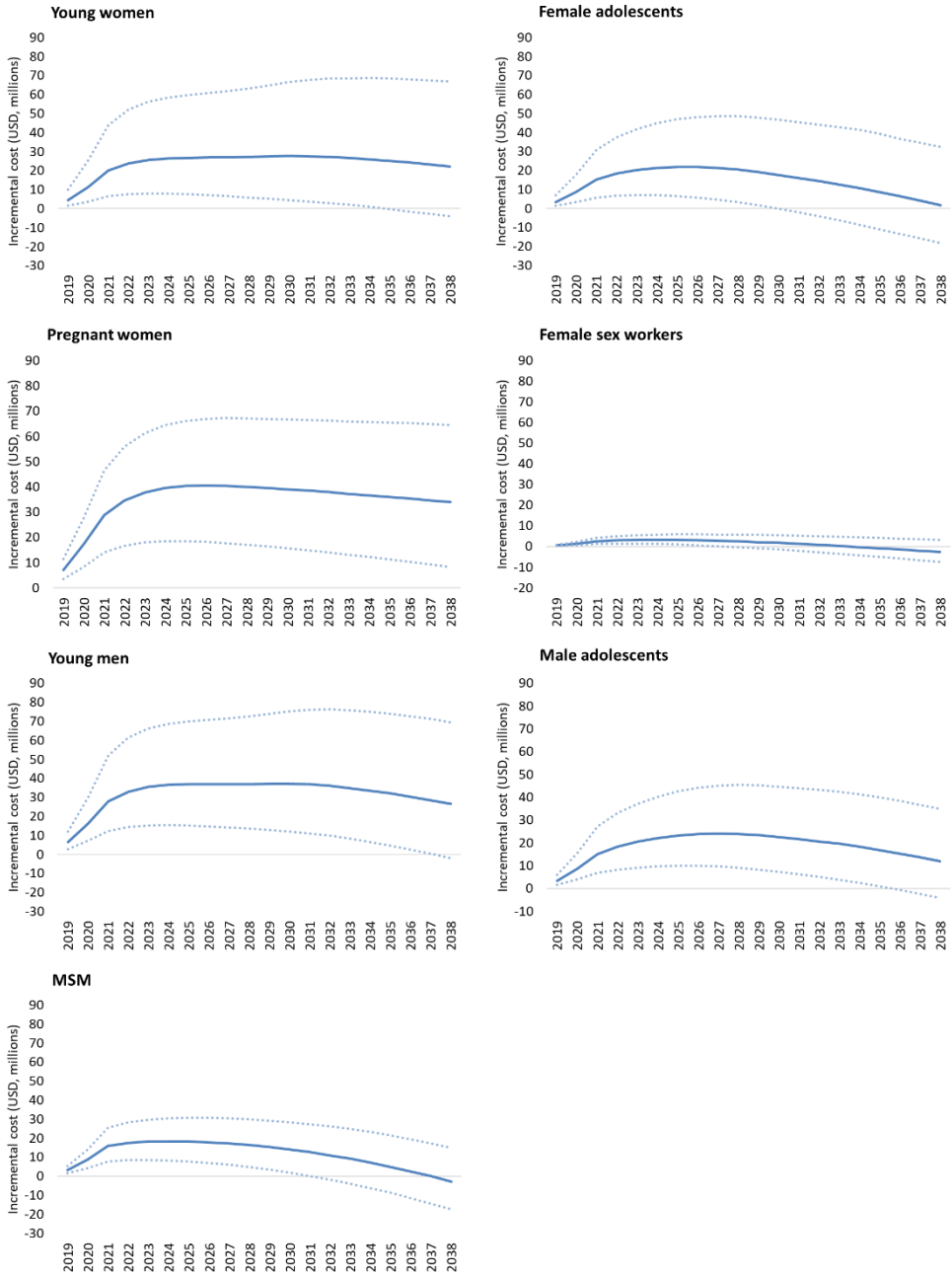
Supplementary Figure 5. Incremental cost of the HIV programme over new HIV infections averted (2019-38), impact of PrEP over baseline, assuming constant PrEP unit cost. Each dot represents the result of one Monte Carlo simulation



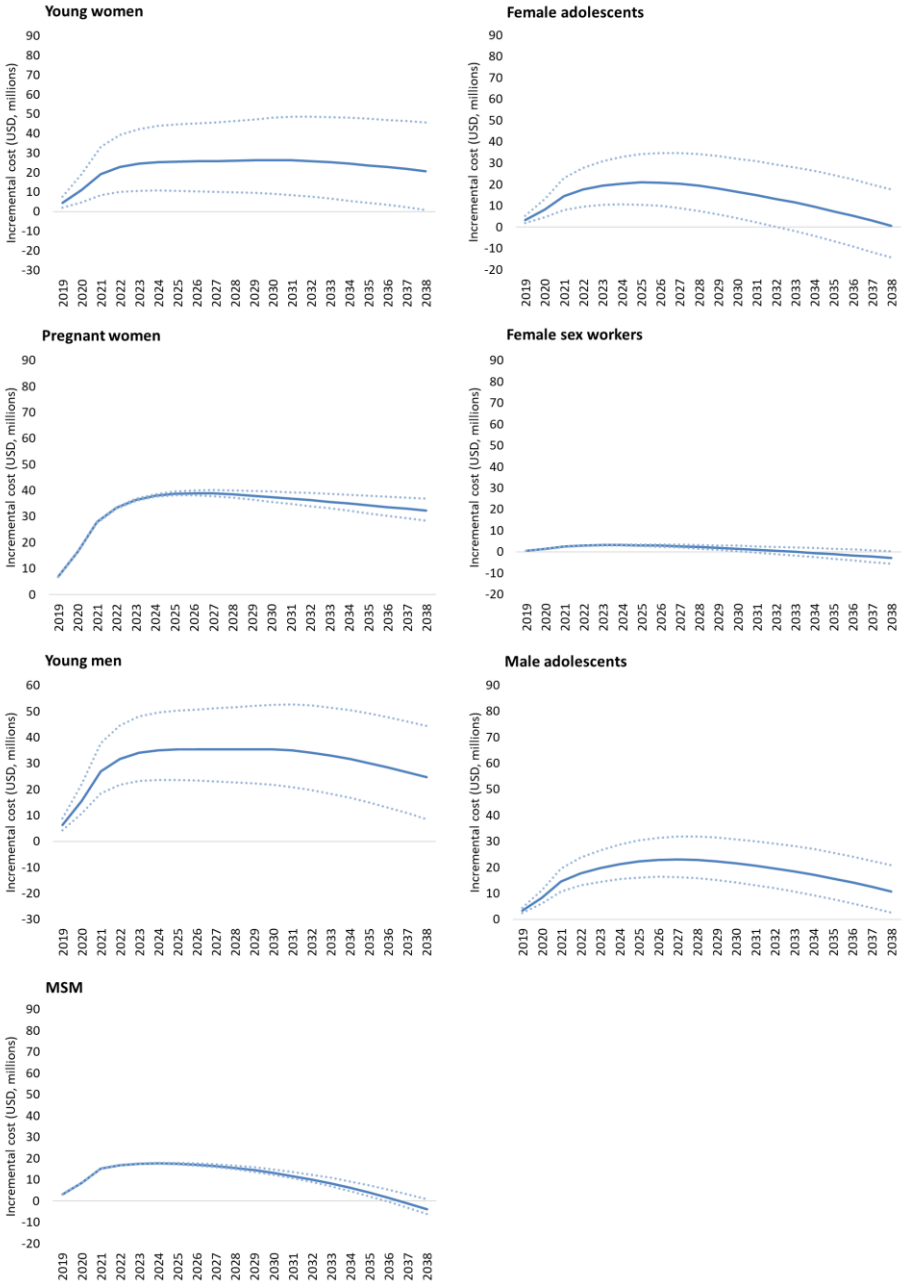
Supplementary Figure 6. Number of HIV infections averted per year by population group, results from probabilistic sensitivity analysis. Solid and dashed lines represent mean and estimated 95% confidence interval



Supplementary Figure 7. Annual incremental cost to the HIV programme by population group, results from probabilistic sensitivity analysis, assuming varying PrEP unit cost. Solid and dashed lines represent mean and estimated 95% confidence interval



Supplementary Figure 8. Annual incremental cost to the HIV programme by population group, results from probabilistic sensitivity analysis (assuming constant PrEP unit cost). Solid and dashed lines represent mean and estimated 95% confidence interval



Chapter 3

The cost effectiveness and optimal configuration of HIV self-test distribution in South Africa: A model analysis

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BMJ Glob Health 6, e005598

Abstract

Background

HIV self-testing (HIVST) has been shown to be acceptable, feasible and effective in increasing HIV testing uptake. Novel testing strategies are critical to achieving the UNAIDS target of 95% HIV-positive diagnosis by 2025 in South Africa and globally.

Methods

We modelled the impact of six HIVST kit distribution modalities (community fixed-point, taxi ranks, workplace, partners of primary healthcare (PHC) ART patients), partners of pregnant women, primary PHC distribution) in South Africa over 20 years (2020-39), using data collected alongside the Self-Testing AfRica (STAR) Initiative. We modelled two annual distribution scenarios: A) 1 million HIVST kits (current) or B) up to 6.7 million kits. Incremental economic costs (2019 USD) were estimated from the provider perspective; assumptions on uptake and screening positivity were based on surveys of a subset of kit recipients and modelled using the Thembisa model. Cost-effectiveness of each distribution modality compared to the status-quo distribution configuration was estimated as cost per life year saved (estimated from life years lost due to AIDS), and optimised using a fractional factorial design.

Results

The largest impact resulted from secondary HIVST distribution to partners of ART patients at PHC (life years saved (LYS): 119,000 (scenario A); 393,000 (scenario B)). However, it was one of the least cost-effective modalities (A: $1,207/LYS; B: $4,106/LYS). Taxi rank distribution was cost-saving under scenario A ($13 million) and predicted to have a moderate epidemic impact (A: 46,000 LYS; B: 98,000 LYS). An optimised scale-up to 6.7 million tests would result in an almost 3-fold increase in LYS compared to a scale-up of status-quo distribution (216,000 vs 75,000 LYS).

Conclusion

Optimisation-informed distribution has the potential to vastly improve the impact of HIVST. Using this approach, HIVST can play a key role in improving the long-term health impact of investment in HIVST.

Key questions

What is already known about this subject?

- HIV self-testing (HIVST) is an acceptable and feasible testing strategy that is also effective in increasing HIV testing uptake.
- Testing strategies which focus on high yield populations (eg. female sex workers) and high-volume distribution modalities (eg. taxi ranks and workplaces) have been found to be more cost-effective than some community-based or any facility-based testing strategies.

What are the new findings?

- Secondary distribution to partners of ART patients has the largest impact in terms of saving life years lost due to AIDS, however it is one of the least cost-effective strategies.
- Taxi rank and workplace distribution is the most cost-effective strategies.
- An optimisation-informed distribution of scaling up HIVST can greatly improve the impact of HIVST, and result in a more cost-effective strategy compared to a status quo distribution of scaling up HIVST.

What are the recommendations for policy and practice?

- Determining the optimal mix of HIVST kit distribution is crucial in ensuring the most effective and cost-effective strategy for national roll-out of HIVST.

Introduction

South Africa has the highest number of HIV infections worldwide, with an estimated 7.8 million people living with HIV (PLHIV) and 5.0 million on antiretroviral therapy (ART) in 2019 (101). Despite having the largest ART programme in the world, over 23% of all deaths in South Africa in 2019 were AIDS-related (102). HIV transmission and AIDS-related deaths can be greatly reduced by identifying PLHIV who are unaware of their HIV status early, linking all PLHIV to ART, and retaining them in care (103). The South African government is dedicated to meeting the UNAIDS 95-95-95 fast-track targets by 2025 (5), which aim to have 95% of PLHIV diagnosed, 95% of those diagnosed on ART and 95% of those on ART virally suppressed by 2025. In 2017, a HIV household survey showed that 85% of South African PLHIV aged 15-64 years had been diagnosed, although men had a lower rate of diagnosis compared to women (80% vs 89%, respectively) (104). Increasing the uptake of HIV testing services (HTS) by introducing novel testing strategies is critical to achieving the UNAIDS target to diagnose 95% of PLHIV in the coming years.

In order to expand HIV testing coverage, the South African National Department of Health (NDoH) has implemented community-based testing to accompany existing conventional HIV testing services, which is most frequently conducted at primary health care (PHC) clinics. Recently, HIV self-testing (HIVST) technology has been introduced to give people the opportunity to self-diagnose their HIV status. HIVST involves a person being able to privately collect their own specimen (most often oral fluid), performing the rapid diagnostic test and interpreting the result themselves, either assisted by HIVST distribution staff or unassisted (30). Recent studies in sub-Saharan Africa, including South Africa, have shown that HIVST is acceptable, feasible and effective in increasing HIV testing uptake (31–33), providing an alternative testing strategy that can overcome socio-structural barriers associated with conventional HTS in a clinic setting, including the stigma associated with accessing testing and limited hours of clinic availability (105).

Furthermore, many health services have been disrupted due to COVID-19 as governments across high HIV prevalence countries instituted lockdowns and other forms of restrictions to curb the spread of COVID-19 (106). Though

many of the restrictions have since been lifted, there remains a concern that with the pandemic still ongoing, people might be reluctant to attend PHC clinics for HIV testing. For this reason, U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and PEPFAR-supported partners have recently recommended scaling up decentralised access to HIVST (107). Since 2016, the Unitaid-funded Self-Testing AfRica (STAR) Initiative started distributing HIVST kits through a variety of approaches/modalities in Malawi, Zambia and Zimbabwe, and later expanded to eSwatini, Lesotho and South Africa. Coordinated economic analyses alongside this roll-out found that the cost per kit distributed (in 2019 US$) was $8.91 in Malawi, $14.70 in Lesotho, $14.90 in Zimbabwe and $17.70 in Zambia using community-based distribution strategies (108,109), $12.82 in circumcision clinics in Zambia (109), and $8.66 in Malawi, $9.15 in Zimbabwe, $5.37 in Zambia, and $13.40 in South Africa when kit distribution was integrated into public primary care facilities (110). A cost-effectiveness analysis of an array of community-based distribution approaches and settings in Sub-Saharan Africa showed these can be cost-effective if implementation is targeted based on HIV prevalence and health benefits, and if costs are considered over a relatively long time horizon (111). In our analysis of South Africa's distribution programme, we found that facility-based distribution modalities had on average higher cost per kit distributed than community-based distribution approaches, which was unlike observations in Zambia and Zimbabwe (112,113).

Previous modelling work by our team in 2019 using preliminary cost and effectiveness data on HIVST from other settings, showed that out of ten testing modalities analysed, HIVST combined with home-based testing would have the greatest impact on the proportion of PLHIV who are diagnosed, increasing the fraction of diagnosed PLHIV to 96.5% by 2030, and would be highly cost-effective compared to currently funded HIV interventions (114). More recently, using data on intermediate outcomes such as person screened positive, tested positive in confirmatory testing and initiated on ART from the STAR-supported HIVST roll-out in South Africa, we established that testing strategies which focus on high yield populations such as female sex workers and high-volume distribution modalities such as taxi rank and workplace distribution were more cost-effective than other community-based or any of the facility-based testing strategies (113).

This work is an update to our previous work, using data collected under the STAR Initiative to inform both effectiveness and cost parameters in the

Thembisa model (101), in order to model the impact and cost-effectiveness of different HIVST distribution modalities over a 20-year time horizon (2020-39), and, based on these outcomes, determine the highest impact and most cost-effective combination of HIVST distribution modalities in a mathematical optimisation.

Methods

Outcomes

To assess the epidemiological impact of different testing strategies, we used the Thembisa model, a deterministic compartmental model set up to simulate HIV testing in South Africa (50). The model stratifies the population by sex and individual age, and further divides the population into a number of sexual behaviour risk groups. Previously the model simulated three HIV testing modalities: testing through antenatal clinics, testing of patients with opportunistic infections and 'general' HIV testing. For each modality, rates of testing uptake are specified by age and sex, based on routine testing data and survey data on the proportions of adults who had ever been tested for HIV (50,115). All individuals are stratified according to their HIV testing history, into one of three compartments: never tested for HIV, previously tested but not diagnosed positive, and diagnosed positive. Newly diagnosed individuals are assigned a probability of starting ART in the month of diagnosis, and a lower monthly rate of ART initiation is assumed for those who do not start ART in the month of diagnosis. The model allows for re-diagnosis of previously diagnosed individuals, with relative rates of testing in previously diagnosed and treated individuals being set in such a way that the model matches historic trends in HIV testing yields (declining from 25.8% in 2004-05 to 6.25% in 2018-19 (116)). A more complete description of the model is provided elsewhere (101).

For this analysis we modelled the impact of six HIVST distribution modalities (fixed-point, taxi ranks, workplace, secondary distribution to partners of ART patients at PHC, secondary distribution to partners of pregnant women at PHC, primary PHC distribution using Thembisa. A more detailed description of each modality is provided in the Appendix (Section 2, Table S1), but briefly- fixed-point distribution involves testing tents set up near busy, pre-selected locations within communities. Taxi rank distribution involves distributing HIVST kits in densely-populated public taxi ranks and train

stations. Facility-based modalities such as secondary distribution through pregnant women and ART patients focussed on the individuals taking the HIVST kits to their partners, while primary PHC is focussed on the individual using the HIVST kit for themselves. Workplace distribution involved primary and secondary distribution in large male-dominated workplaces in industries such as manufacturing, mining, construction, etc.

The impact of HIVST in Thembisa was parameterised using data from the STAR initiative for each of the six modalities that were incorporated into the model, with the exception of primary distribution to PHC (which was conducted by implementing partners and not PHC staff in STAR). Surveys of a subset of 4% of HIVST recipients (n=40,834), conducted telephonically at 2-, 4- and 6-week intervals post distribution, provided information on the numbers of tests used, the age and sex profile of recipients, the self-reported test results (for those test kits that were used) and the proportions of those diagnosed positive who subsequently started ART, for each of the first five HIVST models. For each of these five models, the Thembisa assumptions about the age and sex profile of testers was set to match (approximately) that observed in the STAR data, but because the STAR data are not nationally representative and because HIV prevalence in South Africa is highly heterogeneous, we did not attempt to match the self-reported fraction of HIVST results that were positive (more detailed information is supplied in the Appendix). Model assumptions about test wastage (distributed HIVST kits which were reportedly not used) were also set to match those observed in the STAR data, although these could not be reliably determined in the case of the secondary distribution models, as many of the interviewed individuals did not know if their partner had actually used the test. A more detailed description of each modality and the self-testing extensions to the model is provided in the Appendix.

Data for the sixth model, primary distribution to PHC clients, was not based on STAR data as the only models supported by STAR in South Africa were non-integrated (i.e. using stand-alone distribution staff rather than clinic staff) and as such not representative of likely routine roll-out. Because we lacked data on the uptake of HIVST in primary PHC, we assumed that the patterns of uptake would be the same as for conventional facility-based HTS, with primary PHC distribution of HIVST effectively replacing a proportion of the HIV testing in PHC. To ensure this distribution modality was representative of how it would be conducted within the PHC, we assumed the same

screening positivity as conventional HTS and used the results of previous cost analyses work of conventional HTS at PHC level (114).

Model outcomes reported are life years lost due to AIDS, HIV infections averted and AIDS deaths over 20 years (2020-39). HIV infections are averted both as a result of reduced infectiousness of individuals on ART and an assumed 56% reduction in unprotected sex after HIV diagnosis (101). No specific linkage to prevention services (or change in sexual behaviour) is assumed for people who test negative. Life years lost are calculated with reference to the life expectancies obtained from the West Level 26 lifetable (117).

Cost analysis

To aid comparability across countries, the methods for the analysis of cost and outcomes of HIVST distribution through the six modalities were similar to the other economic analyses under STAR and are described in detail in Matsimela et al (113). Briefly, costs were estimated from the provider perspective using a detailed expenditure analysis complemented by activity-based observations (time in motion analysis) and micro-costing, and included capital cost items such as start-up training, sensitisation, and equipment, as well as recurrent cost items such as personnel, test kits, other supplies, transportation, building operation and maintenance. Research costs and other costs that were only relevant to STAR and not related to routine implementation were excluded. To align the cost of primary HIVST distribution at PHC more closely with services offered within PHC, the cost per test kit distributed through this modality was estimated based on ingredients- and prices adapted from previous work (114). Capital costs were annualised over the 2 years' duration of the project using a 3% discount rate, in keeping with the methods used in other countries.

In order to capture downstream programmatic effects, we modelled the impact of HIVST distribution on the cost and impact of the entire South African HIV programme over a 20-year time horizon, we included, amongst others, the cost of ART, medical male circumcision, condom distribution, prevention of mother-to-child transmission, and conventional HTS with rapid tests through both facility-based and mobile testing modalities (90). Additional information of costs of other interventions included in the HIV programme are shown in Table S2 (Appendix, Section 2). Costs are presented

undiscounted, and converted to 2019 US dollars (USD) using the period average of 14.45 South Africa Rand (ZAR) = 1 USD (118).

Scenarios

We consulted with a stakeholder panel of experts from the National Department of Health and from research organisations focused on HIVST regarding their expected outlook for HIVST distribution for South Africa beyond the STAR initiative, specifically for distribution through the six different modalities under analysis. The result constitutes our baseline scenario, a status-quo distribution, with 60% of HIVST kits assigned to primary PHC distribution, 20% to workplace distribution, 7% to secondary distribution to partners of women attending antenatal care (ANC) at PHC, 5% through fixed point distribution in communities, 5% to taxi rank distribution, and 3% to secondary distribution to partners of ART patients at PHC. For our main analysis, we included two overarching coverage scenarios, defined by the number of HIVST distributed annually. Scenario A assumes that 1 million HIVST kits will be distributed annually, in keeping with the current volumes of programme implementation, while Scenario B represents a target volume, scaling up to a maximum of 6.7 million HIVST kits distributed annually by 2030 (equivalent to replacing 40% of conventional HTS). The consultation also resulted in choosing a target population for each of the six HIVST distribution modalities as well as a "feasible maximum", i.e., a maximum number of people in each target population who can feasibly be screened for HIV with HIVST (see Appendix Section 2, Table S1).

Cost effectiveness analysis

To calculate the incremental cost-effectiveness of each HIVST distribution modality in turn, we assumed that 100% of available HIVST kits would be distributed through one of the six distribution modalities in turn, for both coverage scenarios A and B. We estimated the incremental cost of HIVST as the change in the cost of the entire HIV programme, and calculated the incremental cost per HIV infection averted, cost per life year saved and cost per AIDS death averted over the 20-year time period, incremental to the status quo distribution of 1 million HIVST.

Optimisation

We used a fractional factorial design to determine the optimal set of configurations between the different HIVST distribution modalities, resulting in the largest epidemiological impact and the most cost-effective configuration. This analysis was performed under both coverage scenarios A (1 million HIVST kits annually) and B (6.7 million HIVST kits annually), where we modelled all possible combinations of modalities at set increments, constrained only by the feasible maximum number of target population members reached in each modality. We compared all model runs to the status quo distribution of 1 million HIVST annually. We present different distributions across the different HIVST modalities and the impact on life years saved (LYS) and corresponding cost-effectiveness. Additional results regarding the impact on HIV infections averted are presented in the Appendix (Section 2, Figures S1, S2). We additionally compared the optimal distribution of HIVST in Scenario B to a scenario where the current status quo distribution of test kits was scaled-up to meet the 6.7 million HIVST target. Additional analyses for both scenarios A and B were conducted in which the baseline scenario contained no HIVST are given in the Appendix (Section 2, Figures S3, S4).

Patient and public involvement

Patients were not directly involved in this study; this analysis was conducted using data derived from a previous study (113).

Results

Outcomes

Scenario A

After accounting for uptake, the number of HIVST kits used ranges between 0.5-1.0 million kits across the six modalities (Table 1). Compared to the status quo distribution of HIVST (Table 1), primary distribution of all 1 million HIVST kits annually through PHC was dominated, due to the lower positivity yields compared to the HIVST modalities included in the status quo distribution, increasing new HIV infections and life years lost due to AIDS over 20 years (depicted as negative infections averted or LYS) (Table 2). The distribution strategy with the highest epidemiological impact with respect to saving life years, compared to the status quo, was distributing all HIVST kits

to partners of PHC ART patients, which saved 119,000 (0.3%) life years. All remaining distribution modalities (fixed point, taxi ranks, secondary distribution to partners of ANC clients, workplaces) were more effective than the status quo distribution, and were estimated to save between 40,000-63,000 (0.1%-0.2%) life years and averted 9,000-28,000 (0.4%-1.1%) HIV infections over 20 years.

Scenario B

When scaling up the number of HIVST to 6.7 million kits distributed annually by 2030, exclusive primary distribution to PHC clients was dominated (Table 2). Secondary distribution through PHC ART patients had the highest impact, saving 393,000 (1.1%) life years and averting 112,000 (4.3%) new HIV infections over 20 years (Table 2), while fixed point and workplace distribution modalities had a moderate impact (205,000; 0.6% and 156,000; 0.4% LYS, respectively). Distributing all kits through taxi ranks and partners of ANC clients had the least impact of all distribution modalities (98,000; 0.3% and 66,000; 0.2% LYS, respectively).

Costs

Scenario A

Due to the lower cost per test kit distributed, taxi rank distribution was estimated to be cost-saving compared to the status quo, saving an estimated $13 million over 20 years (Table 2). HIVST distribution to partners of PHC ART patients and ANC clients were the most costly of the distribution strategies ($144 million each over 20 years), while distribution through workplaces and fixed point distribution had an *incremental cost to the HIV programme of $12 million and $22 million, respectively.*

Scenario B

Distributing all HIVST kits through other modalities was more costly compared to the status quo, having an estimated incremental cost ranging between $176 million (for taxi ranks) to $1.6 billion (for distribution to partners of ART patients) over 20 years (Table 2).

Table 1. Description of modelled HIVST distribution modalities

		HIVST					
	Status quo distribution	**Fixed point**	**Taxi ranks**	**Secondary PHC (ANC)**	**Secondary PHC (ART patients)**	**Workplace**	**Primary PHC**
% of kit recipients screened positive		5.7%	5.2%	3.9%	19.9%	6.4%	4.0%
% of screened positive initiating ART		27%	27%	27%	27%	27%	40%
Cost per test kit distributed (2019 USD)	-	5.70	4.74	13.04	12.31	5.44	8.24
Distribution of HIVST into different modalities							
Fixed point	5%	100%	-	-	-	-	-
Taxi ranks	5%	-	100%	-	-	-	-
Secondary PHC (ANC)	7%	-	-	100%	-	-	-
Secondary PHC (ART patients)	3%	-	-	-	100%	-	-
Workplace	20%	-	-	-	-	100%	-
Primary PHC	60%	-	-	-	-	-	100%
Scenario A: Distributing 1 million HIVST per year							
Total HIV tests performed per year (millions)	15.4	15.5	15.5	15.6	15.4	15.5	15.3
HTS	14.5	14.6	14.7	14.8	14.9	14.6	14.3
HIVST	0.9	0.9	0.9	0.8	0.5	0.9	1.0
% of tests that are HIVST	6%	6%	5%	5%	4%	6%	7%
Scenario B: Distributing up to 6.7 million HIVST per year (to replace 40% of conventional HTS)							
Total HIV tests performed per year (millions)	15.4	15.9	15.7	15.6	15.9	15.8	15.3
HTS	14.5	9.6	12.4	14.4	10.5	9.5	9.0
HIVST	0.9	6.3	3.3	1.2	5.4	6.3	6.3
% of tests that are HIVST	6%	40%	21%	8%	34%	40%	41%

Table 2. Impact of HIVST distribution modalities on HIV infections, life years lost due to AIDS and incremental cost (2019 USD) on the HIV programme, over 2020-39, compared to a baseline status quo distribution of 1 million HIVST annually

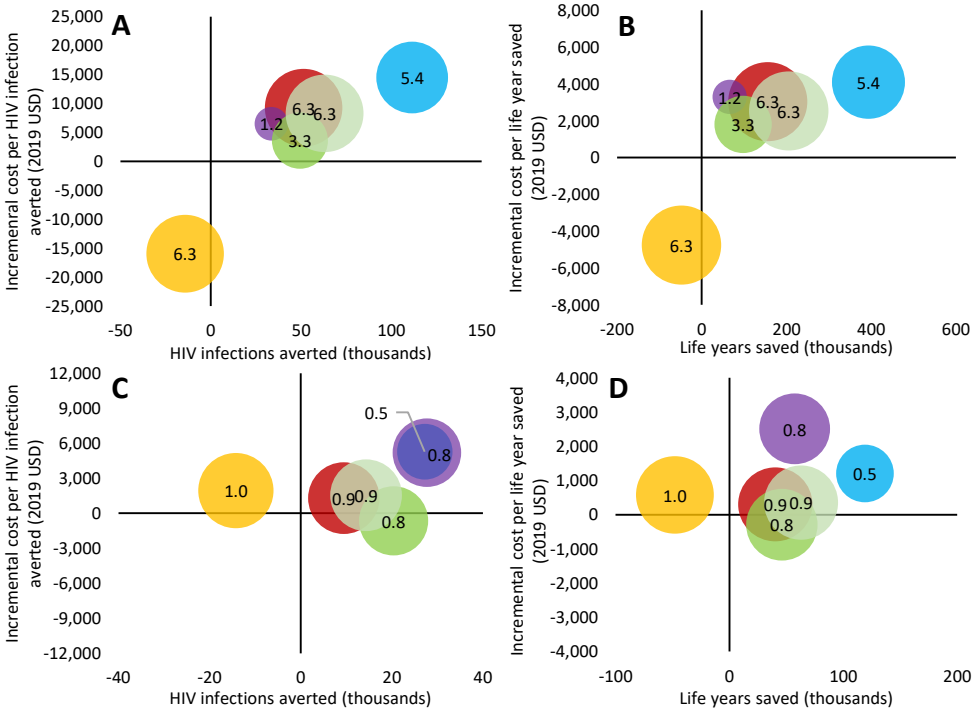
		HIVST					
	Status quo distribution	**Fixed point**	**Taxi ranks**	**Secondary PHC (ANC)**	**Secondary PHC (ART patients)**	**Workplace**	**Primary PHC**
Scenario A: Distributing 1 million HIVST per year							
New HIV infections, millions	2.57	2.55	2.55	2.54	2.54	2.56	2.58
HIV infections averted, thousands (%)		14 (0.6%)	20 (0.8%)	28 (1.1%)	27 (1.1%)	9 (0.4%)	-14 (-0.6%)
Life years lost due to AIDS, millions	36.50	36.44	36.45	36.44	36.38	36.46	36.55
life years saved, thousands (%)		63 (0.2%)	46 (0.1%)	57 (0.2%)	119 (0.3%)	40 (0.1%)	-48 (-0.1%)
AIDS deaths, thousands	1,011	1,010	1,011	1,010	1,008	1,010	1,012
deaths averted, thousands (%)		1.4 (0.1%)	0.70 (0.1%)	0.8 (0.1%)	3.6 (0.4%)	0.9 (0.1%)	-1.0 (-0.1%)
Total cost of the HIV programme	28.79	28.81	28.77	28.93	28.93	28.80	28.76
incremental cost, millions		22	-13	144	144	12	-28
Incremental cost-effectiveness ratio							
cost/infection averted		1,541	Cost-saving	5,186	5,270	1,286	Dominated
cost/life years saved		351	Cost-saving	2,510	1,207	302	Dominated
cost/AIDS death averted		15,797	Cost-saving	173,299	40,300	14,230	Dominated
Scenario B: Distributing up to 6.7 million HIVST per year (to replace 40% of conventional HTS)							
New HIV infections, millions	2.54	2.51	2.52	2.53	2.46	2.52	2.58
HIV infections averted, thousands (%)		63 (2.5%)	49 (1.9%)	34 (1.3%)	112 (4.3%)	51 (2.0%)	-14 (-0.6%)
Life years lost due to AIDS, millions	36.43	36.29	36.40	36.43	36.11	36.34	36.55
life years saved, thousands (%)		205 (0.6%)	98 (0.3%)	66 (0.2%)	393 (1.1%)	156 (0.4%)	-48 (-0.1%)
AIDS deaths, thousands	1,010	1,007	1,010	1,010	1,000	1,008	1,012
deaths averted, thousands (%)		4.6 (0.5%)	1.5 (0.2%)	1.0 (0.1%)	11.1 (1.1%)	3.2 (0.3%)	-1.0 (-0.1%)
Total cost of the HIV programme, billions	29.79	29.31	28.96	29.01	30.40	29.26	29.02
incremental cost, millions		522	176	218	1,615	475	228
Incremental cost-effectiveness ratio							
cost/infection averted		8,283	3,568	6,488	14,488	9,237	Dominated
cost/life years saved		2,543	1,802	3,302	4,106	3,045	Dominated
cost/AIDS death averted		114,438	114,850	227,875	145,395	148,111	Dominated

Cost-effectiveness

Scenario A

With the exception of taxi rank distribution, which was cost-saving, the HIVST distribution modality with the lowest incremental cost effectiveness ratio (ICER) over 20 years was distribution through workplaces ($302/life year saved and $1,286/HIV infection averted) (Figure 1, Table 2). Fixed point distribution was the third most cost-effective ($351/life year saved and $1,541/HIV infection averted), while secondary distribution through ART patients and ANC clients were the least cost-effective distribution modalities ($1,207 and $2,510/life year saved, respectively) (Table 2).

Figure 1. Impact and cost-effectiveness of redistribution all HIVST to different testing strategies, 2020-39. For distributing 1 million HIVST annually, impact on HIV infections averted (A) and life years saved (B); for distributing up to 6.7 million HIVST annually, impact on HIV infections averted (C) and life years saved (D). *Bubble size represents the number of HIVST distributed to each population annually.*



Scenario B

Increasing distribution of HIVST kits up to 6.7 million and directing it all to taxi ranks had the lowest ICER relative to the other distribution modalities, compared to the status quo ($1,802/life year saved and $3,568/HIV infection averted), whereas secondary distribution to partners of ART patients at PHC were the least cost effective ($4,106/life year saved and $14,488/HIV infection averted) (Figure 1) (Table 2). The relative cost-effectiveness of secondary distribution to partners of ANC clients differed from scenario A as these clients were limited to a feasible maximum limit of 1.2 million people who could receive HIVST, thereby curtailing the incremental cost and impact overall.

Optimisation

Scenario A

Distributing the majority (interquartile range (IQR) 38%-63%) of the 1 million HIVST kits through primary PHC led to cost savings over 20 years, compared to the status quo distribution, however this had a relatively small, even harmful, impact on LYS, ranging between -10,000 (i.e. a harmful effect) and 16,000 LYS (Figure 2A). Beyond the cost-saving configurations, ICER/LYS was lowest when a large portion of HIVST kits were distributed to taxi ranks (IQR 6-38%), while there was a mixed distribution for the other modalities: IQR 0%-38% each for fixed point and workplace distribution, IQR 0%-25% for primary distribution to PHC clients, while secondary distribution to partners of ART patients and ANC clients had the lowest allocation (IQR 0%-13%) (Figure 2B). The biggest epidemiological impact resulted from distributing the majority of HIVST (IQR 50-75%) to partners of ART patients (ranging between 32,000 and 46,000 LYS), and these configurations were in the higher range of ICERs with an IQR of $1,900 to $2,300 per life year saved (Figure 2B). Configurations of HIVST distribution relying mainly on secondary distribution to partners of ANC clients (IQR 13%-38%) and primary PHC distribution (0%-38%) were the least cost-effective, with ICERs upwards of $2,000 per life year saved, and even dominated (if 75% or more of HIVST was distributed to primary PHC) (Figure 2B). Similar patterns were obtained when using HIV infections averted as an outcome (Appendix Section 2, Figure S1).

Scenario B

In comparison to the status quo distribution of 1 million HIVST kits distributed annually, if scaled up to 6.7 million HIVST annually, the largest impact was achieved when most HIVST kits (IQR 55%-64%) were distributed to partners of ART patients, saving between 200,000 and 241,000 life years over 20 years, while ICERs for these configurations ranged between $3,309 to $4,300 per life year saved (Figures 3A, 3B). Using the set of configurations that result in the median impact as the optimal distribution strategy (216,000 LYS), the optimal HIVST kit distribution would look as follows: 55% to partners of ART patients, 18% each to fixed point and taxi ranks, 9% to partners of PHC ANC clients and none to workplaces or primary PHC clients. Compared to the status quo distribution of 1 million HIVST annually, an optimised scale-up of distribution to 6.7 million tests annually would result in an almost 3-fold increase in LYS compared to the same volume scale-up at the current status-quo distribution (Table 2) (216,000 vs 75,000 LYS), and it would have a lower ICER ($3,923 vs $5,373 per LYS). The distribution strategy with the lowest ICER/LYS were those where majority of HIVST kits were distributed to fixed point distribution points (Figure 3B). Distributing more than 50% of HIVST kits to primary PHC showed the least impact relative to other configurations (<100,000 LYS), and it was the least cost-effective strategy, with ICERs upwards of $4,500 per LYS (Figures 3A, 3B). We see similar patterns when analysing the impact on HIV infections averted (Appendix Section 2, Figure S2).

Figure 2. A) number of life years saved over the status quo, and B) incremental cost-effectiveness ratio, incremental cost per life year saved (2019 USD); distributing up to 1 million HIVST distributed per year. Status quo: 1 million HIVST distributed to fixed point (5% of HIVST), taxi ranks (5%), secondary PHC (ANC) (7%), secondary PHC (ART patients) (3%), workplace (20%) and primary PHC distribution (60%).

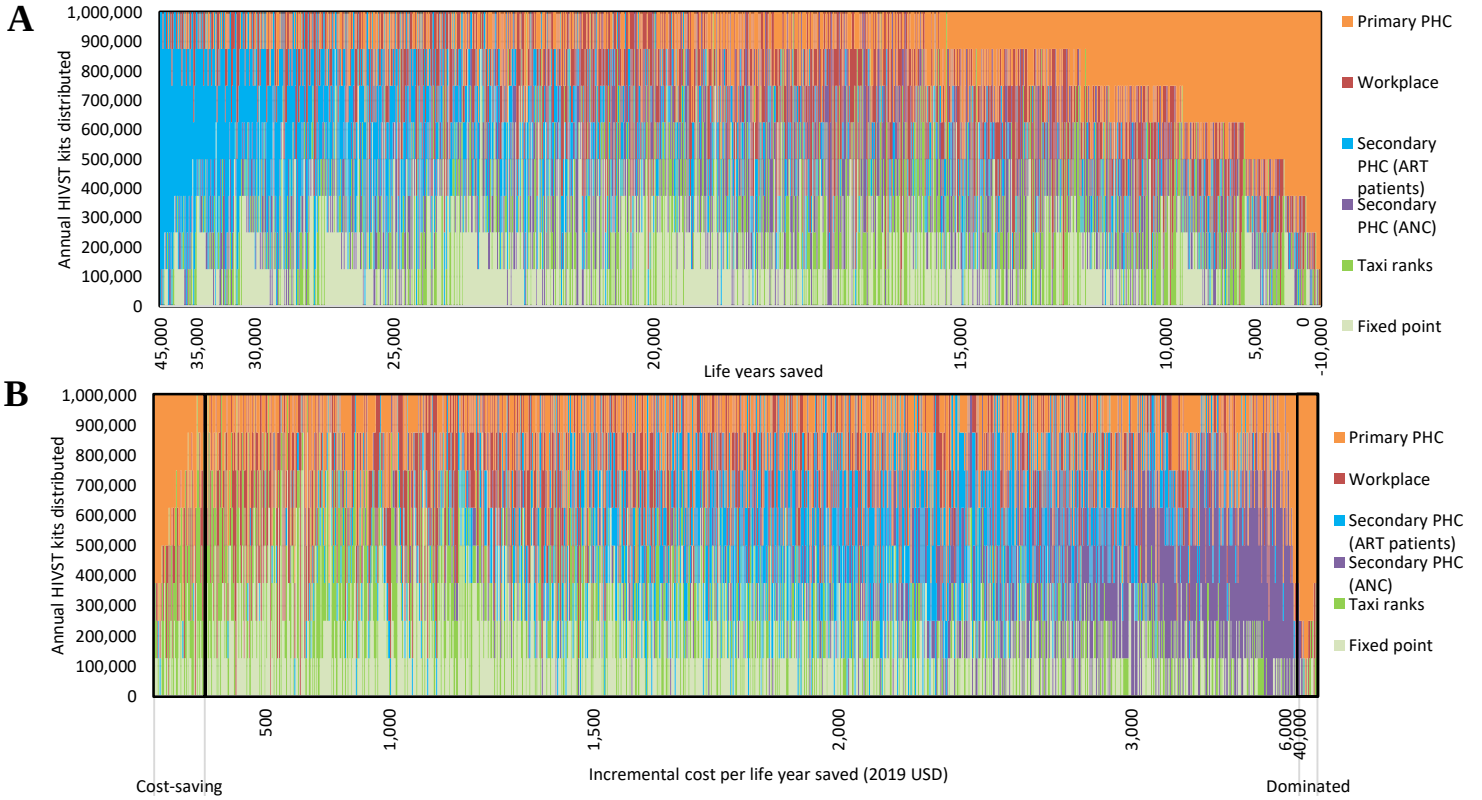
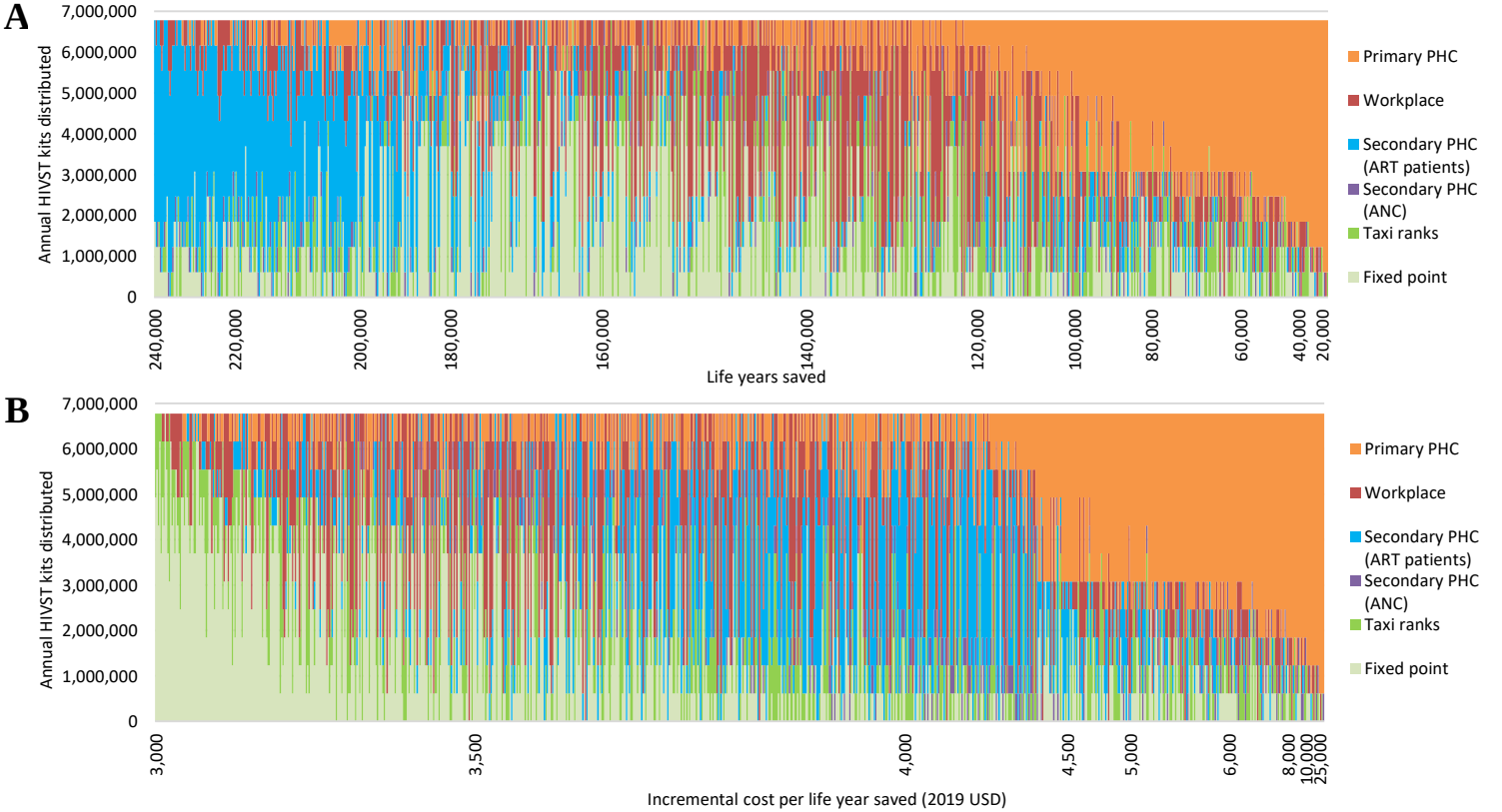


Figure 3. A) number of life years saved over the status quo, and B) incremental cost-effectiveness ratio, incremental cost per life year saved (2019 USD); distributing up to ~6.7 million HIVST per year by 2030. Status quo: 1 million HIVST distributed to fixed point (5% of HIVST), taxi ranks (5%), secondary PHC (ANC) (7%), secondary PHC (ART patients) (3%), workplace (20%) and primary PHC distribution (60%).



Comparing against a baseline of no HIVST

In scenario A, when comparing against a baseline with no HIVST, we see similar patterns of distribution configurations where HIVST distributed mainly to partners of ART patients produced the largest epidemiological impact (ranging 75,000-93,000 LYS), while ICERs are upwards of $2,000 per LYS (Appendix, Section 2, Figure S3). HIVST distributed mostly (>50%) through secondary distribution to partners of ANC clients was the least cost-effective strategy with the highest ICERs amongst all configurations. Distributing a large portion HIVST (>25%) to taxi ranks is the most cost-effective strategy (Appendix, Section 2, Figure S3). When scaling up to 6.7 million HIVST kits distributed annually, compared to a baseline with no HIVST, distribution to partners of ART patients was the strategy that yielded the largest impact (>235,000 LYS), although it had high ICERs relative to the other configurations (>$3,200/life year saved) (Appendix, Section 2, Figure S4). Primary PHC distribution was the least cost-effective (>$4,000/life year saved) and least impactful strategy (<165,000 life year saved). Distributing majority of HIVST kits to fixed points was the most cost-effective strategy compared to other configurations (ICER <$3,000/life year saved) but had a moderate epidemiological impact, ranging between 164,000 and 238,000 LYS (Appendix, Section 2, Figure S4).

Discussion

The distribution of HIVST kits is expected to have a large impact on averting new HIV infections and AIDS deaths over 20 years, compared to a baseline status quo where HIVST kits were already distributed through different modalities with a set distribution pattern (60% to primary PHC, 20% to workplaces, 7% to secondary distribution to partners of ANC clients in PHC, 5% to taxi ranks, 5% to fixed point and 3% to secondary distribution to partners of ART patients). Importantly, we have shown the importance in determining the optimal configuration of testing modalities as HIVST scales up. An optimisation-informed scale-up- instead of proportionally scaling-up the current distribution of HIVST testing modalities- is expected to nearly triple the number of life years saved. Redirecting all HIVST toward any distribution strategy other than primary PHC performs better in terms of saving life years and averting HIV infections over 20 years than the planned status quo; however, results vary in terms of costs and cost effectiveness. We

showed that secondary distribution to partners of ART patients will have the biggest epidemiological impact but will be the least cost-effective strategy due to its high cost, while distribution of HIVST to taxi ranks will be cost-saving but have only a moderate impact on averting HIV infections. Distribution to primary PHC is not cost-effective due to the lower HIV positivity yielded, and may even be dominated compared to other distribution strategies.

There are several limitations to this work. Firstly, cost data for the different distribution strategies was based on an initiative that was managed and implemented by non-governmental organisations, and therefore both cost and screening positivity could change once introduced and managed in the public sector. Secondly, for primary PHC testing we assumed the same screening positivity as conventional HTS. It is plausible that screening positivity could be higher if implemented in the real world as PHC clients concerned about their HIV status might prefer self-screening over conventional HTS within the clinic setting to avoid stigma or have more control over the testing procedure. However, we do posit the screening positivity of primary PHC to remain lower than those of the higher performing distribution strategies, and indeed this was shown to be the case in the vertical, non-integrated PHC testing strategy included in Matsimela et al (113). Thirdly, the model estimates of HIV testing yields were in some cases inconsistent with those reported in the STAR data, suggesting that matching the age and sex profile of HIV test recipients may be insufficient to reasonably capture the different HIV risk profiles associated with different testing modalities. However, the STAR data are not nationally representative, and implementation has not been uniform, with different HIVST modalities being piloted in different areas by different implementers. Some divergence between observed testing yields and yields estimated in a national model is therefore to be expected, and it will be important to continue to monitor testing yields as different HIVST modalities are scaled up nationally. Future work on HIVST should include the evaluation of the different testing strategies once scaled up in the public health system to understand the real cost and screening positivity. The positivity rate may decline differentially between testing modality as demand saturates, and therefore understanding the optimal timing and frequency of testing by modality will need to continue in order to help guide effective implementation.

Conclusion

In evaluating the impact and cost-effectiveness of different HIVST distribution modalities using a HIV transmission model and data collected alongside large-scale routine implementation under the STAR initiative, we were able to generate findings that could help inform policy makers making decisions on the most effective strategy to prioritise for national roll-out: the secondary distribution of HIVST to partners of ART patients. However, this will be a costly approach. The optimal distribution of HIVST is estimated to be a mix between secondary distribution of HIVST kits to partners of ART patients and pregnant women in care at PHC, taxi ranks and fixed point HIVST distribution. Further, in the face of the global COVID-19 pandemic affecting all health services, including HIV testing, scaling up HIVST in order to limit patient contact with health services and providing an option of self-screening to those reluctant to attend a PHC clinic, would assist greatly in maintaining or increasing progress towards testing targets.

Supplementary Appendix

Section 1: Modelling self-testing in Thembisa

Previous versions of Thembisa have not included self-testing. This supplementary material describes extensions made to the Thembisa model to include different forms of self-testing.

We define the following variables:

$\tau_{g,i,s}(x,t)$ is the rate of health worker-administered testing in sexually experienced individuals of age x and sex g, in HIV stage s and with HIV testing history i, in year t;
$\tau'_{g,i,s}(x,t)$ is the rate of health worker-administered testing in virgins of age x and sex g, in HIV stage s and with HIV testing history i;
$S_{g,i,s}(x,t)$ is the rate of self-testing in sexually experienced individuals of age x and sex g, in HIV stage s and with HIV testing history i;
$Z_{g,i,s}(x,t)$ is the rate of any HIV testing (health worker-administered or self-administered) in sexually experienced individuals of age x and sex g, in HIV stage s and with HIV testing history i, in year t.

In HIV-negative individuals ($s = 0$) and acutely-infected individuals ($s = 1$), the total rate of testing is simply

$$Z_{g,i,s}(x,t) = \tau_{g,i,s}(x,t) + S_{g,i,s}(x,t).$$

However, in HIV-seropositive individuals it is necessary to take into account that some of the HIV-positive self-testers seek confirmatory testing, i.e. there could be double-counting of the individuals diagnosed by self-testing and by health worker-administered testing. The total rate of testing is therefore calculated as

$$Z_{g,i,s}(x,t) = \tau_{g,i,s}(x,t) + S_{g,i,s}(x,t)(1 - \gamma \mathrm{I}(s > 1))$$

for $s > 0$, where γ is the fraction of individuals diagnosed through self-testing who seek confirmatory testing by health workers, and $\mathrm{I}(s > 1)$ is an indicator of whether the individual has detectable HIV antibodies (0 if HIV-seronegative, 1 if HIV-seropositive). We set γ to 68%, based in part on the STAR study, in which the proportion of individuals testing positive on self-testing who reported going for confirmatory testing varied between 48% and 74% across modalities. The assumption is also consistent with our previous assumption that the relative rate of linkage to ART services in people who

self-test positive, when compared to that in people who test positive in a health facility, is 0.68 (114).

We consider five types of self-testing:

1. Self-testing through fixed point distribution (a form of community-based distribution)
2. Self-testing kits distributed at taxi ranks
3. Self-testing kits distributed to partners of pregnant women
4. Self-testing kits distributed to partners of ART patients
5. Self-testing kits distributed to employees in workplace settings

The symbol $c_j(t)$ represents the coverage/uptake of self-testing method j (indexed as 1 for fixed point distribution, 2 for taxi ranks, 3 for pregnant women's partners, 4 for partners of ART patients and 5 for employees).

Fixed point distribution

In the case of self-testing through fixed point distribution, our analyses of initial programme data suggest that the age and sex profile of individuals receiving self-testing roughly matches the age and sex profile of people who receive 'general' HIV testing in the Thembisa model (i.e. after excluding testing in antenatal clinics and people with HIV-related symptoms). We therefore set the self-testing rate to

$$\lambda^1_{g,i,s}(x,t) = c_1(t)\, A_g(x,t)\, r^*_i(t),$$

where $A_g(x,t)$ is the same age and sex adjustments that applies in the case of 'general' testing, and $r^*_i(t)$ is the relative rate of testing in individuals with HIV testing history i (1 for individuals who have never been tested or who have only tested negative, 0.5 for untreated HIV-diagnosed individuals and 0.15 for individuals on ART).[1] Figure S1 shows that with the standard age and sex adjustments for 'general' testing the model estimates of patterns of test uptake by age and sex are roughly consistent with the STAR data – although the STAR data suggest lower rates of HIV testing than predicted by the model in the 15-19 and 50+ age groups.

[1] This is consistent with the assumptions made about self-testing in the MicroCOSM model.

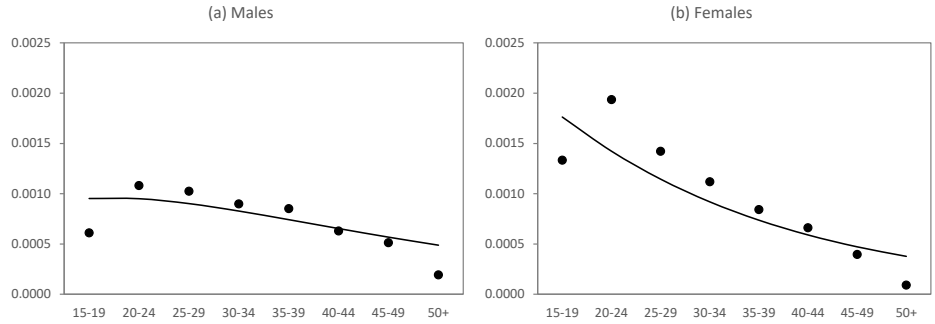


Figure S1. Rates of self-testing through fixed point distribution in Gauteng, 2017-2019
Programme data from the STAR project have been divided by the Thembisa estimates of the size of the sexually experienced population at each age in Gauteng, where most of the distribution through fixed points occurred (dots). Solid lines represent the estimates from the previous equation, scaled by an arbitrary factor to match the relative levels of testing by age and sex.

If we know the total number of self-testing kits distributed through fixed points in year t, $E_1(t)$, then we can approximate the self-testing uptake by the formula

$$c_1(t) = \frac{E_1(t)(1-W_1)}{\sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t) A_g(x,t) r_i^*(t)},$$

where W_1 is the proportion of self-testing kits that are not used ('wastage'), and $N_{g,i,s}(x,t)$ is the size of the sexually experienced population aged x, of sex g, with HIV testing history i, at time t. In the routine data from the STAR programme, most of the self-testing kits distributed through fixed points were used 'on site' (at the point of distribution) and there was thus relatively little wastage; out of 9980 self-testing kits distributed to individuals who were interviewed, 8868 (89%) were used by the individual interviewed or (in a minority of cases) given to someone else. We therefore set W_1 to 11%.

Taxi rank distribution

We adopt a similar approach in modelling the effect of self-test kit distribution through taxi ranks. However, the STAR testing data suggest a different age and sex distribution of test recipients, with relatively high testing

rates in males and in the 20-34 age group. We therefore represent the age and sex adjustment factor by the symbol $A_g'(x,t)$, which is parameterized as

$$A_g'(x,t) = B_g\,(x/25)^{\alpha - 1}\exp(-\sigma(x - 25))$$

where B_g is a scaling factor to represent the effect of sex ($B_1 = 7.5$ for men and $B_2 = 1$ for women), and α and σ are coefficients to represent the effect of age on the rate of testing. Setting α and σ to 14.1 and 0.469 respectively yields a reasonable model fit to the age-specific rates of self-testing through taxi ranks, as shown in Figure S2.

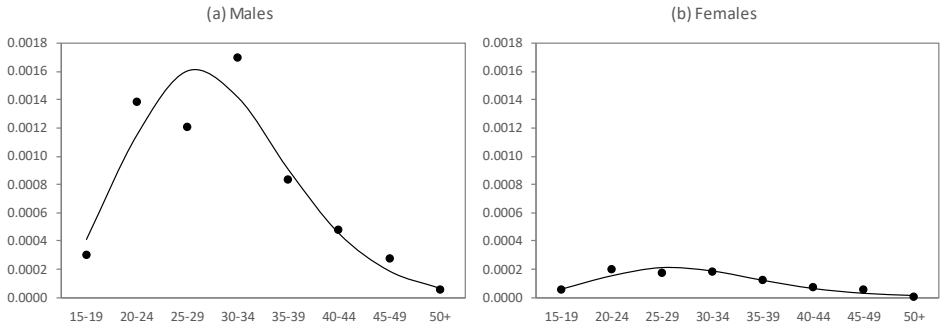


Figure S2. Monthly rates of self-testing through taxi rank distribution in Gauteng, 2018
Programme data from the STAR project have been divided by the Thembisa estimates of the size of the sexually experienced population at each age in Gauteng, where most of the distribution through taxi ranks occurred (dots). Solid lines represent the estimates from the previous equation, scaled by an arbitrary factor to match the relative levels of testing by age and sex.

We set $\lambda^2_{g,i,s}(x,t) = c_2(t)\,A_g'(x,t)\,r^*_i(t)$, where $c_2(t)$ represents the rate of self-testing through taxi ranks in females aged 25. This parameter is calculated in the same way as $c_1(t)$, using recorded numbers of tests distributed through taxi ranks ($E_2(t)$) and observed levels of wastage (W_2). Out of 5922 self-testing kits distributed to individuals who were interviewed after receiving self-testing kits through taxi ranks in the STAR project, 5028 (85%) were used by the individual interviewed or (in a small fraction of cases) given to someone else. We therefore set W_2 to 15%.

Secondary distribution to partners of pregnant women

We model the rate of self-testing in sexually experienced men, using tests distributed to them by pregnant female partners, as

$$\lambda^3_{g,i,s}(x,t) = c_3(t)\, F(x-3,\, t)\, r^*_i(t)\, (1 - W_3),$$

where $F(x, t)$ is the fertility rate in HIV-negative women aged x in year t. The $c_3(t)$ parameter is defined here as the proportion of HIV-positive pregnant women who are given self-testing kits to give to their partners. For the sake of simplicity, we do not incorporate effects of female HIV status and ART use on fertility, which would depend on the male's HIV status. We also assume, for the sake of simplifying the self-testing calculations, that men are on average three years older than their female partners, and that each sexually experienced male has one heterosexual partner (this assumption is made only for the purpose of approximating the effect of secondary distribution through antenatal clinics and does not apply to the rest of the Thembisa model). With these assumptions the modelled relative rates of HIV testing in men, by age, approximate those observed in the STAR data (Figure S3).

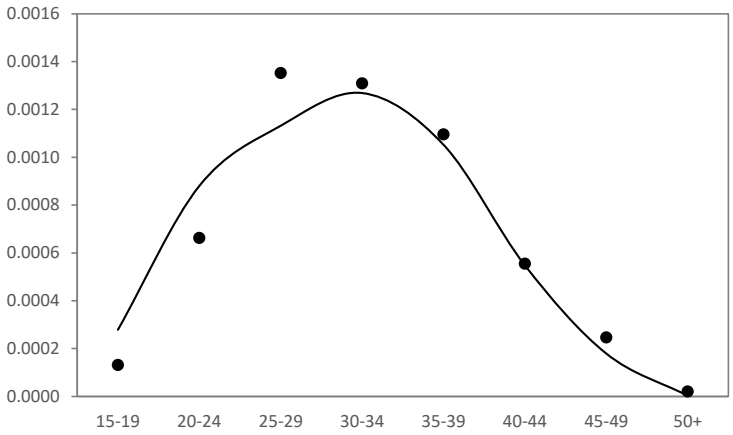


Figure S3. Male rates of self-testing through pregnant partners in Gauteng, 2017-2019
Programme data from the STAR project (numbers of men who were known to have used self-testing kits given to them by their pregnant partners) have been divided by the Thembisa estimates of the size of the sexually experienced male population at each age in Gauteng, where most of the distribution through pregnant women occurred (dots). Solid lines represent

the estimates from the previous equation, scaled by an arbitrary factor to match the relative levels of testing by age.

In the STAR data, 9777 pregnant women who were given self-testing kits to give to their partners were interviewed; all reported that they gave the test(s) to at least one partner, but only 3783 (39%) reported knowing that the partner had actually used the test. This is probably an under-estimate of actual test use, since some men may have used the test without informing their female partners, so we optimistically set W_3, the fraction of tests that are not used by HIV-negative male partners, to 0.12, consistent with the parameters estimated for the previous testing modalities. (It is worth noting that if the male partner is HIV-positive, the probability of the test not being used is $1 - r^*_i(t) \times (1 - 0.12)$.) If we know the total number of self-testing kits distributed through pregnant women in year t, $E_3(t)$, then we can estimate $c_3(t)$ by dividing $E_3(t)$ by the total number of pregnancies in year t.

Secondary distribution to partners of ART patients

We model the rate of self-testing in sexually experienced individuals, following secondary distribution of self-testing kits by sexual partners on ART, as

$$\lambda^4_{g,i,s}(x,t) = c_4(t)\, H_s(g \mid p_0, p_1)\, K_g(x, t)\, r^*_i(t)\, (1 - W_4),$$

where $H_s(g \mid p_0, p_1)$ is the probability that an individual of HIV status s and sex g has an HIV-positive partner (given HIV prevalence levels of p_0 in male partners and p_1 in female partners), and $K_g(x, t)$ is the ART coverage in year t in HIV-positive sexual partners of individuals aged x and of sex g. $H_s(g \mid p_0, p_1)$ is calculated using a formula given in the appendix, based on South African data on levels of seroconcordance in heterosexual relationships. The coverage parameter, $c_4(t)$, is defined as the proportion of ART patients who are given self-testing kits to give to their sexual partners, and W_4 is the proportion of self-test kits distributed that do not get used by sexual partners. Out of 4153 HIV-diagnosed individuals who were given self-testing kits to give to their sexual partners through the STAR project, all reported giving the test to sexual partners, but only 1871 (45%) reported knowing that the test was used. Again, this is likely to be an under-estimate of the fraction of tests actually used. We have therefore set W_4 to 0.12, the same value as assumed for secondary distribution of self-testing kits to partners of pregnant women. If we know the total number of self-testing kits distributed through index

partners in year t, $E_4(t)$, then we can approximate the self-testing uptake by the formula

$$c_4(t) = \frac{E_4(t)}{\sum_i \sum_s \sum_x N_{g,i,s}(x,t) H_s(g \mid p_0, p_1) K_g(x,t)}$$

Note that in this equation (as in the equation for $c_3(t)$) we do not have a wastage term or a testing history adjustment, because the uptake parameter is inclusive of tests that are not used. In contrast, the uptake parameters for the fixed point and taxi rank distribution strategies were exclusive of wastage, and the associated formulas for $c_1(t)$ and $c_2(t)$ therefore excluded wastage.

Distribution through workplaces

Our approach to modelling distribution through workplaces is similar to that for taxi ranks, with a different age distribution from that for general HIV testing. As with fixed point and taxi rank self-test distribution, the STAR data suggest that almost all tests distributed are used by the individuals who receive the tests, and a relatively small fraction are given to others. We therefore ignore secondary distribution, in the interests of simplicity. We model the rate of self-testing in sexually-experienced individuals, through workplace distribution programmes, as

$$\lambda^5_{g,i,s}(x,t) = c_5(t)\ \mathrm{Q}(x, g)\ A^*_g(x,t)\ r^*_i(t),$$

where $\mathrm{Q}(x, g)$ is the rate of employment in individuals aged x, of sex g, and $A^*_g(x,t)$ determines the relative rates of testing uptake by age and sex among employed individuals. The $\mathrm{Q}(x, g)$ parameters are estimated from the 2015 Quarter 3 Labour Force Survey (119), and are shown in Table S1. (We assume rates of employment are zero below age 15 and at ages 65 and older.)

Table S1. Proportion of individuals employed, by age and sex

	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64
Male	2.6%	26.7%	48.3%	54.3%	57.7%	60.3%	59.3%	51.1%	44.9%	24.1%
Female	1.5%	17.4%	35.6%	44.1%	49.0%	48.7%	47.0%	41.4%	35.4%	16.3%

Source: South African Labour Force Survey 2015, Quarter 3 (authors' own calculations).

Similar to the modelling of the age and sex pattern of testing uptake through taxi ranks, we use the following function to represent the age and sex pattern of self-testing in employed populations:

$$A^*_g(x,t) = B^*_g(x/25)^{\alpha^*g-1}\exp(-\sigma^*_g(x-25))$$

where B^*_g is a scaling factor to represent the effect of sex ($B^*_1 = 0.95$ for men and $B_2 = 1$ for women), and α^*_g and σ^*_g are coefficients to represent the effect of age on the rate of testing. Setting α^*_1 and σ^*_1 to 4.59 and 0.153 respectively in men, and setting α^*_2 and σ^*_2 to 2.94 and 0.122 respectively in women, yields a reasonable model fit to the age-specific rates of self-testing through workplaces, as shown in Figure S4. The peak testing rates in males are higher than those in females, despite the B^*_g adjustment being slightly lower for men than for women, which is because of the higher rates of employment in men.

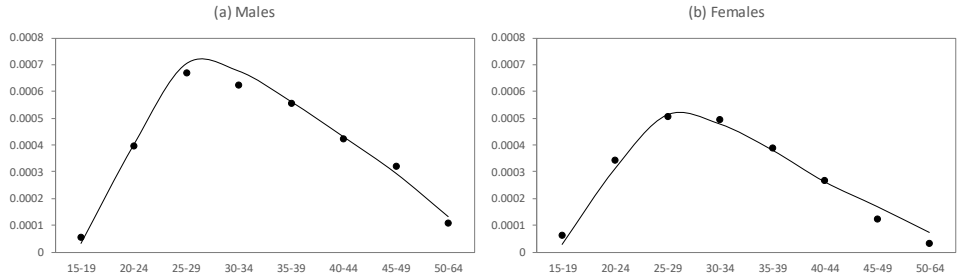


Figure S4. Rates of self-testing through workplaces
Programme data from the STAR project (2017-2020) have been divided by the Thembisa estimates of the size of the sexually experienced population at each age in South Africa (dots). Solid lines represent the estimates from the $\lambda^5_{g,i,s}(x,t)$ equation, scaled by an arbitrary factor to match the relative levels of testing by age and sex.

The coverage parameter $c_5(t)$ is defined as the rate of self-testing through workplace programmes, in employed women aged 25 in year t. We estimate this parameter from the total number of self-tests distributed through campaigns in workplaces in year t, $E_5(t)$, and the assumed fraction of test kits that are not used, W_5:

$$c_5(t) = \frac{E_5(t)(1-W_5)}{\sum_g\sum_i\sum_s\sum_x N_{g,i,s}(x,t)\mathrm{Q}(x,g)A^*_g(x,t)r^*_i(t)}.$$

In the STAR programme, out of 13 308 tests distributed to interviewed individuals, 12 321 (93%) were reported to have been used or given to someone else. We therefore set $W_5 = 0.07$.

Total testing rates and index testing

Table S2 summarizes the data from the STAR programme for the 2017-2020 period, on total numbers of self-testing kits distributed. We assume that this represents the total number of self-test kits distributed, although the STAR programme has also distributed kits through other distribution channels (data forthcoming), and some self-testing kits may be distributed through other providers, or sold through pharmacies.

Table S2. Total self-testing kits distributed in South Africa

Year	Fixed point distribution	Taxi rank distribution	ANC client distribution	Index testing	Workplace testing
2017-18	57,701	155,643	1,107	859	84,713
2018-19	117,215	225,107	9,847	3,798	165,624
2019-2020*	68,720	74,531	10,183	4,923	128,951

ANC = antenatal clinic. * Results for 2020 are only available up to the end of March so are an under-estimate of the true total.

The total rate of self-testing is calculated as

$$S_{g,i,s}(x,t) = \sum_j \lambda^j_{g,i,s}(x,t).$$

The annual rate at which sexually experienced individuals get tested by health workers is calculated as

$$\tau_{g,i,s}(x,t) = b(t)A_g(x,t)r_i(t) + \Omega_s d_i(t) + F_{g,s}(x,t)v_i(t) + S_{g,i,s}(x,t)\gamma \mathrm{I}(s > 1)$$

where $b(t)$ is the base rate of 'general' HIV testing in year t, in individuals who do not have any HIV symptoms and are not pregnant; $A_g(x,t)$ is the adjustment factor to represent the effect of age and sex on the base rate of test uptake; $r_i(t)$ is the adjustment factor to represent the effect of testing history; Ω_s is the annual incidence of OIs in CD4 stage s; $d_i(t)$ is the fraction of OI patients who are tested for HIV in year t; $F_{g,s}(x,t)$ is the fertility rate in sexually experienced women aged x, in HIV stage s, during year t (set to zero for men); and $v_i(t)$ is the proportion of pregnant women who receive HIV testing in year t. The first three terms on the right-hand side of this equation correspond to the three HIV testing modalities previously modelled in Thembisa, and the associated symbols are the same as defined previously (50).

The rate of HIV testing in asymptomatic virgins is assumed to be a multiple φ of the rate of HIV testing in asymptomatic girls aged 15 who are sexually experienced and non-pregnant, i.e.

$$\tau'_{g,i,s}(x,t) = b(t)A_2(15,t)r_i(t)\varphi + \Omega_s d_i(t).$$

For virgins we are therefore excluding antenatal testing (since they would not be pregnant) and self-testing.

Suppose that $G(t)$ is the total number of HIV tests performed by health workers in adults aged 15 and older, in year t. If $V_{g,i,s}(x,t)$ is the number of virgins, at the start of year t, then

$$G(t) \approx \sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)\tau_{g,i,s}(x,t) + V_{g,i,s}(x,t)\tau'_{g,i,s}(x,t).$$

(The relation is not exact because the numbers of individuals in the different strata change over the course of the year, so relying only on the values at the start of the year may lead to some bias.) We use the above calculation to estimate the base rate of testing in year t:

$$\hat{b}(t) = \frac{G(t) - \sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)\{\Omega_s d_i(t) + F_{g,s}(x,t)v_i(t) + S_{g,i,s}(x,t)\gamma I(s>1)\} + V_{g,i,s}(x,t)\Omega_s d_i(t)}{\sum_g \sum_i \sum_s \sum_x N_{g,i,s}(x,t)A_g(x,t)r_i + V_{g,i,s}(x,t)A_2(15,t)r_i\varphi}$$

Sensitivity and specificity of self-testing

Based on a previous review, we assume that self-testing is 100% specific (120). We further assume that self-testing sensitivity depends on the recency of HIV infection: self-testing is assumed to have 0% sensitivity during the acute phase of HIV infection (approximately the first 3 months after HIV acquisition) and 100% sensitivity thereafter. With these assumptions the average sensitivity across all HIV testers is around 96% (101), roughly consistent with sensitivities reported in various studies (120). These sensitivity and specificity assumptions are the same as for conventional HIV testing in Thembisa.

Linkage to ART after diagnosis

In the previous version of Thembisa we assumed that the probability of ART initiation soon after diagnosis depended on the setting in which diagnosis occurred, with the probability being highest in antenatal care settings (95% in the period after 2015), lower in people diagnosed when seeking treatment for HIV-related OIs (78%), and lowest for individuals diagnosed in other settings (40%).

In the new version of the model, we apply the same 40% probability of linkage to individuals who seek confirmatory testing after a positive self-testing result. This means that the actual proportion of all individuals diagnosed through self-testing who link to ART is 27% (40% × 68%, where 68% is the assumed proportion of positive self-testers who seek confirmatory testing). This is consistent with the assumption made in MicroCOSM (also 27%), which was based on rates of linkage observed in other models of community-based testing, prior to the availability of local data on linkage to care after self-testing (114). However, rates of linkage to ART after diagnosis through self-testing are difficult to estimate reliably, and these estimates should be treated with caution (121).

Model results and calibration

Table S3 compares the model estimates of the yield on self-testing with the yields estimated from the STAR data. The model estimates of yield are based only on the tests that were used (i.e. the denominator does not include unused test kits). In the case of the secondary distribution testing modalities (index testing and testing of male partners of pregnant women), there is uncertainty regarding the true yield, because individuals only reported on whether they knew that their partner used the test and whether they knew their partner tested positive. In these cases, a conservative lower bound on the yield would be the total number of known positive results divided by the total numbers of tests distributed to sexual partners. An upper bound on the yield would be the total number of known positive tests divided by the numbers of tests that were known to have been used (although one might argue that this is not an upper bound if partners who test positive are less likely to tell their partners that they used the test, or if they are likely to misreport that they are negative). For both secondary testing modalities, the model estimate of the testing yield falls between the lower and upper bounds estimated from the STAR data, which is reassuring.

Table S3. HIV testing yields, averaged over the 2017-2020 period

	Fixed point distribution	Taxi rank distribution	ANC client distribution	Index testing	Workplace testing
Model estimate	5.73% (5.36-6.09%)	5.18% (4.86-5.45%)	3.91% (3.66-4.15%)	19.9% (19.3-20.4%)	6.44% (6.05-6.74%)
STAR data	3.05%	8.98%	-	-	4.23%
Lower bound	-	-	2.22%	11.0%	-
Upper bound	-	-	5.74%	24.4%	-

ANC = antenatal clinic.

In the case of the fixed point distribution, taxi rank distribution and workplace distribution modalities, however, the yields estimated by the model are very inconsistent with the STAR data. While the model estimates that the three modalities should have relatively similar testing yields (5.2-6.4%), the STAR data suggest that the testing yields on these three modalities are very different. Previous studies have identified taxi ranks as 'hotspots' or locations with high HIV prevalence (122,123), but our model assumes HIV prevalence in taxi ranks is no different from that in the general population (after controlling for age and sex), which may be unrealistic.

Table S4 summarizes the estimates of the testing coverage in each year, for each modality, based on the numbers in Table S1. For all modalities, there was a substantial increase in coverage/uptake between 2017-18 and 2018-19. However, coverage either increased minimally or dropped substantially in the following year, which may be a reflection of the 2019-20 data being incomplete at the time of this analysis.

Table S4. Coverage/uptake of self-testing in South Africa

Year	Fixed point distribution $c_1(t)$	Taxi rank distribution $c_2(t)$	ANC client distribution $c_3(t)$	Index testing $c_4(t)$	Workplace testing $c_5(t)$
2017-18	0.00259	0.00185	0.00099	0.00022	0.01166
2018-19	0.00523	0.00265	0.00803	0.00088	0.02258
2019-20	0.00305	0.00087	0.00833	0.00106	0.01741
Average*	0.00362	0.00179	0.00578	0.00072	0.01722

ANC = antenatal clinic. * The average coverage is assumed to apply in the post-2020 period.

Limitations

The results shown in Tables S3 and S4 are the results obtained using the national version of the Thembisa model. However, almost all of the STAR

data come from Gauteng province, and one could argue that it would be more meaningful to run the Gauteng version of the Thembisa model.

Another limitation is that there is substantial uncertainty regarding the relative rates of testing in previously diagnosed individuals, and these assumptions affect the estimated yield on self-testing (Table S3). We assume that individuals who retest positive are no more likely to initiate ART than individuals who were previously diagnosed and did not get tested, i.e. there are no modelled benefits to retesting individuals who have already been diagnosed. This assumption is unrealistic, as evidence suggests that previously-diagnosed individuals who retest positive are as likely to link to HIV care as individuals who are diagnosed positive for the first time (124,125). However, the assumption is consistent with the assumption made for health worker-administered testing. In future versions of Thembisa we plan to revise these assumptions about linkage to ART after re-diagnosis, to better reflect the benefits of repeat testing.

Appendix A: Predicting HIV seroconcordance in South African couples

For the purpose of modelling index testing, it is necessary to be able to estimate the probability that an individual who tests positive has a positive partner. Suppose that we consider a population of *n* heterosexual couples. We further define *a* to be the number who are concordant positive, *b* the number who are serodiscordant with the female partner positive and the male negative, *c* the number who are serodiscordant with the male partner positive and *d* the number who are concordant negative (Figure A1).

		Male HIV status: Positive	Male HIV status: Negative
Female HIV status	Positive	*a*	*b*
	Negative	*c*	*d*

Figure A1. Numbers of couples by HIV status

We define θ to be the odds ratio relating the odds of HIV infection in the individual to the odds of HIV infection in their partner, i.e. $\theta = ad / bc$. We also define π_0 to be the HIV prevalence in male partners ($(a + c) / n$) and π_1 to be the HIV prevalence in female partners ($(a + b) / n$). These quantities can be estimated from various South African studies, as summarized in Table A1. Estimates of θ appear highly heterogeneous across studies, varying between 2.5 and 32, with the odds ratios generally being highest in the studies in which HIV prevalence is lowest. This is because as HIV prevalence increases in the general population, individuals are relatively more at risk of having acquired HIV from partners other than their current partner, and the strength of association between the individual's HIV status and their partner's status thus becomes weaker.

Table A1. South African studies of seroconcordance in heterosexual couples

Study	*a*	*b*	*c*	*d*	π_0	π_1	θ (95% CI)
Mbulawa *et al* (126)	112	158	44	155	33.3%	57.6%	2.50 (1.62-3.87)
de Bruyn *et al* (127)	302	126	326	671	44.1%	30.0%	4.93 (3.83-6.37)
Kilembe *et al* (128)	245	175	93	394	37.3%	46.3%	5.93 (4.36-8.08)
Lurie *et al* (129)	16	10	25	117	24.4%	15.5%	7.49 (2.78-20.53)
Doherty *et al* (130)	26	50	12	200	13.2%	26.4%	8.67 (3.87-20.06)
2016 DHS (49)	61	44	21	293	19.6%	25.1%	19.34 (10.35-36.55)
Simbayi *et al* (48)	124	134	57	1378	10.7%	15.2%	22.37 (15.37-32.64)
Naik *et al* (131)	11	7	10	201	9.2%	7.9%	31.59 (8.72-115.52)

For the sake of developing a predictive model, we performed a meta-regression on the data in Table A1, using the natural log of the female HIV prevalence as the explanatory variable. (The meta-regression was also done using the log of the male HIV prevalence as the explanatory variable, but this was found to not fit the data as well, so the results of this analysis are not presented here.) The best-fitting model was of the form $\theta(\pi_1) = \exp(0.536) \times \pi_1^{-1.218}$. Figure A2 shows the meta-regression model fit to the data in Table A1.

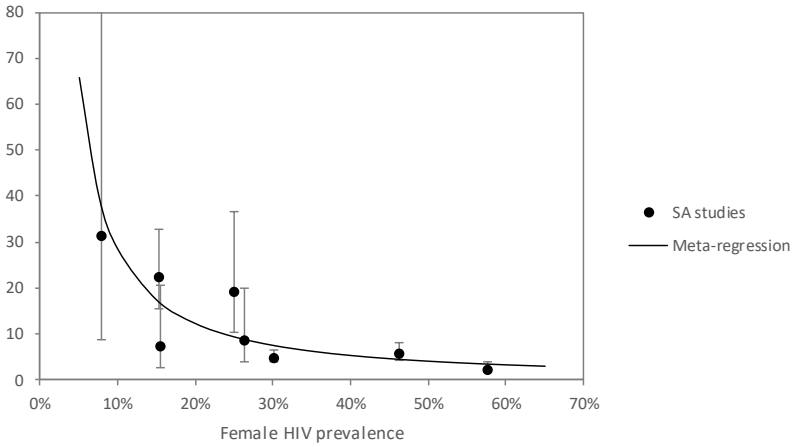


Figure A2. Odds of infection if partner is HIV-positive, relative to odds of infection if partner is HIV-negative

For the purpose of developing a predictive model, we need to be able to estimate a, b, c and d from the parameters $\theta(\pi_1)$, π_0 and π_1. For the sake of simplicity, we will re-express a, b, c and d as proportions that sum to 1, so that $n = 1$, $d = 1 - a - b - c$, $\pi_0 = a + c$, and $\pi_1 = a + b$. Substituting these equations into the odds ratio formula gives

$$\theta(\pi_1) = \frac{a\left(1 - a - \left(\pi_0 - a\right) - \left(\pi_1 - a\right)\right)}{\left(\pi_0 - a\right)\left(\pi_1 - a\right)}.$$

This can be expressed as a quadratic in a; solving for a gives

$$a = \frac{1 + \left(\theta - 1\right)\left(\pi_0 + \pi_1\right) - \sqrt{\left(1 + \left(\theta - 1\right)\left(\pi_0 + \pi_1\right)\right)^2 - 4\left(\theta - 1\right)\theta\pi_0\pi_1}}{2\left(\theta - 1\right)}.$$

The probability that the female partner is positive, given that the male partner is positive, is then $a / (a + c) = a / \pi_0$. Similarly, the probability that the male partner is positive, given that the female partner is positive, is a / π_1. We thus have formulas for predicting partner concordance as a function of the HIV prevalence in males and females, in a population of heterosexual couples.

Section 2: Supplementary results

Table S1. Description of HIVST modalities and feasible maximum number of target populations

Fixed point	
Description	HIV self-test (HIVST) kits distributed at pre-selected locations within local communities. Testing tents are set up near areas of congregation (eg. hostels, taverns and brothels); demonstration of HIVST kit use provided, HIVST kits are distributed to consenting clients. Clients can choose option of self-testing in the tent or can take kit home for private use. For clients screening positive on site, confirmatory testing conducted by a professional provider was offered on site.
Target population description	HIV- adults and undiagnosed HIV+ adults (assuming fixed point distribution will be concentrated in 5 largest metropolitan municipalities)
Feasible maximum number of people	~14 million[1]
Taxi ranks	
Description	Distribution of HIVST kits to commuters, taxi drivers and street vendors in densely populated taxi ranks and train stations, with high foot traffic. Distribution agents provided a demonstration of HIVST kit use and offered kits to interested clients for private use off site.
Target population description	Adults accessing taxis who are HIV negative or undiagnosed PLHIV
Feasible maximum number of people	~3.9 million[2]
Secondary PHC (ANC)	
Description	Women attending their first antenatal care (ANC) visit at a primary healthcare (PHC) clinic were offered HIVST kits, to take home to their current male sexual partner(s) – defined as secondary distribution.
Target population description	Women attending ANC care
Feasible maximum number of people	~1.2 million[3]
Secondary PHC (ART patients)	
Description	HIVST kits offered by to newly diagnosed and previously known HIV-positive clients at a PHC clinic to share with their sexual partner(s) or family members who were unaware of their HIV status.
Target population description	Adults on antiretroviral treatment (ART) + newly diagnosed HIV-positive adults
Feasible maximum number of people	~5.4 million[4]

Workplace	
Description	Workplace distribution was predominantly conducted in a number of male-dominated sectors such as manufacturing, mining, construction, security, petroleum and agriculture. Two types of workplaces included: a) Larger companies without formalised HIV testing programmes or those with low HIV testing uptake were contacted before the distribution event for sensitisation; b) Distribution also took place more ad-hoc and without prior arrangement with management to employees of smaller workplaces such as petrol stations or construction sites.
Target population description	Employed population
Feasible maximum number of people	~10 million[5]
Primary PHC	
Description	This modality involved primary distribution of HIVST for on-site screening of clients attending the clinic for different services including family planning and treatment for sexually transmitted infections.
Target population description	Existing patient population seeking conventional HTS at PHC
Feasible maximum number of people	~15 million[6]

Footnotes:

1. Statistics South Africa Mid-year Population Estimates 2020 in the five largest metro municipalities (City of Cape Town, Ekurhuleni, Johannesburg, Tshwane, eThekwini), combined with provincial-level Thembisa 4.3 estimates of % diagnosed and district-level HIV prevalence statistics from the Naomi model (https://www.hivdata.org.za/)
2. Estimated from worker and higher education population using minibus taxis (Statistics South Africa National Household Travel Survey 2013), combined with HIV prevalence and known diagnosis estimates from Thembisa 4.3
3. Estimates of women attending antenatal care in 2020 from Thembisa 4.3
4. Estimates of adult population on antiretroviral treatment and newly diagnosed HIV+ adults in 2020 from Thembisa 4.3
5. Estimates of employed population from Statistics South Africa. Statistical Release P0277. Quarterly Employment Statistics. December 2019.

Table S2. Unit costs used in the costing of the HIV programme

Intervention	Cost unit	Unit cost (2019 USD)
ART provision per adult (first line regimen, first year)	per person	299.15
ART provision per adult (first line regimen, follow-up years)	per person	196.48
ART provision per adult (second line regimen, follow-up years)	per person	323.64
ART provision per child (first year)	per person	322.39
ART provision per child (follow-up year)	per person	229.20
Early infant male circumcision	per person	43.24
Medical male circumcision (MMC)	per person	86.47
Condom provision (per condom distributed)	per condom	0.05
Prevention of mother-to-child transmission	per person	21.03
Conventional HTS: general (negative)	per test	3.75
Conventional HTS: general (positive)	per test	5.52
Conventional HTS: antenatal care (negative)	per test	3.26
Conventional HTS: antenatal care (positive)	per test	5.01
Conventional HTS: provider-initiated testing and counselling (negative)	per test	3.75
Conventional HTS: provider-initiated testing and counselling (positive)	per test	5.52
Conventional HTS: Mobile testing (negative)	per test	5.76
Conventional HTS: Mobile testing (positive)	per test	6.66
Conventional HTS: Home based testing (negative)	per test	5.76
Conventional HTS: Home based testing (positive)	per test	6.28
Conventional HTS: Partner notification (negative)	per test	3.41
Conventional HTS: Partner notification (positive)	per test	5.32
HIVST: fixed point	per test	5.70
HIVST: taxi ranks	per test	4.74
HIVST: partners of pregnant women	per test	13.04
HIVST: partners of ART patients	per test	12.31
HIVST: primary PHC	per test	8.24

Figure S1. A) number of HIV infections averted over the status quo, and B) incremental cost (2019 USD) per HIV infection averted; distributing up to 1 million HIVST distributed per year. Status quo distribution of 1 million HIVST kits: fixed point (5% of HIVST), taxi ranks (5%), secondary PHC (ANC) (7%), secondary PHC (ART patients) (3%), workplace (20%) and primary PHC distribution (60%).

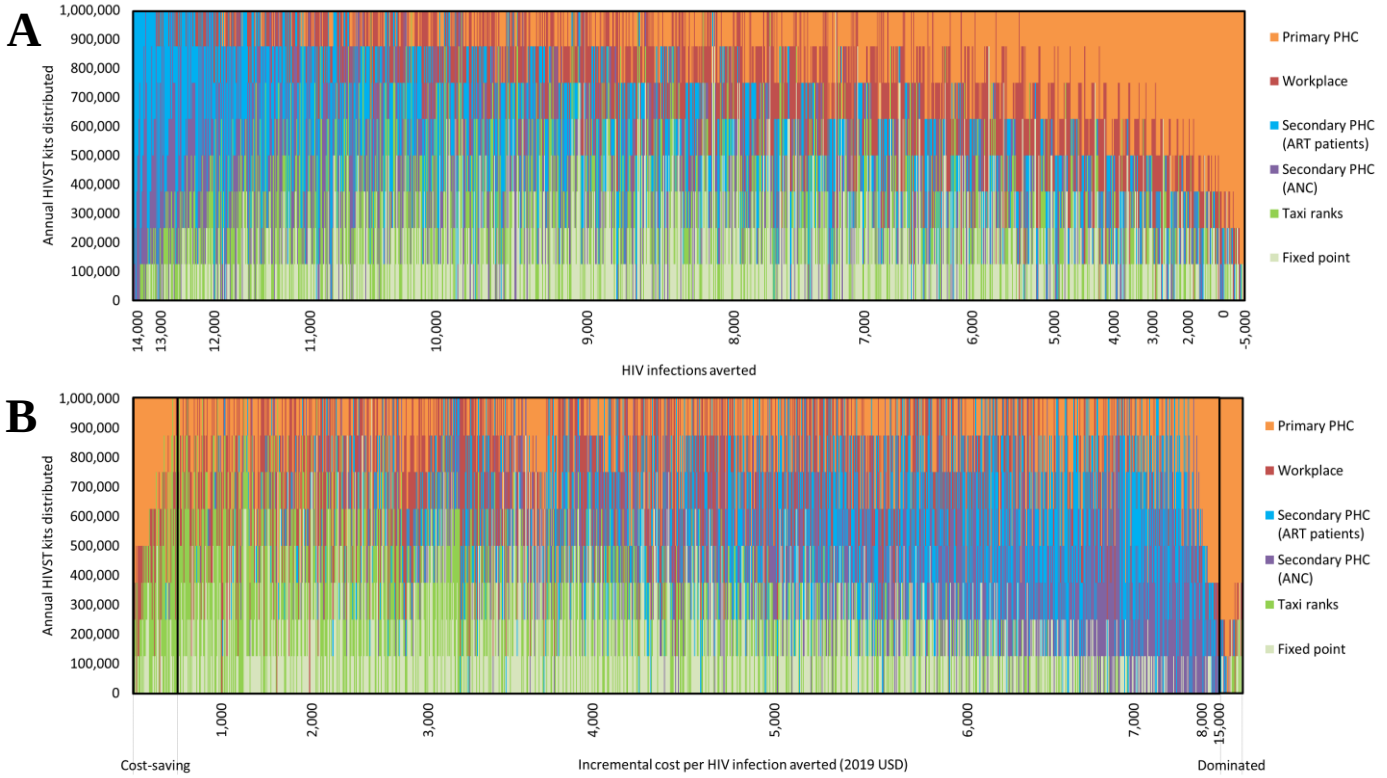


Figure S2. A) number of new HIV infections averted over the status quo, and B) incremental cost (2019 USD) per HIV averted; distributing up to ~6.7 million HIVST per year by 2030. Status quo distribution of 1 million HIVST kits: fixed point (5% of HIVST), taxi ranks (5%), secondary PHC (ANC) (7%), secondary PHC (ART patients) (3%), workplace (20%) and primary PHC distribution (60%)

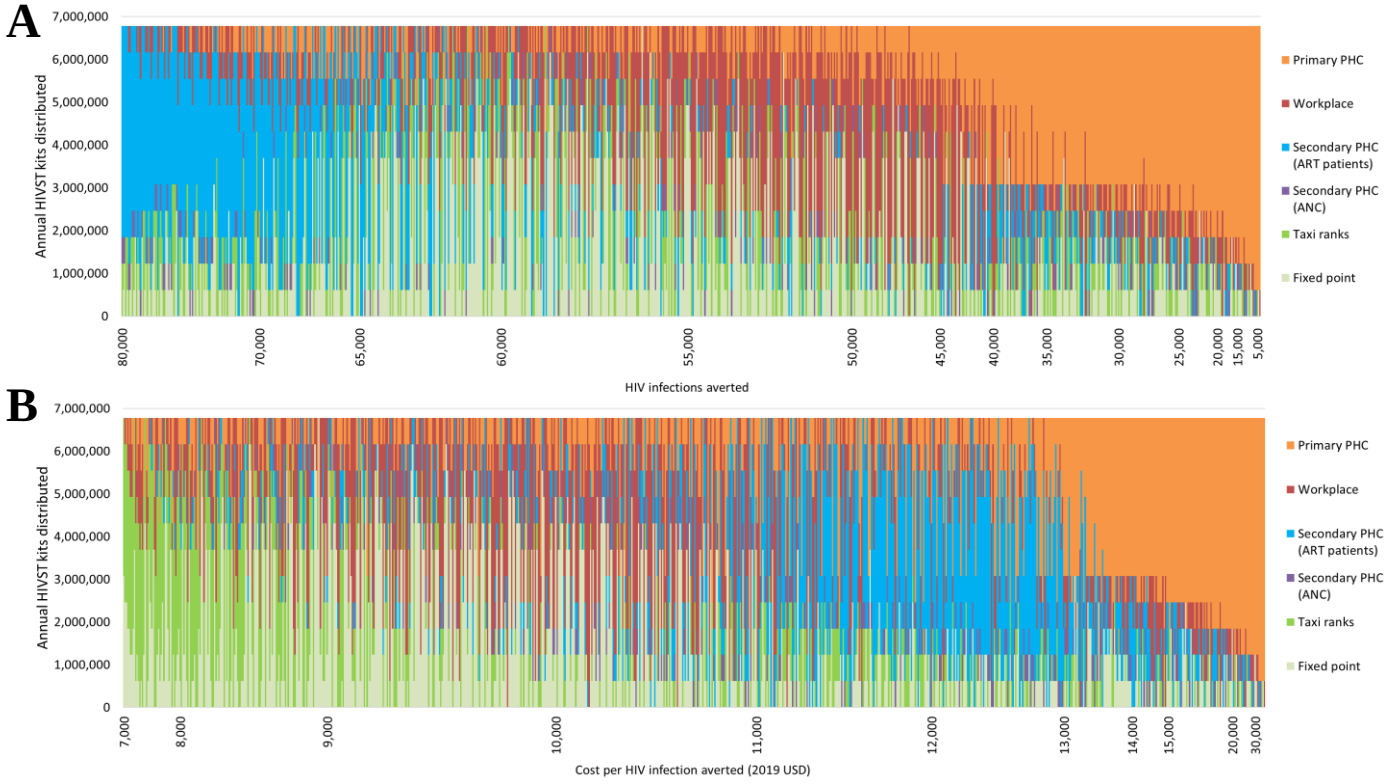


Figure S3. A) number of life years saved over baseline of no HIVST, and B) incremental cost (2019 USD) per life year saved; distributing up to 1 million HIV-ST distributed per year.

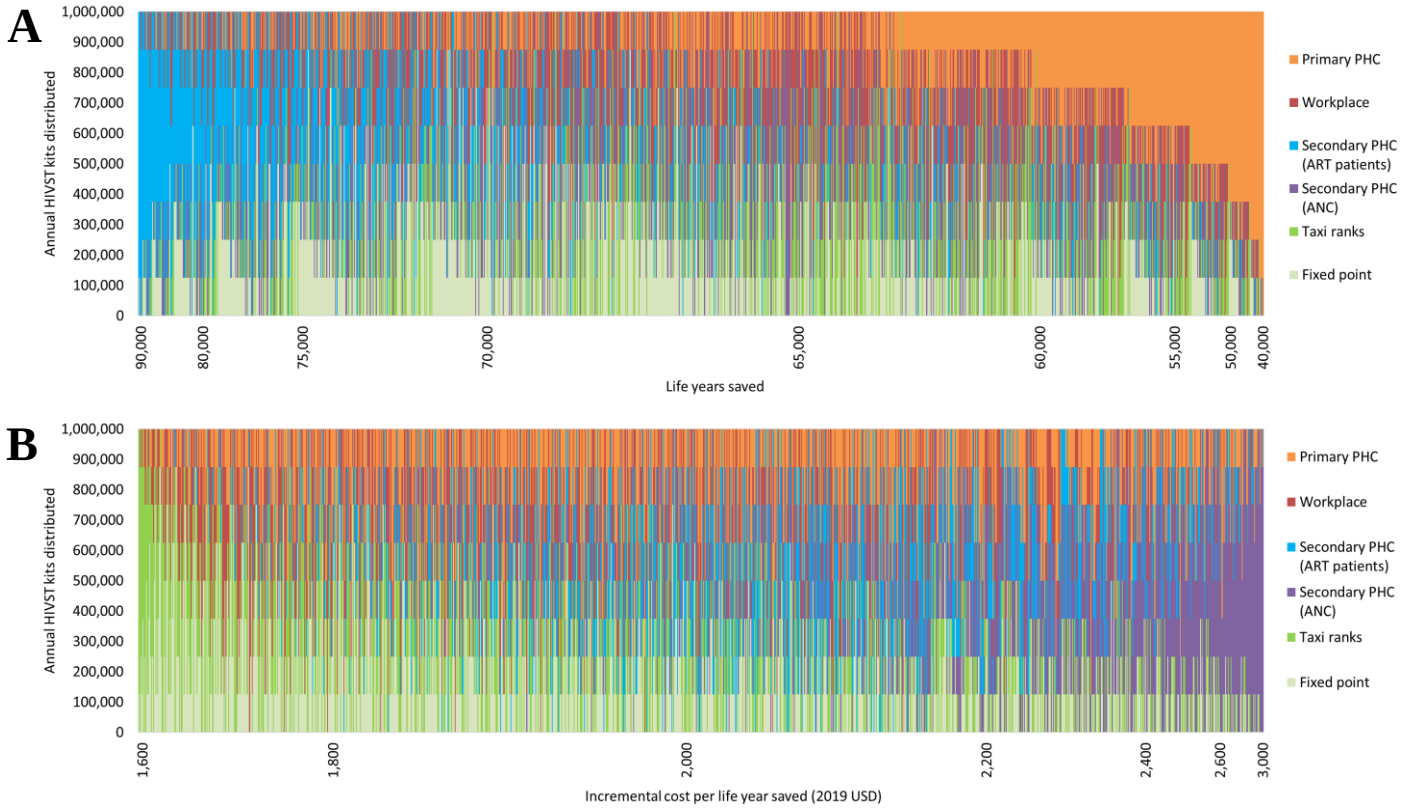
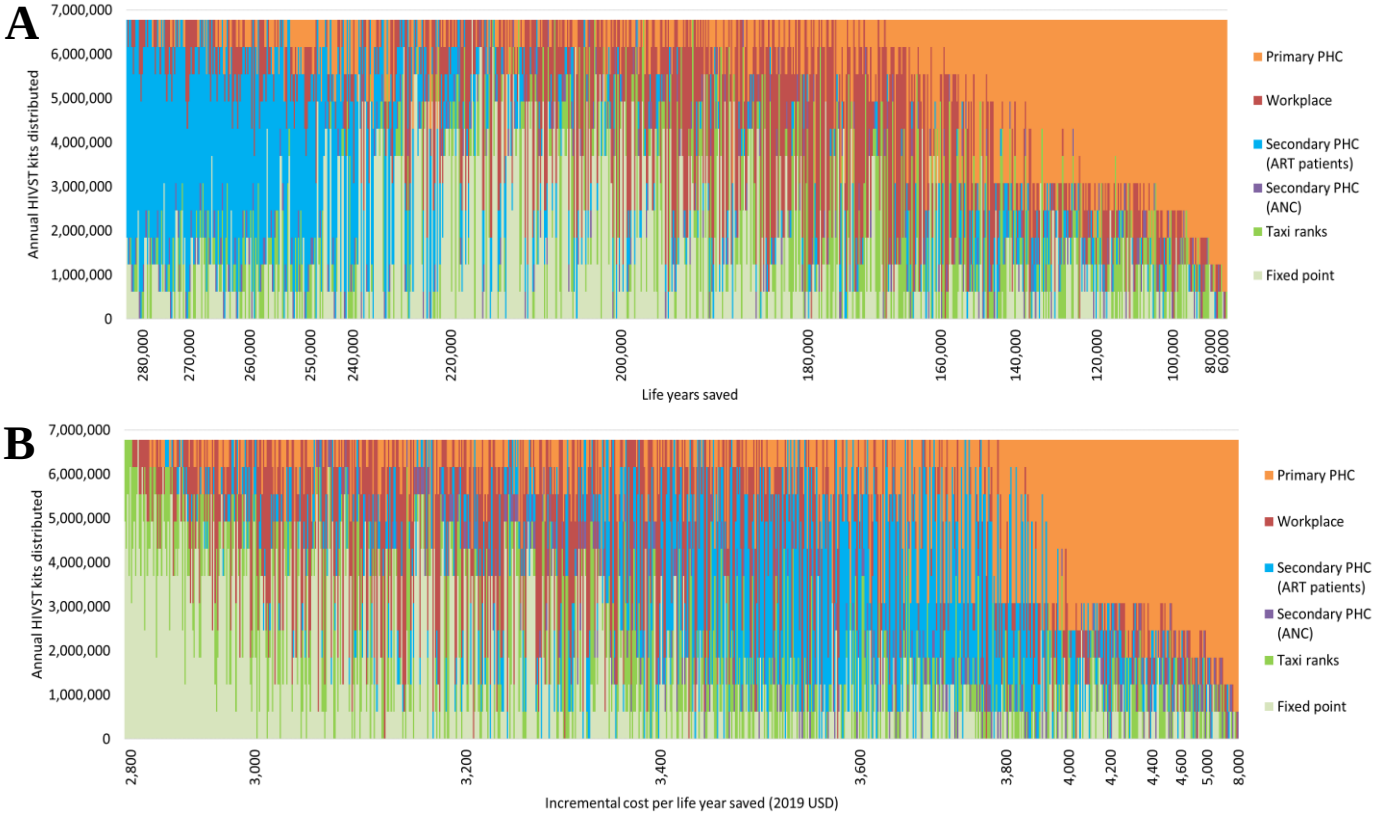


Figure S4. A) number of life years saved over baseline of no HIVST, and B) incremental cost (2019 USD) per life year saved; distributing up to ~6.7 million HIV-ST distributed per year.



Chapter 4

Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and 084 trials: a modelled economic evaluation and threshold analysis

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Summary

Background

Long-acting injectable cabotegravir (CAB-LA), a 2-monthly drug, has been shown to be more effective at preventing HIV infection than daily oral tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC), but its cost-effectiveness in a high-prevalence setting is not known. We estimated the incremental cost-effectiveness of CAB-LA compared to TDF/FTC in South Africa, using methods standard to government planning, and determined the threshold price at which CAB-LA is as cost-effective as TDF/FTC.

Methods

We updated a deterministic model of the South African HIV epidemic with data from the HPTN 083 and 084 trials to evaluate the impact of TDF/FTC and CAB-LA provision to heterosexual adolescents and young women and men, female sex workers, and men who have sex with men. We estimated the average intervention cost, in 2021 USD, using ingredients-based costing, and modelled the cost-effectiveness of two coverage scenarios (medium/high, assuming higher uptake of CAB-LA than TDF/FTC throughout) and, for CAB-LA, two duration sub-scenarios (minimum: same PrEP duration as for TDF/FTC; maximum: longer duration than TDF/FTC) over 2022-2041.

Findings

Across CAB-LA scenarios, 15%-28% of new HIV infections were averted over baseline (current TDF/FTC roll-out) compared to 5%-8% within oral TDF/FTC scenarios. If CAB-LA drug costs were equal to that of TDF/FTC for the same 2-month period, the incremental cost of CAB-LA to the HIV programme was higher than TDF/FTC (5%-14% vs 2%-4%) due to higher assumed uptake of CAB-LA. The cost per infection averted was $6,053-$6,610 (TDF/FTC) and $4,471-$6,785 (CAB-LA). The cost per CAB-LA needed to be less than twice that of a 2-month supply of TDF/FTC to remain as cost-effective, with threshold prices ranging between $9.03/injection (high coverage; maximum duration) and $14.47/injection (medium coverage; minimum duration).

Interpretation

CAB-LA is potentially game-changing for HIV prevention. However, for its implementation to be financially feasible across low- and middle-income countries with high HIV incidence, CAB-LA must be reasonably priced.

Research in context

Evidence before this study

Recent randomized controlled trials (HPTN 083 and HPTN 084) of long-acting injectable cabotegravir (CAB-LA) have found superior effectiveness in preventing HIV acquisition in high risk populations compared to the standard-of-care oral PrEP combination drug tenofovir disoproxil fumarate/ emtricitabine (TDF/FTC). These trials found a risk reduction of 66% in risk in men who have sex with men, transgender women and 89% in young women, compared to oral PrEP. Searching PubMed for (cabotegravir OR rilpivirine) AND injectable AND (prophylaxis OR PrEP OR prevention OR acceptability OR preference) AND (HIV OR human immunodeficiency virus), we found five modelling studies that have evaluated the longer-term impact and/or cost-effectiveness of the provision of CAB-LA as prevention in South Africa, and found it to be cost-effective if targeted towards high-risk individuals. Two additional studies found CAB-LA to be less cost-effective than oral PrEP and concluded that novel financing mechanisms may be required in order to make implementation cost-effective. Between the manufacturer and international organisations, the currently discussed feasible minimum price of CAB-LA for HIV programmes in high-burden, low-resource countries ranges from $16 (excluding capital expenditure) to $270 per patient year on PrEP.

Added value of this study

The introduction of new interventions requires careful consideration of cost as well as impact, especially in resource-limited settings. We estimated the impact and cost-effectiveness of the 2-monthly injectable CAB-LA compared to daily oral TDF/FTC in South Africa, and found it to have a 3-fold higher impact on HIV infections and AIDS deaths compared to TDF/FTC. A threshold analysis estimated the cost per CAB-LA injection would need to be between $9.03 and $14.47 for it to be similarly or more cost-effective compared to daily oral TDF/FTC, and hence acceptable to the South African

government, the main funder of the South African HIV programme. This would place the cost of CAB-LA is between 1 to 2-times that of the current price for TDF/FTC in South Africa, with an upper limit of $101.29/year, approximately 5% of the current list price in the United States.

Implications of all available evidence

Our findings are timely and relevant to the decision-making process of low- and middle-income country (LMIC) governments and donor agencies contemplating whether, and how quickly, to replace or augment oral PrEP by CAB-LA. While CAB-LA has the potential to be a game-changer for HIV prevention, for large scale implementation in high-prevalence settings it would first need to be affordable in these settings, and this will require a multi-partner effort.

Introduction

South Africa has an estimated 7.8 million people living with HIV (PLHIV) and an HIV incidence of 7.79 per 1000 population in 2019 (101). Oral pre-exposure prophylaxis (PrEP) with the combination drug tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) has been shown to be effective in preventing HIV acquisition (34,35), but there are concerns about low adherence and persistent use in many settings, including South Africa (35). In 2015, WHO recommended that oral PrEP be made available to people at substantial risk of acquiring HIV, followed soon thereafter by South African guidelines (132). Since then, new generations of long-acting PrEP have been in development. Most recently, clinical trials (HPTN 083, HPTN 084) conducted across America and sub-Saharan Africa have shown long-acting injectable cabotegravir (CAB-LA) to be highly effective in preventing HIV infection, reducing the risk of HIV acquisition by 66% (95% confidence interval (CI) 38%-82%) in men who have sex with men (MSM) and transgender women, and by 89% (95%CI 68%-96%) in young women, compared to oral TDF/FTC over 12 months (36,37). The latter results have recently been confirmed over a 24-month time period (38). In 2021, the United States Food and Drug Administration (FDA) approved CAB-LA for use in high-risk populations, and in July 2022, WHO recommended it for use in populations at substantial HIV acquisition risk (39). Long-acting injectable products offer an adherence advantage over daily pill taking (133), and across high-risk populations, acceptability studies have shown a strong stated preference for injectable products over oral formulations (134–136). Long-term effective use however will require the user to maintain a 2-monthly visit schedule.

Introducing new drugs require careful consideration of cost, cost-effectiveness, and affordability, especially in countries with severely limited resources. There have been limited studies on the cost and impact of injectable PrEP in sub-Saharan Africa, and only two studies comparing injectable to oral PrEP (66,137–140). Previous modelling studies focussing on South Africa have found that CAB-LA would lead to a substantial reduction of new HIV infections over no PrEP (66,137,138). Of studies evaluating cost-effectiveness; one finding a risk-prioritized strategy cost-effective over 10 years under a threshold of 3x gross domestic product, compared to no PrEP (66); another study finding injectable CAB-LA cost-effective at a price of

<$16/year over 40 years under an arbitrary threshold of <$519/disability-adjusted life year averted (138). Another two modelling studies found injectable PrEP to be less cost-effective than oral PrEP, and concluded that it may require novel financing mechanisms to be implemented (139,140). These analyses were however conducted prior to CAB-LA's effectiveness being known. Discussions of an acceptable price level for high-burden, low-resource countries range between $16-$20 per person year excluding capital expenditure estimated by the Clinton Health Action Initiative based on the costs of producing injectable contraceptives at scale in SSA, and the $240-$270 not-for-profit price considered by the manufacturer. We estimated the impact and cost-effectiveness of 2-monthly injectable CAB-LA compared to daily oral TDF/FTC in South Africa and the threshold cost that would make CAB-LA similarly or more cost-effective compared to TDF/FTC. The South African government base their decisions on affordability and impact rather than a defined cost-effectiveness threshold; in keeping with this, we establish the cost-effectiveness of novel interventions through comparison with that of already-funded interventions with a similar target population, using standard methodology developed for the annual South African HIV Investment Case which is central to HIV programme planning in South Africa (89).

Methods

Epidemiological model

The impact of TDF/FTC and CAB-LA on the HIV epidemic was estimated using Thembisa (version 4.4), a deterministic compartmental HIV transmission model of the South African HIV epidemic (45). The model population is stratified by age, sex, sexual experience, sexual behaviour, marital status, HIV testing history and male circumcision status. The sexually experienced population is divided into two broad sexual risk groups: 'high-risk' (people with a propensity for concurrent partnerships and/or commercial sex) and 'low-risk', with the high-risk group comprising 35% of males and 25% of females. PrEP uptake rates vary by age, sex and risk group. It is assumed that PrEP users have a 10% lower rate of condom use than individuals of the same age and sex who are not using PrEP. Individuals who acquire HIV while on PrEP are assumed to be less likely to transmit HIV than individuals who acquire HIV in the absence of regular HIV testing, as the latter individuals would remain undiagnosed and untreated for longer periods.

TDF/FTC effectiveness, accounting for both efficacy and adherence, is assumed to be 85% for adolescent boys and young men (ABYM) and MSM, and 65% for adolescent girls and young women (AGYW) and female sex workers (FSW) (34,35). Because CAB-LA was trialled against TDF/FTC as a control group, we estimate its effectiveness compared to no PrEP by modifying the trial results, which yields an approximate estimate of 95% effectiveness for CAB-LA (i.e. 0.95 = 1-(1-0.85) x (1-0.66) for MSM; 0.96 = 1-(1-0.65) x (1-0.89) for young women) (36,37). More detail on the epidemiological model, including sources for the main assumptions, are presented in the supplementary material.

Since this study did not include primary human subjects data, no ethical clearance was sought. No health economic analysis plan was developed.

Scenarios and assumptions

We modelled the epidemiological impact over a 20-year time horizon (2022-2041) separately for TDF/FTC and CAB-LA including as target populations FSW, MSM, AGYW (aged 15-24 years), and heterosexual ABYM (aged 15-24 years). We assumed two coverage levels for scaling up each PrEP technology for each population (high and medium coverage), assuming a higher uptake by CAB-LA users, based on studies showing a higher stated preference for injectable products compared to TDF/FTC (136,141,142). PrEP coverage was assumed to increase linearly over a 3-year period. Based on South African PrEP implementation programme data (45), TDF/FTC coverage is assumed to be low (between 0.5% and 3% of the relevant target populations), and the average duration on TDF/FTC is assumed to be 5 months for AGYW and ABYM, and 11 months for MSM, and there is no TDF/FTC uptake in CAB-LA scenarios. We assume that 1-month supply of TDF/FTC at last visit will provide an additional month of protection. For CAB-LA the average duration in the programme was modelled under two sub-scenarios: 1) minimum duration scenario, in which users remain in the programme for a similar time as they would on TDF/FTC; 2) maximum duration scenario, in which users remain on PrEP for longer, i.e. 12 months (AGYW, ABYM) or 24 months (MSM). While annual PrEP initiation rates for the TDF/FTC and CAB-LA minimum duration scenario are based on the assumed coverage for each population, the initiation rates for the CAB-LA maximum duration scenario are fixed to the same rates as the CAB-LA minimum duration scenario, but with longer duration in the PrEP programme

(resulting in higher coverage than in the minimum duration scenario). Key assumptions and scenarios are summarised in Table 1.

Cost and cost-effectiveness

Costs were analysed from the perspective of the provider, the South African government, and reported in 2021 United States dollar (USD), using the average exchange rate of Jan-Oct 2021 (14.61 South African rand = 1 USD) (118). The average cost of PrEP provision was estimated using an ingredients-based approach; the full methodology has been described elsewhere (143). Briefly, PrEP is provided in primary healthcare clinics and includes rapid HIV testing, counselling, provision of condoms, syndromic screening for sexually transmitted infections (STI) with treatment referral, adherence counselling, as well as training, outreach, mobilisation, monitoring and evaluation costs. We varied costs between the first versus follow-up years (where applicable) and populations, capturing differences in HIV and STI prevalence and need for pregnancy tests.

As CAB-LA is not currently available in South Africa, the cost of CAB-LA provision was structured using similar methodology and adjusted by increasing professional nurse time for the injection administration and removing creatinine testing (required for TDF-based PrEP only). We allowed for an oral CAB lead-in, assuming 20% of those who initiate into the programme will opt to start with oral cabotegravir for the first month. The cost structure of CAB-LA provision is presented in the supplementary material (Table S1). Since the cost of the drug in the public healthcare sector is currently unknown, we varied the price of CAB-LA between 1-to-5-fold the 2-monthly price of oral TDF/FTC. Finally, we solve for the optimal price at which CAB-LA is as cost-effective as TDF/FTC. The costs of TDF/FTC and CAB-LA provision for all scenarios are summarised in Table 2.

Table 1. Key modelling assumptions on coverage, duration and effectiveness, coverage of CAB-LA and TDF/FTC scenarios

	Baseline (TDF/FTC only)	TDF/FTC	CAB-LA minimum duration	CAB-LA maximum duration	Source
Coverage scenarios, % coverage in population					
Baseline coverage	3% (FSW); 1% (MSM); 0.5% (AGYW); 0% (ABYM)	-	-	-	TDF/FTC: PrEP implementation data from South African National Department of Health
High coverage	-	30% (FSW, MSM); 10% (AGYW); 10% (ABYM)	50% (FSW, MSM); 40% (AGYW); 20% (ABYM)	67% (FSW, MSM) 60% (AGYW) 35% (ABYM)	TDF/FTC: PrEP implementation data from South African National Department of Health. CAB-LA: informed by acceptability and preference studies (136,141,142)
Medium coverage	-	15% (FSW, MSM); 5% (AGYW); 5% (ABYM)	25% (FSW, MSM); 20% (AGYW); 10% (ABYM)	40% (FSW, MSM); 35% (AGYW); 20% (ABYM)	
Duration in PrEP programme (in months)	5 (FSW, AGYW, ABYM); 11 (MSM)	5 (FSW, AGYW, ABYM); 11 (MSM)	5 (FSW, AGYW, ABYM); 11 (MSM)	12 (FSW, AGYW, ABYM); 24 (MSM)	TDF/FTC: Johnson(45) Long-acting injectable cabotegravir: assumed values
Additional protection since last visit in PrEP programme	+1 month (all populations)	+1 month (all populations)	+3 months (all populations)	+3 months (all populations)	TDF/FTC: assumed values. CAB-LA: Landovitz and colleagues (144)
Total protection duration (in months)	6 (FSW, AGYW,	6 (FSW, AGYW, ABYM);	8 (FSW, AGYW, ABYM); 14 (MSM)	15 (FSW, AGYW, ABYM);	Values estimated from duration in PrEP programme plus additional protection

	Baseline (TDF/FTC only)	TDF/FTC	CAB-LA minimum duration	CAB-LA maximum duration	Source
	ABYM); 12 (MSM)	12 (MSM)		27 (MSM)	
Effectiveness	65% (FSW, AGYW); 85% (ABYM, MSM)	65% (FSW, AGYW); 85% (ABYM, MSM)	95% (all populations)	95% (all populations)	Tenofovir disoproxil fumarate and emtricitabine: Fonner and colleagues (35), Molina and colleagues (63), and McCormack and colleagues (62). Long-acting injectable cabotegravir: Delany-Moretlwe and colleagues (37) and Landovitz and colleagues (36)

Table 2. Average cost of TDF/FTC and CAB-LA provision per person initiated* across scenarios and target populations (2021 USD)

	Female sex workers	Adolescent girls and young women	Heterosexual men	Men who have sex with men (first year)	Men who have sex with men (follow-up year)
TDF/FTC					
Total cost	**78**	**77**	**76**	**116**	**N/A**
Drugs	28 (36%)	28 (37%)	28 (37%)	56 (49%)	N/A
Labs	16 (21%)	16 (21%)	15 (20%)	15 (13%)	N/A
Consumables	3 (3%)	2 (3%)	2 (3%)	4 (4%)	N/A
Staff	23 (29%)	22 (29%)	22 (29%)	29 (25%)	N/A
Overheads	9 (11%)	8 (11%)	8 (11%)	11 (9%)	N/A
CAB-LA minimum duration					
Total cost	**81**	**80**	**78**	**122**	**N/A**
Drugs	37 (45%)	37 (46%)	37 (47%)	65 (53%)	N/A
Labs	10 (12%)	9 (12%)	8 (11%)	9 (8%)	N/A
Consumables	1 (1%)	1 (1%)	1 (1%)	1 (1%)	N/A
Staff	29 (36%)	28 (36%)	28 (36%)	39 (32%)	N/A
Overheads	5 (6%)	5 (6%)	5 (6%)	7 (6%)	N/A
CAB-LA maximum duration					
Total cost	**137**	**137**	**134**	**131**	**105**
Drugs	67 (49%)	67 (49%)	67 (50%)	67 (51%)	56 (54%)
Labs	15 (11%)	16 (12%)	14 (10%)	11 (8%)	6 (5%)
Consumables	2 (1%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)
Staff	46 (33%)	44 (32%)	44 (33%)	44 (34%)	35 (34%)
Overheads	8 (6%)	8 (6%)	8 (6%)	8 (6%)	6 (6%)

Totals may not add up to the sum of the subcomponents due to rounding of all figures to the nearest $1. All values are in 2021 US dollars ($). NA=not applicable. *Duration in the pre-exposure prophylaxis programme differed by population, intervention (tenofovir disoproxil fumarate and emtricitabine or long-acting injectable cabotegravir), and scenario: tenofovir disoproxil fumarate and emtricitabine and long-acting injectable cabotegravir minimum duration scenarios (5 months for adolescent girls, young women, female sex workers, and heterosexual men; 11 months for men who have sex with men); long-acting injectable cabotegravir maximum duration scenarios (12 months for adolescent girls, young women, female sex workers, and heterosexual men; 24 months for men who have sex with men).

We analysed cost-effectiveness over a 20-year time horizon (2022-2041), over a baseline of currently available HIV interventions in South Africa, including the current TDF/FTC programme, high coverages for condom provision, HIV testing services, and medical male circumcision. This allowed us to ascertain the impact of a reduction in HIV incidence on the need for subsequent ART, in addition to existing prevention interventions. The estimation of HIV programme costs followed the same approach as the South

African HIV Investment Case (89). We report on cost effectiveness as cost per HIV infection averted and per life year saved, the metrics most relevant to the decision space of the South African government, in line with the principles of the International Decision Support Initiative (iDSI) reference case for economic evaluation (145). In order to facilitate the use of the results in informing government budgets and an acceptable threshold price for CAB-LA for use in the South African government's negotiations with manufacturers, costs and effects were presented undiscounted over the period modelled.

Sensitivity analysis

We reproduced the main analysis with four modifications: 1) an injection schedule of every 3 months instead of every 2 months for CAB-LA, based on pharmacokinetic data suggesting that longer protection is feasible (144), 2) assuming CAB-LA coverage would be the same as that of TDF/FTC scenarios, 3) testing different discount rates (3%, 4.75% and 6%, instead of 0%), and 4) assuming PCR testing in the HIV diagnostic algorithm. Further, we evaluated the impact of the uncertainty around the following additional key model parameters on the results: intervention effectiveness for both TDF/FTC and CAB-LA, reduction in condom use while on PrEP, annual initiation rate for TDF/FTC, relative annual initiation rate for CAB-LA (to ensure a value consistently higher than the corresponding TDF/FTC scenario), relative rate of PrEP initiation in low-risk heterosexuals, and non-drug costs. To do this we conducted a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation with 1,000 model runs, sampling values from predetermined distributions for each model run (Table S2). We fixed the cost of the CAB-LA drug at 2x the cost of the TDF/FTC drug for this analysis and report median estimates, 2.5th and 97.5th percentiles, and partial rank correlation coefficients quantifying the sensitivity of central model results to changes in these parameters.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Across scenarios, CAB-LA had a large impact on new HIV infections in South Africa, with up to 52,000 infections averted/year over baseline in the high coverage, maximum duration scenario, 42,800 infections averted/year (high coverage, minimum duration), 35,600 infections averted (medium coverage, maximum duration), 26,400 infections averted/year (medium coverage, minimum duration)- a reduction of between 15%-28% of infections over 20 years (Figure 1A). TDF/FTC averted 16,300-9,000 infections annually in high and medium coverage scenarios, respectively, an overall reduction of 4-8% of infections over 20 years. From 2030, HIV infections averted decreased in all CAB-LA scenarios, indicating intervention saturation in the context of declining HIV incidence. HIV incidence was projected to decrease to 0.17% in 2041 at baseline (Figure 1B). CAB-LA reduced incidence to between 0.10% (high coverage, maximum duration) to 0.13% (medium coverage, minimum duration) by 2041, while under the TDF/FTC scenarios HIV incidence declined to 0.14% (high coverage) and 0.16% (medium coverage) by 2041.

CAB-LA was projected to avert between 21,500 (2%) and 43,400 (4%) of AIDS deaths, while TDF/FTC reduced AIDS deaths by 12,400 (1.2%) (high coverage) and 6,500 (0.6%) (medium coverage) over the same time horizon (Figure 1C). Additionally, CAB-LA saved between 57,600 (medium coverage, minimum duration) and 115,700 (high coverage, maximum duration) life years on average per year, while TDF/FTC saved between 32,700 (high coverage) and 17,000 (medium coverage) (Figure 1D), and a 4%-8% reduction in the number of people on ART by 2041 in the CAB-LA scenarios over baseline, compared to a 1%-2% reduction for the TDF/FTC scenarios- a relative 3-to-5-fold reduction due to CAB-LA compared to TDF/FTC (Figure 2A). Though the reduction in ART need will result in a reduction in HIV programme cost, the incremental cost of providing TDF/FTC or CAB-LA at the assumed coverage levels will be more than the savings from the reduction in ART within the next 20 years, increasing total programme cost by 5% (medium coverage) and 10% (high coverage) under CAB-LA, or 2% (medium coverage) and 4% (high coverage) under TDF/FTC (Figure 2B, Table S3). The proportion of the total cost of the HIV programme spent on HIV prevention would be 5% under the baseline scenario, increasing to 8%-10% under TDF/FTC scale-up, and to 11%-14% (medium coverage),

and 17%-20% (high coverage) under CAB-LA, which would further increase at higher prices of CAB-LA (Table S3)- still lower than the UNAIDS recommended 25% to be spent on prevention (146).

Under increased TDF/FTC, the incremental cost-effectiveness ratio (ICER) was $2,309/life year saved (medium coverage) and $2,498/life year saved (high coverage). For CAB-LA to remain as cost-effective as TDF/FTC, the cost of the drug would need to be between 1- and 2-fold that of TDF/FTC (2 months' supply). We estimate the threshold price for CAB-LA per injection to be between $9.03 (CAB-LA high coverage, maximum duration) to $14.47 (CAB-LA medium coverage, minimum duration) if it was to remain as cost-effective as TDF/FTC (Table S4).

The cost-threshold and, hence, acceptable price level for CAB-LA would remain similar if it was administered 3-monthly rather than 2-monthly (Table S5), or had the same coverage as TDF/FTC (though a higher price could be accepted under the minimum duration scenario due to increased effectiveness alone, Table S6), and in discounted analyses (Tables S7-S9). Including PCR testing in the HIV testing algorithm would increase its implementation cost by approximately 60% (annual PCR testing) or approximately 160% (PCR testing every 2 months) and reduce the threshold price to $0.49–6.14 per injection (5–65% of TDF/FTC cost) (Table S10). When accounting for uncertainty, the median HIV infections averted over the 20-year time horizon, compared to baseline, was 238,000 (15,600-400,000) for TDF/FTC, 472,300 (46,700-734,800) for CAB-LA (minimum duration) and 614,000 (81,800-873,700) for CAB-LA (maximum duration) (Table S11). Even under the assumption that the cost of the CAB-LA injectable was 2-fold that of TDF/FTC, 25% and 14% of simulations under the CAB-LA minimum and maximum duration scenarios, respectively, were more cost-effective than the corresponding TDF/FTC simulation (Figure S1), with the 95% confidence interval of the cost threshold price for CAB-LA per injection ranging between $8.80 to $30.80 (Figure S2). Cost per HIV infection averted was most sensitive to PrEP efficacy, relative rate of PrEP uptake by those at low risk of HIV, PrEP initiation rates and the non-drug costs of PrEP provision, while HIV infections averted were most sensitive to PrEP initiation rates and PrEP efficacy (Table S12).

Table 3. Impact and cost-effectiveness of CAB-LA compared to baseline* and oral TDF/FTC compared to baseline, over a 20-year time horizon (2022-41)

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			41.29			
Medium PrEP coverage									
TDF/FTC	2·89	4%	37·00	1%	N/A	42·08	2%	6,053	2,309
CAB-LA minimum duration	2·58	15%	36·19	3%	1x	43·25	5%	4,471	1,705
					2x	44·46	8%	7,211	2,751
					3x	45·66	11%	9,952	3,796
					4x	46·86	13%	12,692	4,842
					5x	48·07	16%	15,433	5,887
CAB-LA maximum duration	2·44	19%	35·81	4%	1x	44·31	7%	5,157	1,978
					2x	46·24	12%	8,447	3,240
					3x	48·16	17%	11,737	4,501
					4x	50·09	21%	15,027	5,763
					5x	52·02	26%	18,317	7,025
High PrEP coverage									
TDF/FTC	2·78	8%	36·68	2%	N/A	42·92	4%	6,610	2,498
CAB-LA minimum duration	2·31	24%	35·41	5%	1x	45·42	10%	5,779	2,145
					2x	47·83	16%	9,147	3,394
					3x	50·24	22%	12,515	4,644

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
					4x	52·64	27%	15,882	5,894
					5x	55·05	33%	19,250	7,144
CAB-LA maximum duration	2·17	28%	35·03	6%	1x	47·10	14%	6,785	2,510
					2x	50·63	23%	10,915	4,038
					3x	54·16	31%	15,045	5,566
					4x	57·70	40%	19,175	7,094
					5x	61·23	48%	23,305	8,622

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population). † Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).

Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Figure 1. Impact of long acting injectable cabotegravir (CAB-LA) and oral PrEP (TDF/FTC) on HIV infections and deaths, 2022–41

Annual (A) HIV infections averted, (B) population HIV incidence, (C) AIDS deaths averted and (D) life years saved over baseline (total population size over time horizon = ~60–73 million). CAB-LA and TDF/are modelled under two coverage scenarios (high and medium); CAB-LA is additionally modelled under both a minimum and maximum duration scenario, described in Table 1.

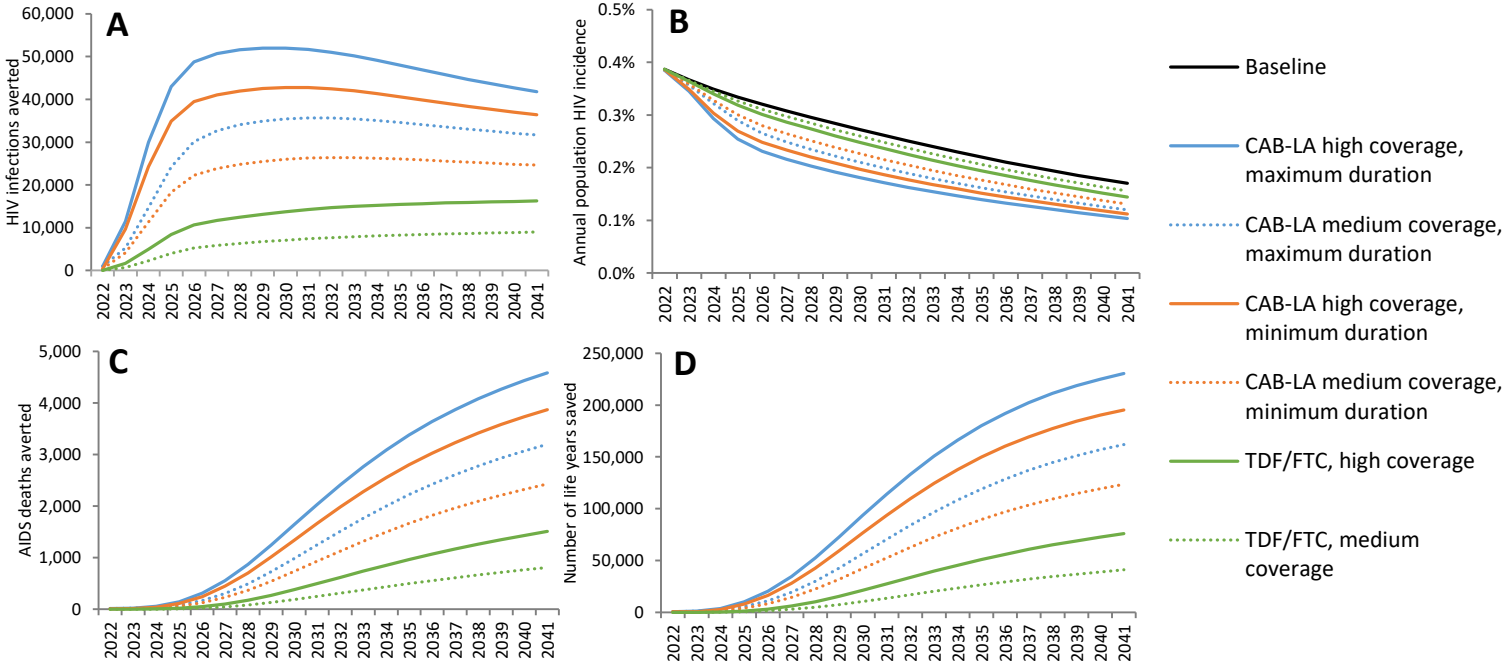
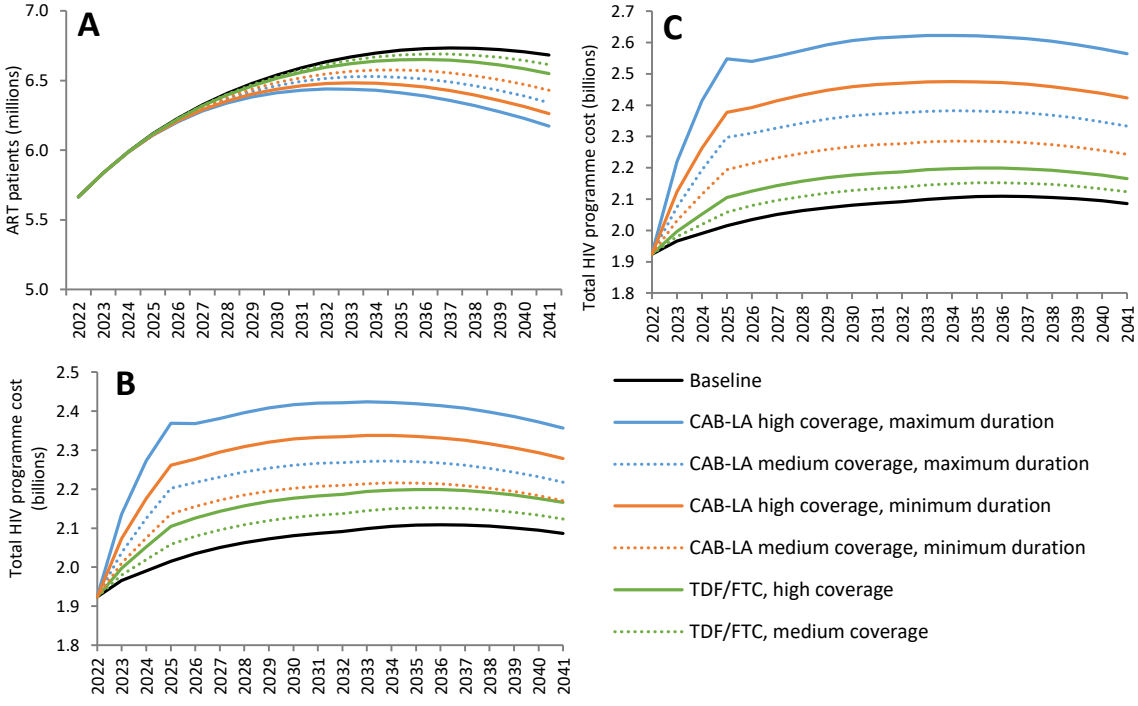


Figure 2. Impact of long acting injectable cabotegravir (CAB-LA) and oral PrEP (TDF/FTC) on patients on ART and HIV programme cost, 2022–41

Annual (A) total patients on antiretroviral treatment (ART) (millions) and total HIV programme cost (billions 2021 USD) if CAB-LA drug price was (B) 1x and (C) 2x that of TDF/FTC



Discussion

Our analysis used a well-validated model of the South African HIV epidemic to show that CAB-LA could avert three times more new HIV infections and save three times more life years over 20 years compared to TDF/FTC under a range of different scenarios. This estimated impact of CAB-LA on HIV infections is similar to other modelling studies (66,137,138). With a higher assumed uptake, the incremental cost of CAB-LA to the HIV programme is likely to be more than that of further scaling up TDF/FTC. Our threshold analysis determined that for our given coverage and duration assumptions, the cost of CAB-LA would need to be between $9.03/injection ($63/year) and $14.47 ($101.29/year) to be as cost-effective as TDF/FTC, with a wider range once uncertainty was factored in ($8.80-$30.80). A strength of our analysis is the certainty around injectable PrEP effectiveness, as previous modelling, conducted prior to the release of trial results (36,37), still incorporated substantial uncertainty. Second, our analysis comprehensively modelled the full cost of the South African HIV response, comprehensively assessing the cost savings associated with more effective PrEP.

It is important to note that the cost of the fixed-dose combination drug TDF/FTC in South Africa is low, at $4.70/month, or $56.39/year for the drug alone, mostly due to the fact that TDF/FTC is a generic formulation and part of first-line ART in the world's largest ART programme, allowing for a significant cost reduction. In contrast, CAB-LA as a recently developed drug is protected under patent laws until 2031 and currently sold at $22,200/year in the US, more than 200-fold the threshold price identified in this analysis (147). Even given the uncertainty in our analysis, it is clear that unless dramatic price reductions take hold, CAB-LA will likely not be an option for HIV prevention for those at highest risk of HIV in LMIC. Options for these reductions include the recently agreed voluntary licenses through the Medicines Patent Pool, a buy-down similar to that establishing a market for HIV self-testing, or a combination of these factors- but given that both depend on the availability of a fairly large target market, additional financial support for implementation and demand creation might be required in order to scale the intervention up quickly enough so that impacts as large as we projected can take hold.

There are several limitations to this analysis. First, though we have programme data on the uptake of TDF/FTC, the real-world uptake of CAB-LA is unknown until it is implemented widely. We assumed uptake of CAB-LA would be higher than that of TDF/FTC in our main analysis and sensitivity analyses, based on acceptability and preference studies (136,141,142); however these may not necessarily translate into real-world choices. Nevertheless, CAB-LA has been shown to be significantly more effective in preventing HIV infection compared to TDF/FTC (38), and if CAB-LA uptake remains at current levels of TDF/FTC uptake, we can still expect large impacts on averting HIV infections. Similarly, duration of effective use of CAB-LA is also unknown, however we consider it a reasonable assumption that duration on CAB-LA would at a minimum be the same as that of TDF/FTC. Second, in the absence of bottom-up cost data, we used an ingredients-based approach to cost PrEP provision. While this could have under- or overestimated the incremental cost required, the cost-of-service provision in a national roll-out would be likely similar between these interventions, with drug cost being the main difference. We also assumed rapid HIV testing across both TDF/FTC and CAB-LA programmes; a change in the diagnostic approach to include polymerase chain reaction (PCR) testing in the CAB-LA programme, to sufficiently detect the presence of virus suppressed by CAB-LA (148), would increase its implementation cost by ~60% (annual PCR testing) or ~160% (2-monthly PCR testing) and reduce the threshold price to $0.49-$6.14/injection (5%-65% of TDF/FTC cost). Third, we modelled PrEP provision to different populations and assumed the relative uptake between these groups to remain constant across scenarios. While selectively targeting particular sub-populations may be more cost-effective, we do expect the same higher uptake in AGYW, FSW and MSM as in the current TDF/FTC programme. In particular, young women already using the widely accepted injectable contraceptives might find CAB-LA more attractive than other groups (149). Fourth, in our current model framework we are not able to model the effect of both TDF/FTC and CAB-LA simultaneously, when in reality there might well be a mix between these two (and future) PrEP technologies. Typically, with each added modality, total demand increases, as seen with other products such as contraceptives for women (150). However, the purpose of our analysis was to determine the price threshold for CAB-LA relative to TDF/FTC, for which an analysis including both modalities was not required. Fifth, adherence to injectable PrEP might be different from that in a clinical trial setting, and this may

compromise effectiveness. Further data on the effectiveness of injectable PrEP in the pharmacokinetic 'tail' after cessation of injections phase will be required in order to model realistically the consequences of such adherence challenges. Finally, a concern could be the potential for an increased risk of drug resistance from acquired infection after stopping the injectable as compared to oral PrEP, because of the longer tail-phase. Given widespread use of dolutegravir-based ART regimens, this could undermine the effectiveness of ART (151). Allowing for such reductions in ART efficacy in our model would offset the cost savings associated with injectable PrEP as more individuals would require more expensive second-line treatment, thus lowering the cost threshold required to achieve similar cost-effectiveness to oral PrEP. CAB-LA studies to date have not observed drug resistance arising specifically during the tail-phase (36,37,148,152); however, this could be a potential, though likely rare, concern in future with higher uptake of CAB-LA.

Though we show CAB-LA to be superior in its impact on the HIV epidemic in South Africa, the budget impact could be significantly more than TDF/FTC if there is a higher uptake, especially if the drug cost/year is more than that of TDF/FTC. Preference studies have suggested that CAB-LA could be a more preferred prevention option over TDF/FTC, including in South Africa; real-world uptake and preference can only be assessed once it is available for use (136,153). However, while CAB-LA has the potential to change HIV prevention, for large-scale implementation across LMICs it first needs to be affordable, and lessons learned from oral PrEP programmes mean that scale-up and demand creation has to be coordinated between all partners and fast enough to build momentum and yield results as high as those projected here.

Supplementary Appendix

Additional details regarding the epidemiological model

A more detailed description of the Thembisa model (version 4.4) is provided elsewhere (45). Here we provide a brief overview of the assumptions most relevant to the current paper.

Modelling of sexual risk behaviour

Thembisa is an integrated demographic and HIV model of the South African population. The demographic component of the model stratifies the population by sex and single year of age. There are two broadly defined risk groups: the 'high-risk' group comprises individuals who have a propensity for concurrent partners and/or commercial sex, and the 'low-risk' group consists of individuals who are serially monogamous and never engage in commercial sex. Within these two broad risk groups there are several sub-groups, defined in terms of sexual experience (virgin/sexually experienced), marital status, and spouse risk group (in the case of married individuals). Female sex workers (FSWs) are modelled as a sub-group within the unmarried high-risk female group, with rates of entry into sex worker being calculated to be sufficient to meet the assumed male demand for commercial sex, and rates of exit from sex work being calculated on the assumption of a three-year average duration of sex work (97,154,155). Men who have sex with men (MSM) are modelled as a sub-group of unmarried sexually-experienced men; due to high rates of heterosexual activity reported by MSM, it is assumed that 30% of sexual contacts are with female partners (156–158). Due to low rates of marriage among South African MSM (156,159,160) and prevailing stigma around same-sex relationships, it is assumed for simplicity that MSM only marry female partners.

Rates of sexual debut depend on age, sex and risk group. After beginning sexual activity, three types of relationship are modelled: once-off contacts between sex workers and clients, short-term (non-cohabiting) relationships, and long-term (marital or cohabiting) relationships. Rates of marriage and union dissolution are assumed to vary by age and sex, based on calibration of the model to marriage prevalence data from censuses and community surveys (161). Rates of male contact with sex workers are assumed to depend on age and marital status, with rates being highest among unmarried men and men

in their thirties. Rates of short-term partnership formation depend on age, sex, risk group and marital status (low-risk individuals, by definition, do not engage in short-term relationships while married), and rates of male short-term partnership formation are calculated to be consistent with female rates, given assumptions about the mean and standard deviation of age differences in short-term relationships. Assumptions about the assortativeness of mixing determine the proportion of high-risk individuals who select partners in the low-risk group and vice versa, for both short-term and long-term relationships.

Coital frequencies are specified on a monthly basis for long-term relationships, and on a per-partnership basis for short-term relationships. Rates of condom use are assumed to depend on age, sex and relationship type, and are assumed to have increased substantially over the 1995-2010 period in response to condom promotion programmes (99). In addition, condom use is assumed to increase after HIV diagnosis and after ART initiation.

Modelling of HIV transmission

The HIV epidemic is seeded in 1985 with an initial HIV prevalence in high-risk individuals aged 15-49. Thereafter the epidemic spreads based on assumptions about the probability of HIV transmission per unprotected sex act. This transmission probability varies in relation to the type of relationship (highest for short-term and MSM relationships), the sex of the susceptible partner, the circumcision status of the susceptible male partner, the HIV stage of the HIV-positive partner (highest during the acute stage of HIV infection and when untreated with a CD4 count of <200 cells/μl), and whether the HIV-positive partner is treated (transmission from treated individuals further depends on assumptions about prevailing levels of viral suppression). Condoms are assumed to be 95% effective in preventing transmission (162,163) and men who are circumcised are assumed to be 60% less likely to acquire HIV during heterosexual sex than uncircumcised men (164). The numbers of HIV-positive individuals and the proportions in different HIV stages are updated at monthly time steps.

Modelling of HIV disease progression

In the absence of treatment, adults who acquire HIV are assumed to progress through five stages of HIV disease: an initial acute stage (lasting an average of 3 months) and four subsequent stages that are defined in terms of CD4

count (≥500, 350-499, 200-349 and <200 cells/μl). Mortality due to AIDS is assumed to occur at CD4 counts of <350 cells/μl. Three types of HIV testing are modelled: testing of pregnant women attending antenatal clinics, testing of patients with opportunistic infection symptoms, and other 'general' HIV testing, with testing rates being assumed to change over time on the basis of routine testing and survey data (50,115). Following HIV diagnosis, a proportion of the newly diagnosed are assumed to initiate ART immediately (if eligible) and the balance are assumed to defer ART initiation. Rates of ART initiation after diagnosis change over time based on changing ART eligibility criteria, and are assumed to be lower at higher CD4 counts. Individuals who start ART are classified according to their baseline CD4 count and the time since first ART initiation; at each ART duration it is further assumed that a certain proportion of patients who have initiated ART are currently interrupting ART (these proportions are calculated from assumptions about annual ART interruption rates and average durations of interruption). Mortality rates in treated patients are assumed to depend on both the baseline CD4 count and the duration since first ART initiation.

Model calibration

The model is calibrated to a number of data sources:

- HIV prevalence data from national antenatal surveys (1991-2015 and 2017), stratified by age
- HIV prevalence data from national household surveys (in 2005, 2008, 2012, 2016 and 2017), stratified by age and sex
- Recorded numbers of deaths in adults (1997-2016), stratified by age and sex
- HIV prevalence data from studies conducted among MSM and FSWs
- National household survey data on the proportion of adults who are receiving ART (2012 and 2017), stratified by sex

For each data source, a likelihood function is specified, representing the model goodness of fit to the data. The model is calibrated using a Bayesian algorithm, with the posterior distribution being estimated by Incremental Mixture Importance Sampling (96).

Modelling of oral PrEP (TDF/FTC)

Effectiveness of oral PrEP

Randomized controlled trials published to date have yielded conflicting estimates of the effectiveness of PrEP, mostly because of differences in PrEP adherence across trials. Although a meta-analysis estimated that PrEP reduced heterosexual transmission and transmission between MSM by 46% and 66% respectively (35), these estimates are probably under-estimates, as most of the evidence included in the meta-analysis came from randomized trials that were conducted prior to the effectiveness of PrEP being established. More recent studies, conducted in the context of known PrEP efficacy, have generally found much higher levels of adherence and effectiveness (62,63,165), suggesting that individuals are more motivated to use PrEP consistently when they know that it works. The assumed effectiveness of PrEP is therefore set to 65% in heterosexuals and 85% in MSM. The assumed effectiveness of 65% in heterosexuals is based on a meta-analysis that found an average 65% reduction in women's HIV risk in studies in which average PrEP adherence was at least 50% (34), and the assumed effectiveness of 85% in MSM is based on the results of the PROUD and IPERGAY studies, which both found 86% effectiveness in MSM (62,63). The assumed greater effectiveness of PrEP in MSM is supported by in vitro evidence of greater drug concentration in rectal tissue when compared to female genital tract tissue (166). There is unfortunately relatively little data on the effectiveness of PrEP in heterosexual men, so we assume effectiveness to be the same as in MSM.

Risk compensation

Although data from randomized trials generally do not show evidence of risk compensation in PrEP recipients (59,64,167), it is difficult to extrapolate from the data collected in these randomized trials, as trial participants would have been counselled on the uncertainty regarding the efficacy of the products that were being evaluated, and even if they believed the study products to be effective, would not have known whether they were receiving the study drug or the placebo. In an analysis of changes in behaviour after the unblinding of the Partners PrEP trial in heterosexual couples, a statistically significant 10% increase was noted in unprotected extramarital sex, amongst individuals who were receiving open-label PrEP (84) A recent meta-analysis of PrEP studies conducted in MSM also found that PrEP use was associated with increased

STI diagnosis (OR 1.26, 95% CI: 0.99-1.54) and increases in condomless sex (168). Based on these two studies, we assume a 10% reduction in condom use among PrEP users. However, it is worth noting that this assumption is subject to much uncertainty; in a more recent study of PrEP uptake in heterosexual sero-discordant couples, no reduction in condom use was observed after PrEP initiation (169).

Oral PrEP discontinuation

Rates at which individuals discontinue PrEP are highly variable between studies, ranging from rates of 0.23 per annum in American MSM (170) to rates of 0.45 and 0.80 per annum in studies that have followed individuals following the completion of randomized controlled trials of PrEP (84,171). In our model we assume an average PrEP duration based on the limited programme data available in South Africa for female sex workers (FSWs) and MSM (Sarah Jenkins, personal communication). We fit simple Weibull models to the data to estimate the time from initiating PrEP to stopping PrEP; in the case of FSWs, a Weibull distribution with a mean of 4.8 months and a shape parameter of 0.45 provides an adequate fit to the data, while in the case of MSM, a Weibull distribution with a mean of 11.1 months and a shape parameter of 0.60 provides an adequate fit to the data (Figure A1). The model does allow previous PrEP users to re-enrol into the PrEP programme, however previous history of PrEP is not tracked separately in the model and we assume that former PrEP users initiate PrEP at the same rate as other eligible individuals.

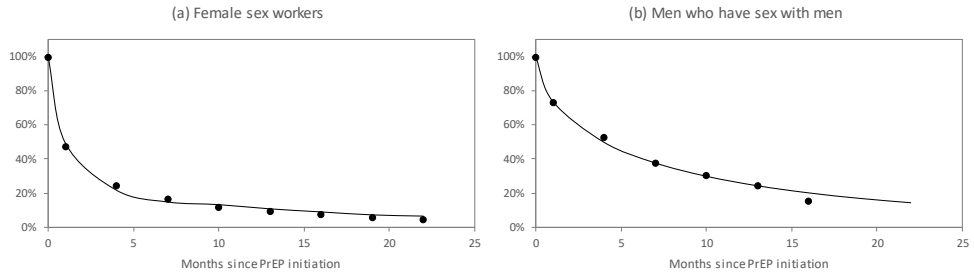


Figure A1. Retention in South African PrEP programmes

Data (represented by dots) are from South African PrEP programmes, as at November 2018 (Sarah Jenkins, personal communication). The solid lines represent Weibull fits to the data.

Effect of risk group on PrEP initiation

Initially, oral PrEP in South Africa was promoted mainly to FSWs and MSM. In recent years there has been increasing promotion of oral PrEP to adolescent girls and young women (AGYW). It is likely that high-risk AGYW initiate PrEP at a greater rate than low-risk AGYW, given that they are more likely to perceive themselves as being at high risk. However, there is a lack of local data on the predictors of PrEP uptake among AGYW. We therefore rely on a study of correlates of PrEP uptake among pregnant Kenyan women (172), assuming those in the low-risk group are 0.33 times as likely to initiate PrEP as those in the high-risk group.

Table S1. Details of cost items, unit cost, quantities and their sources by visit type for CAB-LA provision, for young women (under the assumption that the cost of one CAB-LA injection is the same price the equivalent protection period of oral TDF/FTC, i.e. 2 months' supply = $9.40, and oral CAB cost for 20% of the population is the same as oral TDF/FTC = $4.70; and average duration on CAB-LA was 5 months)

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
Patient-level cost†								
Screening/Initiation								**23.74**
Education/readiness assessment								
Readiness assessment	Staff	Counsellor	0.06	per minute	1	1	Assumption	0.06
STI screening form	Consumables	Patient form	0.01	per form	2	2	Assumption	0.02
HIV testing (screening/initiation)								
1st test (including mark-up for people testing HIV+ that don't initiate PrEP)	Labs	HIV rapid test	0.52	per test	3	1.128	1/(1-HIV prevalence)	0.59
	Staff	Counsellor	0.06	per minute	1	16.128	Data from demonstration projects (personal communication, Kevin Rebe/ Gaby Gomez)	1.01
	Consumables	Gloves	0.07	per pair	4	1.128	1/(1-HIV prevalence)	0.08
	Consumables	Cotton wool swabs	0.02	per swab	5	1.128	1/(1-HIV prevalence)	0.03
2nd test (only if 1st positive)	Labs	HIV rapid test	0.52	per test	3	0.114	HIV prevalence	0.06
	Staff	Counsellor	0.06	per minute	1	1.833	Data from demonstration projects (personal	0.11

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
							communication, Kevin Rebe/ Gaby Gomez)	
	Consumables	Gloves	0.07	per pair	4	0.114	HIV prevalence	0.01
	Consumables	Cotton wool swabs	0.02	per swab	5	0.114	HIV prevalence	0.003
Only in case of discrepant rapid tests	Labs	ELISA	4.12	per test	6	0.02	Assumption	0.08
	Staff	Counsellor	0.06	per minute	1	0.3	Assumption (15 minutes x probability of 0.02)	0.02
	Consumables	Gloves	0.07	per pair	4	0.02	Assumption (1 set x probability of 0.02)	0.001
	Consumables	Needle	0.01	per needle	7	0.02	Assumption (1 set x probability of 0.02)	0.0002
	Consumables	Cotton wool swabs	0.02	per swab	5	0.02	Assumption (1 set x probability of 0.02)	0.0005
Other monitoring tests								
Blood draw and symptom check	Staff	Professional nurse	0.29	per minute	1	15	Assumption	4.38
Alanine aminotransferase (ALT) test	Labs	ALT test	3.39	per test	6	1	Baxter (2013)	3.39
Pregnancy test	Labs	Pregnancy test (urine)	0.28	per test	8	1	One per person	0.28
STI screening (syndromic management)								
STI symptom screen	Staff	Counsellor	0.06	per minute	1	5	Assumption	0.31
Initial Syphilis testing								
Syphilis RPR	Labs	RPR titre	2.41	per test	9	1	One per person (or depending on syphilis prevalence for FSW, MSM)	2.41

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
Counselling and assessment								
Adherence counselling	Staff	Counsellor	0.06	per minute	1	15	Data from demonstration projects (personal communication, Kevin Rebe)	0.94
PrEP dispensing								
CAB-LA	Drugs	Cabotegravir injectable	9.40	per injection	10	0.8	One per person	7.52
Oral CAB lead in	Drugs	Oral Cabotegravir	4.70	per month	10	0.2	One per person	0.94
Prescribing & dispensing	Staff	Professional nurse	0.29	per minute	1	5	Assumption	1.46
	Consumables	Needle	0.01	per needle	7	0.8	Assumption	0.01
	Consumables	Cotton wool swabs	0.02	per swab	5	0.8	Assumption	0.02
Annually								**2.41**
Syphilis RPR	Labs	RPR titre	2.41	per test	9	1	One per person	2.41
Month 1 and Follow-up (all users); Month 2 (for 20% of those opting for a CAB-LA oral lead in; quantities set at 20%)								**13.80**
HIV testing (follow-up)								
1st test	Labs	HIV rapid test	0.52	per test	3	1	One per person	0.52
	Staff	Counsellor	0.06	per minute	1	15	Data from demonstration projects (personal communication, Kevin Rebe/ Gaby Gomez)	0.94
	Consumables	Gloves	0.07	per pair	4	1	One per person	0.07
	Consumables	Cotton wool swabs	0.02	per swab	5	1	One per person	0.02

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
2nd test (only if 1st positive)	Labs	HIV rapid test	0.52	per test	3	0.018	HIV incidence	0.01
	Staff	Counsellor	0.06	per minute	1	0.294	Data from demonstration projects (personal communication, Kevin Rebe/ Gaby Gomez)	0.02
	Consumables	Gloves	0.07	per pair	4	0.018	HIV incidence	0.001
	Consumables	Cotton wool swabs	0.02	per swab	5	0.018	HIV incidence	0.0004
Only in case of discrepant rapid tests	Labs	ELISA	4.12	per test	6	0.02	Assumption	0.08
	Staff	Counsellor	0.06	per minute	1	0.3	Assumption (15 minutes x probability of 0.02)	0.02
	Consumables	Gloves	0.07	per pair	4	0.02	Assumption (1 set x probability of 0.02)	0.001
	Consumables	Needle	0.01	per needle	7	0.02	Assumption (1 set x probability of 0.02)	0.0002
	Consumables	Cotton wool swabs	0.02	per swab	5	0.02	Assumption (1 set x probability of 0.02)	0.0005
Other monitoring tests								
Pregnancy test	Labs	Pregnancy test (urine)	0.28	per test	8	1	One per woman	0.28
STI screening (syndromic management)								
STI symptom screen	Staff	Counsellor	0.06	per minute	1	5	Assumption	0.31
Counselling and assessment								
Adherence counselling	Staff	Counsellor	0.06	per minute	1	10	Data from demonstration projects (personal communication, Kevin Rebe)	0.63

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
PrEP dispensing								
CAB-LA	Drugs	Cabotegravir injectable	9.40	per injection	10	1	One per person	9.40
Prescribing & dispensing	Staff	Professional nurse	0.29	per minute	1	5	Assumption	1.46
	Consumables	Needle	0.01	per needle	7	1	Assumption	0.01
	Consumables	Cotton wool swabs	0.02	per swab	5	1	Assumption	0.02
Re-initiation (First and second re-initiation visits, 4 weeks later)								**3.22**
HIV testing (follow-up, see details in Month 1 visit)								1.69
Other monitoring tests								
Pregnancy test	Labs	Pregnancy test (urine)	0.28	per test	8	1	One per woman	0.28
STI screening (syndromic management)								
STI symptom screen	Staff	Counsellor	0.06	per minute	1	5	Assumption	0.31
Counselling and assessment								
Adherence counselling	Staff	Counsellor	0.06	per minute	1	15	Data from demonstration projects (personal communication, Kevin Rebe)	0.94
Health system costs (per user per year, annually)								**10.30**
Training (nurses)	Staff	Professional nurse	0.29	per minute	11	0.469	Assumption (75min per year online training, 160 clients per yr, 1 per year)	0.14

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
Training (counsellors)	Staff	Counsellor	0.06	per minute	11	0.469	Assumption (75min per year online training, 160 clients per yr, 1 per year)	0.03
Training (peer educators)	Staff	Peer educator	202.95	per month	12	0.000054	Assumption (75min per year online training, 160 clients per yr, 1 per year)	0.01
Training (data capturer)	Staff	Data capturer	0.08	per minute	2	0.469	Assumption (75min per year online training, 160 clients per yr, 1 per year)	0.04
Training system maintenance	Overheads	Training system maintenance	1473.11	per year	14	0.0000007	Assumption (9,400 HCW trained,160 clients per year)	0.0001
Mobilisation								
Outreach campaign	Overheads	Outreach campaign event	13.75	per person	15	0.010	Assumption (proportion initiated out of all reached = 1/100)	0.14
IEC materials	Consumables	IEC material	0.19	per person	13	1.000	Assumption (1 set per client per year)	0.19
Outreach	Staff	Peer educator	202.95	per month	12	0.042	Assumption (15 mins out of 8 hrs for PrEP/160 clients per year)	8.60
M+E								
Patient form	Consumables	Patient form	0.01	per form	2	2.000	1 x 2-page clinical form per year per person on PrEP	0.02
Paper register (A3 page)	Consumables	Paper A3 size	0.02	per page	16	0.075	1 x A3 per month per clinic	0.00
Staff time for monthly reporting	Staff	Data capturer	0.08	per minute	1	4.500	Assumption (60min per month/site)	0.36
Overhead								

	Cost Category	Ingredient	Unit cost (2021 USD)	Cost unit	Source*	Quantity	Quantity source/assumption	Subtotal Cost (2021 USD)
Building maintenance and utilities	Overheads		***7% mark-up on per visit costs, applied to overall cost***					
Drawing patient file	Staff	Clerk	0.07	per minute	1	11.4	Assumption (3 minutes x number of visits per year)	0.77

† Average cost per person initiated is structured based on the types of visits occurring given the average duration each population is on CAB-LA. All populations and duration scenarios have 1 visit for screening/initiation, 1 visit at Month 1 (first year only), 20% of patients with oral CAB-lead in have a visit at Month 2 (first year only). Re-initiation (1) and (2) only occur if clients are on CAB-LA for 12 months or longer. Follow-up visits occur 2-monthly after Month 1 visits and are dependent on the assumed average duration on CAB-LA.
‡ Health systems costs are assumed for each client per year, and training occurs once a year. In addition to these costs, a 7% overhead costs are included for each visit type under patient-level costs to cover utilities and space requirements, as per personal communication with Gaby Gomez.

Source of unit costs:
1. South African Government Salary Scale (2019); 2. South Africa, Global Fund proposal (2013); 3. South African National Department of Health, contract RT41-2017; 4. National Treasury of South Africa, tender RT76-2016; 5. South African National Department of Health, tender HM022015BD; 6. South African National Health Laboratory Service price list (2018); 7. South African National Department of Health, contract HM08-2015SYR; 8. Kendon Medical Supplies Pty Ltd, quote (19 Aug 2019); 9. South African National Health Laboratory Service price list (2017); 10. South African National Department of Health, contract RT71-2019; 11. Clinton Health Access Initiative (2015); 12. Provincial DOH CG Business Plans (2017); 13. Personal communication, Steve Cohen (2015); 14. Personal communication, Hasina Sebudar (2020); 15. RSA Global Fund Grant portfolio budgets (2018)

Table S2. Probability distributions used for parameters varied in the probabilistic sensitivity analysis

Variable	Population	Distribution	Mean, standard deviation
Reduction in condom use while on PrEP	All populations	Beta (0.80, 7.20)	0.10, 0.10
Relative rate of uptake of PrEP in low risk group vs high risk group	Adolescent girls and young women (AGYW), adolescents boys and young men (ABYM)	Beta (1.49, 3.03)	0.33, 0.20
TDF/FTC annual initiation rates	AGYW, ABYM	Uniform(0,0.650)	0.325,0.188
	Female sex workers (FSW)	Uniform(0,2.733)	1.367,0.789
	Men who have sex with men (MSM)	Uniform(0,1.149)	0.574,0.332
CAB-LA annual initiation rates	AGYW, ABYM	Uniform(0,0.40)	0.20, 0.013
	FSW	Uniform(0,0.70)	0.35,0.04
	MSM	Uniform(0,0.70)	0.35,0.04
TDF/FTC effectiveness	AGYW and FSW	Beta (14.14,7.61)	0.65, 0.10
	MSM and ABYM	Beta (9.99, 1.76)	0.85, 0.10
CAB-LA effectiveness	All populations	Beta (3.56, 0.19)	0.95, 0.05
Cost of PrEP provision, excluding drugs (TDF/FTC)	AGYW (first year)	Gamma(12,0.23150)	51, 15
	FSW (first year)	Gamma(12,0.22450)	53, 15
	ABYM (first year)	Gamma(12,0.23469)	51, 15
	MSM (first year)	Gamma(12,0.18962)	63, 18
Cost of PrEP provision, excluding drugs (CAB-LA minimum duration scenario)	AGYW (first year)	Gamma(12,0.26502)	45, 13
	FSW (first year)	Gamma(12,0.25367)	47, 13
	ABYM (first year)	Gamma(12,0.27104)	44, 13
	MSM (first year)	Gamma(12,0.20820)	57, 16
Cost of PrEP provision, excluding drugs (CAB-LA maximum duration scenario)	AGYW (first year)	Gamma(12,0.16907)	70, 20
	FSW (first year)	Gamma(12,0.16750)	71, 20
	ABYM (first year)	Gamma(12,0.17564)	68, 19
	MSM (first year)	Gamma(12,0.18395)	65, 19
	MSM (follow-up year)	Gamma(12,0.24947)	48, 14

Monte Carlo simulation methods were used to conducted with 1,000 model runs, while sampling for the above variables, from the corresponding distribution and shape parameters, for each model run. The number of simulations (N=1,000) was deemed appropriate to achieve an acceptable level of precision (standard error = 0.03), considering the aim of the analysis was to assess the sensitivity of the sampled variables on the main results.

Table S3. Proportion of total cost of HIV programme spent to different areas

				CAB-LA							
				High coverage				Medium coverage			
				Maximum duration		Minimum duration		Maximum duration		Minimum duration	
		TDF/FTC		*CAB-LA drug cost relative to TDF/FTC*							
	Baseline	High coverage	Medium coverage	x1	x2	x1	x2	x1	x2	x1	x2
HIV care and treatment	90%	86%	88%	76%	71%	79%	75%	82%	78%	84%	82%
Prevention	5%	10%	8%	20%	26%	17%	21%	14%	17%	11%	14%
HIV testing	4%	4%	4%	3%	3%	4%	4%	4%	4%	4%	4%
Prevention of mother-to-child transmission	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%
Other	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%	<1%

*__HIV care and treatment includes__: antiretroviral treatment to adults and children, inpatient hospital care to HIV positive patients, palliative care; **Prevention includes:** medical male circumcision, condom distribution, pre-exposure prophylaxis, post-exposure prophylaxis, combination prevention packages to female sex workers; **HIV testing includes**: testing of infants at birth and 10 weeks, general HIV testing at primary health care clinics, HIV testing in antenatal care clinics, provider-initiated HIV testing and counselling, mobile HIV testing, home-based HIV testing, partner notification HIV testing and HIV self-testing; **prevention of mother-to-child transmission** is restricted to mothers who are not already initiated on antiretroviral treatment. **Other includes:** supply chain management and pharmacovigilance programme.

Table S4. Estimated cost threshold per CAB-LA injection to ensure CAB-LA remains as cost-effective as oral TDF/FTC (2021 USD)

Cost per CAB-LA injection solving for	Minimum duration scenario		Maximum duration scenario	
	Medium coverage	***High coverage***	***Medium coverage***	***High coverage***
CAB-LA cost/HIV infection averted = TDF/FTC cost/HIV infection averted	14.47	11.57	11.79	9.03
CAB-LA cost/life year saved = TDF/FTC cost/life year saved	14.47	11.88	11.70	9.33

Table S5. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming that CAB-LA injections are given 3-monthly

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			41.29			
Medium PrEP coverage									
TDF/FTC	2.89	4%	37.00	1%	N/A	42.08	2%	6,053	2,309
CAB-LA minimum duration	2.58	15%	36.19	3%	1x	43.35	5%	4,692	1,790
					2x	44.77	8%	7,921	3,022
					3x	46.19	12%	11,150	4,253
					4x	47.60	15%	14,380	5,485
					5x	49.02	19%	17,609	6,717
CAB-LA maximum duration	2.44	19%	35.81	4%	1x	44.18	7%	4,927	1,889
					2x	46.24	12%	8,445	3,239
					3x	48.30	17%	11,963	4,588
					4x	50.36	22%	15,481	5,937
					5x	52.42	27%	18,999	7,286
High PrEP coverage									
TDF/FTC	2.78	8%	36.68	2%	N/A	42.92	4%	6,610	2,498
	2.31	24%	35.41	5%	1x	45.62	10%	6,052	2,246
					2x	48.45	17%	10,020	3,718

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA minimum duration					3x	51.29	24%	13,989	5,191
					4x	54.13	31%	17,957	6,664
					5x	56.96	38%	21,926	8,137
CAB-LA maximum duration	2.17	28%	35.03	6%	1x	46.85	13%	6,496	2,403
					2x	50.63	23%	10,913	4,037
					3x	54.41	32%	15,330	5,671
					4x	58.19	41%	19,746	7,305
					5x	61.97	50%	24,163	8,939

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population). † Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).

Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S6. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming same coverage for CAB-LA and TDF/FTC

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			41.29			
Medium PrEP coverage									
TDF/FTC	2.89	4%	37.00	1%	N/A	42.08	2%	6,053	2,309
CAB-LA minimum duration	2.83	6%	36.83	1%	1x	41.96	2%	3,449	1,322
					2x	42.41	3%	5,750	2,203
					3x	42.86	4%	8,051	3,085
					4x	43.31	5%	10,352	3,967
					5x	43.76	6%	12,653	4,849
CAB-LA maximum duration	2.73	10%	36.60	2%	1x	42.40	3%	3,843	1,497
					2x	43.16	5%	6,482	2,524
					3x	43.92	6%	9,120	3,551
					4x	44.68	8%	11,758	4,578
					5x	45.44	10%	14,396	5,606
High PrEP coverage									
TDF/FTC	2.78	8%	36.68	2%	N/A	42.92	4%	6,610	2,498
CAB-LA minimum duration	2.67	12%	36.40	3%	1x	42.70	3%	3,984	1,513
					2x	43.59	6%	6,490	2,464
					3x	44.48	8%	8,995	3,416

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
					4x	45.37	10%	11,501	4,367
					5x	46.26	12%	14,007	5,319
CAB-LA maximum duration	2.54	16%	36.08	3%	1x	43.51	5%	4,617	1,765
					2x	44.95	9%	7,621	2,913
					3x	46.40	12%	10,624	4,062
					4x	47.84	16%	13,628	5,210
					5x	49.29	19%	16,631	6,358

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S7. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming a 3% discount rate

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	2.37		17.33			31.27			
Medium PrEP coverage									
TDF/FTC	2.28	4%	17.22	1%	N/A	31.86	2%	6,313	5,264
CAB-LA minimum duration	2.23	6%	17.16	1%	1x	31.78	2%	3,624	3,039
					2x	32.11	3%	5,961	4,998
					3x	32.43	4%	8,297	6,958
					4x	32.76	5%	10,634	8,918
					5x	33.09	6%	12,971	10,877
CAB-LA maximum duration	2.17	9%	17.09	1%	1x	32.11	3%	4,028	3,431
					2x	32.66	4%	6,705	5,711
					3x	33.22	6%	9,382	7,991
					4x	33.77	8%	12,058	10,271
					5x	34.32	10%	14,735	12,551
High PrEP coverage									
TDF/FTC	2.20	7%	17.12	1%	N/A	32.48	4%	6,847	5,665

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA minimum duration	2.12	11%	17.02	1x	1x	32.34	3%	4,149	3,461
				2x	2x	32.98	5%	6,680	5,571
				3x	3x	33.63	8%	9,210	7,681
				4x	4x	34.28	10%	11,740	9,791
				5x	5x	34.92	12%	14,270	11,902
CAB-LA maximum duration	2.02	15%	16.92	2%	1x	32.94	5%	4,789	4,028
					2x	33.99	9%	7,817	6,575
					3x	35.04	12%	10,845	9,122
					4x	36.09	15%	13,873	11,669
					5x	37.15	19%	16,901	14,216

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S8. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming a 4.75% discount rate ρ

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	2.08		11.93			26.87			
Medium PrEP coverage									
TDF/FTC	2.00	4%	11.87	1%	N/A	27.36	2%	6,479	7,764
CAB-LA minimum duration	1.96	6%	11.83	1%	1x	27.30	2%	3,732	4,497
					2x	27.58	3%	6,093	7,342
					3x	27.85	4%	8,454	10,187
					4x	28.13	5%	10,815	13,032
					5x	28.40	6%	13,176	15,876
CAB-LA maximum duration	1.91	8%	11.79	1%	1x	27.58	3%	4,144	5,070
					2x	28.05	4%	6,847	8,378
					3x	28.51	6%	9,550	11,685
					4x	28.97	8%	12,253	14,993
					5x	29.44	10%	14,957	18,300
High PrEP coverage									
TDF/FTC	1.93	7%	11.81	1%	N/A	27.89	4%	6,997	8,331

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA minimum duration	1.87	10%	11.75	1%	1x	27.78	3%	4,252	5,109
					2x	28.32	5%	6,800	8,169
					3x	28.86	7%	9,347	11,230
					4x	29.40	9%	11,894	14,290
					5x	29.94	11%	14,441	17,350
CAB-LA maximum duration	1.79	14%	11.69	2%	1x	28.29	5%	4,897	5,939
					2x	29.17	9%	7,944	9,632
					3x	30.05	12%	10,990	13,326
					4x	30.93	15%	14,036	17,020
					5x	31.81	18%	17,082	20,714

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
ᵖ 4.75% is the South African repurchase rate as of 14 June 2022 (South African Reserve Bank, https://www.resbank.co.za/en/home/what-we-do/statistics/key-statistics/current-market-rates)
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S9. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming a 6% discount rate

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	1.90		9.38			24.23			
Medium PrEP coverage									
TDF/FTC	1.84	3%	9.34	<1%	N/A	24.67	2%	6,602	9,934
CAB-LA minimum duration	1.80	5%	9.31	1%	1x	24.62	2%	3,812	5,764
					2x	24.86	3%	6,192	9,362
					3x	25.10	4%	8,571	12,960
					4x	25.34	5%	10,951	16,558
					5x	25.58	6%	13,330	20,157
CAB-LA maximum duration	1.75	8%	9.28	1%	1x	24.87	3%	4,230	6,493
					2x	25.28	4%	6,954	10,674
					3x	25.69	6%	9,677	14,855
					4x	26.10	8%	12,401	19,036
					5x	26.51	9%	15,125	23,217
High PrEP coverage									
TDF/FTC	1.78	7%	9.30	1%	N/A	25.14	4%	7,109	10,637

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA minimum duration	1.72	10%	9.26	1%	1x	25.04	3%	4,328	6,538
					2x	25.52	5%	6,889	10,406
					3x	26.00	7%	9,450	14,274
					4x	26.47	9%	12,011	18,143
					5x	26.95	11%	14,572	22,011
CAB-LA maximum duration	1.65	13%	9.22	2%	1x	25.50	5%	4,978	7,593
					2x	26.28	8%	8,039	12,262
					3x	27.06	12%	11,101	16,931
					4x	27.83	15%	14,162	21,600
					5x	28.61	18%	17,223	26,270

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S10. Impact and cost-effectiveness of CAB-LA over baseline* and oral PrEP over baseline, over a 20-year time horizon (2022-2041); assuming the HIV diagnostic algorithm under CAB-LA scenarios requires polymerase chain reaction (PCR) testing annually, and at every injection visit

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.02		37.34			41.29			
TDF/FTC									
Medium PrEP coverage	2.89	4%	37.00	1%	N/A	42.08	2%	6,053	2,309
High PrEP coverage	2.78	8%	36.68	2%	N/A	42.92	4%	6,610	2,498
Annual PCR testing in CAB-LA scenarios									
Medium PrEP coverage									
CAB-LA minimum duration	2.58	15%	36.19	3%	1x	44.39	8%	7,069	2,697
					2x	45.60	10%	9,809	3,742
					3x	46.80	13%	12,550	4,787
					4x	48.00	16%	15,290	5,833
					5x	49.21	19%	18,031	6,878

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA maximum duration	2.44	19%	35.81	4%	1x	46.19	12%	8,363	3,207
					2x	48.11	17%	11,653	4,469
					3x	50.04	21%	14,943	5,731
					4x	51.97	26%	18,233	6,992
					5x	53.89	31%	21,523	8,254
High PrEP coverage									
CAB-LA minimum duration	2.31	24%	35.41	5%	1x	47.69	15%	8,954	3,323
					2x	50.10	21%	12,321	4,572
					3x	52.50	27%	15,689	5,822
					4x	54.91	33%	19,057	7,072
					5x	57.32	39%	22,425	8,322
CAB-LA maximum duration	2.17	28%	35.03	6%	1x	50.53	22%	10,798	3,995
					2x	54.06	31%	14,928	5,523
					3x	57.60	39%	19,058	7,051
					4x	61.13	48%	23,188	8,578
					5x	64.67	57%	27,318	10,106
PCR testing 2-monthly in CAB-LA scenarios									

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Medium PrEP coverage									
CAB-LA minimum duration	2.58	15%	36.19	3%	1x	46.35	12%	11,524	4,396
					2x	47.55	15%	14,264	5,441
					3x	48.76	18%	17,005	6,487
					4x	49.96	21%	19,745	7,532
					5x	51.16	24%	22,485	8,577
CAB-LA maximum duration	2.44	19%	35.81	4%	1x	50.60	23%	15,893	6,095
					2x	52.52	27%	19,183	7,357
					3x	54.45	32%	22,473	8,619
					4x	56.38	37%	25,763	9,880
					5x	58.30	41%	29,053	11,142
High PrEP coverage									
CAB-LA minimum duration	2.31	24%	35.41	5%	1x	51.60	25%	14,427	5,354
					2x	54.01	31%	17,795	6,604
					3x	56.42	37%	21,163	7,853
					4x	58.82	42%	24,530	9,103
					5x	61.23	48%	27,898	10,353

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
CAB-LA maximum duration	2.17	28%	35.03	6%	1x	58.61	42%	20,245	7,490
					2x	62.15	51%	24,374	9,017
					3x	65.68	59%	28,504	10,545
					4x	69.22	68%	32,634	12,073
					5x	72.75	76%	36,764	13,601

*Baseline scenario: current roll-out of TDF/FTC as standard of care PrEP (see Table 1 for comparative coverage levels by population).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Note on analysis

The average cost of the CAB-LA scenarios was modified to include polymerase chain reaction (PCR) testing in the HIV diagnostic algorithm in two different scenarios: 1) annually, and 2) 2-monthly. PCR testing is substantially more expensive at $28/test compared to rapid HIV testing as assumed in the main analysis ($0.52/test). Under the annual scenario we assume a PCR test was conducted at screening into the CAB-LA programme, and annually thereafter. Under the 2-monthly scenario we assume a PCR test was conducted at screening, and 2-monthly thereafter.

Incorporating PCR testing, the average cost of CAB-LA provision ranges between $110/user (young men, minimum duration; 40% more expensive than the corresponding scenario/population using HIV rapid testing) to $273 (female sex workers, maximum duration; 99% more expensive) under the annual PCR scenario; it ranges between $167/user (young men, minimum duration; 113% more expensive) to $422 (female sex workers, maximum duration; 207% more expensive) under the 2-monthly PCR scenario. The cost-effectiveness analysis results are presented in Table S10. Assuming PCR testing was part of the HIV diagnostic algorithm on an annual basis, for CAB-LA to be as cost-effective as TDF/FTC, the cost of the CAB-LA injection would need to be $0.49 (maximum duration, high coverage), $3.23 (maximum duration, medium coverage), $3.29 (minimum duration, high coverage) and $6.14 (minimum duration, medium coverage). Under the scenario where PCR testing was 2-monthly, CAB-LA would be less cost-effective than TDF/FTC under all scenarios, irrespective of the cost of the CAB-LA injection.

Table S11. Uncertainty ranges around the impact and cost-effectiveness of CAB-LA and oral PrEP over baseline, over a 20-year time horizon (2022-2041); based on 1,000 Monte Carlo simulations in a probabilistic sensitivity analysis*

figures represent the median estimate with interquartile range in round brackets, and 2.5th and 97.5th percentiles in square brackets.

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
Baseline (BL)	3.03 (2.91-3.13) [2.67-3.34]		37.46 (36.44-38.32) [34.81-39.80]			41.28 (40.81-41.66) [40.04-42.48]			
TDF/FTC	2.79 (2.71-2.89) [2.62-3.01]	8% (4-10%) [1-13%]	36.70 (36.51-36.99) [36.26-37.30]	2% (1-2%) [0-3%]	N/A	42.96 (42.15-43.90) [41.44-45.60]	4% (2-6%) [0-9%]	7,532 (5,884-9,732) [3,585-17,352]	2,843 (2,223-3,659) [1,374-6,564]
CAB-LA minimum duration	2.55 (2.43-2.73) [2.29-2.98]	16% (10-20%) [2-24%]	36.08 (35.73-36.57) [35.32-37.22]	3% (2-4%) [0-5%]	1x	43.70 (42.51-45.00) [41.45-48.05]	6% (3-8%) [0-14%]	5,323 (4,062-6,842) [2,234-9,986]	1,986 (1,528-2,537) [844-3,711]
					2x	45.24 (43.38-47.23) [41.60-51.30]	9% (5-13%) [1-20%]	8,661 (6,859-10,744) [4,412-14,853]	3,242 (2,584-3,999) [1,678-5,474]
					3x	46.80 (44.20-49.40) [41.74-54.74]	12% (7-16%) [1-25%]	11,923 (9,641-14,662) [6,566-19,736]	4,494 (3,632-5,441) [2,517-7,264]

Scenario	New HIV infections		Life years lost due to AIDS		CAB-LA drug cost relative to oral PrEP drug†	Total cost of the HIV programme (2021 USD)		Incremental cost effectiveness (2021 USD)	
	Number [millions]	*% averted over BL*	*Number [millions]*	*% saved over BL*		*Cost [billions]*	*Incremental cost over BL*	*Cost/ infection averted*	*Cost/ life year saved*
					4x	48.35 (45.08-51.51) [41.87-58.28]	15% (8-20%) [1-29%]	15,279 (12,411-18,531) [8,709-24,693]	5,718 (4,681-6,869) [3,325-9,053]
					5x	49.87 (45.92-53.64) [42.01-61.73]	17% (10-23%) [2-33%]	18,603 (15,194-22,371) [10,885-29,924]	6,967 (5,750-8,330) [4,150-10,953]
CAB-LA maximum duration	2.41 (2.28-2.61) [2.15-2.94]	20% (14-24%) [3-29%]	35.70 (35.34-36.26) [34.93-37.13]	4% (3-5%) [1-6%]	1x	44.76 (43.15-46.44) [41.58-50.04]	8% (4-11%) [1-17%]	5,847 (4,404-7,458) [2,425-10,804]	2,184 (1,667-2,779) [938-3,985]
					2x	47.09 (44.53-49.76) [41.83-54.57]	12% (7-17%) [1-24%]	9,765 (7,658-11,902) [4,780-16,372]	3,673 (2,880-4,455) [1,852-6,047]
					3x	49.38 (45.87-52.97) [42.06-59.58]	16% (10-22%) [2-31%]	13,575 (10,810-16,556) [7,093-22,177]	5,123 (4,112-6,161) [2,745-8,148]
					4x	51.77 (47.27-56.21) [42.30-64.43]	20% (13-27%) [2-36%]	17,389 (14,007-21,168) [9,438-27,913]	6,545 (5,321-7,835) [3,660-10,212]
					5x	54.18 (48.65-59.44) [42.54-69.51]	24% (15-31%) [3-41%]	21,226 (17,156-25,786) [11,772-33,580]	7,993 (6,529-9,575) [4,538-12,398]

*Key model parameters which would influence the results were sampled from pre-determined distributions for each of the 1,000 model runs (see Table S2): intervention effectiveness for both TDF/FTC and CAB-LA, reduction in condom use while on PrEP, annual initiation rate for TDF/FTC, relative annual initiation rate for CAB-LA (to ensure a value consistently higher than the corresponding TDF/FTC scenario), relative rate of PrEP initiation in low-risk heterosexuals (i.e. those with no propensity for concurrent partnerships or commercial sex), and cost of PrEP provision (excluding drug cost).
† Drug cost only, excluding cost of provision (staff, lab monitoring, consumables and overhead).
Abbreviations: HIV=Human immunodeficiency virus, AIDS = acquired immunodeficiency syndrome, CAB-LA = long-acting injectable cabotegravir, USD = United States Dollars, BL = Baseline, PrEP = pre-exposure prophylaxis

Table S12. Partial rank correlation coefficients of results from probabilistic sensitivity analysis, by scenario

Parameter	Scenario	Cost per HIV infection averted (2022-2041)	HIV infections averted (2022-2041)	Cost per CAB-LA injection threshold price
Reduction in condom use while on PrEP	CAB-LA maximum duration	0.02	-0.06	0.10
	CAB-LA minimum duration	0.03	-0.07	0.13
	TDF/FTC	0.10	-0.18	N/A
Relative rate of PrEP uptake by those at low risk of HIV	CAB-LA maximum duration	0.94	0.20	-0.01
	CAB-LA minimum duration	0.95	0.20	-0.01
	TDF/FTC	0.73	0.24	N/A
PrEP initiation rates in AGYW and ABYM	CAB-LA maximum duration	0.66	0.92	-0.50
	CAB-LA minimum duration	0.62	0.95	-0.54
	TDF/FTC	0.08	0.98	N/A
PrEP initiation rates in FSW	CAB-LA maximum duration	0.93	0.93	-0.50
	CAB-LA minimum duration	0.93	0.95	-0.54
	TDF/FTC	0.10	0.98	N/A
PrEP initiation rates in MSM	CAB-LA maximum duration	0.93	0.93	-0.50
	CAB-LA minimum duration	0.93	0.95	-0.54
	TDF/FTC	0.10	0.98	N/A
PrEP efficacy in MSM and ABYM	CAB-LA maximum duration	-0.54	0.28	-0.47
	CAB-LA minimum duration	-0.61	0.30	-0.56
	TDF/FTC	-0.67	0.79	N/A
PrEP efficacy in AGYW and FSW	CAB-LA maximum duration	-0.54	0.28	-0.47
	CAB-LA minimum duration	-0.61	0.30	-0.56
	TDF/FTC	-0.64	0.79	N/A
Average cost of PrEP provision for MSM	CAB-LA maximum duration	0.91	0.01	0.32
	CAB-LA minimum duration	0.94	0.01	0.41
	TDF/FTC	0.64	0.03	N/A
Average cost of PrEP provision for AGYW, ABYM and FSW	CAB-LA maximum duration	0.91	0.01	0.32
	CAB-LA minimum duration	0.94	0.01	0.41
	TDF/FTC	0.64	0.03	N/A

Figure S1. Probabilistic sensitivity analysis results comparing the incremental cost per life year saved over 2022-41 across simulations for TDF/FTC to (A) the CAB-LA minimum duration scenario and (B) the CAB-LA maximum duration scenario assuming CAB-LA is 2-fold the cost of TDF/FTC; comparing HIV infections averted over 2022-41 in TDF/FTC to CAB-LA (C) minimum duration scenario and (D) maximum duration scenario

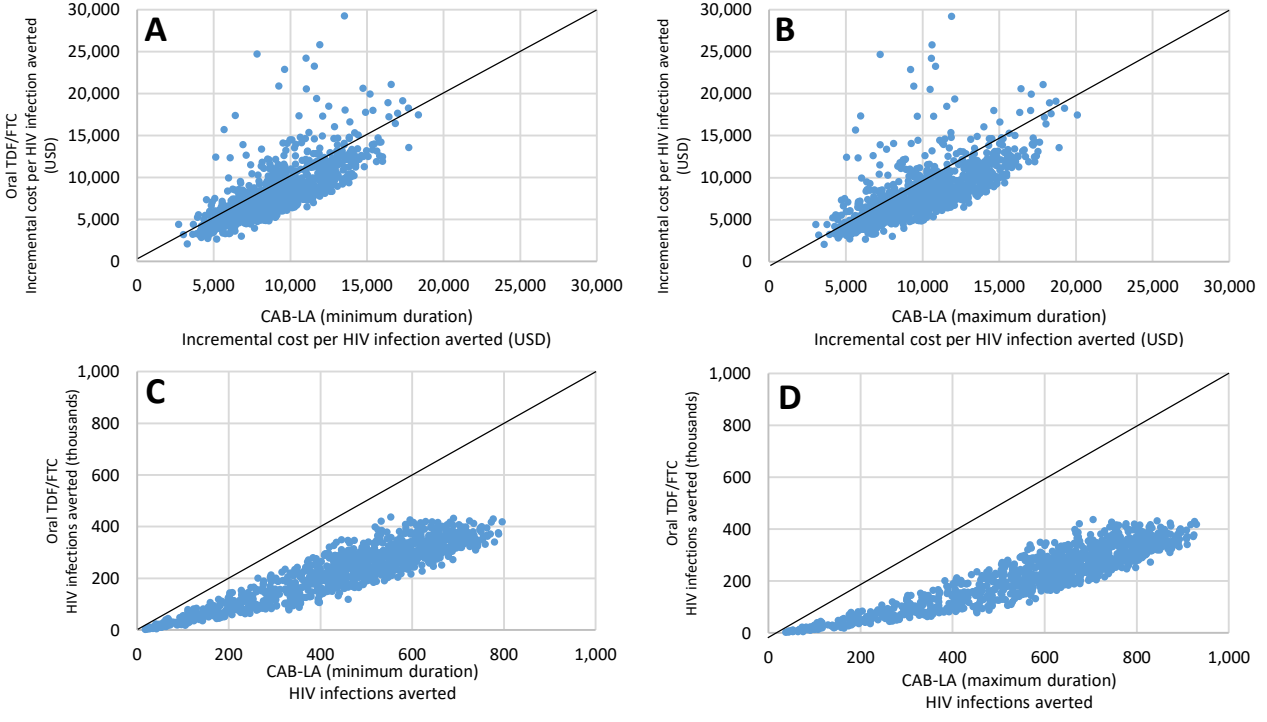
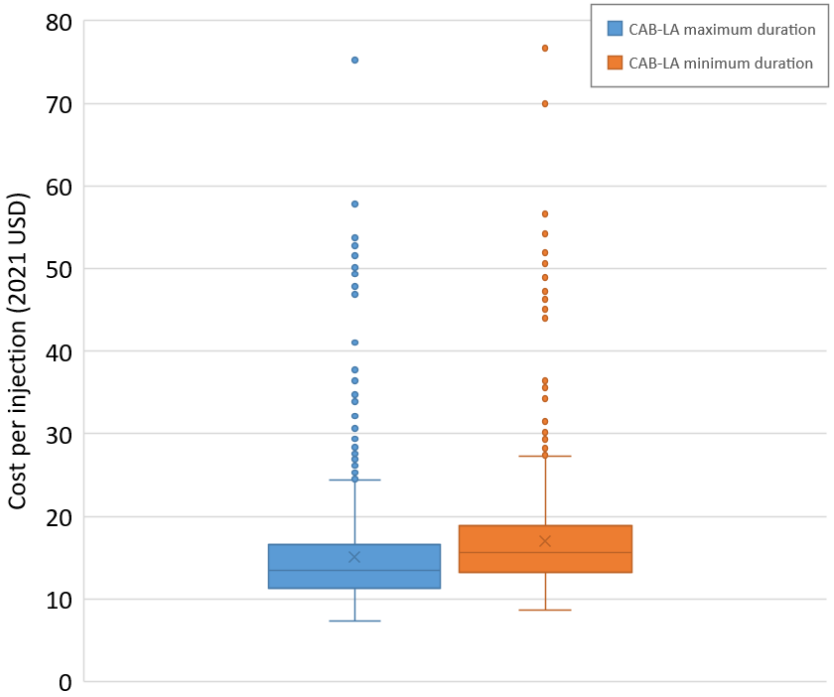


Figure S2. Estimated cost per injection for CAB-LA as calculated based on probabilistic sensitivity analysis



Across all simulations, the cost per CAB-LA injection was a median of $15.60 (interquartile range (IQR) $13.30-$18.90, 2.5th percentile $10.40, 97.5th percentile $30.80) under the minimum duration scenario and $13.50 (IQR $11.30-$16.60), 2.5th percentile $8.80, 97.5th percentile $29.70 under the maximum duration scenario.

Part 2:
Interventions for HIV treatment

Chapter 5

Cost and cost-effectiveness of dolutegravir-based antiretroviral regimens: An economic evaluation of a clinical trial

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AIDS 35, S173–S182

Abstract

Background

HIV programmes world-wide currently make decisions regarding new antiretroviral therapy (ART) regimens with less side-effects and higher resistance barriers which may improve adherence and viral suppression. Economic evaluation helps inform these decisions.

Methods

We conducted an economic evaluation of three ART regimens included in the ADVANCE trial from the provider's perspective: 1) tenofovir alafenamide (TAF)/emtricitabine (FTC)+dolutegravir (DTG) and 2) tenofovir disoproxil fumarate (TDF)/FTC+DTG, compared to 3) TDF/FTC/efavirenz (EFV). We used top-down and bottom-up cost analysis with resource utilisation a) based on trial data and b) adjusted to emulate routine care. We estimated the cost-effectiveness of each regimen as cost per person virally suppressed or retained and per life-year saved, at 48 and 96 weeks.

Results

Though the DTG-based trial arms were 2% more costly than TDF/FTC/EFV, both had slightly lower cost-per-outcome ($9,783 and $9,929/patient virally suppressed for TDF/FTC+DTG and TAF/FTC+DTG, respectively) than TDF/FTC/EFV ($10,365). The trial cost per additional virally suppressed patient, compared to TDF/FTC/EFV, was lower in the TDF/FTC+DTG arm ($2,967) compared to TAF/FTC+DTG ($3,430). In routine care, cost per virally suppressed patient was estimated as similar between TDF/FTC+DTG ($426) and TDF/FTC/EFV ($424), but more costly under TAF/FTC+DTG. Similar results were seen in the cost per additional person retained across scenarios. When modelled over 20 years, TDF/FTC/EFV was more cost-effective than TAF/FTC+DTG ($10,341 vs $41,958/life-year saved).

Conclusion

TDF/FTC+DTG had similar costs per outcome as TDF/FTC/EFV in the routine care scenario, but TDF/FTC+DTG was more cost-effective when modelled over 20 years.

Introduction

South Africa has the largest human immunodeficiency virus (HIV) epidemic globally, with an estimated 7.5 million people living with HIV, and the largest antiretroviral therapy (ART) programme in the world, with 5.2 million accessing HIV treatment in 2019 (173). Since 2013, the standard first-line regimen for HIV treatment has been tenofovir disoproxil fumarate (TDF) combined with efavirenz (EFV) and either lamivudine (3TC) or emtricitabine (FTC). However, this regimen has a low resistance barrier, with 5%-8% of patients developing resistance to the EFV-based regimens (21). In 2013, the United States Food and Drug Administration (FDA) approved the use of the second-generation HIV integrase strand transfer inhibitor (INSTI), dolutegravir (DTG), which had been shown to have better tolerability and less side-effects, and a higher resistance barrier compared with other INSTI (raltegravir (RAL)), protease inhibitors (atazanavir, darunavir (DRV)) and EFV (22–27). There were initial concerns of an association between neural tube defects in babies born to mothers on DTG-based regimens at conception with an incidence of 0.94% (95% confidence interval (CI) 0.37%-2.4%), a 6- to 9-fold increase over non DTG-based regimens (174). However, updated results have since shown the incidence of neural tube defects to be smaller than previously suggested at 0.3% (95% CI 0.13%-0.69%) (175). Since then, several studies in high-income countries, and the WHO global database of individual case safety reports, VigiBase, have shown no association between DTG and neural tube defects (175). Tenofovir alafenamide (TAF), approved by the FDA in 2016 as a successor drug to TDF, has been shown to have an improved side-effect profile and similar viral suppression outcomes in comparison to TDF (176–178).

To establish the effectiveness of DTG- and TAF-based regimens for HIV treatment in the South African setting, the ADVANCE trial was conducted in 2017-2020. The trial was a 96-week randomized phase 3 non-inferiority trial of three ART first-line regimens: 1) TAF/FTC+DTG, 2) TDF/FTC+DTG, and 3) TDF/FTC/EFV. Trial recruitment started in January 2017; 48-week follow-up was completed in May 2019, 96-week follow-up in March 2020. The trial established that at 48 and 96 weeks both the DTG-based regimens were non-inferior compared to the standard regimen at the time (TDF/FTC/EFV) with respect to viral load (VL) suppression. However,

patients in both DTG-based arms experienced substantial weight gain over the course of treatment, a result persisting by 96 weeks post-ART initiation with an increase of 7.1 kilogram (kg) (TAF-based arm) and 4.3 kg (TDF-based arm) over baseline weight, compared to 2.3 kg in the EFV-based arm (178). Additional safety data will be collected in the current extension to 192 weeks, with results expected in 2022. TAF has not yet been included in the WHO recommendations due to limited data on the use in low- and middle-income countries, and in patients with tuberculosis and pregnant women (179).

Based in part on the ADVANCE trial, in 2019 the South African government updated the ART guidelines (180) to include a fixed-dose combination for adults on first-line ART consisting of TDF (300mg), 3TC (300mg), and DTG (50mg) (abbreviated as TLD). These guidelines also provide guidance on how to initiate ART naïve patients on, and switch treatment-experienced patients to, DTG-containing regimens.

A number of studies have evaluated the cost and cost-effectiveness of DTG-containing ART (181–187), with a few studies in sub-Saharan Africa (55,188,189), and TAF/DTG combinations (190,191). Most of them found DTG to be a cost-effective treatment option in both treatment naïve and experienced adults, compared to TDF/FTC/EFV, as well as RAL- and DRV-based regimens. In these studies, cost-effectiveness was determined either in comparison to a threshold based on country-specific gross domestic product (GDP), or based on comparator ART regimens which were dominated.

Here we provide the details of an economic evaluation of the ADVANCE trial in order to provide evidence on the cost-effectiveness of DTG- and TAF-based regimens compared to EFV-based regimens in South Africa, under both a trial and a routine care scenario.

Methods

Cost analysis

We evaluated the trial up to the point where all patients had reached the primary 48-week outcome, which amounted to the calendar period between January 2017 and May 2019, including the time taken to enrol the full cohort. Patient trial data was used to ascertain resource utilisation for laboratory

testing, scheduled/unscheduled visits attended, and the dispensing of medications for concomitant diseases (which included medications dispensed for non-HIV related disease, e.g. diabetes, hypertension, as well as vitamin supplements and contraception), and study drugs (i.e. ART regimen). Concomitant medication records of patients did not specify the number of units dispensed at each visit, and therefore we estimated this quantity based on start and stop dates and usual doses. Site visits were conducted to determine resource utilisation for equipment used during the trial.

Both financial and economic cost were analysed from the provider's perspective using a combination of top-down and bottom-up cost analysis. Financial records of expenditure on equipment, consumables, staff salaries, study drugs, medications for concomitant conditions, laboratory testing and overheads (office/clinic rental, facility fees) were acquired directly from the study sponsor, Ezintsha Wits RHI. The cost of equipment was adjusted to the study period (January 2017 – May 2019) after annualizing costs based on the expected duration of the full trial (4 years), discounting at the average repurchase agreement rate for South Africa in 2019 of 6.5% (192), and multiplying by 2.41 years (the duration of the study period of interest).

The costs of each resource was checked against financial records provided. As not all medications for concomitant diseases dispensed during the trial were found in the pharmaceutical invoices provided, we used the single exit price (SEP) from the 2019 medicine price registry (193), a database of retail medicine prices regulated by the South African government, after determining that the majority of invoices aligned with private sector costs, or, for a select few medication prices for which we did not have an exact price, from the South African public-sector master procurement catalogue (MPC) (194). As the trial drugs DTG and TAF were donated by the manufacturer, we include their market value (ascertained from invoices provided) in the economic cost analysis. Patient-level costs (laboratory testing, ART regimen, medications for concomitant diseases, visit reimbursement) were attributed to the treatment arm which the patient was assigned to at randomization, while staff salaries, costs for equipment, consumables and overheads were assigned to arms based on the number of patient visits in that arm.

Costs that were incurred in 2016-2018 were adjusted to 2019 prices using one of four methods: i) based on guidelines for allowed drug price increases in

the private sector (193); ii) equipment and consumable costs were inflated based on the average annual consumer price index (195), iii) for laboratory costs, the price paid in 2019 was used, and iv) staff salaries were increased by the average annual salary increase calculated from the trial salary data. All costs are presented as 2019 United States Dollar (USD), using the average exchange rate for January to May 2019 (14.13 South African Rand (ZAR) = 1 USD) (118).

Outcomes

We evaluated the trial cost per outcome for two outcomes ascertained at the 48-week endpoint: the number of patients who remain virally suppressed (defined as the number of patients with a viral load of <50 copies/ml at their week 48 visit), and the number of patients retained on ART (defined by the number of patients who had at least 48 weeks of follow-up). DTG- and TAF-based regimens have been shown to have non-inferior, and in some trials superior, rates of viral suppression (22,23,176), and patients on these regimens have also reported a lower number of side-effects and increased tolerability, which may improve patient retention (24).

Routine care scenario adjustment

In order to adjust our cost estimates for trial-induced resource use (such as additional visits, higher staff cadres, and regular laboratory tests for safety reasons), we constructed a routine care scenario representative of care levels at a standard public sector primary health care (PHC) clinic (Table 1). We did this analysis for both the first and second year of ART, using 48- and 96-week trial outcomes respectively and making the assumption that the outcomes would remain the same as in the trial. Fixed costs (staff, equipment, consumables and overheads) were sourced from a recent bottom-up cost analysis of ART provision conducted at a PHC clinic based in Pretoria, South Africa (196), standardised to an average cost per visit and applied to the observed number of visits in each arm, which were capped at 4 in the second year, following national ART guidelines (180). For both ARVs and medications for concomitant diseases, quantities dispensed were based on trial data but prices were sourced from the MPC (194), with the exception of TAF, which is not licensed in South Africa and for which the donated value was used. Laboratory test quantities were based on test frequencies mandated by the current ART guidelines (180), partly adjusted to patient outcome data.

According to guidelines, ART patients are required to have two viral load measures in the first year – at 6 and 12 months after ART initiation, plus an additional viral load if the 6 month measure was >50 copies/ml (180). Patients have one CD4 count measured at 12 months (and a repeat if viral load at 6 months was >1000 copies/ml). Other monitoring tests (full blood count, haemoglobin, creatinine, hepatitis B, pap smear, and, if required, point-of-care tuberculosis diagnostics and pregnancy test) are only required once per patient during the first year of ART. The resulting quantities of laboratory monitoring in the routine care setting are in stark contrast to those in the trial, which conducted more frequent tests- for example, viral load, full blood count and creatinine were tested on average 6 times, and CD4 counts on average 3 times per patient in the first year. Additional laboratory testing not indicated in the ART guidelines was also conducted. For the routine care scenario, laboratory prices were based on 2019 National Health Laboratory Service prices (197).

Table 1. Routine care scenario adjustments

Category	Quantity	Cost (2019 USD)	Cost source
Staff	Adjusted for	$ 15.71 per visit	Long et al
Equipment	number of trial	$ 1.51 per visit	(196)
Consumables	visits per patient	$ 0.09 per visit	
Overheads		$ 3.27 per visit	
Laboratory*			
Viral load	2 per patient (repeat in cases if 6-month viral load >50 copies/ml)	$24.02 per test	National Health Laboratory Service (197)
CD4 count	1 per patient (repeat in cases if 6-month viral load >1000 copies/ml)	$4.71 per test	
GeneXpert tuberculosis test	As per trial data	$13.59 per test	
Creatinine	1 per patient	$2.15 per test	
Hepatitis B surface antigen	1 per patient	$8.91 per test	
Haemoglobin	1 per patient	$1.28 per test	
Full blood count	1 per patient	$4.11 per test	
Pap smear	1 per female patient	$10.93 per test	
Pregnancy test	As per trial data	$0.25 per test	

Category	Quantity	Cost (2019 USD)	Cost source
Drugs			
Medications for concomitant diseases	As per trial data	Variable prices; median cost per unit of medication = $0.04 (interquartile range $0.01 - $0.17)	Master Procurement Catalogue (194)
Study drugs			
TDF/FTC/EFV	As per trial data	$0.22 per pill	Master Procurement Catalogue (194)
TDF/FTC	As per trial data	$0.16 per pill	
DTG	As per trial data	$0.12 per pill	
TAF/FTC	As per trial data	$0.59 per pill	Donated value based on invoices from pharmaceutical companies

*Laboratory quantities based on ART guidelines (180) , and partly adjusted by using patient trial data. Abbreviations: ART=antiretroviral therapy; EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; DTG=dolutegravir; TAF= tenofovir alafenamide

Cost-effectiveness analysis

To assess the long-term cost-effectiveness of DTG-based regimens, we modelled their impact over a 20-year time horizon (2020-2039) using the Thembisa model, a transmission model of the South African HIV epidemic (198). We calculated the cost as the incremental impact on the entire HIV programme. We accounted for differences in retention and viral suppression between regimens using the 96-week outcomes from the ADVANCE trial, and assumed a national scale-up of DTG-based regimens to 20% of adults on first-line ART in 2020, 60% by mid-2021 and 100% thereafter, taking into account current delays in the DTG roll-out. For the cost of ART, we used the routine care cost per patient year, normalized to 12 months. The model assumes that improvements in viral suppression and retention on DTG lead to reductions in HIV transmission, but mortality is assumed to be the same regardless of ART regimen. As the ADVANCE trial did not show a viral suppression benefit after accounting for retention (i.e. viral suppression rates were similar amongst those retained), we included a sensitivity analysis with higher viral suppression, based on a meta-analysis which showed that DTG-based regimens had a 1.87 times odds of viral suppression over EFV-based

regimens (95% credible interval 1.34-2.64) (24); we assumed the same cost and retention benefit as the TDF-based arm in the trial. Key assumptions used or the modelling are shown in Supplementary Table S1.

Sensitivity analysis

We evaluated the impact of uncertainty in three key model parameters (viral suppression, retention and cost of ART per patient year) by conducting a probabilistic sensitivity analysis (PSA) using Monte Carlo simulation. The epidemiological and cost impact of TDF/FTC+DTG compared to TDF/FTC/EFV was assessed 1000 times, randomly drawing parameters' values from appropriate probabilistic distributions (Supplementary Table S2). We report on the cost-effectiveness over the 20-year time horizon (2020-39) with the median estimate and 95%CI using the 2.5th and 97.5th percentiles. The sensitivity of the results to the sampled parameters are quantified using partial correlation coefficients.

Ethics approval

We obtained approval for this study from the Wits Human Research Ethics Committee (Medical) (ref. no. 160606B).

Results

Outcomes

A total of 1,053 patients were enrolled and randomized to one of three treatment arms in the ADVANCE trial, which is described in detail elsewhere (198). Retention on ART by 48 weeks was higher in TDF/FTC+DTG (90%) and TAF/FTC+DTG (88%), compared to the EFV-based regimen (83%) (Table 2). Patients on the EFV-based regimen had a higher rate of discontinuation due to experiencing a serious or intolerable adverse event by week 48 (n=10, 2.8%) compared to those on TDF/FTC+DTG (0 patients) and TAF/FTC+DTG (n=1, 0.3%) (198). Of patients who were not retained by 48 weeks, the proportion who reported an adverse event that was related or possibly related to their ART regimen was highest in the EFV-based arm (50.0%; 30/60) compared to TDF/FTC+DTG (14.7%; 5/34) and TAF/FTC+DTG (14.6%; 6/41). At 48 weeks, the DTG-based arms had higher proportion of viral suppression of those randomized (83% and 82% for TDF/FTC+DTG and TAF/FTC+DTG, respectively) compared to the EFV-

based regimen (77%); however, viral suppression amongst those retained and measured were similar between groups: 94% (292/311) in TDF/FTC+DTG, 95% (287/302) in TAF/FTC+DTG and 95% (269/282) in the EFV-based arm. By 96 weeks, rates of viral suppression remained higher in the DTG-based arms (79% and 78% for TDF/FTC+DTG and TAF/FTC+DTG, respectively) compared to the EFV-based regimen (74%), while 96-week retention also remained higher (82% in DTG-based arms, 77% in EFV-based arm).

Table 2. Trial cost scenario: Summary of costs, outcomes and cost per outcome, by treatment arm (first year (0-48 weeks) only)

	DTG regimens		
	TDF-based (TDF/FTC+DTG)	**TAF-based (TAF/FTC+DTG)**	**EFV-based regimen (TDF/FTC/EFV)**
Resource use			
Number of participants	351	351	351
Visits (total number)	2,503	2,447	2,460
Scheduled visits	*2,348*	*2,326*	*2,283*
Unscheduled visits	155	121	177
Laboratory tests (total number)	49,254	48,553	47,907
Drugs (total drug-months)			
Medications for concomitant diseases	11,973	11,335	11,137
ART regimen	4,283	4,227	4,097
Outcomes at 48 weeks			
Patients virally suppressed (<50 copies/ml)	292	287	269
Patients retained	317	310	291
Total cost (2019 USD) (% of total)			
Staff and consultants	$ 1,976,950 (69.2%)	$ 1,932,720 (67.8%)	$ 1,942,987 (69.7%)
Equipment	$ 25,104 (0.9%)	$ 24,543 (0.9%)	$ 24,673 (0.9%)
Consumables	$ 3,702 (0.1%)	$ 3,619 (0.1%)	$ 3,638 (0.1%)
Overheads			
Facility fees and rental	$ 191,292 (6.7%)	$ 187,012 (6.6%)	$ 188,006 (6.7%)
Trial visit reimbursement	$ 51,296 (1.8%)	$ 50,689 (1.8%)	$ 49,978 (1.8%)
Laboratory	$ 460,868 (16.1%)	$ 452,258 (15.9%)	$ 447,298 (16.0%)
Drugs			
Medications for concomitant diseases	$ 26,862 (0.9%)	$ 28,498 (1.0%)	$ 27,702 (1.0%)
ART regimen	$ 120,753 (4.2%)	$ 170,654 (6.0%)	$ 104,319 (3.7%)

	DTG regimens		
	TDF-based (TDF/FTC+DTG)	**TAF-based (TAF/FTC+DTG)**	**EFV-based regimen (TDF/FTC/EFV)**
Total cost (2019 USD)	**$ 2,856,559**	**$ 2,849,704**	**$ 2,788,317**
Median cost per patient year (2019 USD)			
Staff and consultants	$ 5,529 (68.0%)	$ 5,529 (66.8%)	$ 5,529 (68.5%)
Equipment	$ 70 (0.9%)	$ 70 (0.8%)	$ 70 (0.9%)
Consumables	$ 10 (0.1%)	$ 10 (0.1%)	$ 10 (0.1%)
Overheads			
Facility fees and rental	$ 535 (6.6%)	$ 535 (6.5%)	$ 535 (6.6%)
Trial visit reimbursement	$ 151 (1.9%)	$ 151 (1.8%)	$ 151 (1.9%)
Laboratory	$ 1,364 (16.8%)	$ 1,356 (16.4%)	$ 1,347 (16.7%)
Drugs			
Medications for concomitant diseases	$ 55 (0.7%)	$ 54 (0.7%)	$ 55 (0.7%)
ART regimen	$ 395 (4.9%)	$ 567 (6.8%)	$ 356 (4.4%)
Median (interquartile range)	**$ 8,125 (8,056 - 8,872)**	**$ 8,275 (8,210 - 8,478)**	**$ 8,068 (7,992 - 8,909)**
Total, mean (standard deviation)	**$ 8,138 (1,507)**	**$ 8,119 (1,596)**	**$ 7,944 (1,684)**
Cost per outcome (2019 USD)			
Cost per virally suppressed patient	**$ 9,783**	**$ 9,929**	**$ 10,365**
Cost per patient retained	**$ 9,011**	**$ 9,193**	**$ 9,582**
Incremental cost-effectiveness (2019 USD)			
Cost per additional virally suppressed patient	**$ 2,967**	**$ 3,410**	-
Cost per additional patient retained	**$ 2,625**	**$ 3,231**	-

Abbreviations: EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; DTG=dolutegravir; TAF=tenofovir alafenamide; USD=United States dollars

Resource use

a) Trial resource use

Patients attended 2,460-2,503 scheduled and unscheduled visits during the first 48 weeks of the trial, culminating in approximately 48,000 laboratory tests per arm, 11,000 concomitant drug-months and 4,000 ART drug-months dispensed, with the DTG-based arms having more laboratory tests and drugs

dispensed (both medications for concomitant diseases and ART regimen) (Table 2).

b) Routine care resource use

We assumed the same number of drugs dispensed (medications for concomitant diseases and ART regimen) in the routine care scenario as was the case in the trial (Table 3). Visits and drug quantities were significantly lower in the second year of ART as compared to the first year. Laboratory tests were significantly lower than in the trial, with approximately 2,300 laboratory tests conducted during the first year, and around 300 laboratory tests, either viral load or CD4 count, in the second year (Table 3).

Costs

a) Trial cost scenario

The total economic cost of the trial was $8.49 million over the 48-week outcome study period, including a total of $268,900 in study drugs (DTG and TAF/FTC) donated by the manufacturer, equating to a financial cost of $8.22 million (Table 2). The main cost driver was staff (69%), followed by laboratory testing (16%) and facility fees/rental (7%) (Supplementary Figure S1). Cost drivers did not differ by treatment arm. TDF/FTC+DTG and TAF/FTC+DTG arms were around 2% more expensive than the TDF/FTC/EFV arm. The cost increase was mainly driven by the higher ART cost for DTG and TAF/FTC compared to TDF/FTC/EFV; in the TDF/FTC+DTG arm, a higher number of visits, partly due to higher retention in this group, led to higher fixed costs. Median cost per patient per year was lowest in the TDF/FTC/EFV arm at $8,068 (interquartile range (IQR) $7,992-$8,909), and $8,125 (IQR $8,056-$8,871) and $8,275 (IQR $8,210-$8,478) in the TDF/FTC+DTG and TAF/FTC+DTG arms, respectively.

Table 3. Routine care scenario: Summary of costs, outcomes and cost per outcome, by treatment arm and trial year

	First year (0-48 weeks)			Second year (48-96 weeks)		
	DTG regimens		EFV-based regimen	DTG regimens		EFV-based regimen
	TDF-based (TDF/FTC+DTG)	TAF-based (TAF/FTC+DTG)	(TDF/FTC/EFV)	TDF-based (TDF/FTC+DTG)	TAF-based (TAF/FTC+DTG)	(TDF/FTC/EFV)
Resource use						
Number of patients	351	351	351	310	306	285
Visits (total number)	2,503	2,447	2,460	1,196	1,180	1,104
Laboratory tests (total number)	2,355	2,343	2,296	319	307	290
Drugs (total drug-months)						
Medications for concomitant diseases	11,973	11,335	11,137	2,771	2,307	2,609
ART regimen	4,283	4,227	4,097	3,493	3,393	3,150
Median cost per patient year *(2019 USD)*						
Staff	$110	$110	$110	$63	$63	$63
Equipment	$11	$11	$11	$6	$6	$6
Consumables	$1	$1	$1	$0.4	$0.4	$0.4
Overheads	$23	$23	$23	$13	$13	$13
Laboratory	$76	$76	$69	$24	$24	$24
Drugs						
Medications for concomitant diseases	$26	$26	$25	$9	$8	$8
ART regimen	$119	$297	$90	$102	$255	$77
Total median cost per patient	**$363 (347 - 385)**	**$539 (505 - 558)**	**$335 (315 - 360)**	**$219 (209 - 241)**	**$368 (361 - 384)**	**$194 (184 - 209)**

	First year (0-48 weeks)			Second year (48-96 weeks)		
	DTG regimens		EFV-based regimen	DTG regimens		EFV-based regimen
	TDF-based (TDF/FTC+DTG)	TAF-based (TAF/FTC+DTG)	(TDF/FTC/EFV)	TDF-based (TDF/FTC+DTG)	TAF-based (TAF/FTC+DTG)	(TDF/FTC/EFV)
(interquartile range)						
Mean cost per patient (standard deviation)	$355 (77)	$502 (126)	$325 (92)	$226 (81)	$357 (76)	$198 (47)
Mean cost per patient year (normalised to 12 months)	$386	$546	$352	$281	$441	$241
Cost per outcome						
Cost per virally suppressed patient	$426	$614	$424	$257	$404	$220
Cost per patient retained	$393	$568	$392	$244	$380	$209

Abbreviations: EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; DTG=dolutegravir; TAF=tenofovir alafenamide; USD=United States dollars; ART=antiretroviral therapy

The DTG-based arms had a lower cost per virally suppressed patient compared to the EFV-based regimen arm ($9,783 and $9,929 per virally suppressed patient for TDF/FTC+DTG and TAF/FTC+DTG, respectively, vs. $10,365 per virally suppressed patient for TDF/FTC/EFV (Table 2). The cost per additional virally suppressed patient, compared to the EFV-based regimen, was lower in the TDF/FTC+DTG arm with $2,967 compared to the TAF/FTC+DTG with $3,410 (Table 2). Similarly, the cost per patient retained on ART was lower in the DTG-based arms, with $9,011 for TDF/FTC+DTG and $9,193 for TDF/FTC+DTG, compared to the EFV-based regimen arm which cost $9,582 per patient retained on ART. In comparison to the EFV-based regimen, the cost per additional person retained on ART was again lower in the TDF/FTC+DTG arm vs. the TAF/FTC+DTG arm ($2,625 vs. $3,231, respectively) (Table 2).

b) Routine care scenario

Under the routine care scenario, the overall economic cost was reduced to ~5% of the cost of running the trial. The median cost of medications for concomitant diseases and ART per patient were between 46%-49% and 25-52% that of the trial cost for the first year of ART, respectively (Table 3). Most of the cost reduction were a result of reduced fixed costs, including staff costs, and laboratory testing. Overall, the median cost per patient year was lowest in the TDF/FTC/EFV arm at $335 (IQR $315-$360), and $363 (IQR $347-$385) and $539 (IQR $505-$558) in the TDF/FTC+DTG and TAF/FTC+DTG arms, respectively. By the second year of ART, median cost per patient was lower, due to less visits taking place as well as a reduction in the number of medications for concomitant diseases dispensed. This led to an average cost per patient year (normalized to 12 months) of $281 for TDF/FTC+DTG, $441 for TAF/FTC+DTG and $241 for TDF/FTC/EFV.

In first year of ART in the routine care scenario, the cost per virally suppressed patient and per patient retained in the TDF/FTC/EFV arm was $426 and $393, respectively, similar to that of the TDF/FTC+DTG arm at $424 and $392, respectively. The cost per virally suppressed patient and per patient retained was higher in the TAF/FTC+DTG arm at $614 and $568, driven by the assumed market value of TAF. If TAF were to be licensed for ART use in South Africa these costs would likely decrease. In the second year of ART, cost per virally suppressed patient and per patient retained was relatively higher in the TDF/FTC+DTG arm ($257 and $244, respectively)

than in the EFV-based arm ($220 and $209, respectively), largely due to more medication for concomitant diseases and higher ART regimen costs. Cost per virally suppressed patient and per patient retained remained high in the TAF/FTC+DTG arm ($404 and $380, respectively).

Cost effectiveness

DTG-based regimens were estimated to save between 533,000 (TDF/FTC+DTG) and 563,000 (TAF/FTC+DTG) life years over the EFV-based regimen, and avert 13,000-14,000 AIDS deaths, over 20 years (Table 4), as a result of decreased HIV transmission from patients on ART. TDF/FTC+DTG had a lower incremental cost effectiveness ratio compared to TAF/FTC+DTG for life years saved ($10,341 vs $41,958, respectively) and AIDS deaths averted ($413,196 vs $1,671,834, respectively). Under a higher effectiveness bound, 788,000 life years would be saved and 20,000 AIDS deaths averted; it was most cost-effective with regards to both life years saved and AIDS deaths averted ($6,788 and $266,423, respectively).

In the PSA, 38% of simulations resulted in cost savings of TDF/FTC+DTG compared to TDF/FTC/EFV, mostly due to a lower sampled cost (Figure 1). Around 13% of simulations had a lower retention rate on TDF/FTC+DTG compared to TDF/FTC/EFV, resulting in more AIDS deaths over time. Overall, the median cost per life-year saved over 20 years was $3,119, with a 95% CI of $60,970, while the median cost per AIDS death averted was $126,085 with a 95% CI of $2,402,759. Incremental cost was most sensitive to the cost of ART between in the follow-up years, while life years saved and AIDS deaths averted were most sensitive to relative rates of viral suppression and the rate of ART interruption (Supplementary Table S2).

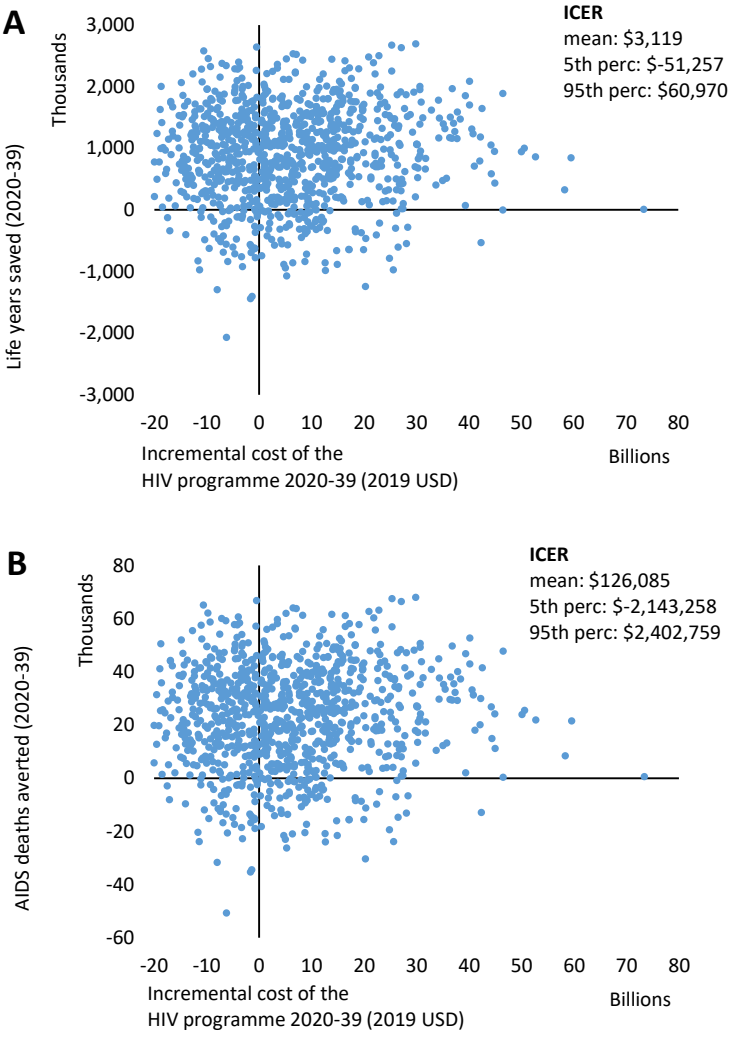
Table 4. Cost-effectiveness of DTG-based regimens compared to EFV-based regimens (2020-2039)

	DTG regimens			
	TDF-based (TDF/FTC+ DTG), trial effectiveness	**TAF-based (TAF/FTC+ DTG), trial effectiveness**	**TDF-based (TDF/FTC+ DTG), higher effectiveness***	**EFV-based regimen (TDF/FTC/EFV)**
Model parameters				
Outcomes				
Retention	82%	82%	82%	77%
VL suppression <400 copies/ml (of those retained)*	96%	97%	N/A	96%
Relative OR to EFV-based regimen	1.00	1.06	1.87	-
Cost inputs (2019 USD)				
Mean cost per person year				
First year	$386	$546	$386	$352
Follow-up year	$281	$441	$281	$241
Results				
Outcomes (2020-39)				
Life years lost, millions	35.97	35.94	35.72	36.51
Life years saved, thousands	533	563	788	-
AIDS deaths, thousands	998	997	991	1,011
AIDS deaths averted, thousands	13	14	20	-
Costs (2020-39) (2019 USD)				
Total cost of HIV programme, billions	$39.25	$57.36	$39.08	$33.73
Incremental cost, billions	$5.5	$23.6	$5.4	-
Incremental cost effectiveness				
Incremental cost per life-year saved	$10,341	$41,958	$6,788	-
Incremental cost per AIDS death averted	$413,196	$1,671,834	$266,423	-

*Viral suppression in the Thembisa model has a threshold of <400 copies/ml, therefore adjusted the outcome in this analysis.

Abbreviations: OR=odds ratio; USD=United States dollars; EFV=efavirenz; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; DTG=dolutegravir; TAF=tenofovir alafenamide

Figure 1. Incremental cost (2019 USD) of the HIV programme against (A) life years saved, and (B) AIDS deaths averted new HIV infections averted (2019-38), impact of TDF/FTC+DTG compared to TDF/FTC/EFV (each dot represents a Monte Carlo simulation from a probabilistic sensitivity analysis)



Discussion

Our analysis shows that the DTG-based regimens were more costly overall, in both the trial and routine care scenarios, which was due to both the higher cost of the ART regimen itself and improved retention in the DTG-based arms resulting in more drug being dispensed; however, due to improvements in the outcomes over the EFV-based regimen arm, the DTG-based regimens had lower cost per virally suppressed patient and cost per person retained in care by 48 weeks – when based on trial cost. Our adjusted routine care scenario resulted in more conservative results, with cost per outcome being similar between TDF/FTC+DTG and TDF/FTC/EFV, implying that on average it will cost the same to achieve similar outcomes with either of these ART regimens in the public sector. However, the DTG-based regimen will result in a higher proportion of virally suppressed patients overall. We identified a likely causal link between ART regimen and patient retention: Patients on the EFV-based arm were more likely to voluntarily withdraw due to adverse events, and among patients not retained by 48 weeks, a larger proportion reported related or possibly related adverse events prior to leaving the trial. Though this will result in higher cost of ART as those on DTG-based regimens remain in care at higher rates, the benefit of patient retention, and possibly higher viral suppression, mean this will be more cost-effective than the EFV-based regimens.

Clinical trials are necessarily significantly more expensive than routine care, but can give some indication of the magnitude of cost differences between regimens, especially when based on data from a randomised trial. In our routine care scenario, overall costs were reduced dramatically, in particular due to reduced fixed costs, and a reduced number of laboratory tests required by standard ART guidelines. Estimating how trial resource use and subsequent costs would have changed in routine care, this type of analysis becomes useful in supplying evidence for policymakers making decisions with regards to implementing novel ART regimens. However, a number of limitations need to be considered alongside this evidence.

Firstly, we assumed that patients would have achieved the same outcomes in the routine care scenario as they did in the trial, despite receiving HIV treatment with less resources (such as higher patient-staff ratios, and less laboratory monitoring). In reality, patients would receive less medications for

concomitant diseases and conditions and less tailored care in public sector compared to a clinical trial. This careful attention to patients may positively impact on trial treatment retention in comparison to public sector health care. Despite this difference between the clinical trial and routine care settings, we would still expect to see relatively improved outcomes on DTG-based regimens, resulting in similar conclusions with respect to cost-effectiveness. Secondly, the ADVANCE trial showed continued, and increasing, weight gain well into the 96-week post-ART initiation period (178), but there is not enough data available to inform assumptions regarding the mortality and subsequent cost impacts of this side-effect beyond two years. While weight gain associated with integrase strand transfer inhibitors (199) more generally might lead to increased health systems cost and mortality in the long run, recent data on the link between obesity and all-cause mortality from a population cohort in South Africa have however shown that individuals who meet clinically-defined criteria for being overweight or obese had a lower risk of all-cause mortality than those with a normal BMI, an effect that was larger in those with a positive HIV status (200). This suggests that the evidence on a link between obesity and mortality in PLHIV in South Africa is unclear at present, and highlights the importance of ongoing economic analysis based on real-world data regarding the frequency and severity of side effects under DTG and their impact on morbidity, patient quality of life, and mortality. Lastly, though we used cost analyses from a South African clinic to estimate fixed costs for our routine care setting, it is possible that this may not be representative of all public health care in South Africa.

Conclusion

Our analysis demonstrated that TDF/FTC+DTG had similar costs per outcome as TDF/FTC/EFV in the routine care scenario, but TDF/FTC+DTG was more cost-effective when modelled over 20 years. We also provided insights into how to translate cost and resource data from a trial into something more representative of routine care, a methodology that is important for both modellers and policy makers as they consider the long-term impact of novel interventions in routine-care settings.

Supplementary Appendix

Section A: Modelling ART initiation, interruption and mortality in Thembisa

Adults who have been diagnosed HIV-positive are assumed to start ART at a rate that changes over time, as ART rollout expands and treatment eligibility criteria change (201). Once individuals have started ART, they are stratified by their time since ART initiation and baseline CD4 category.

ART interruption

The model does not define a separate state to represent individuals who have interrupted ART. However, the model does calculate, for each of the times since ART initiation, the probability that the individual is on ART versus interrupting ART, and these duration-specific probabilities are used in calculating the number of adults currently on ART at any point in time. Figure A1 presents an overview of the theoretical model that we apply to South African data sources, for the purpose of estimating rates of ART interruption and durations of interruption.

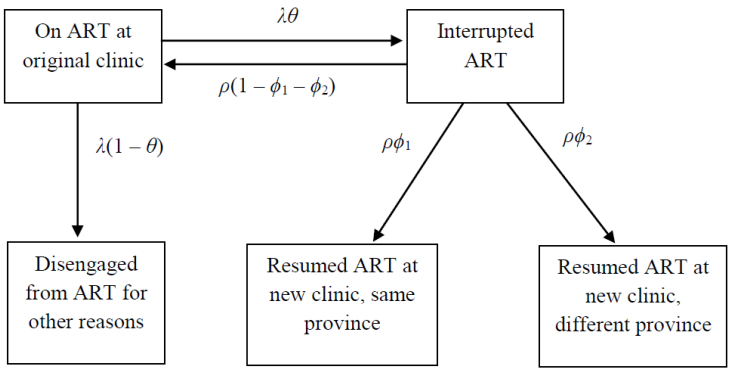


Figure A1. Model of ART interruption and return to care

Patients are assumed to disengage from care at a constant rate λ, but only a proportion θ of these disengagements are assumed to be true ART interruptions. The reasons for other disengagement will vary from study to study, depending on the methods used to classify patients 'lost to follow-up' (LTFU), but will most commonly include patients who have transferred to other ART services (so-called 'silent transfers') and patients who have died without their death being recorded by the clinic at which they were receiving

ART. The patients who interrupt ART are assumed to resume ART at a constant rate ρ, with a proportion ϕ1 of these patients resuming ART at a different clinic within the same province, a proportion ϕ2 resuming ART in a different province, and the remainder resuming ART at the same clinic at which they originally received ART. For the sake of simplicity, we do not consider mortality while interrupting ART, as studies suggest that after excluding the deaths that occur soon after LTFU (which in most cases represent failure to record mortality rather than mortality after a treatment interruption) this is a relatively infrequent occurrence (202,203).

We attempt to estimate the parameters using data from three different South African studies that estimated either rates of treatment interruption or rates of treatment resumption (203–205). Each study follows a different design, and no single study estimates all of these parameters, but by drawing on the estimates from different studies it is possible to determine plausible ranges for the parameters (Table A1).

Table A1. Summary of South African estimates

Parameter and source	Estimate (95% CI)	Comment
Rate of 'true' ART interruption ($\lambda\theta$)		
Kaplan *et al* (203)	0.16-0.19	Likely under-estimate
Kranzer *et al* (204)	0.06	Likely under-estimate
Clouse *et al* (205)	0.10	Likely under-estimate
Rate of ART resumption (ρ)		
Kaplan *et al* (203)	0.92 (0.67-1.32)	-
Kranzer *et al* (204)	0.94 (0.46-1.65)	-
Clouse *et al* (205)	0.70 (0.28-2.60)	-

Table A1 summarizes the estimates of the rate of ART interruption and resumption from the different studies reviewed previously. None of the studies provides a truly unbiased measure of the rate of treatment interruption. The Kaplan and Clouse studies are both likely to under-estimate the true rate because they exclude individuals who interrupted ART and then resumed ART at the same clinic. The Kranzer study also is likely to under-estimate the true rate, as it excludes patients who left the study area (who may have been more likely to interrupt ART), and it followed the patients who remained in the study area intensively (i.e. follow-up may not have been typical of that in the general public health sector). For the purpose of modelling ART

interruptions in Thembisa, we assume a value of 0.2318 for the annual rate of ART interruption.

Pooling the rates of ART resumption estimated in Table A1 and weighting by the inverse of the variance gives an average ART resumption rate of 0.91 (95% CI: 0.68-1.21). We therefore assign a value of 0.90 to the ρ parameter, again noting the need for further work to consider uncertainty around this parameter.

Now consider a simplified model in which mortality after ART initiation is the same regardless of whether individuals remain on ART or interrupt ART. We define I(t) to be the fraction of patients who started ART t years ago who are currently interrupting ART. This fraction can be calculated using the differential equation

$$\frac{d\,I(t)}{dt} = \big(1 - I(t)\big)\lambda\theta - I(t)\rho$$

with the initial condition I(0)=0. Substituting the previously-assumed values of 0.25 and 0.90 for λθ and ρ respectively into the equation, and solving numerically, we get estimates of I(t) of 0.057 for 3 months after ART initiation, 0.152 for 12 months, 0.198 for 24 months, 0.212 for 36 months and 0.216 for 48 months. The values are slightly different from those estimated in a recent analysis, based on African tracing studies, which estimated that the fraction of survivors who had stopped or interrupted ART was 0.100 12 months after ART initiation and 0.265 5 years after ART initiation (206). As this study excluded transient ART interruptions, the lower estimated fraction off ART at 12 months (0.100 compared to 0.152 in our model) is to be expected.

Mortality after ART initiation in adults

HIV-related mortality after ART initiation is assumed to depend on age, sex, baseline CD4 category and time since ART initiation. The mortality rates specified in Table A2 relate to individuals who are aged 35, and these mortality rates are assumed to increase by factors of 1.12 and 1.09 per 10-year increase in age, in men and women respectively.

Table A2. Parameters by HIV disease stage

Parameter	CD4 range 500+	350-499	200-349	<200	Source
Annual male HIV mortality after ART initiation, by baseline CD4‡					
1st 6 months of ART	0.0002	0.0016	0.0146	0.2554	(207)
Months 7-18	0.0009	0.0050	0.0132	0.0613	
Months 19-30	0.0027	0.0085	0.0116	0.0306	
Months 31-42	0.0042	0.0076	0.0076	0.0202	
Months 43+	0.0049	0.0063	0.0063	0.0166	
Annual female HIV mortality after ART initiation, by baseline CD4‡					
1st 6 months of ART	0.0001	0.0016	0.0159	0.2072	(207)
Months 7-18	0.0008	0.0045	0.0101	0.0490	
Months 19-30	0.0020	0.0057	0.0057	0.0235	
Months 31-42	0.0027	0.0034	0.0034	0.0141	
Months 43+	0.0025	0.0025	0.0025	0.0103	

‡ Parameters are adjusted to take into account age effects, and effects of increasing baseline CD4 counts over time.

For the most part these parameters have been determined from a model fitted to data from the IeDEA Southern Africa collaboration (207). However, the IeDEA-SA data relate mainly to individuals who start ART with CD4 counts below 350 cells/μl, and the few patients starting ART at higher CD4 counts are mostly patients who started ART because they qualified on the basis of HIV-related symptoms. Although we lack South African data on mortality in asymptomatic patients starting ART at higher CD4 counts, observational data from high income countries suggest that untreated patients with CD4 counts above 250 cells/μl have similar long-term mortality rates, as long as they start ART before their CD4 count declines below 250 cells/μl (208). We have therefore set the mortality rates of patients starting ART at higher CD4 counts in such a way that the predicted long-term mortality rate in untreated patients with CD4 counts above 500 cells/μl is roughly the same regardless of whether they start ART immediately, defer ART to when their CD4 count drops below 500, or defer ART to when their CD4 count drops below 350.

Within the group of patients starting ART at CD4 counts <200 cells/μl there is substantial heterogeneity in mortality depending on the exact baseline CD4 value. Although the model does not explicitly model variation in mortality rates by CD4 count below the 200 cells/μl cut-off, mortality rates are adjusted to take into account the rate of ART initiation, since high rates of ART initiation would imply that (a) most individuals starting ART at CD4 <200 cells/μl do so soon after their CD4 count falls below 200, and (b) most

untreated individuals with CD4 <200 cells/μl have CD4 counts close to 200. We therefore calculate the theoretical minimum mortality rates that would be expected (both in untreated individuals with CD4 <200 and in treated individuals starting ART with CD4 <200) if ART was started soon after the CD4 count dropped below the 200 threshold. The difference between the mortality rate in Table A2 and the theoretical minimum is reduced by a factor of exp(-mrg(t −)) in year t, where rg (t −) is the average rate of ART initiation in the 3 years prior to year t, in adults of sex g with CD4 <200 cells/μl, and m is a scaling factor with value 5.831 (209). This scaled difference is added to the minimum mortality rate to determine the modelled mortality rate in year t. The adjustments are made only to those ART-naïve adults with CD4 counts <200 cells/μl and those treated adults with baseline CD4 counts <200 cells/μl.

Section B: Additional assumptions for analyses conducted

Supplementary Table S1. Key model assumptions for main analysis

Assumption	TDF-based (TDF/FTC+ DTG), trial effectiveness	TAF-based (TAF/FTC+ DTG), trial effectiveness	TDF-based (TDF/FTC+ DTG) higher effectiveness*	EFV-based regimen (TDF/FTC/EFV)
Relative rate of ART interruption compared to TDF/FTC/EFV	0.7826	0.7826	0.7826	n/a
Proportion of adults starting ART with CD4<200 who are virally suppressed (<400 copies/ml)	0.8996	0.9032	0.9298	0.8996
Cost per patient per year on ART (first year) (2019 USD)	$386	$564	$386	$352
Cost per patient per year on ART (follow-up years) (2019 USD)	$281	$441	$281	$241

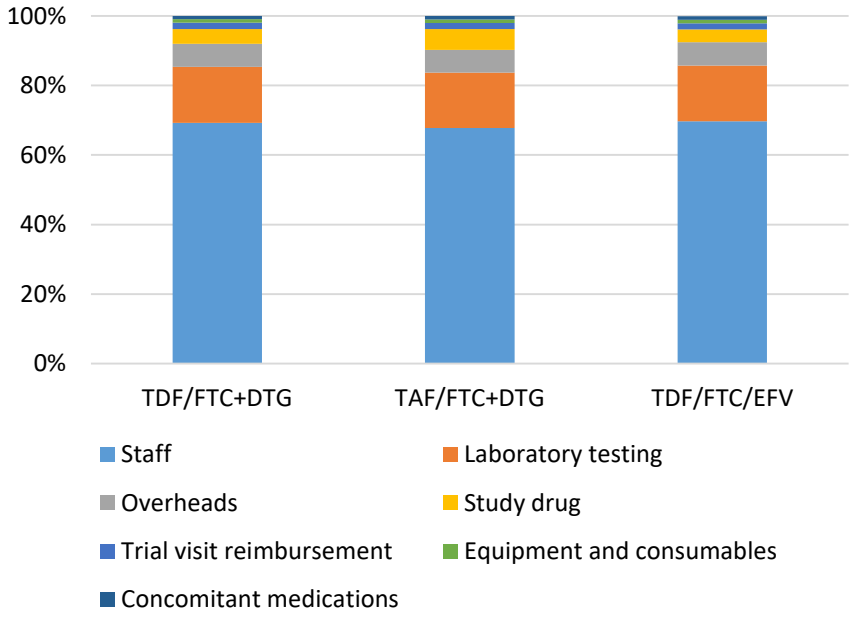
* higher viral suppression, based on a meta-analysis from Kanters et al (2016) which showed that DTG-based regimens had a 1.87 times odds of viral suppression over EFV-based regimens (95% credible interval 1.34-2.64) (24)

Supplementary Table S2. Probability distributions used for parameters varied in the probabilistic sensitivity analysis

Parameter	Regimen arm	Distribution	Mean, standard deviation
Odds ratio of viral suppression relative to TDF/FTC/EFV	TDF/FTC+DTG	Normal (1.87, 0.32)	1.87, 0.32
Relative rate of ART interruption compared to TDF/FTC/EFV	TDF/FTC+DTG	Gamma (6.8053, 8.6957)	0.78, 0.30
Cost of ART per patient year (2019 USD)			
First year	TDF/FTC+DTG	Gamma (18.9191, 0.00347)	386, 88
	TDF/FTC/EFV	Gamma (11.6265, 0.00234)	352, 103
Follow-up years	TDF/FTC+DTG	Gamma (6.2173, 0.00156)	281, 113
	TDF/FTC/EFV	Gamma (16.9117, 0.00497)	241, 59

Section C: Additional results

Supplementary Figure S1. Contribution of cost categories to total cost by trial arm



Supplementary Table S2. Partial rank correlation coefficients of results from probabilistic sensitivity analysis

Parameter varied in model	Incremental cost	Life years saved	AIDS deaths averted
Difference in ART cost for 1st year *(TDF/FTC/EFV - TDF/FTC+DTG)*	-0.008	-0.023	-0.023
Difference in ART cost for follow-up years *(TDF/FTC/EFV - TDF/FTC+DTG)*	-0.996	0.012	0.011
Odds ratio of viral suppression relative to TDF/FTC/EFV	-0.944	-0.995	-0.994
Relative rate of ART interruption compared to TDF/FTC/EFV	-0.100	0.631	0.641

Chapter 6

How soon should patients be eligible for differentiated service delivery models for antiretroviral treatment? Evidence from Zambia

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BMJ Open 12, e064070

Abstract

Objectives: Patient attrition is high the first six months after antiretroviral therapy (ART) initiation. Patients with <6 months ART are systematically excluded from most differentiated service delivery (DSD) models, which are intended to support retention. Despite DSD eligibility criteria requiring ≥6 months on ART, some patients enroll earlier. We compared loss to follow-up (LTFU) between patients enrolling in DSD models early to those enrolled according to guidelines, assessing whether the ART experience eligibility criterion is necessary.

Setting: In a retrospective cohort study using routinely-collected electronic medical record data in Zambia, we assessed adults (≥15 years) who initiated ART between 01/01/2019 and 31/12/2020, evaluating LTFU (>30 days late for scheduled visit) at 18 months for "early enrollers" (DSD enrolment after <6 months on ART) and "established enrollers" (DSD enrolment after ≥6 months on ART). We used a log-binomial model to compare LTFU risk, adjusting for age, sex, location, ART refill interval, DSD model.

Participants: For 6,340 early enrollers and 25,857 established enrollers there were no differences in sex (61% female), age (median 37 years), or location (65% urban). ART refill intervals were longer for established vs early enrollers (72% vs 55% were given 4–6-month refills).

Results: LTFU at 18 months was 3% (192/6,340) for early enrollers and 5% (24,646/25,857) for established enrollers. Early enrollers were 41% less likely to be LTFU than established patients (adjusted risk ratio [95% confidence interval] 0.59 [0.50-0.68]).

Conclusions: Patients enrolled in DSD after <6 months' ART were more likely to be retained than patients established on ART prior to DSD enrolment. A limitation is that early enrollers may have been selected for DSD due to providers' and patients' expectations about future retention. Offering DSD models to ART patients soon after ART initiation may help address high attrition during the early treatment period.

Strengths and limitations

- Our analysis utilized data from Zambia's national electronic medical record system, with records from the entire national HIV treatment cohort over four years (2018-2021) in all ten provinces.
- We report observed outcomes for more than 6,000 antiretroviral treatment (ART) clients who enrolled in differentiated service delivery (DSD) models after less than six months' experience on ART.
- Results reflect large-scale, routine program implementation, rather than clinical trial settings.
- A key limitation is the assumption that patients who were enrolled in DSD models after less than 6 months on ART were selected based on an expectation of good future adherence.
- A further limitation is the potential bias if facilities with better-than-average retention rates were more likely to allow early DSD model enrollment; results may reflect differences in the quality of services as opposed to the relationship between duration on ART before DSD enrollment and retention in care.

Introduction

A critical step toward achieving universal coverage of antiretroviral therapy (ART) for HIV is to support lifelong patient retention in ART programmes. Data from sub-Saharan Africa (SSA), where some 70% of the world's ART patients reside, continue to indicate insufficient retention on ART (210), with about a fifth of all patients lost to care five years after treatment initiation (206). A patient's first six months after initiation are a high risk period for attrition: a Zambian study showed rates of loss to follow-up to be four-fold higher in the first six months of ART treatment compared to the period between six months and 3.5 years thereafter (211).

Since 2016, the World Health Organization (WHO) has recommended differentiated service delivery (DSD) for HIV treatment (30). DSD models such as facility-based individual "fast track" medication pickup and community-based ART refills can increase access and remove barriers to care by adjusting the cadre of provider, location of service delivery, frequency of interactions with the healthcare system, and/or types of services offered to support long-term retention of people established on HIV treatment (28). A recent systematic review reporting on outcomes of patients in DSD models in SSA found that retention in care of those in DSD models was generally within 5% of that for conventional care (29). In Zambia, several DSD models have shown to have similar rates of retention as conventional care 12 months after DSD model entry (212,213). The INTERVAL trial, a cluster-randomized, non-inferiority trial conducted in Malawi and Zambia, found that 6-month ART dispensing was non-inferior in terms of 12-month retention, compared to standard of care (213). DSD models have consistently been found to save substantial time and money for patients themselves, and satisfaction with the models among both providers and patients has been high (213–215).

A major limitation to the scale-up of DSD models to date has been eligibility criteria that limit enrollment to patients who are "stable" or "established on treatment, which is defined as patients who: i) are on first-line ART regimens; ii) have been on ART for at least 6 or 12 months; and iii) have a recent, documented suppressed viral load (213,216–218). Until April 2021, the WHO's definition of "established" included at least 12 months of ART experience; new guidelines require at least 6 months on ART for DSD model eligibility (219). Patients who are newly initiated on ART are thus systematically excluded from stable-patient-specific DSD models and from

the benefits they offer. In the previously cited INTERVAL trial in Malawi and Zambia, 10% of all patients were excluded due to having initiated ART less than 6 months prior (220). For patients not eligible for DSD models, guidelines typically require frequent visits to the healthcare facility and medication dispensing intervals of no more than 3 months (221). In Zambia, all care is differentiated and dependent on the needs of the patient (216), but currently there is no evidence on the outcomes of patients with <6 months ART experience who enroll into DSD models that are typically reserved for stable patients.

Despite existing guidelines limiting DSD eligibility based on time on ART, in practice patients who do not meet guideline-recommended criteria are sometimes enrolled in DSD models for stable patients, due to provider decision, error or patient request. To understand how such patients who are referred early to DSD models fare when participating in DSD models designed for those established on treatment, we analyzed routinely collected medical record data from Zambia to compare rates of retention among patients enrolled into DSD models earlier than guidelines recommend with retention among those who met all eligibility criteria.

Methods

Study population and outcomes

We conducted a retrospective cohort study with data extracted in October 2021 from SmartCare, Zambia's national electronic medical record system (222). We extracted data for patients, aged 15 years or older, reported to have initiated ART between January 2019 and December 2020 at any of 692 health facilities across all 10 provinces. Zambian policy guidelines for this period required patients to be stable on ART before they are considered for DSD enrolment, with stability defined in the 2018 consolidated ART guidelines (216,217) as on ART for at least six months.

We defined patients who enrolled into a DSD model with <6 months of ART as "early enrollers", while a comparison group of patients who enrolled into a DSD model with ≥6 months of ART as "established enrollers". Patients on second-line ART (defined as those dispensed protease inhibitors such as lopinavir, atazanavir or ritonavir) were excluded from this analysis, as they are already known to be at high risk of attrition (223,224). For both early and established enrollers, we assessed loss to follow-up (LTFU) at 18 months

post-ART initiation, with LTFU defined as patients who were reported as "lost to follow-up" or "inactive" in the SmartCare database between 15 and 21 months after ART initiation date. "Inactive" was defined as having missed a scheduled visit by more than 30 days. Rates of LTFU were calculated for early and established enrollers and stratified by DSD model type and ART dispensing duration. DSD models, which had multiple names in the SmartCare database, were grouped into the following categories: 1) adherence groups (community adherence groups, rural/urban adherence groups); 2) extended clinic hours (DSD models designed for clinic access before/after hours or weekends, including scholar models); 3) fast-track (procedures to accelerate dispensing at clinics); 4) home ART delivery; 5) multi-month dispensing (MMD); and 6) community pick-up point (central dispensing units, community retail pharmacies, community ART distribution points, health posts, mobile ART distribution models) (Table 1). These six DSD models were defined for our analysis to be mutually exclusive – patients could only be enrolled in a single model.

Table 1. Differentiated service delivery (DSD) models for HIV treatment in use in Zambia during the study period

Category	Model(s) in category	Description
1. Adherence groups	Community adherence groups	Patient groups, consisting of ±6 members, meeting at an agreed time every 1-3 months. The groups are managed by the patients themselves, and usually meet outside of the health facility. Members collect ART at clinical appoints for other members in a rotating fashion (212).
	Rural and urban adherence groups/clubs	Patient groups, consisting of 20-30 members, meeting at an agreed time every 2-3 months. Groups are often facilitated by the same health care worker or facility-based volunteer, also providing pre-packaged ART (212).
2. Community pick-up point	Central dispensing units	A centralized model for ART distribution, where medication is packed at a centrally located hub and distributed to patients at multiple approved pick-up points. Clinic visits occur every 6 months at the health facility (216).
	Community ART distribution points,	ART refills are provided to patients outside of health facilities, e.g. schools, churches, community centres, community retail pharmacies and health posts (216).

Category	Model(s) in category	Description
	community retail pharmacies, health posts	
	Mobile ART distribution models	A clinical outreach team linked to a facility does 3-monthly clinical assessments at community distribution points. This model is usually used for hard-to-reach areas (216).
3. Extended clinic hours	Before/after-hours models, weekend models, scholar models	These models allow patients to have a clinical visit and collect their ART outside the conventional operation times at the facility (early mornings, evenings and over weekends). These are beneficial to patients with competing priorities (e.g. school or employment).
4. Fast-track	Fast-track	A model that typically involves a separate, shorter queue to dispense ART to stable patients, allowing for a quick patient visit when a clinical visit is not required (225).
5. Home ART delivery	Home ART delivery	Trained community health workers (CHWs) linked to facilities conduct home visits to deliver ART, conduct health screening, monitor adherence, and refer patients as required (212).
6. Multi-month dispensing	Multi-month dispensing	Facility-based model in which the primary goal is to dispense medications for more than one month (usually 6 months). Dispensing is typically done during a clinical facility-based visit.

Statistical analysis

We described the demographics of our study population using descriptive statistics. We compared loss to follow-up risk between early enrollers and established enrollers and Wilson's score interval was used to calculate 95% confidence intervals around proportions. We used a log-binomial regression to calculate risk ratios for loss to follow-up, adjusting for age, sex, urban/rural status, DSD model type and ART dispensing duration. Analyses were also stratified by DSD model type and ART dispensing duration. Further, we also conducted an age-stratified analysis and a sub-analysis restricted to facilities with a higher proportion of early enrollers, with results shown in the supplementary material.

Patient and public involvement

Patients and the public were not involved in the design and conduct of this research.

Results

Study populations

The full SmartCare data set included 1,520,125 unique patients on ART over 2018-2021, of whom 32,197 had enrolled into a DSD model after ART initiation and had an 18-month outcome reported within the 15-to-21-month window (Figure 1). Of these, 6,340 patients were reported to have been enrolled in DSD models <6 months after ART initiation during the study period (early enrollers). The remaining 25,857 patients comprised the comparison group of established enrollers. For early enrollers, median time enrolled in a DSD model at the time of outcome evaluation was 14.7 months (IQR 13.0-16.5); majority (81%, n=20,856) of established enrollers were on DSD models at outcome evaluation at a median of 5.8 months (interquartile range (IQR) 2.9-8.9) (Table 2). Early enrollers and established enrollers were similar with respect to age, sex and urban/rural location. Across both groups, the median age was 37 years (IQR 29 – 44), a majority (61%, 19,580/32,197) were female and most patients resided in urban settings (64%, n=20,618).

Most patients were enrolled in either multi-month dispensing DSD models (65% [n=4,101] of early enrollers and 64% [n=16,552] of established enrollers) or fast-track (15% [n=979] of early enrollers and 24% [n=6,266] of established enrollers) (Table 1). Amongst early enrollers, around half (55%, n=3,477) were dispensed 4-6 months of ART at their most recent ART pickup, 35% (n=2,197) were dispensed 3 months of ART, and 10% (n=636) were dispensed <2 months of ART. Established enrollers had slightly longer dispensing intervals with 72% (n=18,679) dispensed 4-6 months of ART, 22% (n=5,688) dispensed 3 months of ART, and 6% (n=1,476) dispensed <2 months of ART (Table 1).

Figure 1. Flow diagram depicting study population

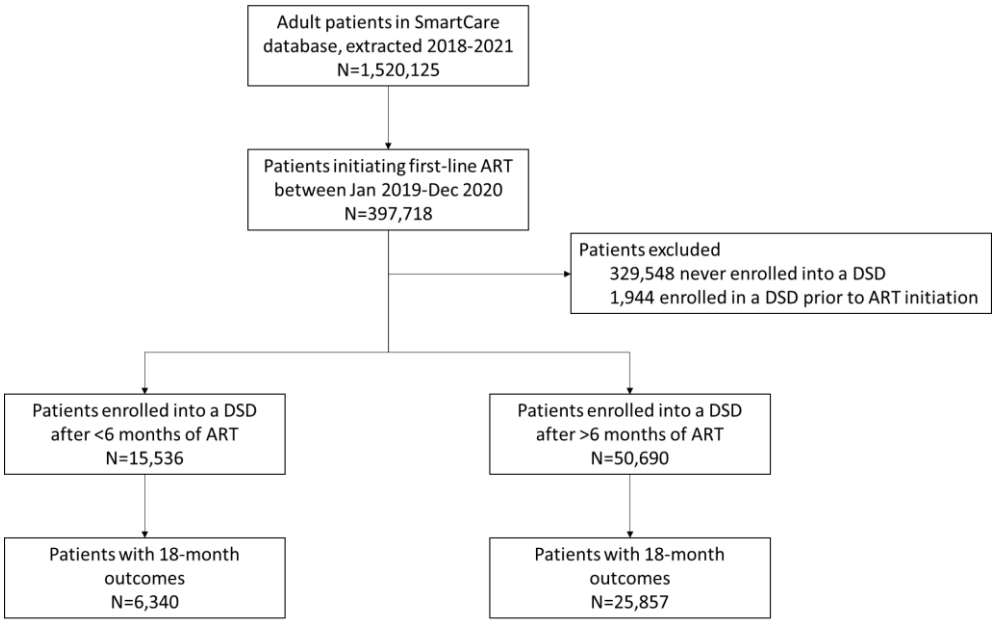


Table 2. Demographics of patients enrolled in differentiated service delivery models

Variable		Early enrollers of DSD models (N=6,340)	Established enrollers of DSD models (N=25,857)
Age in years, median (IQR)		36 (29-44)	37 (29-44)
Age group	15-24	727 (11%)	2,589 (10%)
	25-34	2,069 (33%)	8,346 (32%)
	35-49	2,658 (42%)	11,424 (44%)
	50+	885 (14%)	3,487 (13%)
Sex	Female	3,914 (62%)	15,666 (61%)
	Male	2,426 (38%)	10,191 (39%)
Location	Rural	2,501 (39%)	9,078 (35%)
	Urban	3,839 (61%)	16,779 (65%)
Year of ART initiation	2019	2,897 (46%)	17,346 (67%)
	2020	3,443 (54%)	8,511 (33%)
DSD type	Adherence groups	149 (2%)	508 (2%)
	Community pickup points	671 (11%)	1,461 (6%)

Variable		Early enrollers of DSD models (N=6,340)	Established enrollers of DSD models (N=25,857)
	Extended clinic hours	85 (1%)	97 (<1%)
	Fast-track	979 (15%)	6,266 (24%)
	Home ART delivery	355 (6%)	973 (4%)
	Multi-month dispensing	4,101 (65%)	16,552 (64%)
ART months dispensed	<2 months	636 (10%)	1,476 (6%)
	3 months	2,197 (35%)	5,688 (22%)
	4-6 months	3,507 (55%)	18,679 (72%)
Outcome Year	2020	2,863 (45%)	17,283 (67%)
	2021	3,477 (55%)	8,574 (33%)
Months on ART at outcome, median (IQR)		17.9 (16.4-19.5)	18.4 (16.7-19.8)
On DSD at outcome	Yes	6,340 (100%)	20,856 (81%)
	No	0 (0%)	5,001 (19%)
Months on DSD at outcome, median (IQR)		14.7 (13.0-16.5)	5.8 (2.9-8.9)
Patient outcomes by 18 months after ART initiation	On treatment	6,133 (97%)	24,646 (95%)
	Died	11 (<1%)	31 (<1%)
	Lost to follow-up	192 (3%)	1,169 (5%)
	Stopped ART	4 (<1%)	10 (<1%)
	Stopped DSD	0 (0%)	1 (<1%)

Outcomes

Early enrollers had a slightly lower rate of loss to follow-up (3.0% [95% confidence interval (CI) 2.6%-3.5%]) compared to the established enrollers (4.5% [4.3%-4.8%]) (Table 3). Early enrollers experienced similar or lower loss to follow-up rates than established enrollers across nearly all differentiated models of care. The exception was extended clinic hours: early enrollers enrolled in the extended clinic hours model had a similar rate of loss to follow-up as established enrollers (10.6%; [5.7%-18.9%] vs. 8.2% [4.2%-15.4%], respectively). Across both early and established enrollers, longer dispensing periods were associated with lower rates of loss to follow-up, which increased from 2.5%-3.8% for 4-6-month dispensing to 3.5%-5.3% for 3-month dispensing to 4.1%-10.6% for <2-month dispensing (Table 3). Early enrollers with <2 months dispensing had a lower rate of loss to follow-up than did established enrollers (4.1%; [2.8%-5.9%] vs. 10.6% [9.1%-12.2%]).

Table 3. Relative risk of loss to follow-up at 18 months post-ART initiation for early enrollers of differentiated service delivery (DSD) models

	Proportion of patients lost to follow-up at 18 months, % (95% CI) [n/N]			
	Early enrollers	**Established enrollers**	**Unadjusted risk ratio (95% CI)**	**Adjusted risk ratio* (95% CI)**
All patients	3.0% (2.6% - 3.5%) [192/6,340]	4.5% (4.3% - 4.8%) [1,169/25,857]	0.67 (0.57-0.78)	0.59 (0.50-0.68)
Stratification: DSD model				
Adherence groups	2.7% (1.0% - 6.7%) [4/149]	3.1% (1.9% - 5.1%) [16/508]	0.85 (0.25-2.29)	0.79 (0.23-2.12)
Community pickup points	4.5% (3.1% - 6.3%) [30/671]	3.3% (2.5% - 4.3%) [48/1,461]	1.36 (0.86-2.12)	1.30 (0.81-2.03)
Extended clinic hours	10.6% (5.7% - 18.9%) [9/85]	8.2% (4.2% - 15.4%) [8/97]	1.28 (0.51-3.27)	1.19 (0.43-3.34)
Fast track	3.4% (2.4% - 4.7%) [33/979]	3.6% (3.2% - 4.1%) [227/6,266]	0.93 (0.64-1.31)	0.74 (0.50-1.05)
Home ART delivery	1.4% (0.6% - 3.3%) [5/355]	6.3% (4.9% - 8%) [61/973]	0.22 (0.08-0.50)	0.18 (0.06-0.41)
Multi-month dispensing	2.7% (2.3% - 3.2%) [111/4,101]	4.9% (4.6% - 5.2%) [809/16,552]	0.55 (0.45-0.67)	0.51 (0.41-0.61)
Stratification: ART dispensing duration				
<2 months	4.1% (2.8% - 5.9%) [26/636]	10.6% (9.1% - 12.2%) [156/1,476]	0.39 (0.25-0.57)	0.40 (0.26-0.59)
3 months	3.5% (2.8% - 4.4%) [77/2,197]	5.3% (4.8% - 5.9%) [303/5,688]	0.66 (0.51-0.84)	0.64 (0.49-0.81)
4-6 months	2.5% (2.1% - 3.1%) [89/3,507]	3.8% (3.5% - 4.1%) [709/18,679]	0.67 (0.54-0.83)	0.67 (0.53-0.82)

*Model adjusted for age, sex, location, ART dispensing duration and DSD model type

In an analysis adjusting for age, sex, location, ART dispensing duration, and DSD model type, early enrollers in all DSD model types and dispensing durations were 41% less likely to be lost to follow-up than established enrollers (adjusted risk ratio (aRR) 0.59 [0.50-0.68]) (Table 3). The reduced adjusted risk of being lost to follow-up were similar for patients in adherence groups (aRR 0.79 [0.23-2.12]), multi-month dispensing (aRR 0.51 [0.41-0.61]), home ART delivery (aRR 0.18 [0.06-0.41]) and fast track models (aRR 0.74 [0.50-1.05]). Early enrollers had a statistically insignificant increased risk of being lost to follow-up in the community pick-up point (aRR 1.30 [0.81-2.03]) and extended clinic hours models (aRR 1.19 [0.43-3.34]) compared to the established enrollers.

An age-stratified analysis produced similar results to the main analysis, with early enrollers in each age group being less likely to be lost to follow-up than

established enrollers in the same age group. However, the effect of earlier enrollment in DSD on reduced loss to follow-up appeared less pronounced in patients on 4-6 months' ART dispensing for those aged 25 to 49 years (Appendix Figure S1). In facilities where a larger proportion of all DSD patients enrolled in DSD models early, the trend towards early enrollers performing better persisted with respect to loss to follow-up compared to outcomes for established enrollers (Appendix Figure S2).

Discussion

In nearly all of sub-Saharan Africa, DSD model eligibility criteria require that patients be on ART for a minimum of six months (and in some countries a minimum of 12 months) prior to DSD model enrollment (226). We present a novel analysis from Zambia highlighting good outcomes when newly initiated ART patients (those with less than 6 months' ART experience) are referred early to DSD models. Those referred early to DSD appear to have good outcomes across different DSD models and age categories.

Our data begin to fill in a gap in the evidence base on the validity of time on treatment as an eligibility criterion for DSD models. Because few if any countries permit DSD model enrollment for new initiators, little evidence on their experience in DSD models has been available until now. To date, most reports on DSD outcomes have been limited to people who have spent a significant amount of time on ART prior to DSD model enrollment. In the previously mentioned INTERVAL trial, for example, participants had been on ART for a median of roughly five years at DSD model entry, while patients in a trial of multi-month dispensing in adherence clubs in South Africa had a median duration on ART of 7.3 years at baseline (227).

While ART patients in Zambia have historically been lost to follow-up at high rates in the first few months after ART initiation (211), in our DSD patient population this was less likely to be the case. Our results provide evidence to support the recent revision of WHO guidelines that reduce time on ART from 12 to six months on treatment as part the definition of "established" on ART (219). These findings offer reassurance and evidence to countries that have expanded eligibility as they scale up DSD models (226,228), particularly to support uninterrupted access to HIV treatment during the COVID-19 pandemic, that earlier referral to DSD is possible without compromising patient care. Even if many, or most, of the patients in our "early enrollment" sample were selected deliberately because they were considered at low loss to follow-up risk, our results demonstrate that early eligibility for DSD

models should be considered for at least some patients before they reach six months on ART.

Loss to follow up at 18 months after ART initiation for early and established enrollers averaged 1-11% for all six categories of DSD models studied. We did not observe any programmatically important differences by model or ART experience prior to model enrollment. Where a programmatically important difference did arise, in contrast, was in dispensing intervals. Regardless of how long a patient had been on ART at DSD model enrollment, patients who received ≤2 months of medications at a time were more likely to be lost to follow up than patients who received either 3 months or 4-6 months of medications. This likely reflects providers' assessments of patients' ability to remain on treatment and/or clinical condition. Those regarded as being at higher risk of attrition are asked to come to the clinic for medication refills more often, so that they can be monitored and supported more closely. Ironically, difficulty in accessing the clinic may be the very reason that some patients are at high risk of attrition. For these patients, insisting on shorter refill durations may simply exacerbate whatever challenges they face.

There were several limitations to our analysis. First, we cannot explain why some patients were enrolled in DSD models before reaching six months on ART. As noted above, we assume that patients with <6 months on ART in our sample were not offered DSD model enrollment at random. If providers made accurate clinical decisions about individual patients' risks of attrition, patients in our "early enrollment" cohorts could over-represent patients thought to have low attrition risk. To achieve the results we found, providers would have had to make these decisions correctly at multiple sites across the entire country. If this is the case, our data suggest that the healthcare workers responsible for enrolling patients into DSD models can successfully identify those who will do well with early enrollment. At the same time, if the early enrollers in our data set do comprise patients at lower risk of loss to follow-up, then our results likely underestimate the true rate of loss to follow-up that would occur if early DSD enrollment were to be broadly available, without the benefit of provider selection.

A second limitation is that our data set included only patients reported in the electronic medical record system to have enrolled in a DSD model. It is possible that some patients not in DSD models may be recorded as enrolled, and some who were enrolled may have been missed. Third, bias could occur if facilities with better-than-average retention in care were also more likely to allow early DSD model enrollment. In this case, our results may reflect

differences in facility quality, as well as enrollment timing. An analysis restricted to facilities with >20% early DSD enrolment showed an even lower risk of loss to follow-up among patients enrolled early into DSD models, however, compared to patients with >6 months of ART at DSD entry.

Despite these limitations, our analysis demonstrates that patients on ART for less than six months who are enrolled in existing DSD models can be successfully retained in care and may even fare better than those left in conventional care and only initiate DSD models greater than six months after ART initiation. It is likely that not all patients are ready for less intensive DSD models in their first half-year or year on treatment, but some clearly are. Since DSD models have been shown to be beneficial to patients and in some cases to providers, offering enrollment to newly-initiating ART patients may improve ART programs in general. Future research should look more closely at which patients can be enrolled early and which models of care serve these patients best.

Conclusion

Current policy for DSD model eligibility criteria in Zambia, as in other countries, have required a minimum of 12 months of ART before a patient is considered for DSD enrolment, and more recently, a minimum of six months of ART. In order to change guidelines to allow DSD enrolment sooner after ART initiation (i.e., 6 months or less), large-scale observational evidence, implementation research or trial data demonstrating good patient outcomes among those who enrol in DSD models < six months' post ART initiation would be required. This analysis therefore provides a critical first step towards the reassessment of the delayed DSD enrolment policies, and signals that further research needs to be conducted in other SSA countries to evaluate patient outcomes for early DSD model enrolment.

Data Sharing

The data is owned by the Zambian Ministry of Health and the use of it was approved by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa) and ERES Converge IRB (Zambia). All relevant data is included in the paper and supplementary material. The full data are available upon approval from Zambian Ministry of Health and appropriate ethics committees.

Ethics

This study protocol was approved by ERES Converge IRB (Zambia), protocol number 2019-Sep-030, the Human Research Ethics Committee (Medical) of the University of Witwatersrand, protocol number M190453, and the Boston University IRB H-38823 for the use of data with a waiver of consent.

Supplementary Appendix

Figure S1. Relative risk of loss to follow-up within 18 months of ART initiation for early enrollers of DSD models (ie. after <6 months of ART), stratified by dispensing period and age group (reference group: established enrollers of DSD models with >6 months of ART at DSD enrolment; analysis adjusted for sex and urban/rural status)

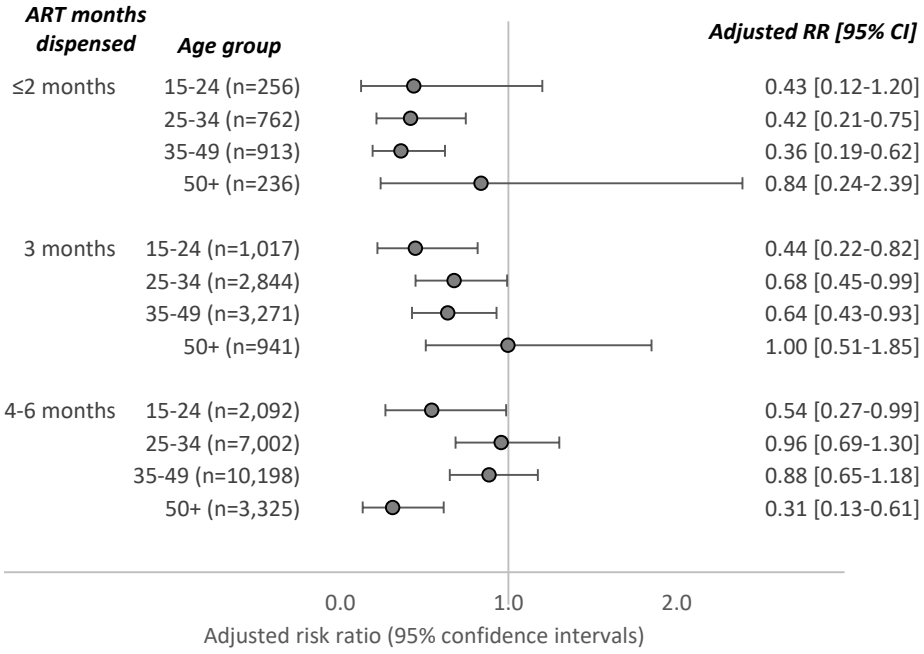
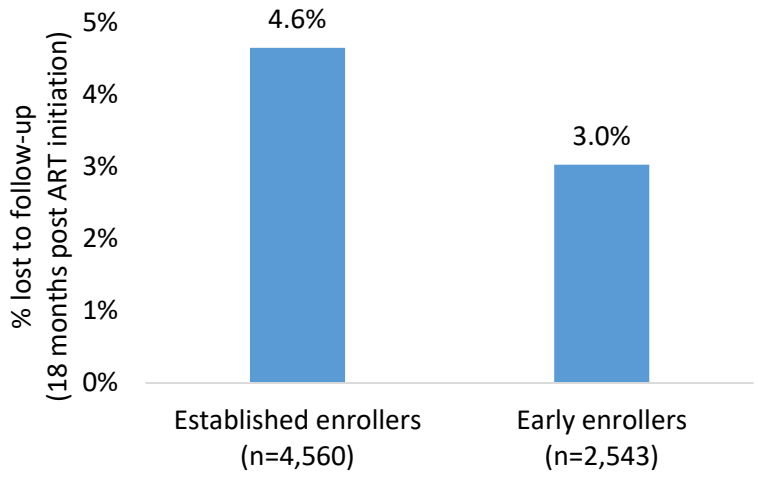


Figure S2. Proportion loss to follow-up by time on ART at DSD entry, limited to N=37 facilities with >20% of DSD patients at each facility classified as "early enrollers"



A potential area of concern was that facilities that had better-than-average retention would be more willing or able to enroll patients into DSD models early and therefore skew the results. We therefore conducted this sub-analysis where we limited the data to those facilities which had substantial proportion of their patients enrolled into DSD models early. Criteria for this analysis limited the data to facilities where: i) ≥20% of patients had early enrollers, and ii) at least 100 patients across both groups (early enrollers and established enrollers). 37 facilities across 8 of 10 provinces were selected for this analysis; 73% (n=27) of facilities were in urban areas. This analysis consisted of 7,103 patients: majority (61%, n=4,351) were female, age group distribution was similar to the main analysis (Table 2) (11%, n=784 were 15-24 years; 35%, n=2,488 were 25-34 years; 43%, n=3,028 were 35-49 years; 11%, n=799 were 50+ years), 81% (n=5,731) of patients were in urban settings. Majority (57%, n=4,028) of patients were enrolled into multi-month dispensing, 29% (n=2,058) were in fast-track, 7% (n=484) were in community pick-up points, 5% (n=350) were in home ART delivery, and <2% were in adherence groups (n=112) and extended clinic hours' groups (n=71).

Results show that in this subset of clinics, early enrollers were less likely to be lost to follow-up (3.0% [77/2,543]), compared to established enrollers (4.6% [212/4,560]). A log-binomial regression assessing risk of loss to follow-up, adjusting for age, sex, urban/rural status, and ART dispensing period estimated that, compared to established enrollers, early enrollers were 40% less likely to be lost to follow-up; adjusted risk ratios (aRR) 0.60 (95% CI 0.46-0.78).

Chapter 7

Transmission reduction, health benefits, and upper-bound costs of interventions to improve retention on antiretroviral therapy: a combined analysis of three mathematical model

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Abstract

Background

In the "Treat All" era, antiretroviral therapy (ART) interruptions contribute a growing proportion of HIV infections and deaths. Many strategies to improve retention on ART cost more than standard-of-care. Research is needed to inform the upper-bound costs at which such interventions should be adopted.

Methods

We compared the infections averted, disability-adjusted life-years (DALYs) averted, and upper-bound costs of interventions that improve ART retention in three HIV models with diverse structures, assumptions, and baseline settings: EMOD in South Africa, Optima in Malawi, and Synthesis in sub-Saharan African (SSA) lower-middle income countries (LMICs). We varied intervention effectiveness, the extent to which interventions could be targeted toward individuals at-risk of interrupting ART, and cost-effectiveness thresholds in each setting.

Findings

Despite simulating different settings and epidemic trends, models produced consistent estimates of health benefit and transmission reduction per increment in retention. The range of estimates was 1.35 ─ 2.60 DALYs and 0.07 ─ 0.16 infections averted over 40 years per additional person-year retained on ART. Upper-bound cost varied by setting and intervention effectiveness. Improving retention by 25% among all people receiving ART, regardless ART interruption risk, had an upper-bound cost per person-year of US$2 ─ $6 per person-year in Optima (Malawi), US$43 ─ $68 in Synthesis (SSA LMICs), and US$28 ─ $180 in EMOD (South Africa). A maximally targeted and effective retention intervention had an upper-bound cost per person-year per person-year of US$93 ─ $223 in Optima (Malawi), US$871 ─ $1,389 in Synthesis (SSA LMICs), and US$1,013 ─ $6,518 in EMOD (South Africa).

Interpretation

Upper-bound costs that could be spent to improve ART retention vary across SSA settings and are likely to be similar or higher than was estimated prior to

implementation of “Treat All.” Upper-bound cost can be increased by targeting interventions to those most at-risk of interrupting ART.

Research in Context

Evidence before this study

Countries hard-hit by the HIV/AIDS pandemic in sub-Saharan Africa have made tremendous progress in expanding access to antiretroviral therapy (ART) since the implementation of “Treat All” guidelines. As a result, a growing proportion of AIDS-related deaths are now believed to occur among ART-experienced individuals who have interrupted treatment. To reduce AIDS-related deaths and transmission associated with ART interruption, retention interventions have been proposed, including multi-month dispensation (MMD), local delivery of medications, health worker and peer support, and mHealth services. While some interventions, such as MMD, are cost-neutral or cost-saving and accordingly are recommended by normative agencies, others incur added costs, and it is not known when they should be implemented. We searched PubMed on October 17, 2021 with the search terms ("upper-bound cost" or "cost-effectiveness" or "willingness to pay" or "willingness-to-pay") AND "retention" AND Africa. We identified one study conducted prior to the implementation of “Treat All,” which simulated a clinical cohort eligible to receive ART with CD4+ T cell count ≤350, estimated an upper-bound cost of US$10 per patient-year of improved retention for patients receiving ART. Seeing as HIV incidence and mortality have declined in the era of “Treat All,” there is concern that the amount countries would be willing to pay to improve retention may be even lower than previously estimated, however, this could be offset by the growing contribution of ART interruptions to HIV mortality and transmission.

Added value of this study

We estimated the impact and upper-bound cost of improving retention with different levels of effectiveness and ability to target patients most-at-risk of ART interruption in the “Treat All” era. Our analysis included a diversity of model structures, assumptions, and baseline settings in order to examine the robustness of these estimates to the sub-Saharan African setting and modeling methodology. We found that models agree regarding the cumulative health and transmission benefits of improving retention over a 40-year time horizon,

but predict different kinetics of how quickly health and transmission benefits will accrue, resulting in more variable estimates at higher annual discounting rates. The lowest predicted upper-bound cost for an untargeted intervention with 50% effectiveness was US$5−$12 from Optima estimates for Malawi, agreeing estimates predating "Treat All." However, another model of SSA LMICs, Synthesis, which includes settings experiencing larger gaps in the HIV care continuum, predicted higher upper-bound cost thresholds. Settings with higher cost-effectiveness thresholds such as South Africa, and/or with an ability to target interventions to those most-at-risk of ART interruptions, would have much higher upper-bound cost thresholds for retention interventions.

Implications of all the available evidence

Although HIV mortality and incidence have fallen in the "Treat All" era, upper-bound costs for improving retention remain similar or higher to previous estimates due to the important contribution of ART interruptions to continued HIV mortality and transmission. These findings should be encouraging to researchers currently investigating strategies to improve ART retention at added cost. Additionally, the results can aid decision-makers in selecting available interventions for implementation, which may include targeting those most-at-risk of ART interruption.

Introduction

Sub-Saharan Africa (SSA) is home to two-thirds of all people living with HIV (PLHIV) (229) who require lifelong treatment with antiretroviral therapy (ART) to safeguard health and reduce HIV transmission. Expanded HIV testing and access to ART, including implementation of "Treat All" guidelines and same-day diagnosis and ART initiation has decreased the proportion of HIV-associated deaths (230) and transmissions (231) among ART-naïve individuals. As a result, ART-experienced individuals, especially those who have interrupted ART, are contributing a growing proportion of HIV mortality and transmission in SSA (232,233). In response, HIV researchers and program implementers are investigating strategies to improve retention of PLHIV on ART (Supplementary Appendix A, Table S1).

Among strategies that have been effective at improving retention, there are some have that have been implemented without incurring additional cost. An example is multi-month dispensing (MMD) of ART, which showed improved retention in randomized trials in SSA (213,234). MMD adoption was accelerated during the COVID-19 pandemic, and, in July 2021, MMD became part of the World Health Organization's Consolidated Guidance on HIV Treatment.

Other strategies to improve retention incur additional cost (235). Examples include financial incentives (236), local delivery of medications (212), individual and group adherence support (237), viral-load-informed adherence counselling (238), and the use of mobile. and wireless technologies to support retention (i.e., mHealth services) (239). Among these strategies, some are implemented for entire patient populations regardless of individual risk of treatment interruption, while others can be implemented targeting patients most at-risk of treatment interruption, which tends to reduce costs.

Prior to "Treat All," analyses suggested that an intervention for all people receiving ART that improves retention by 40% in could be cost-effective if it cost up to US $10 per person-year in SSA lower-middle income countries (LMICs) (240). However, this upper-bound cost may have changed now that SSA countries have implemented "Treat All" and greatly increased ART coverage. We estimated the transmission reduction, health benefits, and upper-bound cost to improve ART retention using three SSA HIV

transmission models with diverse structures, assumptions, and baseline settings, and using a range of economic benchmarks to assess upper-bound costs that could be spent to retain an additional person-year on ART. Our analysis could help to guide researchers and health authorities to prioritize interventions for investigation and implementation.

Methods

Affiliates of the HIV Modeling Consortium (www.hivmodeling.org) were invited to participate in the research if their models could provide annual estimates of incidence, prevalence, mortality, disability-adjusted life years (DALYs), and ART coverage in an SSA setting; could include simulation of ART interruptions and their effect on transmission and mortality; and could reduce the rate of ART interruption by different degrees starting in 2022 and continuing until 2062. The three HIV epidemic models participating in the collaboration met these criteria while having diverse structures, assumptions, and baseline settings (Table 1). Each model took a different approach to simulating the risk of transmission, morbidity, and mortality for ART-experienced PLHIV who have interrupted ART use. Key features of the models are described below and in Table 1, with additional model details and references provided in Supplementary Appendix B.

EMOD

Background: EMOD-HIV, referred to here as EMOD, is individual-based network transmission model of HIV calibrated to epidemic trends in South Africa (241,242).

Disease progression: Rate of progression of untreated HIV disease is assumed to be heterogeneous and age-dependent: for an individual infected at age 20, median survival without treatment is 13.1 years (IQR 8.4 – 18.5 years) whereas for survival for an individual infected at age 50, median survival without treatment is 6.3 years (IQR 4.1 – 8.9 years).

Effect of ART: During untreated chronic HIV infection, CD4 count declines continuously on a square root scale, with median CD4 count of 507 cells/μL (IQR 398 – 613 cells/μL) three months after infection and 19 cells/μL (IQR: 9 – 42 cells/μL) at time of AIDS-related death. While a person is experiencing viral load suppression on ART, transmission is reduced and CD4 count reconstitutes on a square root scale over the first three years, then stabilizes.

ART interruptions: ART interruptions result in resumption of untreated HIV progression based on the age and CD4 count at the time of interruption and return to pre-treatment transmission potential. The annual rate of ART interruptions lasting >1 month was 18.7% prior to implementation of "Treat All" and declined to 3.4% per year by 2020 (243).

Optima

Background: Optima HIV, referred to here as Optima, is a compartmental HIV transmission model calibrated to epidemic trends in Malawi (54,244). The model is disaggregated by sex, 5-year age group, and risk (female sex workers, clients of female sex workers, men who have sex with men, and general population).

Disease progression: HIV progression is defined by category from acute infection, CD4>500, CD4 350-500, CD4 200-350, CD4 50-200, and CD4<50. CD4 count and viral load change at rates depending on ART use and latest reported CD4 count and viral load.

Effect of ART: ART use reduces transmission potential by 50% reduction for unsuppressive ART and 100% for suppressive ART. Mortality both on and off ART depends on latest reported CD4 count and ART status (un/suppressive), varying between 0.08% per year with CD4>500 on suppressive ART to 32.3% for CD4<50 not on ART.

ART interruptions: In the absence of retention programs, ART interruption assumes that individuals would not return to care until CD4<200 is reached via disease progression. The annual rate of ART interruption was assumed to be 12.5% in 2004, declining to 4% per year by 2020 for all people on treatment. For PLHIV with CD4<200, the rate of ART interruption increased from 23% to 29% from 2015 to 2019, representing inconsistent treatment for those with previous interruption (244).

Synthesis

Background: HIV Synthesis is an individual-based HIV model that tracks a simulated population of adults living in SSA LMICs (55,56). HIV transmission is simulated between primary partners, and for non-primary partners, HIV acquisition risk depends on the viral load distribution among people of the opposite sex and in age categories determined by age-sex mixing patterns.

Disease progression: In HIV-positive people, the model tracks CD4 count, viral load, ART regimen, ART adherence, and specific drug resistance mutations. The latter three variables jointly determine at any point in time the antiviral effect of a regimen. HIV mortality risk is dependent on the latest CD4 count, viral load, age and presence of specific AIDS-defining conditions.

Effect of ART: The benefit of ART is via its effect on viral load and CD4 count. ART interruptions cause a rise in viral load to pre-ART level and a decline in CD4 count towards pre-ART level.

ART interruptions: ART interruption rates vary setting scenarios and by factors including pregnancy, ART adherence, ART toxicity, and time on ART (see Supplementary Appendix B). For example, for a non-pregnant, ART-adherent individual with no ART toxicities, interruption rates in the first year of ART range from 0.8% to 4.8% across setting scenarios (245).

Table 1. Characteristics of the EMOD, Optima, and Synthesis HIV models

	EMOD	Optima	Synthesis
Setting	South Africa	Malawi	LMICs in sub-Saharan Africa
Model type	Individual-based	Compartmental	Individual-based
Transmission structure	Age-structured and sex-structured network for coital acts and childbirths	Force-of-infection for sexual (sex-structured) and vertical transmission	Viral load distribution in potential non-primary partners (according to age gender mixing) and primary partner
Untreated HIV disease progression in ART-naive individuals	Age-dependent rate of decline in CD4 count	Fixed rate of progression for each CD4 count category	Viral load changes over time (gradual increase), dependent on gender; CD4 count decline depends on latest viral load; AIDS rate depends on latest CD4 count, viral load, and age
Untreated HIV disease progression in ART-experienced individuals	Age-dependent progression rate starting at CD4 count when ART was interrupted	Same rate as for ART-naive individuals starting from CD4 count at ART interruption	Viral load increases to pre-ART level immediately, CD4 count moves towards pre-ART level gradually
Effect of ART	Recovery of CD4 cell count, suppression of viral load leads to reduced mortality and transmission	Recovery of CD4 cell count, suppression of viral load leads to reduced mortality and transmission	Recovery of CD4 cell count, suppression of viral load leads to reduced mortality and transmission
Baseline rate of ART interruption	Decreasing from 17.8% per year before so-called treat-all era to 3.4% per year by 2020	12.5% per year in 1990 decreasing to 4% per year by 2020 for all people on treatment; increasing from 23% to 29% per year from 2015 to 2019 among people with HIV with CD4 counts of <200 cells per μL, representing inconsistent treatment for those with previous ART interruption	Varies across setting scenarios and by factors including pregnancy, ART adherence, ART toxicity, and time on ART—eg, for a non-pregnant, ART-adherent individual with no ART toxicities, interruption rates range from 0.8% to 4.8% in the first year of ART
Baseline rate of ART re-initiation after interruption	Same rate as ART-naive individuals in the same population group (age, sex, CD4 count, AIDS symptoms, and pregnancy)	All ART-experienced individuals have an opportunity to re-link to care when they reach a CD4 count of <200 cells per μL	Varies across setting scenarios and by factors including pregnancy, sexual risk behaviour, and HIV symptoms

EMOD=EMOD-HIV. LMICs=low-income and middle-income countries. Optima=Optima HIV. Synthesis=HIV Synthesis.

Model scenarios

Models simulated interventions that improve retention on ART beginning on January 1, 2022 and with outputs provided through to January 1, 2062 for a 40-year time horizon of intervention effects. Each model simulated interventions that, for all people on ART within the simulation, reduce the rate of treatment interruption by 25%, 50%, 75%, or 100% relative to the model's no-intervention baseline projection. We performed a bounding analysis for the degree to which retention interventions could be targeted to PLHIV most-at-risk of ART interruptions. Interventions were considered to be maximally targeted to those at-risk of ART interruption if only *incremental* person-years on ART added by the intervention were counted toward intervention cost. Interventions were considered to not be targeted, i.e., to be given to all people on ART regardless of risk of interruption, if *all* person-years on ART were counted toward intervention cost, including individuals who would have remained on ART in the absence of the intervention. For each scenario, standardized annual outputs were provided from each model including incidence and prevalence of HIV, number receiving ART, HIV-related deaths, and DALYs. All models calculated DALYs as the sum of years of life lost to HIV in each year of simulation, plus the years lived with treated and untreated HIV multiplied by respective disability weights from the 2017 Global Burden of Disease Study (246).

Analysis of model outputs

We compared epidemic trends (HIV incidence, prevalence, and mortality) from each model and for each level of improvement in retention. Using outputs for DALYs and new infections, we estimated the numbers of infections and DALYs averted for either (1) each additional person-year on ART relative to baseline, or (2) for each person-year on ART regardless of baseline ART utilization in each model. This served as a bounding analysis for the extent that retention interventions can be targeted to individuals most at-risk of interrupting treatment, with the (1) representing an intervention provided only to individuals who would otherwise have interrupted treatment, and the (2) representing an intervention provided to all people on ART regardless of their risk of ART interruption. Costs and outcomes (infections, DALYs) are reported and are discounted at the same rate (0%, 3%, or 6% per year). The ratios of DALY averted to person-years on ART and infection

averted to person-years on ART were inverted to calculate the number needed to treat (NNT).

Upper-bound costs

We calculated the highest retention intervention cost at which net monetary benefit (NMB) was positive, i.e., where incremental costs of the intervention were smaller than the product of DALYs averted times the cost-effectiveness threshold (CET). Given uncertainty in CETs, we calculated results for a range of CETs and provide equations for calculating results with alternative CETs in Appendix C (parameters for the equations in Tables S3 and S4). In Malawi and other SSA LMICs, we used a CET range of US$500 (247) to US$750 (248) based on cost-effectiveness at the margin of donor-financed HIV services, which generally exceeds the amount that could be afforded through domestic healthcare expenditure alone. For South Africa, where HIV services are primarily domestically funded, we used a range of CET from US$590 per DALY averted (based on opportunity cost at the margin of the South African HIV program (249)) to US$3,525.12 per DALY averted (based on opportunity cost at the margin of all South African domestic healthcare expenditure (250)). Effects of retention on ART coverage were taken into account by incorporating an annual ART cost of $206.75 in South Africa (251) and $165.50 in Malawi (252) and SSA LMICs (253), in addition to the cost of the retention intervention (Table S2). Costs and DALYs were discounted at 0%, 3%, or 6% per year. All costs are reported in 2019 USD.

Role of the funding source

The funder had no role in the study design, the analysis and interpretation of results, the writing of the report, or the decision to submit the paper for publication.

Results

The EMOD, Optima, and Synthesis models produced different epidemic patterns (Figure 1 and Supplementary Appendix D) reflecting their diverse model structures, assumptions, and the different epidemic patterns in the settings being modeled (Table 1). Baseline HIV incidence was the highest in Synthesis and lowest in Optima. Baseline HIV prevalence was similar in EMOD and Synthesis and lower in Optima. Baseline HIV mortality rates were similar in the EMOD and Synthesis models and lower in Optima. For

all three models, increasing ART retention reduced HIV prevalence, incidence, and mortality, with the largest declines in EMOD (Figure 1). Kinetics of the response of the HIV epidemic to improved retention varied widely across models, reflecting the variety of ways in which HIV transmission and disease progression dynamics were modeled. Synthesis manifested the most "front-loaded" response, with incidence and mortality declining immediately upon improvement in retention in 2022. Achieving 100% retention in 2022 would reduce mortality among PLHIV in Synthesis by 51.7% in 2023, compared with the baseline scenario with no change in retention. In contrast, the Optima manifested the most delayed response, with the same intervention reducing mortality by only 3.9% in 2023. EMOD manifested neither the fastest nor slowest response to the intervention – mortality declined by 6.4% in 2023 – but showed the largest decreases in mortality over the 40-year time horizon of analysis.

In all models, health arose both from the direct reduction in mortality among PLHIV who were better retained on ART, and from the avoidance of further HIV infections through maintenance of viral load suppression (Figure 1A and C, and Supplementary Appendix A). Despite wide variation in epidemic patterns, all models produced similar estimates of health benefit and transmission reduction per additional person-year on ART. Health benefit per person-year on ART (Figure 2A) was consistent across models and robust to the degree of improvement in retention and consistent across models with no discounting, but more variable with 3% and 6% annual discounting. Without discounting, all models and retention levels produced estimates within a factor of two of each other, ranging from 1.35 (Optima) to 3.55 (Synthesis) DALYs averted per person-year retained on ART. Discounted at 3% per year, the range of health benefits spanned a factor four, from 0.52 (Optima) to 2.41 (Synthesis) DALYs averted per person-year retained.

Figure 1. Projections of HIV incidence, prevalence, and mortality with improvements to ART retention. *EMOD, Optima, and Synthesis model projections of (A) HIV incidence per 100 person-years among adults aged 15+, (B) HIV prevalence among adults aged 15+, and (C) HIV deaths per 100 PLHIV per year. Graphs show baseline projections with no intervention to improve ART retention (black lines) and improved retention so that treatment interruption rates decline by 25%, 50%, 75%, or 100% (colored lines) at the start of 2022 (gray vertical dashed lines).*

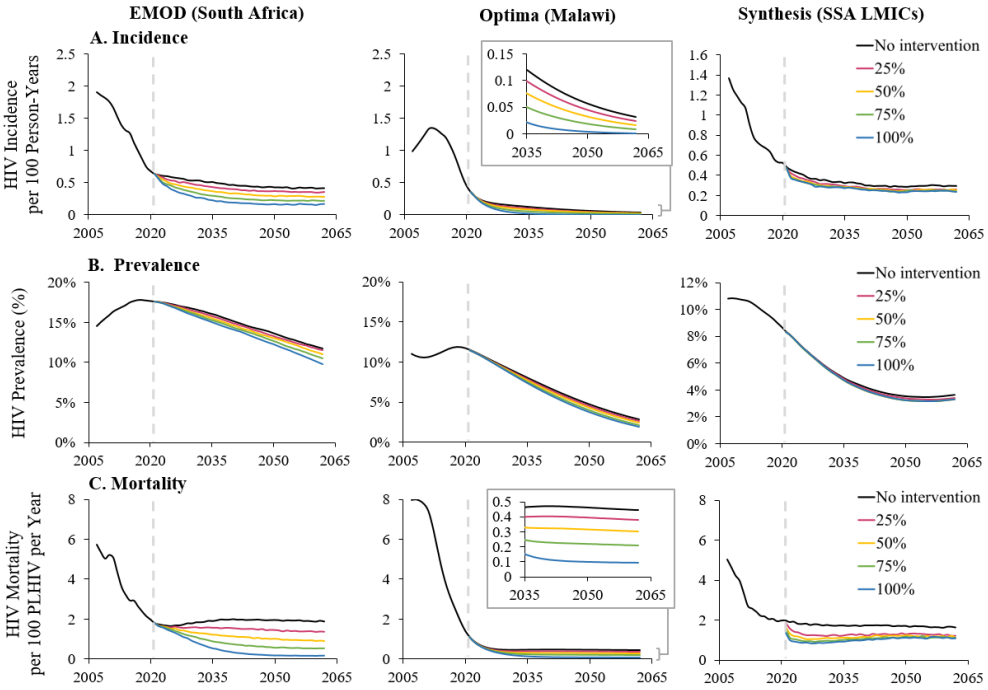
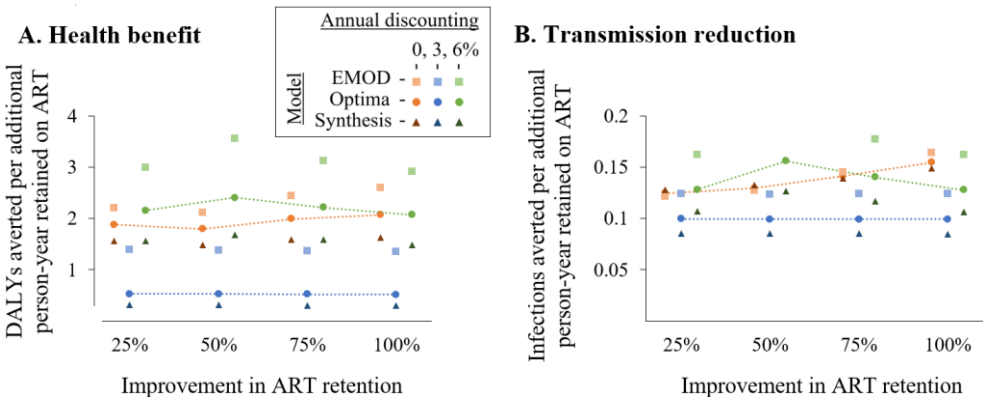


Figure 2. Health benefits and transmission reduction per additional person-year retained on ART with improved retention, representing a maximally targeted retention intervention. *Model estimates from EMOD (orange), Optima (blue), and Synthesis (green) showing the ratios of (A) DALYs averted and (B) HIV infections averted per additional person-year retained on ART, with annual discounting of 0% (light shade), 3% (medium shade), and 6% (dark shade), at different levels of improvement in ART retention (25% to 100%). Inverting these numbers provides estimates of numbers needed to treat (NNT), where the number treated is the additional individuals on ART compared with the no-intervention scenario, i.e., those who would have interrupted ART without improvement to retention.*

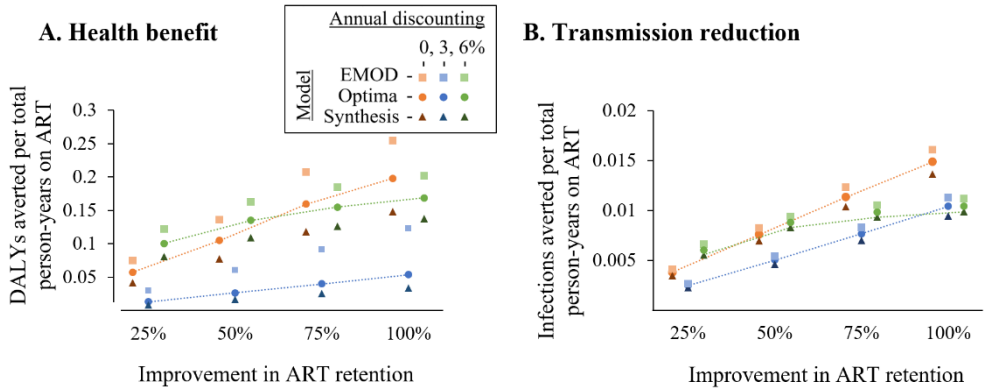


HIV infections averted per additional person retained on ART per year (Figure 2B) were similar across models, levels of improvement in ART retention, and discount rates. Undiscounted estimates ranged from 0.12 (EMOD) to 0.20 (Synthesis) infections per additional person-year on ART, resulting in an NNT range of 4.9 to 8.2 additional person-years needed to be retained on ART in order to avert one HIV infection. Discounted at 3% per year, estimates ranged from 0.10 (Optima) to 0.16 (Synthesis) infections per additional person-year on ART, resulting in an NNT range of 6.4 to 10.1 additional person-years needed to be retained on ART in order to avert one HIV infection.

The infections averted and health benefits per total person-years on ART varied widely across models (Figure 3). As expected, greater improvements in retention resulted in higher impact per person-year on ART in all models, since all individuals on ART were considered to have received an intervention

regardless of whether retention status changed as a result. Synthesis projected the largest impact per person-years on ART. At 50% improvement in retention with 3% discounting, Synthesis projected 0.135 DALYs and 0.009 infections averted per person-year on ART, yielding an NNT of 7.4 to avert one DALY and 114.1 to avert one infection. Optima predicted the smallest impact per person-year on ART. At 50% improvement in retention with 3% discounting, Optima projected 0.026 DALYs and 0.005 infections averted per person-year on ART, yielding an NNT of 37.8 to avert one DALY and 199.4 to avert one infection. Results were less sensitive to discount rate and more sensitive to the model used and to the level of improvement in ART retention.

Figure 3. Health benefits and transmission reduction per total ART use with improved retention, representing a minimally targeted retention intervention. *Model estimates from EMOD (orange), Optima (blue), and Synthesis (green) showing the ratios of (A) DALYs averted or (B) HIV infections averted to total person-years on ART with annual discounting of 0% (light shade), 3% (medium shade), and 6% (dark shade), at different levels of improvement in ART retention (25% to 100%). Inverting these numbers provides estimates of numbers needed to treat (NNT), where the number treated is the total number on ART, regardless of whether or not the intervention changed the retention status.*



Each model produced non-overlapping ranges of upper-bound cost that could be spent to retain an additional individual on ART and remain cost-effective (Table 2 and Supplementary Appendix C), implying substantial variability by setting and model projection. Upper-bound cost was highest in EMOD due to a combination of larger health benefit from improving retention and a higher CET used for South Africa. For a 50% improvement in retention, upper-

bound cost that could be spent per additional person-year retained on ART (e.g., per year of a maximally targeted retention intervention) was US$851 ─ US$5,624 and upper-bound cost per total person-years on ART (i.e., without targeting to those most-at-risk of ART interruption) was US$50 ─ US$329. Upper-bound cost that could be spent per additional person-year retained on ART was lowest for Optima projections due to smaller health benefit from improving retention and a lower CET used for Malawi. For a 50% improvement in retention, upper-bound cost was US$97– US$228 per additional person-year on retained ART and US$5 – US$12 per total person-year on ART.

Table 2. Upper-bound costs to improve ART retention

Retention interventions for people most at risk of ART interruption			Retention interventions for all people on ART		
EMOD	**Optima**	**Synthesis**	**EMOD**	**Optima**	**Synthesis**
25% improvement in ART retention					
90–5,919	99–232	910–1,448	28–180	2–6	43–68
50% improvement in ART retention					
851–5,624	97–228	1,039–1,641	50–329	5–12	58–92
75% improvement in ART retention					
968–6,266	95–225	941–1,494	78–503	7–17	66–105
100% improvement in ART retention					
1,013–6,518	93–223	871–1,389	97–624	10–23	71–113

Cost estimates are in 2019 US$. ART=antiretroviral therapy. EMOD=EMOD-HIV. LMICs=low-income and middle- income countries. Optima=Optima HIV. Synthesis=HIV Synthesis.

Discussion

Despite having diverse model structures, assumptions about the health and transmission effects of treatment interruptions, and baseline settings being represented, the EMOD, Optima, and Synthesis models produced comparable estimates for the health benefits and transmission reductions resulting from each additional person retained on ART for one additional year. Transmission reductions, both discounted and undiscounted over a 40-year time horizon, were similar across all three models. Health gains were similar when undiscounted, but different across models when discounted due to different kinetics of changes in mortality as a result of improved retention. These differences likely reflect different assumptions about HIV disease progression and mortality during treatment interruption. Tracing studies have attempted to quantify outcomes among patients lost to follow-up from clinical cohorts, but have struggled to disambiguate patients who died as a result of ART

interruption from those who appeared to interrupt ART as a result of having died from causes other than AIDS, or from treatment failure occurring without treatment interruption. As a result, models have primarily relied on studies of ART-naïve cohorts prior to the era of "Treat All" to develop assumptions about the role of CD4 count, viral load, aging, and other clinical factors contributing to mortality risk during ART interruptions. Further study of health status during ART interruptions in the "Treat All" era could help to clarify the contribution of ART interruptions to HIV transmission and burden in SSA and help HIV programs to determine when to prioritize retention interventions among competing priorities for HIV care and prevention.

The three models provided different estimates for the health benefits and transmission reductions when a retention intervention is offered to all people on ART, reflecting differences in the HIV care continuum across modeled settings. In South Africa, the "second 90" – i.e., the proportion of people diagnosed with HIV who are on ART – constitutes the largest gap in progress toward the 90-90-90 targets (254). Accordingly, improved retention had a larger impact in South Africa than in Malawi, which as of 2017 had surpassed the second 90 target (255).

Upper-bound costs that could be spent to increase ART retention ranged widely depending on the potential impact of retention in a particular setting, the CET used for the given setting, and the ability to target interventions to PLHIV who would otherwise interrupt ART. Previous analyses, prior to implementation of "Treat All" in SSA, estimated an upper-bound cost threshold of US$10 patient-year on ART for an intervention that improves retention by 40%. This is comparable to the range estimated by Optima (Malawi) without targeting those most-at-risk of interrupting ART. With targeting or a higher CET, and/or in a setting in which improved retention would have greater health impact – such as the range of SSA LMIC settings represented within Synthesis –upper-bound cost to improve retention would be higher than US$10 as has been previously estimated.

Our analysis has several limitations. We assumed that retention interventions would be equally effective at reducing the rate of treatment discontinuation for all people on ART. Studies of specific retention interventions have noted variable effect sizes according to a number of sociodemographic factors, which should be explored further in intervention-specific analyses. We were unable to separate the direct effect of ART retention on the number receiving

ART from the indirect effect of changes to HIV incidence and mortality on the number receiving ART. Further analyses separating these effects could be informative for more detailed costing and to understand differences across models. We assumed that ART would be the cost driver of retention interventions and did not include the population-level effect of improved ART retention on other HIV services such as HIV testing and prevention. We did so because ART is the cost driver of SSA HIV programs (Supplementary Appendix C), and because the impact of improved retention on costs of other services would depend on future policy decisions. For example, reductions in HIV incidence would increase the number of HIV-negative individuals able to receive HIV testing and prevention services, but at sufficiently low HIV incidence, these services might be offered less frequently. Finally, our multi-model approach is both a strength and a limitation. Models with different structures, assumptions, and baseline settings allowed us to capture variability of results across SSA HIV models. However, we did not attempt to standardize individual components of models or systematically evaluate how particular model attributes influenced the estimates provided. Such standardization and "teasing-apart" exercises can help identify the main reasons why model estimates differ, however, performing this type of exercise can run the risk of inducing "groupthink" and losing the diversity of model structures and assumptions that our analysis intended to capture.

Our analysis used a multi-model approach that captures structural model uncertainty and heterogeneity of settings in order to broadly inform research priorities and regional policy guidelines. In order for our analysis to be representative of the range of current and future retention interventions, we used a bounding analysis from 0% to 100% precision of targeting those most-at-risk of interruption. We also used a wide range of CETs. As a result, our analysis carries a wide range of uncertainty and may fail to provide inference for decision-making for certain settings, e.g., when the cost-effectiveness of a particular interventions falls inside the uncertainty range of upper-bound cost. Decision-makers seeking to apply these findings to a specific populations and interventions should consider collaborating with modelers to develop models specific to their populations, settings, and interventions of interest in order to improve accuracy and reduce uncertainty in upper-bound cost estimates. Nevertheless, the impact and upper-bound cost ranges estimated here broadly indicate that the amount HIV programs may be willing to invest in retention interventions is similar or significantly higher in the era

of “Treat All” compared to earlier estimates, notwithstanding recent declines in HIV incidence and mortality. Research on strategies to improve ART retention should be encouraged, especially when it is possible to target those most-at-risk of ART interruption.

Conclusions

Despite declines in HIV incidence and mortality achieved in the “Treat All” era, upper-bound cost to improve ART retention is equal to or higher than has been estimated prior to “Treat All.” Upper-bound cost can be raised well above prior estimates by targeting interventions to those most at-risk of interrupting ART.

Supplementary Appendix

A. Examples of retention interventions and their effect sizes

Numerous studies have tested interventions to improve retention on antiretroviral therapy (ART) among people living with HIV (PLHIV) in Sub-Saharan Africa (SSA). Below we report the effect sizes of a retention interventions in 39 studies spanning 14 SSA countries. Interventions are classified into the categories of community-based service delivery, decentralized care, differentiated care, mHealth, instrumental support, task-shifting, and patient tracing. The studies measured a wide range of effect sizes, suggesting that the intervention type and differences in settings, patient populations, implementation, and study design can lead to different measured outcomes for improvement in retention. For this reason, our modeling study explored a wide range of effectiveness levels for the hypothesized intervention.

Table S1. Measured effect sizes of retention interventions by type, country, and study design.

Intervention type	Year	Country	Study design (sample size)	Intervention	Outcome measurement	Outcome	Ref
Community-based service delivery	2021	Zambia	Prospective cohort study (n=2506)	Four models of care: Community adherence groups, mobile ART, urban adherence groups, home ART.	12-month retention (facility visit between 9-15 months after model entry).	Retention highest in urban adherence groups (95%), followed by community adherence groups (83%), home ART delivery (79%), mobile ART (69%), and standard care (81%).	(212)
	2019	Zimbabwe	Randomized clinical trial (n=94)	Monthly support groups and weekly visits from community health workers.	Increase in self-reported retention in care report for those receiving support from CATS.	Increase in score for intervention participants (3.66 to 3.74, $p<0.001$), decrease in mean score for participants in standard of care (3.86 to 3.31, $p<0.001$).	(256)
	2018	Tanzania	Cluster randomized clinical trial (n=2172)	Delivery of ART by community health workers.	Loss to follow-up (did not return to study facility for study exit assessment or latest viral load not available).	Fewer participants lost to follow-up in standard care group (13.6%) than in the intervention group (18.9%).	(257)
	2017	Mozambique	Retrospective cohort study (n=2406)	Peer-supported community-level ART distribution.	Retained in care at least 6 months.	Participants in intervention group had greater retention at 12-month and 24-months (99.1% and 97.5%) than	(258)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.							
Intervention type	**Year**	**Country**	**Study design (sample size)**	**Intervention**	**Outcome measurement**	**Outcome**	**Ref**
						participants in the standard care group (89.5% and 82.3%, p<0.0001).	
	2016	South Africa	Retrospective cohort study (n=8150)	Community-based adherence clubs lead by community health workers and supported by nurse.	Loss to follow-up (no visits in the first 12 weeks prior to study end).	Participation in intervention groups was associated with 67% reduction in loss to follow-up compared with standard care (aHR 0.33, 95% CI: 0.27-0.40).	(259)
	2015	Kenya	Quasi-experimental two-group study (n=369)	Community-based patient-defined support groups (microclinics) led by community health workers.	Clinic absence (90 more days in the 22-month period after ART initiation).	Intervention participants had one half the rate of clinic absence compared to those in standard care (R 0.48, 95% CI: 0.25-0.92].	(260)
	2014	Mozambique	Retrospective cohort study (n=5729)	Community-level ART distribution and support group.	Retention in care.	Retention at 1 year on ART was 97.7% (95% CI 97.4–98.2); at 2 years, 96.0% (95% CI 95.3–96.6); at 3 years, 93.4% (95% CI 92.3–94.3); and at 4 years, 91.8% (95% CI 90.1–93.2).	(261)
	2012	Zambia	Retrospective cohort study (n=523)	Community-based support teams of volunteers who provide education, referrals, adherence counseling, defaulter tracing, orphan support.	Retained in care (alive and not lost to follow-up).	Participating in the intervention did not have an effect on retention in care (80%) when compared to standard care (82%, p=0.6).	(262)
	2012	South Africa	Prospective cohort study (n=66,953)	Community-based adherence support with weekly visits for one month from community-based health workers.	Loss to follow-up (no clinic visits for 180 days or more)	Lower loss to follow-up in intervention group (aHR 0.63, 95% CI: 0.59-0.68).	(263)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.

Intervention type	Year	Country	Study design (sample size)	Intervention	Outcome measurement	Outcome	Ref
	2011	South Africa	Retrospective cohort study (540)	Community-based adherence support from health workers who provide education, support, and home visits.	Non-retention in case (loss to follow-up or death).	Non-retention in care was lower in intervention group than standard care group (HR 0.62, 95% CI: 0.62-0.68, p=0.001).	(264)
	2010	Kenya	Cluster randomized clinical study (n=208)	Home visits by community health workers to collect data on symptoms, vital signs, and ART adherence, and dispense one-month supply of medications.	Loss to follow-up at study closure	No significant difference in loss to follow-up between intervention (5.2%) and standard care groups (4.5%, p=1.0).	(265)
	2007	Mozambique	Randomized clinical trial (n=350)	6-week modified directly observed therapy, delivered daily by peers.	Retention in care 12 months after starting treatment	More participants in intervention group (84.5%) were retained in care than the standard care group (74.3%, OR=1.8, 95% CI: 1.1-3.3).	(266)
Decentralized care	2015	Kenya	Retrospective cohort study (n=178)	Semi-mobile HIV clinic located near patient homes.	Retention in treatment (ratio of number of scheduled monthly visits attended to total number months in treatment).	Retention did not differ significantly between intervention group (77%) and standard care group (71%, p=0.2).	(267)
	2013	Lesotho	Retrospective cohort study (n=3747)	Care at health centers led by nurses.	Three-year retention in care (in active follow-up at study end).	Retention did not differ significantly between intervention group (68.7%) and standard care (69.7% p=0.81).	(268)
	2012	Malawi	Retrospective cohort study (n=15421)	Care provided by mobile teams at peripheral health facilities, nurse-led initiation of ART and clinical monitoring.	Attrition (deaths and loss to follow-up for more than 2 months).	2- year attrition was lower in the intervention group (9.9 per 100-person years) than in the standard care group (20.8 per 100 person years, 95% CI:19.7-22.0).	(269)
Differentiated care	2018	South Africa	Retrospective cohort study (n=6706)	Community-based adolescent care	Loss to follow-up (at end of study or 5 years on ART, whichever came first)	Fewer participants were lost to follow-up in the intervention group (29.9%) than standard care group (38.9%, aHR 0.60 (95% CI 0.51-0.71); p< 0.0001).	(270)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.

Intervention type	Year	Country	Study design (sample size)	Intervention	Outcome measurement	Outcome	Ref
	2017	Zimbabwe	Randomized clinical trial (n=334)	Decentralized care and structured support visits by community health workers.	Composite outcome: virally unsuppressed, did not start ART, died, or lost to follow-up (no contact with facility for 6 months and not re-entering care elsewhere 18 months after enrolment).	The proportion of participants with the composite outcome was lower in the intervention group (44%) than the standard care group (58%, aOR 0.50, 95% CI 0.28-0.89, p=0.02).	(271)
	2017	Malawi	Case-control study (n=617)	Youth-oriented HIV care.	Not retained in care (lost to follow-up, died, or stopped participation).	Fewer not-retained participants in the intervention group (7.9%) than participants in standard of care (35.2%, p<0.01).	(272)
	2017	South Africa	Retrospective cohort study (n=241)	Adolescent-oriented care.	Retention in care (one clinic visit or pharmacy refill in the prior 6 months).	More participants in intervention group were retained in care (95%) than those participating in standard care (85%, aOR = 8.5; 95% CI 2.3–32.4; p = 0.002).	(273)
	2016	Kenya	Retrospective cohort study (n=269)	Youth and adolescent-oriented care.	Lost to follow-up during the first 6 months of treatment initiation	Participating in youth-oriented services did not improve retention rates (17.0%) when compared to participants in standard care (16.2%, p=0.77).	(274)
	2015	Kenya	Retrospective cohort study (n=924)	Youth-oriented HIV care.	Loss to follow-up (absent from HIV treatment clinic for 4 or more months)	Participating in youth-oriented services was not associated with loss to follow-up (aHR 1.09, 95% CI: 0.80–1.56, p=0.56).	(275)
mHealth	2016	Mozambique	Randomized clinical study (n=830)	Text message reminders.	Retention in care after 12 months of start of treatment	No statistical difference in retention between intervention (93.8%, 95% CI: 90.5-95.7) and standard care (91.0%,95% CI: 87.7-93.4, rate difference-2.8, 95% CI: -0.9-6.4, p=0.139)	(276)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.							
Intervention type	**Year**	**Country**	**Study design (sample size)**	**Intervention**	**Outcome measurement**	**Outcome**	**Ref**
	2015	South Africa	Randomized clinical study (n=230)	Text message reminders.	Retained in care (completed the study).	Greater proportion of participants completed the study in the intervention group (86.1%) than standard care group (75.7%).	(277)
	2012	Cameroon	Randomized clinical trial (n=200)	Motivational text messages.	Retention in care after 6 months of care.	No significant difference in proportion of participants retained in the intervention group (79.2%) and standard care group (83.8%, RR 0.95, 95% CI 0.83-1.08, p=0.399).	(278)
	2010	Kenya	Randomized clinical trial (n=538)	Text message-based support.	Loss to follow-up (unable to reach within 3 months after study end date).	No significant difference in loss to follow-up among participants in the intervention group (6%) and standard care group (10%, RR 1.69, 95% CI: 0.91-3.23, p=0.094).	(279)
Instrumental support	2018	Uganda	Cluster randomized trial (n= 702)	Child savings account for adolescents.	Attrition (at 24 months after enrollment).	Attrition rate in the intervention group (6.5%) was similar to the standard care group (5.5%).	(280)
	2017	Mozambique	Cluster randomized clinical trial (n=2004)	Combination intervention strategy (point-of-care testing, accelerated ART initiation, SMS health messages and appointment reminders; in addition, conditional noncash financial incentives for linkage and retention)	Retention at the diagnosing facility 12 months after diagnosis.	Additional noncash incentives were not associated with improved retention (55%) when compared to combination intervention without incentives (58%, RR 0.95, 95% CI: 0.79-1.13, p=0.45); fewer participants were retained in the standard care group (44%) when compared to the combination intervention strategy (RR 1.32, 95% CI: 0.79-1.13, p=0.004).	(281)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.							
Intervention type	**Year**	**Country**	**Study design (sample size)**	**Intervention**	**Outcome measurement**	**Outcome**	**Ref**
	2017	Swaziland	Cluster randomized trial (n=2201)	Combination intervention strategy (point-of-care testing, accelerated ART, text message reminders, noncash financial incentives.	Retained in care 12 months after testing.	Higher proportion of participants in intervention group retained in care (66%) than standard care group (45%, RR 1.48, 95% CI:1.18-1.86, p=0.002)	(282)
	2014	Chad	Retrospective cohort study (n=509)	Free-of-charge ART.	Loss to follow-up (3 or more months since last visit).	Fewer participants lost to follow up in the intervention group (10%) than standard care group (72.3%, p<0.001).	(283)
	2014	Uganda	Retrospective cohort study (n=2371)	Food or education support, or both.	Loss to follow-up (no contact 90 or more days after scheduled follow-up, dead, or transferred elsewhere).	More participants lost to follow-up in the food support group (42.1%), fewer participants lost to follow in education support group (12.3%), and those who received both interventions (13.7%).	(284)
	2013	Rwanda	Prospective cohort study (n=610)	Daily visit by community health worker, monthly food ration, transportation stipend, accompanied clinic visits by community health workers.	Attrition from treatment during the first year of ART (death, loss to follow-up, or default).	Exposure to the intervention group was strongly associated with a lower risk of attrition (HR, 0.17; 95% CI, .09–.35; p<0.0001)	(285)
	2011	Cameroon	Retrospective cohort study (n=2920)	Price reduction of ART.	Active in care 15 months of follow-up.	Probability of remaining alive and active in care did not significantly different between the two groups (HR 1.1; 95% CI: 0.9-1.2).	(286)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.

Intervention type	Year	Country	Study design (sample size)	Intervention	Outcome measurement	Outcome	Ref
Task-shifting	2014	South Africa	Retrospective cohort study (n=5746)	Down-referral to nurse-managed care.	Loss to follow-up (no contact in 6-month period between end of analysis and study end).	Down-referred patients were more likely to be lost to follow-up than not down-referred patients (aHR 1.36, 95% CI: 1.09-1.69).	(287)
	2013	Malawi	Retrospective cohort study (n=10112)	Nurse-led care.	2-year program attrition (loss to follow-up or death).	Attrition was higher in standard care group when compared to nurse-led group (aIRR 3.03, 95% CI: 2.56-3.59).	(288)
	2013	South Africa	Prospective cohort study (n=2829)	Adherence clubs led by counselors	Composite outcome of death or loss to follow-up (no contact with clinic for at least 6 months).	Participation in the intervention group reduced death or loss to follow-up (HR 0.43, 95% CI: 0.21-0.91).	(289)
	2012	Kenya	Retrospective cohort study (n=4958)	One-stop care clinic with interim visits managed by nurses in the first 3 months of ART initiation.	Loss to follow-up (absent from the clinic for at least 3 months).	Participants in the intervention group were less likely to be lost to follow-up than the standard of care group (aHR 0.62; 95% CI: 0.57-0.67).	(290)
	2012	South Africa	Cluster randomized clinical trial (n= 9252)	Streamlining Tasks and Roles to Expand Treatment and Care for HIV (STRETCH): nurses initiated and prescribe ART.	Retention (alive and in care, with documentation of clinic visit or lab test in previous 6 months) at 12 months after enrollment.	More participants in the intervention group were retained in care (63%) than in the standard care group (58%, RR: 1.10, 95% CI: 1.04-1.16, p<0.001).	(291)
	2011	South Africa	Retrospective matched cohort study (n=2772)	Down-referral of patients to nurse-managed local primary healthcare clinics for continued monitoring and treatment.	Loss to follow-up (3 or more months late for last scheduled visit).	Down-referred patients were less likely become lost to follow-up (1.4%) than those who were not down-referred (4.2%, aHR 0.3, 95% CI: 0.2–0.6).	(292)

Table S1. Measured effect sizes of retention interventions by type, country, and study design.							
Intervention type	**Year**	**Country**	**Study design (sample size)**	**Intervention**	**Outcome measurement**	**Outcome**	**Ref**
Patient tracing	2015	Uganda	Prospective (n=256)	Tracking of patients who missed their clinic appointment for 8–90 days.	Retained in care over 18 months of follow-up.	More participants in the intervention group were retained in care (39%) than those in standard care group (61%).	(293)

B. Extended model descriptions

EMOD

Background: EMOD-HIV (52,294), referred to here as EMOD (295,296), is an individual-based SSA HIV model that includes an age-structured transmission network with short- and long-term sexual partnerships (53,297), individual-level HIV disease progression (52,294), and a detailed continuum of HIV prevention (242,298) and treatment (230,243). Predictions from EMOD have been systematically compared to study results for prospective validation. The model successfully predicted the outcome of a multi-country community-randomized trial in SSA prior to trial unblinding (296). It predicted population-level epidemic trends (prevalence, incidence) in multiple countries ahead of release of survey results (255,295).

Disease progression: Progression of untreated HIV disease is assumed to be age-dependent (299–303). For example, for an individual infected at age 20, median survival without treatment is 13.1 years (IQR 8.4 – 18.5 years) whereas for survival for an individual infected at age 50, median survival without treatment is 6.3 years (IQR 4.1 – 8.9 years) (241,299,300). After an abrupt drop in CD4 count during acute infection, CD4 count is assumed to decline on a square root scale (304,305) during untreated HIV disease. Three months after infection, median CD4 count is 507 cells/μL (IQR 398 – 613 cells/μL) and at time of death median CD4 count is 19 cells/μL (IQR: 9 – 42 cells/μL) (306).

Effect of ART: Initiation of ART reconstitutes CD4 counts on a square root scale by up to 287 cells/μL over the first three years on ART (307,308). Survival on ART is assigned in age/sex strata depending on CD4 count, AIDS clinical stage at time of treatment initiation (or re-initiation), and whether or not individuals are adherent to ART (309–315). Individuals who are adherent to ART are assumed to have a 96% reduction in transmission (17), while individuals who are non-adherent or have interrupted ART are assumed to have no change in their transmission potential.

ART interruptions: The rate of ART interruptions lasting >1 month was 18.7% prior to implementation of Treat All (316–318) and declined to 3.4% per year by 2020 (227,319–321). ART interruptions are assumed to result in resumption of untreated HIV progression based on the age and CD4 count at the time of interruption. Because EMOD simulates an age-structured

transmission network using the same individuals who experience the above-described disease progression and care continuum, the model captures differences in HIV transmission potential among younger ART-naïve individuals versus older ART-experienced individuals.

Sensitivity analyses: Sensitivity of cost and disability-adjusted life years (DALYs) to different model assumptions about ART retention and re-initiation can be found in earlier published work (243,322).

Optima

Background: Optima HIV (54,244), referred to here as Optima, is a compartmental model with populations disaggregated depending on setting. The model for Malawi is disaggregated by sex, 5-year age groups, and risk (female sex workers, clients of female sex workers, and men who have sex with men) and has been validated by in-country stakeholders. HIV acquisition risk depends on characteristics of the individual (number of sexual partners, number of drug injections) and their partnerships (type of sexual interaction, sexual acts per partner, condom use (95% risk reduction), male circumcision status (58% reduction), prevention of mother-to-child transmission (PMTCT) status for mother-to-child transmission (90% reduction), pre-exposure prophylaxis (PrEP) (86% reduction adjusted for adherence) and post-exposure prophylaxis (PEP) (51% reduction adjusted for adherence) use, receptive needle-sharing or opiate substitution therapy, and population status (HIV testing, diagnosis, HIV prevalence, un/suppressive ART use (50% reduction for unsuppressive ART, 100% reduction for suppressive ART), and stage of infection).

Disease progression: Progression of untreated HIV disease is defined as transitions through the following categories: acute infection, CD4>500, CD4 350-500, CD4 200-350, CD4 50-200, and CD4<50.

Effect of ART: CD4 count and viral load change at rates depending on ART use and latest reported CD4 count and viral load. Mortality both on and off ART depends on latest reported CD4 count and ART status (un/suppressive), varying between 0.08% per year with CD4>500 on suppressive ART to 32.3% for CD4<50 not on ART.

ART interruptions: Rates of ART interruption are calibrated to balance the annual number diagnosed, initiated on ART, and receiving ART. Prior to

2021, these numbers were entered annually by stakeholders into the Optima input tables by stakeholders. Starting in 2021, the number on treatment was constrained by the proportion of diagnosed PLHIV that remain linked to care, with loss to follow up rates calibrated to match the reported proportional coverage of diagnosed PLHIV in 2020. Individuals who discontinued care are assumed to return to care when they reach CD4<200 via disease progression.

Sensitivity analyses: Sensitivity analyses of cost and DALYs to model parameters can be found in earlier published work (244).

Synthesis

Background: HIV Synthesis (55,323–325) is an individual-based HIV model that tracks a simulated population of adults with attributes including age, sex, primary and non-primary condomless sex partners, whether currently a female sex worker, HIV testing, male circumcision status, presence of sexually transmitted infections, and use of PrEP. A series of 22 "setting-scenarios" were generated by sampling several parameter values to represent the range of settings and communities in SSA and to incorporate uncertainty in model assumptions (326). HIV transmission is simulated between primary partners, and for non-primary partners, HIV acquisition risk depends on the viral load distribution among people of the opposite sex and in age categories determined by age-sex mixing patterns. In HIV-positive people, the model tracks CD4 count, viral load, and ART.

Disease progression: HIV mortality risk is assessed in each three-month period according to CD4 count, viral load, age, and presence of WHO Stage 3 and 4 AIDS-defining conditions (188).

Effect of ART: The model tracks each HIV-infected individual's ART regimen, ART adherence, and drug resistance mutations. For each drug in the individual's ART regimen, the model calculates the antiviral effect based on the presence of specific drug resistance mutations, drug potency, and level of adherence. The sum of the antiviral effects determines the impact of the drug regimen on viral load, drug resistance, and CD4 count, and hence risk of AIDS and death.

ART interruptions: The underlying rate of interruption of ART is sampled for each setting scenario from a distribution of 0.2%, 0.4%, 0.8% and 1.5% per 3 months, each with a probability of 0.25 (the realized distribution for the 22 setting scenarios was 18%, 27%, 45%, 9%). The actual rate of interruption

depends on several other factors in addition to the underlying rate: presence of current drug toxicity (relative risk = 2, 10, 30, each with probability 0.33 per setting scenario), ART adherence level (relative risk 1.5 if adherence 50-80%, 2 if adherence < 50%; in 25% of setting scenarios these relative rates are increased 2 fold, in 25% of runs they are increased 5 fold), current pregnancy (relative risk 0.01), and more than 1 year from start of ART (relative risk 0.5). In addition, in 20% of setting scenarios there is an effect such that those with recent non-primary condomless sex partners have a 1.5-fold higher risk of interruption. ART interruptions causes a rise in viral load to pre-ART level and a decline in CD4 count towards pre-ART levels (245). Return to care after interruption occurs at a rate of 10% per 3-month period in 40% of setting scenarios, and at rates of 1%, 5%, 30%, and 60% per 3-month period, each in 15% of setting scenarios respectively. The actual rate that applies for a given person is influenced by (i) the lifetime adherence attribute of person, (ii) whether they have developed an HIV related condition, (iii) pregnancy, and (iv) number of sexual partners, where higher numbers of partners are associated with lower likelihood of re-initiating care. In addition, individuals who remain in care but interrupt ART resume ART at 3-monthly rates of 80%, 85%, 90%, and 95%, each in 25% of setting scenarios respectively. The actual rate is then influenced by (i) whether they have developed an HIV related condition, (ii) whether viral load was measured to be >1000 copies/mL for people for whom the clinic is not aware they have interrupted ART, and (ii) pregnancy. Further details about these assumptions can be found in publications (56).

Sensitivity analyses: Sensitivity of cost and DALYs to model parameters related to ART can be found in earlier published work (55,188,245,325).

C. Calculating upper-bound cost with alternative cost-effectiveness thresholds

Upper-bound costs have been calculated for hypothetical interventions with costs that are variable or unknown, such as HIV vaccines (327), long-acting ART (322), and long-acting oral PrEP (328). Upper-bound costs are calculated by determining the net monetary benefit (NMB) of an intervention is positive, when considering the incremental costs and the incremental health benefits multiplied by the cost-effectiveness threshold (CET) for the modeled setting:

$$NMB = CET \times incremental\ DALYs\ averted - incremental\ coss$$

where incremental costs are the cost difference between the intervention and baseline (no intervention) scenarios, and incremental DALYs averted is the difference in DALYs between the intervention and baseline scenarios. Both incremental costs and incremental DALYs are discounted by the same annual discount rate, e.g., 3% per year. Costs and CET use the same currency of 2019 USD. If (NMB) is positive, then the intervention is considered to be cost-effective.

To calculate the upper-bound cost of an intervention, we calculate the maximum possible intervention cost at which NMB does not become negative, i.e., where

$$CET \times incremental\ DALYs\ averted = \ incremental\ costs.$$

Costs include the cost of the retention intervention, as well as the changes to the cost of other HIV services. We assume that ART is the main component of changes to costs of other HIV because it is a cost-driver in SSA HIV programs (90,329), and because the effects of ART on other program costs would depend on policy decisions. For example, improving ART retention reduces HIV incidence the model projections, which increases the number of HIV-negative individuals in the population who could receive HIV testing and HIV prevention, potentially increasing program costs. However, at sufficiently low HIV incidence, some prevention services may no longer be offered to some populations, and HIV testing might be offered less frequently, which would reduce program costs. Therefore, we calculated incremental costs based on the following equation, with ART cost (Table S2) as the only differential cost component outside of the retention intervention:

$$incremental\ costs\ \approx retention\ interventon\ cost + incremental\ person\text{-}years\ on\ ART \times annual\ ART\ cost$$

Table S2. Annual ART cost

Model	Annual ART cost (2019 USD)	Reference
EMOD	$206.75	(251)
Optima	$165.50	(252)
Synthesis	$165.50	(253)

For maximally targeted retention interventions provided only to people who will interrupt ART, the maximum annual cost per person-year receiving a retention intervention, $I_{targeted}$, is related to the CET in a linear fashion, with the incremental DALYs averted per additional person-years retained on ART (main manuscript, Figure 2a) as the slope, and the annual ART cost as the intercept:

$$\max(I_{targeted}) = \frac{incremental\ DALYs\ averted}{incremental\ PY\ retained\ on\ ART} \times CET - annual\ ART\ cost$$

For untargeted retention interventions provided to all people ART, the maximum annual cost per person-year receiving a retention intervention, $I_{untargeted}$, is also related to the CET in a linear fashion, with the incremental DALYs averted per total person-years on ART (main manuscript, Figure 2a) as the slope, as follows:

$$\max(I_{untargeted}) = \frac{incr.\ DALYs\ averted}{total\ PY\ on\ ART} \times CET - \frac{incr.\ PY\ retained\ on\ ART}{total\ PY\ on\ ART} \times annual\ ART\ cost$$

Upper-bound costs with alternative CETs can be calculated using the above equations. For convenience, the slope terms governing the slope (Table S3) and intercept (Table S4) have been calculated. To calculate the upper-bound cost for a retention intervention, multiply a value in Table S3 by the CET and add the corresponding value in Table S4, using the following color-coded equation:

$$upper\text{-}bound\ cost = \textit{value from Table S3} \times CET + \textit{value from Table S4}$$

Table S3. Slope of upper-bound cost equation

		Retention interventions for people most-at-risk of interrupting ART			Retention interventions for all people on ART		
Model		EMOD	Optima	Synthesis	EMOD	Optima	Synthesis
Setting		South Africa	Malawi	SSA LMICs	South Africa	Malawi	SSA LMICs
Improvement in retention	25%	$1.88	$0.53	$2.15	$0.06	$0.01	$0.10
	50%	$1.79	$0.53	$2.41	$0.10	$0.03	$0.14
	75%	$1.99	$0.52	$2.21	$0.16	$0.04	$0.15
	100%	$2.07	$0.52	$2.07	$0.20	$0.05	$0.17

Estimates reported in 2019 USD. SSA LMICs: Sub-Saharan African lower-middle income countries.

Table S4. Intercept of upper-bound cost equation

		Retention interventions for people most-at-risk of interrupting ART			Retention interventions for all people on ART		
Model		EMOD	Optima	Synthesis	EMOD	Optima	Synthesis
Setting		South Africa	Malawi	SSA LMICs	South Africa	Malawi	SSA LMICs
Improvement in retention	25%	$206.75	$165.50	$165.50	$6.30	$4.10	$7.76
	50%	$206.75	$165.50	$165.50	$12.10	$8.35	$9.30
	75%	$206.75	$165.50	$165.50	$16.59	$12.74	$11.60
	100%	$206.75	$165.50	$165.50	$19.80	$17.28	$13.49

Estimates reported in 2019 USD. SSA LMICs: Sub-Saharan African lower-middle income countries.

D. ART coverage and number receiving ART

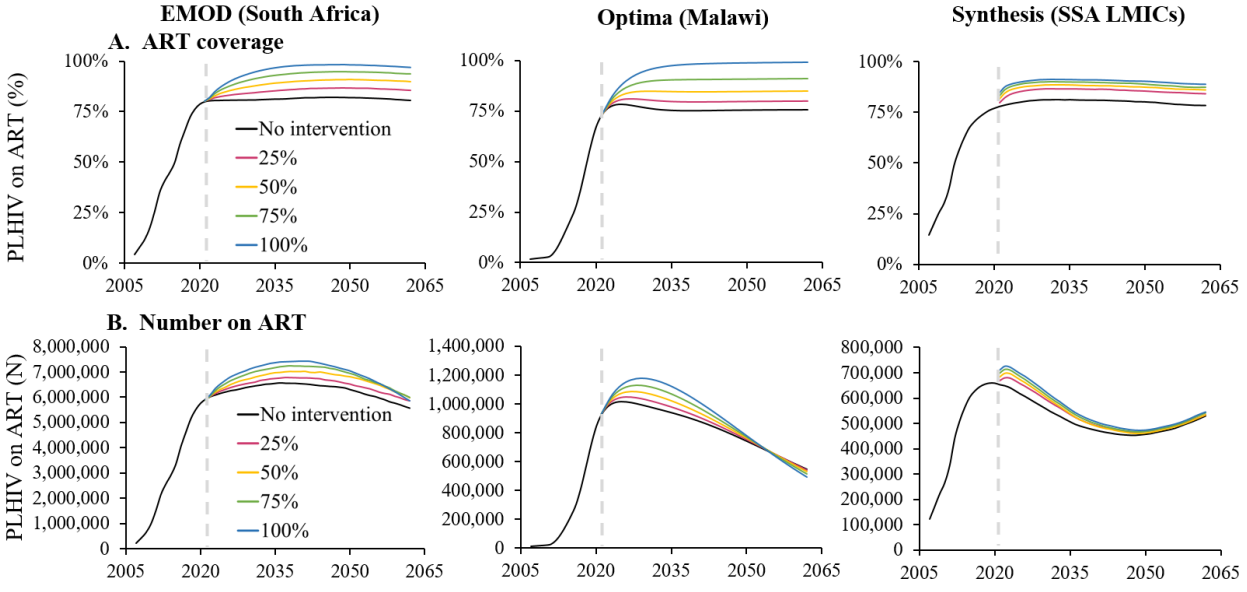


Figure S1. Projections of ART coverage and number on ART with improvements to ART retention. EMOD, Optima HIV, and Synthesis model projections of (A) proportion of PLHIV receiving ART, and (B) number of PLHIV receiving ART.

Part 3: Optimizing a package of interventions for HIV prevention and treatment

Chapter 8

When the only intervention left to optimise is retention: Comparing the 2021 and 2016 South African HIV Investment Cases

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Abstract

Background

Since 2016, annual updates of the HIV Investment Case have identified the optimal mix of HIV interventions in South Africa. Recommendations changed over time due to novel interventions and increasing coverage.

Methods

We updated Thembisa Optimise, an established HIV transmission model combined with an optimisation model incorporating diminishing returns to investment with recent service coverage, survey and cost data. We assessed cost per life year saved for each intervention-coverage option and established the optimal intervention package with and without constraining overall programme cost to HIV budgets committed by government and partners until 2023. Results were evaluated under current and maximal levels of antiretroviral treatment (ART) coverage in those diagnosed HIV-positive (78% vs 95% by 2025).

Findings

Compared to 2016 findings, condom provision continues to be most cost-effective, while medical male circumcision has become less cost-effective given higher coverage especially in adolescents. Pre-exposure prophylaxis for male adolescents/young men and early infant male circumcision are only affordable under the current budget if ART coverage remains at 78%. Achieving 95% ART coverage could, under the current budget, avert three times as many HIV infections and twice as many AIDS deaths over 20 years, compared to the baseline trajectory of 78% coverage. Only achieving 95% ART coverage allows South Africa to both meet the UNAIDS 95-95-95 targets by 2025 and cross the 0.1% incidence threshold required for HIV elimination.

Interpretation

While most interventions have become affordable under the current budget, only maximizing ART retention will significantly increase the South African HIV programme's impact.

Introduction

South Africa is home to more than 8 million people living with HIV, the largest HIV-positive population in the world (101). Many prevention and treatment interventions are already scaled up to high levels of coverage (101). As a result, with 93% of the country's people living with HIV (PLHIV) knowing their status, 72% of diagnosed PLHIV being on antiretroviral treatment (ART), and 92% of PLHIV on ART being virally suppressed, South Africa has reached the first and last of UNAIDS' 90-90-90 targets and is well on its way to reaching the first and last of UNAIDS' 95-95-95 targets- while lagging behind regional neighbours in its attainment of the second target (5,330). According to the latest National AIDS Spending Assessment, the South African government funds about 76% of the HIV response from domestic resources, while external funding has stagnated in recent years (331).

In 2013, the South African National Department of Health (NDOH) and National AIDS Council (SANAC) initiated the application of the UNAIDS investment framework to the South African HIV epidemic (332). The first South African Investment Case covered both the HIV and TB programmes and aimed at informing and, if necessary, changing national HIV and TB policy and strategy, by 1) reviewing all relevant programmes, interventions, and social and programme enablers that could contribute to an efficient HIV and TB response, and 2) calculating the most cost-effective mix of such interventions and enablers (89). The methods used in the South African HIV Investment Case diverge from the UNAIDS framework in a number of ways, most notably by using a rolling baseline against which additional interventions' cost-effectiveness is analysed, in order to take into account the diminishing marginal returns resulting from high baseline coverage levels of most interventions in South Africa (333). In South Africa, the HIV Investment Case is an iterative process, with both inputs and methodology updated and refined on an annual basis. In this paper, we present an update to the Investment Case, produced in 2021, and show how recommendations have changed over time due to novel interventions and increasing coverage, with a focus on the impact of increasing retention on ART towards the attainment of the full 95-95-95 targets.

Methods

Interventions

The 2016 Investment Case process included an intervention selection process which has been described in detail elsewhere (333). This list of interventions has been continuously updated whenever effectiveness data for new interventions became available. In particular, we have added the following interventions:

1. targeted pre-exposure prophylaxis (PrEP) for adolescent girls and young women (AGYW), male adolescents and young men, and men who have sex with men (MSM), with an assumption of successful self-selection based on higher perceived HIV risk;
2. a replacement of efavirenz by dolutegravir in first-line adult ART;
3. HIV self-testing, incorporating six different community- and facility-based self-test kit distribution modalities (primary distribution in fixed community sites, taxi ranks, workplaces, primary healthcare clinics (PHC), and secondary distribution to partners of antenatal clients and partners of index cases in PHC; for more information, see Table S1);
4. an intervention that improves ART retention (as well as linkage to treatment). This intervention was created as a way to ensure that 95% ART coverage pf people with known HIV status would be reached by 2025, in line with the second of the UNAIDS 95-95-95 targets.

We removed a number of interventions as their implementation was different from what had been shown to be effective, in particular social and behaviour change communication campaigns, or because of coverage having reached saturation at baseline, such as polymerase chain reaction (PCR) testing of infants at 6 weeks, and prevention of mother-to-child transmission (now included as general ART). Lastly, the cost of two interventions previously termed “technical efficiency factors”, different general population testing modalities and condom provision in non-traditional outlets, were incorporated into the main interventions (General population HIV testing services (HTS) and Condom availability, respectively).

ART with improved linkage and retention

Improving ART retention is crucial for continued progress towards the second UNAIDS target (95% ART coverage among PLHIV who know their status), the target towards which South Africa lags the most. In the 2021 Investment Case we considered two ART interventions- ART with improved linkage alone, and ART with improved linkage and retention. In the ART with improved retention intervention, ART patients' treatment interruption is assumed to be reduced by 98%, resulting in an increase in the fraction of patients who remain on ART from the current range of 82-87%, depending on time since initiation, to >99% throughout.

In order to identify a set of interventions that would help in attaining such high retention, we reviewed recent literature on retention and re-initiation interventions from both South Africa and internationally, including seven systematic reviews (29,334–337), the most recent of which focussed on differentiated models of care (29). We found that all identified interventions with evidence of a positive impact on retention are already part of the South African guidelines and are funded through the existing budget, though of course their level of implementation might differ from both the literature and between facilities. These interventions include: support clubs for adolescent clients, facility-based psychosocial support and short message service (SMS) reminders for adult clients, community-based peer support, one-on-one counsellor support for pregnant women, and tracing by peer- or community-health workers for those lost to care, as well as adherence clubs and external and facility-based ART pick-up points. Additionally, we identified a number of recently-developed interventions that had not yet been evaluated beyond pilot projects (such as male-focussed peer support, viraemia clubs, high viral load clinic days, welcome back campaigns and family model clubs), rendering their estimated impact in a routine setting highly uncertain. We therefore focussed on only incorporating additional staff needed for hypothetical retention services modelled on the Siyenza campaign, funded as part of the PEPFAR Treatment Surge in 2018 and 2019 (338).

We added the annual cost of facility-level staff employed during the Siyenza campaign who were dedicated towards retention activities, scaled to an estimated 4,200 PHC facilities in South Africa. Since Siyenza staff had been employed through PEPFAR, we adjusted their salaries to public sector salaries wherever an equivalent level existed. The additional staff package for

retention activities includes linkage officers (in 100% of facilities), youth workers (70%), community navigators (50%), ward-based outreach team (WBOT) community health workers (23%), WBOT outreach team leaders (17%), and case managers (17%). The cost of this activity was estimated at approximately $106 million per year (Table S2).

The final included interventions are summarised in Table 1.

Table 1. Interventions included in the HIV Investment Case

Programme area	Intervention	Impact represented in Thembisa
Care and treatment	Antiretroviral treatment (ART) with improved linkage	ART uptake in children and all HIV-positive adults Testing uptake
	ART with improved linkage *and* retention *(new in 2021)*	ART uptake in children and all HIV-positive adults ART retention Testing uptake
Male medical circumcision (MMC)	Early infant male circumcision (EIMC)	EIMC uptake
	MMC promotion across all age groups	MMC uptake
Comprehensive condom programming	Increasing condom availability (including distribution through non-traditional outlets)	Condom use
Key populations services	Pre-exposure prophylaxis (PrEP) for female sex workers (FSW)	PrEP uptake for FSW
	HIV testing services for FSW	Testing uptake in FSW
	PrEP for men who have sex with men (MSM)	PrEP uptake for MSM
HIV testing services (HTS)	Infant testing at birth	Uptake of infant testing at birth
	General population HTS (including workplaces testing, PICT, ANC testing, partner notifications, mobile testing, home-based testing)	Testing uptake
	Testing of adolescents	Testing uptake in adolescents

Programme area	Intervention	Impact represented in Thembisa
	HIV self-testing *(new in 2021)* (including 6 different kit distribution models in an optimised package: fixed point, taxi ranks, workplaces, secondary distribution to partners of ANC clients, secondary distribution to partners of index cases, primary distribution in PHC clinics)	Increase in diagnosis, HTS uptake and linkage to ART
Prevention	PrEP for high risk young women (aged 20-24) PrEP for high risk female adolescents (aged 15-19) PrEP for pregnant women (all ages) PrEP for high risk young men (aged 20-24) PrEP for high risk male adolescents (aged 15-19)	PrEP uptake in respective population

Modelling process and scenarios

We established a new model for the South African HIV Investment Case called Thembisa Optimise, incorporating an established HIV transmission model for South Africa, the Thembisa model (101), and a custom-made cost model (90) as well as a novel optimisation routine described in detail elsewhere (89). The epidemiological model required input data on 1) the definition of the target population for each intervention, and 2) the effectiveness of each intervention. Effectiveness could be expressed as an impact of the intervention on transmission rates or mortality or on programme indicators such as condom usage, increase in adherence, decrease in loss to follow-up, or increase in cases diagnosed, etc.

For each intervention we generated the number of HIV infections averted, and the number of life-years saved for the financial years 2020/21 to 2039/40. Life-years lost were calculated by multiplying the number of deaths due to AIDS in a given age group by the average life expectancy in this age group for a population with low HIV prevalence, counted over the 20-year time horizon of the analysis only. Life expectancy values were based on the West Level 26 life table commonly used in Global Burden of Disease calculations (117).

We present results based on two ART coverage scenarios: 1) 78% ART coverage of those who know that they live with HIV by 2025 (current trajectory, no retention intervention); and 2) 95% ART coverage by 2025 (retention intervention included). Within each, we constructed two sub-scenarios defined by the currently committed budget from the South African government, Global Fund and PEPFAR: (a) Constrained scenario: most cost-effective mix of interventions under the current budget; (b) Unconstrained scenario: interventions scaled up without regard to the budget envelope.

Epidemiological model

The 2021 HIV Investment Case is based on version 4.4 of the Thembisa model (45). Thembisa is an integrated demographic and epidemiological model of the HIV epidemic in South Africa. The model is deterministic and compartmental, dividing the population into a large number of compartments that are defined in terms of demographic, behavioural, intervention exposure and HIV disease characteristics. The population is stratified by sex and age (in months at ages 0-9, and in years at ages 10 and older).

There are two broad risk groups (high and low risk, the former consisting of individuals with a propensity for concurrent partners and commercial sex activity), and within these two risk groups various subgroups are defined, based on sexual experience, marital status and (in the case of married individuals) partner risk group. Female sex workers (FSW) are assumed to be a sub-group of the unmarried high-risk group, and their rate of entry into sex work is assumed to be sufficient to meet the calculated male demand for commercial sex. Rates of marriage and divorce are assumed to depend on age and sex, while rates of entry into non-marital (short-term) relationships depend on age, sex, risk group, marital status and sexual experience. Assumptions about coital frequencies and condom use depend on type of relationship, age and sex. In addition, condom use is assumed to have increased over time, in response to HIV communication and condom distribution programmes.

The model projects the change in the number of individuals in each compartment at monthly time steps, starting in 1985. The model is calibrated to historic HIV prevalence data from antenatal surveys and household surveys, as well as recorded death statistics. Heterosexual HIV transmission probabilities per act of sex are assumed to depend on the HIV disease stage and sex of the infected partner, the age and intervention exposure of the

susceptible partner, the type of relationship and the risk groups of both partners. Thembisa 4.4 has additionally been updated to take into account the impact of the COVID-19 pandemic, including its impact on healthcare seeking behaviour under lockdowns throughout 2020.

Cost-effectiveness analysis and optimisation

We used Thembisa Optimise to calculate the total cost of each intervention as well as the total cost of the HIV response by multiplying the number of people covered with an intervention by the average or unit cost (i.e., the cost per person, person year, test or visit) of the respective intervention. Cost was evaluated from the government perspective, using public-sector prices, and is presented in 2021/22 costs. More details on the underlying cost analysis methods are described elsewhere (90).

Based on the outputs regarding life-years saved and incremental cost, Thembisa Optimise then computed the incremental cost-effectiveness ratio (ICER) for each intervention and scenario, expressed as cost per life-year saved. The ICER calculation is also the basis of the optimisation routine used to generate the two optimisation scenarios. Optimisation was based on cost per life-years saved rather than cost per HIV infection averted, in order to represent the benefits of both prevention and treatment interventions. We examined the impact of scaling each intervention either up or down to any of six coverage levels other than baseline (BL) coverage and a feasible maximum (FM) set at either 95% for existing interventions, 70% for novel interventions, or current policy targets (Table S3). This provided us with a total of 93 intervention-coverage combinations ranked by ICER. In order to be able to use results for budgeting purposes, neither outcomes (life-years saved) nor costs were discounted.

After evaluating each intervention-coverage combination, we iteratively added the most cost-effective option onto the baseline, and re-evaluated the incremental cost-effectiveness of all remaining interventions over this new baseline. This meant we were able to compute the impact of changing coverage with a single intervention on the cost and impact of any other interventions that were affected by it (for example, the reduction in the need for ART as a result of increasing HIV prevention interventions) and, ultimately, the cost and impact of the entire HIV response (89). For the constrained optimisation scenarios, we concluded the process of adding the next most cost-effective intervention once the total cost of the HIV

programme had reached the committed budget for 2020/21 to 2022/23 from the three main funding sources, the South African government, the United States Government and Global Fund (see appendix and Table S4 for more information on calculating the available budget).

Results

Recommended interventions

Under the 78% ART coverage scenario, scaling up all included interventions was estimated to be affordable under the current medium-term budget, whereas under the 95% ART coverage scenario scaling up most interventions was affordable, the exception being PrEP for adolescent males and young men, and early infant male circumcision (EIMC) (Table 2). As a result, for the 78% ART coverage scenario the unconstrained scenario was identical with the constrained scenario, as the total cost fell below the budget constraint. In the following, we will report results for the unconstrained 78% ART coverage scenario only.

Across both ART coverage scenarios, increasing condom distribution to 1 billion condoms/year was a cost-saving intervention, followed by the next most cost-effective intervention, linking 95% of newly diagnosed adults to ART ($115/life year saved) (Table 2). Scaling up infant testing at birth, PrEP for MSM and general population HIV testing services followed as the next cost-effective interventions. At this point, under the 95% ART coverage scenario the ART retention intervention was the next most cost-effective option ($1,470/life year saved), while under the 78% ART coverage scenario instead scaled up adolescent HTS to 95% ($2,228/life year saved). Overall, intervention order remained similar between the ART coverage scenarios, with the exception of medical male circumcision (MMC) which became less cost-effective under the scenario where 95% of ART patients remain on ART, due to diminishing returns to investment.

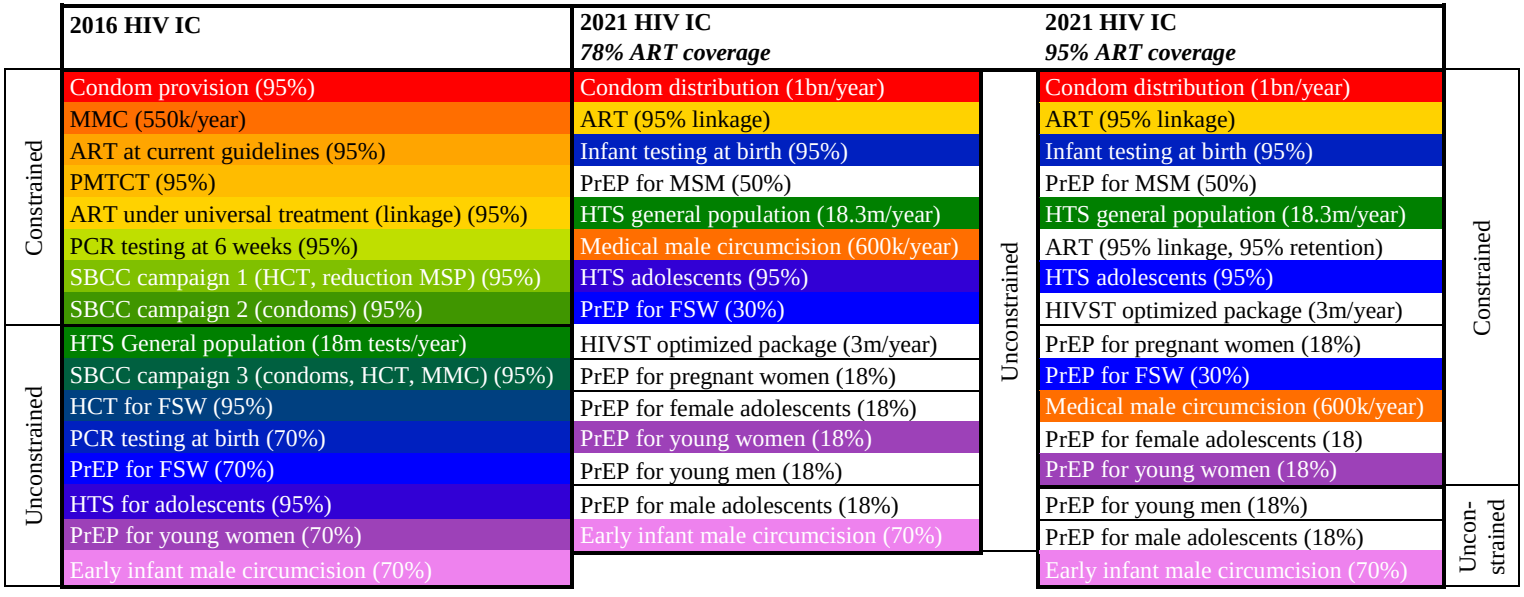
Table 2. List of HIV interventions ranked by cost-effectiveness for two ART coverage scenarios (78% and 95%) – 20-year impact (2021-40); costs in 2021/22 USD

78% ART coverage scenario		**95% ART coverage scenario**	
Intervention (scaled-up coverage)	***Cost per life year saved (USD)***	***Intervention (scaled-up coverage)***	***Cost per life year saved (USD)***
UNCONSTRAINED SCENARIO		**CONSTRAINED SCENARIO**	
Condom distribution (1bn/year)	Cost-saving	Condom distribution (1bn/year)	Cost-saving
ART (95% linkage)	115	ART (95% linkage)	115
Infant testing at birth (95%)	765	Infant testing at birth (95%)	765
PrEP for MSM (50%)	1,107	PrEP for MSM (50%)	1,107
HTS general population (18.3m/year)	1,417	HTS general population (18.3m/year)	1,417
Medical male circumcision (95%)	1,479	ART (95% linkage, 95% ART coverage)	1,470
HTS adolescents (95%)	1,689	HTS adolescents (95%)	2,228
PrEP for FSW (30%)	1,816	HIVST optimized package (3m/year)	2,632
HIVST optimized package (3m/year)	1,861	PrEP for pregnant women (18%)	4,560
PrEP for pregnant women (18%)	2,273	PrEP for FSW (30%)	4,672
PrEP for female adolescents (18%)	4,149	Medical male circumcision (95%)	4,768
PrEP for young women (18%)	8,736	PrEP for female adolescents (18%)	8,181
PrEP for young men (18%)	16,520	PrEP for young women (18%)	16,174
PrEP for male adolescents (18%)	13,249	**UNCONSTRAINED SCENARIO:** Interventions included in addition to above	
Early infant male circumcision (70%)	103,507,912	PrEP for young men (18%)	31,516
		PrEP for male adolescents (18%)	24,536
		Early infant male circumcision (70%)	35,637,752

Comparison with 2016 Investment Case results

A comparison of the results of the 2021 update with the 2016 HIV Investment Case makes it clear that differences in baseline coverage of existing interventions, the addition of new interventions, as well as (to a lesser extent) updates to unit costs and effectiveness assumptions changed the order of recommended interventions substantially (Figure 1). The only constant finding was that maximally increasing condom provision (to 1 billion condoms/year) remained the most cost-effective (and now the only cost-saving) intervention. While ART remained amongst the most cost-effective interventions, MMC retained good cost-effectiveness overall, despite moving down in the ranking compared to the 2016 HIV Investment Case. Reasons for this included: 1) a much higher current baseline coverage than before, 2) a shift in the age distribution of MMC clients to incorporate a recent focus on the youngest age groups, and 3) partially linked to this, a revision to the previous model assumption that MMC uptake would be greater amongst men with the highest level of sexual behavior which resulted in an overestimation of the impact of MMC. PrEP for FSW and for young women ranked higher than in the 2016 Investment Case, partly owing to stronger assumptions regarding targeting of this intervention to clients at higher HIV risk, and a reduction in the estimated cost of implementation. EIMC remained the least cost-effective intervention, as before owing to the choice of projection period (20 years) which did not allow us to capture the full benefit of this intervention.

Figure 1. Comparison of ranked interventions between original 2016 Investment Case and 2021 update



Total cost and budget impact

Under the 78% ART coverage scenario, the total annual cost of the HIV programme remained well below the budget constraint even if all interventions were scaled up, ranging between $1.5-$1.8bn annually (Figure 2). Under the 95% ART coverage scenario, the additional patients retained on ART significantly increased the annual budget. The cost of the constrained scenario remained at a stable level below the 2022/23 budget constraint, even beyond 2023, at around $2bn, and therefore would remain affordable as long as the budget does not decrease. The unconstrained scenario was only marginally more expensive than the constrained scenario (on average an additional $83 million per year), due to only a few interventions being included in addition to those in the constrained scenario.

Programme coverage and impact on the epidemic

Increasing ART retention (95% ART coverage scenario) was responsible for significantly reducing HIV incidence and new HIV infections much sooner than under the current 78% ART coverage trajectory (Figure 2). Improving ART retention resulted in a large cohort of patients requiring ART for the immediate future, until an eventual decline in the total number of people on ART towards the end of the 20-year period. This decline is largely as a result of the increase in condoms, with smaller impacts generated by MMC, PrEP and HTS. Overall, 95% ART coverage was estimated to have a significant impact on reducing AIDS deaths by an estimated average of 9,300/year (relative to baseline), compared to 4,500/year under 78% ART coverage (Figure 2). Finally, despite maximum coverage with all available prevention interventions, only additionally maximising retention towards 95% ART coverage would allow South Africa to both achieve the UNAIDS 95-95-95 targets (by 2025) and cross the 0.1% incidence threshold required for HIV elimination (by 2027) (Figure 2).

Figure 2. Total cost (billions USD) of the HIV programme, excluding inpatient care, and annual epidemiological impacts on key indicators of the HIV epidemic under (A) 78% ART coverage and (B) 95% ART coverage

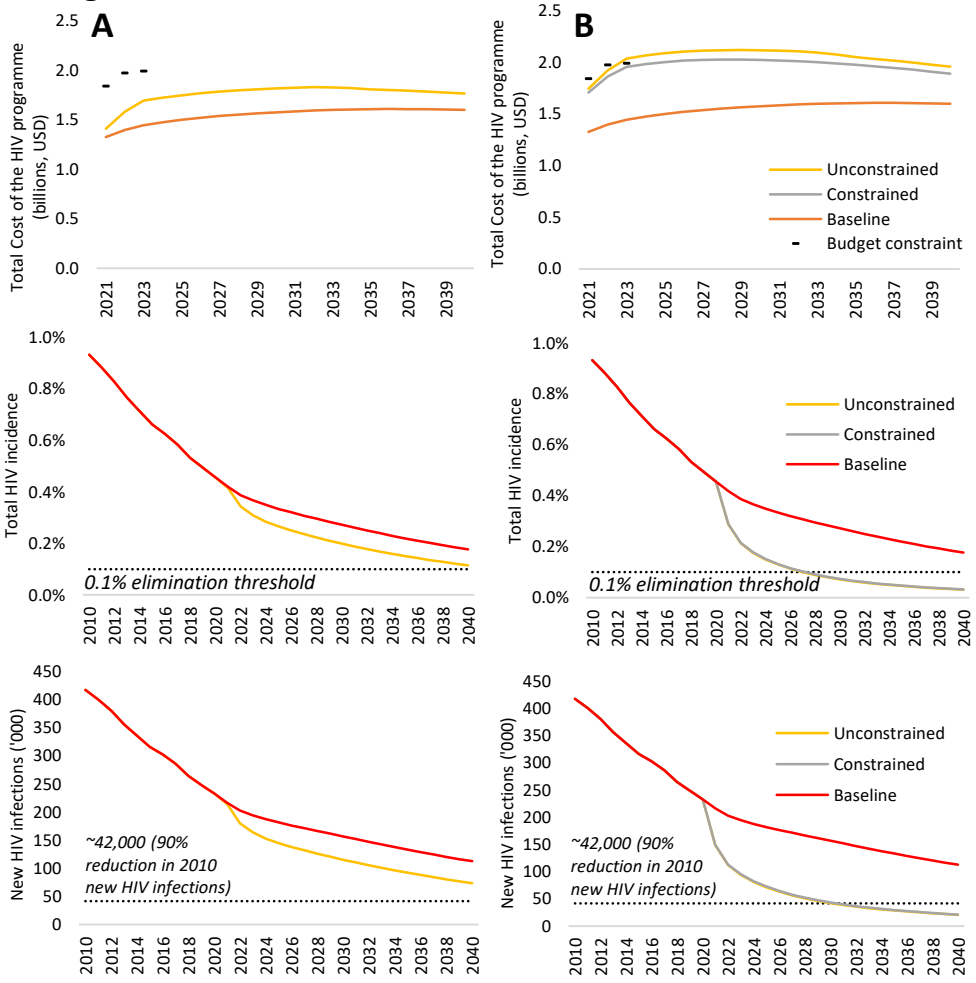
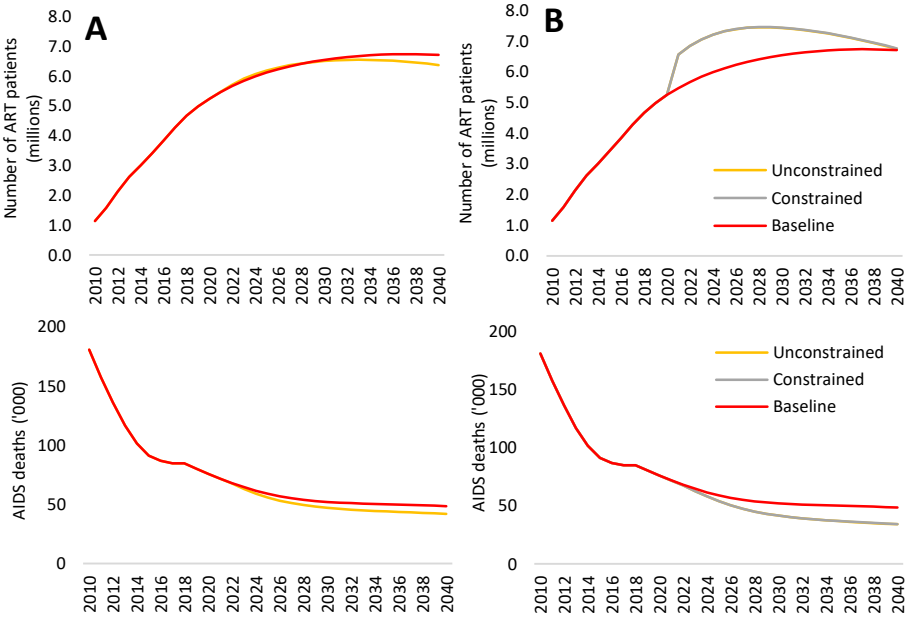


Figure 2. Total cost (billions USD) of the HIV programme, excluding inpatient care, and annual epidemiological impacts on key indicators of the HIV epidemic under (A) 78% ART coverage and (B) 95% ART coverage *(continued)*



Cost effectiveness

If ART retention was maintained at current levels (resulting in 78% coverage overall), compared to baseline, scaling up all interventions would add an incremental cost of $4bn (10%) over 20 years avert 89,000 (8%) AIDS deaths, 700,000 HIV infections (23% of all predicted infections), and save 3.8 million life years (10% of all predicted life years lost to AIDS) (Table 3).

In contrast, achieving a 95% ART coverage was estimated to cost substantially more ($8bn in the constrained, $9.6bn in the unconstrained scenario), but have significantly larger impacts on AIDS deaths (186,000 averted, or 17% of all predicted AIDS deaths), HIV infections (2.1 million averted, or 66% of predicted HIV infections), and life years saved (7.1 million, or 18%). The cost per life year saved under the 78% ART coverage unconstrained scenario was $1,045/life year saved, while under 95% ART coverage it was $1,132/life year saved (constrained scenario) and $1,347/life year saved (unconstrained scenario).

Table 3. Summary of incremental impacts and cost-effectiveness over 20 years (2021-2040)

Baseline (2021-40)		
Total cost of the HIV programme, billions USD	41.1	
New HIV infections, millions	3.1	
AIDS deaths, thousands	1,093	
Life years lost to AIDS, millions	38.8	
	78% ART coverage	**95% ART coverage**
Incremental cost to the HIV programme, billions 2021 USD (%)		
Constrained scenario	n/a	8.0 (+19%)
Unconstrained scenario	4.0 (+10%)	9.6 (+23%)
HIV infections averted, millions (%)		
Constrained scenario	n/a	2.1 (-66%)
Unconstrained scenario	0.7 (-23%)	2.1 (-66%)
AIDS deaths averted, thousands (%)		
Constrained scenario	n/a	186 (-17%)
Unconstrained scenario	89 (-8%)	187 (-17%)
Life years saved, millions (%)		
Constrained scenario	n/a	7.1 (-18%)
Unconstrained scenario	3.8 (-10%)	7.1 (-18%)
Cost per life year saved, 2021 USD		
Constrained scenario	n/a	1,132
Unconstrained scenario	1,045	1,347

Discussion

Our most recent update to the South African HIV Investment Case found that, while most interventions have become affordable under the current, much increased budget, only maximizing ART retention will significantly increase the impact of the South African HIV programme. Altogether, achieving 95% ART coverage could, under the current budget, avert three times as many HIV infections and twice as many AIDS deaths over 20 years, compared to the baseline trajectory of 78% ART coverage, while also allowing South Africa to both meet the UNAIDS 95-95-95 targets by 2025 and cross the 0.1% incidence threshold required for HIV elimination. With regards to individual interventions, compared to 2016 findings, condom provision continued to be the most cost-effective and now only cost-saving intervention, while MMC had become less cost-effective given higher baseline coverage levels especially in adolescents. The least cost-effective interventions, PrEP for male adolescents/young men and early infant male circumcision, were only

affordable under the current budget if ART coverage remained at 78%. HIV self-testing was found to be less cost-effective than conventional HTS, but might still be required to close the last testing gaps.

Our findings need to be interpreted alongside a number of limitations in our methodology. Firstly, our 95% coverage scenario did not incorporate individual interventions known to achieve the necessary levels of 99% retention after treatment initiation. While a number of plausible candidate interventions have shown promise for individual sub-populations, none of these were tested against a comparator, not allowing us to establish their effectiveness and include it into our model. Instead, we simply tested what the impact would be if this level of retention on ART was indeed possible, and added the cost of both a hypothetical staff contingent that might enable such high retention and the cost of the additional client months on ART that would result from such high retention. We are however unable to predict whether this level of retention is feasible or can be achieved with the level of staff whose costs we included. Additionally, our choice of a 20-year time horizon means that some interventions do not appear as beneficial as they would given a longer time horizon, in particular EIMC whose benefits in reducing infection will only become apparent once those circumcised will become sexually active. Lastly, we restricted the range of interventions considered to those with proven effectiveness, which does not necessarily mean that interventions without effectiveness data should not be included in the South Africa response to the HIV epidemic; and while our model was aimed at maximizing the outcome of the programme, by reducing total number of life-years lost, this does not necessarily reduce the unequal distribution of this outcome across subpopulations, for which additional optimization targets would need to be quantified and added into the modelling framework.

Nonetheless, our findings are robust enough to assist in guiding policy development, in particular towards the new HIV National Strategic Plan currently in development.

Supplementary Appendix

Additional interventions

HIV self-testing

We included six HIV self-test (HIVST) kit distribution modalities, with costs and outcomes (HIV positivity, linkage to confirmatory testing and ART initiation for those screened positive) based on our economic analyses of modalities piloted under the STAR project (113). These distribution modalities are:

- primary and secondary distribution in fixed community sites
- primary and secondary distribution in taxi ranks
- primary and secondary distribution in workplaces
- primary distribution in primary healthcare clinics (PHC)
- secondary distribution to partners of antenatal clients in PHC
- secondary distribution to partners of index cases in PHC.

The total number of kits and allocation across these models has been optimised based on a separate analysis using the Thembisa model (339). Table S1 summarises the currently planned policy as well as our optimised option which selected the most effective allocation of kits across modalities that was also more cost-effective than the current policy, while allowing a proportion of tests to be made available for primary distribution at PHCs, a strong policy preference of the NDOH.

Table S1. Allocation of test kits across HIVST modalities under current policy and optimized distribution strategy [2021 USD]

	Current policy allocation	Optimised allocation
Total HIVST kits distributed / year	**638,757**	**3,000,000**
Allocation across modalities (%)		
Fixed community	5%	0%
Taxi rank	5%	12.5%
ANC (secondary)	7%	0%
Index cases (secondary)	3%	75%

	Current policy allocation	Optimised allocation
Total HIVST kits distributed / year	**638,757**	**3,000,000**
Workplace	20%	0%
Primary PHC	60%	12.5%
Cost life year saved	**$912**	**$889**

Calculation of staff quantities cost for retention intervention

Table S2. Number and cost of additional staff assumed for retention intervention, based on facility-level staff added during Siyenza campaign 2018/2019

Staff required	Average staff per site [a]	Average annual salary (2021 USD) [b]	Total Staff required in public sector [c]	Total Staff Cost (2021 USD)
Community health workers	0.1624	2,907	682	1,981,907
Community navigator	0.4943	2,907	2,076	6,034,403
Linkage Officer	1.0520	14,491	4,419	64,029,751
Case Manager	0.1695	8,963	712	6,382,078
Social Work and related professionals	0.0588	28,387	247	7,007,376
WBOT outreach team leader	0.1661	14,630	697	10,203,765
Youth workers	0.6919	2,907	2,906	8,445,921
WBOT community health workers	0.0652	2,907	274	795,631
Psychologists and Vocational Counsellors	0.0091	22,746	38	865,892
			Total	**105,746,725**

[a] estimated from Siyenza project;

[b] where possible, salary acquired from 2019 South African Government Salary scales;

[c] 4,200 health facilities in public sector, multiplied by average staff per site

Selection of outcome metric

Life-years saved as a final outcome metric was selected over HIV infections averted in order to compare interventions across different scenarios and age groups, as a focus on infections averted would have biased the analysis towards interventions for adults. Moreover, the life-years saved measure combines impacts on incidence and mortality and thus permits a comparison of prevention and treatment interventions. Life-years saved was further selected over compound measures such as quality- or disability-adjusted life years since there are only limited data available from South Africa regarding quality weights, and no data regarding disability weights.

Table S3. List of interventions and coverage levels included in the optimisation routine

Intervention	Description	Coverage level tested in optimisation							
		-2	-1	BL	+1	+2	+3	FM (2022/23)	
ART (improved linkage)	Increase ART coverage by increasing linkage to care of newly diagnosed HIV+ patients.	✓	✓	40% linkage	✓	✓	✓	✓	95%
ART (improved linkage and retention)	Increase ART coverage by increasing linkage to care of newly diagnosed HIV+ patients as well as improving retention on ART	✓	✓	77% retention	✓	✓	✓	✓	95%
MMC across all age groups	Men are assumed to get circumcised as a result of programmes that promote MMC as an HIV prevention strategy	✓	✓	430,000	✓	✓	✓	✓	600,000 circumcisions
EIMC†	Circumcision of male infants in their first year of life	✓	✓	10%	✓	✓	✓	✓	70%
Condom availability	Distributing sufficient condoms to ensure that a specified proportion of sex acts will be protected	✓	✓	850m /year	✓	✓	✓	✓	1bn /year
PrEP for FSW	Providing PrEP to FSW only	-	-	9%	✓	✓	✓	✓	30%
PrEP for MSM	Providing PrEP to MSM only	-	-	2%	✓	✓	✓	✓	50%
PrEP for young women	Providing PrEP to young women aged 20-24 only	-	-	2%	✓	✓	✓	✓	18%
PrEP for female adolescents	Providing PrEP to female adolescents aged 15-19 only	-	-	2%	✓	✓	✓	✓	18%
PrEP for pregnant women	Providing PrEP to pregnant women (all ages)	-	-	0%	✓	✓	✓	✓	70%

Intervention	Description	Coverage level tested in optimisation							
		-2	-1	BL	+1	+2	+3	FM (2022/23)	
PrEP for high risk young men	Providing PrEP to high risk young men aged 20-24 only	-	-	0%	✓	✓	✓	✓	18%
PrEP for male adolescents	Providing PrEP to male adolescents aged 15-19 only	-	-	0%	✓	✓	✓	✓	18%
Infant testing at birth	PCR testing of infants at birth	-	-	90%	✓	✓	✓	✓	95%
HIV testing services (HTS) for general population	Conventional HIV testing services for general population	✓	✓	14.3m/ year	✓	✓	✓	✓	18.3m/year (Annual performance plan NDOH)
HTS for adolescents	Dedicated HIV testing drives targeted at adolescents	-	-	22%	✓	✓	✓	✓	95%

Abbreviations: BL=Baseline, FM=Feasible Maximum, ART=antiretroviral treatment, MMC = medical male circumcision, PrEP=pre-exposure prophylaxis, EIMC=early infant male circumcision, PCR=polymerase chain reaction, HTS=HIV testing services, NDoH=National Department of Health

†Although a novel intervention, the model assumed a non-zero baseline for EIMC. We therefore retained the -1 and -2 coverage level scenarios in our analysis.

Available budget

For the calculation of the available budget envelope over the next years, we used a number of data sources. The budget made available by the South African Government was based on the HIV allocation only in the current Conditional Grant budget. We deflated values based on the South Africa Reserve Bank's Consumer Price Index (340) in order for the budget to be comparable with the 2021 nominal costs used in the remainder of the model. The PEPFAR budget was based on the planned budget for 2021/22 (COP21) and assumed to stay the same throughout the projection period-likely an overestimate. The Global Fund budget for the years 2020/21 and 2021/22 was based on the known 2019-2022 allocation. We only included those items that were aligned to Investment Case interventions and costing populations.

The likely GF contribution for 2022/23 was estimated based on the planned 2022-25 allocation, with 40% of the HIV-specific GF budget assumed to be available for general HIV services, based on previous allocations. The resulting budget envelope is summarized in Table S4.

Since the publication of the first Investment Case in 2016, we have continuously updated our modelling suite to take into account changes to the evidence base, intervention coverage and implementation models, and intervention costs, based on recent data from routine implementation (District Health Information System, DHIS) and other NDOH data sources and an update on the ingredients and their quantities and prices for each intervention based on new literature where necessary, and the use of 2020/21 prices throughout.

Table S4. Budget envelope for 2020/21 to 2022/23 based on the three main funders of the South African HIV response [billions 2021 USD]

Funder	2020/21	2021/22	2022/23
South African Government	1.39	1.53	1.54
PEPFAR	0.41	0.41*	0.41*
Global Fund	0.04	0.04	0.04*
Total budget	**1.84**	**1.97**	**1.99**

*assumed targets.

Chapter 9
General Discussion

The aim of this thesis was to demonstrate how epidemiological and health economic modelling methods can be used to shape policy around HIV prevention and treatment services, with an overarching goal of making programmes more impactful and efficient. We do this by evaluating and optimizing individual HIV interventions across the spectrum of HIV prevention and treatment interventions. The modelling methods used in this thesis allow us to simulate and evaluate a wide variety of different implementation strategies, or combinations of interventions, without the need to perform costly and time-consuming trials, or allow us to conduct research which might have been otherwise implausible to conduct in the real world. As modelling can be conducted relatively quickly, it also enables rapid policy development and implementation, while questions remain pertinent.

The research in this thesis has been conducted while directly engaging with the national governments in order to get their input, as well as to disseminate our research results as they were being produced in real time, enabling a live, iterative process to ensure that the work conducted was relevant and answering the right questions. This is evident from my active participation in multiple national working groups including the NDOH PrEP Technical Group, HIV Think Tank and engagement with the National Essential Medicine List Committee at the NDOH.

In this thesis, I demonstrated that oral PrEP can be made more cost-effective, even cost-saving, if sub-populations at high risk of acquiring HIV successfully self-select to take them (Chapter 2) (143). This thesis also found the optimal distribution of HIV self-testing between modalities which will yield higher impacts, and better cost-effectiveness, compared to than the distribution of HIVST between modalities as originally planned by policy-makers (Chapter 3) (339). Chapter 4 extended the work from Chapter 2, by comparing a novel HIV prevention technology, long-acting injectable cabotegravir, to the standard-of-care oral PrEP, and in the process estimated the optimal price threshold for this new HIV prevention intervention (341).

Interventions for HIV treatment were also evaluated using epidemiological and cost modelling methods. In Chapter 5, we demonstrated how a new TDF-based ART drug regimen containing dolutegravir (DTG) is as cost-effective as the standard-of-care regimen at the time (342). In Chapter 6, an analysis investigated current policy on implementation of DSD for HIV treatment and found that the widely-implemented eligibility criteria likely needs to be

reviewed for Zambia (343). Chapter 7 evaluated a combined analysis of three epidemiological models for sub-Saharan Africa was able to determine an upper bound cost for ART retention interventions (344). Lastly, this thesis demonstrates how epidemiological and cost modelling can be used to model all HIV interventions and design an optimal package of interventions to help inform the South African government on the most cost-effective strategy towards reaching the UNAIDS 95-95-95 goals (Chapter 8).

Implications for this research

Part 1: Interventions for HIV prevention

Informing policy-makers on the most optimal strategy of targeting HIV prevention methods, specifically oral PrEP and HIV self-testing; informing national and international price negotiations by estimating the optimal price for the latest available HIV prevention method, CAB-LA.

Chapter 2 estimated the cost of oral PrEP provision in South Africa to be between $129 and $134 per user year, and though more expensive than other available HIV prevention interventions, like condoms and MMC, it demonstrated that targeting PrEP to groups at highest risk of HIV infection will be the more cost-effective strategy, and can even be cost-saving in the longer term. This work was done while engaging with the NDOH PrEP TWG, with regular dissemination of results at quarterly meetings, to aid their decision-making regarding the implementation of the oral PrEP programme.

Chapter 3 directly addressed the question of whether the current NDOH policy of HIVST kit distribution across different modalities was the best possible configuration that can be implemented, for both public health impact and cost-effectiveness. What was initially planned was a distribution where majority (60%) of the HIVST kits would be distributed to the general population attending PHC across South Africa, while smaller portions of the available HIVST kits would be allocated to other modalities included in the analysis- workplace distribution 20%, secondary distribution to partners of women attending ANC 7%, fixed point distribution 5%, taxi rank distribution 5%, secondary distribution to partners of ART patients at PHC 3%. However, my work in this thesis found that the planned distribution was sub-optimal in both impact and cost-effectiveness (339). My work also found that distributing the majority of HIVST kits for primary use by the general population attending PHC could be harmful, and that the biggest impact on

saving life years would occur when distributing majority of HIVST kits to partners of ART patients in the PHC – effectively targeted PHC distribution, instead of to the general PHC population. Through this work I determined the optimal configuration of HIVST kit distribution to maximize impact while being cost-effective: 55% distributed to partners of ART patients in the PHC, 18% each to fixed point and taxi ranks, 9% to partners of PHC ANC clients and none to workplaces or primary PHC clients. When scaling up HIVST kit distribution for South Africa, this optimal distribution produced not only produced a 3-fold bigger impact on life years saved, but was also more cost-effective in terms of having a lower cost per life year saved ($5,373/LYS), compared to the initial policy distribution ($3,923/LYS) between the evaluated HIVST modalities. We had directly engaged, and collaborated, with Dr. Thato Chidarikire, the Director for HIV Prevention Programmes at the South African NDOH, at the time, to disseminate our work them regarding their HIVST distribution policy.

Chapter 4 sought to evaluate the cost-effectiveness of CAB-LA and estimate a price for this novel drug that can be used in price negotiations for the South African market. We found that the cost per injection of the novel cabotegravir can only be around 2-fold the cost of a 2-month supply of standard-of-care oral PrEP to remain as cost-effective, with the price of the drug ranging between $63 and $101 per year (depending on the scenario modelled) – a mere fraction of the current US list price of $22,000 per year. This research was directly disseminated to the NDOH Affordable Medicine Director, in order to aid their price negotiations for the long-acting injectable PrEP for national roll-out in South Africa. Furthermore, this research was presented to the National Essential Medicine List Committee, who are responsible for providing evidence-based recommendations to NDOH for the inclusion of selected medicines for the public sector in South Africa.

Across Chapters 2-4, we were able to use both epidemiological and health economics modelling to inform policy decisions regarding three HIV prevention interventions, specifically informing how to target these to the populations who need it the most, with the overall aim of maximizing impact and improving cost-effectiveness. Further, in Chapter 4 we helped inform policy-makers on the optimal price of CAB-LA in South Africa, should it come into the market, to ensure that it is as cost-effective as current standard-of-care oral PrEP. This latter work is crucial to the decision-making process of the South African government and likely relevant to governments in other

LMIC, and global donor agencies, who are considering how to introduce CAB-LA into current standard-of-care oral PrEP programmes.

Part 2: Interventions for HIV treatment

Re-evaluate existing HIV treatment interventions and their current policies, including the latest ART regimen and interventions used to improved patient retention, across SSA countries, estimating their impact and cost-effectiveness in a way that is useful for policy-makers.

Research in Chapter 5 showed that a newly rolled-out first-line ART regimen, TDF/FTC+DTG, was as cost-effective as the standard-of-care EFV-based regimen, TDF/FTC/EFV, having similar cost per outcomes of $426 and $424 per virally suppressed patient, respectively. This work also showed that over the longer term, TDF/FTC+DTG was more cost-effective than the TAF-containing, equivalent regimen, TAF/FTC+DTG, with $10,341 and $41,958 per life year saved, respectively. Our work in this chapter provided supporting information to policy-makers on the benefits of the roll-out of TDF/FTC+DTG to the ART patient population (180). Further, work conducted in Chapter 5 also demonstrated how one can adjust trial cost and resource utilization data into information that can be used in health economics modelling when assuming routine implementation in the public health sector. Estimating the cost-effectiveness of a national roll-out of TDF/FTC+DTG in a routine-care setting would not have been possible to do timeously without the use of modelling.

We showed in Chapter 6 that patients who are enrolled in DSD models for HIV treatment early (before 6 months of ART compliance) – in contrast to the policy eligibility criteria, are significantly less likely to be lost to follow-up (adjusted risk ratio 0.59, 95% CI 0.50-0.68) compared to patients who enrol in DSD models as per eligibility criteria (where patients require more than 6 months of ART compliance before being considered for DSD enrolment). Though patients in our cohort were likely selected for early DSD model enrolment by healthcare providers based on expected good retention, it is still of vital importance to show to that early eligibility for DSD models can be considered for a subset of patients, and that blanket policy eligibility criteria need not be strictly applied. We conducted this research with direct involvement and input from the Zambian Ministry of Health.

Work conducted in Chapter 7 helped inform the upper-bound cost for HIV treatment retention interventions, while comparing different models across SSA countries. In addition to using different models, the upper-bound costs were estimated separately by % improvement in ART retention and risk population (those most at risk of ART interruption or all people on ART). Our work found that there was substantial variability in the estimated upper-bound costs across models and settings. If targeting those most at risk of ART interruption, to achieve a 50% improvement in ART retention, the upper-bound cost that could be spent per additional person-year retained on ART would be $851-$5,624 (EMOD), $97-$228 (Optima) and $1,039-$1,641 (Synthesis). These estimates were similar or higher than what has been estimated in the past, prior to the "Treat All" era.

By doing a multi-model comparison, we could estimate the incorporate structural model uncertainty and heterogeneity of different populations and settings to inform research priorities more broadly. This research provides important information to policy-makers on how to shape their HIV programmes in order to make it as efficient as possible, as it broadly indicates the amount that governments may be willing to invest in interventions that improve retention in ART programmes, as well as helping to prioritize interventions for implementation. However, the upper-bound estimates are wide as they incorporate much uncertainty; policy makers who would want to apply these estimates to specific sub-populations might need to collaborate with modelling groups to improve the accuracy of model estimates for their specific settings. Overall this work could only be done through modelling, as it would have been impossible to evaluate all combinations of retention improvement and country settings through economic evaluations.

Part 3: Optimizing a package of interventions for HIV prevention and treatment

Designing the optimal package of interventions by applying health economics and epidemiological modelling methods to both HIV prevention and treatment interventions for South Africa with the aim of reaching HIV elimination.

Work conducted in Chapter 8 combines many aspects of this thesis together by modelling several HIV interventions in an effort to design the most optimal package of interventions, while evaluating the impact of maintaining a 95% ART coverage, achievable only through improving retention on ART. Work

in the preceding chapters relate to, or feed directly into, work conducted in Chapter 8. In the HIV Investment Case, we include several HIV prevention interventions: oral PrEP for different target populations (related to work in Chapter 2), HIV testing for the general population, HIV testing for adolescents and PCR testing for infants at birth, the optimized HIVST package (related to work in Chapter 3), condoms, MMC and EIMC. We also include interventions related to ART treatment, namely improving linkage of newly diagnosed individuals and improving retention in care.

In Chapter 8 we found that improving ART retention to reach 95% ART coverage is the only way to achieve the "virtual elimination" threshold (6), despite scaling up all HIV interventions to their feasible maximum, including reaching 95% ART linkage. This work also found that scaling up condom distribution to 1 billion/year was a cost-saving intervention and the next most cost-effective interventions thereafter were ART 95% linkage ($115/life year saved), infant testing at birth 95% coverage ($765/life year saved), PrEP for MSM 50% coverage ($1,107/life year saved), HTS general population 18.3 million tests/year ($1,417/life year saved). Improving ART coverage to 95% through a retention intervention was moderately cost-effective at $1,470/life year saved.

This research was conducted with continuous engagement with the South African NDOH, as well as National Treasury, informing their planned budgets and health outcome targets for the HIV programme.

Limitations

Limitations of modelling methods and input parameters

Data on the uptake and effective use of PrEP and HIV self-testing, as well as duration of use of PrEP is currently limited and this research relied mostly on assumptions based on trial data, open-label studies, and preference studies. Moreover, long-acting injectable PrEP is an intervention not yet widely implemented in SSA and therefore future uptake remains unknown. Furthermore, data used to inform the modelling regarding screening yield and cost of HIV self-testing was collected from an initiative which was implemented by a non-governmental organization, and these could be different if implemented and managed by the public health sector in South Africa.

Modelling methodology allows us to do sensitivity analyses around uptake and duration of use (or other parameters of interest), while incorporating uncertainty around these parameters, with the aim of getting more meaningful answers as to how changes in uptake or duration of use of interventions can influence impact and cost-effectiveness. I conducted extensive sensitivity analyses, including a probabilistic sensitivity analysis for long-acting injectable PrEP. However, parameters could be further refined using preliminary data from implementation studies as these novel interventions are rolled-out in real-time.

In the longer term, real-world uptake and effective use of these interventions in a large-scale roll-out will need to be monitored closely in order to accurately inform future modelling and subsequent impact on the HIV epidemic.

Compared to models which have more comprehensive and realistic sexual networks, Thembisa, as a compartmental model, tends to underestimate how high-risk groups sustain the HIV and STI incidence in the population (92). Therefore, this implies that the impact, and therefore cost-effectiveness, of oral and long-acting PrEP, which was targeted towards high risk groups, could be underestimated in Thembisa.

More generally, these models use the limited data available from clinical trials and other types of studies, usually run by non-governmental organizations, to make assumptions regarding the parameters which are then in turn modelled and generalized to the national population. Programmes or interventions conducted by non-governmental organizations generally tend to have more favourable patient outcomes compared to government-run programmes due to the increased availability of resources in the former. This would lead to an overestimation in the impact these programmes would have if generalized to the national population; however, cost-effectiveness could either be underestimated (if using the higher cost from non-government programmes) or overestimated (if using lower costs from government programmes). More granular data, and possibly geospatial data, and subsequent modelling may be required to ensure that HIV intervention programmes can be targeted accurately and efficiently.

Lastly, in Chapter 8 we model a scenario where we achieve 95% ART coverage through a retention intervention for the treatment programme. There are a number of retention interventions available. However, none of these

have been tested against a standard-of-care comparator and we therefore do not know which intervention would be able to achieve such a high retention and subsequent ART coverage. Though we added the cost of one of these interventions, its impact was theoretical and it remains unclear whether that specific intervention will result in the high retention required. Nevertheless, it was useful to model the potential impact of achieving 95% ART coverage, as it highlights not only the importance of reaching this UNAIDS target for the potential elimination of HIV in South Africa, but also the importance of keeping people engaged in care, particularly as people spend longer durations on ART.

Potential limitations to costing methods

The thesis made use of an ingredients-based costing method for PrEP, for both oral PrEP and long-acting injectable cabotegravir, as real-world cost for a large-scale roll-out had not been evaluated at the time. Our estimate of cost for PrEP provision may be overestimated for two reasons: 1) the cost included additional staff time required for the PrEP services, which, if implemented at all public health care clinics, may not necessarily translate into additional staff hired, 2) the cost included demand creation and training costs, which may be regarded as non-essential in an already overburdened healthcare system once implemented, or at best, become less important as PrEP uptake increases to higher levels. However, if the PrEP programme proves to be unsuccessful at attracting potential clients, government may need to increase spending on demand creation, more than what was estimated in our costing method.

For CAB-LA, we assumed that it would be rolled out in a similar setting as current oral PrEP, and using the current HIV diagnostic algorithm which includes rapid HIV testing. However, due to the long-acting nature of the drug, CAB-LA may suppress the detection of viral load, which means that PCR testing may be required in CAB-LA implementation. As PCR tests are much more expensive than rapid HIV tests, including PCR testing would result in the cost of CAB-LA provision to be vastly more expensive than currently projected. This would mean that in our work where we estimated the price threshold at which CAB-LA would be as cost-effective as oral PrEP, would in turn need to be reduce even more to maintain cost-effectiveness. This lowered price may not be feasibly achieved in terms of its manufacturing cost, even for generic manufacturers, and we may need to accept a higher cost for the implementation for CAB-LA due to the inclusion of PCR testing.

Generalizability

Work in this thesis was mostly done on a South African population (Chapters 2-5, 7 and 8), then for Zambia (Chapter 6) and Malawi and SSA LMIC settings (Chapter 7). The feasibility of extrapolating these findings to other countries would depend on the research or policy questions and the country of interest.

Our findings of high-risk populations being more cost-effective than targeting the general population for oral PrEP would translate into any country, as the assumption of high risk individuals carrying the burden of HIV disease applies across different settings (Chapter 2); however, the incremental cost per HIV infection averted or life year saved would differ substantially between countries as both cost and impact would depend on their HIV epidemic. Oral PrEP would also need to be targeted to different populations in Europe compared to South Africa as the HIV epidemic in the former is more concentrated in the MSM population whereas in South Africa there is much more heterosexual HIV transmission, though MSM are also a high-risk population.

Our work on HIV self-testing in Chapter 3, conducted on a South African population, may not necessarily be generalizable to other countries, even within SSA, as self-testing implementation, uptake and impact could differ from setting to setting. The Unitaid-funded STAR Initiative has implemented HIV self-testing in several countries in SSA and country-specific studies can produce the relevant parameters for future modelling in these countries.

Analysis conducted in Chapter 4, where we estimated the impact of CAB-LA on a South African population could be generalizable to other settings if the underlying assumption of the cost of implementation also hold for those countries, i.e. if the cost of implementation of oral PrEP and CAB-LA – excluding the price of the drugs – are similar, then the only difference dictating cost-effectiveness between these two programmes is the effectiveness of the drugs and the price of the drugs themselves. Of interest is that a modelling study done in the United States, which also estimated the price threshold at which CAB-LA remains as cost-effective as TDF/FTC, found that CAB-LA would need to be between 1- and 2-fold the price of TDF/FTC (345,346). A similar finding to our work, but with higher costs for provision in a different setting altogether. More modelling work needs to be

done in SSA, particularly in those with a high HIV burden, in order to inform policy makers of the optimal price at which CAB-LA remains as cost-effective as standard of care, oral TDF/FTC, if that is one of the relevant criteria for those countries.

Chapter 5 evaluated the cost-effectiveness of a dolutegravir-containing TDF-based ART regimen compared to the standard-of-care first line ART regimen in South Africa. These results are likely to be broadly generalizable given the lower price of manufacturing of dolutegravir-based regimens compared to the previously standard EFV-based regimen, and the improvement of viral suppression for dolutegravir-based regimens would remain the same across all populations.

In Chapter 6 we showed that the DSD model eligibility criteria of needing at least 6 months of ART prior to DSD enrolment, in Zambia, may need to be reconsidered at least for some patients who would be inclined to be 'good adherers'- something that would need to be judged on a patient-to-patient basis by healthcare providers. Patients who are considered good adherers from the very start of ART initiation will always exist in any country, so eligibility criteria need to be flexible in order to accommodate individual needs for ART treatment access.

Our work estimating the upper bound cost for retention interventions was conducted on several country settings in SSA using three different models. This allowed for considerable uncertainty to be taken into account. These would be applicable to all SSA, even with the large uncertainty.

Conclusions and future research

Based on work conducted for this thesis, the following conclusions can be reached:

1. Targeting high risk populations would positively impact on the cost-effectiveness of PrEP and more needs to be done in terms of demand creation to ensure successful self-selection into PrEP programmes.
2. Modelling is a useful tool to evaluate planned implementation and counter it with alternative, impactful and cost-effective strategies to policy-makers in real-time – as we did with HIV self-testing.
3. In South Africa, CAB-LA for PrEP cannot cost more than 2-fold the cost of standard-of-care oral TDF/FTC for it to be as cost-effective as

the standard-of-care. There is a dire need in most LMICs for a highly effective HIV prevention technology such as CAB-LA and the more affordable the manufacturers can make it for those who need it, the more likely people in these countries will be able to benefit from its availability.

4. TDF/FTC+DTG is a cost-effective regimen for HIV treatment when compared to the now-former first line standard-of-care ART regimen and patients will benefit greatly from its continuous roll-out.
5. Eligibility criteria for DSD models need to be evaluated in all SSA countries and programmes may need to be less rigid, and more patient-centric, in order to ensure that these treatment modalities are available to those who are willing and able to adhere to them as soon as they start ART.
6. Multi-model comparisons are informative in modelling potential impact of interventions in different settings, but can produce wide estimates due to the uncertainty in the models. Therefore, policy makers would need to collaborate with modelling groups more closely in order to produce more accurate estimates.
7. Modelling all HIV interventions together is an invaluable exercise as it takes into account several aspects of disease dynamics and the impact of different prevention and treatment interventions. This allows for informative output for the structuring of an HIV programme to ensure it's implemented in the most cost-effective way possible.

Future work for modelling HIV prevention interventions should include the alignment to data outputs from large-scale implementation of these interventions in order to ensure accurate parameterization of models, and the necessary calibration to guarantee accurate model fit. This will also facilitate real-time modelling work and speed up policy development for the most relevant questions for implementation. In order to achieve this effectively and accurately, routine data collection systems would need to be in place to sufficiently capture real-time, or as close to it, uptake of these interventions, effective use and for PrEP, the duration of use. Similarly, new treatment interventions and their subsequent large-scale implementation need to be monitored and understood for the benefit of future modelling work, with the broad goal of informing policy changes as, and when, needed.

It is also vital that future implementation and programmatic research should focus on interventions, or packages of interventions, which can achieve sufficient improvements in ART retention leading to sustained retention in care and ultimately a consistent 95% ART coverage; without this, HIV elimination will not be possible.

Eligibility criteria for DSD models need to be evaluated further, particularly in other settings with high HIV burden and in countries who have implemented DSD models for HIV treatment. This will aid our understanding of how treatment programmes can be further developed to be more patient-centric and how barriers to treatment access can be further reduced to improve linkage and, especially, retention in care to achieve 95% ART coverage.

Chapter 10

Summary in English

The aim of this thesis was to demonstrate how epidemiological and health economic modelling methods can be used to shape policy around HIV prevention and treatment services, with an overarching goal of making programmes more impactful and efficient. We do this by evaluating and optimizing individual HIV interventions across the spectrum of HIV prevention and treatment interventions. We used modelling methods us to evaluate different interventions, implementation strategies, or combinations of interventions, without needing to perform costly and time-consuming trials. These methods also allowed us to conduct research which might have been otherwise implausible to conduct in the real world. As modelling can be conducted relatively quickly, it also enables rapid policy development and implementation, while questions remain pertinent. While conducting the research in this thesis, we engaged directly with the national governments in order to get their input, as well as to disseminate our research results as they were being produced in real time, enabling a live, iterative process to ensure that the work conducted was relevant to policy-makers.

An estimated 25.6 million people were living with HIV (PLHIV) in sub-Saharan Africa (1), of which South Africa accounts for an ~7.5 million of these and Zambia has 1.3 million PLHIV (2,3). Governments from both South Africa and Zambia are committed to meeting the UNAIDS fast-track targets by 2025 (5). These targets aim to have, by 2025, 95% of PLHIV diagnosed, 90% of PLHIV on antiretroviral treatment (ART) and 86% of PLHIV virally suppressed. Zambia is very close to achieving these goals with 91%-90%-87% (3) for the respective target goals. With a much higher burden of HIV compared to Zambia, South Africa is lagging behind with 94%-74%-67% for the respective targets (2). Another target is the "virtual elimination threshold", which was shown through modelling would eliminate HIV if a population-level HIV incidence could be maintained below 0.1% annually (6). As of 2021, Zambia was estimated to have an annual HIV incidence of 0.4% (3) and South Africa, 0.69% (2).

Several prevention and treatment interventions, if implemented widely and efficiently, can assist in reaching the UNAIDS fast-track and HIV incidence targets. These include HIV self-testing (HIVST), pre-exposure prophylaxis (PrEP) technologies, ART, and differentiated service delivery (DSD) models.

HIVST allows people the opportunity to diagnose their HIV status themselves in the privacy of their own homes, and has been shown to be feasible, acceptable and effective at increasing testing uptake in sub-Saharan Africa (31–33). Oral PrEP has been shown to be 65%-85% effective in preventing HIV acquisition in a number of populations (34,35). A newer technology, long-acting injectable cabotegravir (CAB-LA), is 66% [95%CI 38%-82%] effective in preventing HIV in men who have sex with men (MSM) and transgender women, and 89% [95%CI 68%-96%] in young women, compared to oral PrEP (36–38). DSD models are an alternative method of providing a service to a patient in public care. DSD models for HIV treatment can differ from conventional care by the cadre of provider, location of service delivery, frequency of interactions with the healthcare system, and/or types of services offered. These changes can help remove barriers to care, making it easier for patients to access HIV treatment, and support long-term retention to care (28).

This thesis uses health economic and epidemiological modelling methods to understand how to cost-effectively maximize impact of our HIV programmes in order to guide national and international health policy. Broadly, I aimed to achieve the following through my work:

- Informing policy-makers on the most optimal strategy of targeting HIV prevention methods, specifically oral PrEP and HIV self-testing; informing national and international price negotiations by estimating the optimal price for the latest HIV prevention method, CAB-LA.
- Re-evaluating existing HIV treatment interventions and their current policies, including the latest ART regimen and interventions used to improved patient retention, across SSA countries, estimating their impact and cost-effectiveness in a way that is useful for policy-makers.
- Designing the optimal package of interventions by applying health economics and epidemiological modelling methods to both HIV prevention and treatment interventions for South Africa with the aim of reaching HIV elimination.

In this thesis, I demonstrated that oral PrEP can be made more cost-effective, even cost-saving, if sub-populations at high risk of acquiring HIV successfully self-select to take them (Chapter 2). This thesis also found the optimal distribution of HIV self-testing between modalities which will yield

higher impacts, and better cost-effectiveness, compared to than the distribution of HIVST between modalities as originally planned by policy-makers (Chapter 3). Chapter 4 extended the work from Chapter 2, by comparing CAB-LA to the standard-of-care oral PrEP, and in the process, we estimated the optimal price at which CAB-LA remains as cost-effective as oral PrEP. This work is crucial to the decision-making process of the South African government and likely relevant to governments in other low- and middle-income countries (LMIC), and global donor agencies, who are considering how to introduce CAB-LA into current PrEP programmes. We were able to use both epidemiological and health economics modelling to inform policy decisions regarding three HIV prevention interventions, specifically informing how to target these to the populations who need it the most, with the overall aim of maximizing impact and improving cost-effectiveness.

HIV treatment interventions were also evaluated using epidemiological and cost modelling methods. In Chapter 5 we demonstrated how a new TDF-based ART drug regimen containing dolutegravir (DTG) is as cost-effective as the standard-of-care regimen at the time. Further, we demonstrated how one can adjust trial cost and resource utilization data into information that can be used in health economics modelling when assuming routine implementation in the public health sector. Estimating the cost-effectiveness of a national roll-out of tenofovir (TDF)/emtricitabine (FTC)+DTG in a routine-care setting would not have been possible to do timeously without the use of modelling. In Chapter 6, an analysis investigated current policy on implementation of DSD for HIV treatment and found that the widely implemented eligibility criteria likely needs to be reviewed for Zambia. Chapter 7 evaluated a combined analysis of three epidemiological models for sub-Saharan Africa was able to determine an upper bound cost for ART retention interventions. Lastly, this thesis demonstrates how epidemiological and cost modelling can be used to model all HIV interventions and design an optimal package of interventions to help inform the South African government on the most cost-effective strategy towards reaching the UNAIDS 95-95-95 goals (Chapter 8). This research was conducted with continuous engagement with the South African National Department of Health (NDOH), as well as National Treasury, informing their planned budgets and health outcome targets for the HIV programme.

Based on work conducted for this thesis, the following can be concluded: (1) Targeting high-risk populations would positively impact on the cost-effectiveness of PrEP and more needs to be done in terms of demand creation to ensure successful self-selection into PrEP programmes. (2) Modelling is a useful tool to evaluate planned implementation and counter it with alternative, impactful and cost-effective strategies to policy-makers in real-time – as we did with HIV self-testing. (3) In South Africa, CAB-LA for PrEP cannot cost more than 2-fold the cost of standard-of-care oral TDF/FTC for it to be as cost-effective as the standard-of-care. There is a dire need in most LMICs for a highly effective HIV prevention technology such as CAB-LA and the more affordable the manufacturers can make it for those who need it, the more likely people in these countries will be able to benefit from its availability. (4) TDF/FTC+DTG is a cost-effective regimen for HIV treatment when compared to the now-former first line standard-of-care regimen and patients will benefit greatly from its continuous roll-out. (5) Eligibility criteria for DSD models need to be evaluated in all SSA countries and programmes may need to be less rigid, and more patient-centric, to ensure that these treatment modalities are available to those who are willing and able to adhere to them as soon as they start ART. (6) Multi-model comparisons are informative in modelling potential impact of interventions in different settings, but can produce wide estimates due to the uncertainty in the models. Therefore, policy makers need to collaborate with modelling groups in order to produce more accurate estimates. (7) Modelling all HIV interventions together is an invaluable exercise as it takes into account several aspects of disease dynamics and the impact of different prevention and treatment interventions. This allows for informative output for the structuring of an HIV programme ensuring it is implemented in the most cost-effective way possible.

Future work for modelling HIV prevention interventions should include the alignment to data outputs from large-scale implementation of these interventions to ensure accurate parameterization of models, and the necessary calibration to guarantee accurate model fit. This will also facilitate real-time modelling work and speed up policy development for the most relevant questions for implementation.

Nederlandse Samenvatting

Het doel van dit proefschrift was om aan te tonen hoe epidemiologische en gezondheid economische modelleringsmethoden kunnen worden gebruikt om beleid rond HIV-preventie en -behandeling vorm te geven, met als overkoepelend doel programma's effectiever en efficiënter te maken. We doen dit door individuele HIV-interventies over het hele spectrum van HIV-preventie- en behandelingsinterventies te evalueren en te optimaliseren. We gebruikten modelleringsmethoden om verschillende interventies, implementatiestrategieën of combinaties van interventies te evalueren, zonder dure en tijdrovende onderzoeken uit te voeren. Deze methoden stelden ons in staat om onderzoek te doen dat onmogelijk zou zijn geweest om in de echte wereld uit te voeren. Omdat modellering relatief snel kan worden uitgevoerd, maakt het ook een snelle beleidsontwikkeling en -implementatie mogelijk, terwijl vragen relevant zijn. Tijdens het uitvoeren van het onderzoek in dit proefschrift hebben we rechtstreeks contact gehad met de nationale regeringen om hun input te krijgen en om onze onderzoeksresultaten te verspreiden terwijl ze in real-time werden geproduceerd, waardoor een levend, iteratief proces mogelijk werd. Dit zorgde ervoor dat het uitgevoerde werk relevant was voor beleidsmakers.

Naar schatting 25.6 miljoen mensen leefden met HIV (PLHIV) in sub-Sahara Afrika (1), waarvan Zuid-Afrika ongeveer 7.5 miljoen voor zijn rekening neemt en Zambia 1.3 miljoen (2,3). Regeringen van zowel Zuid-Afrika als Zambia hebben zich gecommitteerd om de versnelde doelstellingen van UNAIDS voor 2025 te halen (5). De doelstelling is om tegen 2025 95% van de PLHIV gediagnosticeerd te hebben, 90% van de PLHIV zijn onder antiretrovirale behandeling (ART) en 86% van de PLHIV viraal onderdrukt. Zambia is zeer dicht bij het bereiken van deze doelen met 91%-90%-87% (3). Met een veel hogere HIV-last in vergelijking met Zambia, loopt Zuid-Afrika achter met 94%-74%-67% (2). Een ander doel is de "virtuele eliminatiedrempel", die door modellering werd aangetoond. HIV zou geëlimineerd worden als de HIV-incidentie op populatieniveau onder de 0.1% per jaar zou kunnen worden gehouden (6). Vanaf 2021 had Zambia naar schatting jaarlijkse HIV-incidentie van 0.4% (3) en Zuid-Afrika 0.69% (2).

Verschillende preventie- en behandelingsinterventies kunnen, mits breed en efficiënt geïmplementeerd, helpen bij het bereiken van de UNAIDS fast-track

en HIV-incidentiedoelstellingen. Deze omvatten HIV-zelftesten (HIVST), technologieën voor profylaxe vóór blootstelling (PrEP), ART en modellen voor gedifferentieerde dienstverlening (DSD).

HIVST biedt mensen de mogelijkheid om zelf hun HIV-status te diagnosticeren in de privacy van hun eigen huis, en het is aangetoond dat het haalbaar, acceptabel en effectief is om het gebruik van tests in Sub-Sahara Afrika te vergroten (31–33). Het is aangetoond dat orale PrEP voor 65%-85% effectief is bij het voorkomen van HIV in een aantal populaties (34,35). Een nieuwere technologie, langwerkende injecteerbare cabotegravir (CAB-LA), is 66% [95%CI 38%-82%] effectief in het voorkomen van HIV bij mannen die seks hebben met mannen (MSM) en transgendervrouwen, en 89% [95%CI 68%-96%] bij jonge vrouwen, vergeleken met orale PrEP (36–38). DSD zijn een alternatieve methode voor patiënten in de openbare zorg. DSD-modellen voor HIV-behandeling kunnen verschillen van conventionele zorg door het opleidingsniveau van de aanbieder, de locatie van de dienstverlening, de frequentie van interacties met het gezondheidszorgsysteem en/of de soorten aangeboden diensten. Deze veranderingen kunnen helpen om belemmeringen voor zorg weg te nemen, waardoor het voor patiënten gemakkelijker wordt om toegang te krijgen tot HIV-behandeling, en om langdurige zorgbehoud te ondersteunen (28).

Dit proefschrift maakt gebruik van gezondheid economische en epidemiologische modelleringsmethoden om te begrijpen hoe we op een kosteneffectieve manier de impact van onze HIV-programma's kunnen maximaliseren om het nationale en internationale gezondheidsbeleid te sturen. In grote lijnen heb ik met mijn werk het volgende willen bereiken:

- Beleidsmakers informeren over de meest optimale strategie om HIV-preventiemethoden toe te passen, met name orale PrEP en HIV-zelftesten; het schatten van de prijs van de nieuwste HIV-preventiemethode, CAB-LA, voor nationale en internationale prijsonderhandelingen.
- Opnieuw evalueren van bestaande HIV-behandelingsinterventies en hun huidige beleid, inclusief het nieuwste ART-regime en interventies die worden gebruikt om het behoud van patiënten te verbeteren, in SSA-landen, waarbij hun impact en kosteneffectiviteit worden geschat op een bruikbare manier voor beleidsmakers.

- Ontwerpen van het optimale pakket aan interventies door toepassing van gezondheid economische en epidemiologische modelleringsmethoden op zowel HIV-preventie als behandelingsinterventies voor Zuid-Afrika met als doel HIV-eliminatie.

In dit proefschrift heb ik aangetoond dat orale PrEP kosteneffectiever en zelfs kostenbesparender kan worden gemaakt, als subpopulaties met een hoog risico om HIV op te lopen, er zelf voor kiezen om PrEP te nemen (Hoofdstuk 2). Dit proefschrift vond ook de optimale verdeling van het distribueren van HIV-zelftesten, wat een grotere impact en een betere kosteneffectiviteit zal opleveren dan de distributie van HIVST zoals oorspronkelijk gepland door beleidsmakers (Hoofdstuk 3). Hoofdstuk 4 breidde het werk uit Hoofdstuk 2 uit, door CAB-LA te vergelijken met de standaard orale PrEP, en daarbij schatten we de optimale prijs waartegen CAB-LA even kosteneffectief blijft als orale PrEP. Dit werk is cruciaal voor het besluitvormingsproces van de Zuid-Afrikaanse regering en waarschijnlijk relevant voor regeringen in andere lage- en middeninkomenslanden (LMIC) en wereldwijde donororganisaties, die overwegen hoe ze CAB-LA in de huidige PrEP programma's kunnen introduceren. We waren in staat om zowel epidemiologische als gezondheid economische modellering te gebruiken zodat weloverwogen beleidsbeslissingen genomen konden worden met betrekking tot drie HIV-preventie interventies, met name hoe deze te richten op de bevolkingsgroepen die dit het meest nodig hebben, met als algemeen doel de impact te maximaliseren en de kosteneffectiviteit te verbeteren.

HIV-behandelingsinterventies werden ook geëvalueerd met behulp van epidemiologische en kostenmodelleringsmethoden. In Hoofdstuk 5 hebben we laten zien hoe een nieuw op TDF-gebaseerd ART-medicijn met dolutegravir (DTG) net zo kosteneffectief is als het standaardbehandelingsregime van die tijd. Verder hebben we gedemonstreerd hoe men gegevens, over proefkosten en het gebruik van middelen, kan toepassen als input voor gezondheid economische modellen wanneer wordt uitgegaan van routinematige implementatie in de volksgezondheidssector. Het inschatten van de kosteneffectiviteit van een landelijke uitrol van tenofovir (TDF)/emtricitabine (FTC)+DTG in een routinematige zorgsetting zou niet tijdig kunnen worden gedaan zonder het gebruik van modellen. In Hoofdstuk 6 onderzocht ik met behulp van een analyse het huidige beleid voor de implementatie van DSD voor de behandeling van HIV en ontdekte

dat de wijdverspreide toelatingscriteria waarschijnlijk moeten worden herzien voor Zambia. Hoofdstuk 7 evalueerde een gecombineerde analyse van drie epidemiologische modellen voor Sub-Sahara Afrika en kon een bovengrens voor de kosten voor ART-retentie-interventies bepalen. Ten slotte laat dit proefschrift zien hoe epidemiologische en kostenmodellering kunnen worden gebruikt om alle HIV-interventies te modelleren en een optimaal pakket aan interventies te ontwerpen om de Zuid-Afrikaanse regering te helpen de meest kosteneffectieve strategie te kiezen om de UNAIDS 95-95-95-doelen te bereiken (Hoofdstuk 8). Dit onderzoek werd uitgevoerd in voortdurende samenwerking met het South African National Department of Health (NDOH), evenals met National Treasury, om weloverwogen hun geplande budgetten en gezondheidsresultaten voor het HIV-programma op te stellen.

Op basis van het werk dat voor dit proefschrift is uitgevoerd, kan het volgende worden geconcludeerd: (1) Het richten op populaties met een hoog risico zou een positief effect hebben op de kosteneffectiviteit van PrEP en er moet meer worden gedaan voor het creëren van vraag om succesvolle zelfselectie in PrEP te garanderen. (2) Modellering is een handig hulpmiddel om te evalueren wat er met de geplande implementatie kan worden verwacht, en om beleidsmakers in real-time potentiële impactvolle en kosteneffectieve alternatieven te kunnen bieden - zoals we deden met HIV-zelftesten. (3) In Zuid-Afrika kan CAB-LA voor PrEP niet meer kosten dan het dubbele van orale TDF/FTC om even kosteneffectief te zijn als de standaardbehandeling. Er is in de meeste LMIC's een grote behoefte aan een zeer effectieve HIV-preventietechnologie zoals CAB-LA en hoe betaalbaarder de fabrikanten het kunnen maken voor degenen die het nodig hebben, hoe groter de kans dat mensen in deze landen zullen kunnen profiteren van de beschikbaarheid ervan. (4) TDF/FTC+DTG is een kosteneffectief regime voor HIV-behandeling in vergelijking met het voormalige eerstelijns standaardbehandelingsregime en patiënten zullen enorm profiteren van de doorlopende uitrol ervan. (5) Geschiktheidscriteria voor DSD-modellen moeten in alle SSA-landen worden geëvalueerd en programma's moeten mogelijk minder rigide en meer patiëntgericht zijn om ervoor te zorgen dat deze behandelingsmethoden beschikbaar zijn voor degenen die bereid en in staat zijn zich eraan te houden zodra ze met ART beginnen. (6) Vergelijkingen tussen meerdere modellen zijn een goede basis voor het modelleren van de potentiële impact van interventies in verschillende settingen, maar kunnen brede schattingen opleveren vanwege de onzekerheid

in de modellen. Daarom moeten beleidsmakers samenwerken met modelleringsgroepen om nauwkeurigere schattingen te kunnen maken. (7) Het samen modelleren van alle HIV-interventies is van onschatbare waarde, aangezien daarbij rekening wordt gehouden met verschillende aspecten van de ziektedynamiek en de impact van verschillende preventie- en behandelingsinterventies. Dit maakt informatieve output mogelijk voor het structureren van een HIV-programma, zodat het op de meest kosteneffectieve manier wordt uitgevoerd.

Toekomstige modellen van HIV-preventie interventies zullen afgestemd moeten worden op gegevensoutput van grootschalige implementatie van deze interventies, om nauwkeurige parametrisering van modellen te garanderen. Evenals de noodzakelijke kalibratie om nauwkeurige modelfit te garanderen. Dit zal ook real-time modellering vergemakkelijken en de beleidsontwikkeling versnellen voor de meest relevante vragen voor implementatie.

Chapter 11
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Chapter 12

Author contribution

Chapter 2

Lise Jamieson, Gabriela B. Gomez, Kevin Rebe, Ben Brown, Hasina Subedar, Sarah Jenkins, Natsai Shoko, Linda-Gail Bekker, Leigh F. Johnson, Gesine Meyer-Rath

LJ, LFJ and GMR drafted the manuscript. LJ and GMR developed the unit costs. LFJ developed the epidemiological model. LJ and LFJ performed the epidemiological modelling, while LJ performed the cost modelling and drafted all figures and tables. GBG, KR and BB provided data from South African PrEP implementation studies. HS, SJ and NS provided input from the South African government's early implementation sites. LJ, GMR, LFJ, HS, SJ, NS and LGB conceptualised the analytical framework and scenarios and reviewed results critically. All authors critically reviewed and revised the manuscript, and approved the final manuscript.

Chapter 3

Lise Jamieson, Leigh F. Johnson, Katleho Matsimela, Linda Alinafe Sande, Marc d'Elbée, Mohammed Majam, Thato Chidarikire, Karin Hatzold, Cheryl Johnson, Fern Terris-Prestholt, Brooke Nichols, Gesine Meyer-Rath

LJ and GMR conceptualized the study. LFJ developed the epidemiological model. LJ did the analysis and drafted the manuscript. LJ, GMR and LFJ contributed to the interpretation of the results. All authors contributed to the interpretation of the results, revision and approval of the manuscript.

Chapter 4

Lise Jamieson, Leigh F. Johnson, Brooke E. Nichols, Sinead Delany-Moretlwe, Mina C. Hosseinipour, Prof Colin Russell, Gesine Meyer-Rath

LJ, LFJ, GMR and SDM conceptualised the analytical framework and scenarios. LJ and GMR developed the unit costs and drafted the manuscript. LFJ developed the epidemiological model. LJ performed the modelling and economic analyses. LJ and LFJ accessed and verified all data. SDM and MH provided trial data and key information regarding the implementation to inform cost and epidemiological assumptions, and reviewed scenarios. BEN and CR aided in interpreting the results and worked on the manuscript. LJ and

GMR are responsible for the decision to submit the manuscript. All authors critically reviewed and approved the final manuscript, and share final responsibility for the decision to submit for publication.

Chapter 5

Lise Jamieson, Celicia Serenata, Lebogang Makhubele, Simiso Sokhela, Nkuli Mashabane, Godspower Akpomiemie, Leigh F Johnson, Willem D F Venter, Gesine Meyer-Rath

LJ led the economic evaluation of the trial and conducted all analysis. GMR contributed to the conceptualisation of the analytical framework. LJ and GMR drafted the paper. LFJ built the HIV transmission model and provided input on modelling analysis. WDFV contributed to development of the ADVANCE trial protocol, and oversaw the trial with assistance from CS, SS, LM, NM, GA. Trial data and other information to the running of the trial were provided by GA, CS, SS and NM. All authors reviewed the manuscript, suggested edits and approved the final version.

Chapter 6

Lise Jamieson, Sydney Rosen, Bevis Phiri, Anna Grimsrud, Muya Mwansa, Hilda Shakwelele, Prudence Haimbe, Mpande M Mwenechanya, Priscilla Lumano-Mulenga, Innocent Chiboma, Brooke E Nichols

LJ, BN, SR and AG conceptualized the study. BP, HS, PH, MM, PLM, IC curated data for the study. BP, HS, PH, MMM provided supervision of the study. LJ led data analysis and drafted the paper along with BN, SR and AG. All authors contributed to data interpretation and critically reviewed a revised draft of the manuscript. All authors have read and approved the final manuscript.

Chapter 7

Anna Bershteyn, Lise Jamieson, Hae-Young Kim, Ingrida Platais, Masabho P. Milal, Edinah Mudimu, Debra ten Brink, Rowan Martin-Hughes, Sherrie L. Kelly, Andrew N. Phillips, Loveleen Bansi-Matharu, Valentina Cambiano, Prof Paul Revill, Gesine Meyer-Rath, Brooke E. Nichols

AB, ANP, and BEN designed the study. AB, EM, H-YK, DtB, RM-H, SLK, and ANP produced the model results. LJ, MPM, and AB consolidated and

analysed model results. AB drafted the manuscript. All authors critically reviewed and revised the final manuscript.

Chapter 8

Gesine Meyer-Rath, Lise Jamieson, Ali Feizaddeh, Nthabiseng Khoza, Thato Chidarikire, Teresa Guthrie, Leigh F. Johnson

GMR and LJ prepared the manuscript, developed the analytical framework and developed and updated the custom optimisation model. LJ conducted the analysis. LFJ developed and built the underlying epidemiological model. LFJ, AF, NK, TC and TG contributed towards the analytical framework. TG also contributed data. All authors contributed to the interpretation of data and reviewed the manuscript. All authors read and approved the final manuscript.

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Chapter 2

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Chapter 3

This analysis was funded through the grant "Enhancing the evidence-base of HIV self-testing for young men" (BMGF OPP1189095) to Ezintsha, a division of Wits RHI, and HE^{2}RO.

Chapter 4

Work toward this paper was also funded by the Bill & Melinda Gates Foundation (BMGF) (INV-019496). SDM and MH received funding support from National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH) under Award Numbers UM1AI068619 (HPTN Leadership and Operations Center), UM1AI068617 (HPTN Statistical and Data Management Center), and UM1AI068613 (HPTN Laboratory Center). The content is solely the responsibility of the authors and does not necessarily represent the official views of USAID, the United States Government, or the National Institutes of Health. Funding for the trial, but not this economic analysis, was provided by BMGF (OPP1154174) and ViiV Healthcare.

Chapter 5

This evaluation was funded by the United States Agency for International Development (Unitaid) (2016-07-Wits RHI).

Chapter 6

Funding for the study was provided by the Bill & Melinda Gates Foundation through OPP1192640 to Boston University. The funder had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

Chapter 7

Bill & Melinda Gates Foundation.

Chapter 8

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Chapter 13
About the Author

PhD Portfolio

AMC Graduate School for Medical Sciences

Summary of PhD training, teaching, parameters of esteem and publications

Name PhD student: Lise Jamieson (née Werner)

PhD period: January 2020 – June 2023

Names of PhD supervisor(s) & co-supervisor(s): Prof Colin Russell, Dr Brooke Nichols and Dr Gesine Meyer-Rath

1. PhD training

	Year	ECTS
General courses		
- Good Clinical Practice Refresher, Academic Advance, 12 May 2020	2020	0.14
- TRREE Introduction to Research Ethics 27 Jan 2020	2020	0.14
Specific courses		
- R for HTA in LMICS. Hosted by University College London, University of Bristol. 23 Feb 2022. Virtual.	2022	0.21
Seminars, workshops and master classes		
- Weekly department seminars: Laboratory of Applied Evolutionary Biology (LAEB), University of Amsterdam	2021-2022	1.86
- Bi-monthly multi-continental modelling group research meetings	2021-2022	0.93
Presentations		
Poster presentations:		
- *The cost effectiveness and optimal configuration of oral HIV self-test kit distribution in South Africa: A model analysis.* IAS Conference on HIV Science 2021, 18-21 July 2021.	2021	0.5

- *Retention in care after early enrolment into differentiated service delivery (DSD) models for antiretroviral treatment: a case for policy change in Zambia.* IAS Conference on HIV Science 2021, 18-21 July 2021.	2021	0.5
Oral presentations		
- *HIV prevention investment: modelling different PrEP options for South Africa. Workshop on HIV prevention: Exploring opportunities, challenges, and lessons from 5 years of oral Pre-Exposure Prophylaxis.* National Department of Health, South Africa. 17 Mar 2021, Virtual.	2021	0.5
- *Modelling different PrEP options for South Africa.* National Essential Medicine List Committee, National Department of Health, South Africa, 11 March 2021, Virtual	2021	0.5
- *Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant.* Health Economics and Epidemiology Research Office (HE^2RO)	2021	0.5
- *Early experiences in reducing the time to eligibility for DSD for HIV treatment: data from Zambia.* International AIDS Society and ICAP at Columbia's HIV Coverage, Quality and Impact Network (CQUIN). 3 November 2021. Virtual.	2021	0.5
- *Association between proportion of a facility's ART patients enrolled in a DSD model and outcomes of ART patients not enrolled in Zambia.* Global DSD Research Collaborative, International AIDS Society, 13 June 2022. Virtual.	2022	0.5

- *The relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis: a modelled economic evaluation and threshold analysis in South Africa based on the HPTN 083 and 084 trials.* Long-acting PrEP modelling meeting. Global Impact Advisors. 2-3 March 2023. Virtual	2023	0.5
(Inter)national conferences - *The relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis: a modelled economic evaluation and threshold analysis in South Africa based on the HPTN 083 and 084 trials.* International AIDS Conference, 29 July-2 August 2022, Montreal, Canada - *How soon should patients be eligible for differentiated service delivery models for antiretroviral treatment?* International AIDS Conference, 29 July-2 August 2022, Montreal, Canada	2022 2022	0.5 0.5
Interviews - KYKNET interview on COVID-19 modelling: *25 May 2020* https://m.youtube.com/watch?v=RHkB4VT1VGQ - KYKNET interview on COVID-19 modelling: *07 Jun 2021* - SPOTLIGHT interview on long-acting injectable cabotegravir: 20 Aug 2021 https://www.spotlightnsp.co.za/2021/09/01/in-depth-what-will-it-take-to-bring-hiv-prevention-injections-to-sas-clinics/	2020 2021 2021	0.5 0.5 0.5

- Cape Talk Radio interview on Lancet HIV article on long-acting injectable cabotegravir: *30 Nov 2022* https://www.capetalk.co.za/podcasts/144/afternoon-drive-with-john-maytham/676945/injectable-hiv-prevention-drug-shows-promise	2022	0.5
- In conversation with Lise Jamieson and Gesine Meyer-Rath on cabotegravir for PrEP in South Africa. *Lancet HIV podcast: 14 Dec 2022.* https://www.buzzsprout.com/1062154/11870211	2022	0.5
- En Afrique du Sud, une injection préventive contre le VIH séduit déjà les autorités. Radio France Internationale (RFI). *10 Jan 2023.* https://www.rfi.fr/fr/afrique/20230110-en-afrique-du-sud-une-injection-pr%C3%A9ventive-contre-le-vih-s%C3%A9duit-d%C3%A9j%C3%A0-les-autorit%C3%A9s	2023	0.5
Other		
- Monthly HE^{2}RO journal club meetings	2020-2023	1.71
- Bi-monthly HE^{2}RO research meetings	2020-2023	3.43
- The Launch of the South African HIV Investment Case, 2021 Update. 3 Dec 2021	2021	0.50
- Weekly AMBIT GREAT analysis workshop	2021-2023	2.50
- National HIV Think Tank Research Working Group quarterly meetings. South African National Department of Health	2020-2023	0.43
- Pre-exposure Prophylaxis Technical Working Group quarterly meetings. South African National Department of Health.	2020-2023	0.43

- WHO TC Modelling Group for COVID-19 modelling	2020	1.40
- Programme Committee Meetings for 11th SA AIDS Conference (co-chair member)	2022-2023	0.18

2. Teaching		
	Year	**ECTS**
Tutoring, Mentoring		
- *Mentoring Caroline Govathson on her research projects, assisting with additional analyses*. Health Economics and Epidemiology Research Office (HE^2RO)	2017-2023	1.0
Supervising		
- *Sithabiso Masuku.* Building of software (BASLY) that assists the South African National Department of Health in extracting HIV and TB expenditure data for reports. Health Economics and Epidemiology Research Office (HE^2RO)	2018-2022	1.0
- *Nkgomeleng Lekodeba*. Supervising the work on the ADAPT model, used to optimize Zambia's coverage of differentiated service delivery models. Health Economics and Epidemiology Research Office (HE^2RO)	2022-2023	1.0
- *Mmamapudi Kubjane.* South African TB Investment Case. Health Economics and Epidemiology Research Office (HE^2RO)	2022-2023	1.0

3. Parameters of Esteem	
	Year
Grants - UNITAID (Sub Award; Prime: Wits Reproductive Health and HIV Institute). Economic evaluation of the ADVANCE trial; role: Investigator (PI: Francois Venter)	2019-2020
Awards and Prizes - "Zoom Child Advisor" Award, Health Economics and Epidemiology Research Office (HE2RO)	2020

4. Publications	
Peer reviewed	**Year**
1. **Jamieson, L.**, van Schalkwyk, C., Nichols, B.E., Meyer-Rath, G., Silal, S., Pulliam, J., Blumberg, L., Cohen, C., Moultrie, H., Jassat, W., 2023. Differential in-hospital mortality and intensive care treatment over time: Informing hospital pathways for modelling COVID-19 in South Africa. PLOS Global Public Health [Forthcoming].	2023
2. Bansi-Matharu, L., Mudimu, E., Martin-Hughes, R., Hamilton, M., Johnson, L., ten Brink, D., Stover, J., Meyer-Rath, G., Kelly, S.L., **Jamieson, L.**, Cambiano, V., Jahn, A., Cowan, F.M., Mangenah, C., Mavhu, W., Chidarikire, T., Toledo, C., Revill, P., Sundaram, M., Hatzold, K., Yansaneh, A., Apollo, T., Kalua, T., Mugurungi, O., Kiggundu, V., Zhang, S., Nyirenda, R., Phillips, A., Kripke, K., Bershteyn, A., 2023. Cost-effectiveness of voluntary medical male circumcision for HIV prevention across sub-Saharan Africa: results from five independent models. The Lancet Global Health 11, e244–e255. https://doi.org/10.1016/S2214-109X(22)00515-0	2023
3. **Jamieson, L**., Johnson, L.F., Nichols, B.E., Delany-	2022

	Moretlwe, S., et al, 2022. Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. The Lancet HIV Nov;9(12):e857–67. https://doi.org/10.1016/S2352-3018(22)00251-X	
4.	**Jamieson, L.**, Rosen, S., Phiri, B., Grimsrud, A., Mwansa, M., Shakwelele, H., Haimbe, P., Mukumbwa-Mwenechanya, M., Lumano-Mulenga, P., Chiboma, I., Nichols, B.E., 2022. How soon should patients be eligible for differentiated service delivery models for antiretroviral treatment? Evidence from a retrospective cohort study in Zambia. BMJ Open 12, e064070. https://doi.org/10.1136/bmjopen-2022-064070	2022
5.	Bershteyn, A., **Jamieson, L.,** Kim, H.-Y., Platais, I., et al., 2022. Transmission reduction, health benefits, and upper-bound costs of interventions to improve retention on antiretroviral therapy: a combined analysis of three mathematical models. Lancet Glob Health 10, e1298–e1306. https://doi.org/10.1016/S2214-109X(22)00310-2	2022
6.	Murphy, J.P., Shumba, K., **Jamieson, L.**, Nattey, C., Pascoe, S., Fox, M.P., Miot, J., Maskew, M., 2022. Assessment of facility-level antiretroviral treatment patient status utilizing a national-level laboratory cohort: Toward an understanding of system-level tracking and clinic switching in South Africa. Front. Public Health 10, 959481. https://doi.org/10.3389/fpubh.2022.959481	2022
7.	Phillips, A.N., Bershteyn, A., Revill, P., Bansi-Matharu, L., Kripke, K., Boily, M.-C., Martin-Hughes, R., Johnson, L.F., Mukandavire, Z., **Jamieson, L.,** Meyer-Rath, G., et al., HIV Modelling Consortium, 2022. Cost-effectiveness of easy-access, risk-informed oral pre-exposure prophylaxis in HIV epidemics in sub-Saharan Africa: a modelling study. Lancet HIV 9, e353–e362.	2022

	https://doi.org/10.1016/S2352-3018(22)00029-7	
8.	**Jamieson, L.**, Johnson, L.F., Matsimela, K., Sande, L.A., et al, 2021a. The cost effectiveness and optimal configuration of HIV self-test distribution in South Africa: a model analysis. BMJ Glob Health 6, e005598. https://doi.org/10.1136/bmjgh-2021-005598	2021
9.	**Jamieson, L.**, Serenata, C., Makhubele, L., Sokhela, S., et al, 2021b. Cost and cost-effectiveness of dolutegravir-based antiretroviral regimens: an economic evaluation of a clinical trial. AIDS 35, S173–S182. https://doi.org/10.1097/QAD.0000000000003068	2021
10.	Jo, Y., **Jamieson, L.,** Edoka, I., Long, L., et al., 2021. Cost-effectiveness of Remdesivir and Dexamethasone for COVID-19 Treatment in South Africa. Open Forum Infect Dis 8, ofab040. https://doi.org/10.1093/ofid/ofab040	2021
11.	Edoka, I., Fraser, H., **Jamieson, L.**, Meyer-Rath, G., Mdewa, W., 2021. Inpatient Care Costs of COVID-19 in South Africa's Public Healthcare System. Int J Health Policy Manag. https://doi.org/10.34172/ijhpm.2021.24	2021
12.	Murphy, J.P., Kgowedi, S., Naidoo, N., Girdwood, S., **Jamieson, L.**, Soeteman, D., Resch, S., Meyer-Rath, G., 2021. Role of data from cost and other economic analyses in healthcare decision-making for HIV, TB and sexual/reproductive health programmes in South Africa. Health Policy Plan 36, 1545–1551. https://doi.org/10.1093/heapol/czab071	2021
13.	Nichols, B.E., Cele, R., **Jamieson, L.**, Long, L.C., Siwale, Z., Banda, P., Moyo, C., Rosen, S., 2021. Community-based delivery of HIV treatment in Zambia: costs and outcomes. AIDS 35, 299–306. https://doi.org/10.1097/QAD.0000000000002737	2021
14.	Phillips, A.N., Cambiano, V., Johnson, L., Nakagawa, F., Homan, R., Meyer-Rath, G., Rehle, T., Tanser, F., Moyo, S., Shahmanesh, M., Castor, D., Russell, E., **Jamieson,**	2021

L., Bansi-Matharu, L., Shroufi, A., Barnabas, R.V., Parikh, U.M., Mellors, J.W., Revill, P., 2021. Potential Impact and Cost-Effectiveness of Condomless-Sex-Concentrated PrEP in KwaZulu-Natal Accounting for Drug Resistance. J Infect Dis 223, 1345–1355. https://doi.org/10.1093/infdis/jiz667	
15. **Jamieson, L**., Gomez, G.B., Rebe, K., Brown, B., et al, 2020. The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa. AIDS 34, 883–891. https://doi.org/10.1097/QAD.0000000000002486	2020
16. Johnson, L.F., Patrick, M., Stephen, C., Patten, G., Dorrington, R.E., Maskew, M., **Jamieson, L.,** Davies, M.-A., 2020a. Steep Declines in Pediatric AIDS Mortality in South Africa, Despite Poor Progress Toward Pediatric Diagnosis and Treatment Targets. Pediatr Infect Dis J 39, 843–848. https://doi.org/10.1097/INF.0000000000002680	2020
17. Nichols, B.E., **Jamieson, L**., Zhang, S.R.C., Rao, G.A., Silal, S., Pulliam, J.R.C., Sanne, I., Meyer-Rath, G., 2020. The role of remdesivir in South Africa: preventing COVID-19 deaths through increasing ICU capacity. Clin Infect Dis. https://doi.org/10.1093/cid/ciaa937	2020
Other	**Year**
1. Pearson, C.A.B., Silal, S.P., Li, M.W.Z., Dushoff, J., Bolker, B.M., Abbott, S., van Schalkwyk, C., Davies, N.G., Barnard, R.C., Edmunds, W.J., Bingham, J., Meyer-Rath, G., **Jamieson, L**., Glass, A., Wolter, N., Govender, N., Stevens, W.S., Scott, L., Mlisana, K., Moultrie, H., Pulliam, J.R.C., 2021. Bounding the levels of transmissibility & immune evasion of the Omicron variant in South Africa (preprint). Epidemiology. https://doi.org/10.1101/2021.12.19.21268038	2021

Curriculum Vitae

SUMMARY

Lise Jamieson (née Werner) is a biostatistician and health economist who has worked for the Health Economics and Epidemiology Research Office (HE^2RO), University of Witwatersrand in Johannesburg since April 2015. She holds a Master of Science degree in Statistics from the University of KwaZulu-Natal, and a BSc in Computer Science from the University of Natal. At HE^2RO her research has focused on health economics, epidemiological modelling, and statistical analysis, mainly in HIV, in order to support policy-relevant decisions in South Africa. She has expanded the Thembisa model, an HIV and demographic model for South Africa developed by Leigh Johnson (UCT), helping to develop and integrate it with a costing model and an optimization algorithm, with the aim of optimizing South Africa's HIV programme in response to the HIV epidemic over the next 20 years, with and without the constraints of current government budgets. She works in collaboration with the South African National Department of Health (NDOH) in order to inform their policy decisions and aid decision-making. More recently her work has focused on modelling HIV prevention methods, oral PrEP and long-acting injectable PrEP, and their impact on the HIV epidemic. Notably her recent work has provided policy-relevant research to the NDOH informing their price negotiations for the novel long-acting injectable PrEP, which in turn ensures affordable pricing and access of this intervention to the South African public health sector. She also played an integral role in the South African COVID-19 Modelling Consortium (SACMC), which aimed to provide evidence and data to decision makers across South Africa during the COVID-19 pandemic.

ACADEMIC TRAINING

2020 – present	PhD candidate ***University of Amsterdam, Amsterdam, The Netherlands***
2006-2010	Master of Science (Statistics) *(cum laude)* ***University of KwaZulu-Natal, Pietermaritzburg, South Africa***
2005	Honours (Statistics) ***University of KwaZulu-Natal, Pietermaritzburg, South Africa***
2002-2004	Bachelor of Science (Computer Science and Statistics) ***University of Natal, Pietermaritzburg, South Africa***

ADDITIONAL COURSES AND QUALIFICATIONS

2022	R for HTA in LMICS. Hosted by University College London, University of Bristol. Virtual 23 Feb 2022
2020	TRREE Introduction to Research Ethics 27 Jan 2020
2020	Good Clinical Practice Refresher, Academic Advance, 12 May 2020
2019	Data Artistry Course, Data Innovator (23-24 July 2019)
2017	Good Clinical Practice Refresh (Facilitator: Lesley Burgess), University of Witwatersrand Health Consortium
2014	SAS Advanced Programmer Certification for SAS 9
2013	Bayesian Biostatistics Course, Prof. Emmanuel Lesaffre, hosted by South African Centre for Epidemiological Modelling and Analysis (SACEMA), Stellenbosch, South Africa
2013	Good Clinical Practice and Human Subject Protection course, Collaborative Institutional Training Initiative via Comprehensive International Program of Research on AIDS (CIPRA)

2012 SAS Base Programmer Certification for SAS 9

2010 Basic epidemiology workshop, Prof. Sharon Schwartz hosted by Centre for the AIDS Programme of Research in South Africa (CAPRISA)

2010 Research Policy: Research Ethics, Code of Conduct for Research, University of KwaZulu-Natal, South Africa

2010 Alternative and Adaptive Clinical Trial Design Workshop, Dr. Shein-Chung Chow, hosted by Centre for the AIDS Programme of Research in South Africa (CAPRISA)

2006 Good Clinical Practice and Source Documentation training, Centre for the AIDS Programme of Research in South Africa (CAPRISA)

EMPLOYMENT

2019 – present	Senior Researcher	Health Economics and Epidemiology Research Office, University of the Witwatersrand, South Africa
2018 – 2019	Researcher II	Health Economics and Epidemiology Research Office, University of the Witwatersrand, South Africa
2015 – 2018	Researcher	Health Economics and Epidemiology Research Office, University of the Witwatersrand, South Africa
2006 - 2015	Senior Statistician	Centre for the AIDS Programme of Research in South Africa (CAPRISA)

2006	Statistics Fellow	Centre for the AIDS Programme of Research in South Africa (CAPRISA)

SERVICE RELATED TO PROFESSIONAL WORK

2022 – present	11th SA AIDS Conference Scientific Programme Committee. Dira Sengwe Board. Invited co-chair of Track 6 (Policy, Finance and Ethics).
2020 – present	South African COVID-19 Modelling Consortium. South African National Department of Health. Invited member.
2019 – present	National HIV Think Tank Research Working Group. South African National Department of Health. Invited member.
2015 – present	Pre-exposure Prophylaxis Technical Working Group. South African National Department of Health. Invited member.

AWARDS AND HONOURS

2010	First prize in the annual South African Statistical Association (SASA) post-graduate paper competition
2009	International Society for Clinical Biostatisticians Conference Award for Scientist
2009	Third place for oral presentation at University of KwaZulu-Natal Research Day

INVITED PRESENTATIONS AND INTERVIEWS

2023 *The relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis: a modelled economic evaluation and threshold analysis in South Africa based on the HPTN 083 and 084 trials.* Long-acting PrEP modelling meeting. Global Impact Advisors. 2-3 March 2023.

2023 *En Afrique du Sud, une injection préventive contre le VIH séduit déjà les autorités.* Radio France Internationale (RFI). 10 Jan 2023. https://www.rfi.fr/fr/afrique/20230110-en-afrique-du-sud-une-injection-pr%C3%A9ventive-contre-le-vih-s%C3%A9duit-d%C3%A9j%C3%A0-les-autorit%C3%A9s

2022 *In conversation with Lise Jamieson and Gesine Meyer-Rath on cabotegravir for PrEP in South Africa.* Lancet HIV podcast: 14 Dec 2022. https://www.buzzsprout.com/1062154/11870211

2022 *Modelling long-acting cabotegravir for South Africa.* Symposium on modelling of long-acting PrEP. HIV modelling consortium. 5 Dec 2022

2022 *Modelling long-acting cabotegravir for South Africa.* Cape Talk Ratio. 30 Nov 2022

2022 *Association between proportion of a facility's ART patients enrolled in a DSD model and outcomes of ART patients not enrolled in Zambia.* Global DSD Research Collaborative, International AIDS Society, 13 June 2022. Virtual.

2021 *Early experiences in reducing the time to eligibility for DSD for HIV treatment: data from Zambia.* International AIDS Society and ICAP at Columbia's HIV Coverage, Quality and Impact Network (CQUIN). 3 November 2021. Virtual.

2021 KYKNET interview on COVID-19 modelling: 07 June 2021

2021 *HIV prevention investment: modelling different PrEP options for South Africa.* Workshop on HIV prevention: Exploring opportunities, challenges, and lessons from 5 years of oral Pre-Exposure Prophylaxis. National Department of Health, South Africa (17 Mar 2021)

2021 *Modelling different PrEP options for South Africa.* National Essential Medicine List Committee, South Africa (11 March 2021)

2020 KYKNET interview on COVID-19 modelling: 25 May 2020 https://m.youtube.com/watch?v=RHkB4VT1VGQ

2019 *The South African HIV Investment Case: how we incorporated structural enablers and development synergies.* UNAIDS Technical Consultation on Social Enablers (June 19th-21st, 2019)

2019 *HIV Investment Case 2019 update*. Reflections on SA AIDS 2019: What will we do differently in our HIV response? SANAC Meeting (1 August 2019), Pretoria, South Africa

2019 *Update: The impact and cost-effectiveness of PrEP in South Africa.* National Department of Health, PrEP technical working group meeting (17 January 2018), Pretoria, South Africa

2018 *The impact and cost-effectiveness of PrEP in South Africa*. National Department of Health: Increasing PrEP coverage among the MSM population in South Africa (8 November 2018), Pretoria, South Africa

2018 *The impact and cost-effectiveness of PrEP in South Africa: How modelling helped define PrEP policy.* UNAIDS Shaping PrEP modelling for high burden countries in sub Saharan Africa, Geneva, Switzerland (6 - 8 June 2018)

2018 *The impact and cost-effectiveness of PrEP in South Africa.* National Department of Health, PrEP technical working group meeting (8 June 2018), Pretoria, South Africa

2018 *The cost-of PrEP in South Africa.* National Department of Health, PrEP technical working group meeting (23 June 2018), Pretoria, South Africa

CONFERENCE ORAL PRESENTATIONS

- **Lise Jamieson**, Leigh F. Johnson, Brooke E. Nichols, Sinead Delany-Moretlwe, Mina C. Hosseinipour, Colin Russell, Gesine Meyer-Rath. *The relative cost-effectiveness of long-acting injectable*

cabotegravir versus oral pre-exposure prophylaxis: a modelled economic evaluation and threshold analysis in South Africa based on the HPTN 083 and 084 trials. International AIDS Conference, 29 July-2 August 2022, Montreal, Canada (presentation done on my behalf by Gesine Meyer-Rath)

- **Lise Jamieson**, Sydney Rosen, Bevis Phiri, et al. *How soon should patients be eligible for differentiated service delivery models for antiretroviral treatment?* International AIDS Conference, 29 July-2 August 2022, Montreal, Canada (presentation done on my behalf by Sydney Rosen)
- **Lise Jamieson**, Gesine Meyer-Rath, Gabriela Gomez, Leigh F. Johnson. *The impact of differential uptake by HIV risk group on the effect and cost-effectiveness of PrEP in different populations in South Africa*. International AIDS Economic Network (IAEN), 2018
- **Lise Werner**, Henry Mwambi, Francois van Loggerenberg, Koleka Mlisana and Salim S. Abdool Karim. *Modelling Acute HIV Infection Using Longitudinally Measured Biomarker Data.* South African Statistical Association (SASA) Conference 2011, CSIR International Convention Centre, Pretoria, South Africa
- **Lise Werner**, Henry Mwambi, Francois van Loggerenberg, Koleka Mlisana and Salim S. Abdool Karim. *Modelling Acute HIV Infection Using Longitudinally Measured Biomarker Data Including Informative Drop-out. South African Statistical Association (SASA) Conference 2010, North-West University, Potchefstroom, South Africa*
- **Lise Werner**, Henry Mwambi, Koleka Mlisana and Salim S. Abdool Karim. *Modelling Acute HIV Infection Using Longitudinally Measured Biomarker Data.* UKZN Postgraduate Research Day 2009, University of KwaZulu-Natal, Westville Campus, South Africa
- **Lise Werner**, Henry Mwambi, and Salim S. Abdool Karim. *Joint Modelling of CD4+ cell counts and HIV-RNA. South* African Statistical Association (SASA) Conference 2007, Muldersdrift, South Africa

- **Lise Werner** and Henry Mwambi. *Joint Modelling of CD4+ cell counts and HIV-RNA to describe the evolution of HIV markers. TB and HIV modelling conference 2006, University of Stellenbosch, Stellenbosch, South Africa*

CONFERENCE POSTER PRESENTATIONS

- **Lise Jamieson**, Leigh Johnson, Katleho Matsimela, et al. *The cost effectiveness and optimal configuration of oral HIV self-test kit distribution in South Africa: A model analysis.* IAS Conference on HIV Science 2021, 18-21 July 2021.
- **Lise Jamieson**, Sydney Rosen, Bevis Phiri, et al. *Retention in care after early enrolment into differentiated service delivery (DSD) models for antiretroviral treatment: a case for policy change in Zambia.* IAS Conference on HIV Science 2021, 18-21 July 2021.
- **Lise Jamieson**, Denise Evans, Rebecca Berhan, Nazir Ismail, Samantha Aucock, Kristina Wallengren, Lawrence Long. *Data quality of drug-resistant tuberculosis and antiretroviral therapy electronic registers in South Africa.* SA AIDS Conference 2019, Durban, South Africa
- **Lise Werner**, Henry Mwambi, Francois van Loggerenberg, Koleka Mlisana and Salim S. Abdool Karim. *Exploring CD4 count and viral load evolution in an acutely infected cohort using Joint Modelling.* 30th Annual Conference of the International Society for Clinical Biostatisticians 2009, Prague, Czech Republic

BIBLIOGRAPHY

NCBI:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1Jg064MoQdkQt/bibliography/52488716/public

Google Scholar:

https://scholar.google.com/citations?hl=en&user=XqL1K0gAAAAJ

H-index as of 23 Feb 2023: 29 (last 5 years)

PEER-REVIEWED PUBLICATIONS

2023

- **Jamieson L**, van Schalkwyk C, Nichols BE, Meyer-Rath G, Silal S, Pulliam J, Blumberg L, Cohen C, Moultrie H, Jassat W, 2023. Differential in-hospital mortality and intensive care treatment over time: Informing hospital pathways for modelling COVID-19 in South Africa. *PLOS Global Public Health* [Forthcoming].
- Bansi-Matharu L, Mudimu E, Martin-Hughes R, Hamilton M, Johnson L, ten Brink D, Stover J, Meyer-Rath G, Kelly SL, **Jamieson L**, Cambiano V, Jahn A, Cowan FM, Mangenah C, Mavhu W, Chidarikire T, Toledo C, Revill P, Sundaram M, Hatzold K, Yansaneh A, Apollo T, Kalua T, Mugurungi O, Kiggundu V, Zhang S, Nyirenda R, Phillips A, Kripke K, Bershteyn A, 2023. Cost-effectiveness of voluntary medical male circumcision for HIV prevention across sub-Saharan Africa: results from five independent models. *The Lancet Global Health* 11, e244–e255.

2022

- **Jamieson L**, Johnson LF, Nichols BE, Delany-Moretlwe S, Hosseinipour MC, Russell C, *et al.* Relative cost-effectiveness of long-acting injectable cabotegravir versus oral pre-exposure prophylaxis in South Africa based on the HPTN 083 and HPTN 084 trials: a modelled economic evaluation and threshold analysis. *The Lancet HIV* 2022; Nov;9(12):e857–67.
- **Jamieson L**, Rosen S, Phiri B, Grimsrud A, Mwansa M, Shakwelele H, Haimbe P, Mukumbwa-Mwenechanya M, Lumano-Mulenga P, Chiboma I, Nichols BE, 2022. How soon should patients be eligible for differentiated service delivery models for antiretroviral treatment? Evidence from a retrospective cohort study in Zambia. *BMJ Open* 12, e064070.
- Bershteyn A, **Jamieson L,** Kim H-Y, Platais I, Milali MP, Mudimu E, *et al.* Transmission reduction, health benefits, and upper-bound costs of interventions to improve retention on antiretroviral therapy:

a combined analysis of three mathematical models. *Lancet Glob Health* 2022; 10:e1298–e1306.

- Murphy JP, Shumba K, **Jamieson L**, Nattey C, Pascoe S, Fox MP, Miot J, Maskew M, 2022. Assessment of facility-level antiretroviral treatment patient status utilizing a national-level laboratory cohort: Toward an understanding of system-level tracking and clinic switching in South Africa. *Front. Public Health* 10, 959481.
- Phillips AN, Bershteyn A, Revill P, Bansi-Matharu L, Kripke K, Boily M-C, Martin-Hughes R, Johnson LF, Mukandavire Z, **Jamieson L**, Meyer-Rath G, Hallett TB, Ten Brink D, Kelly SL, Nichols BE, Bendavid E, Mudimu E, Taramusi I, Smith J, Dalal S, Baggaley R, Crowley S, Terris-Prestholt F, Godfrey-Faussett P, Mukui I, Jahn A, Case KK, Havlir D, Petersen M, Kamya M, Koss CA, Balzer LB, Apollo T, Chidarikire T, Mellors JW, Parikh UM, Godfrey C, Cambiano V. Cost-effectiveness of easy-access, risk-informed oral pre-exposure prophylaxis in HIV epidemics in sub-Saharan Africa: a modelling study. *Lancet HIV* 2022; 9:e353–e362.

2021

- Phillips AN, Cambiano V, Johnson L, Nakagawa F, Homan R, Meyer-Rath G, Rehle T, Tanser F, Moyo S, Shahmanesh M, Castor D, Russell E, **Jamieson L**, Bansi-Matharu L, Shroufi A, Barnabas RV, Parikh UM, Mellors JW, Revill P. Potential Impact and Cost-Effectiveness of Condomless-Sex-Concentrated PrEP in KwaZulu-Natal Accounting for Drug Resistance. *J Infect Dis* 2021; 223:1345–1355.
- Pearson CAB, Silal SP, Li MWZ, Dushoff J, Bolker BM, Abbott S, van Schalkwyk C, Davies NG, Barnard RC, Edmunds WJ, Bingham J, Meyer-Rath G, **Jamieson L**, Glass A, Wolter N, Govender N, Stevens WS, Scott L, Mlisana K, Moultrie H, Pulliam JRC. Bounding the levels of transmissibility & immune evasion of the Omicron variant in South Africa; 2021. doi:10.1101/2021.12.19.21268038

- Nichols BE, Cele R, **Jamieson L**, Long LC, Siwale Z, Banda P, *et al.* Community-based delivery of HIV treatment in Zambia: costs and outcomes. *AIDS* 2021; 35:299–306.
- Murphy JP, Kgowedi S, Naidoo N, Girdwood S, **Jamieson L**, Soeteman D, *et al.* Role of data from cost and other economic analyses in healthcare decision-making for HIV, TB and sexual/reproductive health programmes in South Africa. *Health Policy Plan* 2021; 36:1545–1551.
- Jo Y, **Jamieson L**, Edoka I, Long L, Silal S, Pulliam JRC, *et al.* Cost-effectiveness of Remdesivir and Dexamethasone for COVID-19 Treatment in South Africa. *Open Forum Infect Dis* 2021; 8:ofab040.
- **Jamieson L,** Serenata C, Makhubele L, Sokhela S, Mashabane N, Akpomiemie G, *et al.* Cost and cost-effectiveness of dolutegravir-based antiretroviral regimens: an economic evaluation of a clinical trial. *AIDS* 2021; 35:S173–S182.
- **Jamieson L**, Johnson LF, Matsimela K, Sande LA, d'Elbée M, Majam M, *et al.* The cost effectiveness and optimal configuration of HIV self-test distribution in South Africa: a model analysis. *BMJ Glob Health* 2021; 6:e005598.
- Edoka I, Fraser H, **Jamieson L**, Meyer-Rath G, Mdewa W. Inpatient Care Costs of COVID-19 in South Africa's Public Healthcare System. *Int J Health Policy Manag* Published Online First: 25 April 2021. doi:10.34172/ijhpm.2021.24

2020

- Nichols BE, **Jamieson L**, Zhang SRC, Rao GA, Silal S, Pulliam JRC, *et al.* The role of remdesivir in South Africa: preventing COVID-19 deaths through increasing ICU capacity. *Clin Infect Dis* Published Online First: 6 July 2020. doi:10.1093/cid/ciaa937
- Johnson LF, Patrick M, Stephen C, Patten G, Dorrington RE, Maskew M, **Jamieson L**, Davies M-A. Steep Declines in Pediatric AIDS Mortality in South Africa, Despite Poor Progress Toward Pediatric Diagnosis and Treatment Targets. *Pediatr Infect Dis J* 2020; 39:843–848.

- **Jamieson L**, Gomez GB, Rebe K, Brown B, Subedar H, Jenkins S, *et al.* The impact of self-selection based on HIV risk on the cost-effectiveness of preexposure prophylaxis in South Africa. *AIDS* 2020; 34:883–891.

2019

- Phillips A, Cambiano V, Johnson L, Nakagawa F, Homan R, Meyer-Rath G, Rehle T, Tanser F, Moyo S, Shahmanesh M, Castor D, Russell E, **Jamieson L**, Bansi-Matharu L, Shroufi A, Barnabas R, Parikh UM, Mellors JW, Revill P. Potential impact and cost-effectiveness of condomless-sex-concentrated PrEP in KwaZulu-Natal accounting for drug resistance. *J Infect Dis* Published Online First: 18 December 2019. doi:10.1093/infdis/jiz667
- Meyer-Rath G, van Rensburg C, Chiu C, Leuner R, **Jamieson L**, Cohen S. The per-patient costs of HIV services in South Africa: Systematic review and application in the South African HIV Investment Case. *PLoS One* 2019; 14:e0210497.
- **Jamieson L**, Evans D, Berhanu R, Ismail N, Aucock S, Wallengren K, *et al.* Data quality of drug-resistant tuberculosis and antiretroviral therapy electronic registers in South Africa. *BMC Public Health* 2019; **19**:1638.

2018

- Maskew M, **Jamieson L**, Mohomi G, Long L, Mongwenyana C, Nyoni C, *et al.* Implementation of Option B and a fixed-dose combination antiretroviral regimen for prevention of mother-to-child transmission of HIV in South Africa: A model of uptake and adherence to care. *PLoS One* 2018; 13:e0201955.
- Campos NG, Lince-Deroche N, Chibwesha CJ, Firnhaber C, Smith JS, Michelow P, Meyer-Rath G, **Jamieson L**, Jordaan S, Sharma M, Regan C, Sy S, Liu G, Tsu V, Jeronimo J, Kim JJ. Cost-Effectiveness of Cervical Cancer Screening in Women Living With HIV in South Africa: A Mathematical Modeling Study. *J Acquir Immune Defic Syndr* 2018; 79:195–205.
- Brennan AT, **Jamieson L**, Crowther NJ, Fox MP, George JA, Berry KM, *et al.* Prevalence, incidence, predictors, treatment, and control

of hypertension among HIV-positive adults on antiretroviral treatment in public sector treatment programs in South Africa. *PLoS One* 2018; 13:e0204020.

2017

- Thobakgale C, Naidoo K, McKinnon LR, **Werner L**, Samsunder N, Karim SA, *et al.* Interleukin 1-Beta (IL-1β) Production by Innate Cells Following TLR Stimulation Correlates With TB Recurrence in ART-Treated HIV-Infected Patients. *J Acquir Immune Defic Syndr* 2017; 74:213–220.
- Naicker N, Naidoo A, **Werner L**, Garrett N, Majola N, Asari V, *et al.* Efficacy and safety of tenofovir-containing antiretroviral therapy in women who acquired HIV while enrolled in tenofovir gel prophylaxis trials. *Antivir Ther* 2017; 22:287–293.
- Meyer-Rath G, van Rensburg C, Larson B, **Jamieson L**, Rosen S. Revealed willingness-to-pay versus standard cost-effectiveness thresholds: Evidence from the South African HIV Investment Case. *PLoS One* 2017; 12:e0186496.
- Liebenberg LJP, Masson L, Arnold KB, Mckinnon LR, **Werner L**, Proctor E, *et al.* Genital-Systemic Chemokine Gradients and the Risk of HIV Acquisition in Women. *J Acquir Immune Defic Syndr* 2017; 74:318–325.
- **Jamieson L**, Evans D, Brennan AT, Moyo F, Spencer D, Mahomed K, *et al.* Changes in elevated cholesterol in the era of tenofovir in South Africa: risk factors, clinical management and outcomes. *HIV Med* 2017; 18:595–603.
- Chiu C, Johnson LF, **Jamieson L**, Larson BA, Meyer-Rath G. Designing an optimal HIV programme for South Africa: Does the optimal package change when diminishing returns are considered? *BMC Public Health* 2017; 17:143.

2016

- Sobieszczyk ME, **Werner L**, Mlisana K, Naicker N, Feinstein A, Gray CM, *et al.* Metabolic Syndrome After HIV Acquisition in South African Women. *J Acquir Immune Defic Syndr* 2016; 73:438–445.

- Naranbhai V, de Assis Rosa D, **Werner L**, Moodley R, Hong H, Kharsany A, *et al.* Killer-cell Immunoglobulin-like Receptor (KIR) gene profiles modify HIV disease course, not HIV acquisition in South African women. *BMC Infect Dis* 2016; 16:27.
- Maskew M, Fox MP, Evans D, Govindasamy D, **Jamieson L**, Malete G, *et al.* Insights into Adherence among a Cohort of Adolescents Aged 12-20 Years in South Africa: Reported Barriers to Antiretroviral Treatment. *AIDS Res Treat* 2016; 2016:4161738.
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- Garrett NJ, Drain PK, **Werner L**, Samsunder N, Abdool Karim SS. Diagnostic Accuracy of the Point-of-Care Xpert HIV-1 Viral Load Assay in a South African HIV Clinic. *J Acquir Immune Defic Syndr* 2016; 72:e45-48.
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2015

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Chapter 14
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