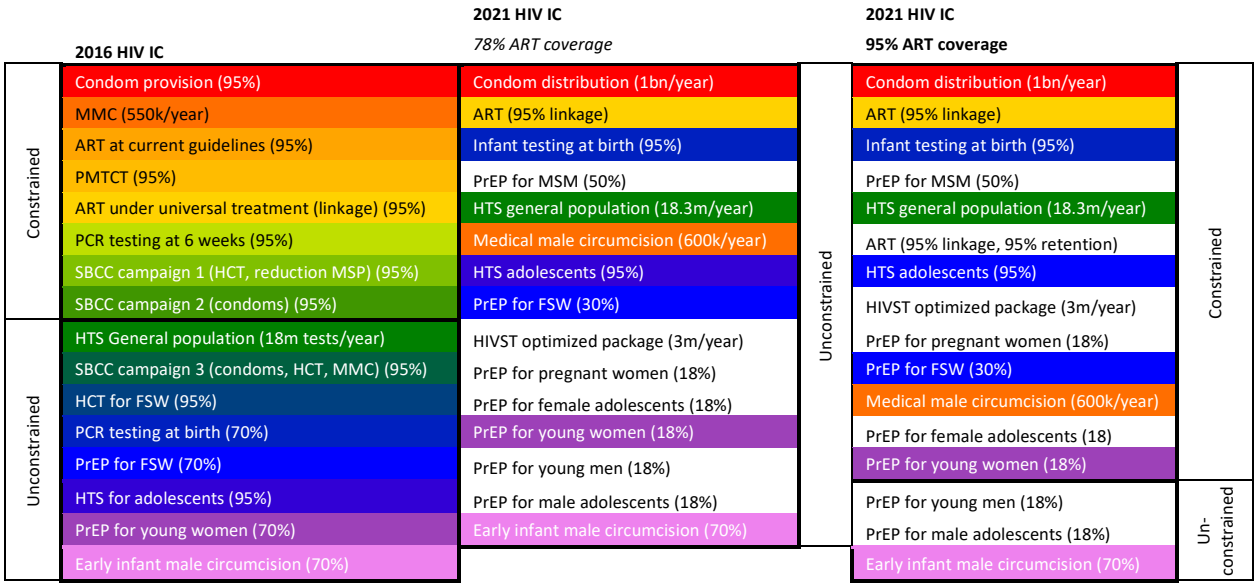
South African HIV Investment Case

Full Report

2021 Update



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Authors: Gesine Meyer-Rath, Lise Jamieson and Leigh Johnson

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Contents

EXECUTIVE SUMMARY

Key summary points:

- Condom provision continues to be the most cost effective (in fact, the only cost saving) intervention, followed now by antiretroviral treatment (ART), infant testing, pre-exposue prophylaxis (PrEP) for men who have sex with men, and general population testing.
- Medical male circumcision (MMC) has become less cost effective at higher coverage levels, but remains good mid-field, and fully affordable.
- HIV self-testing is less cost-effective than conventional HTS but might be required to close last testing gaps.
- PrEP for young men and male adolescents, as well as early infant male circumcision, are only affordable under the current budget if ART retention remains as low as currently (78% by 2025).
- Increasing retention in antiretroviral treatment (ART) is the only way to achieve the second UNAIDS 95-95-95 target, ie, 95% ART coverage.
- With 95% ART coverage under the constrained scenario, we can, over 20 years, avert three times as many new HIV infections and twice as many AIDS deaths, and save twice as many life years compared to 78% ART coverage, compared to the baseline trajectory.
- Under the current 78% ART coverage, scaling up all interventions will add an incremental cost of R58bn (10%) over 20 years, compared to baseline. This is affordable under the current budget.
- Achieving the 95% ART coverage constrained scenario package will cost substantially more than current 78% coverage (at least R117bn over 20 years, of which R80bn is required to maintain 95% ART coverage), but is still affordable under the current budget.
- Of the R80bn needed to increased retention to 95%, about R30bn for human resources for retention, and about R50bn are needed for the additional ART.

Background

South Africa is home to more than 8 million people living with HIV, the largest HIV-positive population in the world. Many prevention and treatment interventions are already scaled up to high levels of coverage. As a result, with 93% of the country's people living with HIV (PLHIV) knowing their status, 74% 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. According to the latest National AIDS Spending Assessment, the government funds about 76% of the HIV response itself, while external funding has stagnated in recent years. In order to further improve allocative efficiency of the available resources, the South African HIV Investment Case set out to identify the optimal mix of interventions against HIV, based on their cost effectiveness, both under the current budget and under an optimal budget. Additionally, given the central gap towards the second UNAIDS target, we added two scenarios, one assuming current ART retention, and the other assuming attainment of the second UNAIDS 95 target by 2025. Here we describe the methods and results of the 2021 update to the HIV Investment Case, including changes to

the modelling suite and input parameters, as well as the results and accompanying recommendations for national HIV policy.

Updates in the 2021 HIV Investment Case

Since 2016, annual updates of the HIV Investment Case set out to determine the optimal package of HIV interventions in South Africa, with the aim improve allocative efficiency of HIV funding from the three main sources- the South African government, PEPFAR and the Global Fund. For this update, we used the latest update of the Thembisa model (version 4.4), recent cost data relevant to the public sector, and a custom-built optimisation routine which considers the cost-effectiveness of each intervention (cost per life year saved) and iteratively adds the most cost effective intervention to a rolling baseline.

The 2021 HIV Investment Case had the following central additions: For the 95% retention scenario in, we included a hypothetical ART retention intervention that aimed at reaching the UNAIDS target of 95% ART coverage. We estimated the cost of such an intervention by evaluating the cost of the Siyenza programme's staff dedicated to retention activities, scaled up a national level (i.e. in all primary healthcare (PHC) facilities), which added an annual cost of R1.5bn annual cost to the HIV programme. We also added an optimised package of HIV self-test distribution models, based on our previous work on the cost-effectiveness of HIV self-testing. This package consisted of distributing HIVST as follows: 75% of self-test kits through secondary distribution to partners of index cases, 12.5% through primary and secondary distribution in taxi ranks and 12.5% in through to primary distribution to PHC clients.

Scenarios

We report on two scenarios, defined by the currently committed budget from SA government, Global Fund and PEPFAR:

- Constrained scenario: most cost effective mix of interventions under the current budget
- Unconstrained scenario: scales up interventions without a regard to the funding envelope.

For defining the budget envelope, the South African Government budget was based on the HIV allocation within the current Conditional Grant budget, with figures deflated based on the Reserve Bank's consumer price index forecast. The PEPFAR budget was based on the planned budget from 2021/22 (COP21), and the Global Fund budget was based on both the 2019-22 and 2022-25 allocation. The resulting total budget envelope was ZAR 26.85 billion in 2020/21, 28.79 billion in 2021/22, and 29.04 billion in 2022/23.

We also present results based on two ART coverage scenarios, defined by the ART retention intervention described above:

- 78% ART coverage by 2025 (current trajectory, no retention intervention)
- 95% ART coverage by 2025 (retention intervention included).

For each scenario, we report on the impact on life years saved, cost per life year saved and cost (and incremental cost) of the HIV programme. Costs are reported uninflated and in 2020/21 South African Rand (ZAR).

Results

Recommended interventions

Under the 78% ART coverage scenario, under the current medium term budget, scaling up all included interventions is affordable, whereas under the 95% ART coverage scenario we can only afford a slightly more limited list of interventions (see Table below).

Across both ART coverage scenarios, increasing condom distribution to 1bn condoms/year is a cost-saving intervention, followed by the next most cost-effective intervention, linking 95% of newly diagnosed adults to ART (R1,674/life year saved) (see Table below). Scaling up infant testing at birth, PrEP for men who have sex with men (MSM) and general population HIV testing services (HTS) follow as the next cost-effective interventions. At this point, under the 95% ART coverage scenario the ART retention intervention is the next most cost-effective option (R21,470/life year saved), while the 78% ART coverage scenario scales up adolescent HTS to 95% (R24,670/life year saved). Overall intervention order remains similar between the ART coverage scenarios, with the exception of medical male circumcision which becomes less cost-effective under the scenario where 95% of ART patients remain on ART, due to diminishing returns.

List of HIV interventions ranked by cost-effectiveness for two ART coverage scenarios (78% and 95%) – 20-year impact (2021-40)

78% ART coverage scenario		**95% ART coverage scenario**	
Intervention (scaled-up coverage)	***Cost per life year saved (ZAR)***	***Intervention (scaled-up coverage)***	***Cost per life year saved (ZAR)***
UNCONSTRAINED SCENARIO		**CONSTRAINED SCENARIO**	
Condom distribution (1bn/year)	Cost-saving	Condom distribution (1bn/year)	Cost-saving
ART (95% linkage)	1,674	ART (95% linkage)	1,674
Infant testing at birth (95%)	11,174	Infant testing at birth (95%)	11,174
PrEP for MSM (50%)	16,176	PrEP for MSM (50%)	16,176
HTS general population (18.3m/year)	20,695	HTS general population (18.3m/year)	20,695
Medical male circumcision (95%)	21,609	ART (95% linkage, 95% ART coverage)	21,470
HTS adolescents (95%)	24,670	HTS adolescents (95%)	32,547
PrEP for FSW (30%)	26,532	HIVST optimized package (3m/year)	38,438
HIVST optimized package (3m/year)	27,183	PrEP for pregnant women (18%)	66,601
PrEP for pregnant women (18%)	33,199	PrEP for FSW (30%)	68,249
PrEP for female adolescents (18%)	60,603	Medical male circumcision (95%)	69,645
PrEP for young women (18%)	127,612	PrEP for female adolescents (18%)	119,494
PrEP for young men (18%)	241,302	PrEP for young women (18%)	236,246
PrEP for male adolescents (18%)	193,520	**UNCONSTRAINED SCENARIO:** Interventions included in addition to above	
Early infant male circumcision (70%)	1,511,925,532	PrEP for young men (18%)	460,355
		PrEP for male adolescents (18%)	358,388
		Early infant male circumcision (70%)	520,555,635

Total cost

Under the 78% ART coverage scenario, the total annual cost of the HIV programme remains well below the budget constraint even if all interventions are scaled up, ranging between R20bn-R25bn annually. Under the 95% ART coverage scenario, the additional patients on ART will significantly increase the annual

budget. The cost of the constrained scenario remains at a stable level below the 2022/23 budget constraint, even beyond 2023, around R29bn, and therefore would remain affordable as long as the budget does not decrease. The unconstrained scenario is only marginally more expensive than the constrained scenario (on average an additional R1.1bn per year) due to only 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) is responsible for significantly reducing HIV incidence (and new HIV infections) much sooner than under the current 78% ART coverage trajectory. Improving ART retention will result in a large cohort of patients requiring ART for the immediate future, until eventual decline in total on ART towards the end of the 20-year period (largely as a result of the increase in condoms, with smaller impacts from MMC, PrEP and HTS). Overall 95% ART coverage will have a significant impact on reducing AIDS deaths by an estimated average of 9,300/year, compared to 4,500/year under 78% ART coverage.

Summary

If we maintain ART coverage at current levels (78%), compared to baseline, scaling up all interventions will add an incremental cost of R58bn (10%) over 20 years and avert 89,000 (8%) AIDS deaths, 700,000 (23%) HIV infections, and save 3.8 million life years (10%). In contrast, achieving a 95% ART coverage will cost substantially more (R117bn constrained, 19% or R140bn unconstrained, 23%), but have significantly larger impacts on AIDS deaths (186,000 averted, 17%), HIV infections (2.1 million averted, 66%), and life years saved (7.1 million, 18%). The cost per life year saved under 78% ART coverage unconstrained scenario is R15,261/life year saved, while under 95% ART coverage it is R16,539/life year saved (constrained scenario) and R19,668/life year saved (unconstrained scenario).

INTRODUCTION

South Africa is home to more than 8 million people living with HIV, the largest HIV-positive population in the world. Many prevention and treatment interventions are already scaled up to high levels of coverage. As a result, with 93% of the country's people living with HIV (PLHIV) knowing their status, 74% 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. According to the latest National AIDS Spending Assessment, the government funds about 76% of the HIV response itself, while external funding has stagnated in recent years.

In 2011, at the UN General Assembly High Level Meeting on HIV and AIDS, countries including South Africa adopted the Political Declaration on HIV/AIDS, pledging to strive to reduce new HIV infections, deaths due to HIV, and HIV-related stigma and discrimination by 50% by 2015. An important component of the Political Declaration was the introduction of the 'investment approach' to achieve substantial and sustainable impacts in the global HIV response by 2015 and beyond [1]. In 2013, the South African National Department of Health (NDOH) and National AIDS Council (SANAC) initiated the application of the investment framework to the South African HIV epidemic. This original South African Investment Case covered both the HIV and the TB epidemics 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.

The methods used in the South African HIV Investment Case and its updates diverge from the original framework in a number of ways, most notably in the use of a rolling baseline against which additional interventions' cost effectiveness was analysed, in order to take into account the very high baseline coverage levels of most interventions in South Africa and the resulting diminishing marginal returns [2]. The Investment Case is an iterative process, and both inputs and methodology have been updated and refined in the last years. This report details the result of the most recent update to the Investment Case and compares the resulting recommendations with those of the original report from 2016 [3].

METHODS

Types of interventions and evidence review process

The original Investment Case process included an intervention selection process which has been described in detail elsewhere [3]. In summary, the selection of interventions was initiated by a stakeholder workshop involving a broad cross-section of academics, implementers and policy makers working in the HIV field in South Africa who suggested interventions across eight programme areas (care and treatment, key populations services, comprehensive condom programming, HIV testing services, social and behaviour change communication, medical male circumcision, prevention, programme and structural enablers and development synergies) as well as published and unpublished evidence for each intervention's effectiveness. The submitted evidence was then reviewed and summarized by a working group for each programme area as well as a team of economists and mathematical modellers using a grading system.

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 PrEP interventions such as PrEP for high risk young men, PrEP for high risk male adolescents and PrEP for men who have sex with men (MSM). Additionally, PrEP provision to all adolescent girls and young women (AGYW) was replaced by targeted PrEP to high-risk AGYW only, with the assumption that people would successfully self-select into the PrEP programme based on their risk of HIV acquisition;
2. a replacement of efavirenz by dolutegravir in first-line adult ART;
3. an ART intervention that improves 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 2020/21, in line with the second of the UNAIDS 95-95-95 targets;
4. HIV self-testing, incorporating six different community- and facility-based self-test kit distribution modalities.

More information on the latter two interventions is available below.

We have additionally removed the following interventions:

1. social and behaviour change communication campaigns, as the currently implemented campaigns do not bear much semblance to those campaigns whose effectiveness had been evaluated and included in the previous version of the Investment Case;
2. PCR testing of infants at 6 weeks, due to its coverage having reached saturation at baseline;
3. prevention of mother-to-child transmission, which is now part of general ART through universal test- and-treat guidelines;
4. condom education as part of the Condom availability intervention, as this is not part of current government policies.

Additionally, the cost of two interventions previously termed "technical efficiency factors", different general population testing modalities and condom provision in non-traditional outlets, have now been incorporated into the main interventions (General population HTS and Condom availability, respectively).

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

Programme area	Intervention	Impact represented in Thembisa
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
	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 uptake in respective population
	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)	

Modelling process and scenarios for analysis

We established a new model for this exercise called Thembisa Optimise, incorporating an established HIV transmission model for South Africa, the Thembisa model [4], and a custom-made cost model [5] as well as a novel optimisation routine described in detail elsewhere [2]. 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 any other intermediate variable or programme indicator, such as condom usage, increase in adherence, decrease in loss to follow-up, or increase in cases diagnosed, etc. Interventions selected in the process described above that did not have evidence of an impact on any of these factors, or that did not have a target population that could be selected in Thembisa Optimise, were excluded from the analysis.

Based on these inputs as well as assumptions regarding survival and HIV transmission embedded in the model, we generated for each intervention: a) the number of HIV infections averted, and b) the number of life-years saved for the financial years 2020/21 to 2039/40. 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 is only limited data are available from South Africa regarding quality weights, and no data regarding disability weights. 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. Life expectancy values were based on the West Level 26 life table commonly used in Global Burden of Disease calculations [6]. Life years lost (or saved) were counted over the 20-year time horizon of the analysis only.

Epidemiological model

The 2021 update of the HIV Investment Case is based on version 4.4 of the Thembisa model [7]. 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 risk 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 programmes and condom distribution programmes.

The model projects the change in the number of individuals in each compartment at monthly time steps, starting in 1985. To ensure that the model results are realistic, 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 been updated to take into account the impact of the COVID-19 pandemic, including the impact on healthcare seeking behaviour under the South African government's Risk-Adjusted Strategy, throughout 2020.

Cost model

Based on outputs from the epidemiological model regarding the numbers of people covered by each intervention, Thembisa Optimise then calculated the total cost of each intervention as well as the total cost of the HIV response by multiplying this number by an average or unit cost (i.e., the per person/ person year/ test/ visit cost) of the respective intervention. Cost was evaluated from the government perspective, using public-sector prices, and is presented in undiscounted, nominal terms, to enable results to inform actual government budgets.

Cost-effectiveness analysis and optimisation

Based on the outputs of life-years saved from the epidemiological model and the incremental cost from the cost model, we 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 each of the two optimisation scenarios. We examined the impact of scaling each intervention either up or down to any of six default coverage levels other than baseline (BL) coverage and a feasible maximum (FM) set at 95% for exiting interventions, 70% for novel interventions, or informed by current policy targets (Table). This provided us with a total of 93 options representing combinations of

interventions and coverage levels that we modelled and ranked by ICER. In order to be able to use results for budgeting purposes, neither outcomes (life-years saved) nor costs were discounted.

In a second step, we added the most cost effective option onto the baseline. We then repeated this process iteratively. 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 increase in ART uptake as a result of increasing HIV testing, or the reduction in the need for ART as a result of increasing HIV prevention interventions, including ART) and, ultimately, the cost and impact of the entire HIV response. For the constrained optimization scenarios we concluded the process of adding the next most cost-effective intervention once the total cost of the 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.

Table 2: List of interventions and coverage levels included in the optimisation routine

Intervention	**Description**	**Coverage level tested in optimisation**							
		-2	-1	BL[1]	+1	+2	+3	FM[2] (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 (model maximum)
Early infant male circumcision (EIMC)[3]	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%
PrEP for high risk young men	Providing PrEP to high risk young men aged 20-24 only	-	-	0%	✓	✓	✓	✓	18%

[1] BL: baseline

[2] FM: feasible maximum

[3] 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.

Intervention	Description	Coverage level tested in optimisation							
		-2	-1	BL[1]	+1	+2	+3	FM[2] (2022/23)	
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 counselling and testing (HTS) of general population		✓	✓	14.3m/ year	✓	✓	✓	✓	18.3m/year (Annual performance plan NDoH)
HTS for adolescents	Dedicated HIV testing drives targeted at adolescents	-	-	22%	✓	✓	✓	✓	95%

Available budget

For the calculation of the available budget envelope over the next years, we used the following data sources:

- The South African Government budget 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 [8] 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 summarised in Table 3.

Table 3: Budget envelope for 2020/21 to 2022/23 based on the three main funders of the South African HIV response [billions 2021 ZAR]

Funder	2020/21	2021/22	2022/23
South African Government	20.34 (76%)	22.31	22.45
PEPFAR	5.97 (22%)	*5.97**	*5.97**
Global Fund	0.54 (2%)	0.51	*0.61**
Total budget	**26.85**	**28.79**	**29.04**

**assumed amounts*

Updates in 2021

Since the publication of the first Investment Case reports, we have continuously updated our modelling suite to take into account changes to the evidence base, intervention coverage and implementation models, and intervention costs. These changes included:

1. an update of baseline coverages with all interventions based on recent data from routine implementation (District Health Information System, DHIS) and other NDOH data sources;
2. the removal of the social and behavior change communication campaigns (see above)
3. 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.

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 [9]. These distribution modalities are:

- distribution in fixed community sites
- distribution in taxi ranks
- distribution in workplaces
- 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 [10]. Table 4 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 4: Allocation of test kits across HIVST modalities under current policy and optimized distribution strategy [2021 ZAR]

	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 (secondary)	3%	75%
Workplace	20%	0%
Primary PHC	60%	12.5%
Cost / life year saved	**R13,326**	**R12,991**

ART with improved linkage and retention

Improving retention in antiretroviral treatment is crucial for continued progress towards the second UNAIDS target (90% ART coverage among PLHIV who know their status)- the target that South Africa lags the most. We now consider two ART interventions- ART with improved linkage alone, and ART with improved linkage *and* retention. In the ART intervention with improved retention, the additional distinction is that ART patient's treatment interruption is reduced by 98%, resulting in patients being more likely to remain on treatment after initiation. This results 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 the recent literature on retention and re-initiation interventions from both South Africa and internationally, including seven systematic reviews [11–15], the most recent of which focussed on differentiated models of care [15]. All identified interventions with evidence of a positive impact on retention, such as support clubs for adolescent clients, facility-based psychosocial support and 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 retention, as well as adherence clubs, external and facility-based drug pick-up points are already part of the South African guidelines and are funded through the existing budget, though of course their level iof implementation might differ from both the literature and between facilities. Additionally, we identified a number of recently developed interventions that have not yet been evaluated beyond pilot projects (such as male focussed peer support, viraemia clubs, high viral load clinic days, welcome back campaign, family model clubs), making it impossible to estimate what their impact in a routine setting would be. We therefore decided to focus on merely incorporating the additional staff needed for hypothetical retention services modelled on the Siyenza campaign that was funded by PEPFAR as part of their Treatment Surge in 2018 and 2019.

In order to approximate the cost of such retention services, we added the annual cost of facilty-level staff emloyed during the Siyenza campaign who were dedicated towards retention activities, scaled to all PHC facilities. 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 R1.5 billion per year.

Scenarios

We present results based on two ART coverage scenarios, defined by the ART retention intervention described above:

- 78% ART coverage by 2025 (current trajectory, no retention intervention)
- 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:

- Constrained scenario: most cost effective mix of interventions under the current budget
- Unconstrained scenario: scales up interventions without regard to the budget envelope.

RESULTS

Recommended interventions

Under the 78% ART coverage scenario, under the current medium term budget, scaling up all included interventions is affordable, whereas under the 95% ART coverage scenario we can only afford a slightly more limited list of interventions (Table 5). This means that for the 78% ART coverage scenario, the unconstrained scenario is identical with the constrained scenario, as the total cost falls 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 is a cost-saving intervention, followed by the next most cost-effective intervention, linking 95% of newly diagnosed adults to ART (R1,674/ life year saved) (Table 5). Scaling up infant testing at birth, PrEP for MSM and general population HIV testing services follow as the next cost-effective interventions. At this point, under the 95% ART coverage scenario the ART retention intervention is the next most cost-effective option (R21,470/ life year saved), while the 78% ART coverage scenario scales up adolescent HTS to 95% (R24,670/ life year saved). Overall intervention order remains similar between the ART coverage scenarios, with the exception of medical male circumcision which becomes less cost-effective under the scenario where 95% of ART patients remain on ART, due to diminishing returns.

Table 5. List of HIV interventions ranked by cost-effectiveness for two ART coverage scenarios (78% and 95%) – 20-year impact (2021-40)

78% ART coverage scenario		**95% ART coverage scenario**	
Intervention (scaled-up coverage)	***Cost per life year saved (ZAR)***	***Intervention (scaled-up coverage)***	***Cost per life year saved (ZAR)***
UNCONSTRAINED SCENARIO		**CONSTRAINED SCENARIO**	
Condom distribution (1bn/year)	Cost-saving	Condom distribution (1bn/year)	Cost-saving
ART (95% linkage)	1,674	ART (95% linkage)	1,674
Infant testing at birth (95%)	11,174	Infant testing at birth (95%)	11,174
PrEP for MSM (50%)	16,176	PrEP for MSM (50%)	16,176
HTS general population (18.3m/year)	20,695	HTS general population (18.3m/year)	20,695
Medical male circumcision (95%)	21,609	ART (95% linkage, 95% ART coverage)	21,470
HTS adolescents (95%)	24,670	HTS adolescents (95%)	32,547
PrEP for FSW (30%)	26,532	HIVST optimized package (3m/year)	38,438
HIVST optimized package (3m/year)	27,183	PrEP for pregnant women (18%)	66,601
PrEP for pregnant women (18%)	33,199	PrEP for FSW (30%)	68,249
PrEP for female adolescents (18%)	60,603	Medical male circumcision (95%)	69,645
PrEP for young women (18%)	127,612	PrEP for female adolescents (18%)	119,494
PrEP for young men (18%)	241,302	PrEP for young women (18%)	236,246
PrEP for male adolescents (18%)	193,520	**UNCONSTRAINED SCENARIO:** Interventions included in addition to above	
Early infant male circumcision (70%)	1,511,925,532	PrEP for young men (18%)	460,355
		PrEP for male adolescents (18%)	358,388
		Early infant male circumcision (70%)	520,555,635

Comparison with 2016 Investment Case results

In comparing the results of the 2021 update with the original 2016 HIV Investment Case, it is 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 have changed the order of recommended interventions substantially (Figure 1). The only constant finding is that increasing condom provision to cover 95% of sex acts remains the most cost-effective (and now the only cost-saving) intervention. While ART remains amongst the most cost effective interventions, MMC retains a good cost-effectiveness overall, however has moved down in the ranking compared to the 2016 HIV Investment Case. Reasons for this include: 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. A number of PrEP interventions, including for MSM, rank higher than in the original Investment Case, partly owing to stronger assumptions regarding targeting of this intervention to clients at higher HIV risk. EIMC remains the least cost-effective intervention, as before owing to the choice of projection period (20 years) which does 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

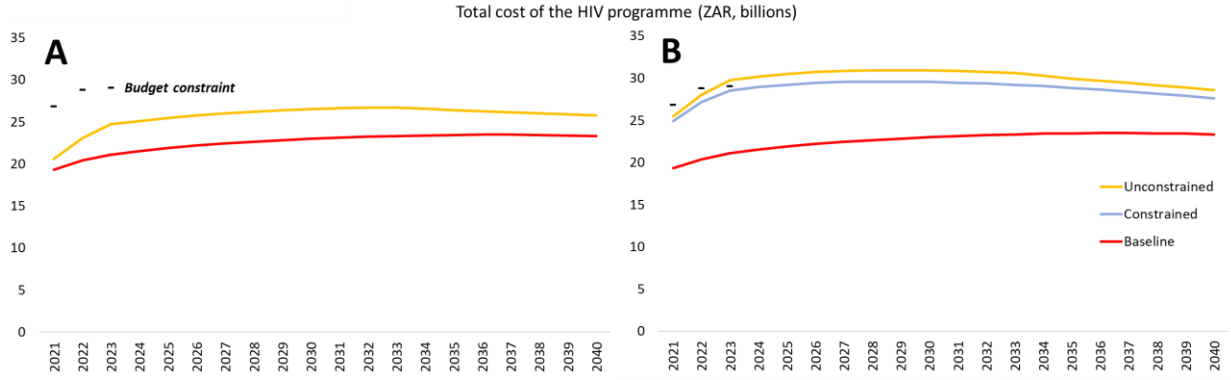
	2016 HIV IC	**2021 HIV IC** *78% ART coverage*		**2021 HIV IC** **95% ART coverage**	
Constrained	Condom provision (95%)	Condom distribution (1bn/year)	Unconstrained	Condom distribution (1bn/year)	Constrained
	MMC (550k/year)	ART (95% linkage)		ART (95% linkage)	
	ART at current guidelines (95%)	Infant testing at birth (95%)		Infant testing at birth (95%)	
	PMTCT (95%)	PrEP for MSM (50%)		PrEP for MSM (50%)	
	ART under universal treatment (linkage) (95%)	HTS general population (18.3m/year)		HTS general population (18.3m/year)	
	PCR testing at 6 weeks (95%)	Medical male circumcision (600k/year)		ART (95% linkage, 95% retention)	
	SBCC campaign 1 (HCT, reduction MSP) (95%)	HTS adolescents (95%)		HTS adolescents (95%)	
	SBCC campaign 2 (condoms) (95%)	PrEP for FSW (30%)		HIVST optimized package (3m/year)	
Unconstrained	HTS General population (18m tests/year)	HIVST optimized package (3m/year)		PrEP for pregnant women (18%)	
	SBCC campaign 3 (condoms, HCT, MMC) (95%)	PrEP for pregnant women (18%)		PrEP for FSW (30%)	
	HCT for FSW (95%)	PrEP for female adolescents (18%)		Medical male circumcision (600k/year)	
	PCR testing at birth (70%)	PrEP for young women (18%)		PrEP for female adolescents (18)	
	PrEP for FSW (70%)	PrEP for young men (18%)		PrEP for young women (18%)	
	HTS for adolescents (95%)	PrEP for male adolescents (18%)		PrEP for young men (18%)	Un-constrained
	PrEP for young women (70%)	Early infant male circumcision (70%)		PrEP for male adolescents (18%)	
	Early infant male circumcision (70%)			Early infant male circumcision (70%)	

Total cost

Under the 78% ART coverage scenario, the total annual cost of the HIV programme remains well below the budget constraint even if all interventions are scaled up, ranging between R20bn-R25bn annually (Figure 2). Under the 95% ART coverage scenario, the additional patients on ART will significantly increase the annual budget. The cost of the constrained scenario remains at a stable level below the 2022/23 budget constraint, even beyond 2023, around R29bn, and therefore would remain affordable as long as the budget does not decrease. The unconstrained scenario is only marginally more expensive than the

constrained scenario (on average an additional R1.1bn per year) due to only a few interventions being included in addition to those in the constrained scenario.

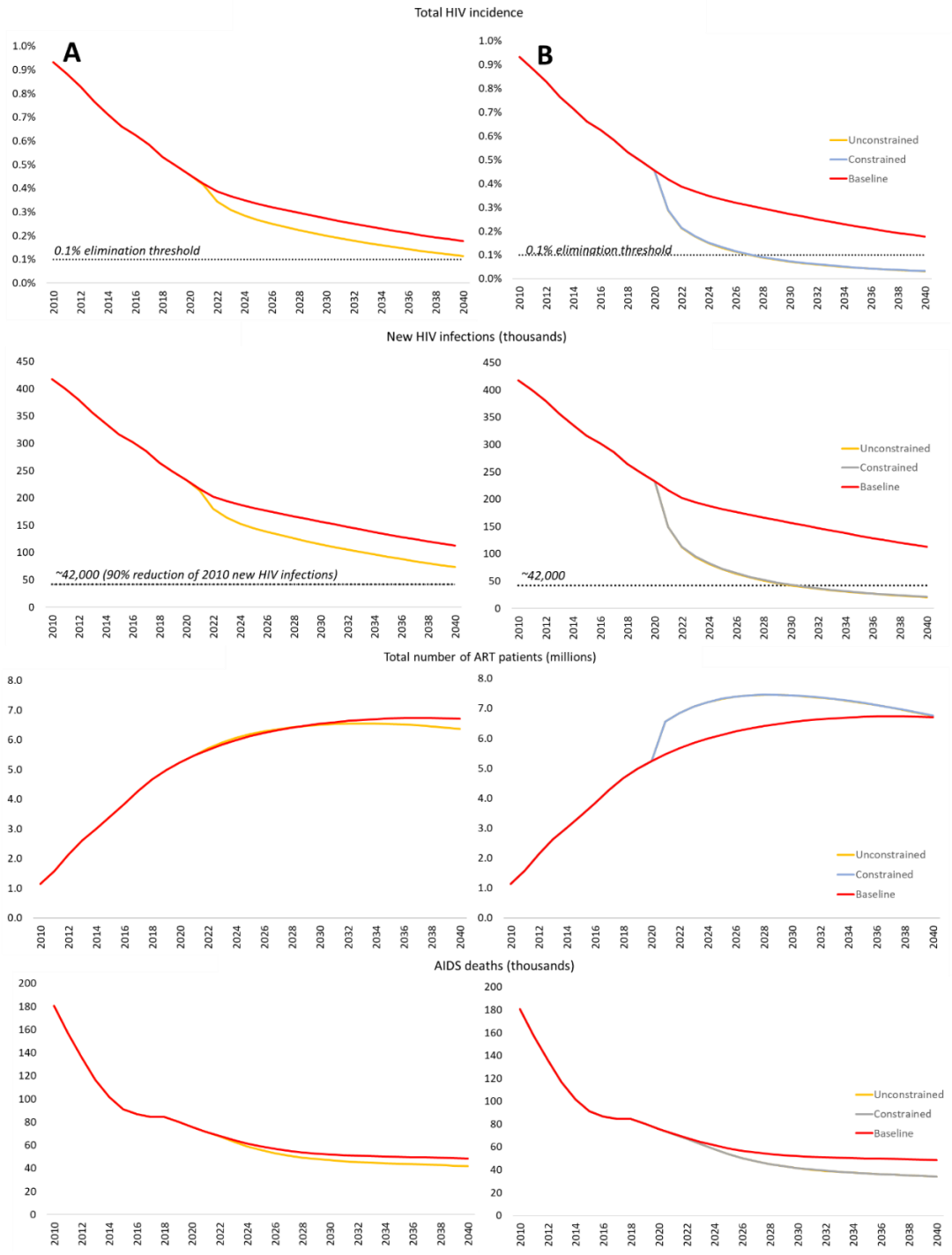
Figure 2. Total cost (ZAR, billions) of the HIV programme, excluding inpatient care, under (A) 78% ART coverage and (B) 95% ART coverage



Programme coverage and impact on the epidemic

Increasing ART retention (95% ART coverage scenario) is responsible for significantly reducing HIV incidence (and new HIV infections) much sooner than under the current 78% ART coverage trajectory (Figure 3). Improving ART retention will result in a large cohort of patients requiring ART for the immediate future, until eventual decline in total on ART towards the end of the 20-year period (largely as a result of the increase in condoms, with smaller impacts from MMC, PrEP and HTS). Overall 95% ART coverage will 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 3).

Figure 3. Annual epidemiological impacts on key indicators of the HIV epidemic with (A) 78% ART coverage and (B) 95% ART coverage



Summary

If we maintain ART retention at current levels (resulting in 78% coverage overall), compared to baseline, scaling up all interventions will add an incremental cost of R58bn (10%) over 20 years and 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 6).

In contrast, achieving a 95% ART coverage will cost substantially more (R117bn in the constrained, R140bn 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 78% ART coverage unconstrained scenario is R15,261/ life year saved, while under 95% ART coverage it is R16,539/ life year saved (constrained scenario) and R19,668/ life year saved (unconstrained scenario).

Table 6. Summary of incremental impacts and cost-effectiveness over 20 years (2021-2040)

Baseline (2021-40)		
Total cost of the HIV programme, billions ZAR	601	
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 ZAR		
Constrained scenario	n/a	117 (+19%)
Unconstrained scenario	58 (+10%)	140 (+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 (ZAR)		
Constrained scenario	n/a	16,539
Unconstrained scenario	15,261	19,668

Our findings need to be interpreted alongside a number of limitations in our methodology. Most importantly, as mentioned, in our 95% coverage scenario we did not incorporate individual interventions know to achieve the necessary levels of 99% retention after initiation- we simply tested what the impact would be if this level of retention was indeed possible, and added the cost of both a hypothetical staff contingent that might bring this about 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 this level of staff. Additionally, as before, 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.

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