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Cost-effectiveness of point-of-care testing with task-shifting for HIV care in South Africa: a modelling study

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Abstract:	Background: The scale-up of “HIV test and treat” has rapidly increased the number of persons on antiretroviral therapy (ART) requiring treatment monitoring in low-resource settings. Decentralized point-of-care (POC) testing for ART monitoring may alleviate burden on centralized laboratories and improve clinical outcomes, but its cost-effectiveness is unknown. Methods: We used primary cost and effectiveness data from the STREAM trial in South Africa, which assessed the impact of POC testing for viral load, CD4 count, and creatinine, with task-shifting from professional to lower-cadre registered nurses compared to laboratory-based testing without task-shifting. We parameterized an agent-based network model, EMOD-HIV, to project the impact of implementing this intervention in South Africa. We assumed POC monitoring increased viral suppression by 9%, enrollment into community-based ART delivery by 25%, and switching to second-line ART by 1%, as reported in STREAM. We evaluated POC scale-up in varying clinic sizes (10-50 patient initiating ART/month) over a 20-year time horizon. We used a cost-effectiveness threshold of $500 USD/disability adjusted life year (DALY) averted for our main analysis. Results: Implementing POC testing at 70% coverage of ART patients was projected to reduce HIV infections by 4.5% and HIV-related deaths by 3.9%. In clinics with 30 ART initiations/month, the intervention was associated with an incremental cost-effectiveness ratio (ICER) of $197/DALY averted; results remained cost-effective when varying background viral suppression, ART dropout, and intervention effectiveness within the 95% confidence bound of the trial results. Assuming POC testing did not increase enrollment into community ART delivery produced an ICER of $1,149, exceeding the cost-effectiveness threshold. At higher clinic volumes (≥40 ART initiations/month), POC testing was cost-saving compared to standard-of-care. At lower clinic volumes (20 patients initiated on ART/month) the ICER was $734/DALY averted. Conclusions: POC testing for ART monitoring with task-shifting is projected to be cost-

	effective in moderately-sized clinics in South Africa.

Cost-effectiveness of point-of-care testing with task-shifting for HIV care in South Africa: a modelling study

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Key words: Point-of-care testing, viral load testing, ART monitoring, sub-Saharan Africa, South Africa, cost-effectiveness, modeling

ABSTRACT

Background: The scale-up of "HIV test and treat" has rapidly increased the number of persons on antiretroviral therapy (ART) requiring treatment monitoring in low-resource settings. Decentralized point-of-care (POC) testing for ART monitoring may alleviate burden on centralized laboratories and improve clinical outcomes, but its cost-effectiveness is unknown.

Methods: We used primary cost and effectiveness data from the STREAM trial in South Africa, which assessed the impact of POC testing for viral load, CD4 count, and creatinine, with task-shifting from professional to lower-cadre registered nurses compared to laboratory-based testing without task-shifting. We parameterized an agent-based network model, EMOD-HIV, to project the impact of implementing this intervention in South Africa. We assumed POC monitoring increased viral suppression by 9%, enrollment into community-based ART delivery by 25%, and switching to second-line ART by 1%, as reported in STREAM. We evaluated POC scale-up in varying clinic sizes (10-50 patient initiating ART/month) over a 20-year time horizon. We used a cost-effectiveness threshold of $500 USD/disability adjusted life year (DALY) averted for our main analysis.

Results: Implementing POC testing at 70% coverage of ART patients was projected to reduce HIV infections by 4.5% and HIV-related deaths by 3.9%. In clinics with 30 ART initiations/month, the intervention was associated with an incremental cost-effectiveness ratio (ICER) of $197/DALY averted; results remained cost-effective when varying background viral suppression, ART dropout, and intervention effectiveness within the 95% confidence bound of the trial results. Assuming POC testing did not increase enrollment into community ART delivery produced an ICER of $1,149, exceeding the cost-effectiveness threshold. At higher clinic volumes (≥40 ART initiations/month), POC testing was cost-saving compared to standard-

of-care. At lower clinic volumes (20 patients initiated on ART/month) the ICER was $734/DALY averted.

Conclusions: POC testing for ART monitoring with task-shifting is projected to be cost-effective in moderately-sized clinics in South Africa.

INTRODUCTION

The majority of the 37 million people living with HIV (PLHIV) globally reside in resource-limited settings.[1] Successful scale-up of antiretroviral therapy (ART) through "test and treat" has transformed HIV from a terminal disease into a manageable chronic illness. PLHIV who are virally suppressed on ART have good clinical outcomes and a near normal life expectancy.[2, 3] Additionally, viral suppression virtually eliminates transmission to sexual partners, providing hope that treatment as prevention can help end the HIV epidemic.[4, 5] Currently, over 25 million individuals receive ART worldwide, and reaching UNAIDS' 95-95-95 targets will dramatically increase number of persons on ART by 2030.[6]

Monitoring the millions of PLHIV in HIV care remains challenging in resource-limited settings. World Health Organization (WHO) recommends routine testing of HIV viral load (VL), CD4 count, and creatinine for patients receiving ART.[7] However, less than 50% of PLHIV on ART in sub-Saharan Africa (SSA) receive routine VL monitoring.[8] Currently, most monitoring tests in SSA are processed in centralized laboratories requiring highly trained staff and specialized equipment. Scale-up is hindered by challenges of timely sample transportation, insufficient capacity to meet demand, and inadequate infrastructure.[9, 10] Further, among patients who receive monitoring, a second clinic visit after several weeks is required to obtain results, which can cause delays in clinical decision making, non-delivery of results, or lack of adherence counseling provision.[8, 11, 12]

Decentralized point-of-care (POC) testing for ART monitoring is a promising strategy to expand testing coverage and improve clinical outcomes by decreasing turn-around time for results and reducing loss-to-follow-up among viremic patients. [13-15] A recent randomized clinical trial (STREAM) evaluated the impact of POC testing for VL, creatinine, and CD4

combined with task-shifted care to lower-cadre nurses compared to standard lab-based testing without task-shifting among ART patients in South Africa. The intervention improved viral suppression and increased referral to ART differentiated service delivery (DSD).[16] However, the economic impact of implementing POC testing for lifelong ART management is uncertain. To inform policy discussions about ART monitoring guidelines, we utilized mathematical modeling to project the health and economic impact of scaling-up the STREAM intervention in South Africa.

METHODS

STREAM clinical trial

We utilized cost and effectiveness data from the STREAM (Simplifying HIV TREAtment and Monitoring) randomized clinical trial.[17] The study was conducted from February 2017 to October 2018 at a large public clinic providing care for a diverse, mobile population in Durban, South Africa. Eligible participants were HIV-positive adults presenting for routine care six months post-ART initiation; individuals who not pregnant, diagnosed with active tuberculosis, requiring acute medical care by a physician were excluded. Participants (N=390) were randomized to receive 1)POC testing for VL, creatinine, and CD4 count testing with same-day counseling and task-shifted care by an enrolled nurse or 2)standard-of-care laboratory testing and care by a professional nurse. All patients received treatment monitoring according to South African and WHO guidelines (**Figure S1**). Individuals with VL>1,000 copies/mL received enhanced adherence counselling and repeat VL testing after two months. If the repeat VL was >1,000 copies/mL, participants were offered to switch to second-line ART. Based on South African guidelines, participants on ART for ≥12 months with two consecutive VL<40 copies/mL

and CD4 count>200 cells/mm^3 were referred to decentralized DSD to collect ART at community pharmacies.

Costs

We conducted a detailed microcosting and time-and-motion observation of the STREAM trial to estimate costs of POC VL, CD4, and creatinine testing, described previously (and in the **Appendix**).[18] Since the equipment component of the test cost depends on number of tests conducted, we calculated POC test cost per patient at varying clinic volumes of 10-50 PLHIV initiating ART/month **(Table 1)**. At higher volumes, instrument costs are spread over a greater number of tests and the cost per test is lower. Centralized laboratory costs were obtained from South African National Health Laboratory Service price lists. HIV tests, ART drugs, and healthcare costs were obtained from literature and inflated to 2018 US dollars (USD).

Table 1: HIV-related healthcare costs for South Africa.

Parameter	Cost
Facility HIV test[19]	
HIV- test	$3.62
HIV+ test	$5.62
ART costs per year (including supply chain)[20]	
1st line regimen*	$90
2nd line regimen§	$318
ART program costs per year (health facility)	$80
ART program costs per year (DSD due to VL <1000)	$40
Health-care for HIV-positive persons not in care[21]	
CD4 count >350 cells per μL	$11
CD4 count >200–350 cells per μL	$39
CD4 count ≤200 cells per μL	$142
End of life care (per death)	$136
Diagnostic tests (centralized laboratory)[18]	
CD4	$6.03
VL test	$25.98
Creatinine	$3.41
Diagnostic tests (POC) by monthly clinic volume[18] ¥	
Clinic volume 10	
CD4	$24.41
VL	$46.51
Creatinine	$9.71
Clinic volume 20	
CD4	$16.09
VL	$33.31
Creatinine	$9.14
Clinic volume 30	
CD4	$13.32
VL	$28.91
Creatinine	$8.96
Clinic volume 40	
CD4	$11.94
VL	$26.71
Creatinine	$8.86
Clinic volume 50	
CD4	$11.11
VL	$25.39
Creatinine	$8.81

ART: antiretroviral therapy, DSD: differentiated service delivery, POC: point-of-care, VL: viral load
*1st line ART regimen consisting of tenofovir, lamivudine, and efavirenz
§2nd line ART regimen consisting of lopinavir/ritonavir
¥Clinic volume refers to the number of patient initiating ART per month

Mathematical model

We adapted a previously developed microsimulation model, EMOD-HIV, described in detail at www.idmod.org/idmdoc and elsewhere.[22] EMOD-HIV is an open-source, stochastic, agent-based model integrating population demography, HIV disease progression, and network-based HIV transmission, configured to match age- and sex-specific propensities to form different sexual partnerships.[23] The model incorporates detailed within-host HIV progression to simulate HIV health and transmission effects and the impact of ART on epidemic dynamics. EMOD includes a highly configurable HIV care cascade, including HIV testing, linkage and retention in care, time-varying treatment eligibility, ART dropout, and heterogeneity in treatment engagement by age and sex. Model validation is shown to reproduce age and sex-specific HIV incidence in KwaZulu-Natal, South Africa as confirmed by epidemiologic and phylogenetic studies.[23-25] The model tracks health outcomes including HIV infections and HIV-related deaths and healthcare utilization, enabling the calculation of economic costs of HIV and disability-adjusted life years (DALYs). We simulated approximately 175,000 individuals per model run.

The model was parameterized with epidemiologic data from South Africa including fertility, mortality, voluntary male circumcision coverage, and health seeking behavior. We calibrated the model to South Africa data on age- and sex-specific HIV prevalence, ART coverage, population size and validated to HIV incidence (**Appendix**). Model calibration was performed using a parallel simultaneous perturbation optimization (PSPO) algorithm which maximizes the pseudo-likelihood of stochastic epidemiological models given observed data and identifies an optimal set of input parameters.[26] We selected 250 model parameter sets using roulette resampling in proportion to the likelihood of each simulation.

Scenarios

In the standard-of-care scenario, we assumed individuals initiating ART received clinical management by a professional nurse and monitoring using centralized laboratory tests. Based on the literature for South Africa, we assumed 3% of ART patients were on second-line regimens, 20% of individuals on ART collected drugs through DSD,[27, 28] and 83% of ART patients were virally suppressed (VL<1000 copies/mL).[29] In the POC intervention scenario, we assumed 70% of individuals on ART received monitoring using POC testing and task-shifted care by an enrolled nurse, based on acceptance rates in the STREAM trial and the assumption that POC testing would not be uniformly rolled out in all HIV clinics in South Africa. The remaining 30% of patients received standard-of-care laboratory monitoring from a professional nurse and were assumed to have the same health outcomes as individuals in the standard-of-care scenario. Among those receiving POC monitoring, we assumed a 1% increase in switching to second line treatment, 25% higher referral to DSD and 9% higher viral suppression on ART, as reported in STREAM. We assumed individuals on ART but not virally suppressed experience 1.96-times the mortality risk of those who are suppressed.[30] Based on clinical data, we estimated that PLHIV on ART with VL<1,000 copies/mL experience a 96% reduction in HIV transmission compared to PLHIV not on ART.[4, 31] Individuals on ART with VL>1,000 copies/mL were estimated to have a 35% reduced risk of HIV transmission compared to those not on ART; due to uncertainty in this parameter, we varied it from 0-70% in sensitivity analyses[4, 31] (See **Appendix** for details).

In all scenarios, we assumed PLHIV on ART received treatment monitoring according to WHO guidelines (**Figure S1**). Individuals found to be unsuppressed (VL>1000) were assumed to have a repeat VL after 2 months with additional adherence counseling.[7]

Cost effectiveness analysis

We calculated incremental cost-effectiveness ratios (ICERs) as difference in costs divided by difference in effects in intervention versus standard-of-care scenarios across each of the 250 parameter sets.[32, 33] We report the mean and 90% model variability of 250 ICERs. We utilized a 20-year time horizon and discounted costs and DALYs at 3% annually.[34] In light of ongoing deliberations regarding the appropriate threshold at which to identify efficient interventions, we utilized two cost-effectiveness thresholds: $500/DALY averted, frequently used in economic evaluations in SSA, and $1,175/ DALY averted, calculated as an appropriate cost-effectiveness threshold for South Africa by a panel of economic experts to reflect the opportunity costs of additional health investment.[20, 35]

Budget impact analysis

We calculated the undiscounted total cost of implementing the POC testing intervention at varying clinic volumes compared to standard-of-care over 5 and 20 years, including intervention and healthcare costs, both incurred and averted.

Sensitivity analyses

In addition to evaluating parameter uncertainty across 250 good-fitting sets, we conducted extensive sensitivity analyses to assess influence of uncertain parameters on results. We varied ART dropout, HIV infectivity if unsuppressed on ART, background viral suppression, clinic size, infectivity on ART if not virally suppressed, intervention impact on viral suppression, intervention impact on switching to both second-line ART and DSD, ART costs, and discount rate.

RESULTS

Table 2 displays the health impact and cost-effectiveness of implementing POC testing with task-shifting for ART monitoring under varying assumptions. In the baseline scenario, assuming 70% coverage of ART patients, the intervention was projected to avert 4.5% of HIV infections and 3.9% of HIV-related deaths. The intervention was cost-saving at clinic volumes of ≥40 patients initiating ART/month. At clinic volumes of 30 patients initiating ART/month, ICERs fell below the $500/DALY averted threshold. At the higher threshold ($1,175/DALY averted), the intervention was cost-effective at clinic volumes of ≥20 monthly ART initiations. Assuming lower background viral suppression on ART (71% vs. 83%) yielded slightly lower HIV infections averted (4.0%) and higher ICERs, although cost-effectiveness results remained the same as the baseline scenario. Similarly, doubling the annual ART dropout rate from 5% to 10% resulted in lower health benefits: 3.8% and 3.7% infections and HIV-related deaths averted, respectively, but cost-effectiveness results remained the same as the baseline scenario. Assuming lower intervention effectiveness (5% increase in viral suppression) nearly halved the projected health benefits (2.2% of HIV-related deaths and HIV infections averted respectively); ICERs were considerably higher, particularly at clinic volumes of 10 and 20 monthly ART initiations, although cost-effectiveness results remained the same. Assuming a higher intervention effectiveness (15% increase in viral suppression) increased health benefits to 6.6% and 6.9% HIV-related deaths and infections averted, respectively; the intervention was considered cost-effective at clinic volumes of ≥20 at the $500/DALY averted threshold. Using the threshold of $1,175/DALY averted, the intervention was cost-effective at all clinic volumes assessed. Similarly, assuming PLHIV on ART with unsuppressed VL had the same HIV transmissibility as PLHIV not on ART resulted in greater infections averted compared to the baseline scenario; the

intervention was cost-effective at the $500/DALY threshold at clinic volumes of ≥20 monthly ART initiations and all clinic volumes were cost-effective at the higher threshold. Conservatively assuming that PLHIV on ART with unsuppressed VL had a 2-fold higher reduction in HIV transmissibility (70% vs. 35%) compared to PLHIV not on ART, resulted in lower intervention health benefits and higher ICERs. At both thresholds, the intervention was cost-effective at clinic volumes with ≥30 monthly ART initiations.

Table 2: Health impact and cost-effectiveness of POC testing intervention across varying assumptions[§]

	Baseline	Lower background viral suppression on ART	2X higher ART dropout	Lower bound intervention effectiveness	Upper bound intervention effectiveness	No reduction in HIV transmission among those on ART w/ VL>1000	2X higher reduction in HIV transmission among those on ART w/ VL>1000
Health Impact (%)							
HIV infections averted	4.5 (1.6, 7.6)	4.0 (0.8, 7.1)	3.8 (1.1, 6.4)	2.2 (0.5, 5.2)	6.9 (3.2, 10.2)	5.6 (2.6, 8.6)	2.6 (-1.0, 6.9)
HIV deaths averted	3.9 (2.0, 6.0)	3.8 (1.7, 5.9)	3.6 (1.7, 5.3)	2.2 (0.1, 4.1)	6.6 (4.4, 8.6)	4.2 (2.3, 6.0)	3.6 (1.2, 5.6)
Cost-effectiveness ($ per DALY averted)							
Clinic volume: 50	-239 (-602, -96)	-229 (-721, -100)	-107 (-245, -36)	-209 (-582, -103)	-358 (-464, -103)	-161 (-281, -98)	-126 (-410, -18)
% under $500 threshold	100%	100%	100%	100%	100%	100%	100%
Clinic volume: 40	-72 (-176, 26)	-50 (-142, 144)	40 (-68, 279)	-45 (-145, 63)	-82 (-125, -79)	-75 (-122, -18)	-39 (-175, 140)
% under $500 threshold	100%	99%	97%	98%	100%	100%	98%
Clinic volume: 30	197 (-27, 863)	242 (-39, 1,051)	280 (-2, 1079)	319 (-14, 908)	49 (-41, 276)	63 (-36, 328)	374 (-17, 1,373)
% under $500 threshold	93%	87%	91%	85%	97%	97%	87%
Clinic volume: 20	734 (93, 2,569)	824 (69, 3,190)	757 (107, 2,546)	1045 (111, 2,960)	305 (58, 890)	339 (63, 1,075)	1,197 (117, 4,567)
% under $500 threshold	72%	66%	68%	49%	88%	85%	58%
Clinic volume: 10	2,348 (436, 7,681)	2,571 (380, 9,720)	2,190 (421, 6,779)	3,226 (494, 9,159)	1,073 (344, 2,738)	1,169 (341, 3,213)	2,451 (503, 8,474)
% under $500 threshold	9%	13%	10%	5%	28%	22%	5%

[§]Values in parenthesis represent 90% model variability across 250 simulations. Values in green represent scenarios where the mean ICER is considered cost-effective at both thresholds of $500 and $1,175 per DALY averted. Values in yellow represent scenarios where the mean ICER is considered cost-effective using only the threshold of $1,175 per DALY averted and values in red exceed both thresholds. VL: Viral load

Lower background viral suppression on ART: 71%; 2X higher ART dropout: 10% annual dropout; Lower bound intervention effectiveness: 5% increase in viral suppression compared to SOC; Upper bound intervention effectiveness: 15% increase in viral suppression compared to SOC; No reduction in HIV transmission among those on ART w/ VL>1000: Individuals on ART with VL>1000 have same HIV transmissibility as those not on ART; 2X higher reduction in HIV transmission among those on ART w/ VL>1000: Individuals on ART with VL>1000 have 70% reduction in HIV transmissibility compared to those not on ART

Figure 1 and **Table S7** show the impact of varying healthcare costs on ICERs in the baseline scenario. Across clinic volumes, ICERs were most sensitive to changes in proportion of patients receiving ART through DSD, which incurs lower ART program costs than clinic-based ART delivery. Doubling the proportion of patients referred to DSD by the intervention (65% vs. 45%) resulted in cost-saving ICERs for clinic volumes of ≥20 monthly ART initiations. Conversely, assuming no intervention impact on DSD (i.e. 20% of patients referred to DSD in both standard-of-care and intervention), yielded ICERs that were no longer cost-saving and exceeded the $500/DALY averted across all clinics volumes. However, using the threshold of $1,175/DALY averted, the intervention was still cost-effective at clinic volumes of ≥30 monthly ART initiations. Increasing the proportion of patients on second-line ART in the intervention scenario (from 1% to 2% higher than standard-of-care) resulted in higher ICERs while assuming no increase in second-line ART by the intervention lowered the ICERs. Neither scenario altered cost-effectiveness results. Similarly, varying ART costs or discount rate (0-6%) minimally impacted ICERs (**Table S8**). Across all sensitivity analyses, ICERs for clinics with 10 monthly ART initiations exceeded both thresholds **(Table S3)**.

Figure 2 and **Table S9** display the 5-year undiscounted healthcare costs of implementing the POC testing intervention at varying clinic volumes and standard-of-care testing for a population of 175,000 adults. Costs ranged from $40.4-44.0 million depending on scenario, with ART drugs and provision making up the majority of costs (>75%). ART monitoring was projected to cost $6.7 million in the standard-of-care scenario and $7.5 million if the POC intervention was implemented in clinics with 50 ART initiations/month. POC ART monitoring costs increased with clinic volume: the intervention cost $8.1 million at clinics with 30 ART initiations/month and $11 million at clinics with 20 monthly ART initiations. Costs increased

slightly each year, ranging from $7.9-9.0 million depending on scenario. At clinic with 50 monthly ART initiations, the intervention cost approximately $168,000 less than standard-of-care over 5 years. At clinic with 40 ART initiations/month, the intervention cost approximately $54,000 more than standard-of-care, indicating that although ICERs show cost-savings over a 20-year time horizon, the intervention would not save costs in the near-term. Incremental costs compared to SOC increased to $423,000 at clinics with 30 ART initiations/month and rapidly increased with lower clinic volume, exceeding 1.16 million at clinic with 20 ART initiations/month. With a 20-year time horizon, annual costs increase over time **(Figure S4)** but intervention costs relative to standard of care decrease over time for all clinic volumes **(Figure S5)**. At clinics with 30 ART initiations/month, the intervention becomes cheaper than standard-of-care by year 2031.

DISCUSSION:

Our model-based analysis assessed the population-level impact of implementing POC testing for VL, CD4 count, and creatinine with task-shifted HIV care in South Africa. We find that the intervention can reduce HIV transmission and HIV-related mortality and is cost-effective in moderately-sized clinics in South Africa. In clinics with ≥30 ART initiations per month, the intervention fell below $500/DALY averted; results were robust to changes in background viral suppression on ART, treatment dropout, intervention effectiveness, and HIV transmissibility on ART. Using a higher threshold of $1,175/DALY averted, the intervention was considered cost-effective at lower clinic volumes of ≥20 monthly ART initiations, which was robust to most sensitivity analyses. At smaller clinic volumes of 10 monthly ART initiations, ICERs exceeded both thresholds in all but the most optimistic sensitivity analyses.

Cost-effectiveness results were most sensitive to changes in proportion of patients referred to DSD by the intervention, which was the main driver of the finding that the intervention resulted in cost-savings at higher clinic volumes. When assuming POC testing did not increase patient referrals to DSD, ICERs exceeded the conservative threshold for all clinic volumes, although the intervention was still cost-effective using the higher threshold ($1,175/DALY averted) at clinic volumes of ≥30 monthly ART initiations. Our results highlight the importance of decentralized services in increasing efficiency of ART delivery. DSD provides a client-centered alterative to standard clinical care that allows stable patients to obtain ART refills from local pharmacies or community groups at lower frequencies (every 3-6 months) than standard-of-care. This reduces patient time spent traveling and waiting for care while also decongesting busy clinics, reducing healthcare worker burnout, and allowing providers to focus on counseling patients most at risk of treatment failure.[36] A systematic review found DSD can improve patient retention in care.[37] As the number of PLHIV on ART rapidly grow in resource-limited settings, decentralized approaches to ART care including DSD and POC testing are becoming increasingly vital to sustainably delivering high-quality care.

The 5-year budget impact analysis shows that, although cost-effective, implementing POC testing for VL, CD4 count, and creatinine requires substantial upfront investment. While the intervention is cost-saving in clinics with ≥50 monthly ART initiations, POC testing would cost approximately $420,000 more than standard of care over 5 years for clinic volumes of 30 monthly ART initiations and more than $1.16 million more for clinic volumes of 20 patients initiated on ART per month. These costs assume a population size of 175,000 so would increase rapidly with coverage of larger populations. However, annual costs compared to standard-of-care decline over time as clinical benefits of POC testing are realized and HIV infections and deaths

averted result in costs savings to the healthcare system. At clinic volumes of ≥30 monthly ART initiations, the intervention eventually becomes cheaper than standard-of-care within a 20-year time horizon. ART drugs and provision made up the vast majority of the costs; however drug monitoring costs are also considerable.

The higher drug monitoring costs in the intervention scenarios relative to standard-of-care are largely driven by costs of POC creatinine, which is considerably more expensive as a POC test. While the cost of CD4 count testing is also higher when administered as POC, the frequency of CD4 testing is low compared to creatinine: WHO guidelines recommend CD4 monitoring only twice in the first year while creatinine testing is recommended 4 times in the first year and annually thereafter to monitor for declines in kidney function due to tenofovir containing ART regimens.[38] However, there is ongoing debate about the value of universal creatinine testing in ART patients as clinically significant tenofovir-related kidney toxicity is uncommon.[39-41] A cost-effectiveness analysis found that routine monitoring of asymptomatic patients on ART for renal toxicity was expensive and rarely improved clinical care in low-resource settings.[42] Instead, targeted monitoring of patients at high risk of renal decline due to clinical indications (e.g. low body mass index, diabetes, or hypertension) is shown to have similar clinical outcomes and is more cost-effective than routine creatinine testing.[43] In the STREAM trial, POC creatinine testing allowed for faster referral of patients to DSD. If future ART guidelines remove the requirement for creatinine testing before DSD referral while also endorsing targeted instead of routine creatinine monitoring, this intervention would likely become more cost-effective.

Our analysis should be viewed in the context of several limitations. We used clinical effectiveness data from a randomized clinical trial; real-world intervention effectiveness may

vary across clinic settings. Further, STREAM enrolled patients without co-morbidities at 6 months post-ART initiation, but our analysis assumes the intervention is provided at ART initiation to 70% of patients on ART. Since patients are more likely to dropout of care in the first 6 months after initiating ART, it is possible that POC testing with immediate adherence counseling would have a greater impact than our modeled results.[44] Yet, it is also possible the intervention provides the highest benefit to patients on ART for at least 6 months and our results overestimate cost-effectiveness. However, our cost-effectiveness results were robust to changes in intervention effectiveness to the upper and lower bounds of the 95% confidence interval of the STREAM trial. Additionally, the STREAM trial tested a package of interventions including POC testing for VL, CD4 count and creatinine along with task-shifted care to an enrolled nurse, so it is not possible to tease out the clinical impact or cost-effectiveness of different parts of the intervention. However, our intervention package is in line with recent recommendations from a WHO expert consultation, which endorsed streamlined approaches for ART provision in limited resource settings, including task-shifting for clinic visits and diagnostic testing, point-of care testing, and community-based ART refill pick-up for stable clients.[45] A combination of evidence-based interventions will likely need to be implemented simultaneously to support high quality ART delivery in SSA. Finally, cost data were collected at one clinic in an urban region of South Africa yet we model average impact of intervention scale-up nationally in South Africa. Although our results provide insights into overall cost-effectiveness of implementing POC testing with task-shifted care in South Africa, we do not account for regional differences affecting costs. While we find that POC testing is cost-effective for moderate/high volume clinics, geospatial modeling of POC VL scale up in Zambia suggest that some low-volume rural clinics may be cost-efficient locations for POC instrument placement because of high costs of

transporting samples to laboratories due to inadequate road infrastructure, long distances, and cold chain failures. Future studies conducting detailed geospatial analyses, including transport networks, are needed to optimize POC testing placement in South Africa. Additionally, if POC instruments are used for other diseases, such as tuberculosis diagnostics, cost-effectiveness would increase.

Reaching the third 95 of UNAIDS global targets, 95% of individuals on ART virally suppressed in less than 10 years requires the efficient mobilization of limited resources in an era of shrinking donor funding.[46] We find that POC testing for VL, CD4, and creatinine with task-shifted care can avert substantial HIV-related morbidity and is cost-effective in moderate/high volume clinics in South Africa. We utilized a well-established network model and accounted for parameter uncertainty across 250 good-fitting parameter sets. Our results were robust to a range of sensitivity analyses. Our findings are similar to other modeling analyses showing POC diagnostics cost-effectively improve patient clinical outcomes in SSA.[47, 48] As countries strive to scale-up high-quality care to a growing number of patients, POC testing combined with client-centered care including referral of stable clients to DSD, can efficiently improve patient outcomes and reach UNAIDS ambitious treatment targets in SSA.

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DECLARATION OF INTERESTS:

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CONTRIBUTIONS

PKD, NG, and MS conceived of the modeling analysis. MS, AB, and EM parameterized the model. MS ran the analysis and wrote the first draft of the paper. AA provided modeling support. KS conducted the microcosting. JD, SAK, CC, NG, PKD, and LRV assisted with data collection of model inputs from the STREAM trial. All authors critically revised and approved the final version of the manuscript.

DATA SHARING

All data used for model calibration are publicly available and can be found in summary tables in the appendix. EMOD-HIV is open-source and available online: www.idmod.org/idmdoc. The STREAM trial results are published and publicly available.

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Figure 1

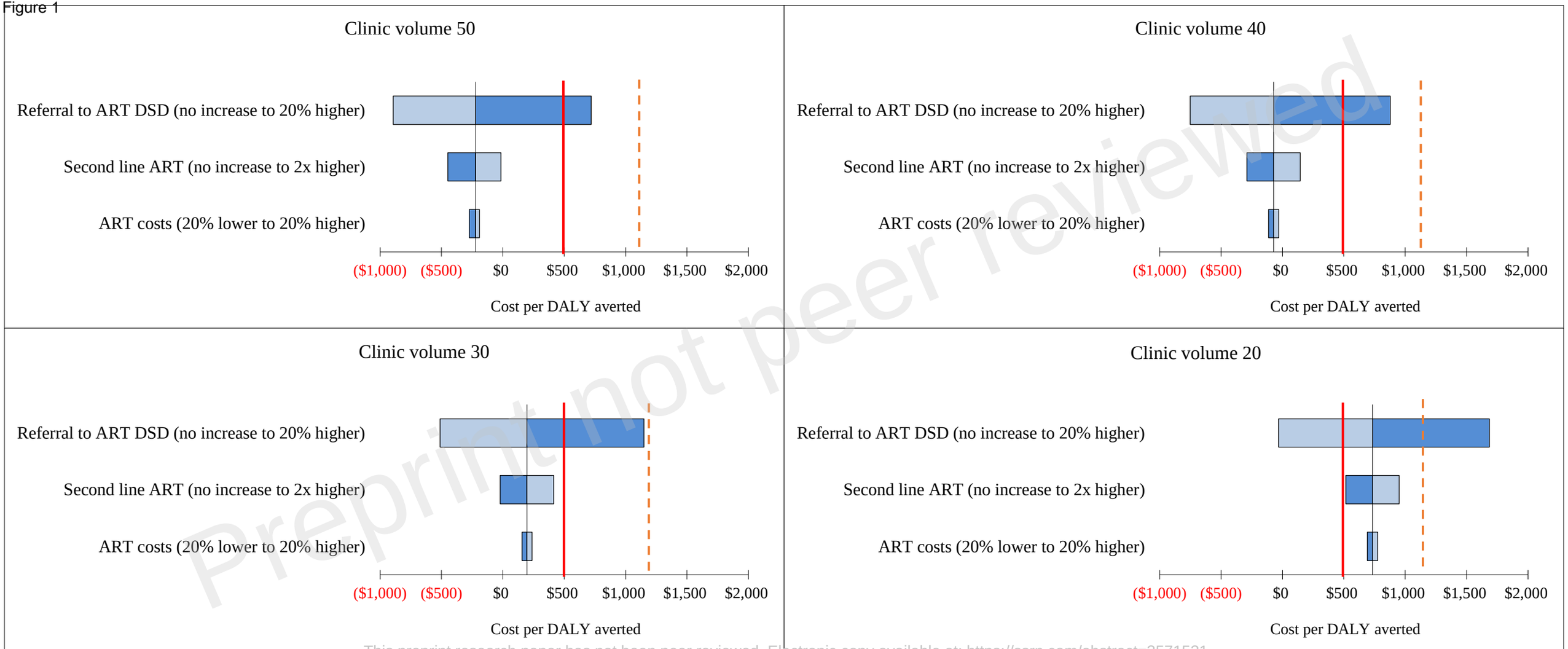
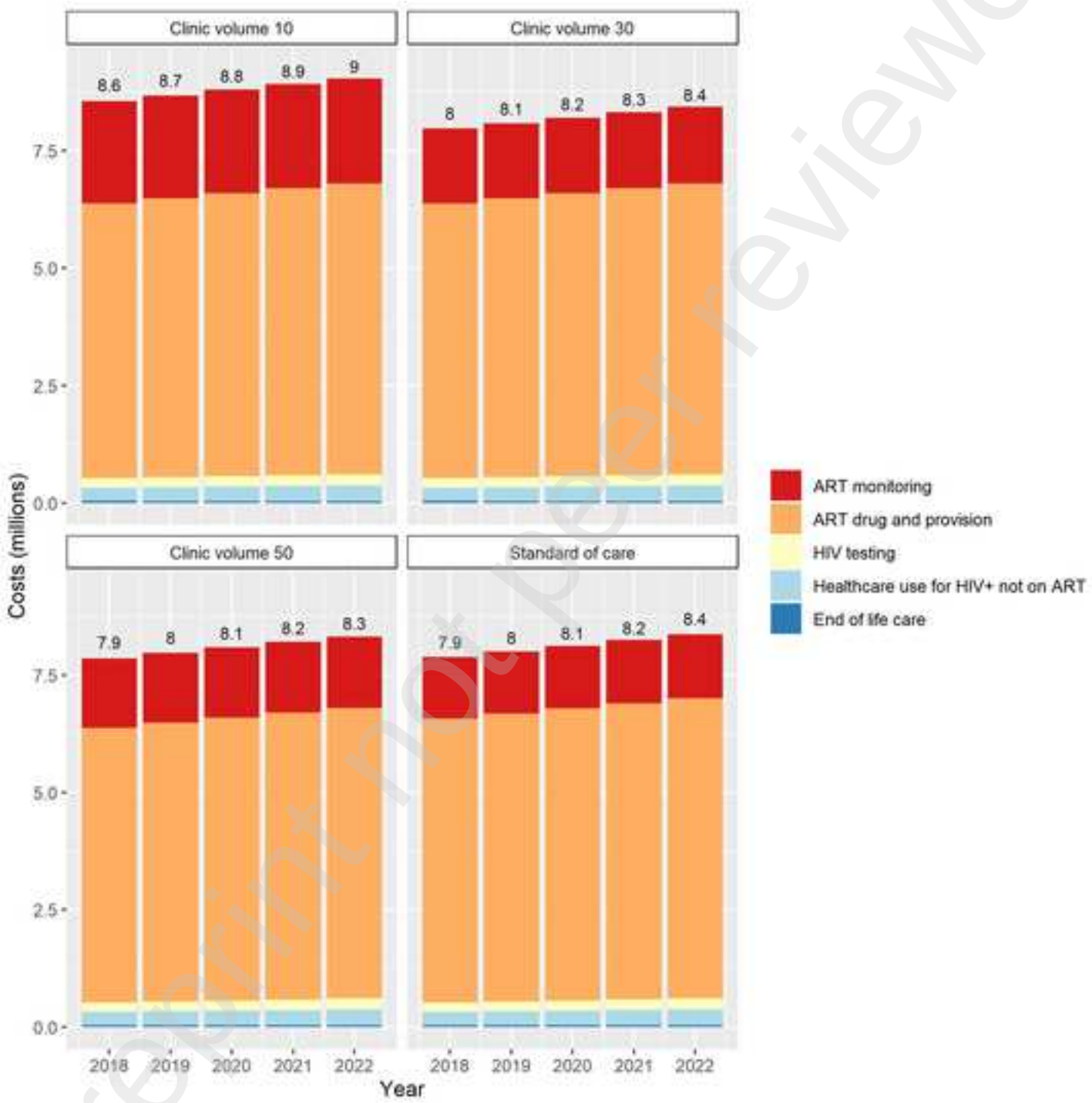


Figure 2



Online Supplemental Appendix

Accompanying the manuscript:

Cost-effectiveness of point-of-care testing with task-shifting for HIV care in South Africa: a modelling study

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Table S1. Model parameters. Select model parameters used to fit the EMOD-HIV transmission model to survey data on prevalence and ART coverage from South Africa. Median and interquartile ranges (IQRs) reported for all dynamic parameters used in the calibration process from 250 best-fitting parameter sets. A full description of all parameters and references available is at: http://idmod.org/docs/hiv/parameter-configuration.html

Parameter	Description	Dynamic	Static value / fitted mean (IQR)	Source
AIDS_Duration_In_Months	The length of time, in months, prior to an AIDS-related death over which the AIDS_Stage_Infectivity_Multiplier is applied	no	9	[1]
AIDS_Stage_Infectivity_Multiplier	Multiplier acting on Base_Infectivity to determine the per-act transmission probability of an individual during AIDS stage	no	4.5	[1]
ART_CD4_at_Initiation_Saturating_Reduction_in_Mortality	The duration from ART enrollment to on-ART HIV-caused death increases with CD4 at ART initiation up to a threshold determined by this parameter value.	no	350	
ART_dropout	Exponentially distributed mean number of days from ART initiation until ART dropout, corresponds to 5% annual dropout.	no	7300	
ART_Link_Max	The right asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time.	yes	0.992 (0.987 - 1)	
ART_Link_Mid	The time of the inflection point in the sigmoid trend of probability of ART linkage (given eligibility) over time.	yes	2005.9 (2005.7 - 2006.2)	
ART_link_Min	The left asymptote for the sigmoid trend of probability of ART linkage (given eligibility) over time.	no	0	
ART_link_Rate	The slope of the inflection point in the sigmoid trend of probability of ART linkage over time. A Rate of 1 sets the slope to a 25% change in probability per year.	no	1	
Base_Infectivity	The probability of transmission when none of the transmission multipliers apply to a coital act (or when all multipliers are set to 1).	yes	0.00144 (0.00138 - 0.00155)	[2]
CD4_At_Death_LogLogistic_Heterogeneity	The inverse shape parameter of a Weibull distribution that represents the at-death CD4 cell count.	no	0.7	
CD4_At_Death_LogLogistic_Scale	The scale parameter of a Weibull distribution hat represents the at-death CD4 cell count.	no	2.96	

CD4_Post_Infection_Weibull_Heterogeneity	The inverse shape parameter of a Weibull distribution that represents the post-acute-infection CD4 cell count.	no	0.2756	
CD4_Post_Infection_Weibull_Scale	The scale parameter of a Weibull distribution that represents the post-acute-infection CD4 cell count.	no	560.43	
Circumcision_Reduced_Acquire	The reduction of susceptibility to HIV by voluntary male medical circumcision (VMMC)	no	0.6	[3-5]
Coital_Act_Rate	Number of coital acts per day for all relationships except commercial ones	no	0.33	
Coital_Act_Rate_Commercial	Number of coital acts per day for commercial relationships	no	0.002739726	
Coital_Dilution_Factor_2_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly two current partners. Represents coital dilution.	no	0.75	
Coital_Dilution_Factor_3_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly three current partners. Represents coital dilution.	no	0.6	
Coital_Dilution_Factor_4_Plus_Partners	The multiplicative reduction in the coital act rate for all relationship types when an individual has exactly three current partners. Represents coital dilution.	no	0.45	
	The maximum asymptote for commercial relationships	no	0.85	
Commercial_Condom_Mid	The year of the inflection point for commercial relationships	no	1999.5	
Commercial_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for commercial relationships	no	0.5	
Commercial_Condom_Rate	The rate proportional to the slope at the inflection point for commercial relationships	no	1	
Commercial_Form_Rate	Exponentially distributed mean number new relationships formed per day for commercial relationships	no	0.15	
Condom_Transmission_Blocking_Probability	The per-act multiplier of the transmission probability when a condom is used	no	0.8	

Days_Between_Symptomatic_And_Death_Weibull_Heterogeneity	The time between the onset of AIDS symptoms and death is sampled from a Weibull distribution; this parameter governs the heterogeneity (inverse shape) of the Weibull.	no	0.5
Days_Between_Symptomatic_And_Death_Weibull_Scale	The time between the onset of AIDS symptoms and death is sampled from a Weibull distribution; this parameter governs the scale of the Weibull.	no	618.34
Delay_Period_Mean	Delay from HIV infection until ART initiation for future ART scale-up scenarios, post 2016 (in days).	no	180
HIV_Adult_Survival_Scale_Parameter_Intercept	Determines the intercept of the scale parameter for the Weibull distribution used to determine HIV survival time. Survival time with untreated HIV infection depends on the age of the individual at the time of infection, and is drawn from a Weibull distribution with shape parameter (see HIV_Adult_Survival_Shape_Parameter) and scale parameter. The scale parameter is allowed to vary linearly with age as follows λ = HIV_Adult_Survival_Scale_Parameter_Intercept + HIV_Adult_Survival_Scale_ Parameter_Slope * Age (in years).	no	21.182
HIV_Adult_Survival_Scale_Parameter_Slope	This parameter determines the slope of the scale parameter for the Weibull distribution used to determine HIV survival time.	no	-0.2717
HIV_Adult_Survival_Shape_Parameter	This parameter determines the shape of the Weibull distribution used to determine age-dependent survival time for individuals infected with HIV.	no	2
HIV_Age_Max_for_Adult_Age_Dependent_Survival	Survival time with untreated HIV infection depends on the age of the individual at the time of infection, and is drawn from a Weibull distribution with shape parameter and scale parameters (See HIV_Adult_Survival_Scale_Parameter_Intercept, HIV_Adult_Survival_Scale_ Parameter_Slope, and HIV_Adult_Survival_Shape_Parameter). Although the scale parameter for survival time declines with age, it cannot become negative. To avoid negative survival times at older ages, this parameter, HIV_Age_Max_for_Adult_Age_Dependent_Survival, determines the age beyond which HIV survival is no longer affected by further aging.	no	50

HIV_Age_Max_for_Child_Survival_Function	The maximum age at which an individual's survival will be fit to the child survival function. If the value of this parameter falls between zero and the age of sexual debut, model results are not sensitive to this parameter as there is no mechanism for children to become infected between infancy and sexual debut.	no	15
HIV_Child_Survival_Rapid_Progressor_Fraction	The proportion of HIV-infected children who are rapid HIV progressors.	no	0.57
HIV_Child_Survival_Rapid_Progressor_Rate	The exponential decay rate, in years, describing the distribution of HIV survival for children who are rapid progressors.	no	1.52
HIV_Child_Survival_Slow_Progressor_Scale	The Weibull scale parameter describing the distribution of HIV survival for children who are slower progressors.	no	16
HIV_Child_Survival_Slow_Progressor_Shape	The Weibull shape parameter describing the distribution of HIV survival for children who are slower progressors.	no	2.7
Informal_Condom_Max	The maximum asymptote for informal relationships	yes	0.355 (0.328 - 0.38)
Informal_Condom_Mid	The year of the inflection point for informal relationships	yes	1999.1 (1997.9 - 2000.2)
Informal_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships	no	0
Informal_Condom_Rate	The rate proportional to the slope at the inflection point for informal relationships		1.947 (1.788 - 2.099)
Informal_Form_Rate	Exponentially distributed mean number new relationships formed per day for informal relationships	yes	0.00096 (0.00083 - 0.00105)
Male_To_Female_Relative_Infectivity_Multiplier_Old	An array of scale factors governing the susceptibility of females relative to males, by age ≥ 25	yes	2.311 (2.187 - 2.43)
Male_To_Female_Relative_Infectivity_Multiplier_Young	An array of scale factors governing the susceptibility of females relative to males, by age < 25	yes	3.755 (2.803 - 4.463)

Marital_Condom_Max	The maximum asymptote for marital relationships	yes	0.213 (0.187 - 0.24)
Marital_Condom_Mid	The year of the inflection point for marital relationships	yes	1995.0 (1994.3 - 1995.7)
Marital_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for marital relationships	no	0
Marital_Condom_Rate	The rate proportional to the slope at the inflection point for marital relationships	yes	3.528 (3.465 - 3.675)
Marital_Form_Rate	Exponentially distributed mean number new relationships formed per day for marital relationships	yes	0.0001 (0.000095 - 0.000111)
Maternal_Infection_Transmission_Probability	The probability of transmission of infection from mother to infant at birth.		0.3
Maternal_Transmission_ART_Multiplier	The maternal transmission multiplier for on-ART mothers.	no	0.03334
preART_Link_Max	The right asymptote for the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	0.870 (0.828 - 0.937)
preART_Link_Mid	The time of the inflection point in the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	1999.1 (1998 - 2000.1)
preART_link_Min	The left asymptote for the sigmoid trend of probability of preART linkage (given eligibility) over time.	yes	0.621 (0.6 - 0.653)
preART_link_Rate	The slope of the inflection point in the sigmoid trend of probability of preART linkage over time. A Rate of 1 sets the slope to a 25% change in probability per year.	no	1
Proportion_Low_Risk	Proportion of the initial population that is low risk	yes	0.497 (0.446 - 0.546)
Sexual_Debut_Age_Female_Weibull_Heterogeneity	The inverse shape of the Weibull distribution for female debut age.	yes	0.052 (0.04 - 0.065)
Sexual_Debut_Age_Female_Weibull_Scale	The scale term of the Weibull distribution for female debut age.	yes	16.401 (16.219 - 16.56)
Sexual_Debut_Age_Male_Weibull_Heterogeneity	The inverse shape of the Weibull distribution for male debut age.	yes	0.037 (0.026 - 0.048)
Sexual_Debut_Age_Male_Weibull_Scale	The scale term of the Weibull distribution for male debut age.	yes	16.623 (16.32 - 16.938)

Sexual_Debut_Age_Min	The minimum age at which individuals become eligible to form sexual relationships.	no	13
Transitory_Condom_Max	The maximum asymptote for transitory relationships	yes	0.584 (0.555 - 0.624)
Transitory_Condom_Mid	The year of the inflection point for transitory relationships	yes	2007.2 (2006.4 - 2007.8)
Transitory_Condom_Min	The minimum asymptote of the probability of condom use per coital act for informal relationships for transitory relationships	no	0
Transitory_Condom_Rate	The rate proportional to the slope at the inflection point for transitory relationships	yes	1.975 (1.839 - 2.038)
Transitory_Form_Rate	Exponentially distributed mean number new relationships formed per day for transitory relationships	yes	0.001291 (0.001219 - 0.001386)
Transitory_Weibull_Heterogeneity	Inverse of the Weibull shape (1/kappa) parameter of relationship duration in years for transitory relationships	no	0.833333333
Transitory_Weibull_Scale	Weibull scale parameter of relationship duration in years for transitory relationships.	no	0.956774771

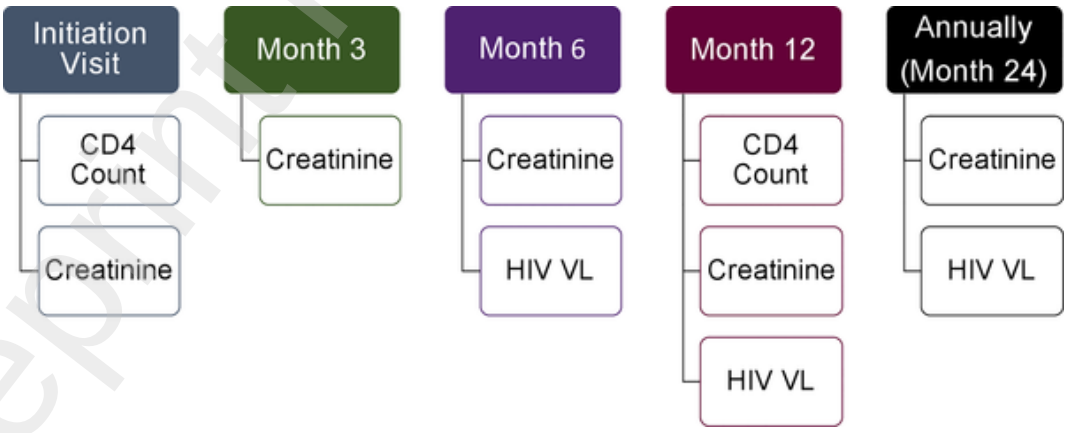
Cost estimates

In the standard of care scenario, we assumed 3% of patients on ART were on second line treatment and 20% of those on ART were participating in Differentiated Service Delivery (DSD) based on the literature for South Africa.[6, 7] Therefore, ART costs were assumed to be weighted average accounting for individuals on second line treatment as well as those participating in DSD. In the intervention scenario, we assumed that 4% of patients on ART were on second line treatment in the and 45% of patients on ART were participating in DSD for ART pick-up at local pharmacies, based on the results from the STREAM clinical trial. Cost estimates of point-of-care monitoring tests were obtained through a detailed microcosting of the STREAM trial from the payer perspective.[8] We conducted time-and-motion observations of sample collection and processing to estimate staff time costs. Expense reports were utilized to estimate consumables, POC instrument and maintenance costs. Capital costs were annualized assuming 5-years of useful life with 3% discounting.[9] Public laboratory tests were obtained from the South African National Health Laboratory Service (NHLS) price lists and costs of nurse time and consumables were added based on the STREAM microcosting.

Table S2. Utility weights for estimating disability-adjusted life-years averted

Health State	DALY Weight	Reference
HIV-negative	0	Salomon *et al.*[41]
HIV-positive CD4>350	0.078	
HIV-positive CD4 200-350	0.274	
HIV-positive CD4<200	0.582	
HIV-positive on ART	0.078	
Dead	1	

Figure S1: Flowchart of WHO monitoring guidelines for patients on ART



Impact of viral suppression on excess mortality among HIV-infected adults on ART

In the model, mortality risk among people living with HIV (PLHIV) on antiretroviral therapy (ART) is dependent on viral load (VL), dichotomized into categories of less than or greater than 1,000 viral copies/mL. To model VL-dependent mortality among PLHIV on ART, we assume that the overall distribution of mortality risk is a weighted average of the VL stratum-specific distributions of mortality risk as follows:

$$\frac{k_t}{\lambda_t}\left(\frac{x}{\lambda_t}\right)^{\lambda_t-1} e^{-\left(\frac{x}{\lambda_t}\right)^{k_t}} = p_s * \left(\frac{k_s}{\lambda_s}\left(\frac{x}{\lambda_s}\right)^{k_s-1} e^{-\left(\frac{x}{\lambda_s}\right)^{k_s}}\right) + p_{ns} * HR_{ns} * \left(\frac{k_s}{\lambda_s}\left(\frac{x}{\lambda_s}\right)^{k_s-1} e^{-\left(\frac{x}{\lambda_s}\right)^{k_s}}\right)$$

where k_t and λ_t are the shape and scale parameters, respectively, of the overall Weibull-distributed mortality risk; k_s and λ_s are the shape and scale parameters, respectively, of Weibull-distributed mortality risk among individuals on ART with <1,000 viral copies/mL; p_s and p_{ns} are the proportion of individuals with less than and greater than 1,000 viral copies/mL, respectively; HR_{ns} is the hazard ratio of death among individuals on ART with viral load great than 1,000 viral copies/mL relative to those with less than 1,000 viral copies/mL; and x indicates time since ART initiation.

As described in our previous modeling work, values for k_t and λ_t are estimated based on observed survival from IeDEA cohorts of individuals initiating ART in 2004-2007 in Côte d'Ivoire, Malawi, and South Africa.[10] The weights applied to the VL strata, p_s and p_{ns}, are based on 2012 estimates of percentage of persons virally suppressed on ART in South Africa, 0.754 and 0.246, respectively.[11] Consistent with other models of HIV transmission dynamics,[12] we assume that this proportion increases over time and stabilizes at 83% by 2018, although we vary this assumption in sensitivity analyses. Based on clinical trial data, we assume that individuals on ART with VL greater than 1,000 viral copies/mL experience a 1.96-fold increase in the risk of death at any given time point.[13]

Substituting these values into the corresponding variables, our equation becomes:

$$\frac{0.34}{123.83}\left(\frac{x}{123.83}\right)^{123.83-1} e^{-\left(\frac{x}{123.83}\right)^{0.34}} = 0.754 * \left(\frac{k_s}{\lambda_s}\left(\frac{x}{\lambda_s}\right)^{k_s-1} e^{-\left(\frac{x}{\lambda_s}\right)^{k_s}}\right) + 0.246 * 1.96 * \left(\frac{k_s}{\lambda_s}\left(\frac{x}{\lambda_s}\right)^{k_s-1} e^{-\left(\frac{x}{\lambda_s}\right)^{k_s}}\right)$$

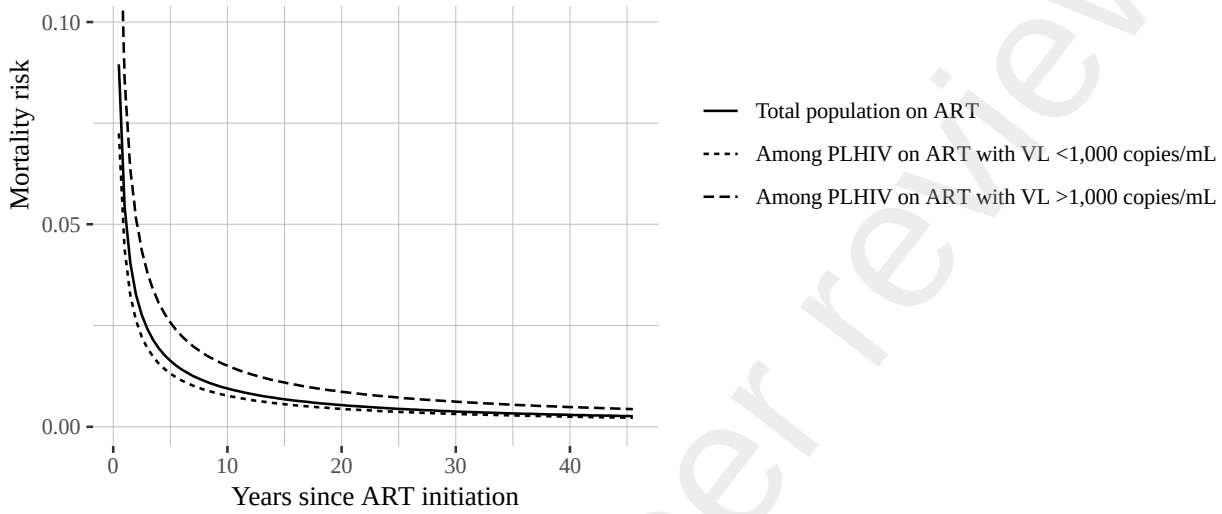
Which is then rearranged as:

$$\frac{\frac{0.34}{123.83}\left(\frac{x}{123.83}\right)^{123.83-1} e^{-\left(\frac{x}{123.83}\right)^{0.34}}}{1.23616} = \frac{k_s}{\lambda_s}\left(\frac{x}{\lambda_s}\right)^{k_s-1} e^{-\left(\frac{x}{\lambda_s}\right)^{k_s}}$$

We assume ranges of possible values for λ_s of [100, 400] and for k_s of [0.01, 0.50], and identify the combination of λ_s and k_s parameter values that minimizes the inequality in equation above, as evaluated by the difference in their squared errors. The resulting parameter values that characterize Weibull-distributed mortality risk among PLHIV on ART with viral load less than 1,000 viral copies/mL are λ_s=302 and k_s

=0.32. This Weibull distribution is multiplied by 1.96 at all time points to infer the mortality risk among PLHIV on ART with viral load greater than 1,000 viral copies/mL (Figure S2).

Figure S2. Weibull distribution of mortality risk among the total population of individuals on ART and stratified by viral load less than/greater than 1,000 viral copies/mL



Transmission risk by viral load among individuals on antiretroviral therapy

We assume that individuals on ART have a reduced risk of transmission, which depends on their VL (stratified as less than or greater than 1,000 viral copies/mL). Based on clinical data, we estimate that individuals on ART with VL <1,000 viral copies/mL experience a reduction in transmission risk of 96%.[14] There is a lack of empiric data on HIV transmission risk among persons on ART who are not virally suppressed (VL >1,000 viral copies/mL). Studies have estimated the relative risk of transmission per $\log_{10}$ increase in viral load is 2.89 among individuals not on ART and 1.88 among individuals on ART (after controlling for relevant covariates).[14, 15] Therefore we assumed the relative reduction in HIV transmission for persons on ART with VL >1,000 viral copies/mL is 1-(1.88/2.89) = 35%. However, to due the uncertainty of this parameter, we varied our assumption in sensitivity analyses from 0-70%.

Table S3: HIV prevalence data by age and sex from population-based surveys for model calibration[¥]

Sex	Age group	Year				
		2002	2005	2008	2012	2017
Men	15-19	0.040	0.032	0.025	0.007	0.047
	20-24	0.080	0.060	0.051	0.051	0.048
	25-29	0.220	0.121	0.157	0.173	0.124
	30-34	0.240	0.233	0.258	0.256	0.184
	35-39	0.180	0.233	0.185	0.288	0.238
	40-44	0.120	0.175	0.192	0.158	0.224
	45-49	0.120	0.103	0.084	0.134	0.248
	50-54	0.050	0.142	0.104	0.155	0.202
	55-59	0.070	0.064	0.062	0.055	0.148
	15-49	0.128	0.117	0.116	0.145	0.148
Women	15-19	0.070	0.094	0.067	0.056	0.058
	20-24	0.170	0.239	0.211	0.174	0.156
	25-29	0.320	0.333	0.327	0.284	0.275
	30-34	0.240	0.260	0.291	0.360	0.347
	35-39	0.140	0.193	0.248	0.316	0.394
	40-44	0.190	0.124	0.163	0.280	0.359
	45-49	0.110	0.087	0.141	0.197	0.303
	50-54	0.080	0.075	0.102	0.148	0.222
	55-59	0.070	0.030	0.077	0.097	0.176
	15-49	0.177	0.202	0.213	0.232	0.263

[¥]Sources: South African National HIV Prevalence, Incidence and Behaviour Surveys (2002, 2005, 2008, 2012 and 2017) from the Human Sciences Research Council (HSRC)[16-19]

Table S4: Number of people on ART by sex (ages 15-49 years) [¥]

Year	Male	Female
2001	2713	3543
2002	5768	7586
2003	9321	12313
2004	17717	24423
2005	34874	59240
2006	66629	123308
2007	118977	228753
2008	186564	367389
2009	277931	548206
2010	402000	781477
2011	558131	1095411
2012	713294	1415016
2013	876749	1732515
2014	1013499	2003014
2015	1130063	2239669
2016	1238815	2518238
2017	1403702	2998170

[¥]Source: South Africa Department of Health Surveys[20]

Table S5: HIV incidence by age and sex[§]

Year	Sex	Age group	HIV incidence	95% LB	95% UB
2012	Male	15 - 24	0.0055	0.0045	0.0065
2012	Female	15 - 24	0.0254	0.0204	0.0304
2012	Male	15 - 49	0.0121	0.0097	0.0145
2012	Female	15 - 49	0.0228	0.0184	0.0274
2017	Male	15 - 24	0.0049	0.0027	0.0071
2017	Female	15 - 24	0.0151	0.0131	0.0171
2017	Male	15 - 49	0.0069	0.006	0.0076
2017	Female	15 - 49	0.0093	0.0071	0.0111

[§]Source: Human Sciences Research Council (HSRC) 2012 and 2018 Surveys[16, 17]

Table S6: Population of South Africa by age and sex¥

Sex	Age group	Year				
		2002	2005	2008	2012	2017
Men	0 - 4	2634839	2651819	2692300	2784372	2886299
	5 - 9	2559246	2570683	2592577	2644720	2767111
	10 - 14	2582620	2565499	2557928	2578751	2636981
	15 - 19	2546968	2596517	2584945	2572032	2587023
	20 - 24	2348165	2488613	2572307	2606447	2594656
	25 - 29	2069939	2215800	2362377	2530034	2612453
	30 - 34	1759391	1899279	2018461	2227862	2488823
	35 - 39	1488894	1568198	1664587	1845019	2131687
	40 - 44	1270053	1324166	1367150	1493652	1731088
	45 - 49	1077752	1122009	1159644	1234887	1398602
	50 - 54	831061	925655	973184	1038560	1147992
	55 - 59	636945	677128	760379	856728	947123
Women	0 - 4	2587465	2602664	2640997	2729586	2825703
	5 - 9	2523770	2535299	2555462	2604517	2719700
	10 - 14	2557891	2533039	2526253	2545219	2603685
	15 - 19	2527828	2568409	2552976	2535920	2555420
	20 - 24	2323512	2451570	2523985	2560705	2550570
	25 - 29	2064262	2167428	2282514	2447992	2550351
	30 - 34	1807453	1906808	1967958	2123170	2394266
	35 - 39	1577255	1648612	1717873	1821711	2039776
	40 - 44	1370835	1434647	1491937	1594914	1745050
	45 - 49	1184477	1243314	1302936	1396666	1541175
	50 - 54	924873	1054059	1124243	1214556	1348848
	55 - 59	727478	783876	898804	1035986	1160340

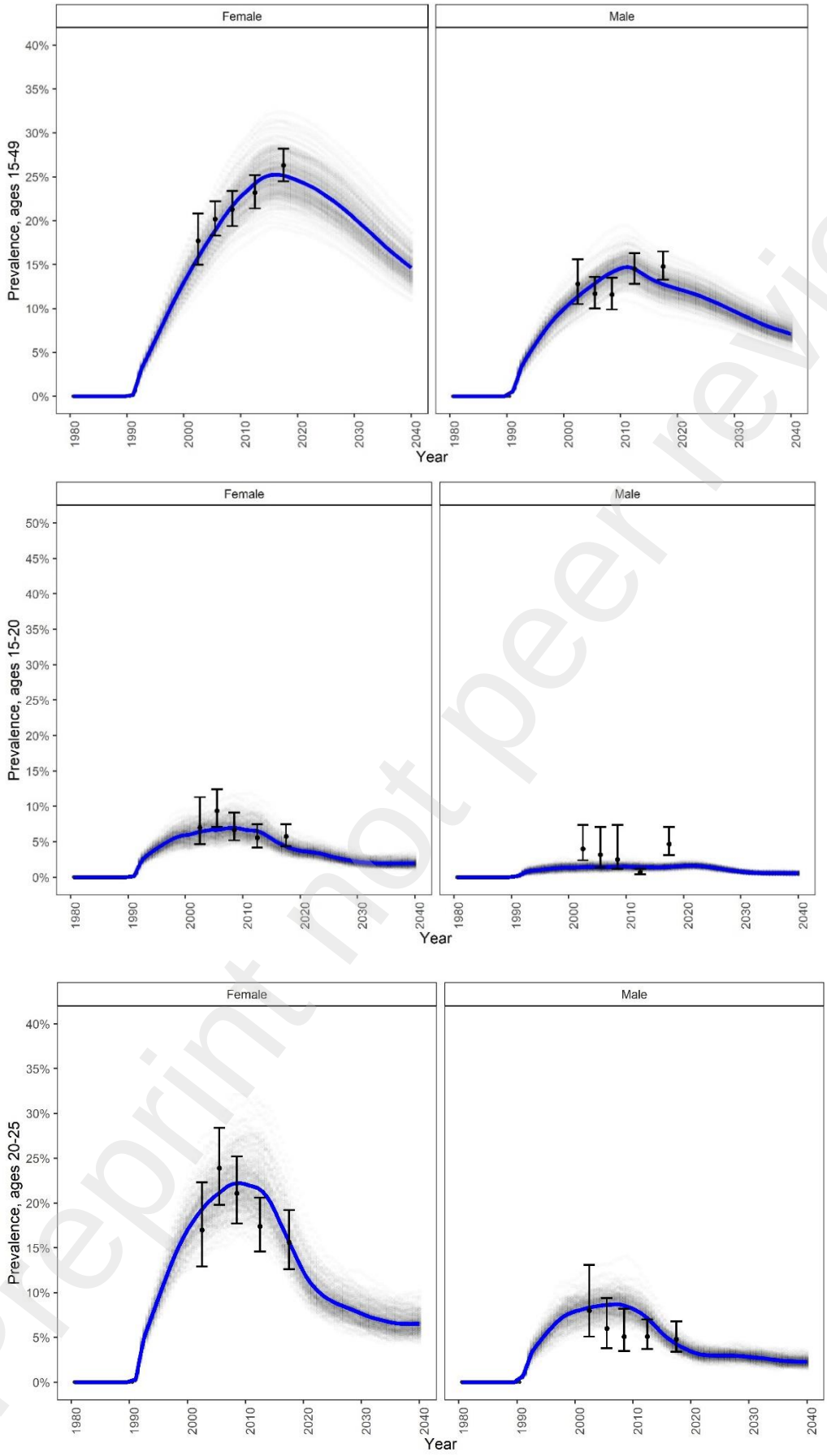
¥Source: United Nations Population Database[21]

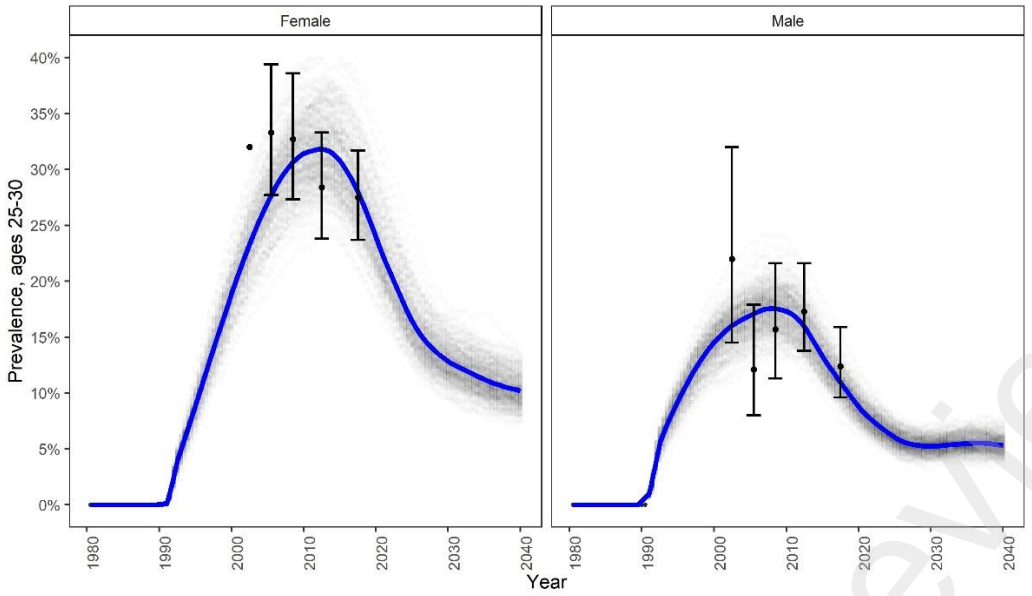
Table S7: Number of voluntary medical male circumcisions conducted in South Africa by age group*

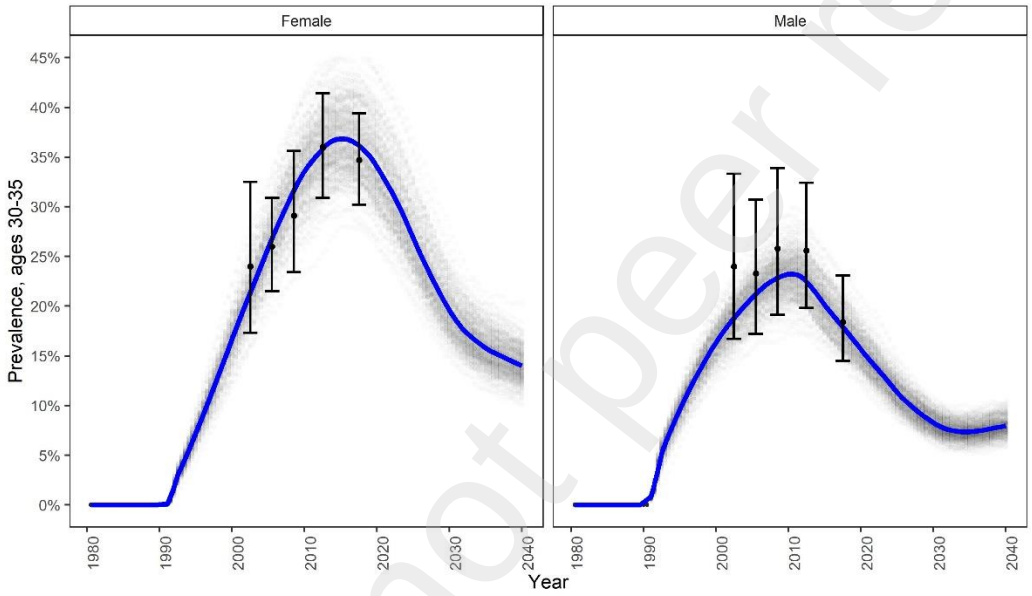
Year	Age Group					
	10 - 14	15 - 19	20 - 24	25 - 34	35 - 49	≥50
2010	55,431	30,552	15,856	18,047	7,864	1,160
2011	137,648	75,866	39,374	44,816	19,527	2,881
2012	175,060	96,487	50,075	56,996	24,834	3,664
2013	156,496	86,255	44,765	50,952	22,201	3,276
2014	199,750	110,095	57,138	65,035	28,337	4,181
2015	199,535	109,976	57,076	64,965	28,306	4,176
2016	165,672	91,312	47,390	53,940	23,502	3,468
2017	203,960	112,415	58,342	66,406	28,934	4,269
2018	279,500	154,050	79,950	91,000	39,650	5,850
2019	258,000	142,200	73,800	84,000	36,600	5,400
2020	236,500	130,350	67,650	77,000	33,550	4,950
2021	215,000	118,500	61,500	70,000	30,500	4,500
2022 onwards	43,000	23,700	12,300	14,000	6,100	900

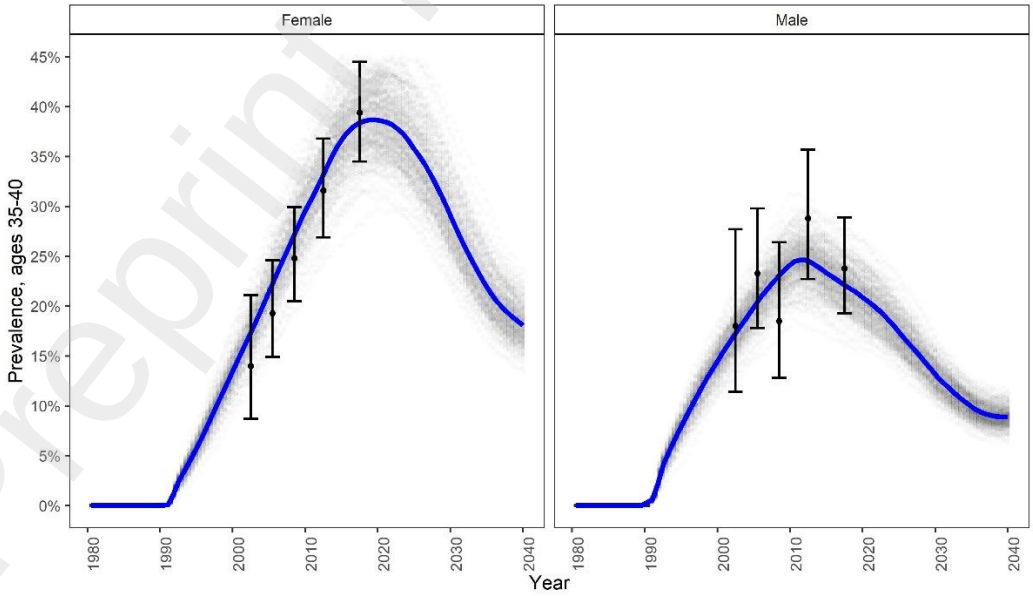
*Source: South Africa Department of Health (unpublished data) and South Africa National Strategic Plan for HIV, TB, and STIs 2017-2022[22]

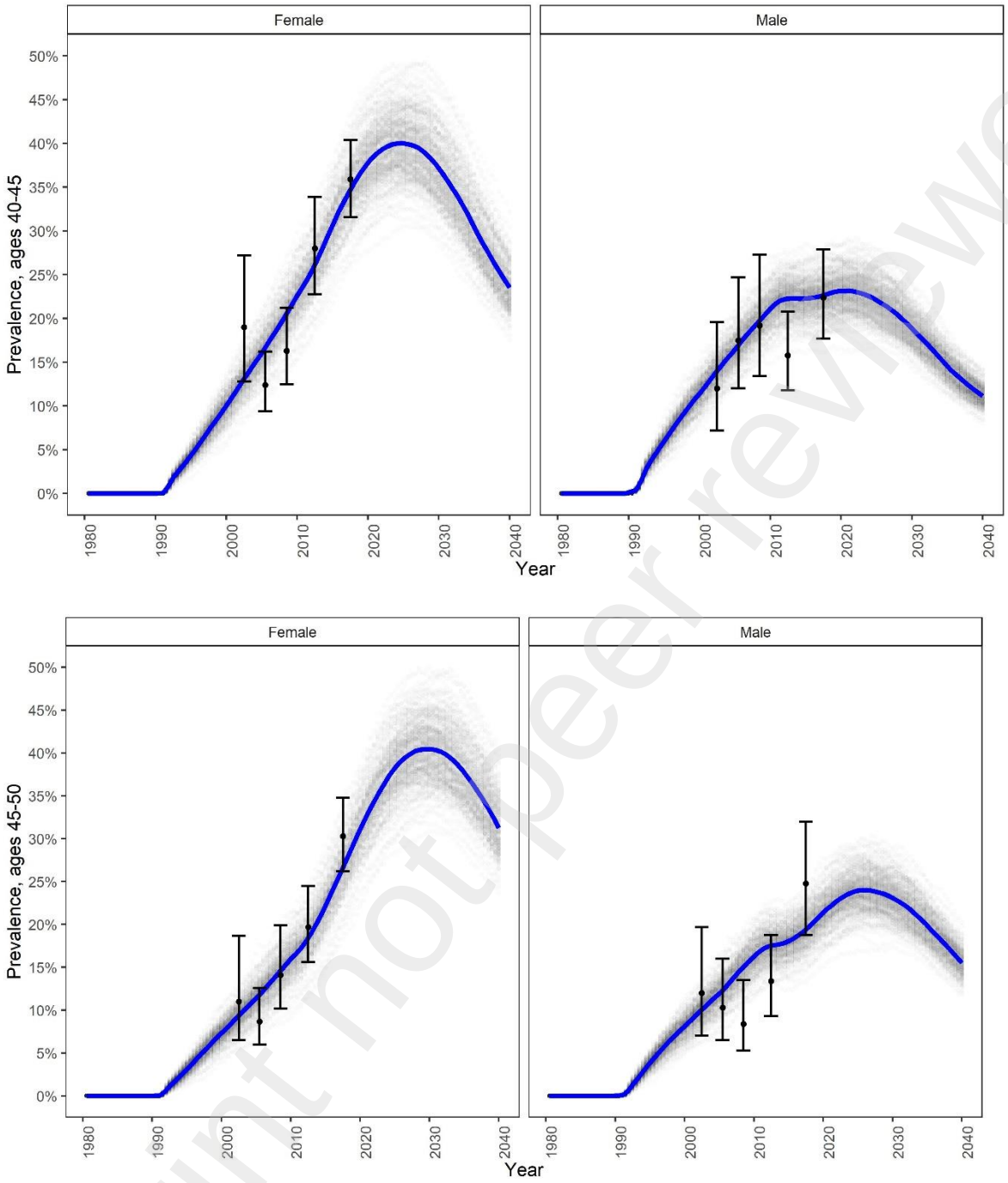
Figure S3: Calibration: Model fit to age-specific and overall prevalence from population-based surveys by sex.*





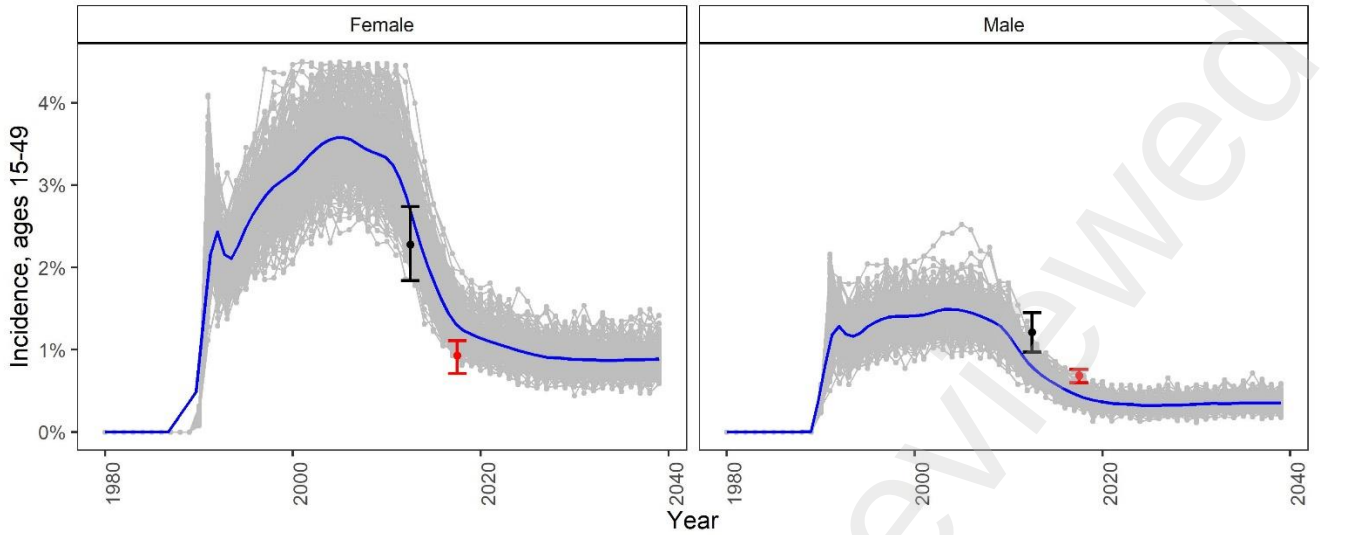


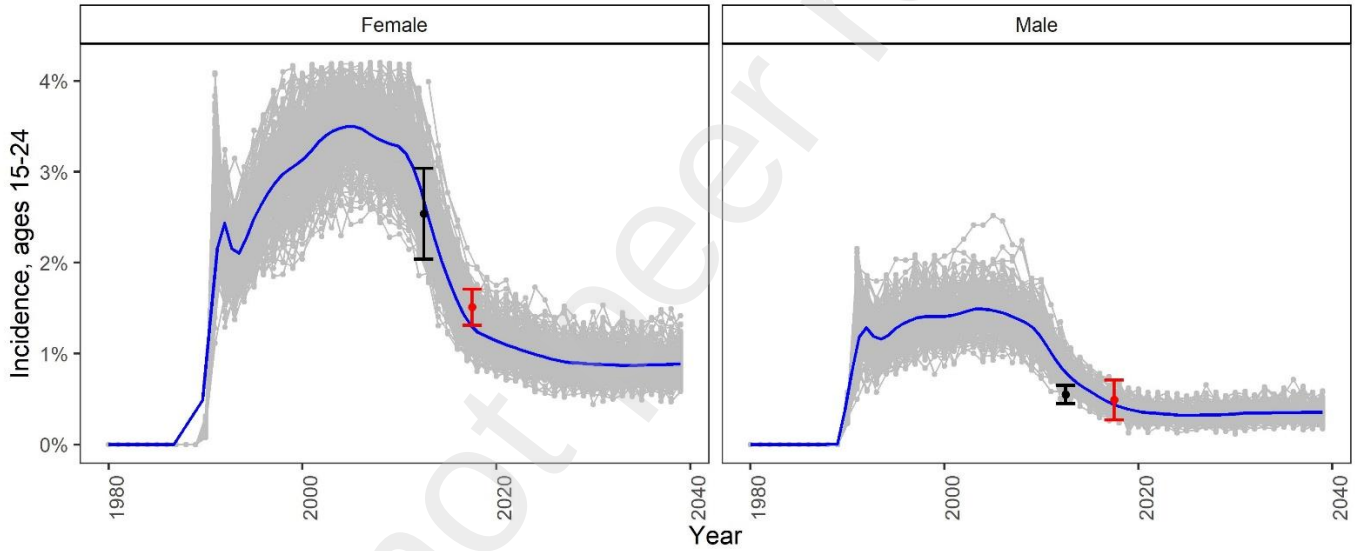


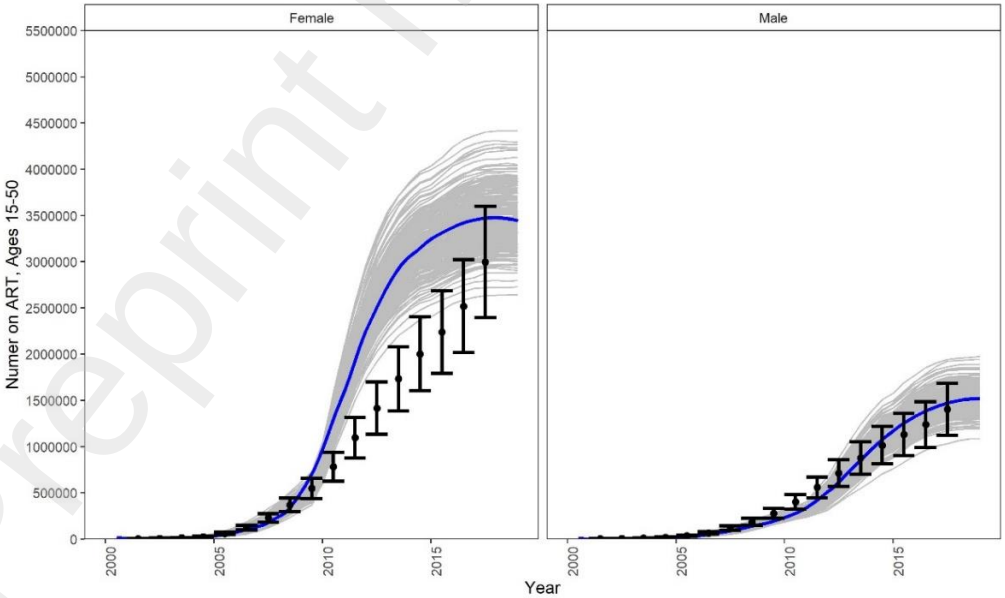


* Points and error bars represent empiric data. 250 good-fitting parameter sets are shown in gray and loess average is shown in blue.

Figure S4: Model fit to HIV incidence and number of person on ART by sex.*







* Points and error bars represent empiric data. 250 good-fitting parameter sets are shown in gray and loess average is shown in blue.

Table S8: Sensitivity analysis[§]

	Baseline	No increase in referral to ART DSD	20% higher referral to ART DSD	2X higher switching to 2nd line ART in intervention	No increase in switching to 2nd line ART in intervention	20% higher ART costs	20% lower ART costs
Cost-effectiveness ($ per DALY averted)							
Clinic volume: 50	-239 (-602, -96)	719 (90, 2,526)	-894 (-2768, -268)	-15 (-95, 179)	-449 (-1262, -149)	-191 (-470, -81)	-274 (-719, -102)
% under $500 threshold	100%	72%	100%	97%	100%	100%	100%
Clinic volume: 40	-72 (-176, 26)	879 (125, 3,034)	-751 (-2277, -237)	145 (-38, 694)	-289 (-765, -108)	-30 (-123, 148)	-113 (-257, -39)
% under $500 threshold	100%	68%	100%	94%	100%	97%	100%
Clinic volume: 30	197 (-27, 863)	1,149 (184, 3,886)	-511 (-1458, -177)	415 (23, 1,559)	-21 (-102, 160)	238 (-25, 1,011)	156 (-30, 719)
% under $500 threshold	93%	56%	100%	84%	97%	91%	93%
Clinic volume: 20	734 (93, 2,569)	1,686 (296, 5,585)	-32 (-110. 122)	951 (140, 3,255)	517 (48, 1879)	775 (96, 2,721)	692 (90, 2,413)
% under $500 threshold	72%	36%	97%	64%	80%	71%	73%
Clinic volume: 10	2,348 (436, 7,681)	3,300 (635, 10,733)	1,404 (276, 5,069)	2,564 (481, 8,375)	2130 (389, 6984)	2,389 (439, 7,828)	2,306 (432, 7,530)
% under $500 threshold	9%	11%	34%	8%	21%	16%	18%

[§]Values in parenthesis represent 90% model variability across 250 simulations. Values in green represent scenarios where the mean ICER is considered cost-effective at both thresholds of $500 and $1,175 per DALY averted. Values in yellow represent scenarios where the mean ICER is considered cost-effective using only the threshold of $1,175 per DALY averted and values in red exceed both thresholds.

Table S9: Sensitivity analysis cont'd[§]

	Baseline	0% discount rate	6% discount rate
Cost-effectiveness ($ per DALY averted)			
Clinic volume: 50	-239 (-602, -96)	-192 (-457, -93)	-250 (-659, -96)
% under $500 threshold	100%	100%	100%
Clinic volume: 40	-72 (-176, 26)	-80 (-169, -9)	-60 (-169, 32)
% under $500 threshold	100%	100%	100%
Clinic volume: 30	197 (-27, 863)	102 (-35, 470)	246 (-19, 1002)
% under $500 threshold	93%	90%	91%
Clinic volume: 20	734 (93, 2,569)	663 (74, 1766)	858 (122, 3102)
% under $500 threshold	72%	78%	64%
Clinic volume: 10	2,348 (436, 7,681)	2,050 (377, 5240)	2695 (502, 9408)
% under $500 threshold	9%	10%	5%

[§]Values in parenthesis represent 90% model variability across 250 simulations. Values in green represent scenarios where the mean ICER is considered cost-effective at both thresholds of $500 and $1,175 per DALY averted. Values in yellow represent scenarios where the mean ICER is considered cost-effective using only the threshold of $1,175 per DALY averted and values in red exceed both thresholds.

Table S10: 5-year budget impact analysis (2018 USD)[¥]

Cost category	Standard of care	Clinic volume 50	Clinic volume 40	Clinic volume 30	Clinic volume 20	Clinic volume 10
ART monitoring	6,664,494	7,471,136	7,692,736	8,062,032	8,802,224	11,025,557
ART drugs and provision	31,075,279	30,107,263	30,107,263	30,107,263	30,107,263	30,107,263
HIV testing	1,093,583	1,093,451	1,093,451	1,093,451	1,093,451	1,093,451
Health-care use for HIV+ not in care	1,548,242	1,547,030	1,547,030	1,547,030	1,547,030	1,547,030
End of life care	209,894	204,547	204,547	204,547	204,547	204,547
Total	**40,591,492**	**40,423,428**	**40,645,027**	**41,014,323**	**41,754,515**	**43,977,849**
Cost difference compared to SOC	**-**	**(168,064)**	**53,535**	**422,831**	**1,163,023**	**3,386,356**

[¥]SOC: Standard of care

Figure S4: 20-year budget impact analysis: Incremental costs by year of POC intervention and standard of care

Figure S5: 20-year cost pressure analysis of intervention incremental costs compared to standard-of-care

¥Dashed green line indicates cost of intervention is the same as standard of care

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