Can the Heterosexual HIV Epidemic be Eliminated in South Africa Using Combination Prevention? A Modeling Analysis

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A modeling analysis

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Abbreviations:

AIDS, acquired immune deficiency syndrome

ART, antiretroviral therapy

CEPAC-I, Cost Effectiveness of Preventing AIDS Complications International

CSW, commercial sex workers

HIV, human immunodeficiency virus

HIV-CDM, HIV Calibrated Dynamic Model

LTFU, loss to follow up

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Abstract

Little is known about how combining efficacious HIV prevention interventions could lead to HIV elimination. We used an agent-based simulation model, the HIV Calibrated Dynamic Model (HIV-CDM), to assess the potential for HIV elimination in South Africa. We examined several scenarios (from continuation of current status quo to perfect targets) with differing combinations of male condoms, adult male circumcision, HIV testing, and early antiretroviral therapy (ART). We varied parameters including: proportion of adult males circumcised, frequency of condom use in sex acts, HIV test acceptance, linkage to care, ART initiation criteria, ART suppression rates, and loss to follow up. Maintaining current levels of combination prevention will lead to increasing HIV incidence and prevalence while the perfect combination scenario is projected to eliminate HIV on a 50-year time scale from 2013 to 2063. Perfecting testing and treatment, without changing condom use or circumcision rates, resulted in 89% incidence reduction but not elimination. Universal adult male circumcision alone resulted in a 21% incidence reduction within 20 years. Substantial decreases in HIV incidence are possible from sufficient uptake of both primary prevention and ART, but with continuation of the status quo, HIV elimination in South Africa is unlikely within a 50-year time scale.

Key Words: agent-based models, HIV, mathematical modeling, South Africa

Researchers and public health officials are cautiously optimistic that the interventions needed to control and potentially eliminate HIV have been identified, but these interventions are inadequately and ineffectively used in many populations. The number of available interventions to curb horizontal HIV transmission has increased as successful trials have proven the efficacy of oral pre-exposure prophylaxis (1-4), treatment as prevention (5), and vaginal microbicides (6). Primary prevention methods, such as condoms (7) and adult male circumcision (8-11), can reduce transmission risk in the absence of antiretroviral treatment. Trials attempting to demonstrate the possibility of control and elimination of HIV in large populations are currently being conducted in Sub-Saharan Africa by scaling up combinations of independently successful HIV intervention programs (12-15).

Along with these trials, mathematical models have been developed to simulate strategies to achieve elimination, defined here as a reduction of HIV incidence to less than one infection per 100,000 person-years (16, 17). Two main types of mathematical models have been used to model HIV transmission: compartmental models track the progress of groups of individuals grouped by particular characteristics (often infection/disease stage) (18) and agent-based models simulate individuals and include individual-level behavior and/or disease progression (19, 20). Agent-based models are especially useful when there is a great deal of heterogeneity and complexity in behavior and biology as observed in HIV epidemics (see (21) for more detail) (22-24).

Several mathematical models have been developed to address the potential for HIV elimination using treatment as prevention and have come to a variety of conclusions about its timeline and feasibility (25-33). While differences in model parameterization and structure have little influence on short term projections (32, 33), some modelers have reported that longer-term elimination is possible even with imperfect testing and treatment interventions (25, 32). Few have studied the change in incidence and the potential for elimination when combinations of non-treatment focused programs, such as condom and circumcision campaigns, are implemented with existing treatment expansion strategies. In light of

UNAIDS's recent fast-track guidelines, which were motivated by mathematical models, it is important to examine progress towards elimination through multiple methods (34). Using the HIV Calibrated Dynamic Model (HIV-CDM) (35), we perform agent-based simulations to estimate the treatment as prevention conditions, alongside non-treatment focused programs, that could lead to HIV elimination and estimate the timeline for this possible elimination.

METHODS

HIV Calibrated Dynamic Model (HIV-CDM) Overview

The HIV-CDM is an agent-based HIV transmission model that has been calibrated to South African prevalence and sexual behavior data from 1990-2002 using a Bayesian melding-like procedure (35). Briefly, the HIV-CDM is linked to the Cost Effectiveness of Preventing AIDS Complications International (CEPAC-I) model (36-39) allowing the HIV-CDM to incorporate detailed disease progression and sexual behavior parameters when evaluating HIV transmission dynamics. HIV-RNA is stochastically assigned by CEPAC-I and, in the absence of treatment, determines the monthly decline in CD4 count, which in turn leads to increased risks of opportunistic infections and HIV-related mortality (40, 41). Individuals receiving antiretroviral therapy (ART) have reductions in their HIV-RNA, which in turn reduces their HIV transmission potential. The HIV-CDM allows individuals to form up to four types of heterosexual partnerships (each with a particular partnership duration and number of sex acts per month) concurrently, with varying partnership acquisition rates. Individuals of both sexes can be either low- or high-risk, forming partnerships at differing rates by the use of a high-risk multiplier. A small proportion of females are commercial sex workers (CSW), for whom all partnerships are assumed to be one-time transactional.

The sexual mixing algorithm is male-driven; women are chosen for partnerships based on a male's preferred age and risk group. The model tracks HIV transmission on a per-act basis between discordant partners. The force of infection is dependent on the infected partners' HIV-RNA and stage of HIV

infection (acute, chronic or late-stage), condom use, and circumcision status of the male partner. Acute infection is defined as the first three months after infection; chronic infection follows and continues until the individual's CD4 count drops below 50/mm^3 (late-stage infection). Each month, for those infected, HIV-RNA, CD4 count, case identification, in-care status, ART status, and opportunistic infections are updated from CEPAC-I. Individuals die in the model either due to HIV/AIDS or from non-HIV related causes (35).

The HIV-CDM was developed and coded in C++. Each model run is initiated with a total population size of 100,000 for a 50-year initialization period and then seeded with 6 HIV cases distributed evenly among high-risk individuals of both sexes and CSW. Random number generation was performed with a fixed seed in order to reproduce perfect counterfactuals in the absence of treatment and to maintain the validity of the calibration procedure. Parameter sets were created for the calibration procedure by simultaneously selecting parameter values randomly from pre-specified distributions for 12 parameters (Web Table 1). These parameter sets were then tested over three phases of calibration procedures which checked for consistent fit to HIV prevalence data, sexual behavior, and incidence data prior to the introduction of ART. At the end of the three phases, each of the parameter sets was assigned a normalized likelihood weight based on its fit to the national 1990-2003 South African HIV prevalence curve using the Levenberg-Marquardt algorithm. This normalized likelihood weight is used to produce a weighted average of all outcomes for the parameter sets that passed all three phases of the calibration procedure. Additional details of the model structure and calibration have been previously published (35).

Primary Prevention. We define a distribution for the proportion of sex acts in which a condom is used for each partnership type at model initiation. Each male randomly draws his own parameters from these distributions to determine with what probability he will use condoms for each partnership type. Condom usage distributions can be changed at any point in time and males redraw their condom use probability for

each partnership type at the start of such an intervention. Condoms are assumed to be 80% effective in all scenarios (Web Table 1) (7).

Male circumcision is modeled in one of two ways. A newborn circumcision program is simulated in which 35% of newborns are circumcised throughout the simulation (Web Table 1). To simulate adult voluntary medical male circumcision interventions, a defined proportion of adult males within a specified age range are circumcised to reach a target proportion. Circumcision is assumed to reduce the per-act HIV transmission probability by 56% (8-10, 42).

Testing and Treatment Cascades. The HIV-CDM structure allows infected individuals to pass through the testing and treatment cascades provided by CEPAC-I (31, 43, 44) and the potential benefits of various testing and treatment assumptions on epidemic dynamics can be examined. In the testing cascade, individuals access care and are offered an HIV test based on clinical symptoms. A proportion of individuals accept HIV tests and a proportion are linked to care if the test is positive. When individuals link to care and subsequently meet the CD4 ART start threshold, they enter the treatment cascade in CEPAC-I (39). Individuals begin treatment according to treatment availability through ART expansion. Those receiving ART have a probability of HIV-RNA suppression (45); for those who reach suppression, a monthly probability of late ART failure is assigned (45). Additionally, individuals can be lost to follow-up at a specified yearly rate (Web Table 1) (46, 47).

A detailed description of historical ART rollout in South Africa for the period between 2002 and 2013 can be found in Web Appendix 1. For the period after 2013, two types of continued ART expansion were considered: slow and rapid. In slow expansion, the amount of available treatment increased at a historical ratio with growing population size. In rapid expansion, all individuals who tested positive for HIV received treatment by 2017 (details in Web Table 2).

Elimination

We defined elimination as achieving an annual HIV incidence of less than 1 new infection per 100,000 person-years. The year at which elimination is reached can be directly estimated from the model incidence output.

Historical ART rollout in the HIV-CDM

In the period between 2002-2013 historical levels of ART following national treatment guidelines were assigned in the HIV-CDM to ensure accurate predictions. Because the model population size is smaller than the true South African population, the number of individuals receiving ART in the model was standardized yearly to historical data from South Africa between 2002 and 2013 and interpolated monthly (see Web Figure 1 and Web Table 2) (48-50). Historical South African treatment guidelines (51-54) were used to assign individuals to treatment in CEPAC-I, assuming availability. These treatment guidelines are summarized in Web Table 3. The eligibility, testing, and treatment access process are outlined in Web Figure 1 and Web Table 3. In cases of limited treatment availability, treatment was assigned to a new individual when an individual on ART died or when treatment availability expanded.

Scenarios

We analyzed primary prevention, testing, and treatment interventions to determine which produce the largest decrease in HIV prevalence and incidence, and largest increase in infections averted. We constructed scenarios to evaluate HIV interventions, starting in 2013 through 2063, by varying multiple parameters (Table 1): the proportion of adult males circumcised; condom usage in each type of partnership; the interval at which individuals get tested for HIV; HIV test acceptance rates; linkage to care rates following a new HIV diagnosis; probability of ART suppression at 6 months; monthly probability of late ART failure; yearly LTFU on ART; and the CD4 threshold for initiation of ART. All other inputs were assumed to remain constant for each of these scenarios (Web Table 1). We assumed perfect HIV test sensitivity and specificity for those with chronic and late-stage HIV infection.

In Scenario 1 (Status Quo Continued), current inputs for testing, treatment, and primary prevention were specified along with a slow expansion of ART (1% increase in treatment slots per year). This scenario was used as the comparator for all analyses. In the perfect scenario (Scenario 2 – Perfect), testing and treatment expanded rapidly to reach universal coverage in 4 years. In Scenario 2, the testing cascade was assumed to be perfect (i.e. everyone was offered a test, accepted it, and was linked to care if positive) with complete HIV suppression (including no late failure) and no losses to follow-up. Additionally, all males were circumcised and condoms were used in all sex acts. We also evaluated improvements to the testing and treatment cascades in the absence of primary interventions (Scenario 3 – Perfect Testing and Treatment Only*)*. In the remaining scenarios (Table 1), we varied primary prevention intervention parameters individually (Scenario 4 – Universal Circumcision, Scenario 5- Universal Condom Usage). Lastly, we examined a higher ART start CD4 threshold (Scenario 6), and estimated the changes in HIV prevalence, incidence and infection averted with a perfect testing cascade (Scenario 7) and perfect treatment components, including no LTFU and perfect HIV suppression (Scenario 8).

Every scenario was evaluated across each of the 564 calibration-derived parameter sets that collectively represent 90% of the posterior probability weight-to-fit to national prevalence and incidence data from 1990-2002 (35). Average results are shown for HIV prevalence, incidence, and infections averted calculated from normalized calibration weights (35).

Robustness of Predictions

The calibration approach used in our model (35) allows testing of the robustness of predictions while varying multiple parameters simultaneously. Parameter-dependence of the findings of the model was assessed by examining how consistently different scenarios are ranked on the value of the outcome measures (incidence, prevalence, and infections averted) using these different parameter sets. For each of the scenarios, annual HIV incidence in 2050 was ranked from highest to lowest across each of the 564

parameter sets. If the same parameter sets were ranked highest for each of the scenarios, one can conclude that results were parameter-set independent and transmission dynamics depended primarily on the scenario of interest. Conversely, if there was wide variety in outcome rankings for each of the scenarios, one may expect that calibrated parameter values mattered in determining the scenario's epidemiologic role in HIV prevention or elimination.

Role of the Testing and Treatment Cascade and Acute Infection Period in Achieving HIV Elimination

We varied assumptions on ideal testing and treatment programs, the use of HIV-RNA as ART start criterion, condom usage in different partnership types (Web Table 4), acute infection period, and elimination thresholds in sensitivity analyses.

To understand the most influential portions of the testing and treatment cascade, we implemented the most ambitious value of each element independently with the status quo assigned for all other parameters (Web Table 4). In Scenarios 9-11, the test interval, test acceptance, and linkage to care are perfected independently, representing improvements to different elements of the testing cascade. In Scenarios 12 and 13, we improved the suppression rates on treatment and LTFU rates to understand the sensitivity of interventions to changes in the treatment cascade.

We examined a high HIV-RNA level for the treatment threshold (HIV-RNA > 30,000 copies/mL, Scenario 14) and additionally examined the use of a lower HIV-RNA level for the ART start criterion by treating individuals with HIV-RNA >10,000 copies/mL (Scenario 15). The HIV-RNA ART start criterion is implemented in the same way as the CD4 ART start criterion in CEPAC-I.

We assessed the sensitivity of model predictions to the extent of condom usage using six different sensitivity scenarios (Web Table 4) since universal condom usage is practically unattainable (55). In Scenario 16, we evaluated CSW condom interventions by modeling all partners of CSW using condoms

during each partnership. In Scenario 17, we evaluated 100% condom use in one-off partnerships (casual and CSW). In Scenario 18, we estimated 100% condom use in casual partnerships. In Scenario 19, we assessed improving condom usage by 50% in all partnership types and by 90% in Scenario 20 compared to status quo values. In Scenario 21, we examined reducing the effectiveness of condoms to 65% (from 80%) in the universal condom usage scenario.

RESULTS

Historical ART Rollout: Validation

When ART was rolled out at historical rates from 2002-2013, our model's average HIV prevalence curve somewhat overestimated the UNAIDS model (50). Despite this, prevalence was comparable to historical antenatal clinic data (56) and Africa Centre Cohort prevalence data (57) in South Africa during the same time period (Web Figure 2).

HIV Elimination

Scenario 1 (status quo in 2013 for all interventions continued) resulted in a 33% increase in prevalence (Figure 1) and a slight increase in incidence (Figure 2) from 2013 to 2063. Only Scenario 2, in which all interventions are perfected, achieved elimination of HIV on a 50-year time scale (Web Figure 3). In this scenario, the year of elimination varied by parameter set from 2046 to 2064, with random variability as incidence rates approached zero. In this setting, elimination was not always permanent; in some simulations, the elimination threshold was reached but incidence increased above it again following small clusters of transmission among high-risk men and their low-risk partners (Web Figure 3, inset).

In the absence of universal primary prevention interventions, the use of perfect testing and treatment (Scenario 3) produced immediate reductions in incidence followed by a slow continuous decline, although elimination was not reached (Figure 2). Of all new infections from 2043-2063, 60% were attributed to infectors in the acute infection period indicating that continued transmissions from acutely infected

individuals prevented further decreases in incidence. Universal condom use (Scenario 5), in the absence of perfect treatment and testing, resulted in a 99% reduction in incidence over 50 years, but only reached elimination for a few parameter sets. The remaining scenarios (6-8) did not produce a weighted average incidence below 1.5 cases per 100 person-years within 50 years (Figure 2) and showed substantial increases in prevalence over 50 years (Figure 1). Short-term reductions in incidence were seen in Scenarios 4 (Universal Circumcision), 6 (Ambitious CD4 Threshold), and 8 (Perfect Treatment Components) within 20 years of the intervention, but these reductions were not maintained; higher steady states were reached at 21%, 11%, and 26% reductions from 2013 incidence, respectively. Perfecting the testing cascade (Scenario 7) reduced incidence little more than the Status Quo due to similar increases in ART slots in both scenarios, which created a bottleneck in downstream treatment with increased testing.

Infections Averted

When compared to the continuation of the Status Quo (Scenario 1), Scenarios 2, 3, and 5 averted 99%, 88%, and 93% of anticipated new infections from 2013 to 2063, respectively (Table 2).

Robustness of Predictions

The ranking of scenarios within parameter sets was most consistent for those scenarios that resulted in dramatic decreases in incidence (Scenarios 2, 3, and 5, Web Figure 4). Among scenarios with modest decreases in incidence (Scenarios 1, 4, 6-8), the order of scenarios was less clear, indicating that the change in outcomes due to these intervention scenarios was more parameter-dependent.

Role of the Testing and Treatment Cascade and Acute Infection Period in Acheiving HIV Elimination

When each element of the testing and treatment cascade is improved to an ambitious value independently, we see minor reductions in HIV incidence and prevalence compared to the situation in which all improvements to the testing and treatment cascade are made at once (Scenario 3). Improvements to the treatment cascade decrease HIV incidence more than improvements to the testing cascade when

implemented independently (Web Figures 5 and 6, Web Table 5), in large part due to the limited availability of ART in these scenarios. Improving 6-month ART suppression rates and reducing LTFU resulted in sustained incidence reductions of 13% and 11%, respectively, over the course of the 50-year simulation, representing the largest reduction of incidence for independent testing and treatment components (Web Figures 5 and 6, Web Table 5).

Using an HIV-RNA threshold to determine ART eligibility led to reductions in HIV incidence over time and dramatic increases in prevalence, but was not superior to the most ambitious CD4 ART start threshold results (Web Figures 7 and 8, Web Table 5). We captured the total potential prevention benefit of this strategy by treating everyone with HIV-RNA > 30,000 copies/mL. Additionally, we observed that modest increases in condom usage led to less dramatic reductions in HIV incidence (Web Figures 9 and 10, Web Table 5).

The magnitude of the epidemic at its peak was found to be proportional to the length of the acute period. Changing the acute infection length had little influence on Scenario 1 but did influence Scenario 2 by making prevention interventions weaker for shorter acute periods. The HIV-CDM was calibrated with a 3-month acute infection period; changing the length of acute infection breaks the calibration and as such results are not shown.

DISCUSSION

We forecasted the potential for multiple HIV prevention interventions to change HIV incidence and prevalence in South Africa over a 50-year time horizon. If all interventions are perfected and combined, elimination is predicted within 50 years. If the testing and treatment cascades are perfected, elimination is within reach but not achieved due to transmissions occurring during acute infection. Continuing current rates of testing and treatment in South Africa does not achieve HIV elimination.

The timeline for HIV elimination after a dramatic scale-up in testing, treatment, and primary prevention interventions was longer than previously predicted (32). This is likely due to the level of detail presented in our model and the use of a more stringent cut-off for elimination than previous analyses (32). Even when considering a less stringent cut-off, such as a sustained 75% reduction in incidence, extreme and implausible conditions need to be met to reach elimination (Scenarios 2, 3, and 5). The variability in our predicted results, due to multiple calibrated parameter sets, adds robustness to our predictions and highlights the importance of rigorously calibrating complex models to multiple data sources.

Despite dramatic reductions in HIV incidence in the most ambitious scenarios, we observed that a group of transmitters, primarily high-risk men transmitting to low-risk women, caused HIV to persist for extended periods of time, delaying elimination. Despite receiving numerous interventions and ART, these high-risk men were having enough sex acts to continue transmitting HIV to their low-risk partners (most high-risk partners had already been infected). The stratification of our model population into high- and low-risk, with a complex risk-, age-, and relationship-dependent sexual mixing structure, the inclusion of CSW, variations in condom usage, appropriate circumcision efficacy, changes in transmission potential as a result of detailed treatment modeling and a thorough calibration procedure distinguish this model from previously published analyses (32).

Improvement in any single aspect of the testing and treatment cascade leads to small overall changes in prevalence and incidence, because failures at other steps limit overall effectiveness. Reducing LTFU or improving ART suppression decrease incidence because they affect viral load and infectiousness, but do not reduce incidence enough on their own to lead to significant changes in prevalence. In these situations, an individual's transmission potential remains high, alongside lower community HIV-RNA and increased access to treatment. Primary prevention interventions, such as condom usage and circumcision, help reduce HIV incidence through a rapid reduction in transmission potential and subsequently influence prevalence on a long-term scale. Despite dramatic decreases in incidence through combined testing and

treatment interventions, we found that it is difficult to move the epidemic towards elimination without universal adoption of the primary prevention methods of circumcision and condom usage, which are more likely unattainable. Future analyses should evaluate the potential that pre-exposure prophylaxis may have as a primary prevention intervention.

This analysis was constrained by assumptions implicit in the model structure. The HIV-CDM does not account for non-heterosexual HIV transmission, and therefore cannot account for prevention benefits or risks via non-heterosexual transmission routes. Furthermore, the model does not account for mother-to-child transmission or infected adolescents entering the sexually active pool. We have not implemented behavioral changes after the start of aggressive testing and treatment interventions that are expected to occur in real-world populations (58). The implementation of multiple concurrent prevention interventions may lead to participant fatigue but neither this nor heterogeneity in testing behavior is examined in this analysis. Finally, we have assessed testing, treatment, and primary prevention at idealized levels. Whether moving each of these components of care from the status quo towards ideal is equally feasible is not clear. Despite these limitations, the HIV-CDM is one of the most detailed individual-based models in the HIV transmission and prevention literature (21) incorporating a great deal of flexibility in modeling both behavior and biology. Additionally, the use of agent-based simulations allowed examination of outcomes for a large range of scenarios, something unattainable in large and complex community randomized trials (24). In developing this model, we have expanded upon the capacity of the CEPAC-I Disease Model to simulate sexual behavior's influence on HIV transmission. The extensive calibration of the HIV-CDM in the era prior to the introduction of ART helps to ensure that the behavior represented in the model produces accurate epidemic dynamics in the absence of ART.

With the continuation of current levels of HIV prevention, testing and treatment in South Africa, we conclude that it will be difficult, and perhaps impossible, to decrease HIV prevalence in the population, partly due to increasing survival on ART. We have shown that even after implementation of an aggressive

and highly optimistic ART expansion, alongside changes in condom usage and circumcision patterns, the potential for HIV elimination would be lower than previously estimated (32). Treatment as prevention produces the greatest reduction in transmission potential in a population when used to "hit hard and fast", as suggested by the recent UNAIDS fast-track guidelines and the Strategic Timing of Antiretroviral Treatment study results (34, 59). In the absence of an effective HIV vaccine, if HIV transmission potential is not reduced quickly and substantially, the number of people on ART is expected to remain high as individual survival outweighs the population-level reduction in transmission. Large upfront investments from governments and international partners would be needed to make this dramatic decrease in incidence possible (60). While increased attention has been given to testing and treatment interventions in Sub-Saharan Africa, primary prevention interventions could also reduce HIV incidence. Efforts towards increasing uptake of primary prevention strategies, such as circumcision and pre-exposure prophylaxis, alongside ongoing prevention efforts, may lead the way to faster and more effective reductions in HIV incidence in South Africa.

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References

1. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *NEJM*. 2010;363(27):2587-2599.
2. Van Damme L, Corneli A, Ahmed K, Agot K, Lombaard J, Kapiga S, et al. Preexposure prophylaxis for HIV infection among African women. *NEJM*. 2012;367(5):411-422.
3. Baeten JM, Donnell D, Ndase P, Mugo NR, Campbell JD, Wangisi J, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *NEJM*. 2012;367(5):399-410.
4. Thigpen MC, Kebaabetswe PM, Paxton LA, Smith DK, Rose CE, Segolodi TM, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *NEJM*. 2012;367(5):423-434.
5. Cohen MS, Chen YQ, McCauley M, Gamble T, Hosseinipour MC, Kumarasamy N, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *NEJM*. 2011;365(6):493-505.
6. Karim QA, Karim SSA, Frohlich JA, Grobler AC, Baxter C, Mansoor LE, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science*. 2010;329(5996):1168-1174.
7. Weller S, Davis K. Condom effectiveness in reducing heterosexual HIV transmission. *Cochrane Database Syst Rev*. 2002(1):CD003255.
8. Auvert B, Taljaard D, Lagarde E, Sobngwi-Tambekou J, Sitta R, Puren A. Randomized, controlled intervention trial of male circumcision for reduction of HIV infection risk: the ANRS 1265 Trial. *PLoS Med*. 2005;2(11):e298.
9. Bailey RC, Moses S, Parker CB, Agot K, Maclean I, Krieger JN, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet*. 2007;369(9562):643-656.
10. Gray RH, Kigozi G, Serwadda D, Makumbi F, Watya S, Nalugoda F, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet*. 2007;369(9562):657-666.
11. Siegfried N, Muller M, Deeks J, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men (Review). *Cochrane Database Syst Rev*. 2009;2:CD003362.
12. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): Rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment-a study protocol for a cluster randomised trial. *Trials*. 2014;15(1):57.
13. Iwuji CC, Orne-Gliemann J, Tanser F, Boyer S, Lessells RJ, Lert F, et al. Evaluation of the impact of immediate versus WHO recommendations-guided antiretroviral therapy initiation on HIV incidence: the ANRS 12249 TasP (Treatment as Prevention) trial in Hlabisa sub-district, KwaZulu-Natal, South Africa: study protocol for a cluster randomised controlled trial. *Trials*. 2013;14(1):230.
14. Novitsky V, Wang R, Bussmann H, Lockman S, Baum M, Shapiro R, et al. HIV-1 subtype C-infected individuals maintaining high viral load as potential targets for the "test-and-treat" approach to reduce HIV transmission. *PLoS One*. 2010;5(4):e10148.
15. Havlir D. Clinical Trials.gov - A service of the U.S. National Institutes of Health. Sustainable East Africa Research in Community Health (SEARCH). http://clinicaltrials.gov/ct2/show/NCT01864603?term=havlir&rank=11. Published April 26, 2013. Updated October 29, 2015. Accessed February 24, 2015.
16. Cori A, Ayles H, Beyers N, Schaap A, Floyd S, Sabapathy K, et al. HPTN 071 (PopART): A Cluster-Randomized Trial of the Population Impact of an HIV Combination Prevention Intervention Including Universal Testing and Treatment: Mathematical Model. *PLoS One*. 2014;9(1):e84511.
17. Boily M-C, Mâsse B, Alsallaq R, Padian NS, Eaton JW, Vesga JF, et al. HIV treatment as prevention: considerations in the design, conduct, and analysis of cluster randomized controlled trials of combination HIV prevention. *PLoS Med*. 2012;9(7):e1001250.
18. Hethcote HW. A thousand and one epidemic models. Frontiers in Mathematical Biology. Heidelberg, Germany: Springer-Verlag Berlin Heidelberg; 1994. p. 504-515.

19. Goodreau SM, Carnegie NB, Vittinghoff E, Lama JR, Sanchez J, Grinsztejn B, et al. What drives the US and Peruvian HIV epidemics in men who have sex with men (MSM)? *PLoS One*. 2012;7(11):e50522.
20. Marshall BD, Friedman SR, Monteiro JF, Paczkowski M, Tempalski B, Pouget ER, et al. Prevention and treatment produced large decreases in HIV incidence in a model of people who inject drugs. *Health Affairs*. 2014;33(3):401-409.
21. Abuelezam NN, Rough K, Seage III GR. Individual-based simulation models of HIV transmission: reporting quality and recommendations. *PLoS One*. 2013;8(9):e75624.
22. Hernán MA. Invited commentary: agent-based models for causal inference—reweighting data and theory in epidemiology. *AJE*. 2015;181(2):103-105.
23. Marshall BD, Galea S. Formalizing the role of agent-based modeling in causal inference and epidemiology. *AJE*. 2014:kwu274.
24. El-Sayed AM, Seemann L, Scarborough P, Galea S. Are network-based interventions a useful antiobesity strategy? An application of simulation models for causal inference in epidemiology. *AJE*. 2013;178(2):287-295.
25. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet*. 2009;373(9657):48-57.
26. Bendavid E, Brandeau ML, Wood R, Owens DK. Comparative effectiveness of HIV testing and treatment in highly endemic regions. *Arch Intern Med*. 2010;170(15):1347-1354.
27. Dodd PJ, Garnett GP, Hallett TB. Examining the promise of HIV elimination by'test and treat'in hyperendemic settings. *AIDS*. 2010;24(5):729-735.
28. Kretzschmar ME, van der Loeff MFS, Coutinho RA. Elimination of HIV by test and treat: a phantom of wishful thinking? *AIDS*. 2012;26(2):247-248.
29. Powers KA, Ghani AC, Miller WC, Hoffman IF, Pettifor AE, Kamanga G, et al. The role of acute and early HIV infection in the spread of HIV and implications for transmission prevention strategies in Lilongwe, Malawi: a modelling study. *Lancet*. 2011;378(9787):256-268.
30. Wagner BG, Kahn JS, Blower S. Should we try to eliminate HIV epidemics by using a "Test and Treat" strategy? *AIDS*. 2010;24(5):775-776.
31. Walensky RP, Paltiel AD, Losina E, Morris BL, Scott CA, Rhode ER, et al. Test and treat DC: forecasting the impact of a comprehensive HIV strategy in Washington DC. *Clin Infect Dis*. 2010;51(4):392-400.
32. Hontelez JA, Lurie MN, Barnighausen T, Bakker R, Baltussen R, Tanser F, et al. Elimination of HIV in South Africa through expanded access to antiretroviral therapy: a model comparison study. *PLoS Med*. 2013;10(10):e1001534.
33. Eaton JW, Johnson LF, Salomon JA, Barnighausen T, Bendavid E, Bershteyn A, et al. HIV treatment as prevention: systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa. *PLoS Med*. 2012;9(7):e1001245.
34. Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *JAIDS*. 1997;16(1):54-62.
35. McCormick AW, Abuelezam NN, Rhode ER, Hou T, Walensky RP, Pei PP, et al. Development, Calibration and Performance of an HIV Transmission Model Incorporating Natural History and Behavioral Patterns: Application in South Africa. *PLoS One*. 2014;9(5):e98272.
36. Yazdanpanah Y, Losina E, Anglaret X, Goldie SJ, Walensky RP, Weinstein MC, et al. Clinical impact and cost-effectiveness of co-trimoxazole prophylaxis in patients with HIV/AIDS in Cote d'Ivoire: a trial-based analysis. *AIDS*. 2005;19(12):1299-1308.
37. Goldie SJ, Yazdanpanah Y, Losina E, Weinstein MC, Anglaret X, Walensky RP, et al. Cost-effectiveness of HIV treatment in resource-poor settings--the case of Cote d'Ivoire. *NEJM*. 2006;355(11):1141-1153.
38. Walensky RP, Wolf LL, Wood R, Fofana MO, Freedberg KA, Martinson NA, et al. When to start antiretroviral therapy in resource-limited settings. *Ann Int Med*. 2009;151(3):157-166.

39. Walensky RP, Wood R, Fofana MO, Martinson NA, Losina E, April MD, et al. The clinical impact and cost-effectiveness of routine, voluntary HIV screening in South Africa. *JAIDS*. 2011;56(1):26-35.
40. Holmes CB, Wood R, Badri M, Zilber S, Wang B, Maartens G, et al. CD4 decline and incidence of opportunistic infections in Cape Town, South Africa: implications for prophylaxis and treatment. *JAIDS*. 2006;42(4):464-469.
41. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126(12):946-954.
42. Mills E, Cooper C, Anema A, Guyatt G. Male circumcision for the prevention of heterosexually acquired HIV infection: a meta-analysis of randomized trials involving 11,050 men. *HIV MED*. 2008;9(6):332-335.
43. Paltiel AD, Weinstein MC, Kimmel AD, Seage III GR, Losina E, Zhang H, et al. Expanded screening for HIV in the United States—an analysis of cost-effectiveness. *NEJM*. 2005;352(6):586-595.
44. Walensky RP, Wood R, Ciaranello AL, Paltiel AD, Lorenzana SB, Anglaret X, et al. Scaling up the 2010 World Health Organization HIV Treatment Guidelines in resource-limited settings: a model-based analysis. *PLoS Med*. 2010;7(12):e1000382.
45. Barth RE, van der Loeff MFS, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis*. 2010;10(3):155-166.
46. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. *PLoS Med*. 2007;4(10):e298.
47. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007–2009: systematic review. *Trop Med Int Health*. 2010;15(s1):1-15.
48. South Africa S. Mid-Year Population Estimates 20132013 27 January 2014. Available from: http://beta2.statssa.gov.za/publications/P0302/P03022013.pdf.
49. Adam MA, Johnson LF. Estimation of adult antiretroviral treatment coverage in South Africa. *SAMJ*. 2009;99(9):661-667.
50. UNAIDS. AIDSinfo Online Database - South Africa. http://www.unaids.org/en/dataanalysis/datatools/aidsinfo/. Accessed August 1, 2013.
51. Rojanapithayakorn W, Hanenberg R. The 100% condom program in Thailand. *AIDS*. 1996;10(1):1-7.
52. Shelton JD, Halperin DT, Nantulya V, Potts M, Gayle HD, Holmes KK. Partner reduction is crucial for balanced "ABC" approach to HIV prevention. *Bmj*. 2004;328(7444):891-893.
53. Saphonn V, Parekh BS, Dobbs T, Mean C, Bun LH, Ly SP, et al. Trends of HIV-1 seroincidence among HIV-1 sentinel surveillance groups in Cambodia, 1999-2002. *JAIDS*. 2005;39(5):587-592.
54. Eyawo O, de Walque D, Ford N, Gakii G, Lester RT, Mills EJ. HIV status in discordant couples in sub-Saharan Africa: a systematic review and meta-analysis. *Lancet Infect Dis*. 2010;10(11):770-777.
55. Potts M, Halperin DT, Kirby D, Swidler A, Marseille E, Klausner J, et al. Rethinking HIV prevention: Public health. *Science*. 2008;320(5877):749-750.
56. National Department of Health South Africa. The 2011 National Antenatal Sentinal HIV and Syphilis Prevalence Survey, South Africa. Pretoria, South Africa: National Department of Health, 2011.
57. Zaidi J, Grapsa E, Tanser F, Newell ML, Barnighausen T. Dramatic increase in HIV prevalence after scale-up of antiretroviral treatment. *AIDS*. 2013;27(14):2301-2305.
58. Bunnell R, Ekwaru JP, Solberg P, Wamai N, Bikaako-Kajura W, Were W, et al. Changes in sexual behavior and risk of HIV transmission after antiretroviral therapy and prevention interventions in rural Uganda. *AIDS*. 2006;20(1):85-92.
59. The INSIGHT START Study Group. Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection. *NEJM*. 2015;373(9):795-807.

60. Resch S, Ryckman T, Hecht R. Funding AIDS programmes in the era of shared responsibility: an analysis of domestic spending in 12 low-income and middle-income countries. *The Lancet Global Health*. 2015;3(1):e52-e61.

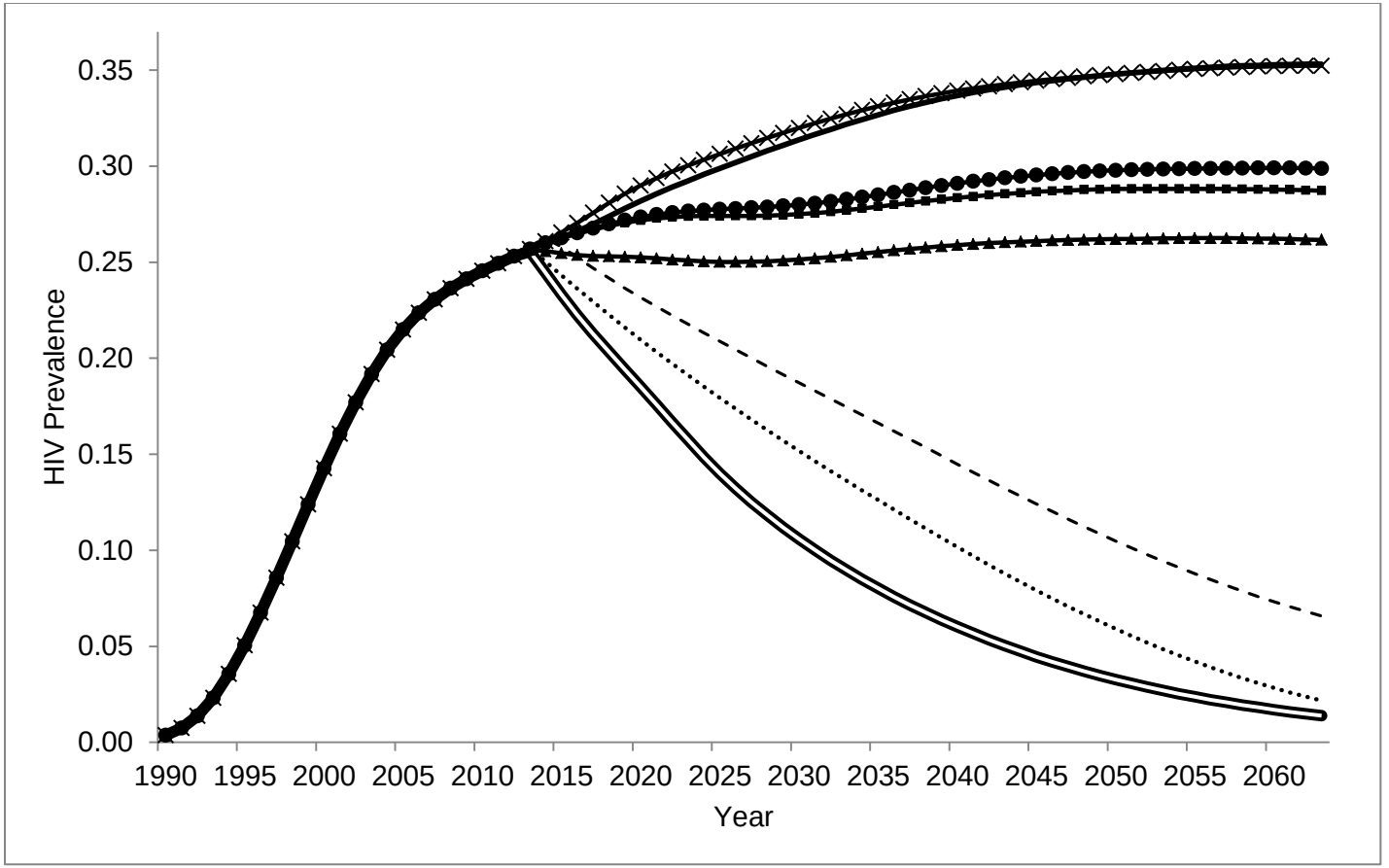


Figure 1. **Human immunodeficiency virus (HIV) prevalence from 1990-2063 in all combination intervention scenarios simulated in South Africa starting in 2013**. HIV prevalence is defined as the total number of living HIV cases among sexually active individuals divided by the total number of sexually active individuals alive at the defined time point. The bold black solid line represents Scenario 1 (Status Quo Continued), black dotted line represents Scenario 2 (Perfect), black dashed line represents Scenario 3 (Perfect Testing and Treatment Only), black line with triangles represents Scenario 4 (Status Quo, Universal Circumcision), double black line represents Scenario 5 (Status Quo, Universal Condom Usage), black line with circles represents Scenario 6 (Status Quo, Ambitious CD4 Threshold), black line with crosses represents Scenario 7 (Status Quo, Perfect Testing Components), and black line with squares represents Scenario 8 (Status Quo, Perfect Treatment Components). All scenarios are defined in Table 1. Prevalence decreases quickly in Scenarios 2, 3, and 5 while prevalence increases in all other scenarios. A steady state is reached in Scenarios 6 and 8.

Abbreviations in figure: HIV= human immunodeficiency virus.

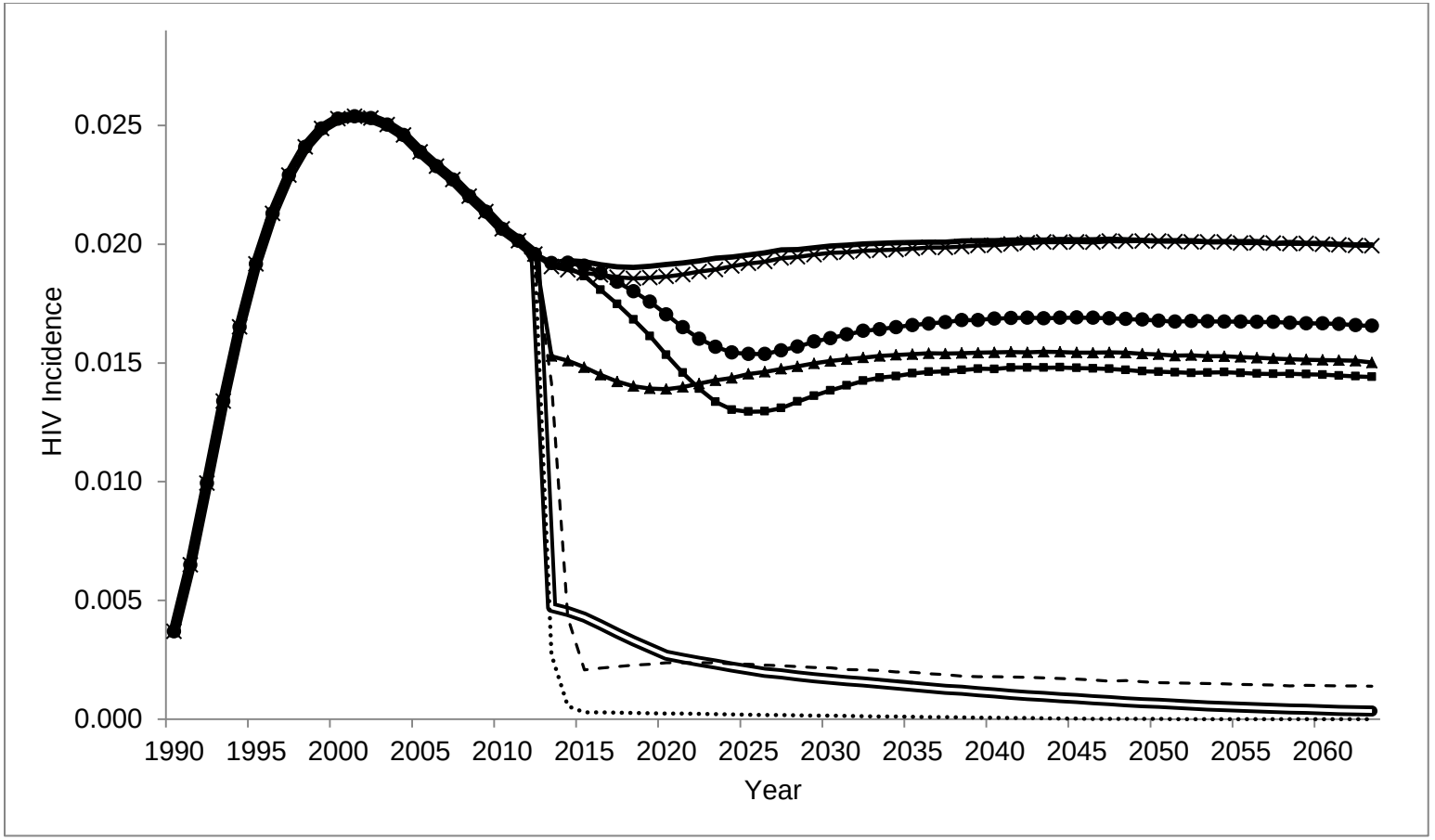


Figure 2. **Human immunodeficiency virus (HIV) incidence from 1990-2063 in all combination intervention scenarios simulated in South Africa starting in 2013**. HIV incidence represents an annual HIV incidence among sexually active individuals. The bold black solid line represents Scenario 1 (Status Quo Continued), black dotted line represents Scenario 2 (Perfect), black dashed line represents Scenario 3 (Perfect Testing and Treatment Only), black line with triangles represents Scenario 4 (Status Quo, Universal Circumcision), double black line represents Scenario 5 (Status Quo, Universal Condom Usage), black line with circles represents Scenario 6 (Status Quo, Ambitious CD4 Threshold), black line with crosses represents Scenario 7 (Status Quo, Perfect Testing Components), and black line with squares represents Scenario 8 (Status Quo, Perfect Treatment Components). All inputs for scenarios are defined in Table 1. HIV incidence decreases dramatically in Scenarios 2, 3, and 5 but only reaches elimination in Scenario 2. Initial HIV incidence decreases are seen in Scenarios 6 and 8 but level off at slightly lower levels from the 2013 incidence.

Abbreviations in figure: HIV= human immunodeficiency virus.

Table 1. Scenario Input Table. Scenarios used to estimate the changes in HIV incidence, prevalence and infections averted varying primary, testing, and treatment interventions on HIV elimination in South Africa from 2013 to 2063.

Scenario	Description	ART Expansion Type	Male Circ Prop at Birth (%)	Condom Usage (%)	HIV Testing Interval	HIV Test Accept Rate (%)	Linkage to Care (%)	ART Supp at 6 mo. (%)	Monthly ART late fail prob (%)	LTFU on ART (%) per year	CD4 ART Start Threshold (2013)
1	**Status Quo Continued**	Slow	35	12-50	1 year	50	46.80	78	0.1	9.90	<350/µl
2	**Perfect**	Rapid	100	100	1 month	100	100	100	0	0	All CD4
3	**Perfect Testing and Treatment Only**	Rapid	35	12-50	1 month	100	100	100	0	0	All CD4
4	**Status Quo, Universal Circumcision**	Slow	100	12-50	1 year	50	46.80	78	0.1	9.90	<350/µl
5	**Status Quo, Universal Condom Use**	Slow	35	100	1 year	50	46.80	78	0.1	9.90	<350/µl
6	**Status Quo, Ambitious CD4 Threshold**	Slow	35	12-50	1 year	50	46.80	78	0.1	9.90	All CD4
7	**Status Quo, Perfect Testing Components**	Slow	35	12-50	1 month	100	100	78	0.1	9.90	<350/µl
8	**Status Quo, Perfect Treatment Components**	Slow	35	12-50	1 year	50	46.80	100	0	0	<350/µl

Abbreviations: accept = acceptance; ART= antiretroviral therapy; circ = circumcision; HIV= human immunodeficiency virus; LTFU = loss to follow-up; mo. = month; prob = probability; prop = proportion; supp = virologic suppression rate.

Table 2. Infections Averted Results. Tabulated total infections, infections averted, and percent averted for all scenarios of an examination for the potential for HIV elimination in South Africa from 2013 to 2063.

Scenario	Description	Total Incident Infections (2013-2063) (No.)	Total Infections Averted (vs. Scenario 1 – Status Quo Continued) (No.)	Percentage of Infections Averted (vs. Scenario 1 – Status Quo Continued) (%)
1	**Status Quo Continued**	278,373	--	--
2	**Perfect**	2,014	276,359	99
3	**Perfect Testing and Treatment Only**	33,858	244,515	88
4	**Status Quo, Universal Circumcision**	219,236	59,137	21
5	**Status Quo, Universal Condom Usage**	20,914	257,459	93
6	**Status Quo, Ambitious CD4 Threshold**	241,162	37,211	13
7	**Status Quo, Perfect Testing Components**	278,648	-275	-0.10[a]
8	**Status Quo, Perfect Treatment Components**	220,823	57,550	21

[a]The increase in infections is due to the recruitment of healthier people for treatment with a more extensive testing campaign. This leaves fewer spots for those who may be more viremic, causing more infections in the long term.

Abbreviations: HIV=human immunodeficiency virus.

Web Table 1. Base-case Inputs for a Model of HIV Elimination in South Africa from 2013-2063.

Parameter (reference)	Value
Population size at model initiation	100,000
Number of births per person per month (56)	0.0022
Proportion of the population who is male (MA, 56)	0.50
Age of first sex (57-59)	17 years
Proportion of newborn males circumcised (57, 58, 60, 61)	0.35
Probability of a female becoming a CSW/Proportion CSW at baseline	0.01-0.04**
Proportion of males in the HR group	0.07-0.4
Proportion of non-CSW females in the HR group	0.01-0.3**
Sexual Partnership Characteristics	
Steady Partnerships	
Duration of partnership[b] (62-64)	10.20 years (SD 7.80 years)
Number of sex acts per partnership per month[c] (65-67)	9
Probability of male condom use per sexual act[d] (%)(59, 68, 69)	12 (SD 6)
Regular Partnership	
Duration of partnership[b] (55, 56)	13.50 months (SD 9 months)
Number of sex acts per partnership per month	4-11**
Probability of male condom use per sexual act (%) (57, 59, 70, 71)	29 (SD 15)
Casual Partnership	
Duration of casual partnership (MA)	1 sexual act
Number of sex acts per partnership per month[c] (MA)	1
Probability of male condom use per sexual act[d](%) (57, 59, 70)	37 (SD 19)
CSW Encounters	
Duration of CSW encounter (MA)	1 sexual act
Number of sex acts per partnership per month[c] (MA)	1
Probability of male condom use per sexual act[d] (%) (68)	50 (SD 25)

Parameter (reference)	Value
Partnership Selection Criteria	
Average number of years younger the female is compared to male partner (steady, regular and casual)[b] (49, 57, 58)	5 (SD 2.50)
Average number of years younger CSW is compared to male partner[b] (72, 73)	13 (SD 6·50)
Sexual Network Parameters	
High-risk multiplier	1-10**
High-risk multiplier CSW	30-100**
Partner acquisition multiplier while in steady partnership or low-risk males	0-1**
Assortativeness parameter for steady, regular, and casual partnerships	0.2-0.8**
Intervention Efficacy	
Circumcision Efficacy (%) (8-10, 40)	56
Condom Efficacy (%) (7)	80
HIV Testing	
Intervention HIV testing interval (MA)	1 year
Average background HIV test frequency (52)	Every 10 years
Sensitivity of HIV test (%) (MA)	100
Specificity of HIV test (%) (MA)	100
Sensitivity in acute phase[a] of HIV test (%) (MA)	0
Linkage to care (%) (52)	46.8
Mean initial CD4 cell count, cells/µl	
Acute, primary[a] HIV infection (74)	884
ART	
CD4 ART start criteria in 2013 (75)	<350 cells/µl
ART Suppression at 6 months (%) (43)	78
Monthly late ART failure probability (%)(43)	0.1
ART program loss to follow-up at 12 mo. (%) (44, 45)	9.9
Natural History	
Mean monthly CD4 decline (cells/µl) by HIV RNA level (39, 76)	

Parameter (reference)	Value
>30,001 copies/ml	6.4
10,001-30,000 copies/ml	5.4
3,001-10,000 copies/ml	4.6
501-3,000 copies/ml	3.7
<500 copies/ml	3.0
Probability of transmission per sexual act by HIV RNA (copies/ml) (66, 67, 77, 78)	
0-500	0.0001
501-3,000	0.0012
3,001-10,000	0.0012
10,001-30,000	0.0014
30,001 +	0.0023
Acute infection[a]	0.0082
Late-stage infection[a] (67)	0.0036

Abbreviations: ART= antiretroviral therapy; CSW= commercial sex worker; HIV=human immunodeficiency virus; HR=high risk; MA ¯ Model assumption; mo.=month;

a Acute infection is the first three months post-infection; chronic infection immediately follows primary infection and continues until the individual's CD4 count drops below 50/mm^3; late-stage infection occurs when the individual's CD4 drops below 50/mm^3.

[b] The duration of partnerships and the average number of years between partners are parameters chosen from a normal distribution with the denoted mean and standard deviation.

[c] The number of sex acts per partnership per month parameter is chosen from a Poisson distribution with the denoted mean (and standard deviation).

[d] The probability of a condom use in each partnership parameter is chosen from a beta distribution. This distribution is converted to a normal distribution with the denoted mean and standard deviation for presentation in table.

** These parameters were varied in the calibration procedure. Each of the 564 parameter sets has a randomly selected value from within these ranges for each of the 12 varied parameters.

Web Appendix 1

Cost-effectiveness of Preventing AIDS Complication International Model (CEPAC-I)

The CEPAC-I Disease Model is a computer-based, state-transition, Monte Carlo simulation model of the progression and outcomes of HIV disease in a hypothetical cohort of patients (1-5). Each individual patient's clinical course is followed from the time of entry into the model until death. A running tally is maintained of all clinical events, the length of time spent in each health state, and the cost and quality of life associated with each health state. Health states are chosen to be both descriptive of a patient's current health (CD4 count, HIV RNA, relevant history, quality of life, and resource use) and predictive of disease progression (immune system deterioration, onset and relapse of OIs (Web Table 6), toxic reactions to medications, resistance to therapy, and mortality) (6-8). The model defines three general categories of health states: chronic, acute, and death. Most of the time, patients reside in one of the chronic states, where progression of disease and immune system deterioration (CD4 decline) take place. Patients who develop an acute complication (eg: an OI or drug-related toxicity) temporarily move to an acute health state, where quality of life is lower and both resource use and mortality rates are higher. Deaths can occur in either a chronic or an acute state and can be attributed to a particular OI, chronic AIDS, or non-AIDS related causes.

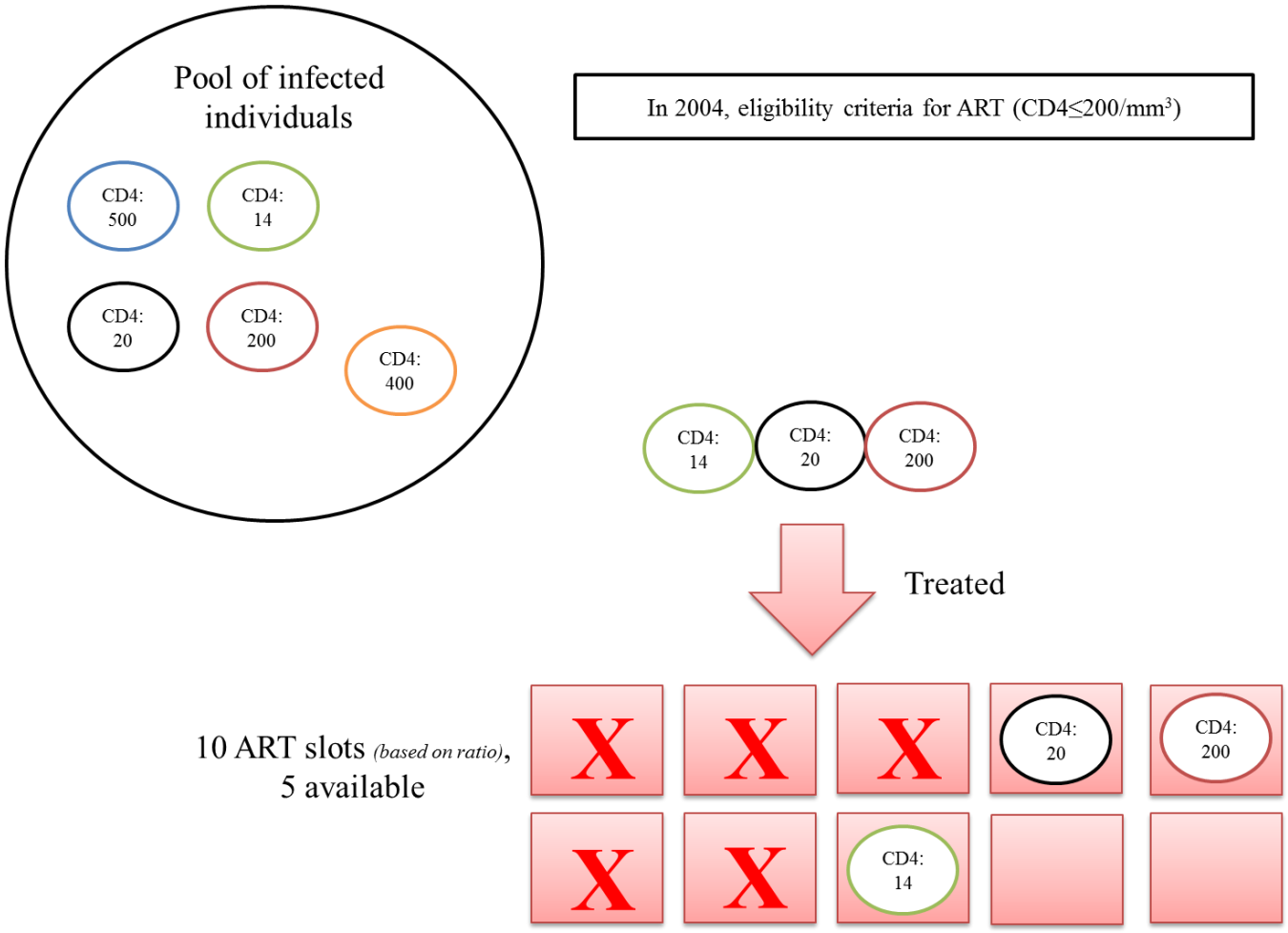
The chronic and acute health states are stratified by: current and nadir CD4 cell count (>500 cells/μL; 301–500 cells/μL; 201–300 cells/μL; 101–200 cells/μL; 51–100 cells/μL; and 0-50 cells/μL) and current and set-point HIV RNA level (>30,000 copies/mL; 10,001–30,000 copies/ mL; 3,001–10,000 copies/ mL; 501–3,000 copies/ mL; 51-500 copies/ mL; 0-50 copies/mL). Upon entry into the model, a patient is randomly assigned to a health state based upon a set of user-specified probability distributions.

At the start of each one-month cycle, the model records the patient's CD4 cell count, HIV RNA, history of acute illness, and current therapies and uses these characteristics to determine the probabilities that indicate movement to a new state in the subsequent month. Monthly probabilities of events are derived from public use datasets and translated into risk functions for the model (9). These risk functions embody the key parameters of the natural history of HIV illness, AIDS, and OIs, including: rates of disease progression, OI risks (Table S5), survival probabilities, and the effects of therapy. The model treats HIV RNA as the primary driver of immune system deterioration, and thus the assigned HIV RNA determines the rate at which the patient's CD4 cell count will decline in the absence of therapy. Patients with a history of OIs have a higher risk of recurrence, depending on CD4 cell count and current use of ART (7).

The efficacy of ART is estimated from data on viral suppression and CD4 cell count change over time, as reported in randomized trials (10-12).

Web Table 2. Rollout Specifications. This table indicates the population size and historical treatment rollout numbers in South Africa from 2002-2013. Because the model population size is smaller than that of the actual South African population, a ratio is calculated from these numbers which is used to scale the model population size to determine the amount of treatment available in the model run. After 2013, assumptions are made about the speed of ART rollout (rapid or slow) by changing the ratio.

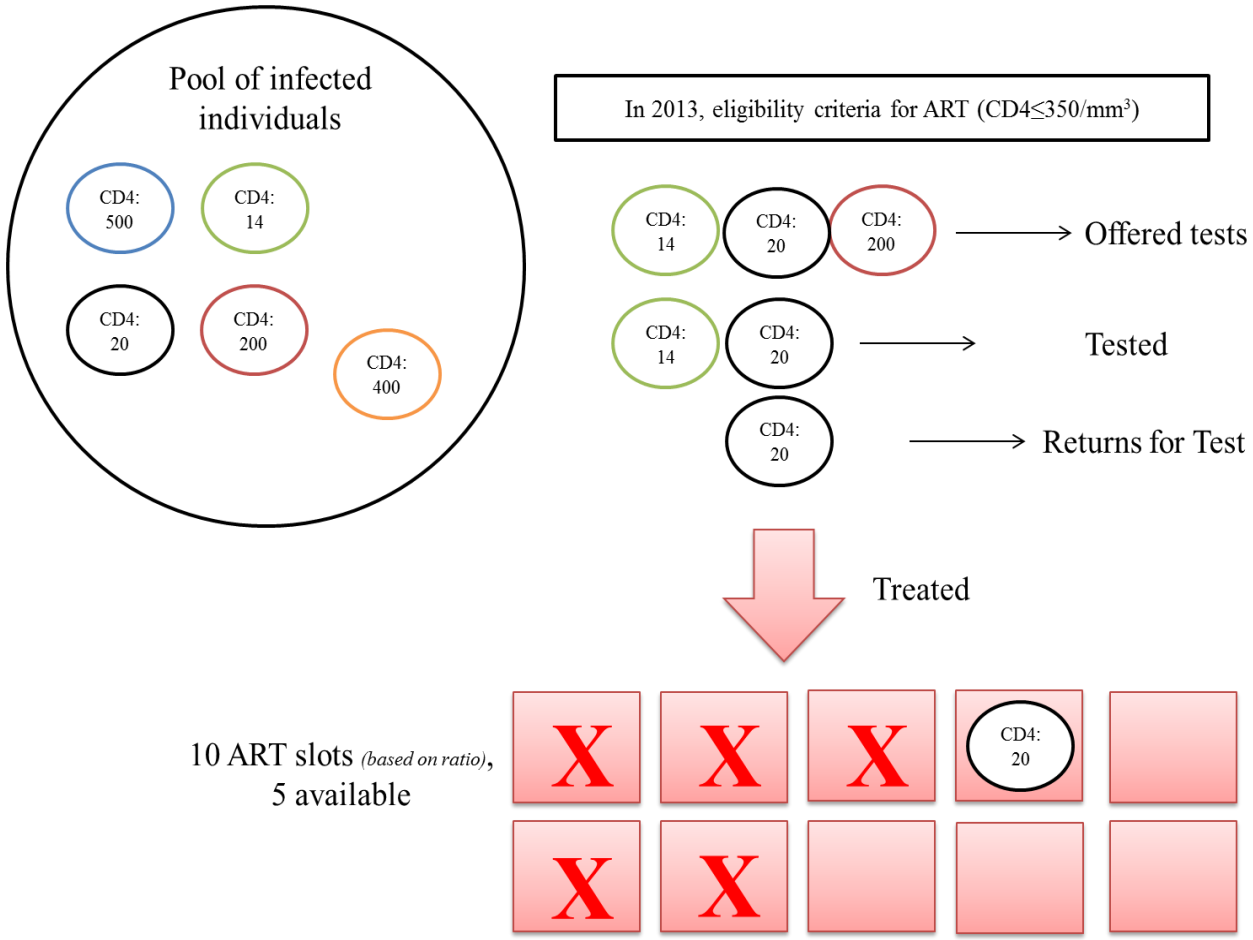
Year	**Population Size** (in millions)(15)	**Historical Number Infected** (in millions)(16)	**Historical Number Being Treated**(16, 17)	**Historical Input Ratio**	**Rapid Input Ratio**	**Slow Input Ratio**
2002	40.00	4.68	15000	0.00040		
2003	41.00	4.95	26000	0.0010		
2004	41.80	5.15	55000	0.0010		
2005	42.50	5.32	206718	0.0050		
2006	43.40	5.46	324754	0.0070		
2007	44.60	5.59	458951	0.010		
2008	45.90	5.72	730183	0.016		
2009	47.40	5.82	971556	0.020		
2010	48.80	5.88	1389865	0.028		
2011	50.10	5.97	1702060	0.034		
2012	52.60	6.07	2150881	0.041		
2013					0.082	0.050
2014					0.16	0.060
2015					0.33	0.070
2016					0.65	0.080
2017					0.99	0.090
2018					0.99	0.10
2019					0.99	0.11
2020					0.99	0.12
2021					0.99	0.13
2022					0.99	0.14
2023					0.99	0.15
2024					0.99	0.16
2025					0.99	0.17
..					..	..
2065					0.99	0.57


Pool of infected individuals
CD4: 500
CD4: 14
CD4: 20
CD4: 200
CD4: 400
In 2004, eligibility criteria for ART (CD4≤200/mm³)
CD4: 14
CD4: 20
CD4: 200
Treated
10 ART slots (based on ratio), 5 available
X
X
X
CD4: 20
CD4: 200
X
X
CD4: 14

(A)


Pool of infected individuals
CD4: 500
CD4: 14
CD4: 20
CD4: 200
CD4: 400
In 2004, eligibility criteria for ART (CD4≤200/mm3)
CD4: 14
CD4: 20
CD4: 200
Random Selection for Slot
10 ART slots (based on ratio), 1 available
X
X
X
X
CD4: 200
X
X
X
X
X

(B)



(C)

Web Figure 1. Testing and treatment cascade in the CDM and CEPAC-I. (A) Prior to 2013, all individuals who are eligible for treatment are put on treatment if there is treatment available. This ensures that all historically available treatment is being used. (B) In the case where there is not enough treatment for all eligible individuals, the available treatment is randomly assigned among those eligible. Treatment becomes available when someone who is receiving treatment dies. (C) After 2013, the testing and treatment cascade probabilities begin to take effect. Individuals who are eligible for treatment are tested and can accept or reject the test. Of those who accept the test, some are linked to care. Once an individual is linked to care, they are given treatment, assuming the availability of treatment.

Web Table 3. Historical ART Treatment Guidelines. Assumptions for access to ART are highlighted in the table for each of the years in which a major treatment guideline was revised. We assumed that the first two years of ART distribution were dominated by individuals with severe OIs. We then followed the treatment guidelines published by the South African Department of Health for the subsequent years until present day.

Year	**Treatment Guidelines**	
	WHO Stage/OI	***CD4***
2002	4	Irrespective
	3	Irrespective, including recurrent or persistent oral thrush and recurrent invasive bacterial infections
2004 (18)	4, 3	Irrespective
	1,2,3	<200/mm^3
2010 (19)	TB	<350/mm^3
	4	Irrespective
	Irrespective	<200/mm^3
2013 (20)	3,4	Irrespective
	Irrespective	<350/mm^3

Web Table 4. Sensitivity Analyses. The parameter values for the scenarios of interest for sensitivity analyses are outlined below.

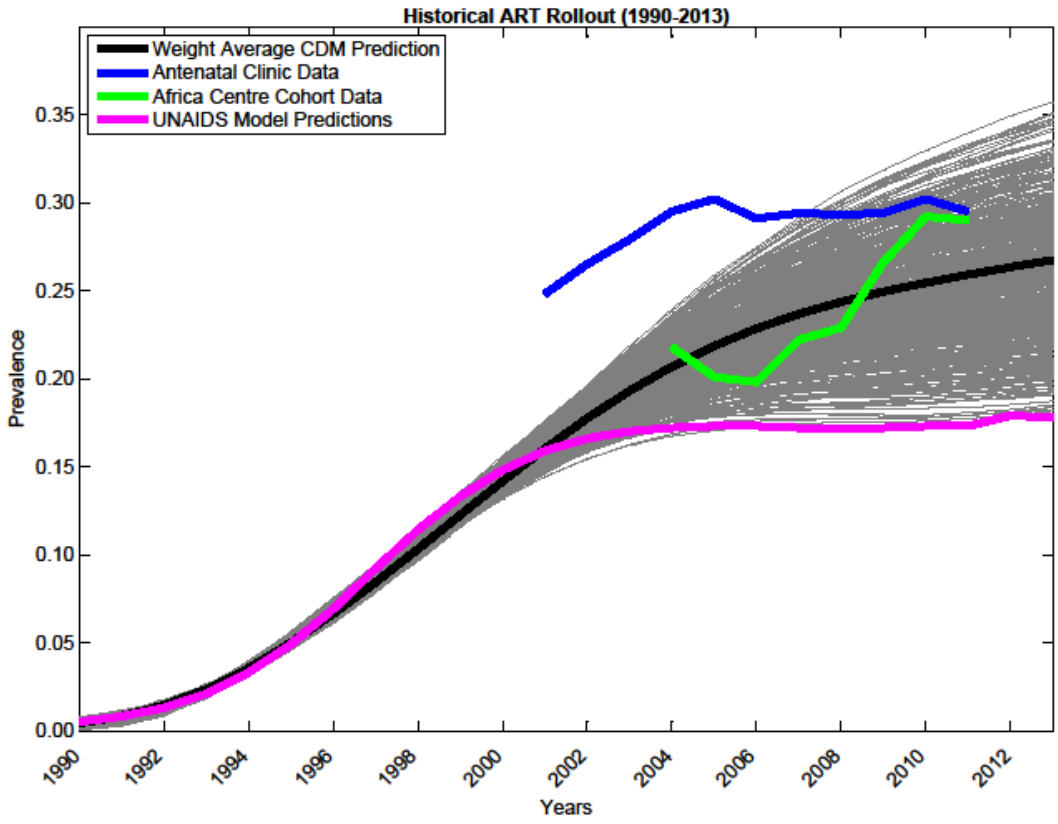
Scenario	ART Expansion Type	Male Circ Prop at Birth (%)	Condom Usage (%)	HIV Testing Interval	HIV Test Accept Rate (%)	Linkage to Care (%)	ART Supp at 6 mo. (%)	Monthly ART late fail prob (%)	LTFU on ART (%)	CD4 Threshold (2013)	HIV RNA Threshold (2013)
Scenario 9 – Status Quo, Perfect test interval	Slow	35	12-50	1 month	50	46.8	78	0.1	9.9	<350	N/A
Scenario 10 – Status Quo, Perfect test accept	Slow	35	12-50	1 year	100	46.8	78	0.1	9.9	<350	N/A
Scenario 11 – Status Quo, Perfect linkage to care	Slow	35	12-50	1 year	50	100	78	0.1	9.9	<350	N/A
Scenario 12 – Status Quo, Perfect suppression	Slow	35	12-50	1 year	50	46.8	100	0	9.9	<350	N/A

Scenario	ART Expansion Type	Male Circ Prop at Birth (%)	Condom Usage (%)	HIV Testing Interval	HIV Test Accept Rate (%)	Linkage to Care (%)	ART Supp at 6 mo. (%)	Monthly ART late fail prob (%)	LTFU on ART (%)	CD4 Threshold (2013)	HIV RNA Threshold (2013)
Scenario 13 – Status Quo, Perfect LTFU	Slow	35	12-50	1 year	50	46.8	78	0.1	0	<350	N/A
Scenario 14 – Status Quo, Ambitious use of HIV RNA threshold for treatment	Slow	35	12-50	1 year	50	46.8	78	0.1	9.9	N/A	>30,000
Scenario 15 – Status Quo, Ambitious use of lower HIV RNA threshold for treatment	Slow	35	12-50	1 year	50	46.8	78	0.1	9.9	N/A	<10,000

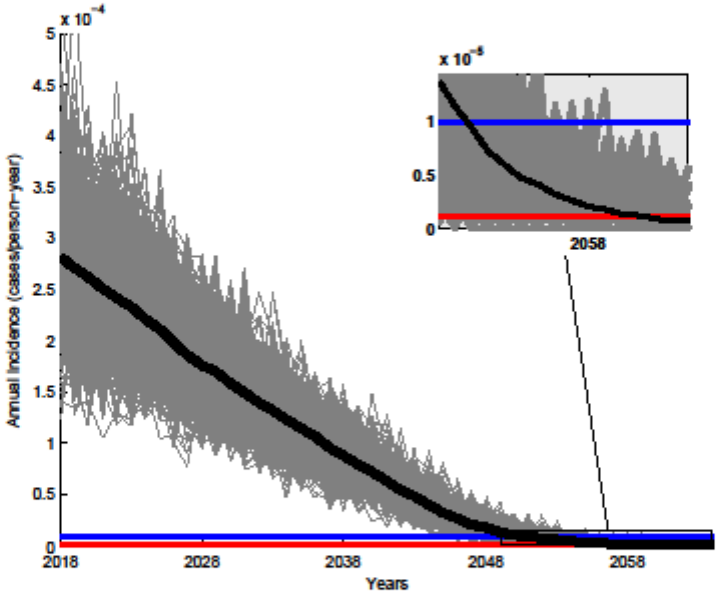
Scenario	ART Expansion Type	Male Circ Prop at Birth (%)	Condom Usage (%)	HIV Testing Interval	HIV Test Accept Rate (%)	Linkage to Care (%)	ART Supp at 6 mo. (%)	Monthly ART late fail prob (%)	LTFU on ART (%)	CD4 Threshold (2013)	HIV RNA Threshold (2013)
Scenario 16 – Status Quo, 100% Condom Usage for CSW Only	Slow	35	Steady: 12 Regular: 29 Casual: 37 CSW: 100	1 year	50	46.8	78	0.1	9.9	<350	N/A
Scenario 17 – Status Quo, 100% Condom Usage for CSW and Casual Partnerships	Slow	35	Steady: 12 Regular: 29 Casual: 100 CSW: 100	1 year	50	46.8	78	0.1	9.9	<350	N/A
Scenario 18 – Status Quo, 100%	Slow	35	Steady: 12 Regular:	1 year	50	46.8	78	0.1	9.9	<350	N/A

Scenario	ART Expansion Type	Male Circ Prop at Birth (%)	Condom Usage (%)	HIV Testing Interval	HIV Test Accept Rate (%)	Linkage to Care (%)	ART Supp at 6 mo. (%)	Monthly ART late fail prob (%)	LTFU on ART (%)	CD4 Threshold (2013)	HIV RNA Threshold (2013)
Condom Usage for Casual Partnerships Only			29 Casual: 100 CSW: 50								
Scenario 19 – Status Quo, 20% Increase in Condom Usage for all Partnership Types	Slow	35	Steady: 14 Regular: 35 Casual: 44 CSW: 60	1 year	50	46.8	78	0.1	9.9	<350	N/A

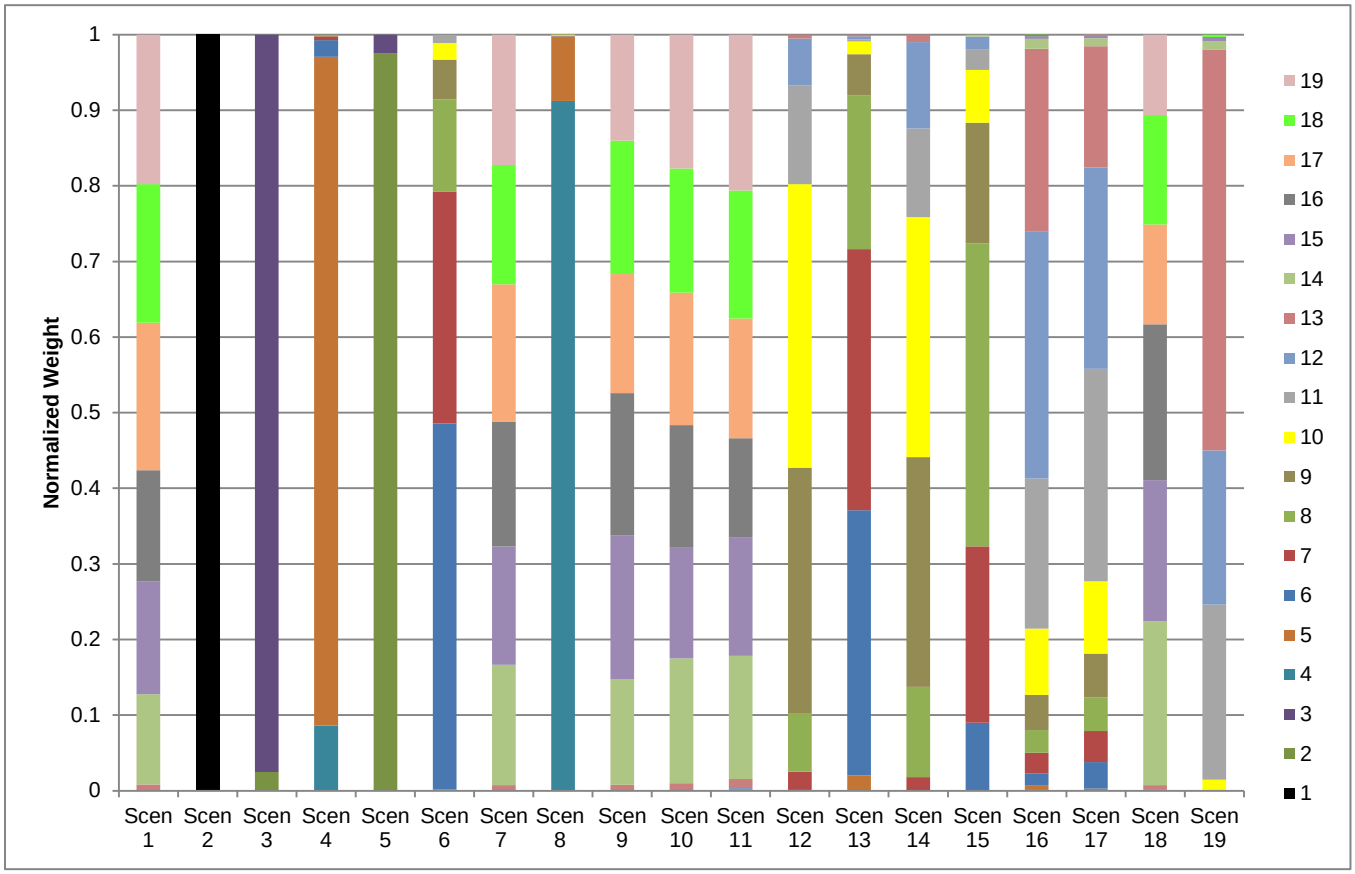
Abbreviations in table: circ = circumcision, prop = proportion, accept = acceptance, supp = suppression rate, mo. = month, LTFU = loss to follow up, prob = probability



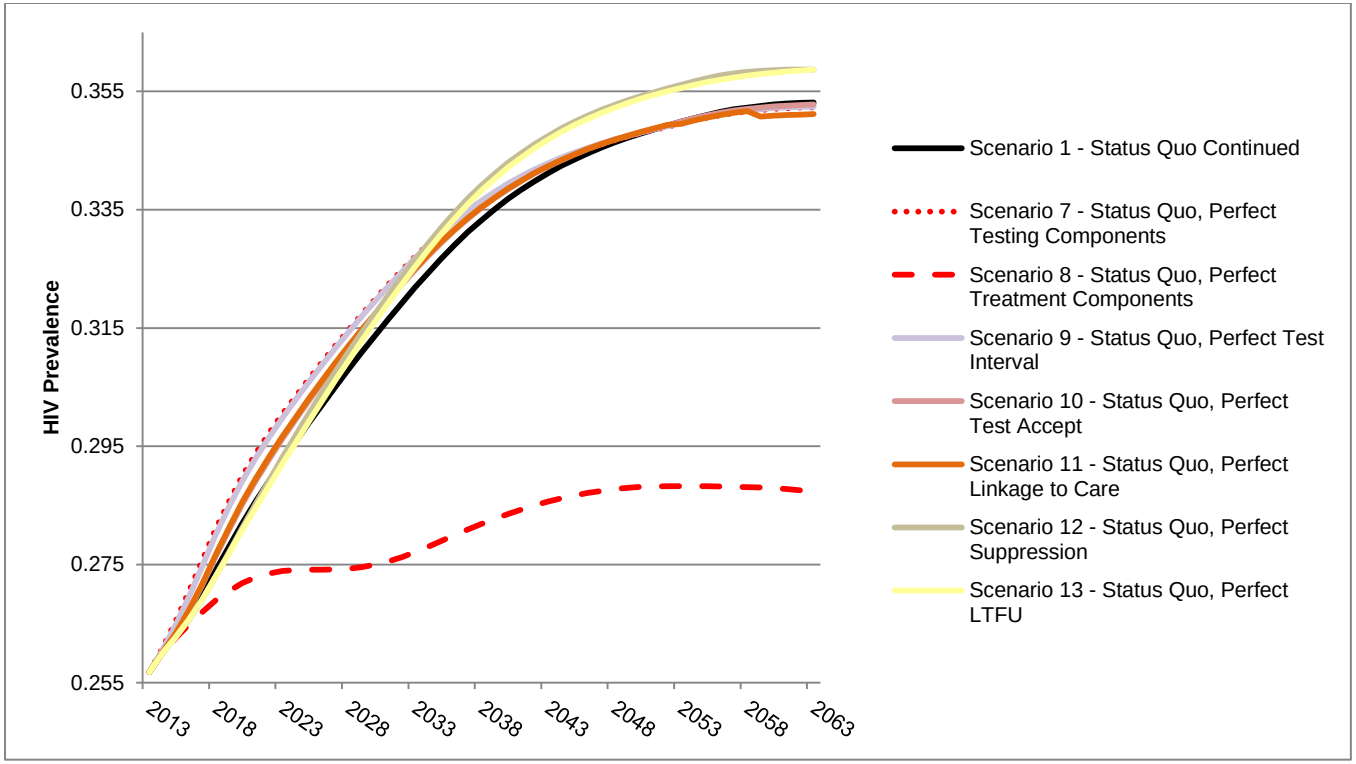
Web Figure 2. Historical ART Rollout (1990-2013). The predicted HIV prevalence from each of the HIV-CDM's 90% weight to fit is depicted above with gray lines, in comparison to South African antenatal clinic data (16) and the Africa Centre Cohort prevalence data (22). The UNAIDS model predictions are much lower after the introduction of ART due to a lack of observed survival benefit of ART.



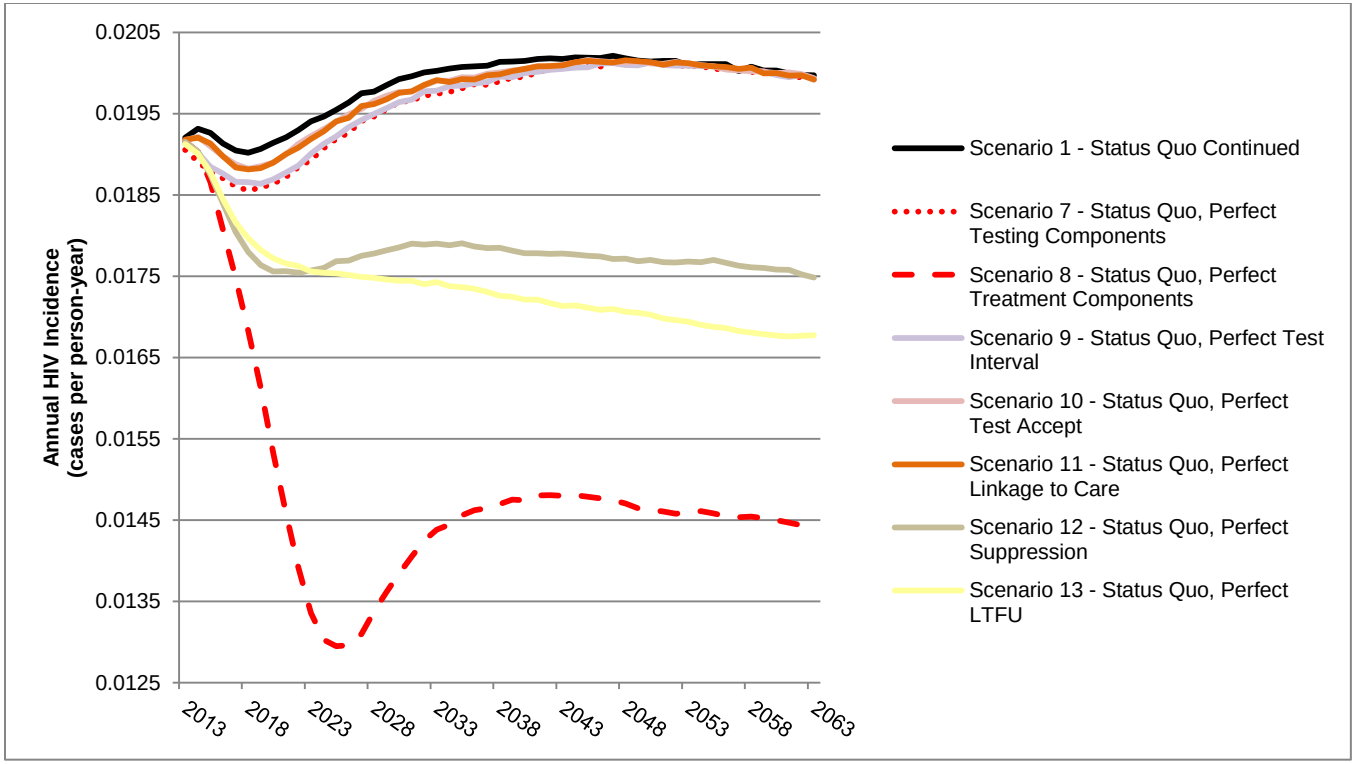
Web Figure 3. Time to Elimination for Perfect Scenario 2. The grey lines in this figure represent each of the 564 parameter sets that contribute the top 90% of the weight to fit from the calibration procedure; the black line represents their weighted average. The horizontal red line represents the elimination threshold of 1 case per 100,000 person-years. The blue line represents an elimination threshold of 1 case per 10,000 person-years. The time to elimination would occur between 2047 and 2063 with an aggressive testing and treatment campaign and perfect primary interventions.



Web Figure 4. Robustness of Incidence Predictions. Boxplots of the relative ranking of scenarios within particular parameter sets. More variation between parameter sets occurs among scenarios with lower reductions in incidence compared to those with higher reductions in incidence.



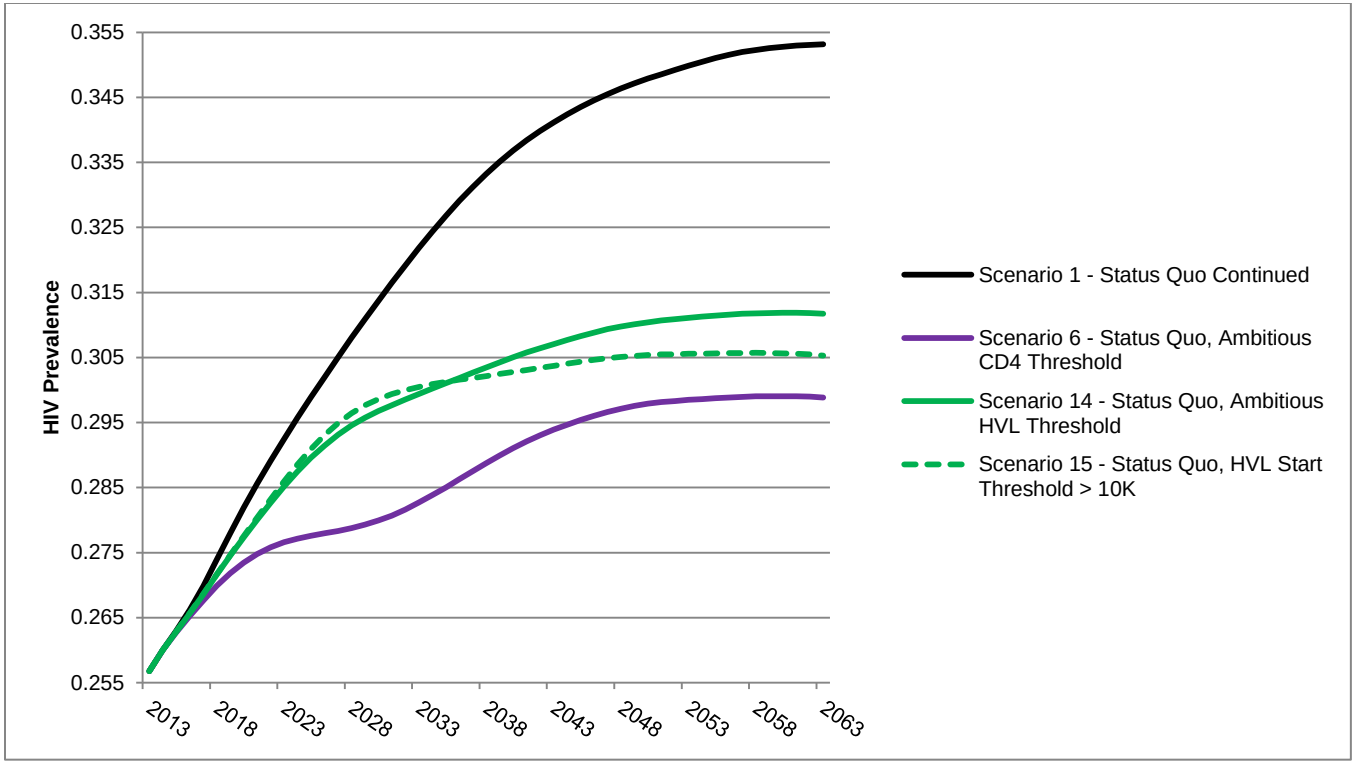
Web Figure 5. HIV Prevalence Curves for Independently Perfect Testing and Treatment Interventions. Independent changes to the testing and treatment cascades do not have a long term impact on the trend for increasing prevalence in South Africa over a 50 year time horizon, with the exception of changes to HIV RNA thresholds, which result in a decrease in HIV prevalence compared with the status quo.



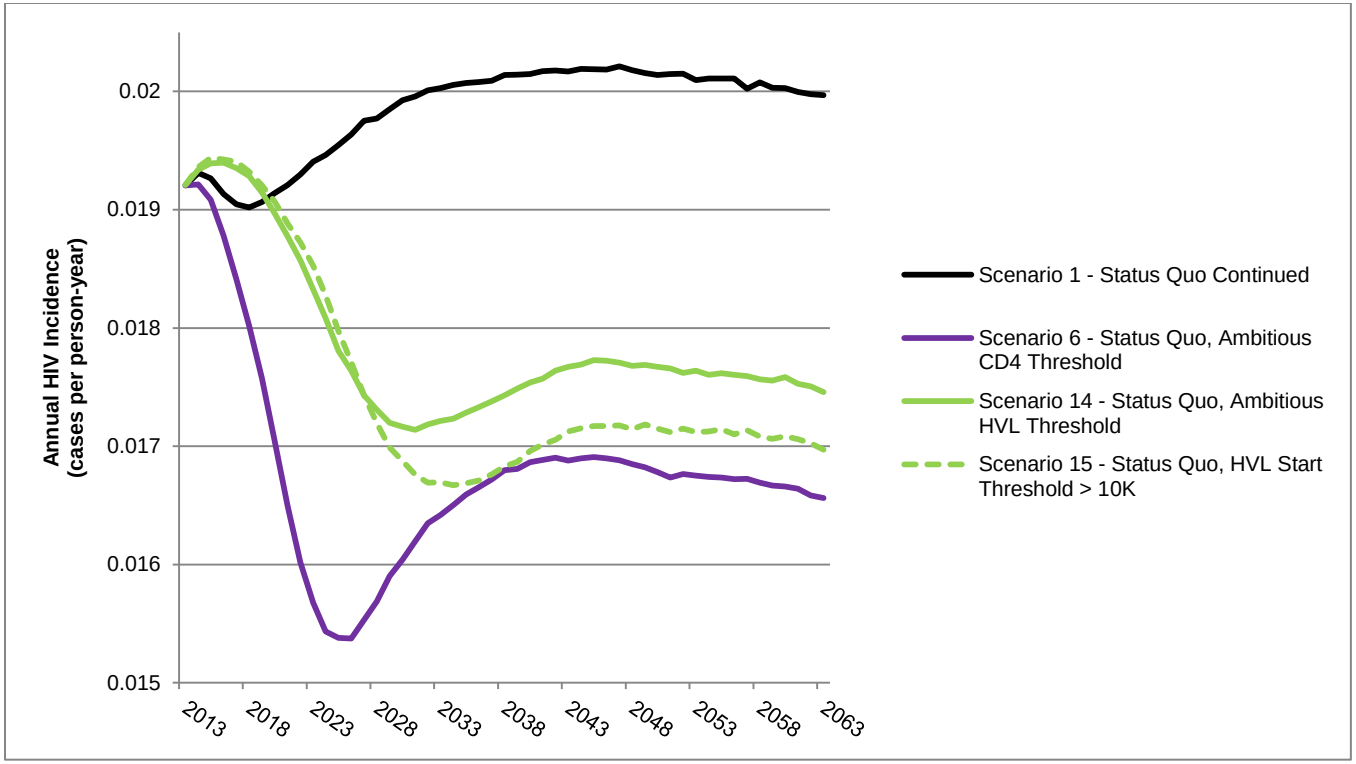
Web Figure 6. HIV Incidence Curves for Independently Perfect Testing and Treatment Interventions. Incidence is reduced slightly for independent changes to the treatment cascade, but no observable differences in incidence are realized with idealized treatment cascade elements.

Web Table 5. Infections Averted for Scenarios 9-19 for Sensitivity Analysis Runs.

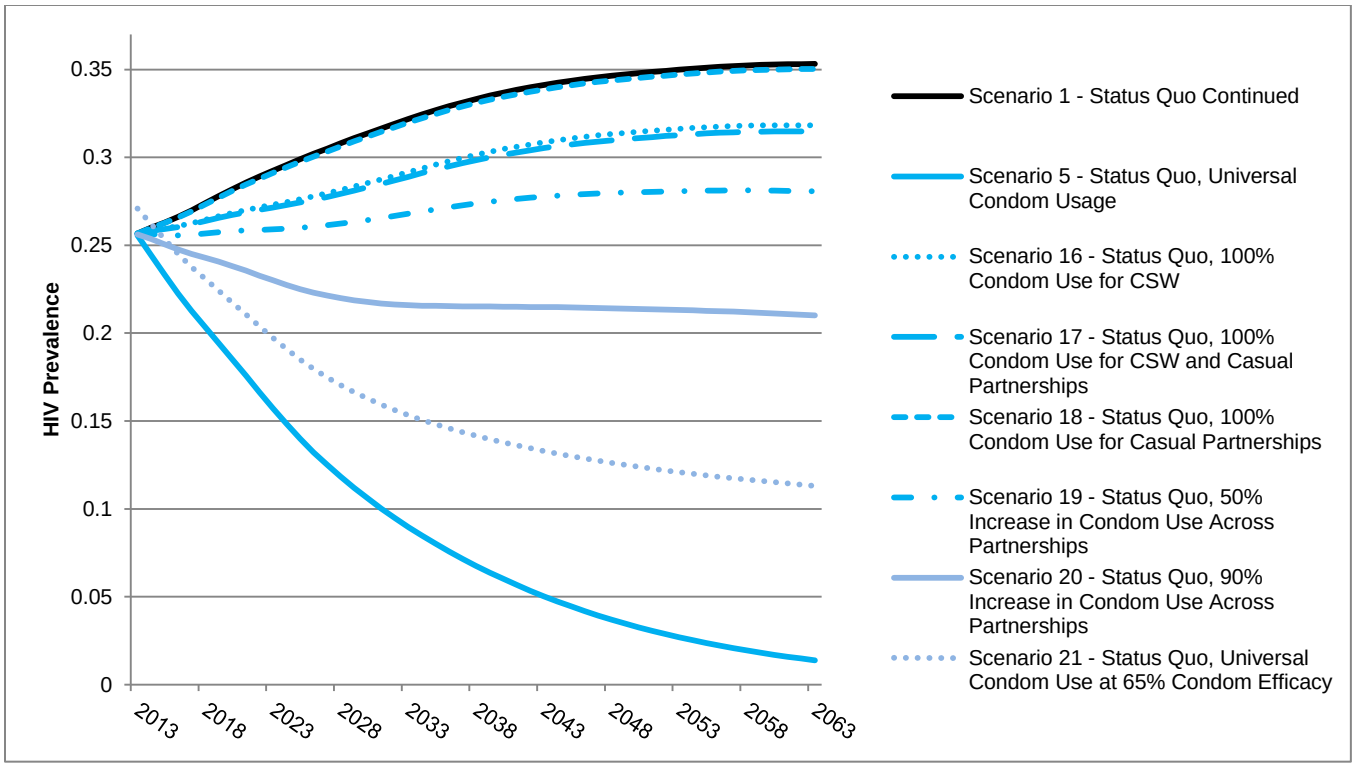
Scenario	Total Incident Infections (2013-2063)	Infections Averted (vs. Scenario 1 - Real)	Percentage of Infections Averted (vs. Scenario 1 – Real)
Scenario 1 – Status Quo Continued	278373	--	--
Scenario 9 – Status Quo, Perfect Test Interval	278636	-263	N/A
Scenario 10 – Status Quo, Perfect Test Accept	278514	-140	N/A
Scenario 11 – Status Quo, Perfect Linkage to Care	558748	-280375	N/A
Scenario 12 – Status Quo, Perfect Suppression	262563	15810	6%
Scenario 13 – Status Quo, Perfect LTFU	256765	21608	8%
Scenario 14 – Status Quo, Ambitious HVL Threshold	252085	26288	9%
Scenario 15 – Status Quo, HVL Start Threshold > 10K	247733	30640	11%
Scenario 16 – Status Quo, 100% Condom Use for CSW	257600	20773	8%
Scenario 17 – Status Quo, 100% Condom Use for CSW and Casual Partnerships	248450	29923	12%
Scenario 18 – Status Quo, 100% Condom Use for Casual Partnerships	276643	1730	1%
Scenario 19 – Status Quo, 20% Increase in Condom Use Across Partnerships	261952	16421	6%



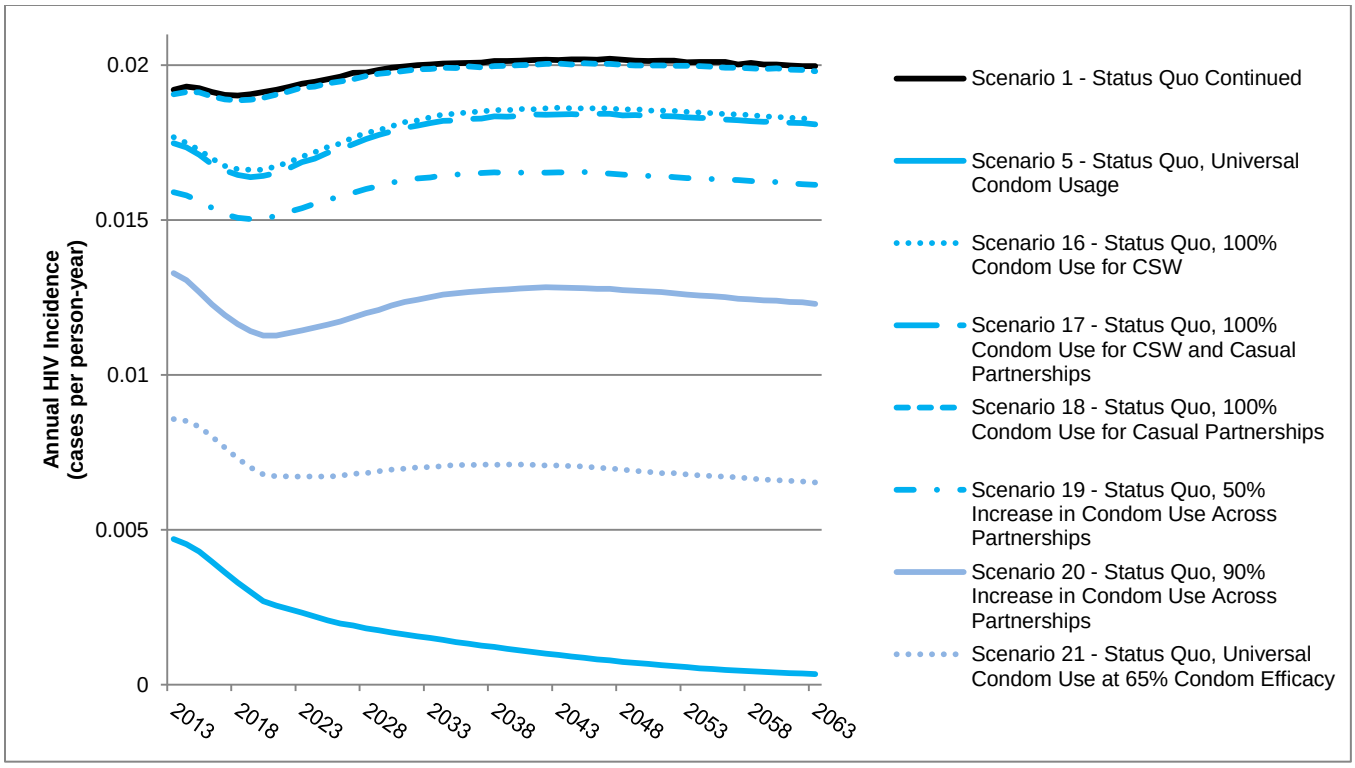
Web Figure 7. HIV prevalence curves for alternate ART starting policies. Test and treat and the alternate test and treat approach (based on a HIV viral load threshold) reduce prevalence over the next 50 years, but a larger reduction is observed with an ambitious CD4 threshold.



Web Figure 8. HIV incidence curves for alternate ART starting policies. Test and treat and the alternate test and treat approach (based on a HIV viral load threshold) reduce incidence over the next 50 years, but a faster and larger reduction is observed with an ambitious strategy of treating everyone regardless of CD4 count (Scenario 6).



Web Figure 9. HIV prevalence curves for alternate condom efficacy interventions. A campaign that focuses on improving condom usage among particular subgroups of the population or among a portion of the population is not as effective at reducing prevalence as a perfect intervention. With modest increases in condom usage across all partnership types (30-60% increase in condom use from Status Quo) we see that prevalence continues to increase over the 50 year period. Only after achieving greater than a 70% increase in condom usage does prevalence decline in the same period. Notably, these reductions are not as large in magnitude as the scenarios in which all partnerships are protected by condom use. The reductions in prevalence are proportional to the efficacy of condom use in all of our sensitivity analyses. Condoms have a larger impact in CSW partnerships than casual partnerships because CSW partnerships are more likely to involve high-risk individuals than casual partnerships. High risk individuals are more likely to be infected in our model structure. Focusing on condom interventions alone does not have a great impact on the epidemic trajectory.



Web Figure 10. HIV incidence curves for alternate condom efficacy interventions. Incidence is only reduced dramatically and quickly in the perfect condom intervention case. In all other variations, condom usage does not impact incidence dramatically. With modest increases in condom usage across all partnership types (30-60% increase in condom use from Status Quo) we see that incidence continues to remain stable over the 50 year period. Only after achieving greater than a 70% increase in condom usage does incidence decline in the same period. Notably, these reductions are not as large in magnitude as the scenarios in which all partnerships are protected by condom use. The reductions in incidence are proportional to the efficacy of condom use in all of our sensitivity analyses. Condoms have a larger impact in CSW partnerships than casual partnerships because CSW partnerships are more likely to involve high-risk individuals than casual partnerships. High risk individuals are more likely to be infected in our model structure.

Web Table 6. **Additional Natural History Input Parameters Used in CEPAC-I**.

Parameter	Value
Natural History	
Percent monthly risk of severe opportunistic infections (%)(21)	
Bacterial	0.08-0.71
Fungal	0.02-2.22
Tuberculosis	0.21-1.96
Toxoplasmosis	0-0.060
Non-tuberculosis mycobacteriosis	0-0.30
Pneumocystis jiroveci pneumonia	0-0.12
Other WHO stage 4-defining diseases	0.25-2.57
Percent monthly risk of mild opportunistic disease (%)	
Fungal	0.59-3.51
Other	2.51-3.10