# Portfolios of Biomedical HIV Interventions in South Africa: A Cost-Effectiveness Analysis

Appendix

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## 1. Overview

We develop a dynamic transmission model of the HIV epidemic in South Africa. The model allows for HIV incidence to change over time and it captures the effects of secondary transmission in the population (i.e., downstream infections that occur due to future transmission caused by primary infected persons). By including a simple model of disease progression, we also project future health outcomes for persons newly infected with HIV. The model accounts for the presence of one or more prevention or treatment programs, at varying coverage levels, and the effect on epidemic and economic outcomes. The model is instantiated with initial conditions based on demographic data in South Africa. We numerically calculate the future course of the epidemic over a 10-year time horizon, and we estimate key epidemic outcomes, including HIV incidence, prevalence, and quality-adjusted life years (QALYs) gained.

Key uncertainties in intervention program efficacy are examined through probabilistic sensitivity analysis. In particular, we append a Monte Carlo simulation to our deterministic compartmental model to randomly sample all model parameters based on a specified probability distribution, and we repeat this 1,000 times. We then show an entire probability distribution on health outcomes (e.g., in *x*% of simulations, more than *y* infections are prevented with portfolio, *z*). The model is implemented in the mathematical programming language Matlab 2012a.

## 2. Population

We include the adult population aged 15 to 49 years in South Africa (Table A1). We subdivide the population based on gender, HIV-infection (uninfected or infected), identification (serostatus-unaware or aware), disease progression if infected (CD4 >350 cells/mm$^3$, CD4 200-350 cells/mm$^3$, CD4 <200 cells/mm$^3$), antiretroviral treatment, and male circumcision status. We estimate current population sizes [1], and HIV prevalence levels among men (15.1%) and women (23.9%).[1-3] We include entry and exit from the population due to non-HIV-related mortality,[4] age maturation,[1] and population growth.[1, 5, 6] Finally, we estimate the fraction of men currently circumcised (40%),[3, 6, 7] the number of persons receiving antiretroviral treatment (350,000 men, 650,000 women),[2] and the fraction of people who received an HIV test in the preceding 12 months (19.9% of men, 28.7% of women)[3] based on the published literature.

## 3. HIV transmission

We include HIV transmission via heterosexual contact, based on published estimates of the probability of transmission (male to female, female to male), number of sexual contacts, and condom use. For sexual behavior, we assume random mixing in the population. The probability of heterosexual HIV transmission between uninfected persons in compartment *i* and infected persons in compartment *j*, at time *t* is:

$$\lambda_{i,j}(t) = n_i(1-u_i\kappa)\left[\frac{X_j(t)n_j(1-u_j\kappa)}{\sum_{\forall k} X_k(t)n_k(1-u_k\kappa)}\right]\sigma_{i,j} \qquad (S1)$$

where $X_i(t)$ refers to the number of persons in compartment *i* at time *t*, $n_i$ and $u_i$ are the average number of sexual partners and condom use by persons in compartment *i*, respectively, and $\kappa$ is condom effectiveness at preventing HIV transmission. The term in square brackets refers to the

behavior-weighted probability of selecting a sexual partner in compartment $j$. The parameter $\sigma_{ij}$ is the per-partner probability of HIV transmission between an infected person in compartment $j$ and an uninfected person in compartment $i$. We adjust the term $\sigma_{ij}$ to reflect differences in transmission based on gender, disease stage, antiretroviral treatment, circumcision, microbicide use, or pre-exposure prophylaxis use, as described in the following section. The effects of HIV screening on sexual behavior are captured in condom use, $u_i$.

## 4. HIV interventions

To account for the effects of prevention and treatment programs on disease transmission and health outcomes, we subdivide the population into 40 mutually exclusive, collective exhaustive compartments (Figure A1). We assume that $\pi_g^s$ is the baseline probability of transmission per heterosexual partnership given no prevention or treatment, where $g \in \{male, female\}$ refers to the gender of the uninfected partner, and $s \in \{CD4 >350, CD4\ 200\text{-}350, CD4 <200\}$ refers to the disease state of the infected partner. We then adjust $\pi_g^s$ and other specific model parameters based on the characteristics of each intervention(s).

### *4.1. HIV screening*

Increased HIV screening and counseling can reduce overall HIV incidence through reduced risky sexual behavior. In particular, we assume that HIV-infected persons who know their HIV status increase overall condom use from 25% to 50%, for their remaining lifetime.[3, 7, 8] We make the conservative assumption that uninfected persons maintain condom use at 25%, regardless of knowing their HIV status. If these individuals do in fact increase condom use

following screening and counseling, then the intervention will have a greater impact on reducing transmission.

*4.2. HIV treatment*

We assume that HIV-infected persons with a CD4 count <350 cells/mm$^3$ are eligible to receive antiretroviral treatment (ART) based on 2010 World Health Organization guidelines. Individuals receiving ART have reduced morbidity and mortality (Table A1), based on published estimates in the literature. In our model, this implies a reduction in disease progression and mortality as well as an increase in quality of life, a decrease in annual HIV-related healthcare costs, and an increase in treatment costs (due to the use of ART).

Additionally, suppressive ART reduces an individual's viral load, subsequently reducing the probability of infecting others. We assume the effectiveness of ART, $\varepsilon_{ART}$, to be 96%, but we vary this from 73% to 99% based on the recent HPTN 052 trial.[9] The probability of HIV transmission between an uninfected person in compartment *i* and an infected person with disease state *s* in compartment *j* who is receiving ART is:

$$\sigma_{i,j} = \pi_g^s(1-\varepsilon_{ART}) \qquad (S2)$$

We assume the effectiveness of ART, $\varepsilon_{ART}$, is the same for both male-to-female and female-to-male HIV transmission, despite differences in baseline transmission probabilities, $\pi_g^s$.

*4.3. Male circumcision*

We assume that male circumcision reduces heterosexual HIV acquisition in uninfected men by 50% ($\varepsilon_C$), but we vary $\varepsilon_C$ from 28% to 66% based on the confidence intervals calculated in meta-analysis of the clinical trials.[10-13] The probability of HIV transmission between an

uninfected, circumcised man in compartment *i* and an infected woman with disease stage *s* in compartment *j* is:

$$\sigma_{i,j} = \pi^{s}_{male}\left(1-\varepsilon_{C}\right) \qquad (S3)$$

*4.4. Microbicide*

Similar to male circumcision, we assume that a vaginal microbicide containing tenofovir reduces HIV acquisition in women who regularly use the microbicide by 39% ($\varepsilon_M$) although we allow $\varepsilon_M$ to vary from 6% to 60% based on the recent CAPRISA 004 trial results in South Africa.[14] The transmission probability between an uninfected woman utilizing a microbicide in compartment *i* and an infected man with disease stage *s* in compartment *j* is:

$$\sigma_{i,j} = \pi^{s}_{female}\left(1-\varepsilon_{M}\right) \qquad (S4)$$

*4.5. Pre-exposure prophylaxis*

We assume that oral pre-exposure prophylaxis (PrEP) reduces the probability of HIV acquisition by 67% $\left(\varepsilon_V^H\right)$ in PrEP recipients with high adherence (who take ≥90% of pills) and by 21% $\left(\varepsilon_V^L\right)$ in PrEP recipients with low adherence (who take <90% of pills). We allow $\varepsilon_V^H$ to vary from 44% to 81%, and $\varepsilon_V^L$ to vary from -31% to 52%,[15-18] where a negative value corresponds to an *increase* in the relative risk of transmission. In our base case, we assume that 50% ($\alpha$) of those on PrEP will have high adherence, a conservative assumption compared to adherence observed in clinical trials, although we vary this value in sensitivity analysis. The transmission probability between an uninfected person with high adherence to PrEP in compartment *i* and an infected person with disease stage *s* in compartment *j* is:

$$\sigma_{i,j} = \pi_g^s \left(1 - \varepsilon_V^H\right) \quad (S5)$$

A similar equation is assumed for individuals with low adherence to PrEP:

$$\sigma_{i,j} = \pi_g^s \left(1 - \varepsilon_V^L\right) \quad (S6)$$

As with ART, we again assume that PrEP has similar effectiveness in both men and women.

*4.6. Combination interventions*

Finally, our model captures the effects of multiple, simultaneous prevention and treatment programs on disease transmission. We compute the joint effectiveness of multiple interventions by assuming the net effectiveness is *multiplicative*. For example, the joint effectiveness of male circumcision and oral PrEP with high adherence is:

$$\varepsilon_{C,V}^H = 1 - \left(1 - \varepsilon_C\right)\left(1 - \varepsilon_V^H\right) \quad (S7)$$

Using our base case numbers, we compute this as: $\varepsilon_{C,V}^H = 1 - \left(1 - 0.50\right)\left(1 - 0.67\right) = 0.835$

We aggregate other combinations of prevention programs in a similar manner.

Because the joint effectiveness of multiple biomedical interventions in yet unknown, we also consider an alternative function that assumes joint effectiveness is the *maximum* of each individual program effectiveness. In our previous example, this would imply:

$$\varepsilon_{C,V}^H = \max\left(\varepsilon_C, \varepsilon_V^H\right) \quad (S8)$$

Using our base case numbers, we compute this as: $\varepsilon_{C,V}^H = \max\left(0.50, 0.67\right) = 0.67$

This approach leads to a more conservative assumption of joint program effectiveness, because it is always lower than the multiplicative scenario.

## 5. Initial conditions

We instantiate the mathematical model using 2010 demographic and epidemiologic data on current population sizes, HIV prevalence levels, and the fraction of the infected population in each disease stage, based on the average time spent in each health state. We then adjust these proportions to account for the use of antiretroviral therapy. We also estimate the fraction of the male population that is circumcised, as well as the fraction of the population who received an HIV test in the preceding 12 months.

## 6. Compartmental model equations

The dynamic compartmental model shown in Figure A1 is characterized by a set of nonlinear differential equations (*S9*)- (*S48*), which define how the system evolves over time due to HIV transmission, disease progression, mortality, and the scale-up of HIV screening, treatment, male circumcision, microbicides, and oral PrEP. The system of equations is given below, followed by a description of each parameter. The health states are shown in Figure A1. For compactness, we allow the term $X_i$ to denote $X_i(t)$.

In equations (*S9*)-(*S48*), we use the following notation:

$\rho_i$ = entry rate for persons in compartment *i*,

$\delta_i$ = death rate for persons in compartment *i*,

$\gamma_i$ = circumcision rate for men in compartment *i*,

$\mu_i$ = microbicide initiation rate for women in compartment *i*,

$\nu_i$ = PrEP initiation rate for persons in compartment *i*,

$\alpha$ = fraction taking PrEP who have high adherence

$\psi_i$ = screening rate for persons in compartment *i*,

$1/\omega$ = average duration of screening status-awareness for uninfected persons,

$\varphi_i$ = treatment initiation rate for persons in compartment *i*,

$\theta_i$ = disease progression rate for infected persons in compartment *i*.

*Male Uninfected*

$$\frac{dX_1}{dt} = \rho_1 \sum_{i=1}^{40} X_i - \left( \sum_{j=21}^{40} \lambda_{1,j}(t) \right) X_1 - \psi_1 X_1 + \omega X_2 - \nu_1 X_1 - \gamma_1 X_1 - \delta_1 X_1 \quad (S9)$$

$$\frac{dX_2}{dt} = -\left( \sum_{j=21}^{40} \lambda_{2,j}(t) \right) X_2 + \psi_1 X_1 - \omega X_2 - \nu_2 X_2 - \gamma_2 X_2 - \delta_2 X_2 \quad (S10)$$

$$\frac{dX_3}{dt} = -\left( \sum_{j=21}^{40} \lambda_{3,j}(t) \right) X_3 - \psi_3 X_3 + \omega X_4 - \nu_3 X_3 + \gamma_1 X_1 - \delta_3 X_3 \quad (S11)$$

$$\frac{dX_4}{dt} = -\left( \sum_{j=21}^{40} \lambda_{4,j}(t) \right) X_4 + \psi_3 X_3 - \omega X_4 - \nu_4 X_4 + \gamma_2 X_2 - \delta_4 X_4 \quad (S12)$$

$$\frac{dX_5}{dt} = -\left( \sum_{j=21}^{40} \lambda_{5,j}(t) \right) X_5 - \psi_5 X_5 + \omega X_6 + \alpha \nu_1 X_1 - \gamma_5 X_5 - \delta_5 X_5 \quad (S13)$$

$$\frac{dX_6}{dt} = -\left( \sum_{j=21}^{40} \lambda_{6,j}(t) \right) X_6 + \psi_5 X_5 - \omega X_6 + \alpha \nu_2 X_2 - \gamma_6 X_6 - \delta_6 X_6 \quad (S14)$$

$$\frac{dX_7}{dt} = -\left( \sum_{j=21}^{40} \lambda_{7,j}(t) \right) X_7 - \psi_7 X_7 + \omega X_8 + (1-\alpha) \nu_1 X_1 - \gamma_7 X_7 - \delta_7 X_7 \quad (S15)$$

$$\frac{dX_8}{dt} = -\left( \sum_{j=21}^{40} \lambda_{8,j}(t) \right) X_8 + \psi_7 X_7 - \omega X_8 + (1-\alpha) \nu_2 X_2 - \gamma_8 X_8 - \delta_8 X_8 \quad (S16)$$

$$\frac{dX_9}{dt} = -\left( \sum_{j=21}^{40} \lambda_{9,j}(t) \right) X_9 - \psi_9 X_9 + \omega X_{10} + \alpha \nu_3 X_3 + \gamma_5 X_5 - \delta_9 X_9 \quad (S17)$$

$$\frac{dX_{10}}{dt} = -\left(\sum_{j=21}^{40}\lambda_{10,j}(t)\right)X_{10} + \psi_9 X_9 - \omega X_{10} + \alpha\nu_4 X_4 + \gamma_6 X_6 - \delta_{10}X_{10} \quad (S18)$$

$$\frac{dX_{11}}{dt} = -\left(\sum_{j=21}^{40}\lambda_{11,j}(t)\right)X_{11} - \psi_{11}X_{11} + \omega X_{12} + (1-\alpha)\nu_3 X_3 + \gamma_7 X_7 - \delta_{11}X_{11} \quad (S19)$$

$$\frac{dX_{12}}{dt} = -\left(\sum_{j=21}^{40}\lambda_{12,j}(t)\right)X_{12} + \psi_{11}X_{11} - \omega X_{12} + (1-\alpha)\nu_4 X_4 + \gamma_8 X_8 - \delta_{12}X_{12} \quad (S20)$$

*Male HIV-Infected*

$$\frac{dX_{13}}{dt} = \left[\sum_{i=1}^{12}\left(\sum_{j=21}^{40}\lambda_{i,j}(t)\right)X_i\right] - \psi_{13}X_{13} - \theta_{13}X_{13} - \delta_{13}X_{13} \quad (S21)$$

$$\frac{dX_{14}}{dt} = \psi_{13}X_{13} - \theta_{14}X_{14} - \varphi_{14}X_{14} - \delta_{14}X_{14} \quad (S22)$$

$$\frac{dX_{15}}{dt} = \theta_{13}X_{13} - \psi_{15}X_{15} - \theta_{15}X_{15} - \delta_{15}X_{15} \quad (S23)$$

$$\frac{dX_{16}}{dt} = \theta_{14}X_{14} + \psi_{15}X_{15} - \theta_{16}X_{16} - \varphi_{16}X_{16} - \delta_{16}X_{16} \quad (S24)$$

$$\frac{dX_{17}}{dt} = \varphi_{14}X_{14} + \varphi_{16}X_{16} - \theta_{17}X_{17} - \delta_{17}X_{17} \quad (S25)$$

$$\frac{dX_{18}}{dt} = \theta_{15}X_{15} - \psi_{18}X_{18} - \delta_{18}X_{18} \quad (S26)$$

$$\frac{dX_{19}}{dt} = \theta_{16}X_{16} + \psi_{18}X_{18} - \varphi_{19}X_{19} - \delta_{19}X_{19} \quad (S27)$$

$$\frac{dX_{20}}{dt} = \theta_{17}X_{17} + \varphi_{19}X_{19} - \delta_{20}X_{20} \quad (S28)$$

*Female Uninfected*

$$\frac{dX_{21}}{dt} = \rho_1 \sum_{i=1}^{40} X_i - \left( \sum_{j=1}^{20} \lambda_{21,j}(t) \right) X_{21} - \psi_{21} X_{21} + \omega X_{22} - \nu_{21} X_{21} - \mu_{21} X_{21} - \delta_{21} X_{21} \quad (S29)$$

$$\frac{dX_{22}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{22,j}(t) \right) X_{22} + \psi_{21} X_{21} - \omega X_{22} - \nu_{22} X_{22} - \mu_{22} X_{22} - \delta_{22} X_{22} \quad (S30)$$

$$\frac{dX_{23}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{23,j}(t) \right) X_{23} - \psi_{23} X_{23} + \omega X_{24} - \nu_{23} X_{23} + \mu_{21} X_{21} - \delta_{23} X_{23} \quad (S31)$$

$$\frac{dX_{24}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{24,j}(t) \right) X_{24} + \psi_{23} X_{23} - \omega X_{24} - \nu_{24} X_{24} + \mu_{22} X_{22} - \delta_{24} X_{24} \quad (S32)$$

$$\frac{dX_{25}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{25,j}(t) \right) X_{25} - \psi_{25} X_{25} + \omega X_{26} + \alpha \nu_{21} X_{21} - \mu_{25} X_{25} - \delta_{25} X_{25} \quad (S33)$$

$$\frac{dX_{26}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{26,j}(t) \right) X_{26} + \psi_{25} X_{25} - \omega X_{26} + \alpha \nu_{22} X_{22} - \mu_{26} X_{26} - \delta_{26} X_{26} \quad (S34)$$

$$\frac{dX_{27}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{27,j}(t) \right) X_{27} - \psi_{27} X_{27} + \omega X_{28} + (1-\alpha) \nu_{21} X_{21} - \mu_{27} X_{27} - \delta_{27} X_{27} \quad (S35)$$

$$\frac{dX_{28}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{28,j}(t) \right) X_{28} + \psi_{27} X_{27} - \omega X_{28} + (1-\alpha) \nu_{22} X_{22} - \mu_{28} X_{28} - \delta_{28} X_{28} \quad (S36)$$

$$\frac{dX_{29}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{29,j}(t) \right) X_{29} - \psi_{29} X_{29} + \omega X_{30} + \alpha \nu_{23} X_{23} + \mu_{25} X_{25} - \delta_{29} X_{29} \quad (S37)$$

$$\frac{dX_{30}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{30,j}(t) \right) X_{30} + \psi_{29} X_{29} - \omega X_{30} + \alpha \nu_{24} X_{24} + \mu_{26} X_{26} - \delta_{30} X_{30} \quad (S38)$$

$$\frac{dX_{31}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{31,j}(t) \right) X_{31} - \psi_{31} X_{31} + \omega X_{32} + (1-\alpha) \nu_{23} X_{23} + \mu_{27} X_{27} - \delta_{31} X_{31} \quad (S39)$$

$$\frac{dX_{32}}{dt} = -\left( \sum_{j=1}^{20} \lambda_{32,j}(t) \right) X_{32} + \psi_{31} X_{31} - \omega X_{32} + (1-\alpha) \nu_{24} X_{24} + \mu_{28} X_{28} - \delta_{32} X_{32} \quad (S40)$$

*Female HIV-Infected*

$$\frac{dX_{33}}{dt} = \left[\sum_{i=21}^{32}\left(\sum_{j=1}^{20}\lambda_{i,j}(t)\right)X_i\right] - \psi_{33}X_{33} - \theta_{33}X_{33} - \delta_{33}X_{33} \quad (S41)$$

$$\frac{dX_{34}}{dt} = \psi_{33}X_{33} - \theta_{34}X_{34} - \varphi_{34}X_{34} - \delta_{34}X_{34} \quad (S42)$$

$$\frac{dX_{35}}{dt} = \theta_{33}X_{33} - \psi_{35}X_{35} - \theta_{35}X_{35} - \delta_{35}X_{35} \quad (S43)$$

$$\frac{dX_{36}}{dt} = \theta_{34}X_{34} + \psi_{35}X_{35} - \theta_{36}X_{36} - \varphi_{36}X_{36} - \delta_{36}X_{36} \quad (S44)$$

$$\frac{dX_{37}}{dt} = \varphi_{34}X_{34} + \varphi_{36}X_{36} - \theta_{37}X_{37} - \delta_{37}X_{37} \quad (S45)$$

$$\frac{dX_{38}}{dt} = \theta_{35}X_{35} - \psi_{38}X_{38} - \delta_{38}X_{38} \quad (S46)$$

$$\frac{dX_{39}}{dt} = \theta_{36}X_{36} + \psi_{38}X_{38} - \varphi_{39}X_{39} - \delta_{39}X_{39} \quad (S47)$$

$$\frac{dX_{40}}{dt} = \theta_{37}X_{37} + \varphi_{39}X_{39} - \delta_{40}X_{40} \quad (S48)$$

## 7. Health and economic outcomes

We numerically solve the system of nonlinear differential equations (*S9*)-(*S48*) using a Runge-Kutta 4$^{th}$-order method with variable time steps. The model computes the number of individuals in each compartment over time. We then calculate the following health and economic outcomes over a 10 year time horizon: HIV prevalence, new HIV infections, discounted costs and health benefits (quality-adjusted life years), and incremental cost-effectiveness ratios. We calculate HIV prevalence for men and women using the following equations.

$$\text{Male HIV prevalence at time } t = \frac{\sum_{i=13}^{20} X_i(t)}{\sum_{i=1}^{20} X_i(t)} \quad (S49)$$

$$\text{Female HIV prevalence at time } t = \frac{\sum_{i=33}^{40} X_i(t)}{\sum_{i=21}^{40} X_i(t)} \quad (S50)$$

We calculate the number of new HIV infections that occur among men and women over the time horizon, $T$ (10 years).

$$\text{Male HIV infections} = \int_0^T \sum_{i=1}^{12} \sum_{j=33}^{40} \lambda_{i,j}(t) X_i(t) dt \quad (S51)$$

$$\text{Female HIV infections} = \int_0^T \sum_{i=21}^{32} \sum_{j=13}^{20} \lambda_{i,j}(t) X_i(t) dt \quad (S52)$$

We calculate total health benefits for the population, measured in discounted quality-adjusted life years (QALYs). We assume an infinite time horizon to account for health benefits occurring after the time horizon, where $q_i$ corresponds to the quality of life factor for persons in compartment $i$.

$$\text{QALYs} = \int_0^\infty e^{-rt} \sum_{i=1}^{40} q_i X_i(t) dt \quad (S52)$$

We similarly compute total discounted costs for the entire population, as the sum of annual healthcare costs for persons in each compartment, $c_i$, as well as total intervention costs. Thus, total costs include the direct costs of the interventions and related healthcare costs over the

specified time horizon (10 years), as well as future discounted lifetime costs for all persons alive at the end of the time horizon. All costs are converted to 2010 international dollars, which are equivalent to U.S. dollars calculated using purchasing power parity (PPP) exchange rates.

Finally, we calculate the incremental cost-effectiveness ratio (ICER) of each portfolio strategy, relative to the status quo and the next-best strategy on the cost-effectiveness frontier.

$$\text{ICER} = \frac{Costs_{Intervention} - Costs_{StatusQuo}}{QALYs_{Intervention} - QALYs_{StatusQuo}} \qquad (S53)$$

## 8. Model calibration

We calibrate our epidemic model to recent estimates from the Actuarial Society of South Africa (ASSA), based on their ASSA2008 model (Figure A2). We systematically vary key model parameters until we obtain a close fit to data since 2006. We choose to use only more recent data because of possible differences in behavior during the earlier part of the epidemic. We compare our model's projection to data on HIV incidence in the population, and we find a close fit from 2006 to 2012. From 2012 onwards, our model projects that HIV incidence will continue to decline, as more people initiate ART and other prevention programs (e.g., voluntary male circumcision, HIV screening and counseling) continue to increase. Our model results are slightly lower than ASSA projections, which assume relatively constant HIV incidence from 2010. We believe our model is conservative because if baseline incidence is indeed higher than our model projects, then a portfolio of partially effective interventions will have a greater impact and likely be more cost-effective.

## 9. Optimal portfolio

Using our deterministic model parameters, we determine the optimal portfolio given a particular budget constraint. For computational tractability, we discretize the level of each intervention implemented as follows:

1) Male circumcision: 0, 0.10, 0.20, 0.3, 0.4 (annual rate)
2) Microbicide: 0%, 25%, 50%, 75%, 100% (utilization)
3) PrEP: 0%, 10%, 20%, 30%, 40%, 50% (utilization)
4) ART: 37%, 50%, 60%, 70%, 80%, 90%, 100% (utilization)
5) Screening: every three years, two years, one year, six months (frequency)

This creates 4,200 different combinations of interventions. For each portfolio combination, we apply our deterministic model to estimate future HIV infections, costs, and QALYs over a 10 year time horizon. We show the *efficient frontier* or the portfolio that maximizes QALYs gained (Figure A4), for varying levels of investment (x-axis). We also show some illustrative portfolios for different budget levels (Table A2). With a limited state space of 4,200 portfolios, the deterministic model runtime is approximately 10 hours (Intel Core i7, 2.67 GHz, 8 GB RAM).

## 10. Monte Carlo simulation

Although several recent trials have shown statistically significant reductions in HIV transmission due to male circumcision, vaginal microbicides, and PrEP, there is still uncertainty in the expected effectiveness of these programs if implemented in practice, due to potential variations in adherence, sexual behavior, biological susceptibility, etc. Moreover, the joint effectiveness of implementing one or more interventions simultaneously is unknown. To

account for uncertainty in program effectiveness and other model parameters, we layer a Monte Carlo simulation on top of our dynamic compartmental model, which entails the following steps:

a) Assign a random variable, $\mathbf{Y_i}$, for each uncertain parameter and specify a probability distribution. For male circumcision, vaginal microbicide, and PrEP, we assume the intervention's relative risk reduction follows a lognormal distribution based on the sampling distribution obtained from the clinical trials (Table 1). The "effectiveness" of an intervention is thus 1-(relative risk), as defined in the clinical trials.

Male circumcision: $\mathbf{Y_1} \sim Normal(-0.6932, 0.1914)$

$$\varepsilon_C = 1\text{-}exp(\mathbf{Y_1})$$

Microbicide: $\mathbf{Y_2} \sim Normal(-0.4855, 0.2180)$

$$\varepsilon_M = 1\text{-}\ exp(\mathbf{Y_2})$$

PrEP (High): $\mathbf{Y_3} \sim Normal(-1.1087, 0.2757)$

$$\varepsilon_V^H = 1\text{-}exp(\mathbf{Y_3})$$

PrEP (Low): $\mathbf{Y_4} \sim Normal(-0.2357, 0.2561)$

$$\varepsilon_V^L = 1\text{-}\ exp(\mathbf{Y_4})$$

ART: $\mathbf{Y_5} \sim Normal(-3.2189, 0.8408)$

$$\varepsilon_{ART} = 1\text{-}\ exp(\mathbf{Y_5})$$

For HIV screening, we assume a uniform distribution on the average condom use following screening and counseling for HIV-infected persons.

Condom use: $\mathbf{Y_6} \sim Uniform(0.25,0.75)$

For all other model parameters, we assume *independent*, *uniform* probability distributions over the ranges shown in Table 1.

b) On each simulation iteration, draw a random sample from each probability distribution.

$$\mathbf{Y_1} = y_1$$

$$\dots$$

$$\mathbf{Y_n} = y_n$$

c) Holding this set of values ($y_1, \dots, y_n$) fixed, numerically solve the system of differential equations *(S9)-(S48)* and calculate epidemic outcomes.

d) Repeat step (c) for each intervention portfolio considered.

e) Repeat steps (b)-(d) for $N$ iterations. We present results for $N$=1,000 iterations.

f) Report the distribution of simulation outcomes, including HIV infections prevented, HIV prevalence, costs, and QALYs.

The model run time is approximately 60 minutes for each intervention portfolio considered, given 1,000 iterations (Intel Core i7, 2.67 GHz, 8 GB RAM).

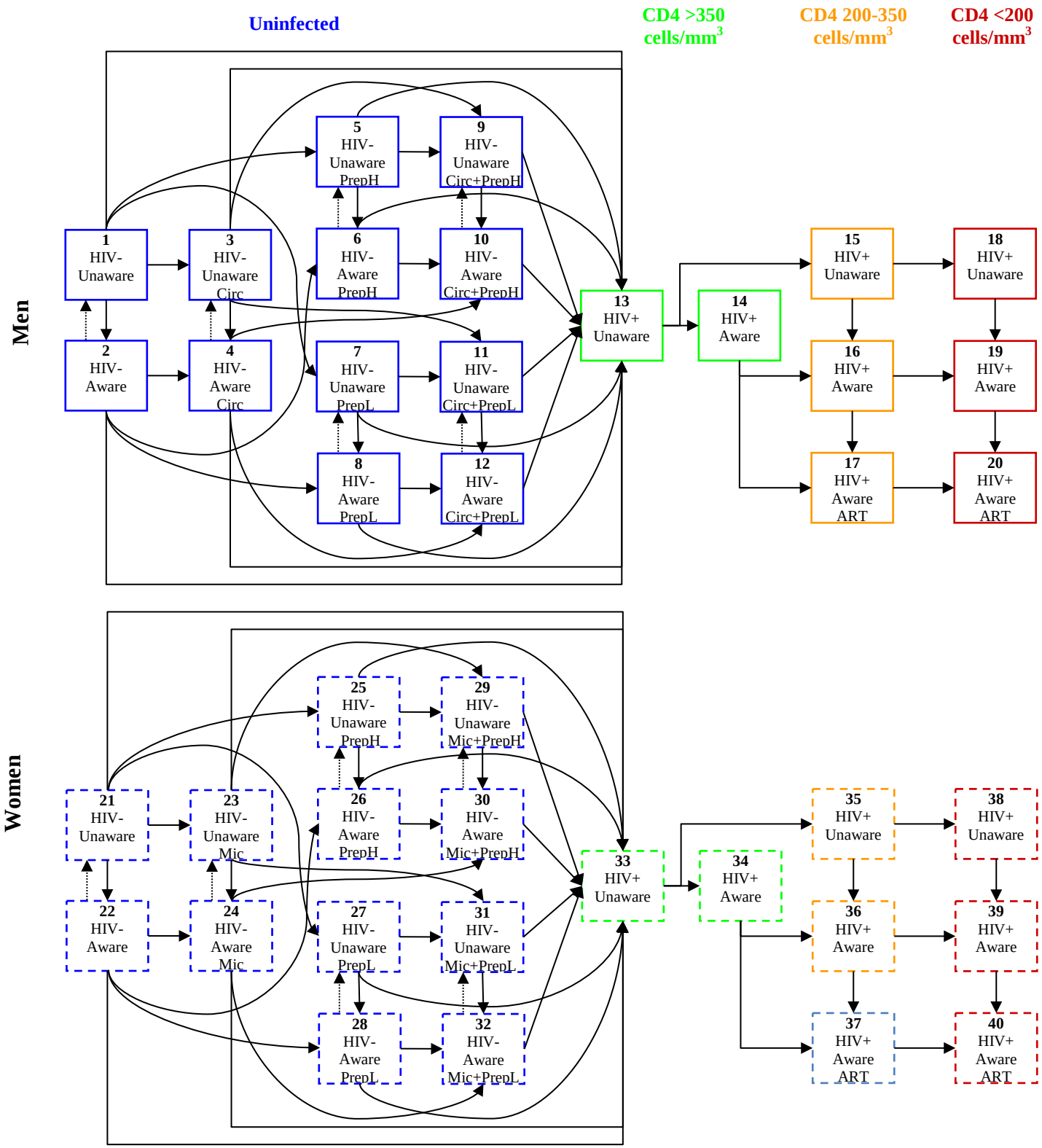



**Figure A1.** Schematic model diagram where boxes represent cohorts of men (solid outline) and women (dashed outline) in each disease stage. Transitions occur due to disease transmission, progression, mortality, or prevention or treatment initiation. Unaware = Serostatus-unaware, Aware = Serostatus-aware, PrepH = Pre-exposure prophylaxis (oral) with high adherence, PrepL = Pre-exposure prophylaxis (oral) with low adherence, Circ = Circumcision, Mic = Microbicide (vaginal), ART = Antiretroviral Therapy.

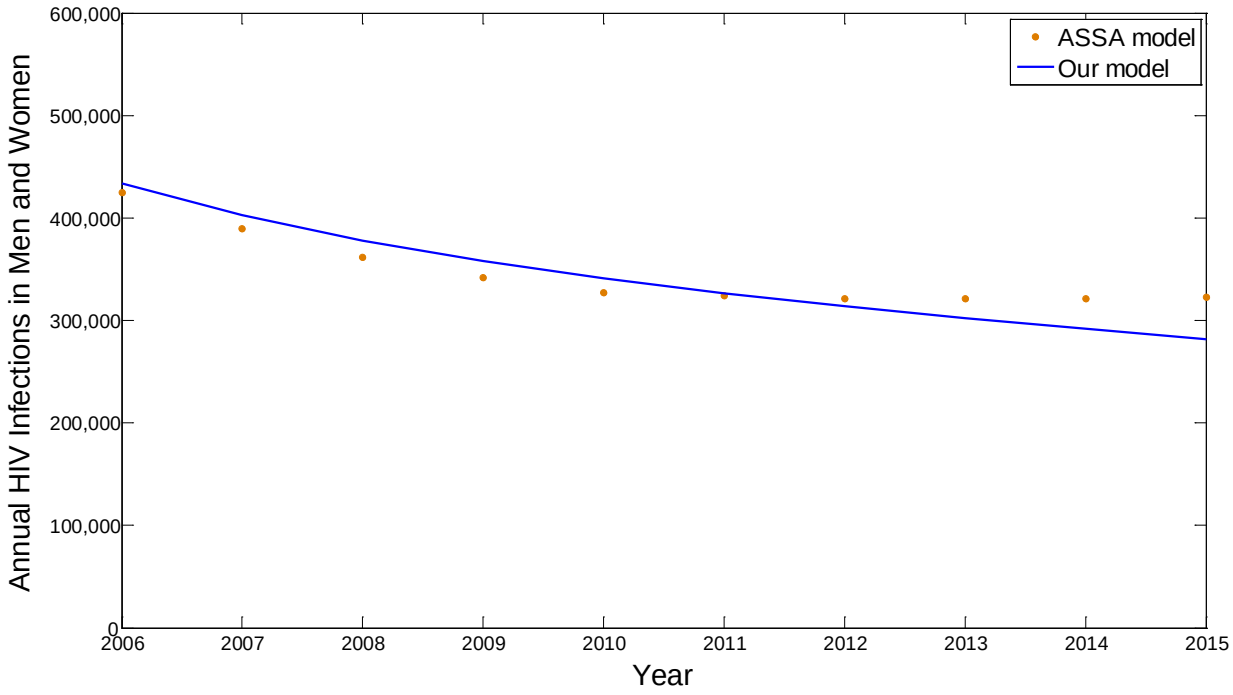



**Figure A2.** Model calibration.
Historical and projected annual new HIV infections (2006-2015) using our model (blue line) or based on the model (orange dots) from the Actuarial Society of South Africa (ASSA), 2011.[19]

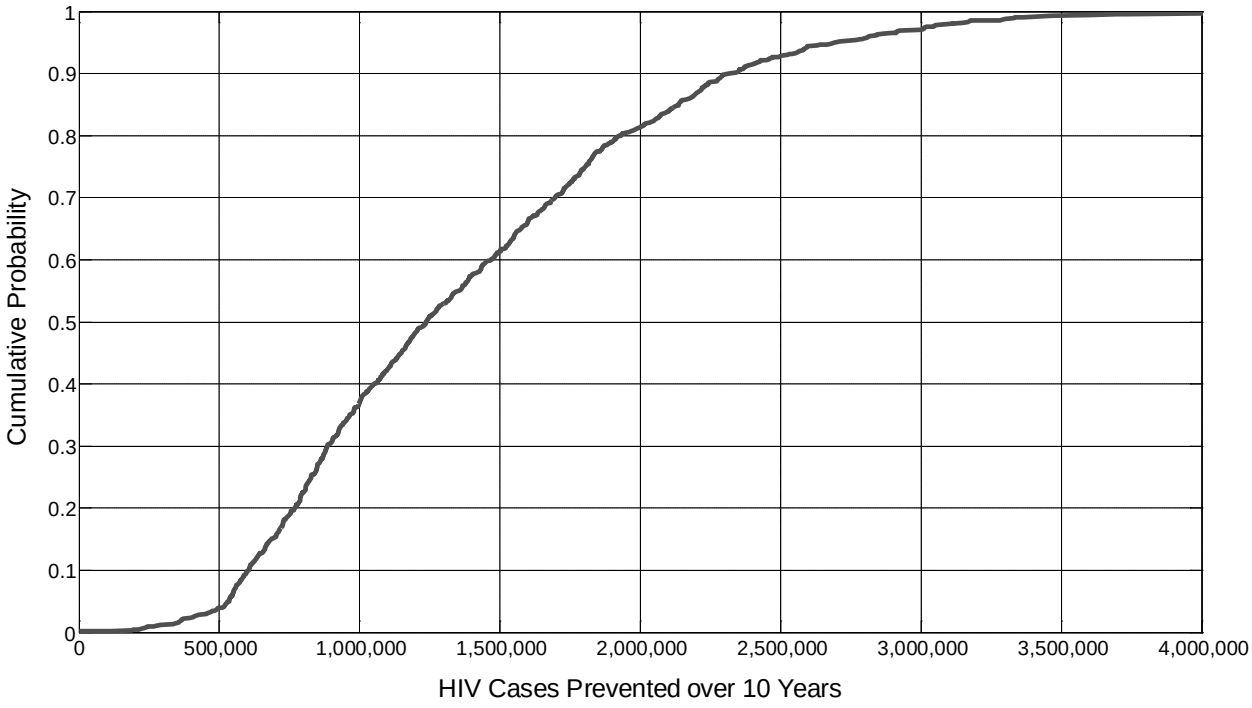
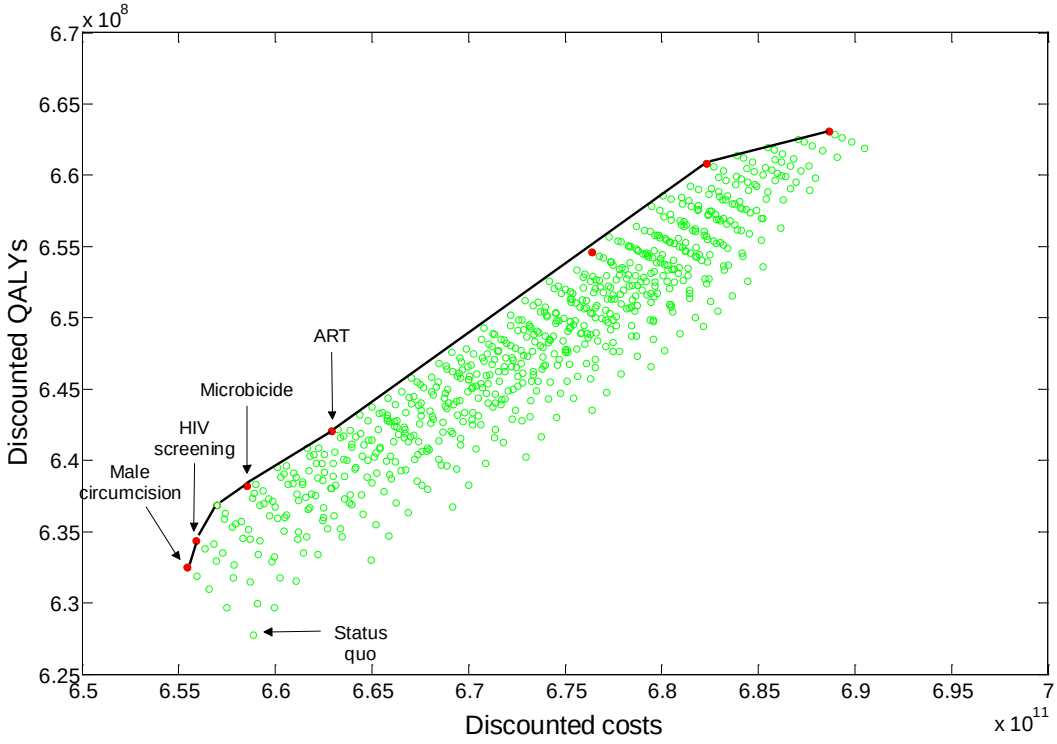



**Figure A3.** Cumulative distribution of HIV infections prevented over 10 years.
A cumulative probability distribution showing the number of HIV cases averted over 10 years with a combination portfolio compared to the status quo, given a Monte Carlo simulation with 1,000 iterations.

(a)




(b)

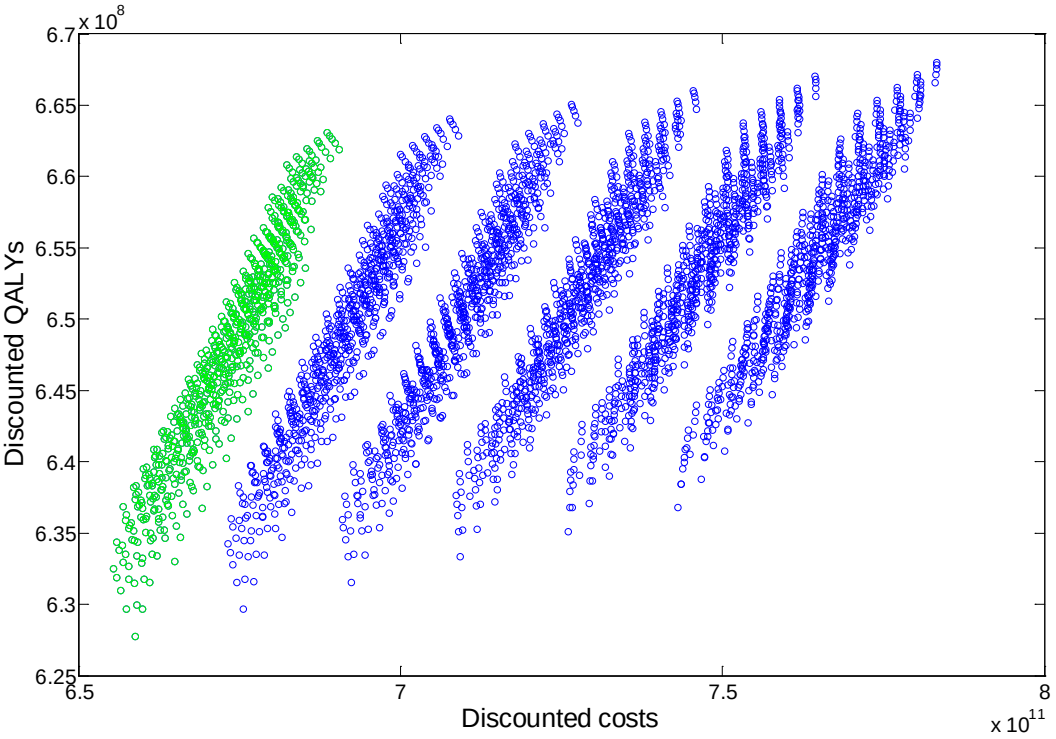



**Figure A4.** Optimal portfolio for a given budget.

(a) Discounted costs and discounted QALYs over 10 years are shown for 700 portfolios (excluding PrEP). The labels indicate when each intervention enters the optimal portfolio, and the black line corresponds to the efficient frontier. The red points show illustrative optimal portfolios for different budget levels (Table A2).

(b) Discounted costs and discounted QALYs over 10 years are shown for 4,200 portfolios (including PrEP).

**Table A1.** Summary of key model parameters.

| Parameter | Value | Range | Source |
|---|---|---|---|
| **Demographic Parameters** | | | |
| Total population (15-49 years) | | | |
| Men | 13,204,600 | 13.0-13.5 million | [1] |
| Women | 13,814,600 | 13.5-14.0 million | [1] |
| HIV prevalence | | | |
| Men | 15.1% | 12-18% | [1-3] |
| Women | 23.9% | 20-25% | [1-3] |
| Mortality rate (non-HIV-related) | | | |
| Men | 0.028 | 0.02-0.03 | [4] |
| Women | 0.028 | 0.02-0.03 | [4] |
| Maturation rate | | | |
| Men | 0.0162 | 0.015-0.020 | [1, 20] |
| Women | 0.0185 | 0.015-0.020 | [1, 20] |
| Entry rate (including growth rate) | | | |
| Men | 0.0548 | 0.05-0.06 | [1, 5, 6] |
| Women | 0.0571 | 0.05-0.06 | [1, 5, 6] |
| | | | |
| **Disease Parameters** | | | |
| Disease mortality rate | | | |
| CD4 >350 cells/$mm^3$ | 0.01 | 0.005-0.02 | [21-23] |
| CD4 200-350 cells/$mm^3$ | 0.04 | 0.02-0.05 | [21-23] |
| CD4 200-350 cells/$mm^3$ on ART | 0.01 | 0.005-0.02 | [21-23] |
| CD4 <200 cells/$mm^3$ | 0.40 | 0.25-0.50 | [21-23] |
| CD4 <200 cells/$mm^3$ on ART | 0.13 | 0.10-0.40 | [21-23] |
| Disease progression rate | | | |
| CD4 >350 cells/$mm^3$ | 0.125 | 0.10-0.20 | [21-23] |
| CD4 200-350 cells/$mm^3$ | 0.30 | 0.20-0.50 | [21-23] |
| CD4 200-350 cells/$mm^3$ on ART | 0.10 | 0.05-0.20 | [21-23] |
| Quality-of-life factor | | | |
| Uninfected | 1.0 | - | [24] |
| CD4 >350 cells/$mm^3$ | | | |
| Status-unaware | 0.91 | 0.68-1.0 | [25-28] |
| Status-aware (first year) | 0.84 | 0.63-1.0 | [25-30] |
| Status-aware (subsequent years) | 0.89 | 0.67-1.0 | [25-30] |

| Parameter | Value | Range | Source |
|---|---|---|---|
| CD4 200-350 cells/mm$^3$ | | | |
| Status-unaware | 0.79 | 0.59-0.99 | 25-28, 31 |
| Status-aware | 0.72 | 0.54-0.90 | 25-28 |
| On ART | 0.83 | 0.62-1.0 | 25-28 |
| CD4 <200 cells/mm$^3$ | | | |
| Status-unaware | 0.72 | 0.54-0.90 | 25-28 |
| Status-aware | 0.72 | 0.54-0.90 | 25-28 |
| On ART | 0.82 | 0.62-1.0 | 25-28 |
| **Sexual Behavior Parameters** | | | |
| Annual number of sexual partners | 2.5 | 1-3 | 7 |
| Condom effectiveness | 90% | 75-99% | 4 |
| Annual transmission probability per partnership ($F_{HIV+} \rightarrow M_{HIV-}$) | | | |
| CD4 >350 cells/mm$^3$ | 0.06 | 0.04-0.08 | 32-36 |
| CD4 200-350 cells/mm$^3$ | 0.08 | 0.06-0.10 | 32-36 |
| CD4 <200 cells/mm$^3$ | 0.10 | 0.08-0.12 | 32-36 |
| Annual transmission probability per partnership ($M_{HIV+} \rightarrow F_{HIV-}$) | | | |
| CD4 >350 cells/mm$^3$ | 0.08 | 0.06-0.10 | 32-36 |
| CD4 200-350 cells/mm$^3$ | 0.10 | 0.08-0.12 | 32-36 |
| CD4 <200 cells/mm$^3$ | 0.12 | 0.10-0.14 | 32-36 |
| **Screening Parameters** | | | |
| Proportion who received HIV test in past 12 months | | | |
| Men | 19.9% | - | 3 |
| Women | 28.7% | - | 3 |
| Proportion of HIV-infected population who is status-aware | 35% | - | 3 |
| Average duration of status-awareness in uninfected population | 1 year | - | Assumed |
| Annual symptom-based case finding rate | | | |
| CD4 200-350 cells/mm$^3$ | 0.1 | 0-0.2 | Assumed |
| CD4 <200 cells/mm$^3$ | 0.1 | 0-0.2 | Assumed |
| Condom use among status-unaware persons | 25% | 20-50% | 3, 7, 8 |
| Condom use among status-aware persons | | | |

| Parameter | Value | Range | Source |
|---|---|---|---|
| Uninfected | 25% | 20-50% | [3, 7, 8] |
| HIV-infected | 50% | 25-75% | [3, 7, 8] |
| **Treatment Parameters** | | | |
| Number of people receiving ART | | | |
| Men | 350,000 | - | [2] |
| Women | 650,000 | - | [2] |
| Proportion currently receiving ART | | | |
| CD4 <200 cells/mm$^3$ (2006 guidelines) | 56% | - | [2] |
| CD4 <350 cells/mm$^3$ (2010 guidelines) | 37% | - | [2] |
| Reduction in sexual infectivity due to ART | 96% | 73-99% | [9] |
| **Circumcision Parameters** | | | |
| Proportion of males circumcised | 40% | - | [3, 6, 7] |
| Reduction in HIV acquisition among men due to circumcision | 50% | 28-66% | [10-13] |
| **Microbicide Parameters** | | | |
| Reduction in HIV acquisition among women due to vaginal microbicide (tenofovir gel) | 39% | 6-60% | [14] |
| **Pre-exposure Prophylaxis (PrEP) Parameters** | | | |
| Reduction in HIV acquisition due to oral PrEP | | | |
| High adherence | 67% | 44-81% | [15-18] |
| Low adherence | 21% | -31-52% | [15-18] |
| Proportion on PrEP with high adherence | 50% | - | Assumed |
| **Costs Parameters (2010 international dollars)** | | | |
| Annual HIV-related healthcare costs | | | |
| CD4 >350 cells/mm$^3$ | $640 | $500-900 | [22] |
| CD4 200-350 cells/mm$^3$ | $950 | $800-1,200 | [22] |
| CD4 200-350 cells/mm$^3$ on ART | $846 | $800-1,200 | [22] |
| CD4 <200 cells/mm$^3$ | $4,747 | $4,000-6,000 | [22] |
| CD4 <200 cells/mm$^3$ on ART | $1,082 | $500-2,000 | [22] |
| Annual per capita health expenditures | $856 | $750-1,000 | [37] |
| Annual cost of ART | | | |

| Parameter | Value | Range | Source |
|---|---|---|---|
| First-line regimen | $800 | $400-1,000 | [38] |
| Second-line regimen | $1,200 | $600-2,000 | [38] |
| Cost of HIV testing and counseling | | | |
| HIV- | $10 | $5-25 | [39, 40] |
| HIV+ | $25 | $10-50 | [39, 40] |
| Cost of male circumcision | $70 | $50-100 | [41] |
| Cost of oral PrEP | $800 | $400-1,000 | Assumed |
| Annual cost of vaginal microbicide | $100 | $50-300 | Assumed |
| Annual discount rate | 3% | - | [42] |

**Table A2.** Optimal portfolio given a particular budget.

| Incremental costs over 10 years | Incremental QALYs over 10 years | Optimal Portfolio | | | | |
|---|---|---|---|---|---|---|
| | | ART | Screening | Circumcision | Microbicide | PrEP |
| -$3.4B | 4.8M | Status quo | Every 3 yr | 0.4 | 0% | 0% |
| -$2.9B | 6.7M | Status quo | Every 2 yr | 0.4 | 0% | 0% |
| -$0.3B | 10.4M | Status quo | Annual | 0.4 | 25% | 0% |
| $4.1B | 14.3M | 50% | Annual | 0.4 | 0% | 0% |
| $17.5B | 26.9M | 80% | Every 6 mo | 0.4 | 0% | 0% |
| $23.5B | 33.1M | 100% | Every 6 mo | 0.4 | 0% | 0% |
| $29.8B | 35.3M | 100% | Every 6 mo | 0.4 | 100% | 0% |
| $124.4B | 40.3M | 100% | Every 6 mo | 0.4 | 100% | 50% |

Illustrative optimal portfolios are shown, for different budget levels ("Incremental costs over 10 years"). Each portfolio falls on the efficient frontier, which represents the portfolio maximizing QALYs for a given budget level (also shown in red in Figure A4).

**Appendix References**


**1.** Statistics South Africa. *Mid-year population estimates.* Pretoria, South Africa 2010.

**2.** Joint United Nations Programme on HIV/AIDS (UNAIDS). *Report on the global AIDS epidemic.* Geneva 2010.

**3.** Shisana O, Rehle T, Simbayi L, et al. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2008: A turning tide among teenagers?* Cape Town: HSRC Press; 2009.

**4.** Andersson KM, Owens DK, Vardas E, Gray GE, McIntyre JA, Paltiel AD. Predicting the impact of a partially effective HIV vaccine and subsequent risk behavior change on the heterosexual HIV epidemic in low- and middle-income countries: A South African example. *J Acquir Immune Defic Syndr.* Sep 1 2007;46(1):78-90.

**5.** Statistics South Africa. *Mid-year population estimates.* Pretoria, South Africa 2008.

**6.** Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization. *Sub-Saharan Africa AIDS epidemic update regional summary.* 2007.

**7.** South Africa Department of Health, Medical Research Council. *South Africa demographic and health survey 2003.* Pretoria: Department of Health; 2007.

**8.** Shisana O, Rehle T, Simbayi L, et al. *South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005*. Cape Town: HSRC Press; 2005.

**9.** Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* Aug 11 2011;365(6):493-505.

**10.** Siegfried N, Muller M, Deeks JJ, Volmink J. Male circumcision for prevention of heterosexual acquisition of HIV in men. *Cochrane database of systematic reviews (Online).* 2009(2):CD003362.

**11.** 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.* Nov 2005;2(11):e298.

**12.** Bailey RC, Moses S, Parker CB, et al. Male circumcision for HIV prevention in young men in Kisumu, Kenya: a randomised controlled trial. *Lancet.* Feb 24 2007;369(9562):643-656.

**13.** Gray RH, Kigozi G, Serwadda D, et al. Male circumcision for HIV prevention in men in Rakai, Uganda: a randomised trial. *Lancet.* Feb 24 2007;369(9562):657-666.

**14.** Abdool Karim Q, Abdool Karim SS, Frohlich JA, et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science.* Sep 3 2010;329(5996):1168-1174.

**15.** Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med.* Aug 2 2012;367(5):399-410.

**16.** Cohen MS, Baden LR. Preexposure prophylaxis for HIV--where do we go from here? *N Engl J Med.* Aug 2 2012;367(5):459-461.

**17.** Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med.* Aug 2 2012;367(5):423-434.

**18.** Van Damme L, Corneli A, Ahmed K, et al. Preexposure prophylaxis for HIV infection among African women. *N Engl J Med.* Aug 2 2012;367(5):411-422.

**19.** Actuarial Society of South Africa (ASSA). *ASSA AIDS and Demographic Model.* 2011.

**20.** Wang H, Dwyer-Lindgren L, Lofgren KT, et al. Age-specific and sex-specific mortality in 187 countries, 1970-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2013;380(9859):2071-2094.

**21.** Badri M, Bekker LG, Orrell C, Pitt J, Cilliers F, Wood R. Initiating highly active antiretroviral therapy in sub-Saharan Africa: an assessment of the revised World Health Organization scaling-up guidelines. *AIDS.* May 21 2004;18(8):1159-1168.

**22.** Badri M, Cleary S, Maartens G, et al. When to initiate highly active antiretroviral therapy in sub-Saharan Africa? A South African cost-effectiveness study. *Antivir Ther.* 2006;11(1):63-72.

**23.** Cleary SM, McIntyre D, Boulle AM. The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa--a primary data analysis. *Cost Eff Resour Alloc.* 2006;4:20.

**24.** Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. *Med Decis Making.* Apr-Jun 1993;13(2):89-102.

**25.** Holtgrave DR, Pinkerton SD. Updates of cost of illness and quality of life estimates for use in economic evaluations of HIV prevention programs. *Journal of the Acquired Immune Deficiency Syndrome Hum Retrovirol.* September 1, 1997 1997;16(1):54-62.

**26.** Honiden S, Sundaram V, Nease RF, et al. The effect of diagnosis with HIV infection on health-related quality of Life. *Qual Life Res.* Feb 2006;15(1):69-82.

**27.** Schackman BR, Goldie SJ, Freedberg KA, Losina E, Brazier J, Weinstein MC. Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. *Med Decis Making.* 2002;22:27-38.

**28.** Tengs TO, Lin TH. A meta-analysis of utility estimates for HIV/AIDS. *Med Decis Making.* Nov-Dec 2002;22(6):475-481.

**29.** Sanders GD, Bayoumi AM, Sundaram V, et al. Cost-effectiveness of screening for HIV in the era of highly active antiretroviral therapy. *N Engl J Med.* Feb 10 2005;352(6):570-585.

**30.** Bayoumi AM, Redelmeier DA. Economic methods for measuring the quality of life associated with HIV infection. *Qual Life Res.* Sep 1999;8(6):471-480.

**31.** Salomon JA, Vos T, Hogan DR, et al. Common values in assessing health outcomes from disease and injury: disability weights measurement study for the Global Burden of Disease Study 2010. *Lancet.* Dec 15 2013;380(9859):2129-2143.

**32.** Abbas UL, Anderson RM, Mellors JW. Potential impact of antiretroviral therapy on HIV-1 transmission and AIDS mortality in resource-limited settings. *J Acquir Immune Defic Syndr.* Apr 15 2006;41(5):632-641.

**33.** Downs AM, de Vincenzi I. Probability of heterosexual transmission of HIV: relationship to the number of unprotected sexual contacts. European Study Group in Heterosexual Transmission of HIV. *J Acquir Immune Defic Syndr Hum Retrovirol.* Apr 1996;11:388-395.

**34.** Hollingsworth TD, Anderson RM, Fraser C. HIV-1 transmission, by stage of infection. *J Infect Dis.* Sep 2008;198:687-693.

**35.** Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med.* Mar 30 2000;342(13):921-929.

**36.** Wawer MJ, Gray RH, Sewankambo NK, et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis.* May 2005;191:1403-1409.

**37.** World Health Organization. *World health statistics 2010.* Geneva 2010.

**38.** Meyer-Rath G, Pillay Y, Blecher M, et al. Total cost and potential cost savings of the national antiretroviral treatment (ART) programme in South Africa 2010 to 2017. Paper presented at: XVIII International AIDS Conference; July 21, 2010; Vienna, Austria.

**39.** Bassett IV, Giddy J, Nkera J, et al. Routine voluntary HIV testing in Durban, South Africa: The experience from an outpatient department. *J Acquir Immune Defic Syndr*. 2007;46(2):181-186.

**40.** Forsythe S, Arthur G, Ngatia G, Mutemi R, Odhiambo J, Gilks CF. Assessing the cost and willingness to pay for voluntary HIV counselling and testing in Kenya. *Health Policy Plan.* 2002;17(2):187-195.

**41.** Kahn JG, Marseille E, Auvert B. Cost-effectiveness of male circumcision for HIV prevention in a South African setting. *PLoS Med.* Dec 2006;3(12):e517.

**42.** Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.