Model structure

Overview

The mathematical model is designed to represent heterosexual HIV transmission at the *population level* in KwaZulu-Natal province in South Africa, a mature generalised HIV epidemic, and the impact of interventions including Antiretroviral Therapy (ART), Pre-Exposure Prophylaxis (PrEP), condom use and male circumcision, operating either in isolation or in combination. This approach affords insights into how these interventions could affect rates and patterns of HIV transmission, and how combinations of different forms of interventions could operate together.

The model population is divided into compartments that are distinguished by sex, age, infection stage, sexual behaviour and exposure to different types of interventions, with events (e.g. infection, death, ART initiation, etc.) represented as movement between these compartments[1-3]. The model is population-based and deterministic, meaning that individuals and partnerships are not explicitly tracked, and that the results hold only for large populations.

In the model, the natural history of HIV infection is divided into stages (Fig.S1). Individuals becoming infected move from the 'Susceptible' compartment to progress through six consecutive compartments representing stages of HIV infection. These are: 'Acute Infection', a subsequent stage when CD4 count is above 350 cells per microliter, a stage when CD4 count is between 350 and 200 cells per microliter, an 'AIDS (early)' stage, an 'AIDS (advanced)' stage and lastly, an 'AIDS (severe)' stage. Infectiousness of infected individuals varies over the course of infection, with a peak of infectiousness in the 'Acute infection' phase and a period of heightened infectiousness in the 'AIDS (advanced)' phase[4].

Heterogeneity in sexual behaviour is incorporated in the model by stratifying men and women into risk groups according to their average effective partnership formation rate. The distribution between these strata and the mean partnership change rates for men and women is estimated through calibrating the model to HIV prevalence and incidence data from KwaZulu-Natal.

HIV transmission occurs through heterosexual sexual partnerships. Although these are instantaneous in the model, the influence of variation in duration of partnership is reflected by specifying the rate of infection through the partnership as a function of the number of sex acts in partnerships per year. That is, short-term partnerships effectively have a low number of sex acts in total, whilst partnerships maintained over a year would have a higher number of sex acts. Those in the higher risk groups tend to form more partnerships, but each of these partnerships comprises fewer sex acts and higher condom use. The probability of HIV transmission per sex act for those in the chronic stage of infection is based on the most recent meta-analysis [5], with the

relative infectiousness according to stage of infection based on data from serodiscordant couples in Rakai, Uganda [4].
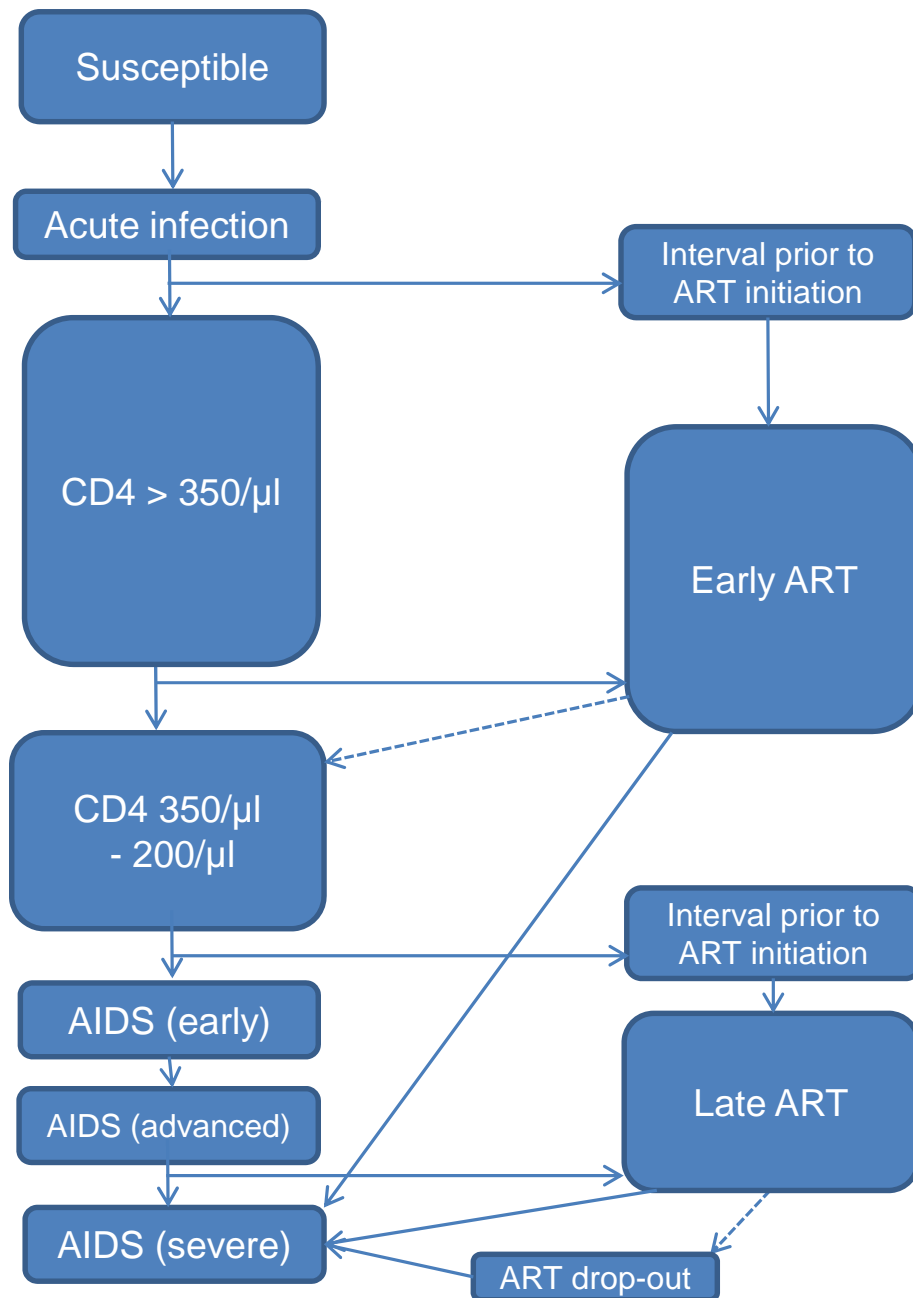
FigureS1. Flow diagram illustrating model representation of the natural history of HIV infection and ART initiation. Dashed arrows indicate treatment drop-out.

The impact of condom use is to reduce the chance of transmission in the sex acts in which they are used. Thus, there are two parameters specifying the impact of condom use – (i) efficacy in preventing transmission in a sex act if they are used correctly; and (ii) usage in sex acts (proportion of sex acts in a partnership in which they are used, which can vary by partnership type). Usage changes over time to reflect the increase in condom use in KwaZulu-Natal [6, 7]. Repeated cross-sectional surveys indicate that, reported condom use at last sex has increased markedly in KwaZulu-Natal; from 26.7% in 2002 to 36.3% in 2005 to 66.2% in 2008[6].

The influence of male circumcision is incorporated by dividing the male population into two groups – circumcised men and uncircumcised men. Circumcised men are less likely to acquire HIV infection by a fixed multiplicative factor per sex act with infected women. The probability of transmission of infection per sex act is assumed to be the same from circumcised men and from uncircumcised men to women. The proportion of men in the model starting sex that enter the circumcised group corresponds to the proportion of men that are circumcised at birth or during adolescence. The rate of movement from the uncircumcised to the circumcised group corresponds to the rate of circumcision achieved by an intervention providing adult medical male circumcision.

PrEP use is incorporated in the model by dividing the population into two parts – those receiving PrEP and those not receiving PrEP. The influence of PrEP is to reduce the risk of acquisition of HIV by a fixed multiplicative factor per sex act. This factor represents biological efficacy of PrEP and is defined separately for transmission - (i) from infected men to uninfected women; and (ii) from infected women to uninfected men. A proportion of male PrEP user's and female PrEP user's sex acts are protected by PrEP. These sex-specific proportions represent adherence. Individuals infected whilst using PrEP are assumed to have the same infectiousness as those infected not using PrEP. Coverage of PrEP is age and sex specific and is reached after a given period following the introduction of PrEP. PrEP users stop taking PrEP after an amount of time.

ART can be initiated for the population with four programme types, specified with different initiation rules. Treatment can be initiated an average of one year after infection (i.e. as soon as infection will be detected on average in an intense programme), or when an individual's CD4 count drops below 350, 200, or 100 cells per microliter. In Fig.S1, 'Early ART'in general usage refers to the first two criteria while 'Late ART' refers to the last two criteria. In these analyses 'Early ART' is used to refer only to the first criterion (i.e. initiated an average of one year after infection). ART initiation below a CD4 count of 100 is used to represent the pattern of actual ART initiation in recent years in South Africa[8-10]. Individuals initiating ART when their CD4 count drops below 200 do so after a certain waiting time[8]. Due to clinical need, no waiting time is assumed for individuals who are put on treatment when their CD4 drops below 100. Drop outs from the 'Late ART' category progress to the AIDS (severe) stage after a period of slightly heightened infectiousness represented by the 'ART drop-out' compartment in Fig.S1. ART is assumed to extend the survival of treated individuals (depending on whether ART is initiated 'early' or 'late') while reducing their infectiousness[11, 12].

The model was calibrated by selecting parameters varied within pre-specified bounds. The behavioural parameters and the baseline transmission probability were calibrated as these are difficult to empirically estimate reliably.The data used were: (1) HIV prevalence estimates for KwaZulu-Natal and their associated confidence intervals reported in population surveys carried out in 2002, 2005, and 2008[6]; and(2) an incidence estimateand its confidence interval from the period 2003 to 2006reported by the Africa Center for Health and Population Studies[13]. Age-specific rates of partnership formation were adjusted to produce age and sex specific incidence curves matching the relative levels of age and sex specific incidence from the Africa Centre for Health and population studies[14].

Technical Specifications

The model is a deterministic compartmental model defined by a set of ordinary differential equations which are solved numerically using software custom-written by the authors in Matlab 7.13. The state variables are denoted by $X_{l,k,a}^{s,p}$: s refers to HIV status (s=0 susceptible, s=1 acute infection, s=2 chronic infection with CD4 >350 cells/µL, s=3 chronic infection with CD4 >200 cells/µL but <350 cells/µL, s=4 AIDS (early) with CD4 <200 cells/µL, s=5 AIDS (advanced) with heightened infectiousness, s=6 AIDS (severe), s=7 interval before early ART, s=8 early ART, s=9 interval before late ART, s=10 late ART, s=11 drop out from late ART; p refers to PrEP status (p=1 not receiving PrEP, p=2 receiving PrEP); l refers to level of risk activity (l=1 low risk, l=2 intermediate risk, l=3 high risk); k refers to sex and male circumcision (k=1 females, k=2 uncircumcised males, k=3 circumcised males); a refers to age in single years (from a=1 (15 years), a=2 (16 years), to a=40 (54 years)).

Natural history of infection

The model is specified by the following ordinary differential equations:

The equations describing the susceptible individuals are:

$$\frac{dX_{l,k,1}^{0,p}}{dt} = \mu N \Psi_{(l,k,p,1)} - (\lambda_{l,k,1}^{p} + \mu_1)X_{l,k,1}^{0,p} + f(1) + g(k) + h(k,p,a) \quad \text{for } a = 1$$

$$\frac{dX_{l,k,a}^{0,p}}{dt} = -(\lambda_{l,k,A}^{p} + \mu_a)X_{l,k,a}^{0,p} + f(a) + g(k) + h(k,p,a) \quad \text{for } a \neq 1$$

(1)

The equations describing the infected individuals are:

$$\frac{dX_{l,k,a}^{1,p}}{dt} = \lambda_{l,k,A}^{p} X_{l,k,a}^{0,p} - (\sigma_1 + \mu_a)X_{l,k,a}^{1,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{2,p}}{dt} = (1-\phi_1)\sigma_1 X_{l,k,a}^{1,p} - (\sigma_2 + \mu_a)X_{l,k,a}^{2,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{3,p}}{dt} = \left(1-\phi_2\right)\sigma_2 X_{l,k,a}^{2,p} + \xi_E X_{l,k,a}^{8,p} - (\sigma_3 + \mu_a)X_{l,k,a}^{3,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{4,p}}{dt} = \left(1-\phi_3\right)\sigma_3 X_{l,k,a}^{3,p} - (\sigma_4 + \mu_a)X_{l,k,a}^{4,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{5,p}}{dt} = \sigma_4 X_{l,k,a}^{4,p} - (\sigma_5 + \mu_a)X_{l,k,a}^{5,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{6,p}}{dt} = \left(1-\phi_4\right)\sigma_5 X_{l,k,a}^{5,p} + \omega_E X_{l,k,a}^{8,p} + \omega_L X_{l,k,a}^{10,p} + \tau_D X_{l,k,a}^{11,p} - (\gamma + \mu_a)X_{l,k,a}^{6,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{7,p}}{dt} = \phi_1\sigma_1 X_{l,k,a}^{1,p} - (\kappa + \mu_a)X_{l,k,a}^{7,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{8,p}}{dt} = \kappa X_{l,k,a}^{7,p} + \phi_2\sigma_2 X_{l,k,a}^{2,p} - (\omega_E + \xi_E + \mu_a)X_{l,k,a}^{8,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{9,p}}{dt} = \phi_3\sigma_3 X_{l,k,a}^{3,p} - (\tau_I + \mu_a)X_{l,k,a}^{9,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{10,p}}{dt} = \phi_4\sigma_5 X_{l,k,a}^{5,p} + \tau_I X_{l,k,a}^{9,p} - (\omega_L + \xi_L + \mu_a)X_{l,k,a}^{10,p} + f(a) + g(k)$$

$$\frac{dX_{l,k,a}^{11,p}}{dt} = \xi_L X_{l,k,a}^{10,p} - (\tau_D + \mu_a)X_{l,k,a}^{11,p} + f(a) + g(k)$$

…(2)

For a given infection stage, hazards of progression to the next stage are given by the rates σ_s ($s=1, 2, 3, 4, 5$). The AIDS (early) stage is defined by the mean time between the state of infection when CD4 count falls below 200 copies/μL and viremic rebound 19 months, on average, prior to death.The AIDS (advanced) stage is a characterization of the 9month period of heightened infectiousness before the AIDS (severe) stage, which is a 10 month period of no transmission risk as per Hollingsworth et. al.[4].Mortality in the AIDS (severe) stage is denotedin

the model by the parameter γ. A limitation of this model is that AIDS-related mortality only applies to this final AIDS (severe) stage, whereas in reality some infected individuals may die of AIDS-related illnesses at higher CD4 counts. The degree to which this leads to an overestimation of the impact of ART on incidence depends on the extent to which this occurs. The model can be refined to incorporate AIDS-related mortality at higher CD4 counts when sufficient data become available.

Several representations of ART initiation are possible in the model. The proportion initiating ART on average one year following infection is controlled by ϕ_1 which determines the proportion of those moved to the interval prior to early treatment $X_{l,k,a}^{7,p}$, as a result of an intervention starting from time $t_{ART\,all\,CD4}$. ART initiation at a threshold of CD4<350 is represented by ϕ_2 which controls the proportion of those eligible (CD4<350) moved to early treatment $X_{l,k,a}^{8,p}$ as a result of intervention starting from time $t_{ART\,350}$. Similarly, the time dependent parameters $\phi_{3(t)}$ and $\phi_{4(t)}$ respectively control the proportion of those moved to late treatment $X_{l,k,a}^{10,p}$ once CD4 drops below 200 and 100, starting from time $t_{ART\,200}$. Individuals initiating ART early or late are moved to early or late ART compartments $X_{l,k,a}^{8,p}$ or $X_{l,k,a}^{10,p}$ and are assumed to survive on average $\frac{1}{\omega_E}$ or $\frac{1}{\omega_L}$ years before progressing to the AIDS (severe) stage, respectively. Individuals drop out from early and late ART at a rate of ξ_E and ξ_L, respectively.

Demography

The model is stratified by single years of age from 15 to 54 years. Individuals progress from one age compartment to the next at a rate of Δ (with $\Delta = 1$). Ageing of individuals is represented by:

$$f(a) = \Delta X_{l,k,a-1}^{s,p} - \Delta X_{l,k,a}^{s,p} \qquad for\ a \geq 2$$

…(3)

$\Psi_{(l,k,p,a)}$ is the matrix of population distribution in the year the epidemic starts (t_0) over each l, k, p, a stratum and it is defined in terms of: (i) $\psi_{f(l)}$ and $\psi_{m(l)}$ which are the proportion of females and males in each risk activity group; and (ii) f_a which is the proportion of the population in each year of age, with $\sum_{a=1}^{40} f_a = 1$. The parameter f_{cm} gives the fraction of circumcised males.

The total number in the population (N) and $\Psi_{(l,k,p,a)}$ are given by:

$$N = \sum_{l=1}^{3} \sum_{k=1}^{3} \sum_{p=1}^{2} \sum_{a=1}^{40} \left(\begin{array}{c} X_{l,k,a}^{0,p} + X_{l,k,a}^{1,p} + X_{l,k,a}^{2,p} + X_{l,k,a}^{3,p} + X_{l,k,a}^{4,p} + X_{l,k,a}^{5,p} \\ + X_{l,k,a}^{6,p} + X_{l,k,a}^{7,p} + X_{l,k,a}^{8,p} + X_{l,k,a}^{9,p} + X_{l,k,a}^{10,p} + X_{l,k,a}^{11,p} \end{array} \right)$$

…(4)

$$\Psi_{(l,k,p,a)} = \begin{cases} \frac{1}{2}\psi_{f(l)}\,f_a & \text{any } l;\ k=1;\ p=1;\ \text{any a;} \\ \frac{1}{2}\psi_{m(l)}f_a(1-f_{cm}) & \text{any } l;\ k=2;\ p=1;\ \text{any a;} \\ \frac{1}{2}\psi_{m(l)}f_a f_{cm} & \text{any } l;\ k=3;\ p=1;\ \text{any a;} \end{cases}$$

…(5)

Individuals enter the population as susceptible 15 year olds,the distribution of whom is defined by the population distribution matrix over each $l, k, and\ p$ stratum($\Psi_{(l,k,p,1)}$), given by:

$$\Psi_{(l,k,p,1)} = \begin{cases} \frac{1}{2}\psi_{f(l)} & \text{any } l;\ k=1;\ p=1;\ \text{a=1 (15 years);} \\ \frac{1}{2}\psi_{m(l)}(1-f_{cm}) & \text{any } l;\ k=2;\ p=1;\ \text{a=1 (15 years);} \\ \frac{1}{2}\psi_{m(l)}f_{cm} & \text{any } l;\ k=3;\ p=1;\ \text{a=1 (15 years);} \end{cases}$$

…(6)

The model assumes age-specific death rates of μ_A and a fixed demographic birth rate of μ .

Infection and sexual network

Force of infection

The per capita force of infection $\lambda_{l,k,A}^{p}$ is the force of infection experienced by individuals of each sex and circumcision status (if male), risk group, PrEP status and five year age group from the infected population of the opposite sex at a given time. The force of infection is the per capita rate at which susceptible individuals acquire infection. Characteristics of an individual (l, k, p, and A (where A is five year age group (A=1,2….8))) are distinguished from those of their sexual partners by means of a prime (i.e. l', k', p′, and A′(where A' is five year age group)).The force of infection is calculated by five year age group and then applied to each individual year of age in that group.

The force of infection depends on the pattern of partnership formation between different risk and five year age groups and on the probability of transmission per partnership, and is defined as:

for women:

$$\lambda_{l,1,A}^{p} = \sum_{l'}\sum_{k'}\sum_{p'}\sum_{A'}\sum_{s'}\left[c_{g,A,l}\rho_{g,A,l,A',l'}\left(\frac{X_{l',k',A'}^{s',p'}}{\sum_{k'=2}^{3}\sum_{p'}\sum_{s'}X_{l',k',A'}^{s',p'}} \right)z_{l,1,p,s',l',k',p'} \right]$$

for men:

$$\lambda_{l,k,A}^{p} = \sum_{l'}\sum_{p'}\sum_{A'}\sum_{s'}\left[c_{g,A,l}\rho_{g,A,l,A',l'}\left(\frac{X_{l',1,A'}^{s',p'}}{\sum_{p'}\sum_{s'}X_{l',1,A'}^{s',p'}} \right)z_{l,k,p,s',l',1,p'} \right]$$

…(7)

Probability of transmission per partnership

The probability of transmission per partnership depends on: (i) the probability of transmission per coital act; and (ii) the number of coital actsduring the partnership (which depends on the risk group of each partner). The probability of transmission per coital act depends on:an individual's sex, circumcision status (if male), PrEP use and adherence (if using PrEP), as well as their partner's stage of infection (including ART use), sex, circumcision status (if male) and PrEP use, in addition to the degree of condom use in the partnership (which depends on the risk group of each partner).

A baseline transmission probability from uncircumcised males to females is assumed (β_{0}). The difference in acquisition and transmission per sexual act for other factors (e.g. stage of infection) is specified with respect to this baseline transmission probability using a multiplicative factor.The probability of HIV transmission per sex act is given by $\beta_{p,k}^{s',k'}$ and depends on: s' (partner's HIV-status), k' (partner's sex, and circumcision status (if male)), p (individual's PrEP status) and k (individual's sex, and circumcision status (if male)).PrEP and male circumcision are assumed to reduce the risk of acquisition but not onward transmission (if breakthrough infection occurs while on PrEP).

The number of sex acts in a partnership depends on the risk group of both partners and is given by the matrix $n_{sex}(l,l')$. Condom use is incorporated as a proportion of sex acts in which condoms are used, via the matrix $CU(l,l')$, which defines condom use in a partnership between an individual's risk group l and their partner's risk group l', modulated by any increase in condom use due to changes over time $\overline{q}_{(t)}$. The efficacy of condoms is given by ϖ. The level of adherence to PrEP is incorporated as a proportion of sex acts protected by PrEP, for male (P_m) and female (P_f) PrEP users.

The probability of transmission per partnership $z_{l,k,p,s',l',k',p'}$ is defined as:

For women and uncircumcised men not receiving PrEP:

$$z_{l,k,1,s',l',k',p'} = 1 - \left((1 - \beta_{1,k}^{s',k'}\varpi)^{\chi}\right)\!\left((1 - \beta_{1,k}^{s',k'})^{\overline{\chi}}\right)$$

For women receiving PrEP:

$$z_{l,1,2,s',l',k',p'} = 1 - \left((1 - \beta_{2,1}^{s',k'}\varpi)^{\chi\ P_f}\right)\!\left((1 - \beta_{2,1}^{s',k'})^{\overline{\chi}P_f}\right)\!\left((1 - \beta_{2,1}^{s',k'}\varpi)^{\chi\ (1-P_f)}\right)\!\left((1 - \beta_{2,1}^{s',k'})^{\overline{\chi}(1-P_f)}\right)$$

For uncircumcised men receiving PrEP:

$$z_{l,2,2,s',l',k',p'} = 1 - \left((1 - \beta_{2,2}^{s',k'}\varpi)^{\chi\ P_m}\right)\!\left((1 - \beta_{2,2}^{s',k'})^{\overline{\chi}P_m}\right)\!\left((1 - \beta_{2,2}^{s',k'}\varpi)^{\chi\ (1-P_m)}\right)\!\left((1 - \beta_{2,2}^{s',k'})^{\overline{\chi}(1-P_m)}\right)$$

For circumcised men not receiving PrEP:

$$z_{l,3,1,s',l',k',p'} = 1 - \left((1 - \beta_{1,3}^{s',k'}\varpi)^{\chi}\right)\!\left((1 - \beta_{1,3}^{s',k'})^{\overline{\chi}}\right)$$

For circumcised men receiving PrEP:

$$Z_{l,3,2,s',l',k',p'} = 1 - ((1 - \beta_{2,3}^{s',k'} \varpi)^{\chi P_m})((1 - \beta_{2,3}^{s',k'})^{\overline{\chi} P_m})((1 - \beta_{2,3}^{s',k'} \varpi)^{\chi (1-P_m)})((1 - \beta_{2,3}^{s',k'})^{\overline{\chi}(1-P_m)})$$

…(8)

where:

$$\chi = CU(l,l')\overline{q}_{(t)} n_{sex}(l,l')$$

$$\overline{\chi} = (1 - CU(l,l')\overline{q}_{(t)}) n_{sex}(l,l')$$

…(9)

That is, χ is the number of sex acts protected by condoms in a partnership between an individual of risk group l and their partner of risk group l' and $\overline{\chi}$ is the number of sex acts not protected by condoms in a partnership between an individual of risk group l and their partner of risk group l'.

Sexual Mixing

The mixing pattern is defined with respect to sex, five year age group and behavioural risk group. The proportion of sexual partnerships that an individual of sex g (where $g=1$ refers to females and $g=2$ to males), 5 year age group A and behavioural risk group l forms with an individual of the opposite sex, age group A' and risk group l', is given by $\rho_{g,A,l,A',l'}$, and is defined as:

$$\rho_{1,A,l,A',l'} = \varepsilon_A \varepsilon_l \left(\delta_{A,A'} \ \delta_{l,l'} \right) + (1-\varepsilon_A)\varepsilon_l \left(\delta_{l,l'} \frac{c_{2,A',l'} \sum\limits_{k'=2}^{3}\sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',k',A'}}{\sum\limits_{A'} c_{2,A',l'} \sum\limits_{k'=2}^{3}\sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',k',A'}} \right)$$

$$+ \varepsilon_A (1-\varepsilon_l) \left(\delta_{A,A'} \frac{c_{2,A',l'} N_{g'}(A',l')}{\sum\limits_{l'} c_{2,A',l'} \sum\limits_{k'=2}^{3}\sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',k',A'}} \right) + (1-\varepsilon_A)(1-\varepsilon_l) \left(\frac{c_{2,A',l'} N_{g'}(A',l')}{\sum\limits_{A'}\sum\limits_{l'} c_{2,A',l'} \sum\limits_{k'=2}^{3}\sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',k',A'}} \right)$$

$$\rho_{2,A,l,A',l'} = \varepsilon_A \varepsilon_l \left(\delta_{A,A'} \ \delta_{l,l'} \right) + (1-\varepsilon_A)\varepsilon_l \left(\delta_{l,l'} \frac{c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}}{\sum\limits_{A'} c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}} \right)$$

$$+ \varepsilon_A (1-\varepsilon_l) \left(\delta_{A,A'} \frac{c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}}{\sum\limits_{l'} c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}} \right) + (1-\varepsilon_A)(1-\varepsilon_l) \left(\frac{c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}}{\sum\limits_{A'}\sum\limits_{l'} c_{1,A',l'} \sum\limits_{p'}\sum\limits_{s'} X^{s',p'}_{l',1,A'}} \right)$$

Note: $\sum\limits_{A'}\sum\limits_{l'} \rho_{g,A,l,A',l'} = 1$

(10)

The parameter $c_{g,A,l}$ gives the mean number of partners in a year per individual of sex g in age group A and risk group l. The degrees of assortativity in mixing with respect to age and with respect to risk are given by ε_A and ε_l, respectively. The identity matrix with respect to risk is given by the Kronecker delta $\delta_{l,l'}$, whereby:

$$\delta_{l,l'} = \begin{cases} 1, & if \ l = l' \\ 0, & if \ l \neq l' \end{cases}$$

Mixing with respect to age group is offset such that women mixing assortatively with respect to age form partnerships with men five years older and men mixing assortatively with respect to age form partnerships with women five years younger, as has been reported in KwaZulu-Natal (particularly among spousal partnerships) [15]. Thus, the mixing matrix with respect to age $\delta_{A,A'}$ is given by:

for women: for men:

$$\delta_{A,A'} = \begin{cases} 1, & if \ A = A'+1 \\ 0, & if \ A \neq A'+1 \end{cases} \quad \delta_{A,A'} = \begin{cases} 1, & if \ A = A'-1 \\ 0, & if \ A \neq A'-1 \end{cases}$$

…(11)

In order to balance the number of sexual partnerships, a method developed by Garnett and Anderson is used, whereby a discrepancy matrix D_{A_2,l_2,A_1,l_1} is defined to calculate the discrepancy between males and females regarding the number of partnerships formed with respect to each age and risk group[16], where A_2 and l_2 are the age and risk group of the male partner, and A_1 and l_1 are the age and risk group of the female partner. It is calculated as:

$$D_{A_2,l_2,A_1,l_1} = \frac{\rho_{2,A,l,A',l'} c_{2,A,l} \sum_{k=2}^{3} \sum_{p} \sum_{s} X_{l,k,A}^{s,p}}{\rho_{1,A,l,A',l'} c_{1,A,l} \sum_{p} \sum_{s} X_{l,1,A}^{s,p}}$$

…(12)

The extent to which balancing of the number of sexual partnerships is male-driven or female-driven is determined by the parameter θ. When $\theta = 1$, balancing is male-driven, that is, the number of partnerships formed by females is adjusted such that the number of partnerships formed by females is equal to the number formed by males. Equally, when $\theta = 0$, balancing is female-driven, and when $\theta = 0.5$ the sexes compromise equally. Balancing of sexual partnerships is carried out with respect to both partner's age and risk groups and is represented by:

$$\rho_{2,A,l,A',l'} \rightarrow D_{A_2,l_2,A_1,l_1}^{(\theta-1)} \rho_{2,A,l,A',l'}$$

$$\rho_{1,A,l,A',l'} \rightarrow D_{A_2,l_2,A_1,l_1}^{(\theta)} \rho_{1,A,l,A',l'}$$

…(13)

Interventions

In addition to the ART intervention parameterized in equations (1) and (2), male circumcision and PrEP are incorporated dynamically in the model. To simulate the intervention moving

uncircumcised men to the circumcised classes, the function $g(k)$ is included in equations (1) and (2):

$$for \ \ t \le t_{Circ}$$
$$\eta_C = 0$$
$$for \ \ t > t_{Circ}$$
$$g(1) = 0$$
$$g(2) \ = \ \frac{dX_{l,2,a}^{s,p}}{dt} - \eta_C X_{l,2,a}^{s,p}$$
$$g(3) \ = \ \frac{dX_{l,3,a}^{s,p}}{dt} + \eta_C X_{l,2,a}^{s,p}$$

…(14)

To simulate an intervention whereby PrEP is provided to uninfected individuals, the function $h(k,p,a)$ is included in equations (1):

$$h(k,1,a) = \ \frac{dX_{l,k,a}^{0,1}}{dt} - \eta_{P,A(t)} X_{l,k,a}^{0,1} + \Theta X_{l,k,a}^{0,2}$$
$$h(k,2,a) = \ \frac{dX_{l,k,a}^{0,2}}{dt} + \eta_{P,A(t)} X_{l,k,a}^{0,1} - \Theta X_{l,k,a}^{0,2}$$

…(15)

The parameter η_C gives the scale-up rate for male circumcision. It is a constant per-capita rate and is defined separately for men aged 15 to 24 years and for men aged 25 to 54 years. It is assumed that men can be circumcised regardless of infection status, and if infected, regardless of stage of infection. Scale-up ceases once coverage of circumcision reaches a threshold, defined separately for men aged 15 to 24 years and for men aged 25 to 54 years.The parameter $\eta_{P,A,(t)}$ representsthe age and timedependent rate at which individuals are initiated on PrEP. The average rate of scale-up of PrEP is defined by r_g , where g represents sex (g=1,2).PrEP is scaled-up such that coverage increases linearly over a defined time period $(1 / r_g)$ to reach a sex and age specific coverage level $P_{g,A}$ (where A represents five year age group (A=1,2….8)), at which level coverage remains constant thereafter:

for $t \leq t_{\mathrm{Pr}\,EP}$

$$\eta_{P,\mathrm{A},(t)} = 0$$

for $t_{\mathrm{Pr}\,EP} < t \leq (t_{\mathrm{Pr}\,EP} + 1/r_g)$

for women : $\quad \eta_{P,\mathrm{A},(t)} = \left[(t - t_{\mathrm{Pr}\,EP}) r_1 P_{1,\mathrm{A}} \right] - \left[\dfrac{\sum_l X_{l,1,\mathrm{A}}^{0,2}}{\sum_l \sum_p X_{l,1,\mathrm{A}}^{0,p}} \right]$

for men : $\quad \eta_{P,\mathrm{A},(t)} = \left[(t - t_{\mathrm{Pr}\,EP}) r_2 P_{2,\mathrm{A}} \right] - \left[\dfrac{\sum_l \sum_{k=2}^{3} X_{l,k,\mathrm{A}}^{0,2}}{\sum_l \sum_{k=2}^{3} \sum_p X_{l,k,\mathrm{A}}^{0,p}} \right]$

for $t > (t_{\mathrm{Pr}\,EP} + 1/r_g)$

for women : $\quad \eta_{P,\mathrm{A},(t)} = \begin{cases} P_{1,\mathrm{A}} - \left[\dfrac{\sum_l X_{l,1,\mathrm{A}}^{0,2}}{\sum_l \sum_p X_{l,1,\mathrm{A}}^{0,p}} \right] & \text{if } P_{1,\mathrm{A}} > \left[\dfrac{\sum_l X_{l,1,\mathrm{A}}^{0,2}}{\sum_l \sum_p X_{l,1,\mathrm{A}}^{0,p}} \right] \\[4ex] 0 & \text{otherwise} \end{cases}$

for men : $\quad \eta_{P,\mathrm{A},(t)} = \begin{cases} P_{2,\mathrm{A}} - \left[\dfrac{\sum_l \sum_{k=2}^{3} X_{l,k,\mathrm{A}}^{0,2}}{\sum_l \sum_{k=2}^{3} \sum_p X_{l,k,\mathrm{A}}^{0,p}} \right] & \text{if } P_{2,\mathrm{A}} > \left[\dfrac{\sum_l \sum_{k=2}^{3} X_{l,k,\mathrm{A}}^{0,2}}{\sum_l \sum_{k=2}^{3} \sum_p X_{l,k,\mathrm{A}}^{0,p}} \right] \\[4ex] 0 & \text{otherwise} \end{cases}$

…(16)

where $t_{\mathrm{Pr}\,EP}$ is the time at which implementing the PrEP interventionbegins, $1/r_g$ is the time taken to reach the defined age and sex specific coverage and $X_{l,k,\mathrm{A}}^{0,p}$ is the number of susceptible individuals in a five year age group. PrEP scale-up ceases once the age and sex specific coverage thresholdsare reached. Individuals cease using PrEP after a mean duration on PrEPof $1/\Theta$.

Parameter tables

Natural history of infection

Parameter	Symbol	Value	Sources
Mean duration of acute infection	$1/\sigma_1$	0.25 years	
Mean duration from end of acute infection to CD4350	$1/\sigma_2$	4.55 years	
Mean duration from CD4350 to CD4200	$1/\sigma_3$	3.50 years	
Mean duration from CD4 <200 to viremic rebound	$1/\sigma_4$	1.12 years	[4, 17]
Mean duration of viremic rebound before AIDS (severe)	$1/\sigma_5$	0.75 years (9 months)	
AIDS (severe) mortality rate	γ	1/0.833 (10 month period before death)	

Table S1. Natural history of infection parameters. The *mean* survival time from seroconversion to death in the model is 11.0 years.

Demography

Parameter	Symbol	Value	Source
Initial population size (15-54 year olds)	N_0	2.466×10^6	See Fig.S6 for population size over time [18]
'Birth' rate	μ	0.051	Calibrated
Fraction of males circumcised in KwaZulu-Natal	f_{cm}	0.268	[19]

Table S2. Demographic parameters.

Symbol	Age group	Value	Source
μ_{15-19}	15-19	0.00131	
μ_{20-24}	20-24	0.00266	
μ_{25-29}	25-29	0.00352	
μ_{30-34}	30-34	0.00434	[20]
μ_{35-39}	35-39	0.00521	
μ_{40-44}	40-44	0.00707	
μ_{45-49}	45-49	0.00881	
μ_{50-54}	50-54	0.01336	

Table S3. Age-specific mortality rates.

Symbol	Age group	Value	Source
f_{15-19}	15-19	0.19	
f_{20-24}	20-24	0.18	
f_{25-29}	25-29	0.16	
f_{30-34}	30-34	0.13	[21]
f_{35-39}	35-39	0.11	
f_{40-44}	40-44	0.09	
f_{45-49}	45-49	0.08	
f_{50-54}	50-54	0.06	

Table S4. Age-specific initial population distribution of 15-54 year olds. Based on 1985 population pyramid.

Infection and sexual network

Parameter	Symbol	Value (range)	Notes
Condom use in partnerships between individuals of low and medium risk groups	$CU(1,1)$ $CU(1,2)$ $CU(2,1)$ $CU(2,2)$	0.0316 (0, 0.1)	Cannot be directly estimated from data
Condom use in partnerships between individuals of low/medium and high risk groups	$CU(3,1)$ $CU(3,2)$ $CU(1,3)$ $CU(2,3)$	0.0932 (0.05, 0.2)	Cannot be directly estimated from data
Condom use in partnerships between individuals in the high risk group	$CU(3,3)$	0.3116 (0.3, 0.6)	Cannot be directly estimated from data
Degree of condom non-use during sex acts reached over a time span of 2-12 years (a value of 1 corresponds to no change in condom use)	$\bar{q}$	0.72 (0.28,1)	Based on reported levels of increase in condom use in the 2002-2008 Human Sciences Research Council (HSRC)South African National Surveys[6] and that this increase had started by 1998[7]
Year condom use started to increase	t_c	1995 (1994, 2002)	Representative value based on what is reported by observational studies on sexual behavior and in the HSRC surveys[6, 7, 22]
Time span for increase in condom use (years)	τ_c	11 (2,12)	Representative

Fraction of women in low risk group	$\psi_f(1)$	0.986 (0.65,0.99)	Representative
Fraction of non-low risk women in the highest risk group	$\dfrac{\psi_f(3)}{1-\psi_f(1)}$	0.426 (0.1,0.9)	Representative
Fraction of men in low risk group	$\psi_m(1)$	0.775 (0.6,0.99)	Representative
Fraction of non-low risk men in the highest risk group	$\dfrac{\psi_m(3)}{1-\psi_m(1)}$	0.55 (0.2,0.9)	Representative
Year epidemic starts	t_0	1980 (1978, 1987)	The first AIDS cases in South Africa were reported in the 1980s [23] and data from US Census Bureau suggests that the HIV epidemicbegan to spread in South Africa much later than it did in other Sub-Saharan African countries [24]

Table S5. Calibrated behavioural parameters. The parameter determining epidemic start time was also calibrated. The term 'representative' indicates a plausible choice for the range within which the parameter value lies.

Parameter	Symbol	Value	Source
Number of sex acts per partnership between individuals in the low risk group and individuals in the medium & high risk groups	$n_{sex}(1,1)$ $n_{sex}(1,2)$ $n_{sex}(1,3)$ $n_{sex}(2,1)$ $n_{sex}(3,1)$	100	Estimated based on reported frequency of sex in marital relationships in Southern Africa [25]
Number of sex acts per partnership between individuals in the medium and high risk groups	$n_{sex}(2,2)$ $n_{sex}(2,3)$ $n_{sex}(3,2)$ $n_{sex}(3,3)$	2	Representative

Table S6. Number of sex acts per partnershipbetween individuals in different risk groups.

Parameter	Symbol	Value	Source
Degree of assortativity of sexual mixing with respect to risk group (a value of 1.0 indicates fully assortative)	ε_l	0.54	Cannot be directly estimated from data.
Degree of assortativity of sexual mixing with respect to age group (a value of 1.0 indicates fully assortative)	ε_A	0.80	Cannot be directly estimated from data. Mixing with respect to age is offset such that women tend to form partnerships with men who are 5 years older on average [15, 26]
The extent to which the demand for partnerships is 'male driven'	θ	0.50	Demand for partnerships is assumed to be determined equally by both sexes.

Table S7. Parameters determining sexual mixing and balancing of partnerships.

	Women			Men		
	Low	Medium	High	Low	Medium	High
	$c_{1,A,1}$	$c_{1,A,2}$	$c_{1,A,3}$	$c_{2,A,1}$	$c_{2,A,2}$	$c_{2,A,3}$
15-19	1.30	11.31	20.89	1.78	11.95	46.38
20-24	1.00	8.72	16.10	1.02	6.83	26.50
25-29	1.13	9.90	18.28	2.55	17.07	66.25
30-34	1.15	10.02	18.50	2.23	14.95	58.04
35-39	1.24	10.84	20.02	1.30	8.70	33.79
40-44	1.01	8.84	16.32	1.02	6.83	26.50
45-49	0.65	5.66	10.44	1.17	7.85	30.48
50-54	0.89	7.78	14.36	1.83	12.29	47.70

Table S8.Age and sex specific partner acquisition rates $c_{g,A,l}$ .Values are representative.

Parameter	Symbol	Value	Source
Baseline transmission probability from uncircumcised males in the asymptomatic stage to females in a single act of unprotected sex	β_0	0.000755	Varied within a pre-defined range: 0.0005 - 0.0008 Representative range captures impact of other risk factors not explicitly in the model, such as other STIs[5, 27]
From population with acute infection	$\beta_{p,k}^{1,k'}$	26	[4]
From population with chronic infection with CD4 >350 cells/μL	$\beta_{p,k}^{2,k'}$	1	The baseline transmission probability is assumed from the end of acute infection until the period of heightened infectiousness 19-10 months before death, as per Hollingsworth et. al.[4]
From population with chronic infection with CD4 >200 cells/μL but <350 cells/μL	$\beta_{p,k}^{3,k'}$	1	
From population in AIDS (early)	$\beta_{p,k}^{4,k'}$	1	
From population in AIDS (advanced)	$\beta_{p,k}^{5,k'}$	7	[4]
From population in AIDS (severe)	$\beta_{p,k}^{6,k'}$	0	[4]

From population in the interval before early ART	$\beta_{p,k}^{7,k'}$	1	
From population in early ART	$\beta_{p,k}^{8,k'}$	0.04	[11]
From population in the interval before late ART	$\beta_{p,k}^{9,k'}$	1	
From population in late ART	$\beta_{p,k}^{10,k'}$	0.04	[11]
From population who have dropped out of ART	$\beta_{p,k}^{11,k'}$	3.56	Estimated
From women	$\beta_{p,k}^{s',1}$	1	Assumes that transmission from male to female is the same as that from female to male [27, 28].
From uncircumcised men	$\beta_{p,k}^{s',2}$	1	
From circumcised men	$\beta_{p,k}^{s',3}$	1	Assumes no effect of circumcision on onward transmission [29]
To circumcised men	$\beta_{p,3}^{s',k'}$	0.4	Circumcised males have a 60% reduced risk of acquisition [30-32]
To individuals using PrEP	$\beta_{2,k}^{s',k'}$	0.253	Assumes that PrEP reduces the risk of acquisition by 74.7% if used
Condom efficacy		0.1	Assumes condoms provide 90% protection from infection

Table S9. Factor increments in transmission probability per sex act with respect to baseline transmission probability (β_0).

Interventions

ART introduction, scale-up and criteria for initiation

In the model, 'late' ART is scaled-up over two periods. The first period (2004-2013) reflects what has happened in KwaZulu-Natal since ART became available in 2004. The proportions receiving ART were calibrated to fit to data on the number of individuals who have ever started ART in KwaZulu-Natal, according to Department of Health data. The second period (2013 onwards) allows 'late' ART coverage to reach higher levels, such that complete coverage at CD4 200 can be reached prior to introducing earlier ART initiation. The parametersused in the baseline scenario are given in table S10.

Parameter	Symbol	Value	Source
Late ART			
Period 1 (2004-2013)			
Year ART is introduced	t_{ART200}	2004	ART introduced in KwaZulu-Natal in 2004, with the government ART programme starting in March 2004[9, 33-35]
Scale-up period		5 years	
Proportion who initiate ART onceCD4 reaches 100	$\phi_{4(1)}$	0.329	Calibrated to Department of Health data
Proportion who initiate ART (after an interval) once CD4 reaches 200	$\phi_{3(1)}$	0.371	Calibrated to Department of Health data
Period 2 (2013 onwards)			
Scale-up period		5 years	
Proportion who initiate ART once CD4 reaches 100	$\phi_{4(2)}$	0.329	
Proportion who initiate ART (after an interval) once CD4 reaches 200	$\phi_{3(2)}$	0.371	
Rate of initiating late ART (after CD4 200)	τ_I	1 year	Representative. Bassett et. al. reporta median 6.6 month interval between diagnosis and ART initiation among ART-eligible individuals (CD4<200) in urban KwaZulu-Natal (Durban), however only 39% of ART-eligible individuals initiated ART

			within 12 months [8].
ART survival (rate of progressing to AIDS (severe)) – late initiation (CD4<200)	ω_L	0.105	The survival probability (p) reported by Mahy et. al. of 0.9[36] was converted to a per capita mortality rate (r), using: $$p = 1 - e^{-rt}$$
Rate of progressing to AIDS (severe) following drop-out of late ART	τ_D	5	Representative
Dropout rate	ξ_L	0.07	The KwaZulu-Natal Department of Health report a rate of 7 per 100 PY for 'interruption' [9]. This rate is assumed for dropout.
Early ART			
CD4 350			
Year initiation threshold is increased to CD4 350	$t_{ART\,350}$	No ART coverage at CD4 350 in baseline scenario	
Proportion who initiate ART once CD4 reaches 350	ϕ_2	No ART coverage at CD4 350 in baseline scenario	
1 year after infection (independent of CD4 count)			
Year ART initiation independent of CD4 count begins	$t_{ART\,allCD4}$	No ART coverage independent of CD4 in baseline scenario	
Proportion who initiate ART independent of CD4	ϕ_1	No ART coverage independent of CD4 in baseline scenario	
Rate of initiating ART independently of CD4 count	κ	1.33 (9 months)	The value of κ is such that individuals receiving ART independently of CD4 count, do so on average 1 year after infection
ART mortality (rate of progressing to AIDS (severe)) - early initiation (CD4>200)	ω_E	0.013	Kitahata et. al. report a crude death rate of 1.3 deaths per 100 person years among individuals receiving early ART (in the United States and Canada) [37].
Dropout rate	ξ_E	0.07	The dropout rate for early ART is assumed to be the same as that for late ART [9].

**Table S10.** Baseline ART parameters and assumptions.

Additional figures

Baseline prevalence and incidence
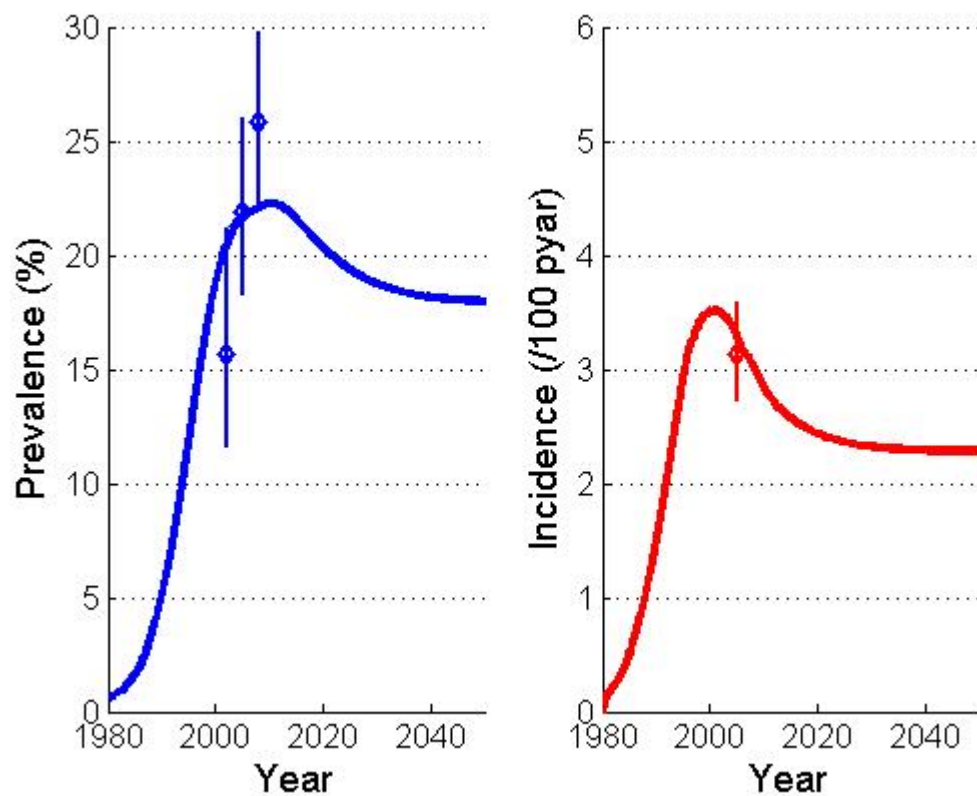
FigureS2. Baseline prevalence (15-49 year olds) and incidence (15-54 year olds) over time. Prevalence estimates for 15-49 year olds in KwaZulu-Natal from population surveys by the Human Sciences Research Council [6] and an incidence estimate for 15-54 year olds from the Africa Center for Health and Population Studies [13] were used for calibration.
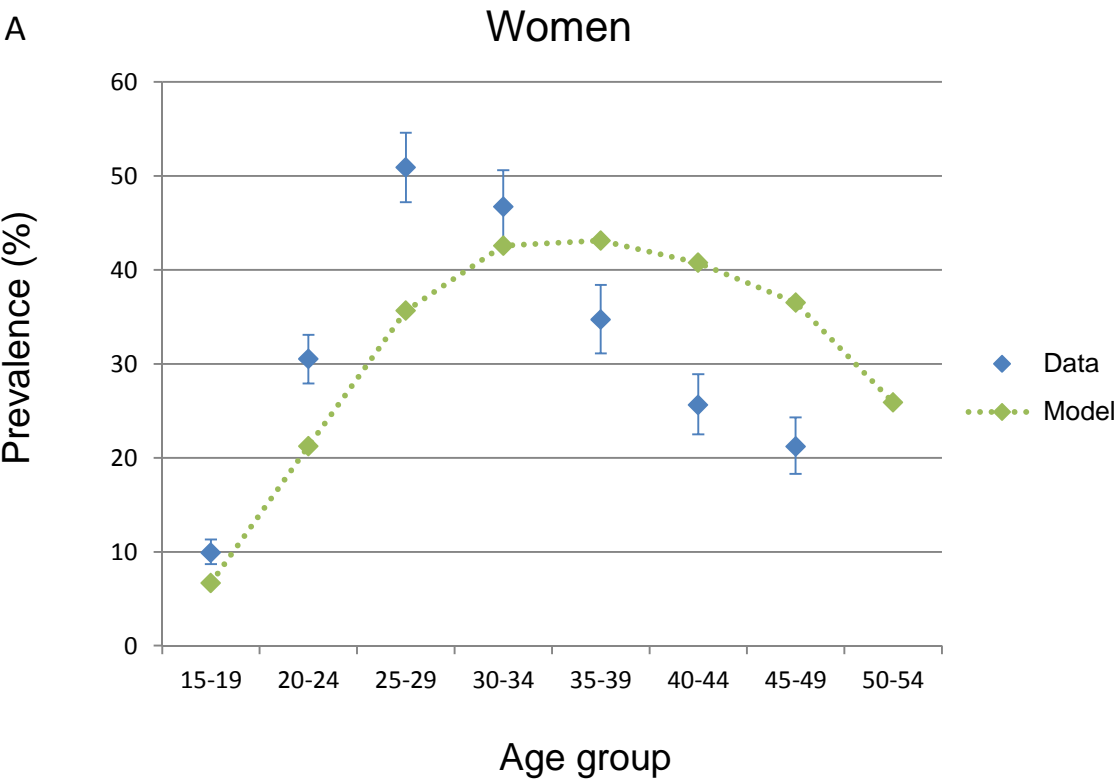
Age and sex specific incidence

A

Women

B

Men
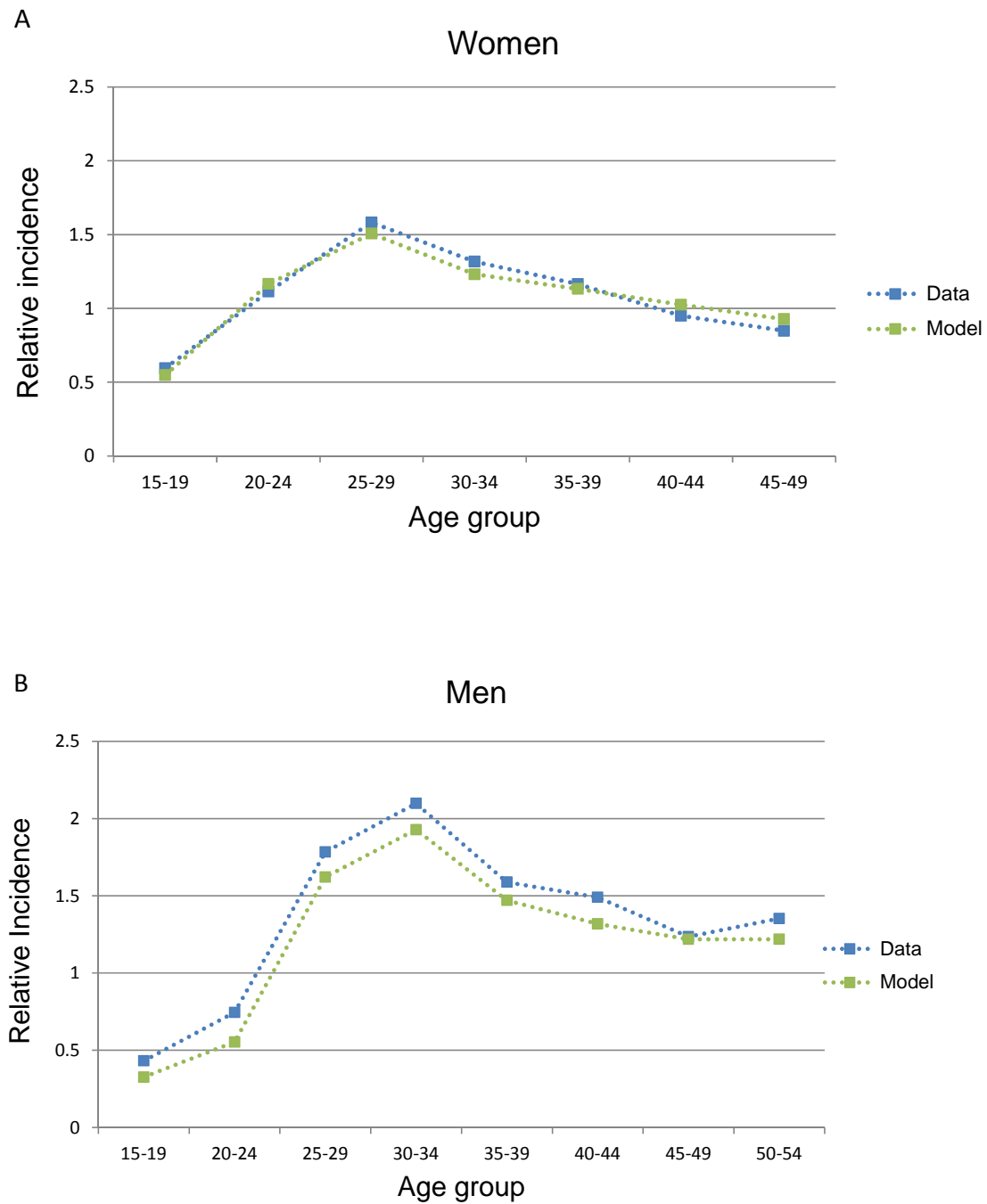
FigureS3. Relative HIV incidence with respect to age for (A) women and (B) men in 2004.

A

Women

B

Men
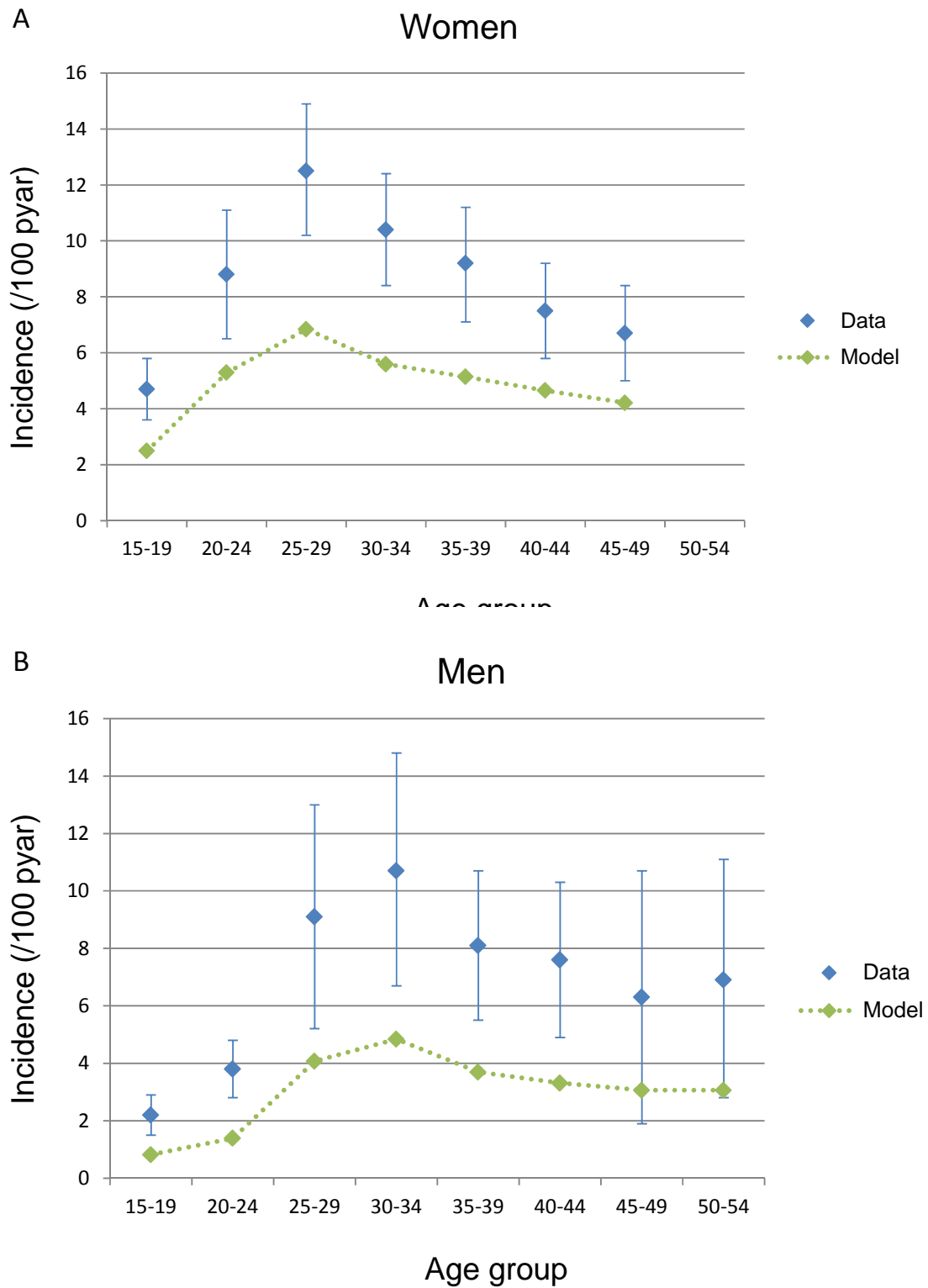
FigureS4. HIV incidence with respect to age for (A) women and (B) men in 2004. Model estimates are compared to data from the Africa Centre Demographic Surveillance Area [14].

Age and sex specific prevalence

A

Women

B

Men
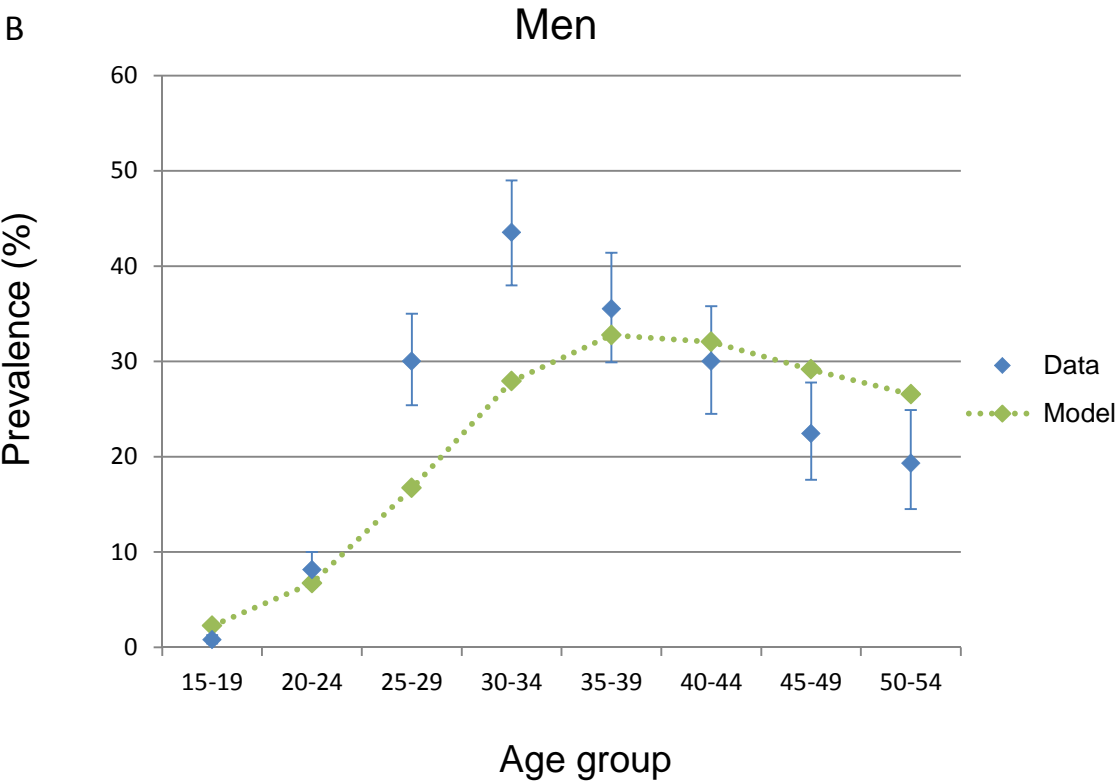
FigureS5. HIV prevalence with respect to age among (A) women and (B) men in 2004. Model estimates are compared to data from the Africa Centre Demographic Surveillance Area[33].Prevalence data from residents were used and no data were availble for 50-54 year old women.

Despite calibrating to overall incidence and prevalence in the population and calibrating to sex and age-specific trends in incidence, discrepancies in age-specific prevalence occurred.

Population size
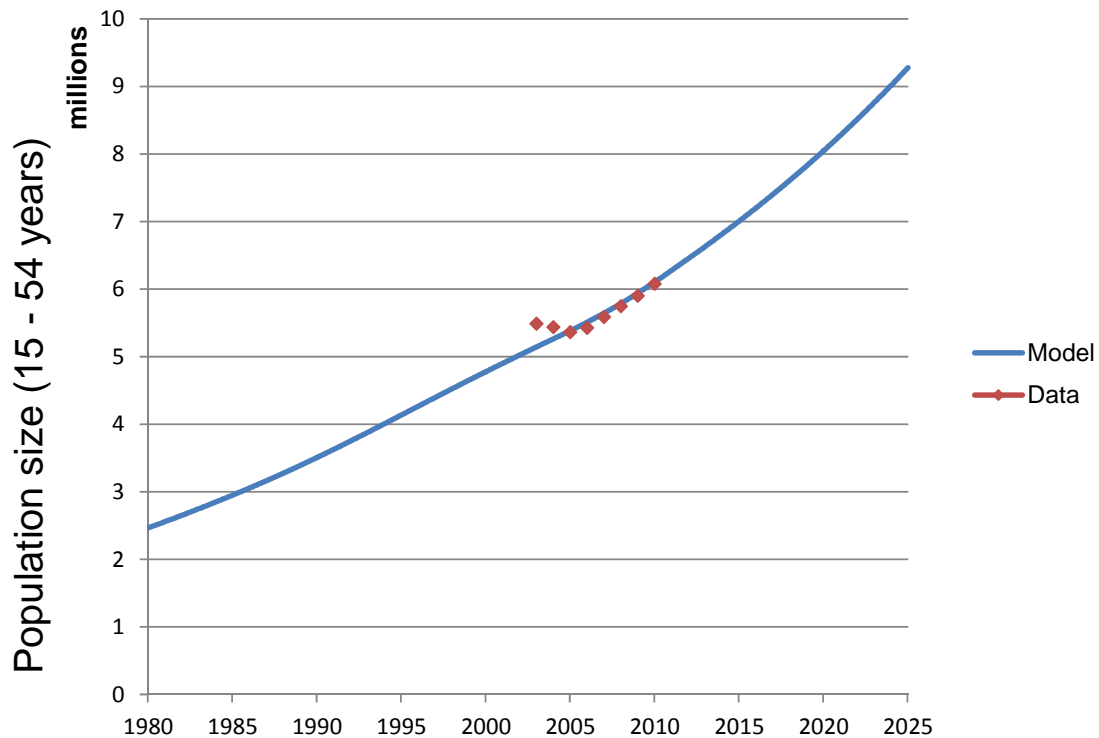
Figure S6. Simulated population size of 15-54 year olds over time. Data points represent mid-year population estimates for KwaZulu-Natal from Statistics South Africa [18].

Supplementary methods

Calculation of Quality Adjusted Life Years

HIV-status	Utility weight
Uninfected	1.0
HIV infected: CD4>350	0.94
HIV infected: CD4 350 - 200	0.82
HIV infected: CD4 <200	0.70
On ART	0.94
Dropped out of ART	0.82

Table S11. Assumed utility weights for states of infection and treatment in the model. These weights are obtained from a meta-analysis by Tengs and Lin that assigned a weight of 0.70 for AIDS, 0.82 for symptomatic HIV infection and 0.94 for asymptomatic HIV infection [38].

Calculation of PrEP effectiveness

The functional effect size (FE) of PrEP (referred to as 'effectiveness' in the main text)for a given 'intrinsic efficacy' (e) and level of 'adherence' (a) is calculated as:

$$FE = 1 - \frac{1 - \left\{ (1-\beta)^{2*n(1-a)} (1-(1-e)\beta)^{2*na} \right\}}{1 - (1-\beta)^{2*n}}$$

…(16)

This calculation is based on the assumption of an average of 48condom unprotected sex acts per year (n), anaverage follow-up period of two years and an average per sex act transmission probability (β) of 0.001[27].This calculation provides an approximation to estimates of efficacy observed in a clinical trial setting and is intended as a guide only.

An intrinsic efficacy of 75% and adherence level of 95% were assumed for all analyses. Together these produce a functional effect size of 70%, based on the above formula. The sensitivity of the functional effect size to the assumption regarding the number of condom unprotected sex acts per year was explored.It was found that it does not have a strong influence on the functional effect

size, with each additional 5 condom unprotected sex acts producing a 0.1% decrease in the functional effect size of PrEP.

The sensitivity of the functional effect size to the assumption regarding duration of follow-up was also investigated. Functional effect size was found to decrease slightly with increasing duration of follow-up, with an effect size of 0.695, 0.690 and 0.685 calculated for durations of follow-up of 3,4 and 5 years, respectively.

Supplementary results

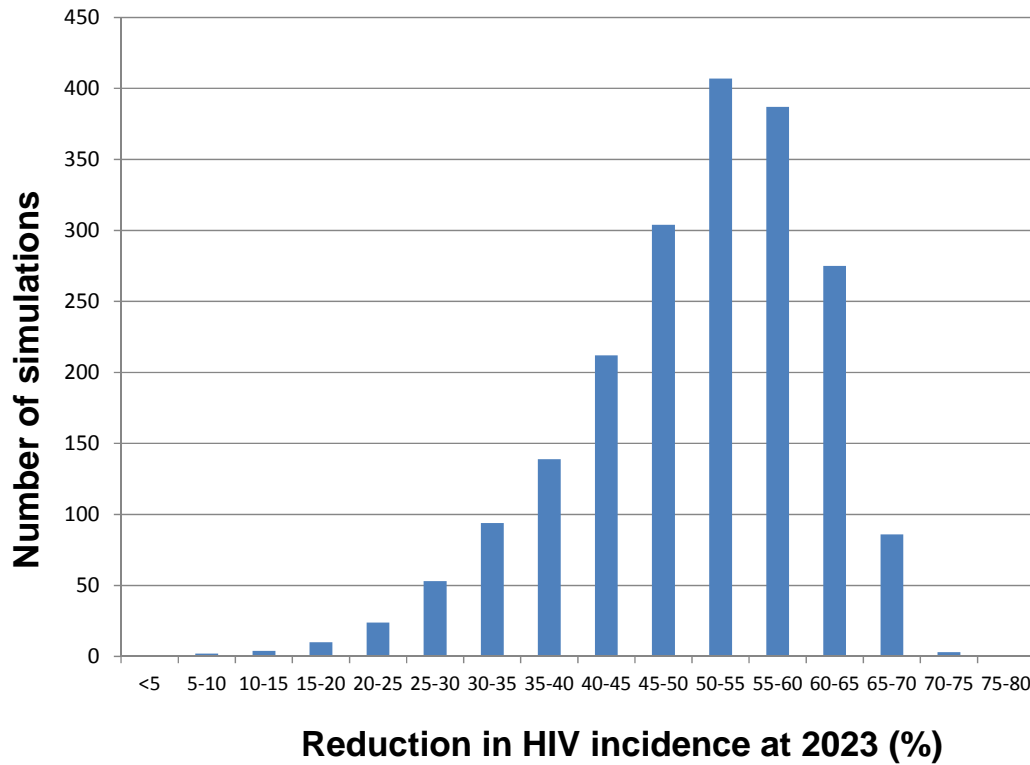### What is the optimal role for PrEP in combination with ART?
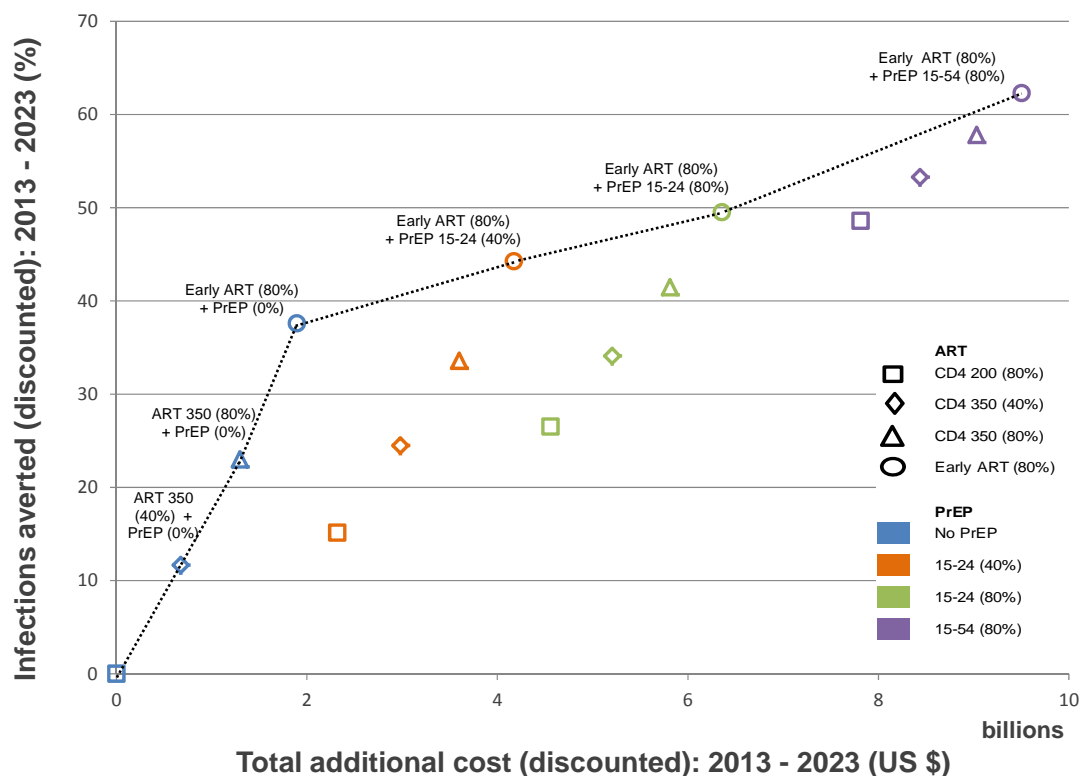
Figure S7. ART and PrEP in combination. The total additional cost versus impact (in terms of the percentage of infections averted), for intervention compared to baseline, for various combinations of ART and PrEP interventions from 2013 to 2023.Male circumcision is not scaled-up in the baseline scenario,nor in any of the intervention scenarios. PrEP effectiveness is assumed to be 70% in each scenario. Cost and impact are discounted at an annual rate of 3%. 1 billion = 1,000,000,000.
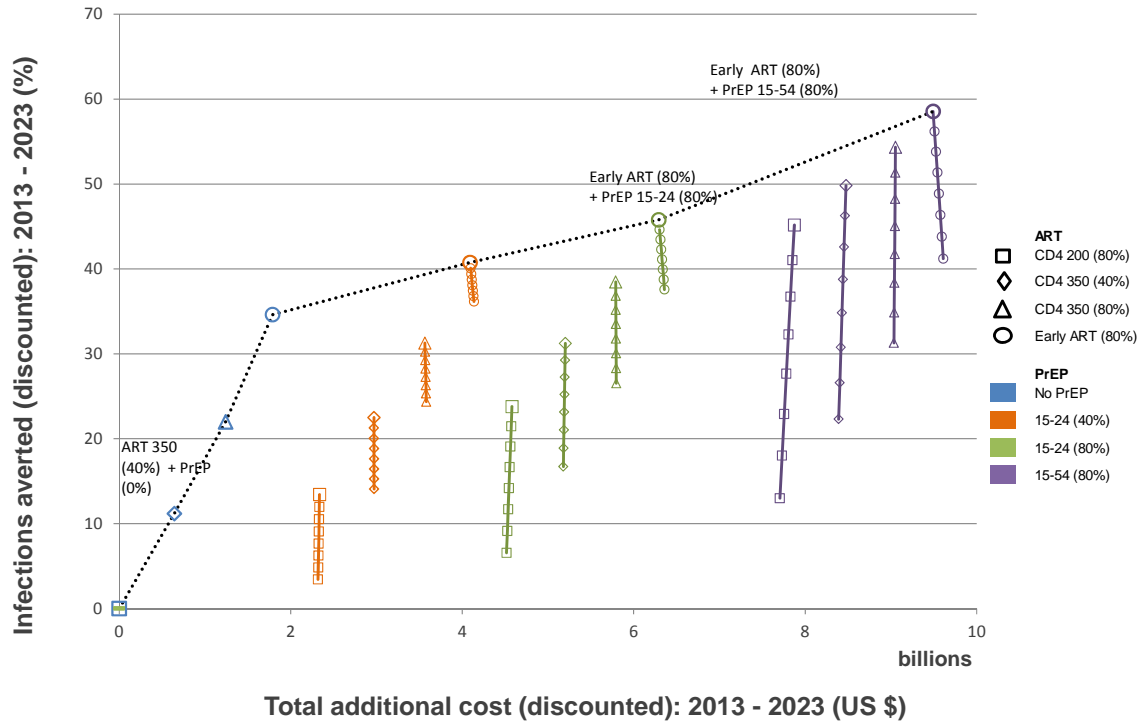
Figure S8. The sensitivity of the impact and cost of ART and PrEP in combination, with respect to level of PrEP adherence.Each of the twelve scenarios which include a PrEP intervention are repeated for a PrEP adherence level of 85%, 75%, 65%, 55%, 45%, 35% and 25% (illustrated by descending data points and connected by a solid line for each ART and PrEP combination scenario). PrEP effectiveness is assumed to be 70% in each scenario. Cost and impact are discounted at an annual rate of 3%. 1 billion = 1,000,000,000.

Figure S9. Reduction in HIV incidence at 2023 as compared to 95% coverage of ART for those with CD4<350 from 2013 onwards,based on2,000 simulations of different levels of coverage of male circumcision, early ART and PrEP (for 15-24 year olds).
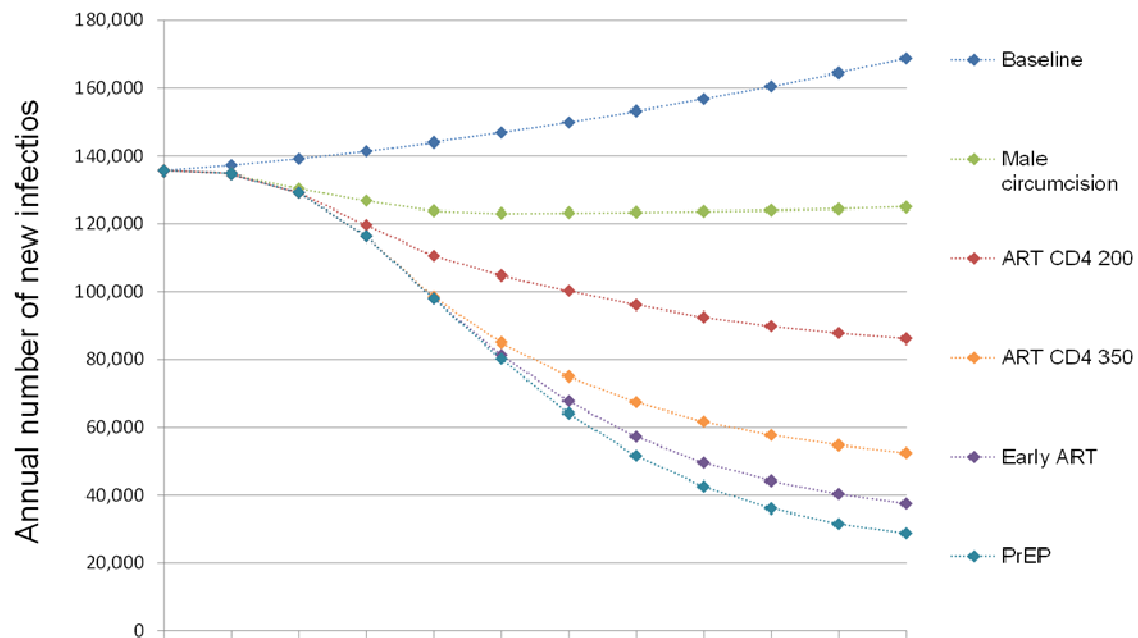
Figure S10: The impact of combination prevention on the annual number of new HIV infections. The impact on new HIV infections of (i) a male circumcision intervention (ii) plus complete ART coverage at CD4 200 (iii) plus very high ART coverage at CD4 350 (iv) plus early ART (v) plus PrEP. Although incidence is declining gradually from 2013 to 2023 in the baseline scenario, the annual number of new infections increases steadily, due to population growth.

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