Supplement Material

Overview of Mathematical Model

To investigate the community level impact of male circumcision on HIV prevalence in a general sub-Saharan population, we employed a previously validated stochastic compartmental model which simulates transmission of HIV and one STI in a heterosexual population in which the intervention is introduced (1-3). Individuals in the population are heterogeneous with respect to sexual activity and are stratified into classes with different rates of sexual partner acquisition. The STI was modelled with two compartments representing infected or not infected. HIV infection has been modelled with 5 states representing susceptible, early and acute infection, asymptomatic infection, pre-AIDS and AIDS. Flow of individuals between states is based on flow rates determined from specified parameters or from force of infection equations. Flow rates are instantly updated following each event. Flow of individuals through different HIV states is unidirectional, whereas individuals can recover from STI and be reinfected. Infection rates for different HIV susceptible individuals in the population depend on their sexual activity, their HIV or STI infection status, HIV and STI prevalence in their partners, and strength of HIV-STI interaction as cofactors of transmission and circumcision status.

Males from the general population are recruited for a male circumcision intervention according to a set time and coverage rate. Male circumcision efficacy against HIV and STI are specified in each simulation. The model generates HIV and STI prevalence and incidence rates by sex and sexual activity class over a 20 year period post-introduction of a circumcision intervention.

We compared HIV prevalence and incidence under different scenarios of effectiveness of a male circumcision program against HIV infection in two epidemiological settings corresponding low and high prevalence of HIV and STI and three levels of efficacy against STI while fixing the efficacy against HIV.

Model parameters and scenarios simulated

Model parameter inputs for the two epidemiological settings corresponding to high (scenario A) and low (scenario B) STI prevalence (averaging B: 3.7% versus A: 22.3% over 20 years), HIV prevalence (but with equivalent average HIV prevalence (B: 16.4% versus A: 29.8%) and HIV incidence rates (B: 1.9 versus A: 5.9 per 100 person-years) in the general male and female population are provided in Table 1 (1,8-26). Model outputs in terms of HIV and STI prevalence are also given.

The sexual behaviour parameters (i.e. distribution of the sexual activity classes and the rate of sexual partner acquisition) for the low STI scenario were selected to agree with infection rates in Kisumu region of Kenya observed from the UNIM male circumcision trial (4-6) and the 2003 Kenyan Demographic and Health Survey (7) at year 15 to 17 after the beginning of the simulated epidemic. Remaining parameters for HIV and STI transmission probabilities (1,8,10-12,16-18), duration of the different HIV states [1,8-15) and duration of STI infection (19-21) were estimated based on other published studies. The presence of STI in the HIV-infected sexual partner increases the per partnership probability of HIV transmission by a factor of 4 (a_1=4), while STI in the HIV-susceptible increases HIV transmission by a factor of 3 (α_2=3). Similarly, HIV infection in either partner increases STI transmission by a factor of 1.5 (b_1=1.5, b_2=1.5).

The higher STI prevalence scenario (A) was obtained from the lower scenario (B) by increasing the average duration of STI infection to 1.33 years from 6 months. Because this change increases HIV infection rates given the interaction between HIV and STI, we introduced a compensating decrease in HIV transmission probabilities of 40% during the early stage of infection. In scenario A, the rate of sexual partner change by sex and sexual activity class also needed to be modified in order to maintain similar HIV infection rates by sex and sexual activity class between scenarios.

Parameter values for male circumcision efficacy against HIV (E_s^{HIV}), modelled as a reduction in males' susceptibility to infection upon exposure was fixed at 60% (6,23,24), while efficacy against STI (E_s^{STI}) varied between low and high values (0%, 40% and 70%). Low E_s^{STI} (~0-20%) reflects the efficacy of MC on Chlamydia and HSV while high E_s^{STI} (~60-80%) reflects efficacy against chancroid and syphilis (25,26). We assumed that male-to-female HIV transmission was unchanged by circumcision status.

For each scenario of low and high STI prevalence scenario and each low to high value for MC efficacy against STI (6 scenarios in all), we recruited for circumcision 75% of males who are uninfected with HIV but who may be either positive or negative for STI infection. The duration of simulations was 20 years post-initiation of the circumcision intervention.

Details of the stochastic mathematical model and the Monte Carlo simulations

The model consists of ten disease states representing five different stages of HIV infection (h=1, …,5) and two states of STI infection (s=1,2)(Supplement figure 1). HIV susceptibles are labelled with the superscript h=1, full blown AIDS patients with h=5, HIV infecteds in the acute (h=2), asymptomatic (h=3) and pre-AIDS (h=4) stages have different degrees of infectiousness. Individuals in any of the HIV stages can be either susceptible (s=0 or infected with the STI (s=1). The number of individuals in the population in HIV infection state h, STI infection state s, activity class i and of sex k at time t, is given by $X_{k,i}^{h,s}(t)$. The sexually active population is stratified by sex (k=1 for women, k=2 for men) and by sexual activity class defined by the rate of sexual partner acquisition. Six activity classes are defined (i=1,…,6) where at one extreme are individuals of low sexual activity (i=1,2) and at the other are high activity individuals (i=3,4,5,6). Transition events between states occur by infection, progression to disease, departure from the sexually active population or immigration into the population. Given a stratification of two sexes and six sexual activity classes, 336 possible events can occur (2 sexes x 6 classes x 28 possible events) in the absence a circumcision intervention, as defined in Supplement figure 1a-b and Table 2.

Upon commencement of the circumcision intervention in the defined population, a fixed number of individuals flow from the general population to circumcised compartments (Supplement figure 1b). The number circumcised at time t of disease state h, state i, sex k and activity class i is given by $Z_{k,i}^{h,s}(t)$. The number of possible events after the trial begins is 660 (2 sexes x 6 activity classes x 55 events), as given in Table 2.

In the stochastic simulations, a random sequence of individual events is generated where each of the 660 possible events occurs with probability $P_{r,k,i}(t) = R_{r,k,i}(t) / S(t)$ where $S(t) = \sum_{r,k,i} R_{r,k,i}(t)$. The event chosen at each step of the sequence is determined by a random number generator according to the 660 probabilities. The time a person of sex k and class i spends in a specific state r before making a transition is assumed to be exponentially distributed with mean $1/\ R_{r,k,i}(t)$. Furthermore, the time between any two events is exponentially distributed with mean $S^{-1}(t)$. The time of occurrence s of chosen event r can be determined by choosing a random number from a uniform distribution and setting it equal to F(s) in the equation $F(s) = 1 - \exp(-S(t)s)$ and solving for s. Thus by an iterative process, a sequence of events and their time of occurrence is generated. With each new event all rates including forces of infection are automatically updated.

Key event flows in the model include force of HIV infection ($\lambda_{k,i}^{0}(t)$ if STI negative, and $\lambda_{k,i}^{1}(t)$ if STI postive) and STI infection ($\rho_{k,i}^{0}(t)$ if HIV negative, and $\rho_{k,i}^{1}(t)$ if HIV positive). The effect of treatment is assumed to reduce these forces of infection by an amount 1-E_s^{STI} and 1- E_s^{HIV}, where E_s^{STI} and E_s^{HIV} are efficacy of circumcision against STI and HIV respectively. The force of HIV infection for sex k and activity class i at time t in the general population is given by:

$$\lambda_{k,i}^{0}(t) = m_{k,i}(t) \sum_{j=1}^{6} \left[\varphi_{k,i,j}(t) \cdot \left(\frac{\sum_{h=2}^{4} \beta_{k^*,j,i}^{h} \cdot (X_{k^*,j}^{h,0}(t) + Z_{k^*,j}^{h,0}(t))}{NA_{k^*,j}(t)} \right) + \varphi_{k,i,j}(t) \cdot a_1 \left(\frac{\sum_{h=2}^{4} \beta_{k^*,j,i}^{h} \cdot (X_{k^*,j}^{h,1}(t) + Z_{k^*,j}^{h,1}(t))}{NA_{k^*,j}(t)} \right) \right]$$

Here, $m_{k,i}$ (t) is the annual rate of partner acquisition of persons of sex k and class i, and $\beta_{k^*,j,i}^{h}$ is the per partnership HIV transmission probability from a person in HIV infection phase h, sex k* and class j to opposite sex k and class i. The term $\varphi_{k,i,j}(t)$ describes the mixing matrix elements. This is essentially the probability that an individual of sex k and class i chooses a partner of opposite sex k* and class j(28). $NA_{k^*,j}$(t) is the total sexually active population of sex k* and class j. The term a_1 is a multiplicative factor increasing the probability of transmission of HIV when the HIV infected partner is also infected with STI. Thus, $\lambda^0_{k,i}(t)$ is a function of the rate of sexual partner change, the HIV transmission probability, HIV prevalence and epidemiological interaction between HIV and STI.

The force of HIV infection in an STI infected individual is $\lambda^1_{k,i}(t) = a_2\lambda^0_{k,i}(t)$, where a_2 is a multiplicative factor increasing the probability of transmission of HIV when the HIV susceptible is infected with STI. Values for the above parameters used in the simulations are given in Table 1.

The force of HIV infection for the circumcised group is given by $\lambda^{0*}_{k,i}(t) = (1 - E_S^{HIV})\lambda^0_{k,i}(t)$ and $\lambda^{1*}_{k,i}(t) = (1 - E_S^{HIV})\lambda^1_{k,i}(t)$, where E_H is the reduction in susceptibility to HIV due to circumcision.

The force of STI infection in HIV susceptibles of sex k and class i is given by:

$$\rho^0_{k,i}(t) = m_{k,i}(t)\sum_{j=1}^{6}\xi_{k*,j,i}\varphi_{k,i,j}(t)\left[\frac{\sum_{h=2}^{4} X^{h,1}_{k*,j}(t) + Z^{h,1}_{k*,j}(t)}{NA_{k*,j}(t)} b_1 + \frac{X^{1,1}_{k*,j}(t) + Z^{1,1}_{k*,j}(t)}{NA_{k*,j}(t)}\right].$$

Here $\xi_{k*,j,i}$ is the per partnership transmission probability of STI from sex k* and sexual activity class j to opposite sex k and class i. Unlike for HIV transmission probabilities, the values for STI transmission probabilities do not change by sexual activity class. We have chosen these values because STI transmission probabilities for bacterial STIs are high and are less affected by number of sex acts within a partnership. In addition, we are not trying to represent the exact biology of a given STI, and the STI needs to reflect a number of different aetiologies. The parameter b_1 is a multiplicative factor increasing the probability of STI transmission when the STI-positive partner is also HIV positive. In our model we set $b_1 = b_2 = 1.5$. The force of STI infection in a HIV positive individual of sex k and class i is given by $\rho^1_{k,i}(t) = b_2\rho^0_{k,i}(t)$, where b_2 is a multiplicative factor increasing the probability of STI transmission when the STI susceptible individual is HIV positive. The force of STI infection for the circumcised group is given by $\rho^{0*}_{k,i}(t) = (1 - E_S^{STI})\rho^0_{k,i}(t)$ and

$\rho^{1*}_{k,i}(t) = (1 - E^{STI}_{S})\rho^{1}_{k,i}(t)$, where E_S^{STI} is the reduction in susceptibility to STI due to circumcision.

The term $\varphi_{k,i,j}(t)$ are the elements of the mixing matrix which gives the probability that person of sex k and class i chooses a partner of opposite sex $k*$ and class j, and is given by (28-30)

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$$\varphi_{k,i,j}(t) = \frac{W_{k,i,j} \cdot NA_{k*,j}(t) \cdot m_{k*,j}(t)}{\sum_j W_{k,i,j} . NA_{k*,j}(t) . m_{k*,j}(t)} .$$

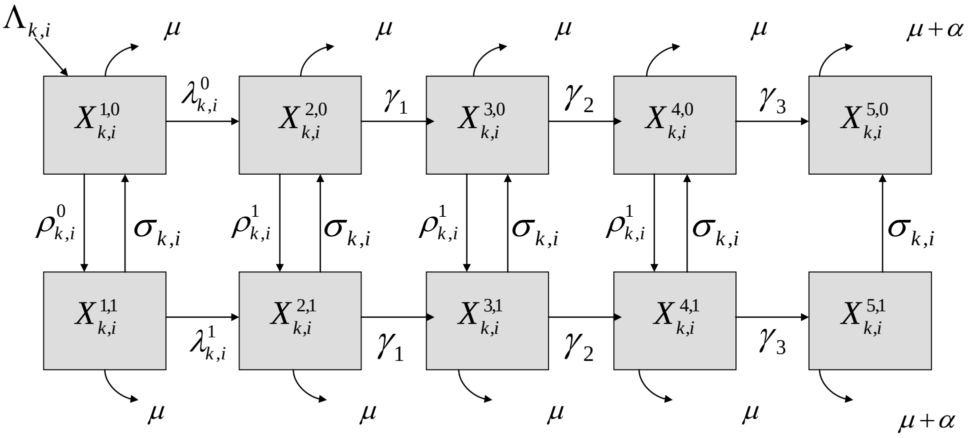
Thus, the row elements of the matrix must satisfy $\sum_j \varphi_{k,i,j}(t) = 1$. Here, $NA_{k*,j}(t)$ is the number of sexually active individuals of sex $k*$ and class j at time t, $m_{k*,j}(t)$ is the number of annual sexual partners and $W_{k,i,j}$ is a preference weight that person sex k and class i has for partner of opposite sex $k*$ and class j. If all elements $W_{k,i,j} = 1$, then mixing is proportional and there is no preference between different classes. In our simulations mixing was proportional.

In order for the model to remain valid, the mixing must remain balanced as the simulation is running over time. That is, the number of partnerships that individuals of sex k and class i has with individuals of opposite sex $k*$ and class j must be equal to the number of partnerships that individuals of sex $k*$ and class j has with person of sex k and class i. The mixing balance equations are

$$NA_{k,i}(t) \cdot m_{k,i}(t) \cdot \varphi_{k,i,j}(t) = NA_{k*,j}(t) \cdot m_{k*,j}(t) \cdot \varphi_{k*,j,i}(t) .$$

As the numbers of individuals with each age and class change with time, particularly due to AIDS-related mortality, these equations become unbalanced and the annual number of partners $m_{k,i}(t)$ requires updating. For this, the value of $m_{k,i}(t)$ for females of the lowest sexually activity class ($i = 1$) is held constant throughout the simulations, the other values of $m_{k,i}(t)$ are selected according to the balance equations as defined in Boily et al(28).

Supplement figure 1a – Stochastic compartmental mathematical model of HIV infection and co-circulating STI in the general population. $X_{k,i}^{h,s}(t)$ represents the number of individuals in the general population at time t of sex k and sexual activity class i with HIV infection status h and STI status s. Flows indicate the 28 possible events.



Supplement Figure 1b – Additional compartments in stochastic compartmental mathematical model to represent the circumcised population from time t. $Z_{k,i}^{h,s}(t)$ is the number of circumcised males at time t of sex k=2 and sexual activity class i with HIV infection status h and STI status s. Circumcision reduces the rate of HIV infection according to $\lambda_{k,i}^{0*}(t) = (1 - E_S^{HIV})\lambda_{k,i}^{0}(t)$ and $\lambda_{k,i}^{1*}(t) = (1 - E_S^{HIV})\lambda_{k,i}^{1}(t)$ and the rate of STI infection according to $\rho_{k,i}^{0*}(t) = (1 - E_S^{STI})\rho_{k,i}^{0}(t)$ and $\rho_{k,i}^{1*}(t) = (1 - E_S^{STI})\rho_{k,i}^{1}(t)$ where E_s^{HIV} and E_s^{STI} are the efficacy of circumcision against HIV and STI.

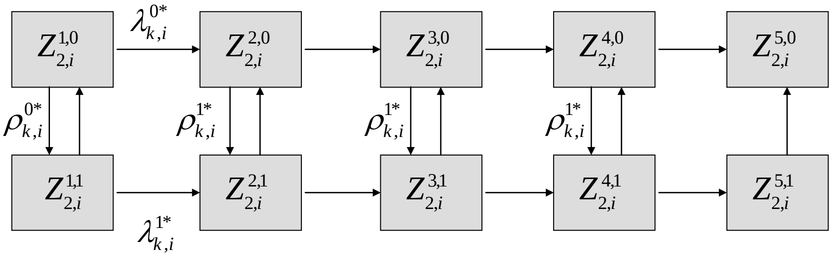


Table 2- Events and flow rates of individuals between disease states in general population and circumcised compartments.

Event r	**Description of events for general population**	**Gross Rate (number individuals per year) $\mathbf{R_{r,k,i}(t)}$**
1	Recruitment into sexually active population	$R_{1,k,i}(t) = \Lambda_{k,i}(t)$
2	Departure from sexually active population (DFSA) of STI- / HIV- individuals	$R_{2,k,i}(t) = \mu X_{k,i}^{1,0}(t)$
3	DFSA of STI-/HIV+ infecteds in first disease state	$R_{3,k,i}(t) = \mu X_{k,i}^{2,0}(t)$
4	DFSA of STI-/HIV+HIV infecteds in second disease state	$R_{4,k,i}(t) = \mu X_{k,i}^{3,0}(t)$
5	DFSA of STI-/HIV+HIV infecteds in third disease state	$R_{5,k,i}(t) = \mu X_{k,i}^{4,0}(t)$
6	Departure of AIDS patients who are STI-	$R_{6,k,i}(t) = (\mu + \alpha) X_{k,i}^{5,0}(t)$
7	HIV infection of STI-negative susceptibles	$R_{7,k,i}(t) = \lambda_{k,i}^{0}(t) X_{k,i}^{1,0}(t)$
8	Progression to second state of HIV infection for STI-	$R_{8,k,i}(t) = \gamma_1 X_{k,i}^{2,0}(t)$
9	Progression to third state of HIV infection for STI-	$R_{9,k,i}(t) = \gamma_2 X_{k,i}^{3,0}(t)$
10	Progression to AIDS for STI-	$R_{10,k,i}(t) = \gamma_3 X_{k,i}^{1,0}(t)$
11	Infection with STI for HIV- individuals	$R_{11,k,i}(t) = \rho_{k,i}^{0}(t) X_{k,i}^{1,0}(t)$
12-14	Infection with STI for HIV+ individuals	$R_{r,k,i}(t) = \rho_{k,i}^{1}(t) X_{k,i}^{..,0}(t)$
15-19	Recovery from STI for HIV+ and HIV-	$R_{r,k,i}(t) = \sigma_{k,i}(t) X_{k,i}^{..,1}(t)$
20-23	DFSA for STI+	$R_{r,k,i}(t) = \mu X_{k,i}^{..,1}(t)$
24	Death rate of AIDS patients who are STI+	$R_{24,k,i}(t) = (\mu + \alpha) X_{k,i}^{5,1}(t)$
25	HIV infection of STI+ positive susceptibles	$R_{25,k,i}(t) = \lambda_{k,i}^{1}(t) X_{k,i}^{1,1}(t)$
26	Progression to second state of HIV infection for STI+	$R_{26,k,i}(t) = \gamma_1 X_{k,i}^{2,1}(t)$
27	Progression to third state of HIV infection for STI+	$R_{27,k,i}(t) = \gamma_2 X_{k,i}^{3,1}(t)$
28	Progression to AIDS for STI+	$R_{28,k,i}(t) = \gamma_3 X_{k,i}^{4,1}(t)$

Description of events in circumcised individuals

29-55	Defined analogously to general population	
34	HIV infection of STI-negative susceptibles	$R_{34,2,i}(t)=(1-E_S^{HIV})\lambda_{2,i}^{0}(t)Z_{2,i}^{1,0}(t)$
38	Infection with STI for HIV- individuals	$R_{38,2,i}(t)=(1-E_S^{STI})\rho_{2,i}^{0}(t)Z_{2,i}^{1,0}(t)$
39-41	Infection with STI for HIV+ individuals	$R_{r,2,i}(t)=(1-E_S^{STI})\rho_{2,i}^{1}(t)Z_{2,i}^{h,0}(t)$
52	HIV infection of STI+ positive susceptibles	$R_{79,2,i}(t)=(1-E_S^{HIV})\lambda_{2,i}^{1}(t)Z_{2,i}^{1,1}(t)$

Table 1- Parameter input values used in model simulations for low and high STI prevalence and output values for HIV and STI prevalence and HIV incidence.

Symbol	Description of epidemiological parameters	Parameter value	References
$\gamma_1,\ldots,\gamma_3$	Rate of progression between 3 stages of HIV infection. Duration of stage 1 is $1/\gamma_1$ = 4.4 months, stage 2 is $1/\gamma_2$ =6.5 yrs, stage 3 is $1/\gamma_3$ = 2 yrs.	γ_1 = 2.75 γ_2 = 0.154 γ_3 = 0.5	(1,8-15)
$\beta^h_{k^*,j,i}$	Per partnership probability of transmission of HIV from individual of sex k*, sexual activity class j and infection phase h (h=2,3,4) to partner of opposite sex k and class i. Values given are transmission probabilities for females (k*=1) of low activity class (j= 1,2 = lowf) or high activity class (j=3,...,6 = highf) to males of low activity class (i= 1,2 = lowm) or high activity class (i=3,...,6 = highm). Transmission probabilities for male to female are double of these below.		
High Scenario (A)	$\beta^2_{1,lowf,lowm} = 0.048$ $\beta^3_{1,lowf,lowm} = 0.0032$	$\beta^4_{1,lowf,lowm} = 0.051$	(1,8,10-12,16-18)
	$\beta^2_{1,lowf,highm} = 0.026$ $\beta^3_{1,lowf,highm} = 0.0017$	$\beta^4_{1,lowf,highm} = 0.026$	
	$\beta^2_{1,highf,lowm} = 0.015$ $\beta^3_{1,highf,lowm} = 0.001$	$\beta^4_{1,highf,lowm} = 0.0071$	
	$\beta^2_{1,highf,highm} = 0.015$ $\beta^3_{1,highf,highm} = 0.001$	$\beta^4_{1,highf,highm} = 0.0071$	
Low Scenario (B)	$\beta^2_{1,lowf,lowm} = 0.048$ $\beta^3_{1,lowf,lowm} = 0.0032$	$\beta^4_{1,lowf,lowm} = 0.051$	
	$\beta^2_{1,lowf,highm} = 0.026$ $\beta^3_{1,lowf,highm} = 0.0017$	$\beta^4_{1,lowf,highm} = 0.026$	
	$\beta^2_{1,highf,lowm} = 0.015$ $\beta^3_{1,highf,lowm} = 0.001$	$\beta^4_{1,highf,lowm} = 0.0071$	
	$\beta^2_{1,highf,highm} = 0.015$ $\beta^3_{1,highf,highm} = 0.001$	$\beta^4_{1,highf,highm} = 0.0071$	
$\sigma_{k,i}$	Recovery rate of STI infection. Duration of infection is $1/\sigma_{k,i}$ = 6 months or 1.33 years for all sexes k and activity classes i.	High scenario (A): $\sigma_{k,i}$ = 0.75. Low scenario(B): $\sigma_{k,i}$ = 2.0.	(19-21)
$\xi_{k,j,i}$	Per partnership probability of transmission of STI from infected individual of sex k and sexual activity class j to partner of opposite sex k* and class i.	$\xi_{k,i,j}$ = 0.15 for all k,i,j	(19-21)
a_1, a_2	Enhancement of HIV transmission given STI infection. a_1 is the relative risk (multiplicative factor) for increased susceptibility to HIV given STI infection in the partner. a_2 is the relative risk of increased susceptibility to HIV given STI infection in self.	a_1 = 4 a_2 = 3	(22,27)
b_1, b_2	Enhancement of STI transmission given HIV infection. b_1 is the relative risk (multiplicative factor) for increased suceptibility to STI given HIV infecion in the partner. b_2 is the relative risk of increased susceptibility to STI given HIV infection in the self.	b_1=1.5 b_2 =1.5	(27)
α	Mortality rate due to AIDS	$1/\alpha$ = 1 year	(13-15)
$m_{k,i}$	Annual rate of sexual partner change. $m_{k,i}$ is the number of new sexual partners per	Low scenario: $m_{k=1,i=1\ldots6}$ =	Assumed

	year for person of sex k and sexual activity class i. k=1 represents females; k=2 males.	1.0 3.5 5 10 50 75 $m_{k=2,i=1\ldots6}$ = 1.5 5.0 10 15 20 25 High scenario: $m_{k=1,i=1\ldots6}$ = 1.5 4.0 6 12 35 40 $m_{k=2,i=1\ldots6}$ = 1.0 3.5 5 10 25 35	
$pp_{k,i}$	Percentage of population by activity class i for class k at start of HIV epidemic.	$pp_{k=1,=1\ldots6}$= 55 20 10 10 2.5 2.5 $pp_{k=2,=1\ldots6}$= 50 30 5 5 5 5	Assumed
μ	Rate of departure from sexually active population ($1/\mu$ = 35 yrs)	μ = 0.02857	Assumed
Population	Size of population	100 000	Assumed
Coverage	Percentage of HIV-negative males recruited for circumcision	75%	Assumed
Incidence- HIV (This is a model output)	Average incidence rate of HIV in general population over 20 years	High scenario (A): 5.9 per 100 person-years Low scenario (B): 1.9 per 100 person-year	(4-6)
Prevalence – HIV (This is a model output)	Prevalence of HIV in general population over 20 years	High scenario(A): 29.8% Low scenario (B): 16.4%	(4-6)
Prevalence – STI (This is a model output)	Prevalence of STI in general population over 20 years	High scenario(A): 22.3% Low scenario(B): 3.7%	(4-6)
E_s^{HIV}	Efficacy of circumcision against HIV	E_s^{HIV} = 60%	(6,23,24)
E_s^{STI}	Efficacy of circumcision against STI	E_s^{STI} = 0%, 40%, 70%	(25,26)

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