Technical description of model

The model is a development of a previous model developed by Peter Vickerman and described in Williams et al. (2006). The original model simulated the transmission of HIV and two curable STIs resulting from heterosexual contacts between a number of sub-populations within the male and female population. The model has been adapted to include the heterosexual transmission of Herpes simplex virus type 2 (HSV-2), one of the curable STIs has been adapted to mimic the natural history of Treponema pallidum (syphilis), and the female sex worker population has been stratified into those FSWs that have a low and high frequency of clients per month.

The model is formulated in the C programming language as a set of deterministic ordinary differential equations that describe the movement of individuals between discrete sub-populations – based upon their sex, sexual behaviour, STI and HIV infection status. These are described in turn below.

In the model, the population is divided by sex (r = 0 and r = 1 denotes males and females respectively) into a number of sub-groups with four different levels of sexual activity (j = 0, sexually inactive, j = I, just has long-term ‘main’ sexual partners, j = 2, has main and casual sexual partnerships, j = 3 and 4, has main, casual and commercial sexual partnerships). The population is also divided into four HSV-2 infection stages (i = 0 to 3, with 0 being uninfected, 1 being the initial primary infection stage; 2 being the asymptomatic stage and 3 being the symptomatic recurrence phase). The subscripts r,p,k denote the sex, sexual activity and HSV-2 infection status, respectively, of a partner of an individual of sub group r,j,i.

As with other HIV compartmental models, each behavioural sub-group is divided into those that are susceptible to HIV infection (x), those that are recently HIV infected and in the initial high viraemia phase (y), those who have progressed into the low-viraemia phase (z) and those with symptomatic high viraemia (v). Those with AIDS are chronically ill, and are assumed to cease being sexually active. New individuals enter the susceptible population at a fixed per capita recruitment rate (A) equivalent to the sum of those leaving the model through HIV related and unrelated mortality and migration. The overall number in the modelled population is represented by the term n. Susceptibles become infected with HIV at a per capita rate that is determined by the per-capita risk associated with their sexual behaviour (\( \pi_{ax} \)). When a susceptible becomes infected with HIV they are initially highly infectious (for an average period 1/\( \psi \)). The model, individuals remain in the population until they cease sexual activity due to AIDS, die or migrate out of the population. The non-HIV related movements out of the population are summed and represented by the parameter \( \Psi \).

Female sex workers continue sex work for a period (average duration 1/\( \eta_{ij} \), for r = 1 and j = 3 and 4) before returning to the general population and are replaced by new female sex workers from the sexually active general population. Similarly, clients remain as clients for a period (average duration 1/\( \eta_{ij} \), for r = 0 and j = 3 and 4) before returning to the general population and being replaced by new clients from the sexually active general population. The parameter \( \eta_{ij} \) is zero for j = 0, 1 and 2. The female sex workers and clients only return to the corresponding infection categories amongst the sexually active individuals that have just main (j = 1) or main and casual partnerships (j = 2), with the proportion going to each being dependant on the relative size of each groups. In addition, the female sex workers and clients are only replaced by individuals from the j = 1 and j = 2 behavioural categories, but from all HIV and HSV-2 infection states, with the number from each category being dependant on the relative number in that category.

Eq. (1) describes the HIV infection dynamics amongst the population including the population movements into and out of the FSW and client groups:

\[
\frac{dx_{0}}{dt} = \eta_{0}A_{r} - x_{0}(\pi_{ax} + \Psi + \eta_{j}) + \frac{b_{y} + b_{z}}{r_{FX}} \sum_{y_{a}=1,2,3,4} \eta_{ax} y_{ax} \sum_{y_{a}=1,2,3,4} n_{ay} \eta_{av}\]

\[
\frac{dx_{1}}{dt} = x_{0} \pi_{ax} - h_{ax}(\psi_{r} + \xi + \eta_{j}) + \frac{b_{y} + b_{z}}{r_{FX}} \sum_{y_{a}=1,2,3,4} \eta_{ax} y_{ax} \sum_{y_{a}=1,2,3,4} n_{ay} \eta_{av}\]

\[
\frac{dx_{2}}{dt} = x_{1} \pi_{ax} - h_{ax}(\psi_{r} + \xi + \eta_{j}) + \frac{b_{y} + b_{z}}{r_{FX}} \sum_{y_{a}=1,2,3,4} \eta_{ax} y_{ax} \sum_{y_{a}=1,2,3,4} n_{ay} \eta_{av}\]

\[
\frac{dx_{3}}{dt} = \Omega_{x_{3}} - z_{x_{3}}(\psi_{r} + \xi + \eta_{j}) + \frac{b_{y} + b_{z}}{r_{FX}} \sum_{y_{a}=1,2,3,4} \eta_{ax} y_{ax} \sum_{y_{a}=1,2,3,4} n_{ay} \eta_{av}\]
where $\delta_{jk}$ equals one if $j = p$ and zero otherwise. The probability that a susceptible becomes HIV infected per unit time from unprotected sex ($\pi_{sex}$) is one minus the probability of not getting infected over this time. The probability of not becoming infected per unit time is the product of the probabilities of not being HIV infected from any sexual act with any sexual partner from each behavioural sub-group. If we let $d_{0ij}$, $d_{1ij}$ and $d_{2ij}$ denote the total number of main, casual and commercial sexual partners that an individual in sub-group $[r',p,k]$ has per unit time, then mathematically, the probability that a susceptible becomes HIV infected from their sexual partnerships ($\pi_{sex}$) per unit time is given by:

$$\pi_{sex} = 1 - \prod_{r'p} (1 - \varphi_{0r'pik})^{d_{0r'pik}} (1 - \varphi_{1r'pik})^{d_{1r'pik}} (1 - \varphi_{2r'pik})^{d_{2r'pik}}$$

Equation 1

Two components make up the mixing function $\varphi_{0r'pik}$. Firstly, an individual has a probability $\mathcal{C}$ that they will choose a main partner of the same sexual activity, and otherwise their main partnerships are chosen depending on the number of main partnerships provided by different sub-groups. The probability $\mathcal{C}$ determines how assortative or random the mixing is, with 1 being complete like with like assortative mixing and 0 being random mixing. The mixing function $\varphi_{0r'pik}$ has the following form:

$$\varphi_{0r'pik} = (1 - \mathcal{C}) \sum_{r'p} \varphi_{r'pik} + \mathcal{C} \sum_{r'p} \varphi_{r'pik}$$

Equation 2

The form and derivation of the $\varphi_{0r'pik}$ function is a development of the formulation by Garnett and Anderson [46]. The product $d_{0r'}\varphi_{0r'pik}$ then gives the total number of main sexual partnerships an individual from sub-group $[r',p,k]$ forms with those from sub-group $[r',p,k]$. The functions $\varphi_{1r'pik}$ and $\varphi_{2r'pik}$ and calculated similarly except mixing is assumed to be random (proportional to the number of casual or commercial partnerships provided by that group) and $\varphi_{1r'pik} > 0$ only when $j > 1$ (only individuals in classes $j = 2,3$ and 4 have casual partnerships) and $\varphi_{2r'pik} > 0$ only when $j > 2$ (only individuals in classes $j = 3$ and 4 have commercial partnerships).

The parameter $\varphi_{0r'pik}$ is the product of the probability that an individual from that behavioural and HSV-2 infection state is infected and the probability that the infected main partner transmits HIV to the susceptible individual per unit time (defined as $D_{0r'pik}$). The probabilities of HIV transmission between a susceptible and an infected individual per unit time are estimated using a Bernoulli formulation based on Weinstein et al. (1989). If in each unit of time, an individual in sub-group $[r,j,i]$ has $m_i$ sex acts with each main sexual partner; $f$ is the probability that a condom is used per sex act; $e$ is the per sex act efficacy of the condom; $\beta$, is the probability of HIV transmission per sex act from sex $r'$ to sex $r$; $\alpha$, is the extent to which STI co-infection of either partner increases the probability of HIV transmission, and $\alpha_{hi1}$ and $\alpha_{hi2}$ are the extent to which the initial and symptomatic high viraemia phases increase the probability of HIV transmission, then $D_{0r'pik}$ can be written:

$$D_{0r'pik} = 1 - \left(1 - \left(\frac{Y_{r'pik}}{Y_{r'pik}}\right)\left(1 - \frac{\Gamma_{r'pik} + \Phi_{r'pik} + \Theta_{r'pik}}{Y_{r'pik} + \Gamma_{r'pik} + \Phi_{r'pik} + \Theta_{r'pik}}\right)\right)\left(1 - \frac{\varphi_{0r'pik}}{\varphi_{0r'pik} + \varphi_{1r'pik} + \varphi_{2r'pik}}\right) + \left(1 - \left(\frac{Y_{r'pik}}{Y_{r'pik}}\right)\left(1 - \frac{\Gamma_{r'pik} + \Phi_{r'pik} + \Theta_{r'pik}}{Y_{r'pik} + \Gamma_{r'pik} + \Phi_{r'pik} + \Theta_{r'pik}}\right)\right)\left(1 - \frac{\varphi_{0r'pik}}{\varphi_{0r'pik} + \varphi_{1r'pik} + \varphi_{2r'pik}}\right)$$

Equation 3

where $y^s$ denotes the number infected with an STI and $\Phi = [t]$, $E = [t]$, $F = [t]$, $G = 1$, $Q = 1$, $V = [t]$, $\Omega = [t]$.

Equation 4

The corresponding probabilities $\varphi_{1r'pik}$ and $\varphi_{2r'pik}$ (probabilities that a susceptible will become HIV infected per unit time from their casual or commercial partnerships), and $D_{1r'pik}$ and $D_{2r'pik}$ (probabilities that a susceptible will become HIV infected per unit time from their casual or commercial partnerships).
from their infected casual or commercial partnerships) are calculated in exactly the same way except that there are different levels of condom use for casual and commercial sexual partnerships and only certain individuals have casual (j = 2,3, and 4) and commercial partnerships (j = 3 and 4).

STI dynamics

The model also simulates the transmission of syphilis, HSV-2 and a generic bacterial STI (representing Neisseria gonorrhoeae (Ng) and Chlamydia trachomatis (Ct)) between sexual partners. In brief, once individuals are infected with Ng/Ct, they become susceptible again at a fixed rate. Once individuals are infected with HSV-2, they remain infected for life. They first enter the initial infection stage, then progress to asymptomatic infection from which they repeatedly have short symptomatic recurrences[1]. When individuals are infected with syphilis, they enter the primary/secondary phase of infection, then progress to latent infection where they remain, if not treated. If syphilis cases are treated in the primary/secondary stages for syphilis), then for each partnership the probability that a susceptible is infected with a STI per unit time (defined as \( \psi_{ij,pk} \)) is:

\[
\psi_{ij,pk} = \frac{\beta_{ij,pk}}{\mu_j} - [\beta_{ij}((1 - fe)(1 - s))]^{m}
\]

Equation 6

If we let \( x' \) denote the number susceptible to an STI, and \( y' \) the number infected, then the transmission dynamics of the SIS STI can be described using the following set of deterministic differential equations:

\[
\frac{dx'}{dt} = n_{gj}A_j - x' \left( \pi_x + \psi_x + n_{gj} + \frac{\psi_{xg}}{n_{gp}} \right) + \mu_j x' + \frac{\beta_{j1} + \beta_{j2} \sum_{y = 1,2} \sum_{r = 1,4} \eta_{yrw} \sum_{y = 1,4} \eta_{ywr} \sum_{y = 1,4} \eta_{ywr}}{\mu_j}
\]

\[
\frac{dy'}{dt} = x' \left( \pi_x + \psi_x + n_{gj} + \frac{\psi_{xg}}{n_{gp}} \right) + \mu_j y' + \frac{\beta_{j1} + \beta_{j2} \sum_{y = 1,2} \sum_{r = 1,4} \eta_{yrw} \sum_{y = 1,4} \eta_{ywr} \sum_{y = 1,4} \eta_{ywr}}{\mu_j}
\]

Equation 7

For this we assume that individuals remain infected for a fixed period of time \((1/\mu_x)\), and then become susceptible to the STI once more, and the parameter \( \Psi \) is the rate at which susceptibles and infecteds leave due to HIV morbidity (acquiring AIDS) because a proportion \( \frac{\psi_{xg}}{n_{gp}} \) of the individuals in sub-group \([r,j,i,]\) will be in the symptomatic HIV phase.

For syphilis, the dynamics are similar to those described for the first STI (equation 7) except there are three stages of infection, primary (\( y'^p \)), latent (\( y'^l \)) and resistant or immune (\( y'^i \)) and individuals susceptible to syphilis are denoted by \( x'^s \).

For syphilis, if individuals are treated when in the primary or secondary stage (at a rate \( \alpha_j \)) then they become susceptible again, whereas if they are treated in the latent stage (at a rate \( \alpha_j \)) then they are assumed to become resistant to infection for a certain duration \((1/\theta)\). If individuals are not treated then they stay in the primary or secondary stage for an average duration \(1/\theta\) and then enter the latent phase where they remain until treated. The differential equations in Eq. (8) describe the syphilis model:
Equation 8

**HSV-2 dynamics**

HSV-2 infection states are modelled as an index (i) of all other state variables. This means that HIV and HSV-2 are modelled in a way that all possible co-infection states are modelled explicitly. The model structure used for HSV-2 is described in detail by Foss et al. (2008) with there being four HSV-2 infection states (i = 0..3). The probability that a susceptible is infected with a HSV-2 per unit time (defined as $\phi_{type}$) uses the same formulation (equation 6) as for the other STIs except that there are different transmission probabilities for primary, latent/asymptomatic and recurrent HSV-2.

HSV-2 infection is modelled in a similar manner to the other STIs with slight modifications. The index i denotes the stage of HSV-2 infection and stratifies all behavioural and HIV states. The susceptible population (i = 0) becomes infected with probability $\pi_{0i}$. After infection individuals move into a short initial/primary infection stage (denoted by i = 1) with average duration $1/\gamma$. From this initial infection stage individuals move into the latent/asymptomatic low level infectious shedding stage (i = 2). Individuals in the latent stage can move in to a symptomatic recurrent phase (i = 3) at rate $\varsigma$ which differs for those who are HIV positive, before returning back to the asymptomatic phase at an average rate $\varpi$. Individuals with HSV-2 are assumed to remain infected for life. The differential equations for HSV-2 for individuals in a generic HIV state ‘q’ are as shown below (equation 9). With $\Psi$ only being present if the generic HIV state is the symptomatic z state and the replacement of susceptibles only occurring in the HIV susceptible state unless a bacterial STI or HSV-2 for those co-infected with HIV. The infectivity of HSV-2 is also increased if the individual is co-infected with HIV, and the susceptibility to infection with HSV-2 is increased in those infected with HIV.

References


Model parameter derivation

**Yearly increase in condom use over years**

From collating different data sources (see Table 1) a range was produced for the consistency of condom use at the time of the round 1 FSW IBBA in each district. Then, to estimate the condom use in other years, the round 2 FSW IBBA data from each setting was used to reconstruct the average yearly increase in consistent condom use for before and after the start of the intervention (2004 in Belgaum and 2003 in Mysore)[35]. This was done by firstly looking at when FSWs report they started using condoms consistently (in the round 2 IBBA survey), and then using this to estimate the percentage of FSWs that used condoms consistently in each year by dividing the number that
used condoms consistently in that year by the number that reported still being a FSW in that year.

For Mysore, the FSW IBBA R2 condom reconstruction analysis estimates that the percentage of FSWs using condoms consistently increased on average by 3.4% (2.0–8.8%) per year from 2001–03 and by 12.2% (8.7–15.7%) per year from 2003–07. In contrast, the average increase in the percentage of FSWs using condoms consistently in Belgaum increased by 12.4% (8.0–16.7%) per year from 2001–04 and by 4.8% (2.4–7.3%) per year from 2004–08. The same yearly increase was assumed to apply to the increase in the overall consistency of condom use in the last sex act as used in the model but negative lower bounds were set to zero.

**HSV-2 transmission probabilities**

Studies suggest that the HSV-2 transmission probability is about 0.001 per sex act over all infection stages for men to

Supplementary Table 1: Biological model input parameters used to obtain the baseline Mysore and Belgaum model fits.

<table>
<thead>
<tr>
<th>Types of model input</th>
<th>Definition of model input</th>
<th>Model inputs for: Male Female</th>
<th>Reference for model input value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiological</td>
<td>Average duration of Ng/Ct (months)/s</td>
<td>2–5</td>
<td>[5] but also depends on level of STI treatment.</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sex worker</td>
<td>0.5–3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Average duration of syphilis stages (months)</td>
<td>4.5–6</td>
<td>Available data was reviewed by [3]</td>
</tr>
<tr>
<td></td>
<td>Primary and secondary stage (without treat)</td>
<td>1–5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary and secondary stage (with treat)</td>
<td>2–24</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune/resistant phase</td>
<td>2–60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration in months of Initial high viraemia phase</td>
<td>4–6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic high viraemia phase</td>
<td>6–18</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV and symptomatic high viraemia transmission</td>
<td>75–92</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Primary stage</td>
<td>0.36–0.66</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Symptomatic recurrence</td>
<td>0.1–0.15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rate of HSV-2 symptomatic recurrences (per month)</td>
<td>0.09–0.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>while HIV negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rate of HSV-2 symptomatic recurrences (per month) when HIV positive</td>
<td>1.3–2×rate in HIV negatives</td>
<td>[24,25]</td>
</tr>
<tr>
<td></td>
<td>Condom efficacy per sex act</td>
<td>80–95%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative condom efficacy for HSV-2 compared to HIV</td>
<td>50%–100%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probability of HIV transmission per sex act:</td>
<td>Male to female:</td>
<td>0.0008 (0.0006–0.0011)</td>
</tr>
<tr>
<td></td>
<td>Female to male:</td>
<td>0.0004 (0.0001–0.0014)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Probability of STI transmission per sex act:</td>
<td>Ngs/Ct</td>
<td>0.05–0.2</td>
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<td></td>
<td>Syphilis (male to female):</td>
<td>0.1–0.3</td>
<td>[3]</td>
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<tr>
<td></td>
<td>Ratio for female to male syphilis transmission</td>
<td>0.33–1.0</td>
<td>Supplementary material</td>
</tr>
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<td></td>
<td>Probability of HSV-2 transmission per sex act for males to females: HSV-2 Primary stage</td>
<td>0.003–0.25</td>
<td>Supplementary material</td>
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<tr>
<td></td>
<td>HSV-2 latent/asymptomatic shedding stage</td>
<td>0.0005–0.002</td>
<td>Supplementary material</td>
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<td></td>
<td>HSV-2 symptomatic recurrence stage</td>
<td>0.003–0.15</td>
<td>Supplementary material</td>
</tr>
<tr>
<td></td>
<td>probability compared to male to female transmission probability</td>
<td>0.2–0.33</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Transmission probabilities</td>
<td>Male to female:</td>
<td>1.2–2.5</td>
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<tr>
<td></td>
<td>Female to male:</td>
<td>2.1–3.3</td>
<td>[34]</td>
</tr>
<tr>
<td></td>
<td>Average syphilis cofactor per sex act</td>
<td>1.5–5</td>
<td>[28]</td>
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<tr>
<td></td>
<td>Average HSV-2 cofactor per sex act for increasing HIV infectivity:</td>
<td>Primary phase</td>
<td></td>
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<tr>
<td></td>
<td>Asymptomatic/latent phase</td>
<td>1–1.7</td>
<td>[28]</td>
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<tr>
<td></td>
<td>Symptomatic recurrence phase</td>
<td>1–5</td>
<td>[28]</td>
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<tr>
<td></td>
<td>Average HSV-2 cofactor per sex act for increasing HIV susceptibility:</td>
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<td></td>
<td>Asymptomatic/latent phase</td>
<td>1–4.75</td>
<td>[28]</td>
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<tr>
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<td>Symptomatic recurrence phase</td>
<td>1.5–19</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>Sexual transmission multiplicative co-factor during:</td>
<td>Initial HIV high viraemia phase</td>
<td>9.2 (4.5–18.8)</td>
</tr>
<tr>
<td></td>
<td>Symptomatic high viraemia phase</td>
<td>7.3 (4.5–11.9)</td>
<td>[28]</td>
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<tr>
<td></td>
<td>Cofactors for increasing HSV-2 transmission</td>
<td>HIV cofactor per sex act for increasing HSV-2 susceptibility</td>
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<tr>
<td></td>
<td>Cofactors for increasing HIV transmission</td>
<td>Average Ngs/Ct cofactor per sex act</td>
<td>1.2–5</td>
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<td></td>
<td>Average syphilis cofactor per sex act</td>
<td>2.1–3.3</td>
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<td>Average HSV-2 cofactor per sex act for increasing</td>
<td>Primary phase</td>
<td>1–5</td>
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<td>HIV infectivity -</td>
<td>Asymptomatic/latent phase</td>
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<td>Symptomatic recurrence phase</td>
<td>1–5</td>
<td>[28]</td>
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<td></td>
<td>Average HSV-2 cofactor per sex act for increasing</td>
<td>HIV susceptibility -</td>
<td>1.5–19</td>
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<td></td>
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<td>1–4.75</td>
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<td>1.5–19</td>
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<td>Symptomatic high viraemia phase</td>
<td>7.3 (4.5–11.9)</td>
<td>[28]</td>
</tr>
</tbody>
</table>

† signifies a parameter that is varied in the HIV and HSV-2 biological parameter sets in the second stage of the model fitting.
women using condoms and that it is normally 3–5 times lower for females to males [23,36,37]. Viral load and transmission data suggests HSV-2 could be 1–3 times more transmissible during a symptomatic recurrence compared to the asymptomatic period [18,23,38,39], and although Kim et al. [23] found no relationship between the number of lesions and HSV-2 transmission, they did find recent infection made HSV-2 transmission twice as likely.

Because individuals will be mainly in the asymptomatic period, the transmission probability for this period for men to women was set to be around the average found in other studies with it varying from 0.0005–0.002 because of any condom use effect and other uncertainties. The transmission probability for the asymptomatic period for women to men was set to be 2–5 times less than this and was set to be 1–3 times larger for symptomatic recurrences and 1–5 times larger for primary infection. However, both the cofactors for the symptomatic recurrences and primary infection were also weighted due to the fact that asymptomatic shedding only occurs for about 4–15% of the asymptomatic period [16, 18, 38, 40] so use extra multiplicative cofactor of 6.7–25.

**HSV-2 cofactor per sex act for increasing HIV infectivity**

Using the observed relationship between plasma viral load (PVL) and HIV incidence reported by Quinn et al. [41], recently published trials looking at the effect of Acyclovir and Valacyclovir on HIV PVL [42–48] suggest that HSV-2 may increase HIV transmission by 27–44%. Other shedding studies suggest that HSV-2 may increase HIV transmission by up to 157% [24,49–53]. However, the newly completed ‘partners in prevention’ HSV-2 suppressive treatment trial suggests HSV-2 may have less effect on HIV transmission (press release at aidsmap: http://www.aidsmap.com/en/news/DD6C1B64–07DA-45C8-8B97-0B2230CFF4D.asp accessed 19th June 2009). HSV-2 ulcers may also have an increased HIV transmission cofactor but only up to about twice that of asymptomatic shedding [53–55].

A cofactor of 1.0–2.57 was assumed for asymptomatic shedding. However, this was scaled down because asymptomatic HSV-2 shedding only occurs for about 4–15% of the asymptomatic period amongst HIV negatives [16,18,38,40], but then it was scaled up because asymptomatic shedding occurs 2–3 times more often amongst HIV-infecteds [24,49–53]. During symptomatic recurrences and primary infection the cofactor was assumed to be 1–2 times the asymptomatic shedding cofactor of 1.0–2.57.

**HSV-2 cofactor per sex act for increasing HIV susceptibility**

If HSV-2 infected but without GUD then Corey et al. found that the risk of HIV transmission is 4.75 times higher than if not HSV-2 infected and without GUD, whereas if they are HSV-2 infected with GUD then the risk is 7.75 times higher [56]. Also Williams et al. [57] showed that individuals with primary HSV-2 have 2.46 (1.5–4.0) times the risk of acquiring HIV compared to people with prevalent HSV-2, and Freeman [58] showed that prevalent HSV-2 infection increases the chance of HIV acquisition by 2.7–3.1 times compared to people without HSV-2. However, new trials looking at the effect of HSV-2 suppressive treatment on HIV acquisition have shown no effect [45, 59] and so maybe HSV-2 does not increase the chance of HIV acquisition.

The cofactor for HIV acquisition for primary HSV-2 infection and symptomatic recurrences was assumed to be 1.5–4 times the cofactor for the asymptomatic period. The cofactor for the asymptomatic period was assumed to be 1–4.75 to include the Corey finding and the recent trial results.

**HIV cofactor per sex act for increasing HSV-2 infectivity**

Studies have found that there are about 2–3.0 times more asymptomatic HSV-2 shedding episodes if an individual is HIV positive [24,49–53], and the viral load is possibly higher by 0.5–0.7 log_{10} copies/ml [50,52].

For the asymptomatic/latent period, HIV infection was assumed to increase HSV-2 infectivity by 2–4 times to take into account the increase in asymptomatic shedding periods and the possible increase in HSV-2 viral load. For the primary infection period and during symptomatic recurrences, the possible increased viral load was assumed to increase HSV-2 infectivity by 1–2.5 times.

**The model fitting algorithm**

A two stage fitting algorithm was used to obtain multiple model fits to available HIV, syphilis, HSV-2 and Ng/Ct prevalence data from the round 1 FSW IBBA surveys for Belgaum (October 2005) and Mysore (August 2004) and HIV prevalence data from the round 1 client IBBA surveys (October 2007 for Belgaum and December 2006 and April 2009 for Mysore). The model was not fit to any other rounds of the FSW IBBA surveys (July 2008 for Belgaum and December 2006 and April 2009 for Mysore), which were used to validate the model fits. The model was not fit to general population HIV/HSV-2 prevalence data from the GPS (2007 for Belgaum and 2006 for Mysore) or ANC surveys - this was used in the model analysis.

In the first stage of the fitting algorithm, 100 parameter sets were randomly sampled from the non-setting specific syphilis and Ng/Ct parameter uncertainty ranges (Ng/Ct and syphilis transmission probabilities and duration of primary and secondary syphilis without treat), and for each of these, 1,000 FSW/client sexual behaviour and
setting specific syphilis and Ng/Ct parameter sets were sampled. Every combined parameter set (100,000 for each setting) was used to run to equilibrium the Ng/Ct and syphilis components of the model for FSWs/clients with no condom use, and then to the time of the round 1 IBBA FSW survey while condom use increased as described in table 2. Any parameter set that fit the 95% confidence intervals (CI) of the round 1 FSW syphilis and Ng/Ct prevalence was kept as a 'stage 1 model fit' for that setting.

For each 'stage 1 model fit' for Belgaum and Mysore, 200 HIV/HSV-2 biological parameter sets were sampled ([parameters in supplementary Table 1). For each parameter combination, the full FSW/client component of the model was run, firstly until all STIs reached equilibrium without HIV transmission and then until 2009 with HIV seeded in 1987 and condom use increasing as in table 1. Any model runs that fit the 95% CI of the round 1 HSV-2 and HIV prevalence were kept as a 'stage 2 model fit'.

Lastly, only those model fits with non-setting specific HIV/STI parameters that produced model fits in both setting were accepted as 'full model fits' and used in the model analysis. These model fits were validated against HIV prevalence data from the round 2/3 FSW IBBA and STI prevalence data from the round 1 client IBBA from both settings.

Supplementary Figure 1: Comparison of the model projected Ng/Ct, syphilis and HSV-2 prevalence (median is middle line, 25%/75% percentiles are limits of boxes and 2.5%/97.5% percentiles are whiskers) with data estimates (with 95% confidence bounds) from the round 1 FSW and client IBBA surveys. Model was fit to FSW data but not client data.

Comparison of the prior and posterior parameter distributions

Because many model parameter sets were rejected in the model fitting process it is likely that the posterior distributions (i.e. the parameter values used in the full model fits) for many of the model parameters will differ from their prior distribution (i.e. the parameter range used in the model fitting process). In summary, among the Mysore and Belgaum model fits most model parameters had similar ranges (posterior ranges) to the original uncertainty range assigned to the parameter (prior range), including the increase in condom use over recent years (supplementary figure 3). However, notable exceptions that had a posterior range < 80% the size of the prior range are shown in supplementary figure 2, and included (posterior ranges shown in brackets): HIV transmission probabilities, which had reduced upper bounds (male to female 0.00063–0.00098, female to male 0.00016–0.00102); primary (0.029–0.175) and recurrent (0.021–0.109) phase HSV-2 transmission probabilities which had reduced lower/upper bounds; asymptomatic phase HSV-2 transmission probability (0.0010–0.0020) which was skewed towards its upper bound; cofactor increase in HIV infectivity when an individual is asymptomatically shedding HSV-2, which was skewed to its lower bound (1.0–1.3); and lastly the duration of the HIV asymptomatic period, which had reduced lower/upper bounds (58–77 months).
**Supplementary Figure 3**: Condom use in last sex act in model fits for Belgaum and Mysore (median, 2.5%, 25%, 75% and 97.5% percentiles of model projections) compared with the percentage of FSWs using condoms always from the round 2 FSW IBBA condom reconstruction (with 95% confidence bounds)

3a. Belgaum

3b. Mysore

**Parameter correlations in the full model fits**

Many of the model parameters were correlated across the different full model fits. The parameters that had correlation coefficients above 0.4 and had visible correlations are shown in figure 4, with all correlations being easily understandable. For example, if the duration of Ng/Ct infection is shorter then the Ng/Ct transmission probability has to be higher so that the Ng/Ct prevalence amongst sex workers at the time of the round 1 IBBA is within the 95% confidence intervals. Also, if the duration of the symptomatic high viraemia phase in longer then the HIV transmission probability has to be lower so that the sex worker HIV prevalence fits the round 1 IBBA data. Lastly, if the rate of symptomatic
recurrences is higher than the HSV-2 transmission probability during the latent/asymptomatic phase does not have to be as high to attain the sex worker HSV-2 prevalence in round 1 IBBA.

**Supplementary Figure 4:** Scatter plots of the correlated model parameters

a. Correlation between the duration of Ng/Ct in sex workers and the transmission probability for Ng/Ct per sex act

![scatter plot 1](image1)

b. Correlation between the duration of the symptomatic high viraemia phase and the HIV transmission probability per sex act for females to males

![scatter plot 2](image2)
c. Correlation between the rate of symptomatic HSV-2 recurrences and the HSV-2 transmission probability in the latent/asymptomatic shedding period

Supplementary Figure 5: A comparison of the model projections (median is middle line, 25%/75% percentiles are limits of boxes and 2.5%/97.5% percentiles are whiskers) with data estimates (with 95% confidence bounds) for the general population HIV or HSV-2 prevalence.

a. HIV projections for Mysore
b. HIV projections for Belgaum

![Diagram of HIV prevalence for Belgaum](image)

- Data
- Model with main/casual bridging infections
- Model with main/casual bridging infections and low risk infections

Belgaum female HIV prevalence & Belgaum male HIV prevalence

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c. HSV-2 projections for Mysore

![Diagram of HSV-2 prevalence for Mysore](image)

- Data
- Model with main/casual bridging infections
- Model with main/casual bridging infections and low risk infections

Mysore female HSV2 prevalence & Mysore male HSV2 prevalence
d. HSV-2 projections for Belgaum

**Supplementary Figure 6**: Correlation between client population size and the model projected overall HIV prevalence in Belgaum and Mysore.

a. Mysore.
Supplementary Figure 7: Proportion of yearly incident HSV-2 infections in males and females that result from different types of sexual partnership in Mysore and Belgaum (defined as attributable fraction in figure). Projections show median with 2.5% and 97.5% percentiles. Low-risk females are assumed to have the same sexual activity as reported by men in the GPS.

7a. Mysore incident infections in men
7b. Mysore incident infections in females

Supplementary figure 8: Relative reduction in overall HIV incidence over 5 years due to different interventions that achieve a 20% reduction in HIV transmission risk in different partnership types.
a. Mysore

References


b. Belgaum


