Supplementary material

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, $j = 1$, 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 (h), those who have progressed into the low-viraemia phase

(y) and those with symptomatic high viraemia (z). 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 (Λ_r) 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 (π_{sex}). When a susceptible becomes infected with HIV they are initially highly infectious (for an average period $1/\nu$). They then enter a long period of low infectivity (average duration $1/\Omega$) before entering the symptomatic high infectivity phase (for an average period $1/\Psi$). In 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 Ψ_r.

Female sex workers continue sex work for a period (average duration $1/\eta_{rj}$, 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 $1/\eta_{rj}$, 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 η_{rj} 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 depending 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:

$$\frac{dx_{rji}}{dt} = n_{rji}\Lambda_r - x_{rji}\left(\pi_{sex} + \psi_r + \eta_{rj}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}x_{rui}\sum\limits_{\forall w}n_{rjw} - x_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dh_{rji}}{dt} = x_{rji}\pi_{sex} - h_{rji}\left(\psi_r + \nu + \eta_{rj}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}h_{rui}\sum\limits_{\forall w}n_{rjw} - h_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dy_{rji}}{dt} = \nu h_{rji} - y_{rji}\left(\psi_r + \Omega + \eta_{rj}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}y_{rui}\sum\limits_{\forall w}n_{rjw} - y_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dz_{rji}}{dt} = \Omega y_{rji} - z_{rji}\left(\psi_r + \Psi + \eta_{rj}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}z_{rui}\sum\limits_{\forall w}n_{rjw} - z_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

Equation 1

where δ_{jp} equals one if $j = p$ and zero otherwise. The probability that a susceptible becomes HIV infected per unit time from unprotected sex (π_{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 $d0_{rj}$, $d1_{rj}$ and $d2_{rj}$ denote the total number of main, casual and commercial sexual partners that an individual in sub-group $[r,j,i]$ has per unit time, then mathematically, the probability that a susceptible becomes HIV infected from their sexual partnerships (π_{sex}) per unit time is given by:

$$\pi_{sex} = 1 - \prod_{\forall pk}(1 - \varphi0_{rjipk})^{d0_{rji}\rho0_{rjipk}}(1 - \varphi1_{rjipk})^{d1_{rji}\rho1_{rjipk}}(1 - \varphi2_{rjipk})^{d2_{rji}\rho2_{rjipk}}$$

Equation 2

where the function $\varphi0_{rjipk}$ $\varphi1_{rjipk}$ and $\varphi2_{rjipk}$ are the probabilities that a susceptible in sub-group $[r,j,i]$ will become HIV infected per unit time from a main, casual or commercial sexual partnership with an individual in sub-group $[r',p,k]$, and $\rho0_{rjipk}$, $\rho1_{rjipk}$ and $\rho2_{rjipk}$ are the probabilities that individuals within sub-group $[r,j,i]$ form main, casual or commercial sexual partnerships with individuals from $[r',p,k]$, with different levels of sexual activity (j and p) and HSV-2 status (i and k).

Two components make up the mixing function $\rho0_{rjipk}$. Firstly, an individual has a probability '$\mathcal{E}$' 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 $\mathcal{E}$ 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 $\rho0_{rjipk}$, has the following form:

$$\rho0_{rjipk} = (1 - \varepsilon)\frac{d0_{r'p}n_{r'pk}}{\sum\limits_{\forall p,k} d0_{r'p}n_{r'pk}} + \varepsilon\delta_{jp}\frac{d0_{r'p}n_{r'pk}}{\sum\limits_{\forall k} d0_{r'p}n_{r'pk}},$$

Equation 3

The form and derivation of the $\rho0_{rjipk}$ function is a development of the formulation by Garnett and Anderson [46]. The product $d0_{rj}\rho0_{rjipk}$ then gives the total number of main sexual partnerships an individual from sub-group $[r,j,i]$ forms with those from sub-group $[r',p,k]$. The functions $\rho1_{rjipk}$ and $\rho2_{rjipk}$ and calculated similarly except mixing is assumed to be random (proportional to the number of casual or commercial partnerships provided by that group) and $\rho1_{rjipk} > 0$ only when $j > 1$ (only individuals in classes $j = 2,3$ and 4 have casual partnerships) and $\rho2_{rjipk} > 0$ only when $j > 2$ (only individuals in classes $j = 3$ and 4 have commercial partnerships).

The parameter $\varphi0_{rjipk}$ 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 $D0_{rjipk}$). 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_j 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; β_r is the probability of HIV transmission per sex act from sex r' to sex r; α_s is the extent to which STI co-infection of either partner increases the probability of HIV transmission, and α_{hi1} and α_{hi2} are the extent to which the initial and symptomatic high viraemia phases increase the probability of HIV transmission, then $D0_{rjipk}$ can be written:

$$D0_{rjipk} = 1 - \left[\begin{array}{l}\left(1 - \frac{y^s_{r'pk}}{n_{r'pk}}\right)\left(1 - \frac{y^s_{rji}}{n_{rji}}\right)\frac{[\Gamma h_{r'pk} + \Phi y_{r'pk} + \Theta z_{r'pk}]}{y_{r'pk} + h_{r'pk} + z_{r'pk}}\\ + \left[1 - \left(1 - \frac{y^s_{r'pk}}{n_{r'pk}}\right)\left(1 - \frac{y^s_{rji}}{n_{rji}}\right)\right]\frac{[Hh_{r'pk} + Ey_{r'pk} + \Omega z_{r'pk}]}{y_{r'pk} + h_{r'pk} + z_{r'pk}}\end{array}\right]$$

Equation 4

where y^s denotes the number infected with an STI and

$$\Phi = [^1 \quad E = [^1$$
$$\Gamma = [^1 \quad H = [^1$$
$$\Theta = [^1 \quad \Omega = [^1$$

Equation 5

Here the variables Φ, E, Γ, Θ, Ω and H denote the probabilities that a susceptible person, who is having sex with an HIV infected person, does not become HIV infected per unit time in the following different situations; neither partner has a particular STI and the HIV infected partner is not in the initial high viraemia phase (Φ); at least one partner has an STI and the HIV infected partner is not in the initial high viraemia phase (E); neither partner has an STI but the HIV infected partner is in the initial high viraemia phase (Γ); neither partner has an STI but the HIV infected partner is in the symptomatic high viraemia phase (Θ); at least one partner has an STI, and the HIV infected partner is in the symptomatic high viraemia phase (Ω); at least one partner has an STI, and the HIV infected partner is in the initial high viraemia phase (H). Eqs. (4) and 5 are extended to include the possibilities of each partner having a curable STI or syphilis or HSV-2, but are not shown here for simplicity. The overall cofactor for when two STIs are present or when in a high viraemia phase of HIV is additive.

The corresponding probabilities $\varphi1_{rjipk}$ and $\varphi2_{rjipk}$ (probabilities that a susceptible will become HIV infected per unit time from their casual or commercial partnerships), and $D1_{rjipk}$ and $D2_{rjipk}$ (probabilities that a susceptible will become HIV infected per unit time

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 infection stage, then they become susceptible, whereas they become temporarily immune[2–4] if they are treated during latent infection.

For the bacterial STI an SIS model structure was adopted, whereas for syphilis there are four classes: susceptible, primary and secondary infected, latent infected and resistant. Both HIV susceptible and HIV infected individuals can acquire an STI. The per capita probability of STI transmission per unit time (π_s) is analogous to the per capita probability of HIV infection per unit time (π_{sex}) (*equation 2*) but only primary and secondary syphilis cases are assumed to be infectious. If the probability of STI transmission per sex act is β_{std}, and y^s is the number infected with an STI (only those in the primary or

secondary stages for syphilis), then for each partnership the probability that a susceptible is infected with a STI per unit time (defined as φ^s_{rjipk}) is:

$$\varphi^s_{rjipk} = \frac{y^s_{r'pk}}{n_{r'pk}}(1 - [1 - \beta_{std}(1 - fe)]^{m_j})$$

Equation 6

If we let x^s denote the number susceptible to an STI, and y^s the number of infecteds, then the transmission dynamics of the SIS STI can be described using the following set of deterministic differential equations:

$$\frac{dx^{rji}_s}{dt} = n_{rji}\Lambda_r - x^{rji}_s\left(\pi_s + \psi_r + \eta_{rj} + \frac{\Psi z_{rji}}{n_{rji}}\right) + \mu_r y^{rji}_s + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}x^s_{rui}\sum\limits_{\forall w}n_{rjw} - x^{rji}_s\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dy^{rji}_s}{dt} = x^{rji}_s\pi_s - y^{rji}_s\left(\mu_r + \psi_r + \frac{\Psi z_{rji}}{n_{rji}}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}y^s_{rui}\sum\limits_{\forall w}n_{rjw} - y^{rji}_s\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

Equation 7

For this we assume that individuals remain infected for a fixed period of time ($1/\mu_r$), and then become susceptible to the STI once more, and the parameter Ψ is the rate at which susceptibles and infecteds leave due to HIV morbidity (acquiring AIDS) because a proportion $\frac{z_{rji}}{n_{rji}}$ of the individuals in sub-group [r,j,i,] will be in the symptomtic 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^{tp}), latent (l^{tp}) and resistant or immune (r^{tp}) and individuals susceptible to syphilis are denoted by x^{tp}.

For syphilis, if individuals are treated when in the primary or secondary stage (at a rate ω_{rj}) then they become susceptible again, whereas if they are treated in the latent stage (at a rate σ_{rj}) then they are assumed to become resistant to infection for a certain duration ($1/\upsilon$). 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:

$$\frac{dx^{tp}_{rji}}{dt} = n_{rji}\Lambda_r - x^{tp}_{rji}\left(\pi_s + \psi_r + \eta_{rj} + \frac{\Psi z_{rji}}{n_{rji}}\right) + \omega_{rj}y^{tp}_{rji} + \upsilon r^{tp}_{rji} + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}x^{tp}_{rui}\sum\limits_{\forall w}n_{rjw} - x^{tp}_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dy^{tp}_{rji}}{dt} = x^{tp}_{rji}\pi_s - y^{tp}_{rji}\left(\theta + \omega_{rj} + \psi_r + \frac{\Psi z_{rji}}{n_{rji}}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}y^{tp}_{rui}\sum\limits_{\forall w}n_{rjw} - y^{tp}_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dl^{tp}_{rji}}{dt} = y^{tp}_{rji}\theta - l^{tp}_{rji}\left(\sigma_{rj} + \psi_r + \frac{\Psi z_{rji}}{n_{rji}}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}l^{tp}_{rui}\sum\limits_{\forall w}n_{rjw} - l^{tp}_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dr^{tp}_{rji}}{dt} = l^{tp}_{rji}\sigma_{rj} - r^{tp}_{rji}\left(\upsilon + \psi_r + \frac{\Psi z_{rji}}{n_{rji}}\right) + \frac{\delta_{j1} + \delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum\limits_{u=3,4}\eta_{ru}r^{tp}_{rui}\sum\limits_{\forall w}n_{rjw} - r^{tp}_{rji}\sum\limits_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

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 φ_{rjipk}^{h}) 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 π_h. 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 ς which differs for those who are HIV positive, before returning back to the asymptomatic phase at an average rate ϖ. 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 Ψ 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 portion of the incoming population are assumed to be HIV or HSV-2 infected.

$$\frac{dq_{rj0}}{dt} = n_{rj}\Lambda_r - q_{rj0}(\pi_h + \psi_r + \Psi) + \frac{\delta_{j1}+\delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum_{u=3,4}\eta_{ru}q_{ru0}\sum_{\forall w}n_{rjw} - q_{rj0}^{tp}\sum_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dq_{rj1}}{dt} = q_{rj0}\pi_s - q_{rj1}(\gamma + \psi_r + \Psi) + \frac{\delta_{j1}+\delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum_{u=3,4}\eta_{ru}q_{ru1}\sum_{\forall w}n_{rjw} - q_{rj1}^{tp}\sum_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dq_{rj2}}{dt} = q_{rj1}\gamma + q_{rj3}\varpi - q_{rj2}(\varsigma + \psi_r + \Psi) + \frac{\delta_{j1}+\delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum_{u=3,4}\eta_{ru}q_{ru2}\sum_{\forall w}n_{rjw} - q_{rj2}^{tp}\sum_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

$$\frac{dq_{rj3}}{dt} = q_{rj2}\varsigma - q_{rj3}(\varpi + \psi_r + \Psi) + \frac{\delta_{j1}+\delta_{j2}}{\sum\limits_{\forall w,v=1,2} n_{rvw}}\left[\sum_{u=3,4}\eta_{ru}q_{ru3}\sum_{\forall w}n_{rjw} - q_{rj3}^{tp}\sum_{\forall v,u=3,4}\eta_{ru}n_{ruv}\right]$$

Equation 9

Modified susceptibility / infectivity dependant on STI infection status

The model is structured so that the degree of infectivity of those infected and / or susceptibility to infection are modified according to the individual's infection status for other infections. Susceptibility to HIV infection and HIV infectivity are increased in those infected with syphilis (only primary and secondary syphilis), bacterial STI or HSV-2 (with different cofactors for each stage of HSV-2). There is also a different rate of symptomatic recurrence of 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

Foss AM, Vickerman PT, Chalabi Z, Mayaud P, Alary M, Watts C. Dynamic modelling of herpes simplex virus type 2 (HSV-2) transmission: issues in structural uncertainty. *Bulletin of Mathematical Biology* 2008 (in press).

Weinstein MC, Graham JD, Siegel JE, Fineberg HV. *Cost-effectiveness analysis of AIDS prevention programs: concepts, complications and illustrations.* Turner CF, Miller HG, Moses LE, editors. Confronting AIDS. Washington DC: National Academy Press; 1989. p. 471-499.

Williams JR, Foss AM, Vickerman P, Watts C, Ramesh BM, Reza-Paul S, Washington RG, Moses S, Blanchard J, Lowndes CM, Alary M, Boily M-C. What is the achievable effectiveness of the India AIDS initiative intervention among female sex workers under target coverage? Model projections from southern India. *Sex Transm Infect* 2006;82(5):372-80.

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

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

Types of model input	Definition of model input	Model inputs for: Male Female	Reference for model input value
Epidemiological	Average duration of Ng/Ct (months)s		
	Males	2–5	[5] but also depends on level of STI treatment.
	Females	2-12	
	Sex worker	0.5–3	
	Average duration of syphilis stages (months)		
	Primary and secondary stage (without treat)	4.5–6	Available data was reviewed by [3]
	Primary and secondary stage (with treat)	1–5	
	Latent phase (including treatment)	2-24	
	Immune/resistant phase	2-60	
	Duration in months of		
	Initial high viraemia phase	4–6†	[6,7]
	Symptomatic high viraemia phase	6–18†	
	HIV and symptomatic high viraemia	75–92†	[8,9]
	Average duration of HSV-2 stages (months)		
	Primary stage	0.36–0.66†	[10–16]
	Symptomatic recurrence	0.1–0.16†	[12,14,17–20]
	Rate of HSV-2 symptomatic recurrences (per month) while HIV negative	0.09–0.41†	[10,12,14,15,21–23]
	Rate of HSV-2 symptomatic recurrences (per month) when HIV positive	1.5–2×rate in HIVnegatives†	[24,25]
	Condom efficacy per sex act	80–95%†	[26,27]
	Relative condom efficacy for HSV-2 compared to HIV	50%-100%†	Little data, thought to be less efficacy than for HIV
Transmission probabilities	Probability of HIV transmission per sex act:		
	Male to female:	0.0008 (0.0006–0.0011) †	[28]
	Female to male:	0.0004 (0.0001–0.0014) †	
	Probability of STI transmission per sex act:		
	Ng/Ct	0.05–0.2	[29–33]
	Syphilis (male to female):	0.1–0.3	[3]
	Ratio for female to male syphilis transmission	0.33–1.0	
	Probability of HSV-2 transmission per sex act for males to females:		Supplementary material
	HSV-2 Primary stage	0.003–0.25†	Supplementary material
	HSV-2 latent/asymptomatic shedding stage	0.0005–0.002 †	Supplementary material
	HSV-2 symptomatic recurrence stage	0.003–0.15†	Supplementary material
	Factor difference for female to male HSV-2 transmission probability compared to male to female transmission probability	0.2–0.33 †	Supplementary material
Cofactors for increasing HIV transmission	Average Ng/Ct cofactor per sex act	1.2–2.5†	[34]
	Average syphilis cofactor per sex act	2.1–3.3†	
	Average HSV-2 cofactor per sex act for increasing HIV infectivity -		Supplementary material
	Primary phase	1–5†	Supplementary material
	Asymptomatic/latent phase	1–1.7†	Supplementary material
	Symptomatic recurrence phase	1–5†	Supplementary material
	Average HSV-2 cofactor per sex act for increasing HIV susceptibility –		
	Primary phase	1.5–19†	Supplementary material
	Asymptomatic/latent phase	1–4.75†	Supplementary material
	Symptomatic recurrence phase	1.5–19†	Supplementary material
	Sexual transmission multiplicative co-factor during:		
	Initial HIV high viraemia phase	9.2 (4.5–18.8) †	[28]
	Symptomatic high viraemia phase	7.3 (4.5–11.9) †	
Cofactors for increasing HSV-2 transmission	HIV cofactor per sex act for increasing HSV-2 susceptibility	1†	Little data – assume no effect
	HIV cofactor per sex act for increasing HSV-2 infectivity:		
	Primary phase	1–2.5†	Supplementary material
	Asymptomatic/latent phase	2–4†	Supplementary material
	Symptomatic recurrence phase	Same as primary†	

† signifies a parameter that is varied in the HIV and HSV-2 biological parameter sets in the second stage of the model fitting.

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

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-45C8-8B97-0B22230CFF4D.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 October 2008 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.

a. Mysore
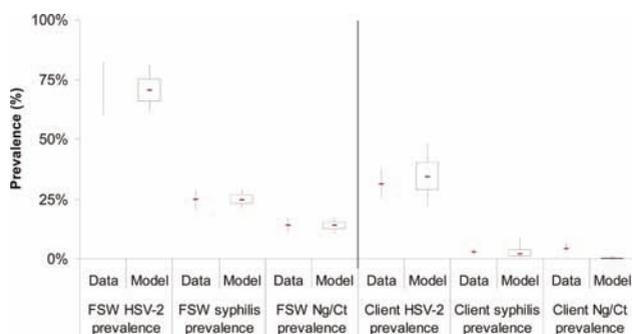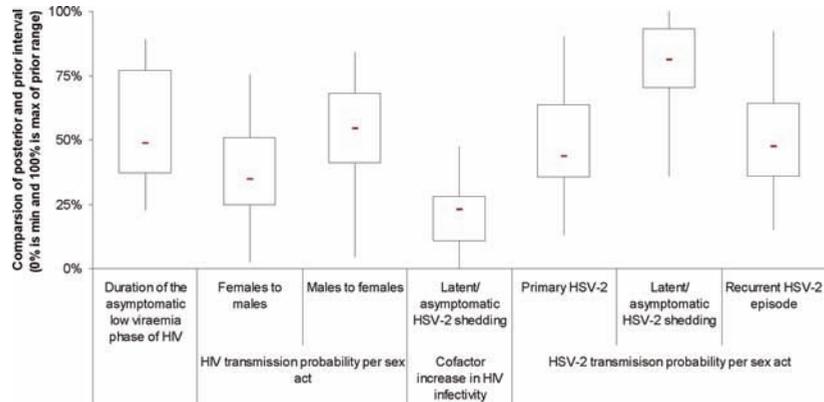

b. Belgaum
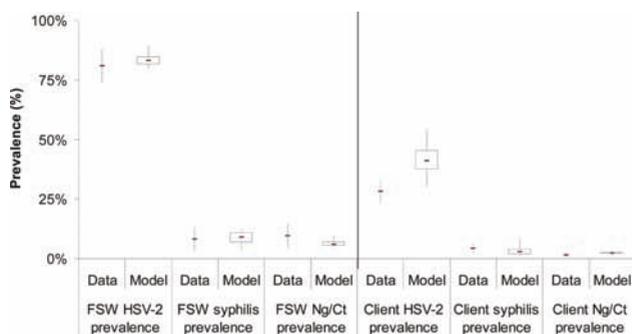
### Comparison of the prior and posterior parameter distributions

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 2: Comparison of posterior distributions of the model parameters (median is middle line, 25%/75% percentiles are limits of boxes and 0%/100% percentiles are whiskers) whose posterior parameter range was less than 80% that of the prior parameter range.
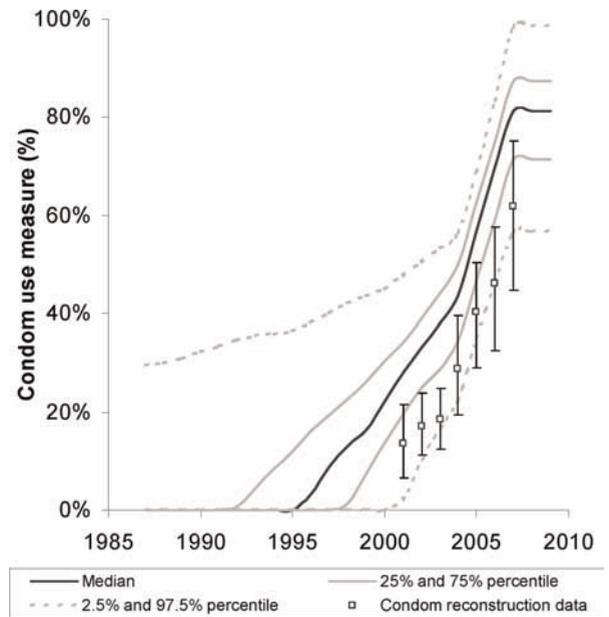

Supplementary Figure 3: Condom use in last sex act in model fits for Belgaum and Mysore (median, 2.5%, 25%, 75% and 97.5% percentiles of model projections) compared with the percentage of FSWs using condoms always from the round 2 FSW IBBA condom reconstruction (with 95% confidence bounds)

3a. Belgaum
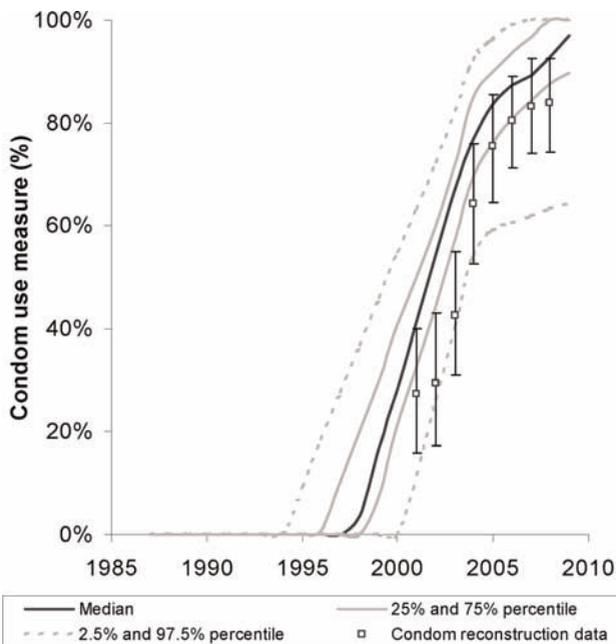
3b. Mysore

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
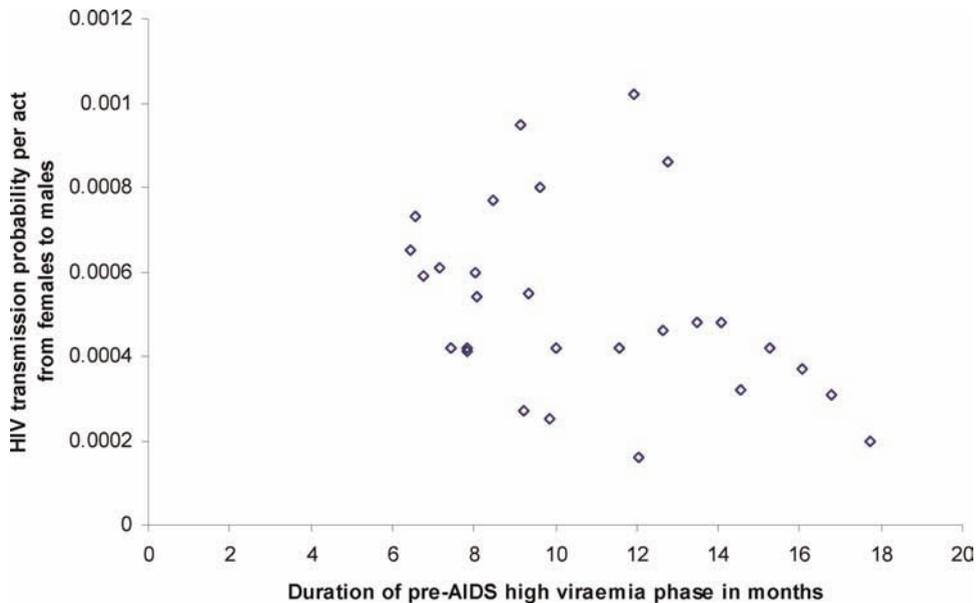
recurrences is higher then the HSV-2 transmission probability during the latent/asymptomatic phase does not have to be as high to attain the sex worker HSV-2 prevalence in round 1 IBBA.

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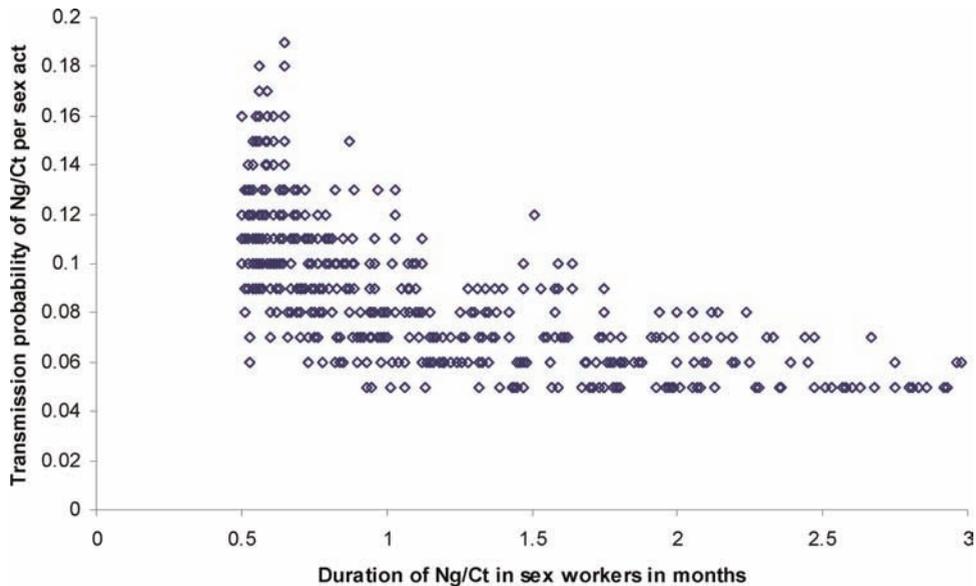
b. Correlation between the duration of the symptomatic high viraemia phase and the HIV transmission probability per sex act for females to males

c. Correlation between the rate of symptomatic HSV-2 recurrences and the HSV-2 transmission probability in the latent/asymptomatic shedding period
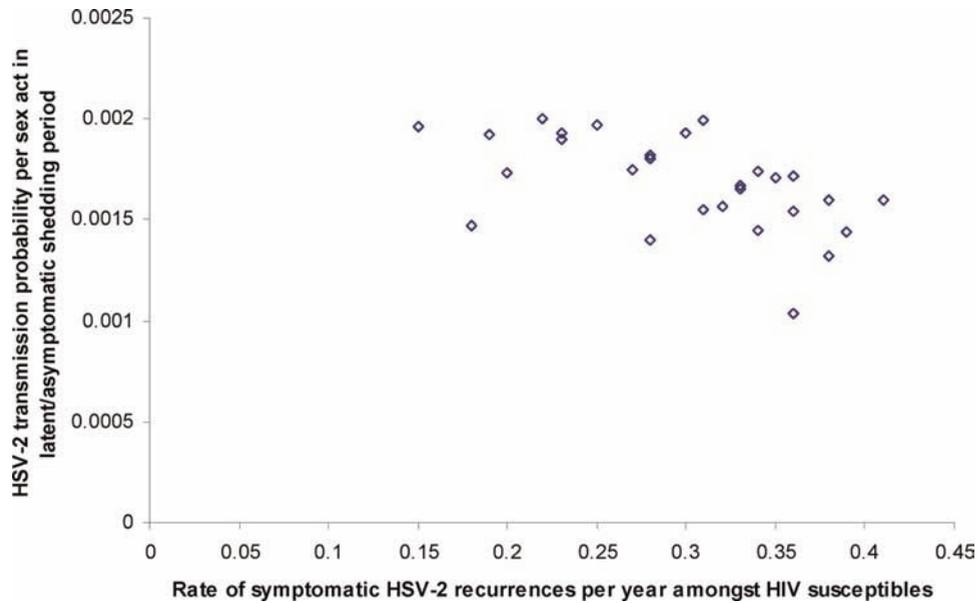

Supplementary Figure 5: A comparison of the model projections (median is middle line, 25%/75% percentiles are limits of boxes and 2.5%/97.5% percentiles are whiskers) with data estimates (with 95% confidence bounds) for the general population HIV or HSV-2 prevalence.
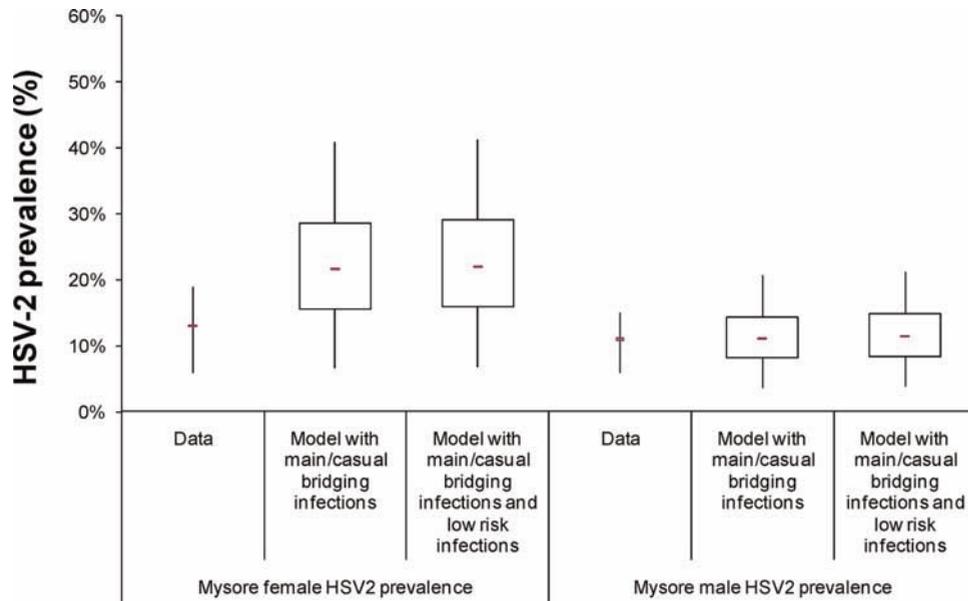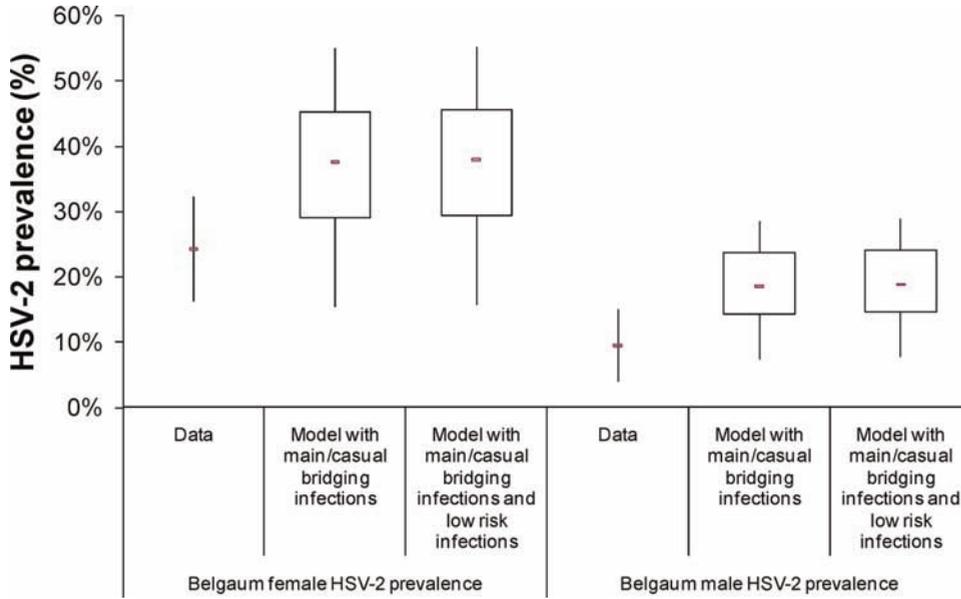
a. HIV projections for Mysore

b. HIV projections for Belgaum

Belgaum female HIV prevalence — Belgaum male HIV prevalence

c. HSV-2 projections for Mysore
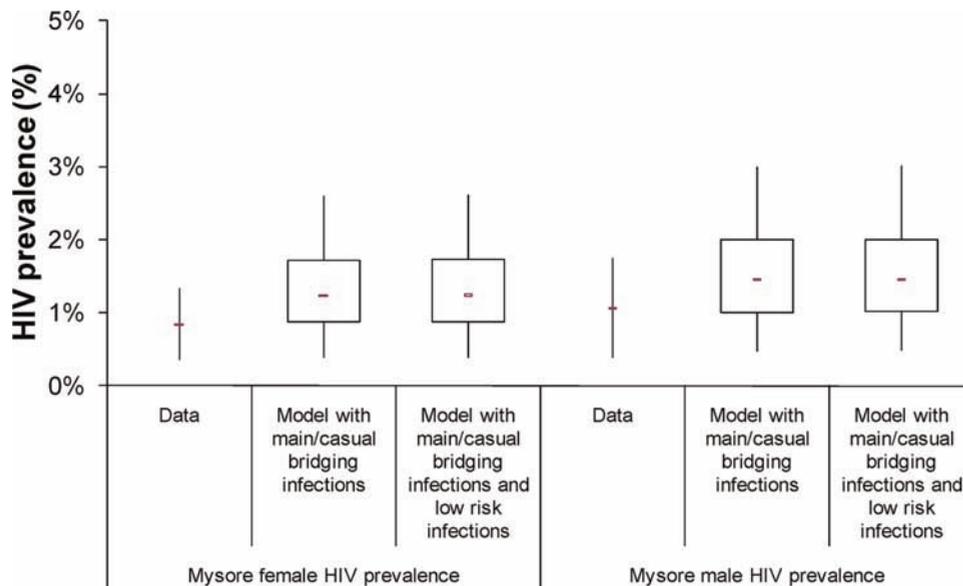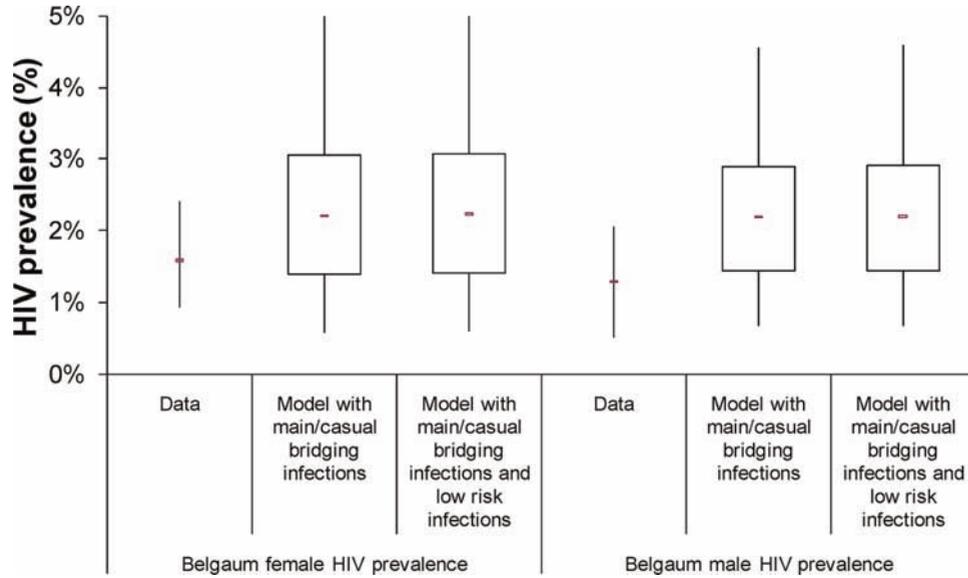
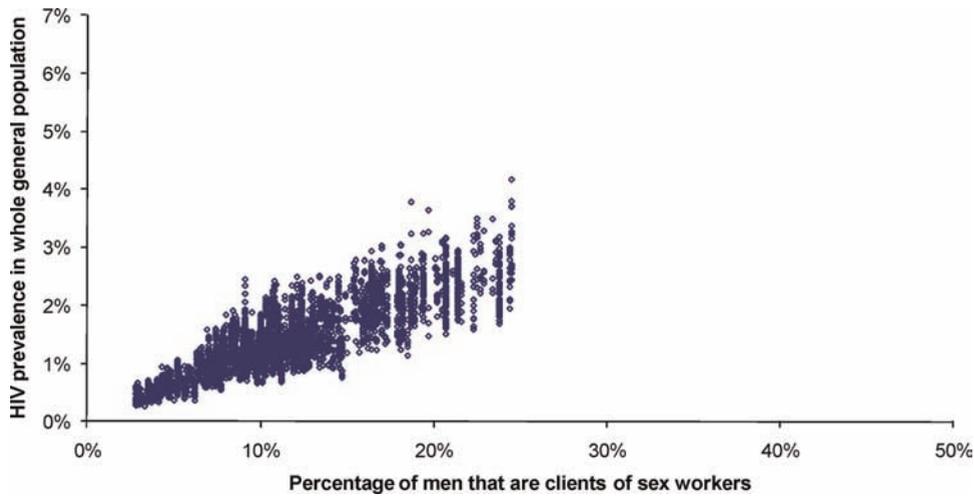Mysore female HSV2 prevalence — Mysore male HSV2 prevalence
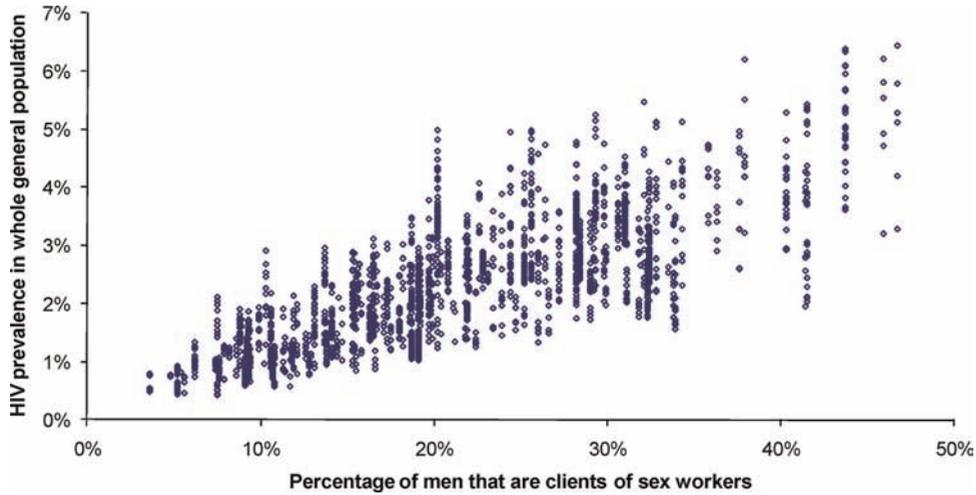
d. HSV–2 projections for Belgaum

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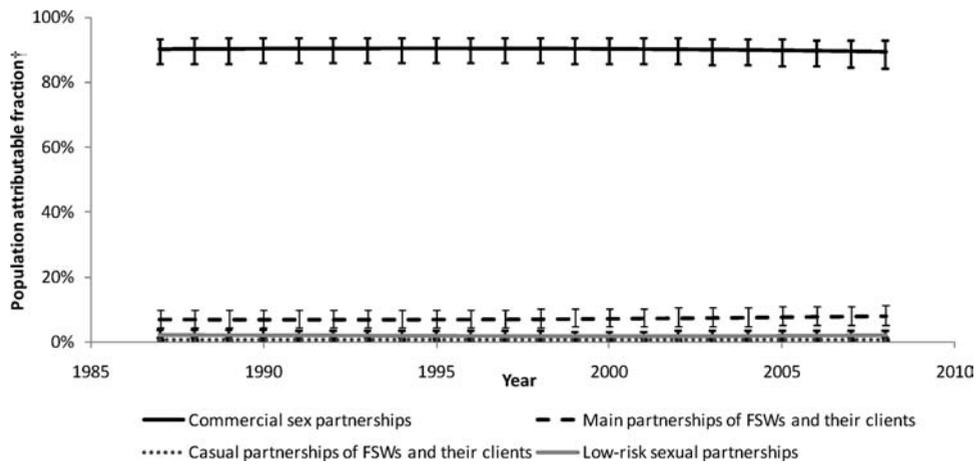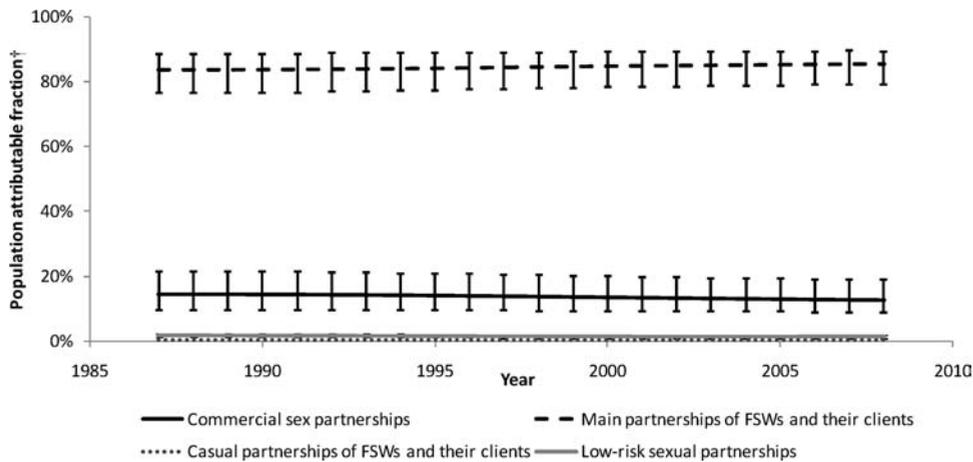
a. Mysore.

b. Belgaum

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 Begaum (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.
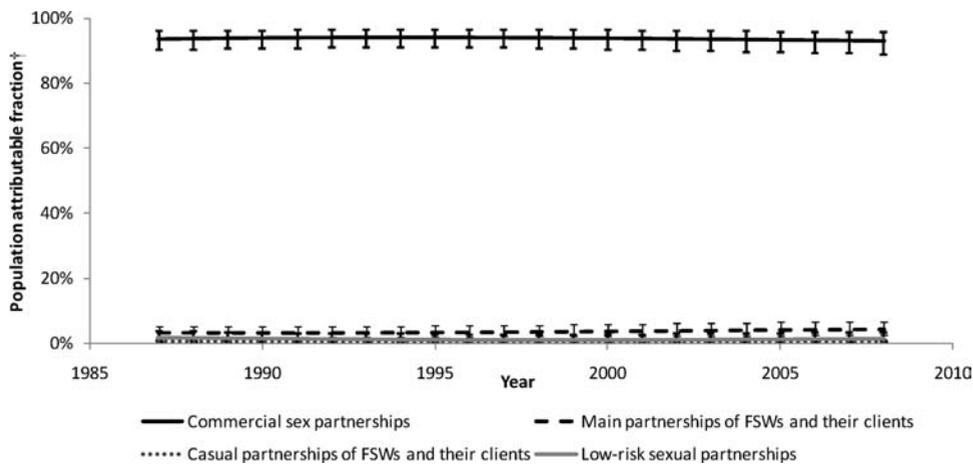
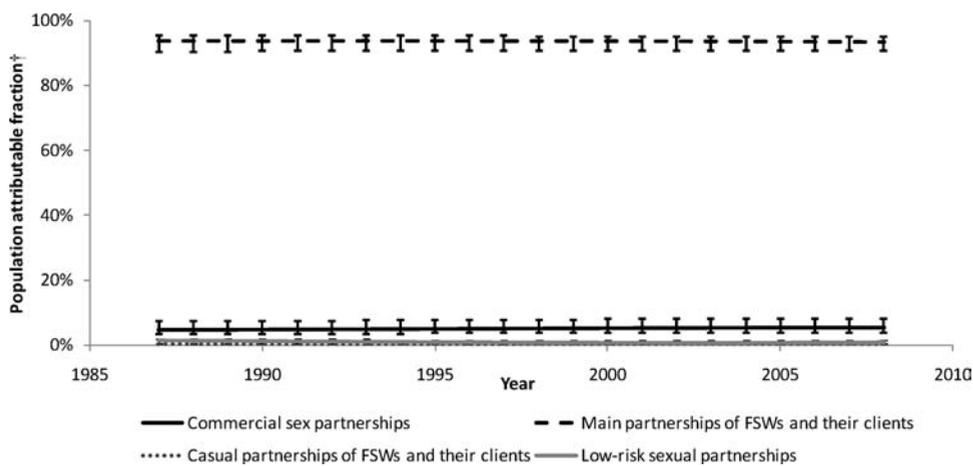7a. Mysore incident infections in men

7b. Mysore incident infections in females

Commercial sex partnerships — Main partnerships of FSWs and their clients
•••••• Casual partnerships of FSWs and their clients —— Low-risk sexual partnerships

7c. Belgaum incident infections in men

Commercial sex partnerships — Main partnerships of FSWs and their clients
•••••• Casual partnerships of FSWs and their clients —— Low-risk sexual partnerships

7d. Belgaum incident infections in females

Commercial sex partnerships — Main partnerships of FSWs and their clients
•••••• Casual partnerships of FSWs and their clients —— Low-risk sexual partnerships

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
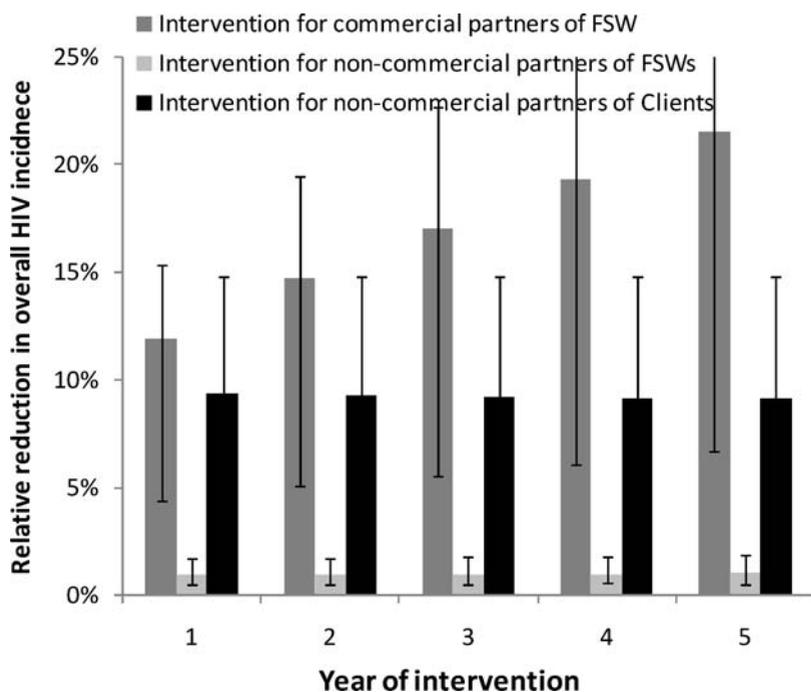
b. Belgaum
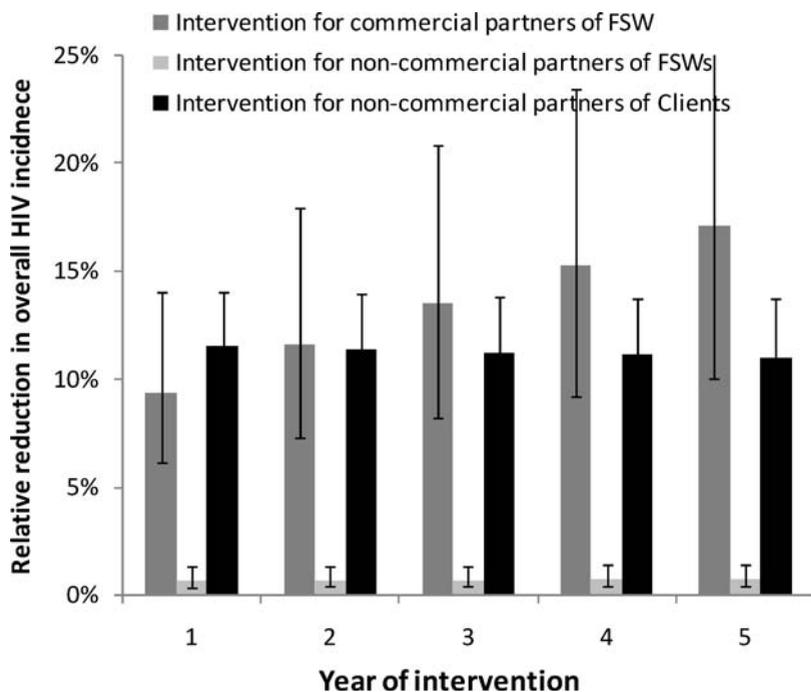
References

1. Foss A, Vickerman P, Chalabi Z, Mayaud P, Alary M, Watts C. Dynamic modelling of herpes simplex virus type-2 (HSV-2) transmission: issues in structural uncertainty. *Bulletin of Mathematical Biology* 2009, **71**:720-749.

2. Grassly NC, Fraser C, Garnett GP. Host immunity and synchronized epidemics of syphilis across the United States. *Nature* 2005, **433**:417-421.

3. Garnett GP, Aral SO, Hoyle DV, Cates W, Jr., Anderson RM. The natural history of syphilis. Implications for the transmission dynamics and control of infection. *Sex Transm Dis* 1997, **24**:185-200.

4. Pourbohloul B, Rekart ML, Brunham RC. Impact of mass treatment on syphilis transmission: a mathematical modeling approach. *Sex Transm Dis* 2003, **30**:297-305.

5. Korenromp EL, Sudaryo MK, de Vlas SJ, Gray RH, Sewankambo NK, Serwadda D, *et al.* What proportion of episodes of gonorrhoea and chlamydia becomes symptomatic? *Int J STD AIDS* 2002, **13**:91-101.

6. Boily MC, Baggaley RF, Wang L, Masse B, White R, Hayes R, *et al.* Heterosexual risk of HIV-1 infection per sexual act: a systematic review and meta-analysis of observational studies. *Lancet Infectious Diseases* 2009, **In press**.

7. Wawer MJ, Gray RH, Sewankambo NK, Serwadda D, Li X, Laeyendecker O, *et al.* Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005, **191**:1403-1409.

8. Grover G, Shivraj SO. Survival pattern of reported HIV infected individuals in the city of Delhi (India). *J Commun Dis* 2004, **36**:83-92.

9. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis* 2003, **36**:79-85.

10. Benedetti JK, Zeh J, Corey L. Clinical reactivation of genital herpes simplex virus infection decreases in frequency over time. *Ann Intern Med* 1999, **131**:14-20.

11. Cheong WK, Thirumoorthy T, Doraisingham S, Ling AE. Clinical and laboratory study of first episode genital herpes in Singapore. *International Journal of STD & AIDS* 1990, **1**:195-198.

12. Corey L, Adams HG, Brown ZA, Holmes KK. Genital herpes simplex virus infections: clinical manifestations, course, and complications. *Ann Intern Med* 1983, **98**:958-972.

13. Corey L, Fife KH, Benedetti JK, Winter CA, Fahnlander A, Connor JD, *et al.* Intravenous acyclovir for the treatment of primary genital herpes. *Ann Intern Med* 1983, **98**:914-921.

14. Corey L, Wald A. Chapter 21: Genital herpes. In: *Sexually Transmitted Diseases.* Holmes KK, Mardh P, Sparling PF, *et al.* (Holmes KK, Mardh P, Sparling PF, *et al.*s). Third ed. USA: McGraw-Hill; 1999: 285-312.

15. Diamond C, Selke S, Ashley R, Benedetti J, Corey L. Clinical course of patients with serologic evidence of recurrent genital herpes presenting with signs and symptoms of first episode disease. *Sex Transm Dis* 1999, **26**:221-225.

16. Koelle DM, Benedetti J, Langenberg A, Corey L. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* 1992, **116**:433-437.

17. Guinan ME, MacCalman J, Kern ER, Overall JC, Jr., Spruance SL. The course of untreated recurrent genital herpes simplex infection in 27 women. *N Engl J Med* 1981, **304**:759-763.

18. Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. Frequent genital herpes simplex virus 2 shedding in immunocompetent women. Effect of acyclovir treatment. *J Clin Invest* 1997, **99**:1092-1097.

19. Wald A, Zeh J, Selke S, Warren T, Ashley R, Corey L. Genital shedding of herpes simplex virus among men. *J Infect Dis* 2002, **186 Suppl 1**:S34-39.

20. Wald A, Zeh J, Selke S, Warren T, Ryncarz AJ, Ashley R, *et al.* Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* 2000, **342**:844-850.

21. Benedetti J, Corey L, Ashley R. Recurrence rates in genital herpes after symptomatic first-episode infection. *Ann Intern Med* 1994, **121**:847-854.

22. Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. Recurrences after oral and genital herpes simplex virus infection. Influence of site of infection and viral type. *N Engl J Med* 1987, **316**:1444-1449.

23. Kim HN, Wald A, Harris J, Almekinder J, Heitman C, Corey L. Does frequency of genital herpes recurrences predict risk of transmission? Further analysis of the valacyclovir transmission study. *Sex Transm Dis* 2008, **35**:124-128.

24. Schacker T, Zeh J, Hu HL, Hill E, Corey L. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* 1998, **178**:1616-1622.

25. Conant MA, Schacker TW, Murphy RL, Gold J, Crutchfield LT, Crooks RJ. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS* 2002, **13**:12-21.

26. Pinkerton SD, Abramson PR. Effectiveness of condoms in preventing HIV transmission. *Social Science and Medicine* 1997, **44**:1303-1312.

27. Pinkerton SD, Abramson PR, Turk ME. Updated estimates of condom effectiveness. *J Assoc Nurses AIDS Care* 1998, **9**:88-89.

28. Boily MC, Baggaley RF, Wang L, Masse B, White R, Hayes R, et al. Heterosexual risk of HIV-1 infection per sexual act: a systematic review and meta-analysis of observational studies. *Lancet Infectious Diseases* 2009, **9**:118-129.

29. Holmes KK, Johnson DW, Trostle HJ. An estimate of the risk of men acquiring gonorrhea by sexual contact with infected females. *Am J Epidemiol* 1970, **91**:170-174.

30. Lycke E, Lowhagen GB, Hallhagen G, Johannisson G, Ramstedt K. The risk of transmission of genital Chlamydia trachomatis infection is less than that of genital Neisseria gonorrhoeae infection. *Sex Transm Dis* 1980, **7**:6-10.

31. Hooper RR, Reynolds GH, Jones OG, Zaidi AA, Wiesner PJ, Latimer KP. Cohort study of venereal disease. 1: The risk of gonorrhoea transmission from infected women to men. *American journal of Epidemiology* 1978, **108**:136-144.

32. Ruijs GJ, Schut IK, Schirm J, Schroder FP. Prevalence, incidence, and risk of acquiring urogenital gonococcal or chlamydial infection in prostitutes working in brothels. *Genitourinary Medicine* 1988, **64**:49-51.

33. Quinn SC, Gaydos C, Shepherd ME, Bobo L, Hook EW, 3rd, Viscidi R, et al. Epidemiologic and micro-biologic correlates of Chlamydia trachomatis infection in sexual partnerships. *JAMA* 1996, **276**:1737-1742.

34. Rottingen J, Cameron DW, Garnett GP. A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV. *Sexually Transmitted Diseases* 2001, **28**:579-595.

35. Lowndes C, Alary M, Verma S, Demers E, Bradley JE, Jayachandran AA, et al. Assessment of intervention impact in the absence of baseline data: 'reconstruction' of condom use time trends using retrospective analysis of survey data. *STI* 2010, **86**:i49-i55.

36. Wald A, Langenberg AG, Link K, Izu AE, Ashley R, Warren T, et al. Effect of condoms on reducing the transmission of herpes simplex virus type 2 from men to women. *JAMA* 2001, **285**:3100-3106.

37. Corey L, Wald A, Patel R, Sacks SL, Tyring SK, Warren T, et al. Once-daily valacyclovir to reduce the risk of transmission of genital herpes. *N Engl J Med* 2004, **350**:11-20.

38. Wald A, Huang ML, Carrell D, Selke S, Corey L. Polymerase chain reaction for detection of herpes simplex virus (HSV) DNA on mucosal surfaces: comparison with HSV isolation in cell culture. *J Infect Dis* 2003, **188**:1345-1351.

39. Mertz GJ, Schmidt O, Jourden JL, Guinan ME, Remington ML, Fahnlander A, et al. Frequency of acquisition of first-episode genital infection with herpes simplex virus from symptomatic and asymptomatic source contacts. *Sex Transm Dis* 1985, **12**:33-39.

40. Mark KE, Wald A, Magaret AS, Selke S, Olin LP, Huang M-L, et al. Rapid onset and clearance of genital HSV reactivations in immunocompetent adults: the virus is usually "on". *17th International Society for Sexually Transmitted Diseases Research*. Seattle, Washington, USA 29 July – 1 August 2007.

41. Quinn TC, Wawer MJ, Sewankambo N, Serwadda D, Li C, Wabwire Mangen F, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *New England Journal of Medicine* 2000, **342**:921-929.

42. Nagot N, Ouedraogo A, Foulongne V, Konate I, Weiss H, Vergne L, et al. Reduction of HIV-1 RNA levels with therapy to suppress Herpes Simplex Virus. *N Engl J Med* 2007, **356**:16-25.

43. Zuckerman R, Luchetti A, Whittington L. HSV-2 suppression with valaciclovir reduces rectal and blood plasma HIV-1 levels in HIV-1 seropositive HSV-2 seropositive men: a randomised double blind placebo-controlled crossover trial. *Journal of infectious diseases (in press)* 2007.

44. Baeten JM, Strick LB, Lucchetti A, Whittington WL, Sanchez J, Coombs RW, et al. Herpes simplex virus (HSV)-suppressive therapy decreases plasma and genital HIV-1 levels in HSV-2/HIV-1 coinfected women: a randomized, placebo-controlled, cross-over trial. *J Infect Dis* 2008, **198**:1804-1808.

45. Celum C, Wald A, Hughes J, Sanchez J, Reid S, Delany-Moretlwe S, et al. Effect of aciclovir on HIV-1 acquisition in herpes simplex virus 2 seropositive women

and men who have sex with men: a randomised, double-blind, placebo-controlled trial. *Lancet* 2008, **371**:2109-2119.

46. Dunne EF, Whitehead S, Sternberg M, Thepamnuay S, Leelawiwat W, McNicholl JM, *et al.* Suppressive acyclovir therapy reduces HIV cervicovaginal shedding in HIV- and HSV-2-infected women, Chiang Rai, Thailand. *J Acquir Immune Defic Syndr* 2008, **49**:77-83.

47. Ouedraogo A, Nagot N, Vergne L, Konate I, Weiss HA, Defer MC, *et al.* Impact of suppressive herpes therapy on genital HIV-1 RNA among women taking antiretroviral therapy: a randomized controlled trial. *Aids* 2006, **20**:2305-2313.

48. Baggaley RF, Griffin JT, Chapman R, Hollingsworth TD, Nagot N, Delany S, *et al.* Estimating the public health impact of the effect of herpes simplex virus suppressive therapy on plasma HIV-1 viral load. *Aids* 2009.

49. Schacker T, Hu HL, Koelle DM, Zeh J, Saltzman R, Boon R, *et al.* Famciclovir for the suppression of symptomatic and asymptomatic herpes simplex virus reactivation in HIV-infected persons. A double-blind, placebo-controlled trial. *Ann Intern Med* 1998, **128**:21-28.

50. Mbopi-Keou FX, Gresenguet G, Mayaud P, Weiss HA, Gopal R, Matta M, *et al.* Interactions between herpes simplex virus type 2 and human immunodeficiency virus type 1 infection in African women: opportunities for intervention. *J Infect Dis* 2000, **182**:1090-1096.

51. Augenbraun M, Feldman J, Chirgwin K, Zenilman J, Clarke L, DeHovitz J, *et al.* Increased Genital Shedding of Herpes Simplex Virus Type 2 in HIV-Seropositive Women. *Ann Intern Med* 1995, **123**:845-847.

52. Nagot N, Foulongne V, Becquart P, Mayaud P, Konate I, Ouedraogo A, *et al.* Longitudinal assessment of HIV-1 and HSV-2 shedding in the genital tract of West African women. *J Acquir Immune Defic Syndr* 2005, **39**:632-634.

53. LeGoff J, Weiss HA, Gresenguet G, Nzambi K, Frost E, Hayes RJ, *et al.* Cervicovaginal HIV-1 and herpes simplex virus type 2 shedding during genital ulcer disease episodes. *Aids* 2007, **21**:1569-1578.

54. Serwadda D, Gray RH, Sewankambo NK, Wabwire-Mangen F, Chen MZ, Quinn TC, *et al.* Human immunodeficiency virus acquisition associated with genital ulcer disease and herpes simplex virus type 2 infection: a nested case-control study in Rakai, Uganda. *J Infect Dis* 2003, **188**:1492-1497.

55. Nagot N, Ouedraogo A, Konate I, Weiss HA, Foulongne V, Defer MC, *et al.* Roles of clinical and subclinical reactivated herpes simplex virus type 2 infection and human immunodeficiency virus type 1 (HIV-1)-induced immunosuppression on genital and plasma HIV-1 levels. *J Infect Dis* 2008, **198**:241-249.

56. Corey L, Wald A, Celum CL, Quinn TC. The effects of herpes simplex virus-2 on HIV-1 acquisition and transmission: a review of two overlapping epidemics. *J Acquir Immune Defic Syndr* 2004, **35**:435-445.

57. Williams BG, Gouws E, Ramjee G, Karim SA. Response to Brown et al., 'Incident and prevalent herpes simplex virus type 2 infection increases risk of HIV acquisition among women in Uganda and Zimbabwe'. *Aids* 2007, **21**:2356-2357.

58. Freeman EE, Weiss HA, Glynn JR, Cross PL, Whitworth JA, Hayes RJ. Herpes simplex virus 2 infection increases HIV acquisition in men and women: systematic review and meta-analysis of longitudinal studies. *Aids* 2006, **20**:73-83.

59. Watson-Jones D, Weiss HA, Rusizoka M, Changalucha J, Baisley K, Mugeye K, *et al.* Effect of herpes simplex suppression on incidence of HIV among women in Tanzania. *N Engl J Med* 2008, **358**:1560-1571.