What is the burden of heterosexually-acquired HIV due to HSV-2? Global and regional model-based estimates of the proportion and number of HIV infections attributable to HSV-2 infection: appendix

Contents

1. Model description

1.1. Model overview

The model is represented by a set of coupled differential equations, which represent the flow of individuals between the stages of HIV and HSV-2 infections and movement between age and sexual activity groups (Figure S1).

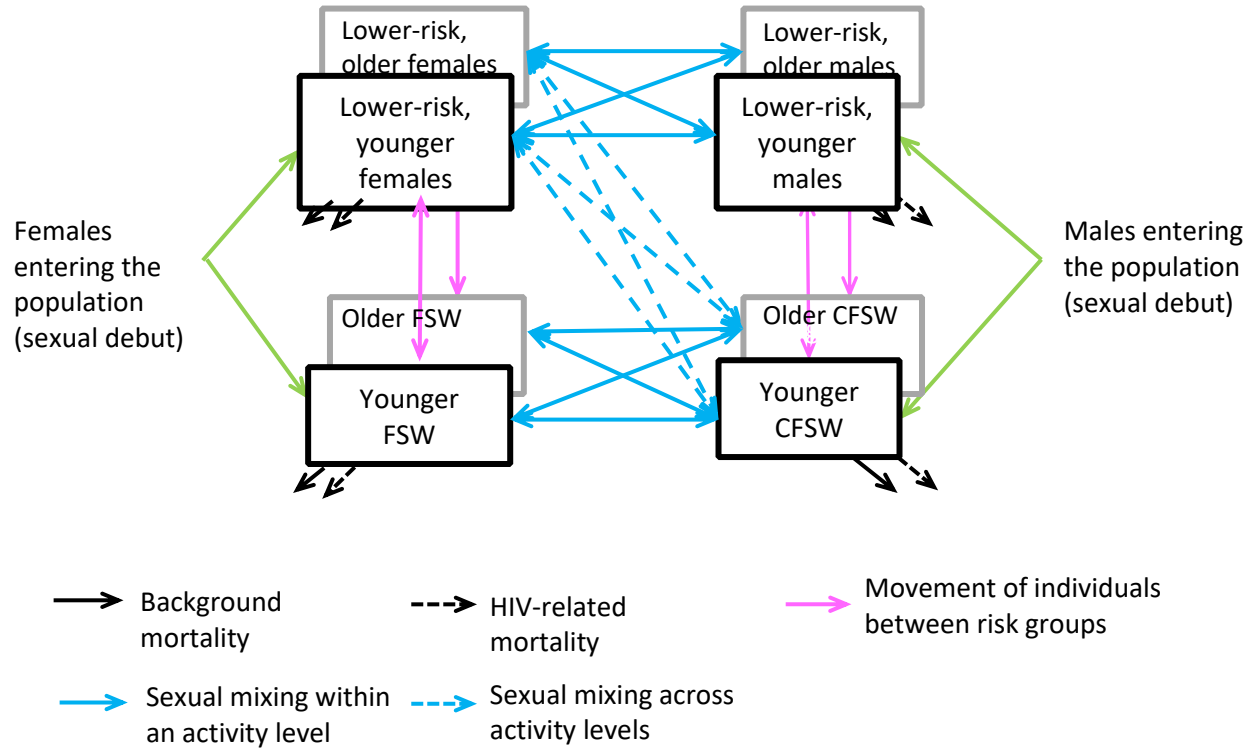


Figure S1: Schematic of the population demographic structure and sexual behaviours. The model divides the population into "younger" (15–24 years old, shown at forefront) and "older" individuals (25–49 years old, compartments shown at back in grey). Sexual contacts are heterosexual (only occur between males and females) which can form within and across age groups (according to the model sexual mixing matrix calculations) – shown as solid blue arrows. Sexual contacts can occur between clients of female sex workers (CFSWs) and lower-risk females (dashed blue arrows) but cannot occur between female sex workers (FSWs) and lower-risk males. For clarity, ageing to the older age group and exiting the model population, and mortality in the older age group compartments, are not shown.

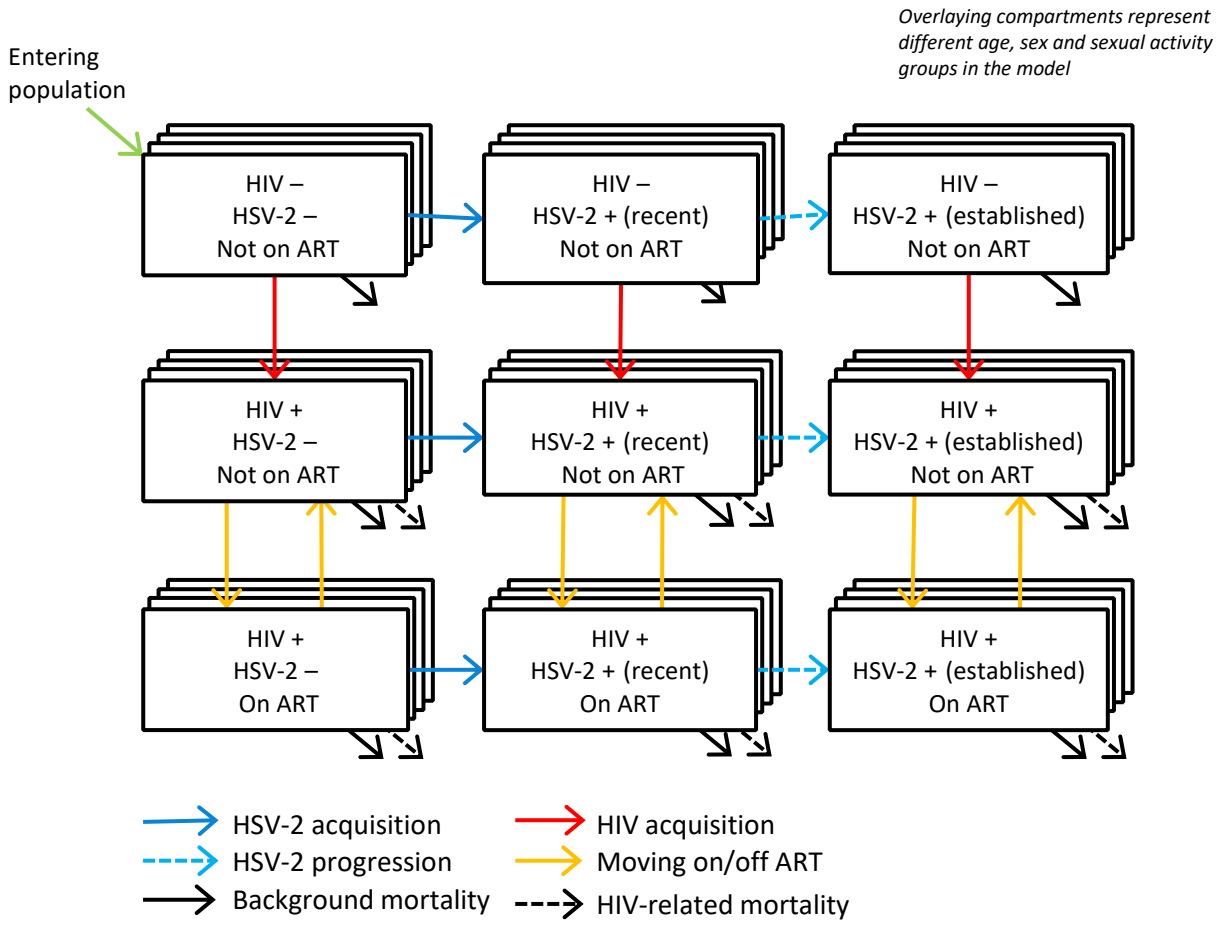


Figure S2: Flows between HSV-2 and HIV infection status.

1.2. Differential equations

Uninfected:

$$\frac{dX_{ra}^{11}(t)}{dt} = E_{ra}(t) + M_{ra}^{11}(t) + ageing_{(a-1)}X_{r(a-1)}^{11}(t) + K_{ra}^{is}(t) - \left(\lambda_{ra}^{HIV,1}(t) + \lambda_{ra}^{HSV,1}(t) + \mu_r + ageing_a\right)X_{ra}^{11}(t)$$ (equation 1)

HSV-2-infected (recent infection):

$$\frac{dX_{ra}^{12}(t)}{dt} = M_{ra}^{12}(t) + \lambda_{ra}^{HSV,1}(t)X_{ra}^{11}(t) + ageing_{(a-1)}X_{r(a-1)}^{12}(t) + K_{ra}^{is}(t) - \left(\lambda_{ra}^{HIV,2}(t) + \theta + \mu_r + ageing_a\right)X_{ra}^{12}(t)$$ (equation 2)

HSV-2-infected (established infection):

$$\frac{dX_{ra}^{13}(t)}{dt} = M_{ra}^{13}(t) + \theta X_{ra}^{12}(t) + ageing_{(a-1)}X_{r(a-1)}^{13}(t) + K_{ra}^{is}(t) - \left(\lambda_{ra}^{HIV,3}(t) + \mu_r + ageing_a\right)X_{ra}^{13}(t)$$ (equation 3)

HIV-infected:

$$\frac{dX_{ra}^{21}(t)}{dt} = M_{ra}^{21}(t) + \lambda_{ra}^{HIV,1}(t)X_{ra}^{11}(t) + \delta_r X_{ra}^{31}(t) + ageing_{(a-1)}X_{r(a-1)}^{21}(t) + K_{ra}^{is}(t) - \left(\lambda_{ra}^{HSV,2}(t) + \tau_r + \mu_r + \alpha^{HIV} + ageing_a\right)X_{ra}^{21}(t)$$ (equation 4)

HIV/HSV-2 coinfected (recent HSV-2 infection):

$\frac{dX_{ra}^{22}(t)}{dt} = M_{ra}^{22}(t) + \lambda_{ra}^{HSV,2}(t)X_{ra}^{21}(t) + \lambda_{ra}^{HIV,2}(t)X_{ra}^{12}(t) + \delta_r X_{ra}^{32}(t) + ageing_{(a-1)}X_{r(a-1)}^{22}(t) + K_{ra}^{is}(t) - (\theta + \tau_r + \mu_r + \alpha^{HIV} + ageing_a)X_{ra}^{22}(t)$ (equation 5)

HIV/HSV-2 coinfected (established HSV-2 infection):

$\frac{dX_{ra}^{23}(t)}{dt} = M_{ra}^{23}(t) + \lambda_{ra}^{HIV,3}(t)X_{ra}^{13}(t) + \theta X_{ra}^{22}(t) + \delta_r X_{ra}^{33}(t) + ageing_{(a-1)}X_{r(a-1)}^{23}(t) + K_{ra}^{is}(t) - (\tau_r + \mu_r + \alpha^{HIV} + ageing_a)X_{ra}^{23}(t)$ (equation 6)

HIV-infected (on ART):

$\frac{dX_{ra}^{31}(t)}{dt} = M_{ra}^{31}(t) + \tau_r X_{ra}^{21}(t) + ageing_{(a-1)}X_{r(a-1)}^{31}(t) + K_{ra}^{is}(t) - \left(\lambda_{ra}^{HSV,3}(t) + \delta_r + \mu_r + \alpha^{ART} + ageing_a\right)X_{ra}^{31}(t)$ (equation 7)

HIV-infected (on ART, recent HSV-2 infection):

$\frac{dX_{ra}^{32}(t)}{dt} = M_{ra}^{32}(t) + \lambda_{ra}^{HSV,3}(t)X_{ra}^{31}(t) + \tau_r X_{ra}^{22}(t) + ageing_{(a-1)}X_{r(a-1)}^{32}(t) + K_{ra}^{is}(t) - (\theta + \delta_r + \mu_r + \alpha^{ART} + ageing_a)X_{ra}^{32}(t)$ (equation 8)

HIV-infected (on ART, established HSV-2 infection):

$\frac{dX_{ra}^{33}(t)}{dt} = M_{ra}^{33}(t) + \theta X_{ra}^{32}(t) + \tau_r X_{ra}^{23}(t) + ageing_{(a-1)}X_{r(a-1)}^{33}(t) + K_{ra}^{is}(t) - (\delta_r + \mu_r + \alpha^{ART} + ageing_a)X_{ra}^{33}(t)$ (equation 9)

The state variable $X_{ra}^{is}(t)$, represent the number of individuals in each diseases stage at time t , where i denotes the HIV status (i=1 to 3, for uninfected, infected not on ART, and infected on ART, respectively) and s denotes the HSV-2 status (s=1 to 3, for uninfected, recently infected (< 1 year, parameter θ), and > 1 year since infection, respectively), r denotes risk group (r=1 and 2 represent lower-risk females and FSWs and 3 and 4 represent lower-risk males and CFSWs, respectively), a denotes age group ($a = 1$ for 15 to 24 years old and $a = 2$ for 25 to 49 years old).

Individuals of risk r and younger age group ($a = 1$) enter the model at an annual net rate of $E_{ra}(t)$ which depends on mortality rates and expected population growth ε, as described in detail in equations 10-11. These entering individuals are susceptible to both infections, with a small fraction of them directly entering the higher risk groups.

For young, lower-risk populations ($a = 1, r = 1,3$):

$E_{ra}(t) = ageing_2 \sum_{i,s} X_{r2}^{is}(t) + \mu_r \sum_{i,s,a'} X_{ra'}^{is}(t) + \alpha^{HIV} \sum_{s,a'} X_{ra'}^{2s}(t) + \alpha^{ART} \sum_{s,a'} X_{ra'}^{3s}(t) + \frac{\varepsilon X_{ra}^{is}(t)}{\sum_{i,s,a'} X_{ra'}^{is}(t)} - \sum_{i,s} M_{ra}^{is}(t)$ (equation 10)

For young, higher-risk populations ($a = 1, r = 2,4$):

$E_{ra}(t) = \varepsilon \frac{\varepsilon X_{ra}^{is}(t)}{\sum_{i,s,a'} X_{ra'}^{is}(t)}$ (equation 11)

Individuals in all disease stages can leave the population at an sex specific per capita background mortality death rate (μ_r) and are assumed to age in and out of their age group a at a rate $ageing_a$ (as described in equations 12):

$$ageing_a = \begin{cases} \frac{1}{10} if\ a = 1\ (15 - 24\ y.o.) \\ \frac{1}{25} if\ a = 2\ (25 - 49\ y.o.) \end{cases}$$ (equation 12)

At each time step, a number $M_{ra}^{is}(t)$ of individuals leave the lower-risk populations and enter the higher-risk populations number in order to balance all deaths and ageing in the higher-risk populations (equations 13-15).

For lower-risk females ($r = 1$):

$M_{1a}^{is}(t) = -\frac{X_{1a}^{is}(t)}{\sum_{i\prime,s\prime} X_{1a}^{i\prime s\prime}(t)}(Ageing_2 \sum_{i\prime,s\prime} X_{22}^{i\prime s\prime}(t) + \mu_2 \sum_{i\prime,s\prime,a\prime} X_{2a\prime}^{i\prime s\prime}(t) + \alpha^{HIV} \sum_{s\prime,a\prime} X_{2a\prime}^{2s\prime}(t) + \alpha^{ART} \sum_{s\prime,a\prime} X_{2a\prime}^{3s\prime}(t))$ (equation 13)

For lower-risk males ($r = 3$):

$M_{3a}^{is}(t) = -\frac{X_{3a}^{is}(t)}{\sum_{i\prime,s\prime} X_{3a\prime}^{i\prime s\prime}(t)}(Ageing_2 \sum_{i\prime,s\prime} X_{42}^{i\prime s\prime}(t) + \mu_4 \sum_{i\prime,s\prime,a\prime} X_{4a\prime}^{i\prime s\prime}(t) + \alpha^{HIV} \sum_{s\prime,a\prime} X_{4a\prime}^{2s\prime}(t) + \alpha^{ART} \sum_{s\prime,a\prime} X_{4a\prime}^{3s\prime}(t))$ (equation 14)

For higher-risk populations ($r = 2,4$):

$M_{ra}^{is}(t) = -M_{(r-1)a}^{is}(t)$ (equation 15)

Otherwise it is equal to zero.

Also, turnover between the higher- and lower-risk populations is accounted for by $K_{ra}^{is}(t)$ which is balanced in order to have constant proportions of FSWs and CFSWs among all females and all males, respectively (equations 16-19). The rate of higher-risk individuals leaving sex work/being clients of sex workers is ω_r (see next section for more details)

For higher-risk females ($r = 2$):

$K_{2a}^{is}(t) = \frac{X_{1a}^{is}(t)}{\sum_{i\prime,s\prime} X_{1a}^{i\prime s\prime}(t)} \sum_{i\prime,s\prime} \omega_2 X_{2a}^{i\prime s\prime}(t) - \omega_2 X_{2a}^{is}(t)$ (equation 16)

For higher-risk males ($r = 4$):

$K_{4a}^{is}(t) = \frac{X_{3a}^{is}(t)}{\sum_{i\prime,s\prime} X_{3a}^{i\prime s\prime}(t)} \sum_{i,s} \omega_4 X_{4a}^{is}(t) - \omega_4 X_{4a}^{is}(t)$(equation 17)

For lower-risk females ($r = 1$):

$K_{1a}^{is}(t) = \omega_2 X_{2a}^{is}(t) - \frac{X_{1a}^{is}(t)}{\sum_{i\prime,s\prime} X_{1a}^{i\prime s\prime}(t)} \sum_{i,s} \omega_2 X_{2a}^{i\prime s\prime}(t)$(equation 18)

For lower-risk males ($r = 3$):

$K_{3a}^{is}(t) = \omega_4 X_{4a}^{is}(t) - \frac{X_{3a}^{is}(t)}{\sum_{i',s'} X_{3a}^{i's'}(t)} \sum_{i,s} \omega_4 X_{4a}^{i's'}(t)$ (equation 19)

Susceptible individuals in risk group r and age a get infected with HIV at a rate (per capita force of infection) $\lambda_{ra}^{HIV,s}(t)$ (equation 20, see below) or infected with HSV-2 at a rate $\lambda_{ra}^{HSV,i}(t)$ (equation 21).

1.3. Model structure – Demography

Higher-risk individuals (FSWs, CFSWs) remain at higher-risk for a fixed duration before leaving the higher-risk group and moving to the lower-risk population (ω_r). These individuals are replaced by an equal number of lower-risk individuals of the same age and sex, and HIV/HSV-2 status reflecting the sex and age specific prevalence in the lower-risk population (equations 13-15). Lower-risk individuals leaving the model through death or ageing are replaced by HIV and HSV-2 negative younger lower-risk individuals.

To reflect population growth and size estimates of the 15-49 population of each region over time, younger susceptible individuals are introduced into all risk groups in the model at specific rates. Also, individuals leaving the higher-risk population through HIV-related and non-HIV related death or ageing are replaced by lower-risk individuals of the same sex with HIV and HSV-2 infection statuses representative of the lower-risk population of that age and sex (equations 13, 14).

1.4. Force of HIV infection

HIV-uninfected individuals become HIV-infected at a per capita force of infection $\lambda_{ra}^{HIV,s}(t)$ described in equation 20:

$\lambda_{ra}^{HIV,s}(t) = \phi_{ra}^{HIV}(t) \cdot RR_{ra}^{HIV-A,s} \cdot \left[\sum_{\tilde{r}=1}^{4} \sum_{\tilde{a}=1}^{2} na_{ra\tilde{r}\tilde{a}} \cdot Pr_{\tilde{r}\tilde{a}}^{HIV} \cdot \sum_{\tilde{\imath}=2}^{3} \sum_{\tilde{s}=1}^{3} (1 - ART_{HIV}^{\tilde{r}\,\tilde{s}}) \cdot RR^{HIV-T,\tilde{s}}\right]$ (equation 20)

Here, r still denotes an individual's risk group, a denotes their age group and s represent their HSV-2 infection status. Their partner's age group and risk group are denoted as $\tilde{a}$ and $\tilde{r}$, respectively, and $\tilde{\imath}$ and $\tilde{s}$ represent their partner's HIV and HSV-2 statuses, respectively.

The term $na_{ra\tilde{r}\tilde{a}}$ gives the number of sexual acts between individual ra and partner $\tilde{r}\tilde{a}$ per year. More precisely, the model assumes that HIV infection can occur during sex acts between 1) FSWs and their CFSWs ("sex acts 1"), 2) CFSWs and their lower-risk female partners ("sex acts 2"), and 3) between lower-risk individuals ("sex acts 3") (Figure S1). The model assumes that FSWs have a high annual number of sex acts with CFSWs, irrespective of FSW and CFSW age (random age-mixing). CFSWs are also assigned an annual number of sex acts with lower-risk females, irrespective of CFSW age. However, the model does reflect age-assortative mixing and age-difference between partners for "sex acts 2", as relatively few sex acts occur between younger CFSWs and older lower-risk females, and the majority of the sex acts of older CFSWs are with younger lower-risk females. The sexual contacts between lower-risk individuals ("sex acts 3") are modelled in a similar way to "sex acts 2", were age-assortative and we used the same prior distribution of the number of sex acts. The number of sex acts

between groups are balanced at each time step so that the total number of sex acts that any group A has with a group B is equal to the total number of acts group B has with group A.

The force of infection for HIV first depends on the HIV prevalence in the partner's sex/age/risk group. which is denoted as $Pr_{\tilde{r}\tilde{a}}^{HIV}$ for the partner's risk and age group. The HIV force of infection allows for two cofactor effects: increased acquisition risk to HIV for an HSV-2-infected individual ($RR_{ra}^{HIV-A,s}$) (conservative scenario) and increased HIV transmission risk when a partner is coinfected with both HIV and HSV-2 ($RR^{HIV-T,\tilde{s}}$) (liberal and fully liberal scenarios). Values of $RR_{ra}^{HIV-A,s}$ were sampled for each sex among those with recent infection, and for each sex risk-level combination with established infection, whereas $RR^{HIV-T,\tilde{s}}$ was assumed not to vary by recency of HSV-2 infection or demographic characteristics.

We also account for reduced HIV transmission risk of an HIV-infected partner receiving anti-retroviral therapy (ART) with the term $ART_{HIV}^{\tilde{r}\,\tilde{s}}$. $ART_{HIV}^{\tilde{r}\,\tilde{s}}$ is calculated as the product of the proportion of the partners population on ART that are virally supressed (vls_ART) with the efficacy of successful ART in decreasing per-act HIV transmission risk $e\_ART_{T\_HIV}^{\tilde{s}}$, as we assumed that individuals who are not virally supressed have the same transmission risk as individuals not on ART. In the fully liberal scenario, HSV-2-infected individuals on ART transmit HIV at a slightly higher rate compared to those on ART that are HSV-2-susceptible, with $e\_ART_{T\_HIV}^{\tilde{s}>1} = e\_ART_{T\_HIV}^{\tilde{s}=1} \cdot RR_{HSV/ART-T}^{HIV}$, with $RR_{HSV/ART-T}^{HIV}$ being $\neq 1$ only under this scenario. The increase in ART coverage across and during simulations is described in the next section. The term $RR_{HSV/ART-T}^{HIV}$ reflects the reduction in the efficacy of ART in reducing HIV transmission risk due to HSV-2, and is always set to 1, except under the fully liberal scenario.

The final parameter defining the HIV force of infection term is the global per-act transmissibility parameter $\phi_{ra}^{HIV}(t)$ which reflects the decreasing per-act risk of HIV acquisition over time due to increases in condom use and male circumcision coverage. This global per-act transmissibility parameter is the product of a time-varying parameter reflecting both HIV-specific intervention levels $Int_{ra}^{HIV}(t)$ (condom use and male circumcision coverage) and efficacies in reducing per-act risk of HIV transmission, a set of risk ratios ($RR\_I_{ra}^{HIV}$) which account for intervention-level differences between risk groups, and a parameter capturing per-act HIV-specific infection risk β_{ra}^{HIV} (equation 21):

$$\phi_{ra}^{HIV}(t) = RR\_I_{ra}^{HIV}(1 - Int^{HIV}(t)) \cdot \beta_{ra}^{HIV} \text{ (equation 21)}$$

Here, the HIV intervention level parameter $Int_{ra}^{HIV}(t)$ is a time-varying meta-parameter which reflects both intervention coverage of the two interventions and their efficacy at the sex-act level, it takes the form of a sigmoidal curve function which increases over time. The general shape was selected upon a review of intervention coverages over time in each WHO region (see Intervention supplementary document), and it is first computed upon lower-risk younger male populations, and is controlled by providing start $s\_Int_s^{HIV}$ and end values $s\_Int_e^{HIV}$, a gradient of change $s\_Int_g^{HIV}$ and the inflection point ($s\_Int_i^{HIV}$) parameters, described in equation 22:

$$b = (s\_Int_s^{HIV} - s\_Int_e^{HIV})\left(\frac{1}{1+e^{s\_Int_g^{HIV}(s\_Int_i^{HIV}-s\_Int_s^{HIV})}} - \frac{1}{1+e^{s\_Int_g^{HIV}(s\_Int_i^{HIV}-s\_Int_e^{HIV})}}\right)$$

$$c = f_0 - \frac{b}{1+e^{s\_Int_g^{HIV}(s\_Int_i^{HIV}-s\_Int_s^{HIV})}}$$

$$Int_{r,a}^{HIV}(t) = \frac{b}{1+e^{s\_Int_g^{HIV}(s\_Int_i^{HIV}-t)}} + c \text{ (equation 22)}$$

Different intervention levels for the other subgroups $Int_{ra}^{HIV}(t)$ are obtained by multiplying $Int_{r=3,a=1}^{HIV}(t)$ by a set of multiplicative risk ratios ($RR\_Int_{ra}^{HIV}$). The per-act HIV risk parameter β_{ra}^{HIV} is an acquisition probability per sex-act, first sampled for a male individual ('base risk'), then derived for older and younger females separately using two independent risk-ratios $RR\_\beta_1^{HIV}$ and $RR\_\beta_2^{HIV}$.

Upon HIV infection, individuals uninfected (equation 4) or infected with HSV-2 (equations 5-6) enter the HIV untreated compartment (equations 7-9) where they are subjected to a background and an extra HIV specific per capita mortality rate (α^i , which dependent on their ART status).

1.5. Force of HSV-2 infection

HSV-2 susceptible individuals ($s = 1$) become infected with a per capita force of infection ($\lambda_{ra}^{HSV,i}(t)$, equation 13) which is given below. Once an individual has become infected with HSV-2 they are defined as having "recent" HSV-2 infection for the first year of infection ($s = 2$). After this time they progress to established HSV-2 infection ($s = 3$). As HSV-2 infection is life-long, individuals retain this status until exiting the model. The primary difference between recent and established HSV-2 infection is that recent infection is associated with higher HSV-2 transmission risk, but we also assume that the level of interactions between HSV-2 and HIV depend on this recency of HSV-2 infection.

The per capita force of infection for HSV-2 resembles the force of infection for HIV (equation 23):

$$\lambda_{ra}^{HSV,i}(t) = \phi_{ra}^{HSV}(t) \cdot RR_{ra}^{HSV-A,i} \cdot \left[\sum_{\tilde{r}=1}^{4}\sum_{\tilde{a}=1}^{2} na_{ra\tilde{r}\tilde{a}} \cdot Pr_{\tilde{r}\tilde{a}}^{HSV} \cdot \sum_{\tilde{\imath}=1}^{3}\sum_{\tilde{s}=2}^{3} RR^{HSV-T,\tilde{\imath}} \cdot RR_{ART-T}^{HSV,\tilde{\imath}}\right] \text{ (equation 23)}$$

Note that i represents an individual's HIV status (including whether they are on ART). The HSV-2 prevalence in a partner's age and risk group is denoted by $Pr_{\tilde{r}\tilde{a}}^{HSV}$. In the fully liberal scenario, the model allows for three additional HSV-2 cofactor effects: 3) increased HSV-2 transmission risk for a partner who is coinfected with both HSV-2 and HIV ($RR^{HSV-T,\tilde{\imath}}$), 4) decreased HSV-2 transmission risk if an individual is on ART (vs HIV-infected not on ART) ($RR_{ART-T}^{HSV,\tilde{\imath}}$), and 5) decrease in the efficacy of ART in reducing HIV transmission risk ($RR_{HSV/ART-T}^{HIV}$).

The final parameter is the global transmissibility parameter for HSV-2, $\phi_{ra}^{HSV}(t)$, which is modelled in much the same way as the global HIV parameter (equation 24):

$\phi_{ra}^{HSV}(t) = RR\_I_{ra}^{HSV}(1 - Int^{HSV}(t)) \cdot \beta_{ra}^{HSV}$ (equation 24)

where β_{ra}^{HSV} is the per-act HSV-2 infection risk parameter, initially defined for all susceptible males, which is multiplied by a set of multiplicative risk ratios ($RR\_\beta_1^{HSV}$ and $RR\_\beta_2^{HSV}$) in order to generate different HSV-2 acquisition risks for younger and older females (cf males) as well as multiplied by $RR\_\beta_3^{HSV}$ to reflect higher risk of HSV-2 transmission during the first year of infection, and a time-varying HSV-2 intervention level parameter, $Int^{HSV}(t)$, reflecting both coverage and efficacy of condom use and male circumcision for younger lower-risk males partnered with younger lower-risk females. We did not find any estimates for transmission according to whether the HSV-2 infection is recent (<1 year) or established (>1 year), either absolute or relative (RR). However, in our first WHO estimates of the burden of genital ulcer disease (GUD),[1] the ratio of number of GUD days per HSV-2-infected individual was approximately 1.1 comparing recent to established infections, while a study which examined viral shedding and lesions in the first year since infection acquisition versus after the first year found a ratio of about 1.4 for shedding and 1.1 for lesions.[2] Based on these values, we selected a range of 1.2-1.4 for $RR\_\beta_3^{HSV}$.

The parameter $Int_{ra}^{HSV}(t)$ takes the form of a sigmoidal function and is entirely independent of the equivalent HIV parameter, reflecting the differing efficacies of the interventions between the two infections. Once again, differences in intervention coverage and efficacy between age and risk groups were modelled using a set of risk ratios specific to HSV-2 ($RR\_I_{ra}^{HSV}$). These are constructed in the same way as for HIV but are entirely independent parameters. Once infected, individuals move from recent to established HSV-2 infection after 1 year on average (rate $\theta = 1$).

1.6. Changes in ART coverage over time

After 1996, HIV-infected individuals can initiate ART at a per capita rate $\tau_r(t)$ and drop out at rate δ_r, which varies by sex. Treated HIV-infected individuals (X_{ra}^{3s}) have a reduced HIV-related mortality rate ($\alpha^{ART} = \alpha^{HIV} \times RR_{\alpha}^{ART}$) and a reduced transmission risk, as described in the HIV force of infection section.

ART initiation rates are allowed to vary over time, being set to zero for the pre-ART period from model initiation to introduction of ART (1996), after which they can vary linearly within five separate periods: 1996-1999, 2000-2004, 2005-2009, 2010-2018, 2018+. For simplicity, we assume that ART coverage varies only by sex (i.e. not by age or risk group), that ART drop-out rates and the proportion of those on ART that are virally suppressed (vls_ART) are constant over time.

1.7. Model initiation

At model initiation in 1982, there is a set proportion of FSWs among females and CFSWs among males. We also assume a small fraction of the population is HIV-infected, while the initial prevalence of HSV-2 is seeded to similar level as in the 2012 estimates[3] within each group, with 5% of HSV-2-infected individuals being assumed to be in the "recent" infection stage.

1.8. Cofactor scenarios

The different scenarios under which tPAF of HSV-2 on incident HIV infections were described in the main manuscript and in the Table 1. More details on the cofactors parametrisation are shown in the section 2 of this supplement.

1.9. Model fitting overview

For each WHO region, the model was parameterised and fitted using a Bayesian framework that accounts for uncertainties in parameters and fitting outcomes. This involved the following steps: 1) defining plausible *prior* range of values for each parameter (Tables S1-2), 2) using Latin hypercube sampling to randomly select 20 million different combinations of parameter sets, 3) using the model with each sampled parameter set to simulate the relevant demographic and epidemiological fitting outcomes, 4) selecting the subset of (up to 100) parameter sets (i.e. the *posterior* parameter sets) that produce model outcomes that are consistent with empirical estimates, i.e. that fit within every predefined 95% confidence interval of the 27 (26 for the European and East-Mediterranean regions) empirical fitting outcome estimates (details below and Table S3), 5) using the *posterior* parameter sets to produce baseline model estimates from the posterior parameter sets

The number of fitting outcomes was slightly lower for the European and East-Mediterranean regions as pooled estimates of the prevalence of HIV and HSV-2 among CFSWs were not available in all regions.
For each region, the model was simultaneously fitted to the following demographic and epidemiological empirical data available (Table S3):

The estimated number of incident heterosexual HIV infections in each region/sex/age group among non-PWID individuals in 2015, which were derived from estimates of 1) the total annual HIV incidence and 2) the distribution of incident infections occurring among heterosexuals in 2015[4] (Table S2). No estimates of HIV prevalence among heterosexual non-PWID were available at the WHO region level, but the model was fitted to HIV prevalence estimates among FSWs in each region and CFSWs in Africa (data were too scarce for the other regions).[5,6]

Sex/age-specific HSV-2 prevalence estimates, which were based on a literature review of HSV-2 prevalence worldwide over 2000-2012,[3] and published pooled estimates of HSV-2 prevalence among FSWs and CFSWs, where available.[7] The modelled cofactors were fitted to published pooled estimates of HIV incidence rate ratios (IRRs) by HSV-2 status and recency of HSV-2 infection (i.e. the ratio of the HIV incidence rate among individuals with <1 year of infection versus among those HSV-2-uninfected, and similarly for >1 year of infection versus uninfected), among females and males separately[8] (Table 1). We fitted simulations on the HIV prevalence ratio by HSV-2 status, based on a literature search (Figure S3).

Finally, the model was further fitted to region-specific UNAIDS estimates of ART coverage by sex over time.[9]

We also compared our predicted HSV-2 incidence rate estimates with previously published model-based estimates for 2003 and 2012 for each WHO region.[1,3] Our predicted HSV-2 prevalence by sex/age combinations for the years 2003 and 2016 were also compared to pooled estimates from two systematic reviews of HSV-2 prevalence calculated over the period 1966-2003[1] and 2004-2018.[10]

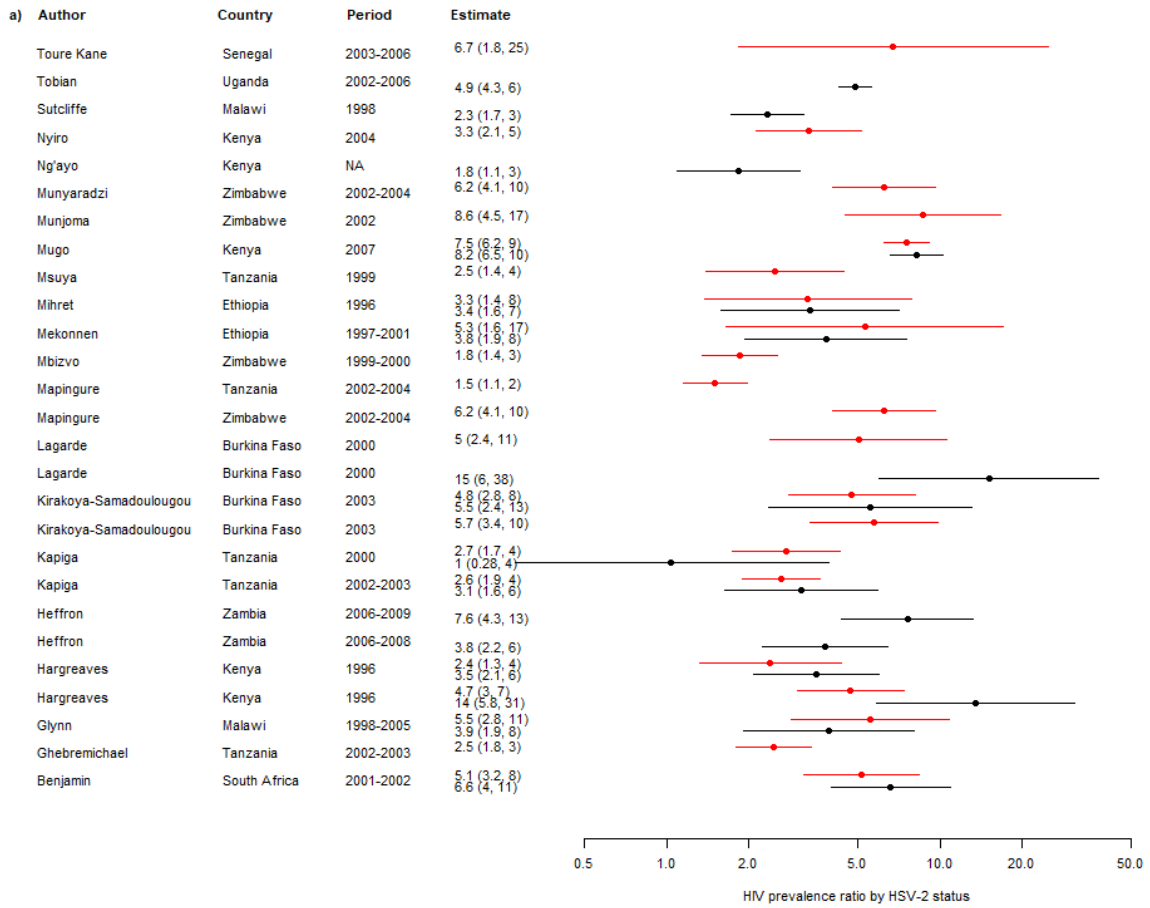
1.10. HIV fitting and comparison data

Estimates of the number of incident HIV infections by WHO region, age and sex, for the heterosexual, non-PWID population, was derived using two sources of data from UNAIDS. The first source is the estimate of the total number incident HIV infections by WHO region, age and sex, for the general population for the year 2015.[9] The second data source is an estimate of the fraction of the total number of incident HIV infections in 2015 that occur among MSM, PWID and other risk groups in each WHO region (Table S2).[4] These estimates did not include uncertainty bounds. The two datasets were combined by removing the number of infections occurring among MSM from the number of infections occurring among males, and the number of infections occurring among PWID from the number of infections occurring among female and males. The uncertainty in the number of incident infections occurring among heterosexuals non-PWID were further expanded in the case of the Europe and Western Pacific regions to allow the model to reflect more realistic ratios of number of incident HIV infections by sex. The HIV prevalence among higher-risk populations were adapted from[11] for FSWs, and sourced from[6] for African CFSWs.

1.11. HSV-2 fitting and comparison data

Estimates of HSV-2 prevalence and incidence by WHO region, age and sex for general populations were available for 2003, 2012, and 2016. Details on the estimation methods are available in the corresponding papers.[1,3,10] In brief, for the 2003 estimates we searched for studies published up to 2005 and used data from any study year. For the 2012 estimates we searched for newly published studies up to 2014 which could also contribute data and applied a cut-off study year of 2000, whereas the 2016 estimates derived from data from 2004 onwards except for Eastern Mediterranean where studies from 2000 onwards are used. Thus, for each estimate year, data were taken from across a range of study years, with large overlap in the data used between estimate years. Estimates were generated by pooling prevalence values by age (15-49 years by 5-year age-band) and sex for each WHO region. A constant-incidence model was applied to each set of pooled prevalence values by age for each WHO region separately by sex to calibrate incidence and obtain smoothed prevalence by single year of age. Smoothed prevalence and calibrated incidence were then applied to population numbers for the relevant estimate year. Only data from general populations were used. We used prevalence adjusted for the sensitivity and specificity of the assay used to maintain comparability since adjusted estimates were only available for 2012. Lower and upper bounds around the 2003 estimates were calculated using the relative uncertainty of the 2012 estimates for the same population. For this study we expanded the uncertainty around the 2012 HSV-2 prevalence estimates in the Eastern Mediterranean region, as the estimates for the male population were 4 times lower than for the female population, and up to 6 times lower than the 2003 estimates among males.

We used HSV-2 prevalence data from all these literature reviews to generate pooled estimates of HSV-2 prevalence separately for FSWs and clients of CFSWs. For the pooling, we used unadjusted prevalence values from studies conducted in 2000 or later for those ages within the range 15-49 years. Estimates were available for these risk groups for all regions, with the exception that no estimates of HSV-2 prevalence were available for clients of FSWs for Africa, Europe or Eastern Mediterranean (Table S3).



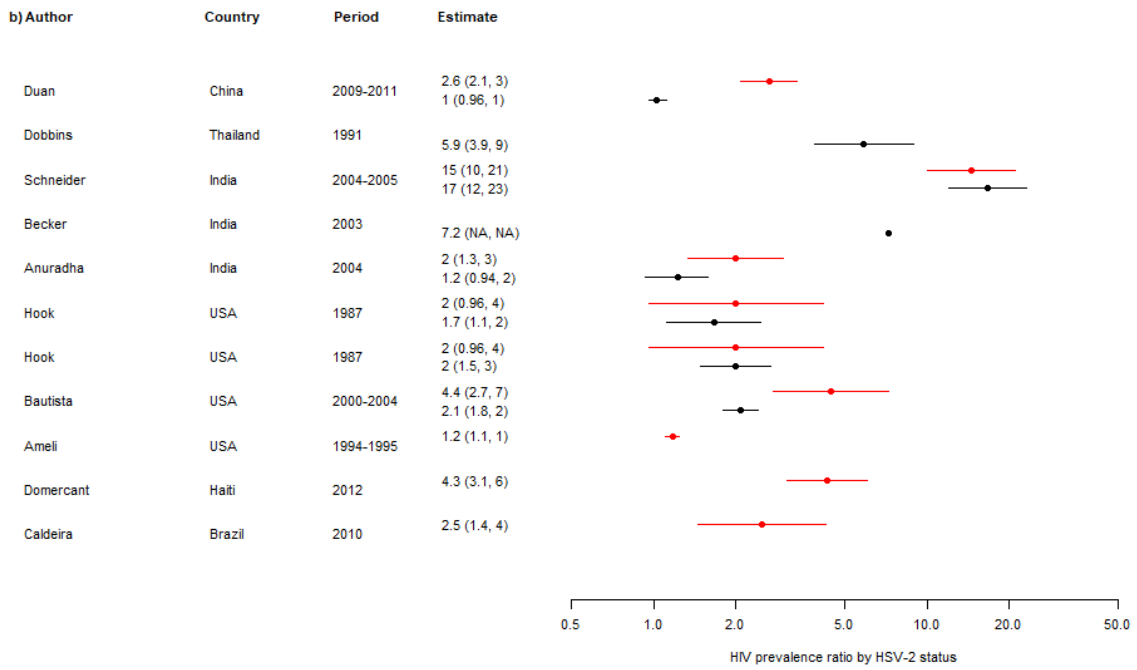


Figure S3: Published empirical estimates of the HIV prevalence ratio by HSV-2 status (HIV prevalence among those HSV-2-infected over among those HSV-2-uninfected) within studies conducted in a) Africa[12-33] b) outside Africa[34-52], among females (red), and males (dark).

Table S1: Description of model parameters with initial condition ranges (priors) and sources.

Parameter	Symbol	Prior	References
Demography / population structure			
Average life expectancy for females (years)	$\frac{1}{\mu_{ra}}, r = 1,2$	Varies by WHO region – see Table M3	[53]
RR for the average life expectancy for males (cf females)	-	Varies by WHO region – see Table S3	[53]
Total population size at start of simulation (millions)	-	Varies by WHO region – see Table S3	[53]
Yearly population growth rate	ε	Varies by WHO region – see Table S3	[53]
FSW population size (fraction of females that are FSWs)		Varies by WHO region – see Table S3	Adapted from [5]
CFSW population size (fraction of males that are CFSWs)		Varies by WHO region – see Table S3	[6] for Africa
Turnover rates between higher and lower-risk groups	$K_{ra}^{is}(t)$	Varies by WHO region – see Table S3	Adapted from [54]
Model-related parameters			
Start year of simulation	N/A	1982	-
End year of simulation	N/A	2030	-
Parameters informing per-act HIV infection risks			
Per-act infection risk for HIV (younger, lower-risk males partnered with younger lower-risk females)	β_{ra}^{HIV}	[0.0004,0.002]	Assumption – fitted to data
RR of per-act HIV infection risk for older female (cf male)	$RR\_\beta_1^{HIV}$	[1,2]	Assumption – fitted to data
RR of per-act HIV infection risk for younger female (cf older female)	$RR\_\beta_2^{HIV}$	[1.5,2.5]	Assumption – fitted to data
Parameters informing the time-varying sigmoidal meta-parameter representing intervention levels for HIV[a]			
Starting value (simulation start)	$s\_Int_s^{HIV}$	[0.01,0.1][b]	Assumption of very low coverage and efficacy of interventions – fitted to data
End value (simulation end)	$s\_Int_e^{HIV}$	[0.3,0.6]	Assumption – fitted to data
Time at which value is halfway between start and end value (turnpoint)	$s\_Int_i^{HIV}$	[1992,2002]	Assumption – fitted to data
Shape gradient	$s\_Int_g^{HIV}$	[0.05,0.9]	Assumption – fitted to data
RRs which increase intervention levels for HIV relative to the younger lower-risk male group[c]			
RR for female (cf male)	$RR\_Int_{r=1-2\,a}^{HIV}$	[0.5,1] [b]	Assumption – fitted to data
RR for older female (cf younger female)	$RR\_Int_{r=1-2\,a}^{HIV}$	[0.5,1]	Assumption – fitted to data
RR for older male (cf younger male)	$RR\_Int_{r=3-4\,a}^{HIV}$	[0.5,1]	Assumption – fitted to data
RR for FSWs (cf lower-risk female)	$RR\_Int_{r=2\,a}^{HIV}$	[1,2]	Assumption – fitted to data

RR for CFSWs is higher-risk (cf lower-risk female)	$RR\_Int^{HIV}_{r=4\,a}$	[1,2]	Assumption – fitted to data
Parameters informing the per-act infection probability of HSV-2			
RR which multiplies the infection risk for HIV to obtain the infection probability for established HSV-2 infection (for males)	RR^{s}_{HSV-T}	[1,2.5]	Based on the HSV-2/HIV prevalence ratio – fitted to data
RR of HSV-2 transmission risk during recent HSV-2 infection stage (cf established infection)	$RR\_\beta^{HSV}_{3}$	[1.2,1.4]	Based on numbers of GUD by recency of infection in [55] and [2]
RR for older female (cf male)	$RR\_\beta^{HSV}_{1}$	[1,2]	Assumption – fitted to data
RR for younger female (cf older female)	$RR\_\beta^{HSV}_{2}$	[1.5,2.5]	Assumption – fitted to data
Parameters informing the time-varying sigmoidal meta-parameter representing intervention levels for HSV-2[a]			
Starting value (simulation start)	$s\_Int^{HSV}_{s}$	[0.01,0.1] [b]	Assumption – fitted to data, same prior as for HIV
End value (simulation end)	$s\_Int^{HSV}_{e}$	[0.3,0.6]	Assumption – fitted to data
Time at which value is halfway between start and end value (turnpoint)	$s\_Int^{HSV}_{i}$	[1992,2002]	Assumption – fitted to data, same prior as for HIV
Shape gradient	$s\_Int^{HSV}_{g}$	[0.05,0.9]	Assumption – fitted to data, same prior as for HIV
RRs which increase intervention levels for HSV-2 relative to the younger lower-risk male group			
RR for female (cf male)	$RR\_Int^{HSV}_{r=1-2\,a}$	[0.5,1] [b]	Assumption – fitted to data
RR for older female (cf younger female)	$RR\_Int^{HSV}_{r=1-2\,a}$	[0.5,1]	Assumption – fitted to data
RR for older male (cf younger male)	$RR\_Int^{HSV}_{r=3-4\,a}$	[0.5,1]	Assumption – fitted to data
RR for FSWs (cf lower-risk female)	$RR\_Int^{HSV}_{r=2\,a}$	[1,2]	Assumption – fitted to data
RR for CFSWs is higher-risk (cf lower-risk female)	$RR\_Int^{HSV}_{r=4\,a}$	[1,2]	Assumption – fitted to data
Parameters related to ART dynamics			
Proportion of population on ART who are virally supressed	vls_ART	Varies by WHO region – see Table S3	
Efficacy of ART in reducing per-act HIV transmission risk for those who are virally supressed	$e\_ART^{\tilde{s}}_{T\_HIV}$	[0.96,1]	Assumed based on [56]. Varies by partner HSV-2 status in the fully liberal scenario.
Time of ART starting in the model	-	1996	ART first available
Time of end of first ART period	-	2000	Assumption – based on fit to data This year was chosen as it is approximatively the year where ART roll-out really started in African countries
Time of end of second ART period	-	2005	Assumption – based on fit to data
Time of end of third ART period	-	2010	Assumption – based on fit to data
Time of end of fourth ART period	-	2018	Assumption – based on fit to data
Time of end of fifth ART period	-	2030	
Parameters related to ART initiation and dropout. The values reflect both changes in the different guidelines (or when they chose to follow WHO guidelines, and local implementation), which leads to large ranges of uncertainty.			
RR for change in ART initiation rate over 1996-2000 (vs 2010-2018)	-	Varies by WHO region – see Table S3	Assumption – fitted to data

RR for change in ART initiation rate over 2000-2005 (vs 2010-2018)	-	Varies by WHO region – see Table S3	Assumption – fitted to data
RR for change in ART initiation rate over 2005-2010(vs 2010-2018)	-	Varies by WHO region – see Table S3	Assumption – fitted to data
RR for change in ART initiation rate over 2018-2030 (vs 2010-2018)	-	Varies by WHO region – see Table S3	Assumption about the 2018-2030 period
Yearly rate of ART initiation for lower-risk females over 2010-2018	τ_1 (over 2010-2018)	Varies by WHO region – see Table S3]	Conservative estimate – fitted to data
RR for change in ART initiation rate for males (cf females)	-	Varies by WHO region – see Table S3	Assumptions based on ART coverages by sex from UNAIDS
Yearly rate of ART drop-out	δ_1	0.08	Discrepancy in estimates, around 3% in [57] (The ANRS 12222 Morbidity/Mortality Study Group 2013), vs 20% for individuals within the first year of treatment [58].
Average life expectancy (years) from HIV acquisition to death, in absence of ART	α^{HIV}	Varies by WHO region – see Table S3	[59,60]
RR for the average number of years an individual is HIV-infected and on ART before death (vs not on ART), is used to calculate the duration from HIV acquisition to death, on ART	RR_{α}^{ART}	[1/4,1/2]	Adapted from ALPHA network data on declines in HIV-related deaths during before and after ART scale-up [61].
Average number of years in the higher-risk group for females	$\frac{1}{\omega_2}$	Varies by WHO region – see Table S3	[54]
Average number of years in the higher-risk group for males	$\frac{1}{\omega_4}$	Varies by WHO region – see Table S3	[54]
Parameters reflecting sexual activity			
Annual number of sex acts of FSWs	-	[200,1000]	Assumption – fitted to data
Weekly number of sex acts of CFSWs with lower-risk females	-	2	Assumed
Weekly number of sex acts of lower-risk females with lower-risk males	-	2	Assumed
Average number of years with a recent HSV-2 infection	θ	1	By definition
Proportion of HSV-2-infected individuals that are in the "recent" stage of the infection in 1982	-	5%	Average equilibrium state after 10 years, over simulations
Proportion of total initial population who are female	-	Varies by WHO region – see Table S3	[53]
Proportion of the initial female population who are younger	-	Varies by WHO region – see Table S3	[53]
Proportion of the initial male population who are younger	-	Varies by WHO region – see Table S3	[53]
Proportion of the initial female population who are higher-risk	-	Varies by WHO region – see Table S3	[5]

Proportion of the initial male population who are higher-risk	-	Varies by WHO region – see Table S3	[5]

ART – antiretroviral treatment; cf – comparison group; CFSWs – clients of FSWs; FSWs – female sex workers; N/A – not applicable; RR – risk ratio.

[a] Time-varying sigmoidal meta-parameters representing intervention levels for HIV and HSV-2, primarily reflecting coverage and efficacy of male circumcision and condom use and representing coverage/efficacy for all for younger lower-risk males partnered with younger lower-risk females. The model runs until 2030, so the parameters also reflect future increases in intervention coverage.

[b] For the Eastern Mediterranean region only: start values of $s\_Int_s^{HIV}$ and $s\_Int_s^{HSV}$ sampled uniformly in [0.1-0.3] and $RR\_Int_{ra}^{HIV}$ and $RR\_Int_{ra}^{HSV}$ sampled uniformly in [0.5-0.75] to reflect high coverage of male circumcision in this region.

[c] Uncertainty bounds were chosen to reflect the fact that the circumcision parameter (meta-parameter) affects both females and males, and that condom use is higher among higher-risk and younger populations.

Table S2: Description of model parameters and data varying by WHO region with initial condition ranges (priors) and sources.

Parameter	Africa	Americas	South-East Asia	Europe	Western Pacific	Eastern Mediterranean	References
Parameters reflecting demography							
Average life expectancy for females (years)	53	66	59	66	64	60	[53] for the period 2010-2015
RR for the average life expectancy for males (cf females)	0.95	0.92	0.94	0.90	0.94	0.96	[53] for the period 2010-2015
Total population size at start of simulation (1982) (millions)	182	316	533	401	699	124	[53]
Proportion of females among all 15-49 at start of simulation	50%	50%	49%	50%	49%	48%	[53]
Yearly population growth rate	0.029 throughout	Time-dependant (0.022 in 1982, 0.016 in 1995, 0.001 in 2030)	Time-dependant (0.024 in 1982, 0.02 in 1995, 0.002 in 2030)	Time-dependant (0.008 in 1982, 0.001 in 1995, 0 in 2030)	Time-dependant (0.22 in 1982, 0.01 in 2000, 0 in 2030)	Time-dependant (0.032 in 1982, 0.03 in 2003, 0.017 in 2030)	[53]
Initial proportion of 15-49 years old that are 15-24 years old (1982)	F: 42% M: 42%	F: 34% M: 35%	F: 37% M: 38%	F: 30% M: 31%	F: 36% M: 36%	F: 41% M: 41%	[53]
Parameters reflecting key populations characteristics							
Proportion of FSWs among all females	0.41-1.88%	0.16-1.52%	0.26-0.67%	0.46-0.97%	0.26-0.67%	0.94-2.78%	[5a]
Average duration of sex work in years	5-6	10-12	2-4	8.4-10	2-4	5-6	[54b]
Proportion of CFSWs among all 15-49 years old males	3-16%	3-16%	3-16%	3-16%	3-16%	3-16%	[6] for Africa
Average duration as a CFSW in years	2-10	10-20	20-40	10-20	20-40	2-10	[54]
Parameters reflecting mortality							
Average duration from HIV infection to death in years (median duration in years)	14.9 (10.3)	15.8 (10.9)	14.9 (10.3)	15.8 (10.9)	14.9 (10.3)	14.9 (10.3)	[59,62]
Parameters related to ART uptake							
Proportion of population on ART who are virally supressed	73-79%	80-85%	85%	69-83%	85%	76%	Estimated from [58] for the year 2017, among all HIV-positive[c]
Yearly rate of ART initiation among HIV+ females over the 4th period (=past few years)	[0.5,0.7]	[0.3,0.7]	[0.3,0.7]	[0.3,0.5]	[0.2,0.4]	[0,0.1]	Assumption – fitted to data

RR ART initiation over the different ART periods (cf 2010-2018)	1st: [0,0.001] 2nd: [0.01,0.1] 3rd: [0.1,0.4] 5th: [1,2]	1st: [0,0.1] 2nd: [0.1,0.3] 3rd: [0.3,0.7] 5th: [1,2]	1st: [0,0.001] 2nd: [0.01,0.1] 3rd: [0.1,0.4] 5th: [1,2]	1st: [0,0.2] 2nd: [0.1,0.4] 3rd: [0.4,0.8] 5th: [1,2]	1st: [0,0.1] 2nd: [0.1,0.2] 3rd: [0.2,0.5] 5th: [1,2]	1st: [0,0.2] 2nd: [0.1,0.4] 3rd: [0.4,0.8] 5th: [1,2]	Assumption – fitted to data
RR ART initiation among HIV+ males (cf HIV+ females)	[0.6,0.9]	[1-1.3]	[0.6,0.9]	[1-1.3]	1	1	Based on UNAIDS ART coverage ratios by sex
Data related to the estimates of incident HIV infections in 2015 (used to triangulate fitting data)							
Proportion of incident HIV infections in 2015 occurring among MSM	7%	43%	20%	9%	25%	25%	[4]
Proportion of incident HIV infections in 2015 occurring among PWID	2%	4%	7%	36%	15%	53%	[4]

[a] Estimates only available for a different regional grouping. Range for Africa selected by combining the UNAIDS estimates for east/southern africa, and west/central central (min of the two estimates lower bound, max of the two estimates upper bounds) [5]. Rrange for Americas selected as the interquartie range for the UNAIDS latin America estimate. Range for south east Asia chosen by combining the UNAIDs estimatea for Asia and Pacific. Range for Europe selected by combining UNAIDS estimates for East Europen and central Asia. Range for Eastern Mediterranean chosen by combining the full range of UNAIDS estimates North Africa and Middle East. Western Pacific range chosen by combining estimates for UNAIDS Asia and Pacific regions.

[b] Estimates unavailable for two WHO regions: The Eastern Mediterraean range was assumed to be the same as the range from Africa, whereas the Western Pacific range was assumed to be the same as the South-East Asia estimate

[c] Estimates only available for a different regional grouping: the Africa range was selected based on the estimates for West and central Africa (73%) and East and Southern Africa (79%). The range for the Americas was selected based on the estimates for Latin America (85%), Western and Central Europe and North America (83%), and Caribbean (70%). The South-East Asia and Western Pacific ranges were selected based on the estimates for the UNAIDS Asia and the Pacific region (85%). The range for the Europe region was selected based on the estimates for Eastern Europe and Central Asia (69%) and the Western and Central Europe and North America (83%) regions. The range for the Eastern Mediterranean region was selected based on the estimate for the UNAIDS Middle East and North Africa region (76%).

Table S3: Model fitting outcomes

Outcome	Africa	Americas	South-East Asia	Europe	Western Pacific	Eastern Mediterranean	References
HSV-2 prevalence in all populations (2012)							
Overall	24.5-40.0%	10.2-20.5%	3.6-16.0%	4.0-12.5%	4.0-16.6%	6.2-18.0%[b]	[3]
All females	30.0-47.1%	13.7-24.6%	4.8-14.8%	5.2-17.8%	6.6-20.9%	10.0-29.4%[b]	[3]
Younger females	18.6-33.8%	5.7-11.3%	2.0-6.4%	2.7-7.8%	2.7-10.2%	7.4-21.6%[b]	[3]
Older females	38.1-56.5%	17.3-30.7%	6.2-19.1%	6.1-21.4%	8.1-25.3%	11.6-34.0%[b]	[3]
All males	19.1-32.6%	6.7-16.3%	2.4-17.0%	2.8-7.3%	1.6-12.5%	2.6-7.6%[b]	[3]
Younger males	9.3-19.0%	2.7-7.3%	1.0-10.6%	1.1-5.3%	0.6-5.2%	1.6-4.7%[b]	[3]
Older males	26.1-42.4%	8.6-20.7%	3.1-20.4%	3.4-8.1%	2.0-15.7%	3.2-9.2%[b]	[3]
HSV-2 prevalence in higher-risk populations (year)							
FSWs	52.9-75.3% (2007)	66.7-94.5% (2003)	42.2-73.9% (2006)	42.7-80.5% (2006)	45.9-71.3% (2008)	2.0-84.0% (2007)	Extended ranges based on a literature review
CFSWs	NA	1.2-47.5 (2007)	23.3-34.7% (2007)	NA	11.5-22.5% (2007)	NA	As above
Number of incident HIV infections (2015) (thousands)							
Overall	711-1247	65-99	69-161	47-135[a]	32-108[a]	7-16	Triangulation of UNAIDS estimates [4,9]
All females	437-768	31-52	33-81	18-50[a]	11-39[a]	3-8	As above
Younger females	163-438	13-24	15-38	4-12[a]	3-10[a]	1-3	As above
Older females	152-408	16-30	17-46	14-39[a]	8-29[a]	2-5	As above
All males	265-484	32-50	35-82	32-82[a]	21-72[a]	4-9	As above
Younger males	25-192	8-18	13-37	5-14[a]	4-19[a]	1-2	As above
Older males	49-361	18-38	18-51	25-77[a]	14-63[a]	3-8	As above
HIV prevalence in higher-risk groups							
FSWs (year)	34.1-39.3% (2007)	3-21% (2017)	0.2-7.7% (2007)	0-21.9% (2007)	1.4-7.1% (2007)	1-3.5% (2007)	Extended ranges based on [11]
CFSWs (year)	4.3-8.9% (2007)	NA	NA	NA	NA	NA	[6]
HIV incidence-rate ratio by HSV-2 infection status							

All females recently infected by HSV-2 (vs HSV-2 uninfected)	4.5-11.5	4.5-11.5	4.5-11.5	4.5-11.5	4.5-11.5	4.5-11.5	[8]
All females with established HSV-2 infection (vs HSV-2 uninfected)	1.8-3.4	1.8-3.4	1.8-3.4	1.8-3.4	1.8-3.4	1.8-3.4	As above
All males recently infected by HSV-2 (vs HSV-2 uninfected)	2.2-10.1	2.2-10.1	2.2-10.1	2.2-10.1	2.2-10.1	2.2-10.1	As above
All males with established HSV-2 infection (vs HSV-2 uninfected)	2.2-4.3	2.2-4.3	2.2-4.3	2.2-4.3	2.2-4.3	2.2-4.3	As above
HIV prevalence ratio by HSV-2 infection status							
All HSV-2 infected females (vs all HSV-2 uninfected females)	1.5-10	1.5-10	1.5-10	1.5-10	1.5-10	1.5-10	Based on a scoping review of published estimates (presented in figure S3)
All HSV-2 infected males (vs all HSV-2 uninfected males)	1.5-10	1.5-10	1.5-10	1.5-10	1.5-10	1.5-10	As above
ART coverage							
All females (2012)	28-44%	36-66%	21-42%	30-42%	25-44%	6-14%	[9]
All females (2017)	51-81%	47-86%	39-79%	42-59%	47-84%	12-27%	[9]
All males (2012)	21-35%	39-70%	16-33%	32-47%	18-34%	6-13%	[9]
All males (2017)	37-62%	47-86%	30-63%	42-63%	44-81%	12-25%	[9]

[a] Ranges extended in order to reflect more realistic ratios of number of incident infections by sex.

[b] Ranges extended in order to better reflect uncertainty and significantly higher HSV-2 prevalence estimates for the 1966-2003 period in this region.

2. HSV-2/HIV cofactors

There may be multiple associations between HSV-2 and HIV/ART ("cofactor effects"). However, the strength of evidence for each of these associations is variable. Thus, model results were presented for three separate scenarios: (i) a conservative scenario incorporating only the best-characterised association (for which there is strongest evidence), i.e., HSV-2 on HIV acquisition; (ii) a liberal scenario additionally incorporating an effect of HSV-2 on HIV transmission risk (for which there is weaker evidence); (iii) a fully liberal scenario additionally incorporating further associations, including modifying effects of ART (but for which the evidence may be even weaker). Tables 1 and S4 shows the parameter distributions used for each cofactor effect.

2.1. Cofactor literature search

A systematic review was available only for the effect of HSV-2 on HIV acquisition risk.[8] For the remaining associations (namely HSV-2 on HIV transmission risk, HIV on HSV-2 acquisition and transmission, efficacy of ART in reducing the per-act increase in HSV-2 acquisition risk due to HIV, efficacy of ART in reducing the per-act increase in HSV-2 transmission due to HIV, effect of HSV-2 on the efficacy of ART in reducing HIV transmission risk; Table S4), we conducted scoping reviews to parameterise these as follows. First, topic experts were consulted to identify published empirical and modelling studies which estimated the relevant cofactor effects. The references lists of these studies were also reviewed to identify additional potentially-relevant references. Empirical data were extracted as far as possible, meaning that for modelling studies, we attempted to identify the original data informing model parameters. Second, we conducted keyword PubMed searches to identify any additional, key studies. A standardised data extraction form was used; extracted information included author, publication year, title, study years, location, population characteristics (sex, age, risk population, etc.), length of follow-up, comparison groups, outcome definition, estimate measure, estimate value, and 95% confidence intervals (95%CI) or other estimate of uncertainty. This search strategy was conducted between October and December 2018.

2.2. Estimating the cofactor effect of HSV-2 on HIV acquisition risk

Estimates of the cofactor effect of HSV-2 on HIV acquisition risk, $RR_{ra}^{HIV-A,s}$, were taken from the most recent systematic review and meta-analysis of longitudinal studies comparing HIV incidence in those HSV-2-infected and those HSV-2-uninfected and reporting adjusted RR (HR, IRR or OR all pooled together; a meta-regression showed estimate measure did not influence the results).[8] A summary of the available pooled RR is given in Table S5.

Triangular distributions of $RR_{ra}^{HIV-A,s}$ were created using the pooled point estimate as the distribution mode, the first integer higher than the pooled estimate upper bound as the upper bound of the distribution, 1 as the lower bound of the distribution. These were used to fit the model on the HIV incidence rate by HSV-2 status separately among all females and all males with recent and established HSV-2 infection. We applied the pooled RR for recently-acquired HSV-2 infection for general population females to all females, but the pooled RR for recently-acquired HSV-2 infection for general population females and males combined to all males, due to only one study informing RR estimates for general population males. We applied the pooled RR for established HSV-2 infection for general population females and for general population

males to lower-risk females and males, respectively. The pooled RR for established HSV-2 infection for FSWs was used for FSWs. The pooled RR for established HSV-2 infection for MSM was used for CFSWs, as no direct RR estimate was available.

Table S4: Summary table of HIV/HSV-2 cofactor effects used in the modelling analyses for conservative, liberal and fully liberal scenarios. These scenarios reflect assumptions regarding the influence of each infection on the other infection

Cofactor parameter	Types of studies, data, and estimates	How the empirical estimates are used in the model	Best empirical estimate (95%CI) or [range]	Parameter ranges and distributions[1] used in the model	Strength of evidence and sources
Conservative and both liberal scenarios					
Cofactor effect of HSV-2 on HIV acquisition risk per sex act ($RR_{ra}^{HIV-A,s}$)	Longitudinal studies comparing HIV incidence in those HSV-2-infected and those HSV-2-uninfected reporting adjusted RR (HR, IRR or OR)	*1) Inform model parameters:* empirical adjusted RR estimates are used to define wide prior $RR_{ra}^{HIV-A,s}$ model parameter (i.e. the per-act increase in HIV acquisition risk among those infected with HSV-2 compared to those HSV-2-uninfected) *2) Inform model fit:* model estimates of the IRR for all females and all males with recent or established HSV-2 infection (4 groups) are fitted to 95%CI of the corresponding empirical adjusted RR estimates	*Recently HSV-2-infected:* All females: 7.2 (4.5-11.5) All males: 4.7 (2.2-10.1) *Established HSV-2 infection:* Lower-risk females: 2.5 (1.8-3.4) Lower-risk males: 3.1 (2.2-4.3) FSWs: 1.5 (0.8-2.7) CFSWs: 1.8 (1.5-2.2)	*For 1)* *Recently HSV-2-infected ($RR_{ra}^{HIV-A,s=2}$):* All females: T(7.2,1,12) All males: T(4.7,1,11) *Established HSV-2 infection ($RR_{ra}^{HIV-A,s=3}$):* Lower-risk females: T(2.5,1,4) Lower-risk males: T(3.1,1,5) FSWs: T(1.5,1,3) CFSWs: T(1.8,1,3) *For 2)* *Recently HSV-2-infected:* All females: [4.5-11.5] All males: [2.2-10.1] *Established HSV-2 infection:* All females: [1.8-3.4] All males: [2.2-4.3]	Strong: based on direct HIV incidence data from systematic review of 55 studies – estimates available by sex and risk group;[8] see section 2.2
Liberal and fully liberal scenarios only					
Cofactor effect of HSV-2 on HIV transmission risk per sex act ($RR^{HIV-T,\tilde{s}}$)	(A) Longitudinal studies comparing HIV incidence in partners of those HIV-HSV-2 co-infected and partners of those HIV-infected but HSV-2-uninfected,	*Inform model parameter:* A summary RR estimate, based on empirical studies, is used to define plausible parameter ranges for increases in per-act transmission risk $RR^{HIV-T,\tilde{s}}$ (i.e. increase in	1.33 (range 1.00-1.93)	All females and males ($RR^{HIV-T,\tilde{s}}$): T(1.33,1,1.93)	Medium: indirect evidence from biological data from epidemiological studies; see section 2.3

Cofactor parameter	Types of studies, data, and estimates	How the empirical estimates are used in the model	Best empirical estimate (95%CI) or [range]	Parameter ranges and distributions[1] used in the model	Strength of evidence and sources
	reporting adjusted or unadjusted RR (HR, IRR or OR) (B) Cross-sectional studies reporting the HIV prevalence in partners of those HIV-HSV-2 co-infected and partners of those HIV-infected but HSV-2-uninfected, reporting adjusted or unadjusted RR (HR, IRR or OR) (C) Epidemiological studies comparing HIV plasma viral load and/or genital viral shedding in HIV-infected people who are HSV-2-infected and those who are HSV-2-uninfected, reporting adjusted RR (HR, IRR or OR)	per-act HIV transmission risk of HSV-2-infected individuals compared to HSV-2-uninfected)			
Fully liberal scenario only					
Cofactor effect of HIV on HSV-2 transmission risk per sex act ($RR^{HSV-T,\bar{I}}$)	(A) Longitudinal studies comparing HSV-2 incidence in partners of those HSV-2-HIV co-infected and partners of those who are HSV-2-infected but HIV uninfected, reporting adjusted or unadjusted RR (HR, IRR or OR) (B) Epidemiological studies comparing frequency of genital HSV-2 shedding in those HSV-2-HIV-co-infected and those HSV-2-infected but HIV uninfected, reporting adjusted RR (HR, IRR or OR)	*Inform model parameter:* the parameter $RR^{HSV-T,\bar{I}}$ reflects the average increase in per-act HSV-2 transmission risk from HIV infected individuals not on ART compared to HIV-uninfected individuals	2.55 (95%CI 1.39-4.68)	All females and males ($RR^{HSV-T,\bar{I}}$): T(2.55,1.39,4.68)	Medium: no direct evidence. Based on pooled estimate from 4 studies; but using indirect comparisons of HSV-2 shedding frequency; [63-66] see section 2.4

Cofactor parameter	Types of studies, data, and estimates	How the empirical estimates are used in the model	Best empirical estimate (95%CI) or [range]	Parameter ranges and distributions[1] used in the model	Strength of evidence and sources
Efficacy of ART in reducing the per-act increase in HSV-2 transmission risk due to HIV per sex act ($RR_{ART-T}^{HSV,\tilde{\imath}}$)	(A) Longitudinal studies comparing HSV-2 incidence in partners of those HSV-2-HIV co-infected on ART and partners of those HSV-2-HIV co-infected not on ART reporting adjusted or unadjusted RR (HR, IRR or OR) B) Epidemiological studies comparing frequency of genital HSV-2 shedding in those HSV-2-HIV co-infected on ART and those HSV-2-HIV co-infected not on ART reporting adjusted RR (HR, IRR or OR)	*Inform model parameter:* $RR_{ART-T}^{HSV,\tilde{\imath}}$ is multiplied by the cofactor $RR^{HSV-T,\tilde{\imath}}$ to obtain the increase in per-act HSV-2 transmission risk among HIV-infected individuals on ART compared to HIV-uninfected	0.58 (95%CI 0.37-0.92)	All males and females ($RR_{ART-T}^{HSV,\tilde{\imath}=3}$): T(0.58,0.37,0.92), and =1 if $\tilde{\imath} < 3$	Medium: no direct evidence. Based on pooled estimate from 4 studies; but using indirect comparisons of HSV-2 shedding frequency; [66-69] see section 2.5
Cofactor effect of HSV-2 on the efficacy of ART in reducing HIV transmission risk ($RR_{HSV/ART-T}^{HIV}$)	A) Longitudinal studies comparing HIV incidence in partners of those HSV-2-HIV co-infected on ART and partners of those HIV-infected but HSV-2-uninfected on ART reporting adjusted or unadjusted RR (HR, IRR or OR) B) Epidemiological studies comparing HIV plasma viral load and/or genital viral shedding in those HSV-2-HIV co-infected on ART and those HIV-infected but HSV-2-uninfected on ART reporting adjusted RR (HR, IRR or OR)	*Inform model parameter:* the cofactor $RR_{HSV/ART-T}^{HIV}$ is multiplied by the reduction of per-act HIV transmission risk among those HSV-2-uninfected on ART (vs HIV infected not on ART) $e\_ART_{T\_HIV}^{s=0}$ to obtain the decrease in HIV transmission risk when on ART and HSV-2-infected, compared to HIV transmission risk when not on ART	Most recent studies of type A) suggest that there is currently almost no HIV transmission when the infected partner is virally suppressed[56,70], suggesting that the rate of transmission is very low in that case, and HSV-2 attributable risk even lower. Most recent studies of type B) suggest that suppressive herpes therapy decreases HIV genital shedding among women on ART[71], and that that HSV-2 was associated with cervicovaginal HIV RNA[72], but no parameter estimate could be derived	All females and males ($RR_{HSV/ART-T}^{HIV}$): U(0.95-1)	Weak/medium, see section 2.6
Not modelled					

Cofactor parameter	Types of studies, data, and estimates	How the empirical estimates are used in the model	Best empirical estimate (95%CI) or [range]	Parameter ranges and distributions[1] used in the model	Strength of evidence and sources
Cofactor effect of HIV on HSV-2 acquisition risk per sex act	Longitudinal studies comparing HSV-2 incidence in those HIV infected and those HIV uninfected reporting adjusted or unadjusted RR (HR, IRR or OR)	--	1.77 (95%CI 0.91-3.45)[43]	Omitted from model due to limited evidence	Poor: only 1 relevant study identified; see section 2.7
Efficacy of ART in reducing the per-act increase in HSV-2 acquisition risk due to HIV per sex act	Longitudinal studies comparing HSV-2 incidence in those HIV infected on ART and those HIV infected not on ART reporting adjusted or unadjusted RR (HR, IRR or OR)	--	0.73 (95%CI 0.41-1.32)	Omitted from model due to limited evidence	Poor: only 1 relevant study identified; see section 2.8

95%CI = 95% confidence interval; ART = antiretrovial therapy; CFSWs = clients of female sex workers; FSWs = female sex workers; HR = hazard ratio; IRR = incidence rate ratio; OR = odds ratio; P = peak value; PVL = plasma viral load; RR = risk ratio. [1]Distributions of parameter ranges were used to generate model 95% credible intervals using the following distributions according to parameter type: U = uniform distribution; T = triangular distribution. For triangular distributions, the mode is indicated by the first value.

Table S5: Pooled relative risk (RR) estimates of HIV acquisition attributable to HSV-2 infection and number of studies informing RR estimate, by time since HSV-2 infection, risk population, and sex[7,8].

Population	Established HSV-2 infection		Recently-acquired HSV-2 infection	
	No. of studies informing RR estimate	Pooled adjusted RR (95%CI)	No. of studies informing RR estimate	Pooled adjusted RR (95%CI)
General population[1]	22	2.7 (2.2-3.4)	6	4.7 (2.2-10.1)
o Females only	11	2.5 (1.8-3.4)	5	7.2 (4.5-11.5)
o Males only	10	3.1 (2.2-4.3)	1	1.1 (0.4-3.1)
o Both sexes	1	8.7 (1.1-67.2)	--	--
MSM[2]	7	1.8 (1.5-2.2)	1	2.8 (0.8-9.9)
FSWs[3]	7	1.5 (0.8-2.7)	1	3.0 (1.6-5.3)
Other higher-risk[4,5] - Females and/or males	11	Pooling not performed[6]	--	--

[1]All studies were in Africa. [2]Four of the studies informing the RR estimate for established HSV-2 infection were in the Americas, and one each in South-East Asia, Western Pacific and World (more than one WHO region). The one study informing the RR estimate for recently-acquired HSV-2 infection was in the Americas. [3]Six of the studies informing the RR estimate for established HSV-2 infection were in Africa, and one in South-East Asia. The one study informing the RR estimate for recently-acquired HSV-2 infection was in Africa. [4]Higher-risk populations were female bar, hotel, and food and recreational facility workers, serodiscordant couples, male trucking company employees, male military conscripts, attendees of STI clinics, and women reported as being "high-risk". [5]Six of the studies informing the RR estimate for established HSV-2 infection were in the Americas, four in South-East Asia, and one in Western Pacific. [6]Range of individual study estimates 0.5 (0.2-1.1) to 4.3 (1.5-12.4).

2.3. Estimating the cofactor effect of HSV-2 on HIV transmission risk

The model required the cofactor effect of HSV-2 on HIV transmission risk, $RR^{HIV-T,\tilde{s}}$, to be expressed in terms of an average effect per sex act regardless of symptoms. A number of different empirical evidence sources could potentially inform this parameter: 1) discordant couple studies which estimate relative risk per sex act or incidence rate ratios, 2) cross-sectional studies which estimate relative risk per partner, and 3) studies comparing HIV viral load (either genital shedding or plasma viral load (PVL)) between HSV-2-infected and -uninfected individuals, which can be used to derive relative risk per sex act. Per act estimates tend to report relative risk of HIV transmission where the HIV-transmitting individual (the index case) has symptomatic HSV-2 infection, or GUD from any cause, while per partner estimates tend to report relative risk for HSV-2 infection over a longer time period, which likely covered periods of both symptomatic and asymptomatic HSV-2 infection for the index case.

2.3.1. Estimates from discordant couple studies

We did not identify any published studies which estimated an *average* per act RR of the effect of HSV-2 on HIV transmission risk, $RR^{HIV-T,\tilde{s}}$. In an HIV discordant couple study in Rakai, Uganda, Gray *et al.* [73] reported a per act adjusted RR for genital ulcer disease (GUD) due to any cause of 2.58 (95%CI 1.03-5.69) which we assumed was the same as that for symptomatic HSV-2, RR_{symp}^{HIV-T}. The same study found no evidence of increased HIV transmission among all those HSV-2-infected. This suggests that the cofactor effect per sex act during asymptomatic periods of HSV-2 infection, RR_{asymp}^{HIV-T}, is 1.00.

The average per sex act cofactor effect can be expressed as an average of these two values as follows:

$$RR^{HIV-T,\tilde{s}} = (1-\xi_D)RR_{asymp}^{HIV-T} + \xi_D RR_{symp}^{HIV-T} \quad \text{(equation 25)}$$

where ξ_D is the proportion of time with HSV-2 symptomatic recurrences among HIV-infected/HSV-2-infected individuals, averaged across all HIV stages. We used an estimate for ξ_D of 14.5% (95%CI 9.6-19.9%) (Table S6). Using equation 25 and estimates of RR_{symp}^{HIV-T} and RR_{asymp}^{HIV-T} informed by Gray *et al.*, our estimate for $RR^{HIV-T,\tilde{s}}$ using discordant couple data is **1.23 (range 1.00-1.93)**.

Table S6: Parameter inputs informing calculation of the per sex act cofactor effect of HSV-2 on HIV transmission risk

Parameter	Value (range)	Source
ξ_D	14.5% (9.6-19.9%)	Proportion of time with GUD during HSV-2 infection (HIV-infected/HSV-2-infected individuals)*
p	0.0038 (0.0013-0.0110)	Boily *et al.* 2009[74]
τ_P	18 months (12-36)	Gray *et al.* 2001[73]
n	8.9 acts/month (7.0-10.5)	Gray *et al.* 2001[73]

*Duration of primary HSV-2 episodes reported by Benedetti *et al.* was <19 days (n=182), 20-34 days (n= 124) and ≥35 days (n=20).[75] Assuming a mean for the <19 days category of 10 days, and that for the ≥35 days category as 40 days, the average duration of primary HSV-2 episodes is 18.3 days. Cheong *et al.* 1990 reported a mean duration of primary HSV-2 infection of 14.1 days (13.9 days for women, 15.5 days in men) among 54 patients.[76] Corey *et al.* 1983 reported a mean duration of 19.0 days among 268 patients. [77] The average of these, weighted for sample size, is 18.2 days. With no standard deviations or standard errors provided by the studies, we calculated the standard error of the Benedetti *et al.* 1994 data with our assumed category midpoints (=9.8) and used this to infer the 95% confidence interval for our estimate as 17.2-19.3 days. We have used estimates of proportion of time with symptomatic recurrence during HSV-2 infection, while dually infected with HIV, from Freeman *et al.* 2007,[78] based on duration of HSV-2 stages: 2 years, latent phase: 10 years, late latent phase: rest of life; early latent phase ulcer recurrence average every 2.5 months for men, 3 months for women; latent phase ulcer recurrence average every 6 months for men, 8 months for women; no ulcer recurrence during late latent phase. Duration of recurrent ulcers: average 1 week. Freeman *et al.* assumed frequency and duration of ulcerative recurrences are each quadrupled during symptomatic and AIDS HIV stages. Our range for proportion of time with symptomatic HSV-2 recurrences is produced by varying this -fold increase between 3 and 5.

2.3.2. Estimates from cross-sectional studies

Latif *et al.*[79] reported that men with a history of GUD (again, not specifically HSV-2) were significantly more likely to have a wife who was seropositive for HIV-1 (RR 1.94; 95%CI 1.62-15.13). If we assume that this RR reflects the cofactor effect for HSV-2-mediated GUD then this can be used to calculate an alternative estimate for $RR^{HIV-T,\tilde{s}}$, by using assumptions regarding the number of sex acts per partnership and the HIV transmission probability per partnership.

$RR^{HIV-T,partner}$ can be expressed as: $RR^{HIV-T,partner} = \frac{q_1}{q_0}$ (equation 26)

where q_0 represents the HIV transmission probability per partnership for HIV-infected/HSV-2-uninfected index partners: $q_0 = 1-(1-p)^{n\tau_P}$ (equation 27)

where p = average HIV transmission probability per sex act for HIV-infected/HSV-2-uninfected index partners, τ_P = a representative follow-up duration of HIV discordant couples (months), n = average coital frequency (acts/month), and q_1 represents the HIV transmission

probability per partnership for HIV-infected/HSV-2 positive index partners:

$$q_1 = 1 - \left(1 - RR_{asymp}^{HIV-T} \times p\right)^{(1-\xi_D)n\tau_P}\left(1 - RR_{symp}^{HIV-T} \times p\right)^{\xi_D n\tau_P} \quad \text{(equation 28)}$$

Substituting in equations (26) to (28) the $RR^{HIV-T,partner}$ value informed by Latif *et al.*[79] and assuming that the cofactor effect of HSV-2 during asymptomatic HSV-2 periods is zero (RR_{asymp}^{HIV-T}=1) an alternative, much higher estimate for RR_{symp}^{HIV-T} is 18.0 (range 1.0-175.1). Substituting this into equation (25) produces an alternative estimate for $RR^{HIV-T,\tilde{s}}$ using cross-sectional data of **3.47 (range 1.01-26.2).**

2.3.3. Estimates from HIV viral load studies

HSV-2 suppression trials have resulted in mean 0.3-0.5 $\log_{10}$ decreases in HIV plasma viral load (PVL) with acyclovir or valacyclovir treatment, with the exception of a small study (n=32) which found a larger reduction (-1.23 log10 copies/ml) and a null finding recorded by Tanton *et al.* 2010[80] (**Table S7**). The meta-analytic summary estimate for these studies is a PVL reduction of 0.40 $\log_{10}$ copies/mL (95%CI 0.28-0.51) with HSV-2 suppressive therapy.[81]

This difference in HIV PVL can be translated into the per act cofactor effect using the relationship between PVL and HIV transmission probability per sex act defined by Quinn *et al.*[82]: each $\log_{10}$ increase in PVL is associated with a 2.45-fold increase in per act HIV transmission risk:

$$RR^{HIV-T,\tilde{s}} = \frac{p^{HSV,\tilde{s}}}{p} = 2.45^{log_{10}(V^{HSV,\tilde{s}}/V)} \quad \text{(equation 29)}$$

where $p^{HSV,\tilde{s}}$ is the average HIV transmission probability per sex act for HIV-infected/HSV-2-infected index partners, V the HIV PVL of HIV-infected/HSV-2-uninfected individuals, $V^{HSV,\tilde{s}}$ the HIV PVL of HIV-infected/HSV-2-infected individuals. This formula gives an $RR^{HIV-T,\tilde{s}}$ of **1.43 (1.29-1.58)**. It is important to note that this might be an underestimate since 1) HSV-2 treatment does not fully suppress the effect of HSV-2 on HIV, and 2) its effect is larger at the genital tract than at the systemic level. While several studies have evaluated the impact of HSV-2 infection on genital HIV, there are no data available analogous to Quinn *et al.*[82] which relate genital HIV measurements to transmission risk.

Table S7: Summary of studies examining the effect of HSV-2 suppressive therapy on HIV PVL.

Study	Therapy	N	PVL difference (log10 copies/ml)
Celum 2010[83]	ACV	3302	-0.25 (-0.29, -0.22)
Tanton 2010[80]	ACV	419	0.02 (-0.09, 0.13)
Delany 2009[84]	ACV	288	-0.27 (-0.41, -0.13)
Reynolds 2011*[85]	ACV	440	-0.46 (-0.51, -0.42)
Dunne 2008[86]	ACV	128	-0.43 (-0.56, -0.02)
Schacker 2002[87]	ACV	12	-0.28 (-0.54, -0.19)
Baeten 2008[88]	VAL	20	-0.26 (-0.33, -0.23)
Zuckerman 2007[89]	VAL	20	-0.33 (-0.42, -0.35)
Nagot 2007[90]	VAL	136	-0.53 (-0.72, -0.32)
Roxby 2011*[91]	VAL	148	-0.40 (-0.50, -0.21)

Petri 2011*[92]	VAL	24	-0.40 (-0.64, -1.07)
Mugwanya 2011[93]	VAL	32	-1.23 (-1.38, -0.28)

Data taken from Barnabas and Celum 2012.[81] *Conference abstract only. ACV – acyclovir; PVL – HIV plasma viral load; VAL – valacyclovir.

2.3.4. Combining evidence

All three methods for estimating $RR^{HIV-T,\tilde{s}}$ are subject to limitations and biases. However, the method based on cross-sectional data requires data from the largest number of data sources and therefore has the greatest degree of uncertainty, and produces an unrealistically high cofactor estimate. We therefore used the midpoint of the estimates from the remaining two methods for the distribution mode and the widest range for the lower and upper bounds, i.e. **1.33 (range 1.00-1.93)**, and assumed a triangular distribution.

2.4. Estimating the cofactor effect of HIV on HSV-2 transmission risk

For the effect of HIV on HSV-2 transmission risk, $RR^{HSV-T,\tilde{\imath}}$, we did not find any cross-sectional studies of HSV-2 transmission among discordant couple. We did identify studies the effect of HIV on HSV-2 shedding and on HSV-2 viral load. Here, we considered the frequency of HSV-2 shedding (which is irrespective of viral load) as the best proxy for HSV-2 transmission risk, assuming increases in shedding with HIV status translate into the same effect on transmission risk. In the original treatment to prevent transmission clinical trial for HSV-2,[94] the reduction in HSV-2 shedding was greater than the reduction in acquisition, however there was considerable overlap between the two estimates.

We found four longitudinal studies comparing the frequency of HSV-2 genital shedding in those HIV-infected and HIV-uninfected. The first, among women and men in Uganda, found an unadjusted RR of 1.4 (95%CI 0.9-2.1) for the proportion of days with HSV-2 shedding among those HIV-infected versus HIV-uninfected, based on anogenital swabbing three times daily for six weeks.[64] The second, among women in the US, found an OR of 4.1 (95%CI 1.0-27.4) which seems to be an adjusted OR.[63] This OR compared point prevalence of HSV-2 shedding from vulvar and cervical specimens among those HIV-infected versus HIV-uninfected. The third study, among MSM in the US, found an OR of 3.3 (95%CI 1.1-9.9), which also seems to be adjusted.[65] This OR compared proportion of days with HSV-2 shedding among those HIV-infected versus HIV-uninfected, based on swabbing of the penile shaft, urethra and rectum four times daily for 60 days. A fourth study, among women in the placebo group of two randomised controlled trials of HSV-2 suppressive therapy in Burkina Faso, reported on the percentage of days with HSV-2 shedding in those HIV-uninfected (11/253; 4.3%) versus HIV-infected (comparison is those not on HAART; 119/767; 15.5%).[66] We calculated the RR from (119/767)/(11/253) = 3.57, standard error of the log RR = sqrt(1/exposed cases - 1/N exposed + 1/unexposed cases - 1/N unexposed) = sqrt((1/119) - (1/767) + (1/11) - (1/253)) and error factor (ER) = exp (1.96 * standard error of the log RR) giving an unadjusted RR=3.57 (95%CI 1.96-6.51) using 95%CI (RR) = RR/EF to RR*EF. Log estimates of these 4 estimates were pooled in Stata using the 'metan' command and calculating the standard error of the log RR from (ln(UCB)-ln(LCB))/(2*1.96) where UCB and LCB are the upper and lower confidence bounds, respectively, and exponentiating the pooled log RR to obtain the pooled RR of **2.55 (95%CI 1.39-4.68)**. These were used as the mode, lower and

upper bounds, respectively, of a triangular distribution and assuming these estimates are applied at the per-act level.

2.5. Estimating the efficacy of ART in reducing the per-act increase in HSV-2 transmission risk

For the modifying effect of ART on HSV-2 transmission risk per sex act RR_{ART-T}^{HSV}, we did not find any studies of HSV-2 transmission, so, as for the cofactor effect of HIV on HSV-2 transmission risk, we used an indirect method to estimate this cofactor effect based on frequency of HSV-2 shedding comparisons, and again assuming this translates into the same effect on transmission risk. We found four longitudinal studies of frequency of HSV-2 genital shedding in those HIV-infected on ART versus those HIV-infected not on ART. The first was among high-risk women in Burkina Faso and measured the proportion of visits on which HSV-2 was present, based on cervicovaginal swabs.[67] This study had a follow-up visit frequency of 3-6 months, and an adjusted OR of 0.34 (95%CI 0.2-0.6) was found. The second study, among women and men in Canada, and based on daily swabbing for both HSV-1 and HSV-2 for 28 days found an adjusted OR of 1.05 (95%CI 0.43-2.58) based on the proportion of days with HSV shedding[68]. The third study, among women in the placebo group of two randomised controlled trials of HSV suppressive therapy in Burkina Faso, had data on the percentage of days with HSV-2 shedding in those HIV-infected on HAART and those not on HAART, finding an adjusted RR comparing those on HAART to those not on HAART and CD4 cell count > or = to 500 cells/μl of adjusted RR of 0.95 (95%CI 0.52-1.73)[66]. The fourth, among women and men in the US, and based on daily swabbing for at least 45 consecutive days, found an adjusted OR 0.35 (95%CI 0.22-0.56) based on the proportion of days with HSV-2 shedding.[69]

We also found data from a study among women and men in the US which measured proportion of days with HSV-1 or HSV-2 shedding based on daily samples of genital secretions for at least 30 consecutive days, and found a RR of 0.72 (95%CI 0.47-1.1).[95] We did not use the data from this study due to the age of the study: at that time, those initiating ART had low CD4 counts, meaning their chance of having HSV-2 shedding and GUD were greater than those not on ART (not withstanding any effect of ART itself). We also found one study which only reported data on HSV-2 shedding among those initiating ART, which showed an increase in HSV-2 shedding with ART.[96] We did not use the data from this study because we required RR estimates averaged for time since ART initiation: starting ART may increase the risk of IRIS-related increased HSV-2 shedding and symptomatic disease. Three other studies only looked at the association between ART use and genital ulcer disease.[38,97,98]

Log estimates were pooled in Stata using the 'metan' command and calculating the standard error of the log RR from (ln(UCB)-ln(LCB))/(2*1.96) where UCB and LCB are the upper and lower confidence bounds, respectively, and exponentiating the pooled log RR to give the pooled RR of **0.58 (95%CI 0.37-0.92)**. In the model, the parameter RR_{ART-T}^{HSV} reflecting this risk ratio was sampled with a triangular distribution, using this pooled RR and its confidence interval as distribution mode and bounds, respectively. This risk ratio was then multiplied by the cofactor $RR^{HSV-T,\tilde{\imath}}$ to obtain the increase in per-act HSV-2 transmission risk among HIV infected individuals on ART (compared to the per-act HSV-2 transmission risk among HIV-uninfected).

2.6. Estimating the cofactor effect of HSV-2 on ART on HIV transmission risk

Here, RRs reported by studies comparing HIV incidence in partners of those HSV-2-infected on ART and partners of those HSV-2-uninfected on ART could be used, or RRs reported by studies comparing HIV plasma viral load and/or genital viral shedding in those HSV-2-infected on ART and those HSV-2-uninfected. Two studies conducted in Burkina Faso found an increased quantity of genital HIV-1 RNA among women on ART who were HSV-2-infected (versus HSV-2-uninfected),[72] and that suppressive herpes therapy was associated with lower HIV shedding and less genital HIV RNA among women on ART,[71] suggesting that HSV-2 infection could increase the occurrence of HIV transmissions among those on ART. None of these publications could directly provide a ready estimate of the decrease in per-act HIV transmission risk when on ART and HSV-2-infected (compared to on ART and HSV-2-uninfected). However, more recent studies suggest that there is currently almost no HIV transmission when the infected partner on ART is virally suppressed,[56,70] suggesting that the current rate of breakthrough HIV infection is very low, and the risk of breakthrough HIV infection attributable to HSV-2 is even lower. Whilst differences in HIV shedding among PLHIV on ART by HSV-2 infection status could simply reflect the overall effect of HSV-2 on HIV transmission risk, another recent study conducted among PLHIV with ART treatment failure suggested that HSV-2 may lead to selection of HIV resistant variants (either in genital tract or plasma) and subsequent ART failure[99], but this study had important methodological limitations. The study was cross-sectional, only included patients already with treatment failure, the prevalence of HSV-2 (30%) was much lower than expected in such HIV population, and several confounders such as other STI's or vaginal flora were not measured. Based on this lack of evidence, we only included this cofactor to measure the population-level impact of this hypothetical effect and assumed that the maximum possible impact of HSV-2 on the ART efficacy in reducing HIV transmission would be to reduce it by a relative 5%. In the model, the parameter $RR^{HIV}_{HSV/ART-T}$, was multiplied by the per-act efficacy of ART in reducing the HIV transmission risk (among those HSV-2-uninfected) $e\_ART^{s=0}_{T\_HIV}$ to obtain the decrease in per-act HIV transmission risk when on ART and HSV-2-infected, compared to the per-act HIV transmission risk of those not on ART.

2.7. Estimating the cofactor effect of HIV on HSV-2 acquisition risk

For the effect of HIV on HSV-2 acquisition risk, RRs reported by studies comparing HSV-2 acquisition in HIV-infected and HIV-uninfected individuals could be used. We only found one empirical study of HSV-2 incidence in those HIV-infected versus those HIV-uninfected within the same study (conducted among US adolescents), which reported an unadjusted OR of **1.77 (95%CI 0.91-3.45)**.[43] Based on the limited available evidence, this cofactor effect was omitted from our analyses.

2.8. Estimating the efficacy of ART in reducing the per-act increase in HSV-2 acquisition risk due to HIV

For the modifying effect of ART on HSV-2 acquisition risk, RRs reported by studies comparing HSV-2 acquisition in HIV-infected individuals on ART versus HIV-infected individuals not on ART could be used. The same study reporting HSV-2 incidence in those HIV-infected versus those HIV-uninfected, among US adolescents, reported HAART coverage (unclear whether at baseline or time of seroconversion) among HSV-2 seroconverters versus HSV-2

non-serocoverters (in a nested case control analysis).[43] This study found that 12/33 HSV-2 seroconverters and 30/63 HSV-2 non-serocoverters were on HAART. We calculated the RR from (12/42)/(21/54) = 0.73, standard error of the log RR = sqrt(1/exposed cases - 1/N exposed + 1/unexposed cases - 1/N unexposed) = sqrt((1/12) - (1/42) + (1/21) - (1/54)) and error factor (ER) = exp (1.96 * standard error of the log RR) giving an unadjusted RR of **0.73 (95%CI 0.41-1.32)** using 95%CI (RR) = RR/EF to RR*EF. There are also data from a study in French Guiana,[100] which reported HRs for the incidence of *symptomatic* genital herpes according to time since HAART initiation, compared to those not on HAART. These HRs were all greater than 1 (comparing to no HAART), with the highest HR for HAART <2 months' duration, and decreasing thereafter. The HR of 1.2 for HAART >6 months is within our range. Based on the limited available evidence, this cofactor effect was omitted from our analyses.

3. Trends in condom use and male circumcision coverage within WHO regions

3.1. Model assumptions

Based on the review hereby summarised, the model assumes a decrease in per-act HIV and HSV-2 transmission risk over time in each of the 6 WHO regions due to the combine effect of overall increase in condom use and prevalence of male circumcision. Due to the paucity of data in several regions, a time-varying sigmoidal shape parameter was used in the force of infection to reflect the combined trends in condom use and male circumcision over time, as well as their efficacy (see Methods section of this appendix). The coverage of effect of ART and viral suppression on HIV and HSV-2 risk and HIV mortality was modelled explicitly, in order to be able to apply the relevant cofactor effects.

3.2. Data summary

The condom and male circumcision trends as depicted below were primarily sourced from data from DHS[101], UNAIDS[58] and World Bank,[102] which was completed by other literature for WHO regions with scarce data. The condom use indicators available are summarized in the Table S8. The DHS only collects data on one male circumcision indicator (i.e. 'percentage of men who report being circumcised'). Condom use amongst female sex workers (FSW) was based on the indicator from UNAIDS Key Population atlas.

Data from the DHS was extracted using the 'rdhs' R package.[103] To visualise region-level trends in intervention coverage, we calculated region and sex-specific weighted trends of estimates using linear regression. Weighting across countries in a specific region was done based on the size of a country's entire population (from UNDP in 2015).

Table S8: Available indicators (Yes/No) on condom use across WHO regions in the DHS, World Bank, and UNAIDS data (green = displayed in this appendix).

REGION	Africa	South East Asia	Eastern Mediterranean	Europe	Americas	Western Pacific	Sources
Ever use of condom, by sex	Y	N	Y	N	N	N	DHS
Ever use of condom (married), by sex	Y	N	Y	N	N	N	DHS
Ever use of condom (sexually active unmarried) by sex	Y	N	N	N	N	N	DHS
Current use of condom, women (All Women)	Y	Y	Y	Y	Y	Y	DHS
Current use of condom, women (married)	Y	N	Y	N	N	N	DHS
Current use of condom, women (sexually active unmarried)	Y	N	N	N	N	N	DHS
Young (wo)men using a condom at last sexual intercourse	Y	N	N	N	N	N	DHS
Condom use at last high-risk sex (with a non-marital, non-cohabitating partner), by sex	Y	Y*	N	Y	Y	Y	DHS
Condom use during higher-risk sex (with multiple partners), by sex	Y	N	N	N	N	N	DHS
Young (wo)men using a condom during premarital sex	Y	N	N	N	N	N	DHS
Condom use at last paid sexual intercourse	Y	Y	N	Y	Y	Y	DHS
Condom use at last sex (% of total population aged 15-49)	Y	N	N	N	N	N	World Bank
Condom use amongst sex workers - where sex workers are defined as female, male and transgender adults and young people who receive money or goods in exchange for sexual services, either regularly or occasionally	Y	Y	Y	Y	Y	Y	UNAIDS key population Atlas

* Not stratified by sex; [a] Where available, data for FSW were used otherwise, data combining FSWs, MSWs and/or transgender was used

3.3. Summary of findings

Condom use: Despite the prevalence of condom-use amongst the general population as well as sex workers and their clients vary widely across different WHO regions, overall condom use appears to have increased globally between 1980 and 2018. This is confirmed by a UN report on global contraceptive use, which estimates that between 1970 and 2015 the global contraceptive prevalence has almost doubled going from 36% to 64%.[104] Condom use amongst FSW has been higher than the general population across all regions. With the lowest percentage of FSW reporting using a condom in the Eastern Mediterranean region.

Male circumcision: It is estimated that around 38% of men worldwide are currently circumcised, however this number varies widely between regions.[105] In some regions such as the Middle East, North and West Africa as well as Central Asia the practice is almost universal [106] and the prevalence of male circumcision has been consistently high over time. Regions with lower rates of circumcision have reported varying trends over time. In the European region, where male circumcision has typically remained relatively low, prevalence appears to have decreased over time. In contrast, circumcision prevalence appear to have slight increased recently in Eastern and Southern Africa, most likely reflecting recent roll out of voluntary medical male circumcision (VMMC) programs by international agencies.[107] Male circumcision prevalence has remained consistently low in America over time, except in the United States with a relatively high prevalence, which also appears to be increasing.

3.4. African region

Data availability: The estimates of condom use and circumcision were primarily based on data extracted from the DHS. Although the DHS has data on several condom use indicators, we used the indicators with the most data points available (condom use at last "high-risk sex" or among younger populations). Data on condom use among the younger population (15-24) was available from the World Bank,[108] whereas data for FSWs and clients of sex workers was extracted from the DHS and UNAIDS Key Population Atlas, respectively.[109]

Condom Use

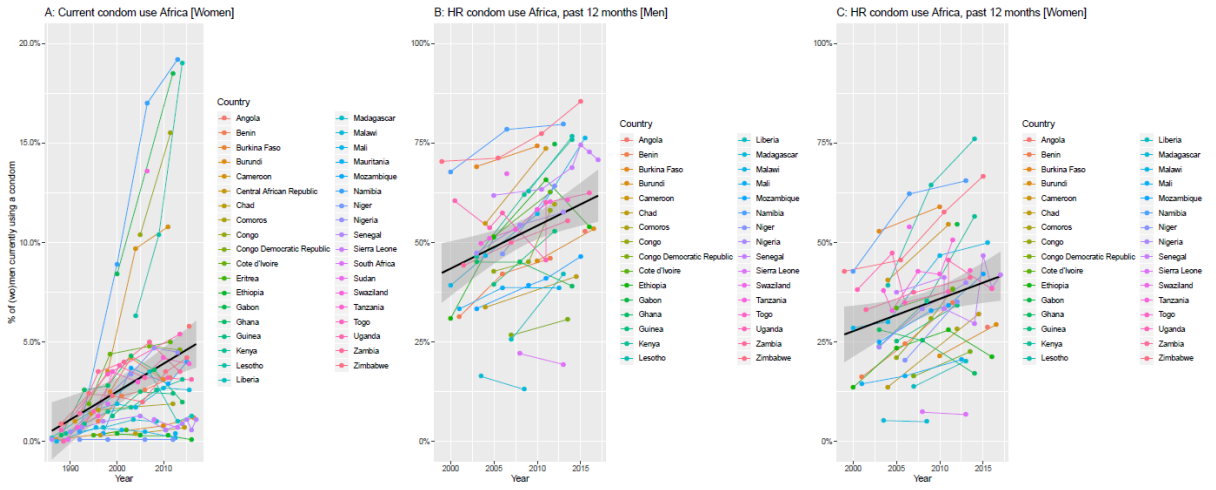


Figure S4 Summary of condom use in the African region from DHS data for : A) women who are currently using a condom (annual increase of 0.10%); Proportion reporting condom use at last high-risk sex (non-marital, non-cohabiting partner in the last 12 months) among B) women (annual increase of 0.84% C) men (annual increase of 1.04%).

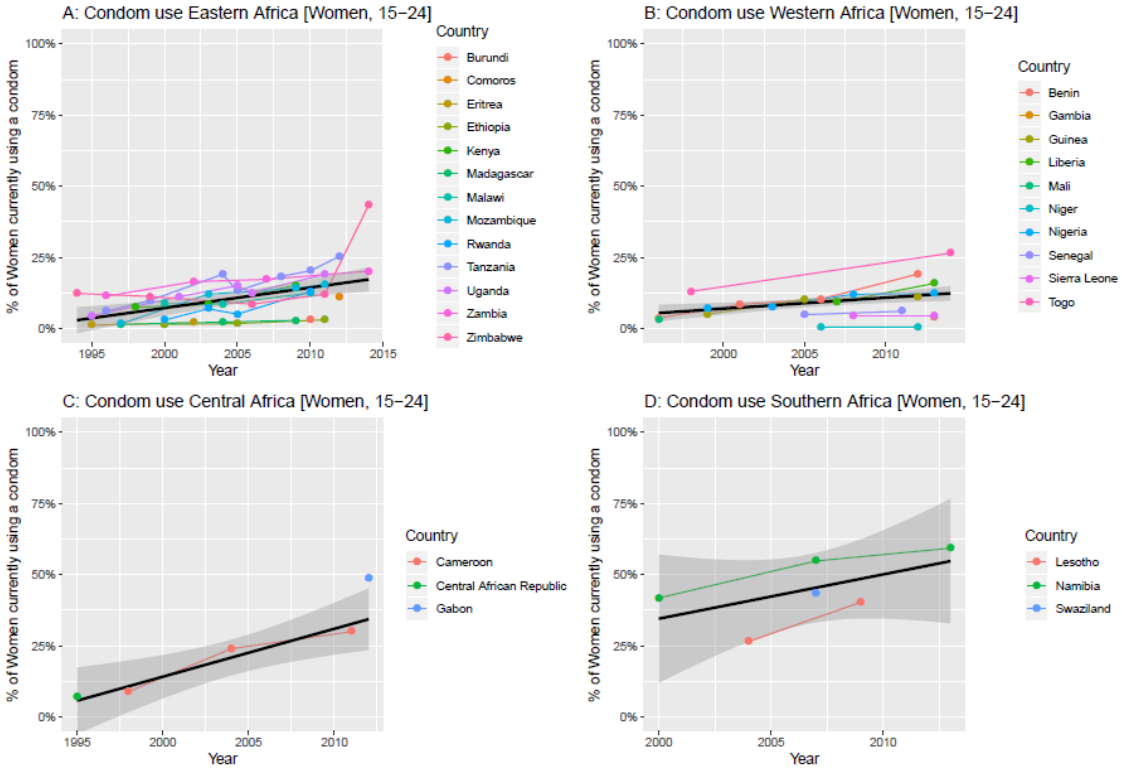


Figure S5 World Bank data on condom use at last intercourse in the past 12 months among younger women (15-24 years old), per WHO region: A) Eastern Africa (annual increase: 0.7%), B) Western Africa (annual increase: 0.4%, C) Central Africa (annual increase 1.7%), D) Southern Africa (annual increase 1.6%).

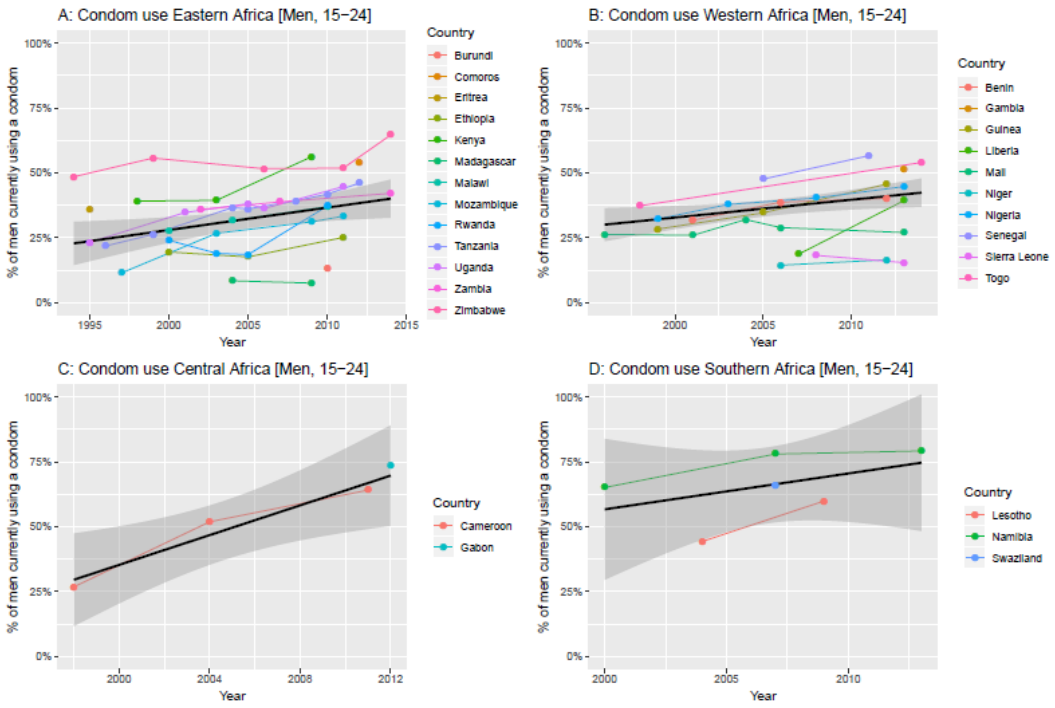


Figure S6: World Bank data on condom use at last intercourse in the past 12 months among younger men (15-24 years old), per WHO region: A) Eastern Africa (annual increase: 0.86%), B) Western Africa (annual increase: 0.68%, C) Central Africa (annual increase 2.87%), D) Southern Africa (annual increase 1.38%)

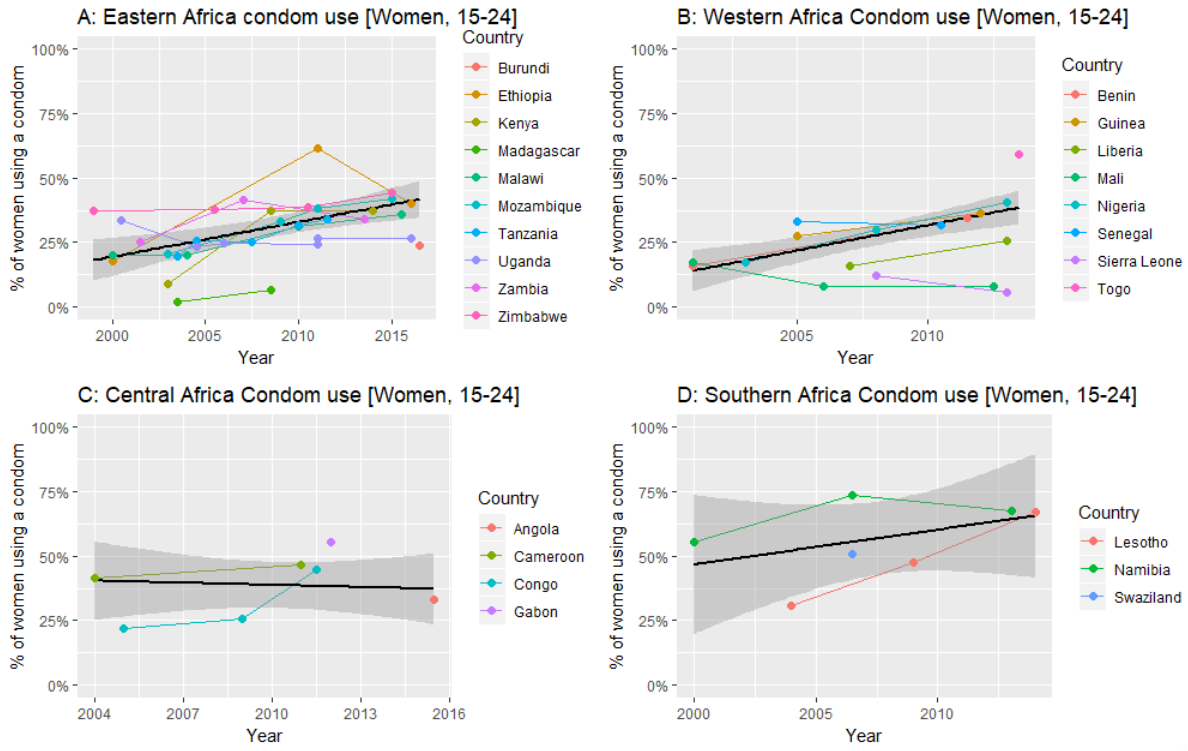


Figure S7: DHS data on condom use at last intercourse in the past 12 months among younger women (15-24), per African region: A) eastern Africa (annual increase: 1.36%), B) Western

Africa (annual increase: 1.96%, C) Central Africa (annual increase -0.28%), D) Southern Africa (annual increase 1.35%)

The DHS also collects data on the same indicator as presented in Figure S5 and S6, however with slightly different outcomes. Figure S7 shows the trend for young women (15-24) and condom use at last intercourse (among those having sex in the past 12 months) (A: 1.36%, B: 1.96%, C: -0.28%, D: 1.35%)

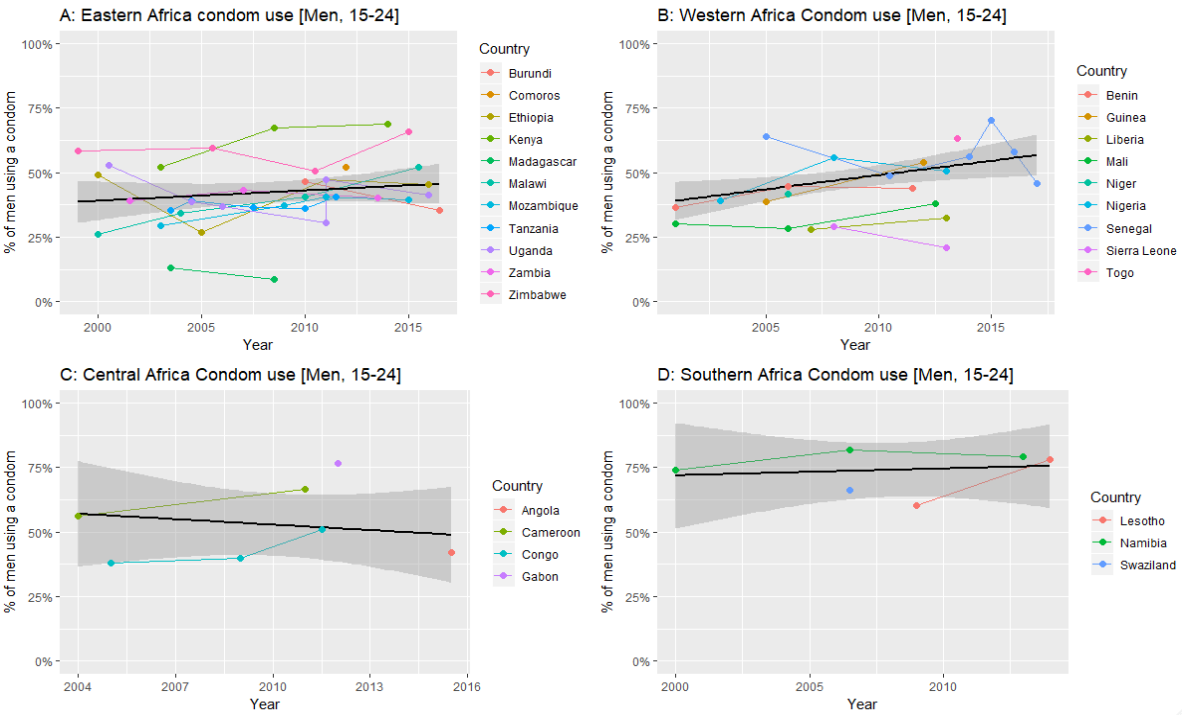


Figure S8: DHS data on condom use at last intercourse (among those having sex in the past 12 months) among younger men (15-24 years old), per African region: A) eastern Africa (annual increase: 0.4%), B) Western Africa (annual increase: 1.11%, C) Central Africa (annual increase -0.07%), D) Southern Africa (annual increase 0.26%)

Condom use amongst FSW and clients of FSW

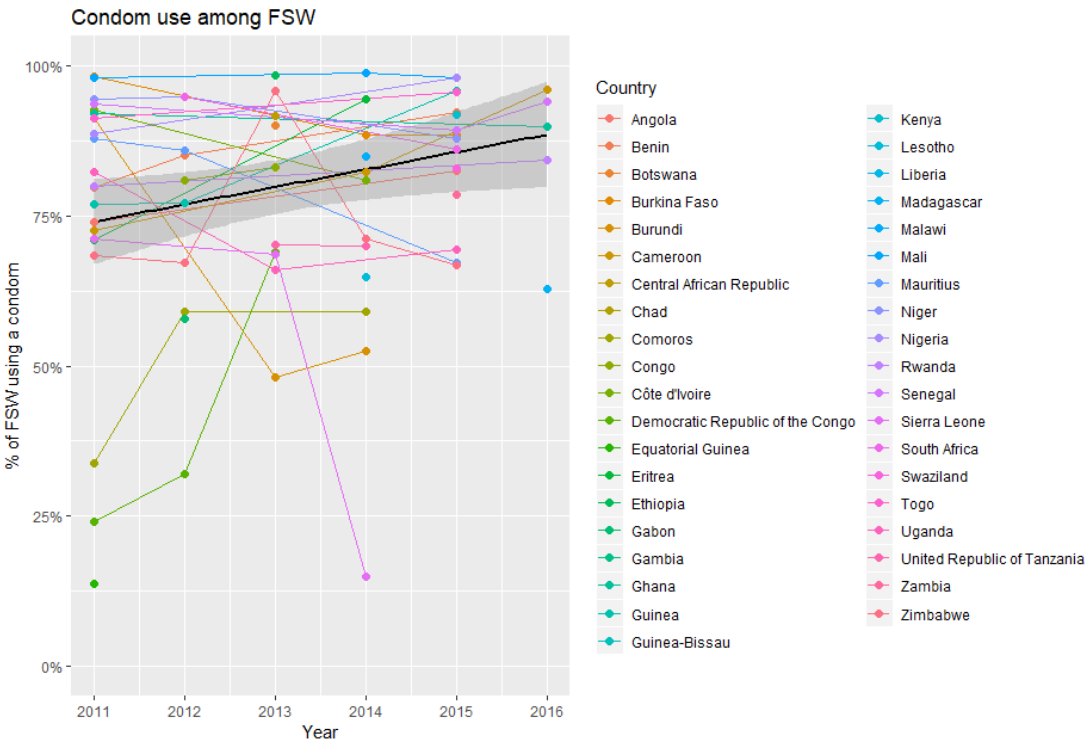


Figure S9: Percentage of FSW reporting using a condom during their last commercial sex act WHO African region from the UNAIDS Key Population Atlas (annual increase: 2.91%)

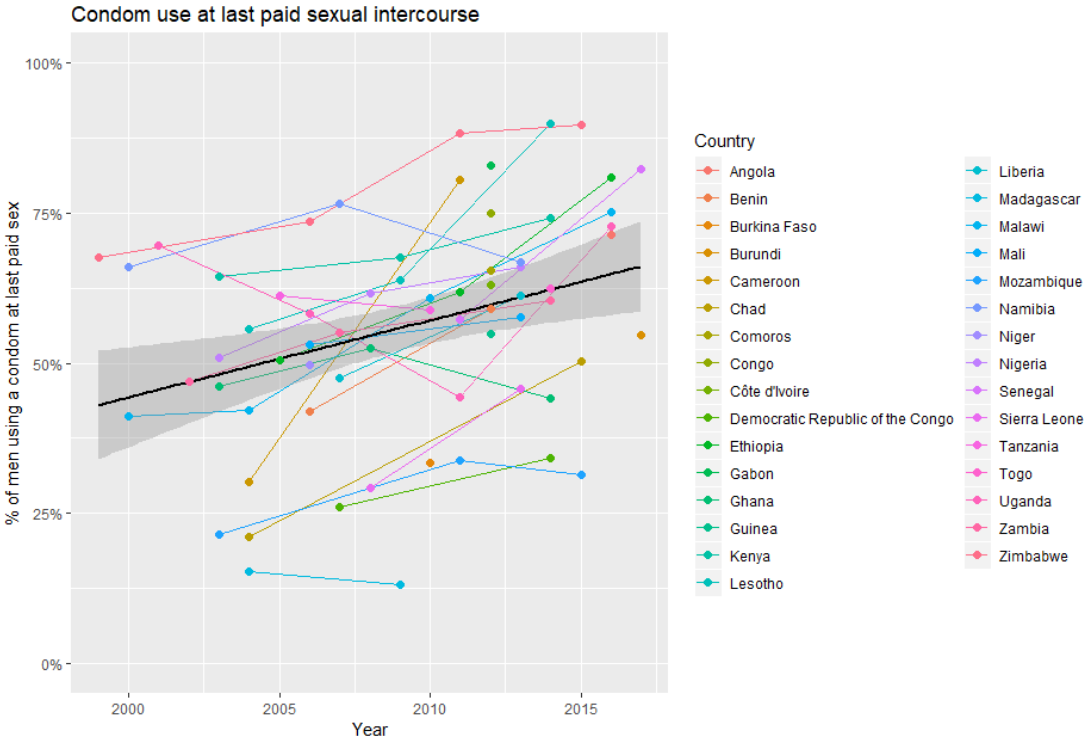


Figure S10: DHS data on condom use at last paid sex (amongst men who paid for sex in the last 12 months) in WHO African region (annual increase: 1.28%).

Male Circumcision

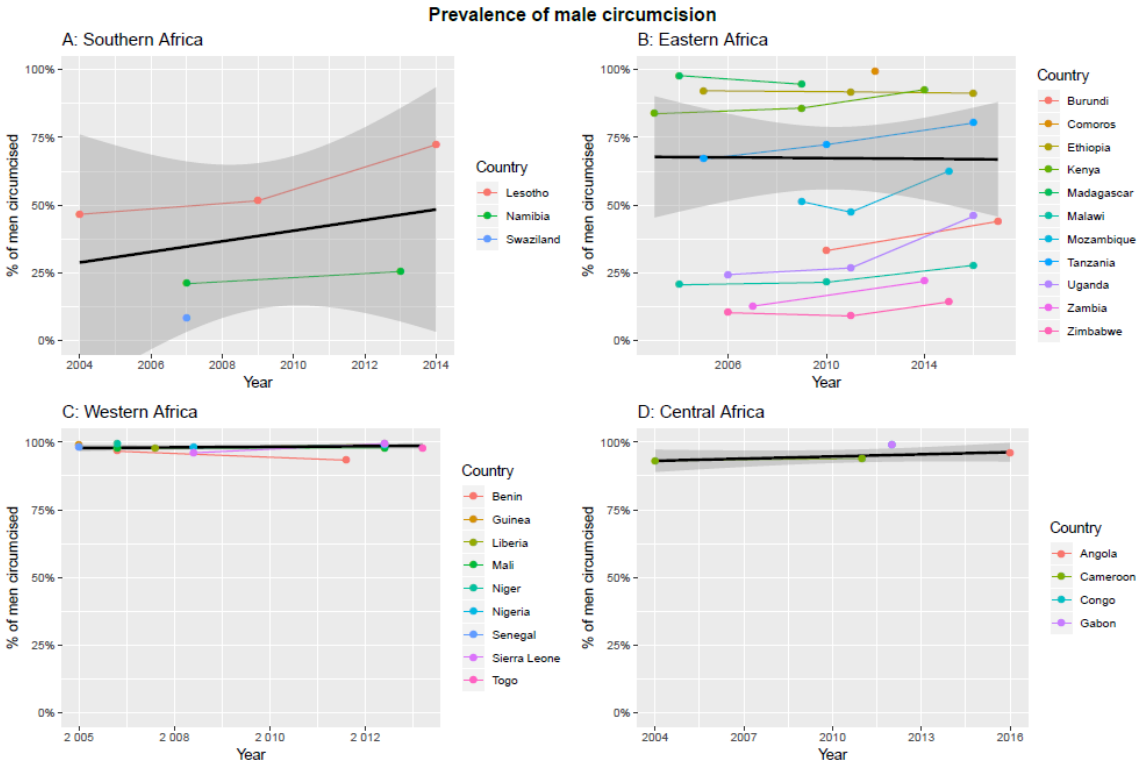


Figure S11: DHS data on variation in prevalence of male circumcision across WHO African region over time: A) Southern Africa (lower, increasing) , B) Eastern Africa (lower, stable), C) Western Africa (high, stable) , D) Central Africa (high, stable). However, male circumcision has increased further in recent year following efforts to scale up male circumcision as a preventive intervention following results of three clinical trials demonstrating that it reduces HIV acquisition risk.[110]

3.5. Americas region

Data availability: Condom use information for WHO America region was primarly based on the DHS data on 3 indicators. Data on condom use amongst FSW was taken from the UNAIDS Key Population Atlas. As t no DHS data was available for large countries within the region (e.g. Brazil and the United States), a literature search was conducted to confirm that the trends from the DHS were applicable to the rest of the region.

Condom use

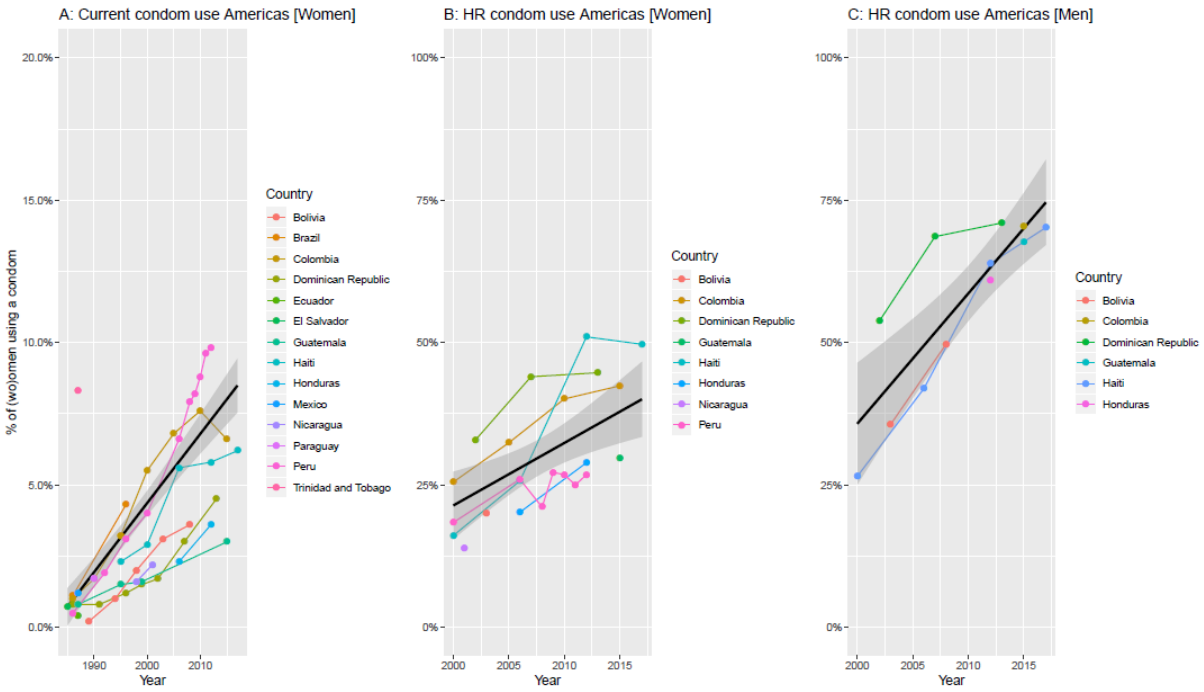


Figure S12 Summary of condom use in the America region from DHS data for : A) women who are currently using a condom (annual increase of 0.24%); Proportion reporting condom use at last high-risk sex (non-marital, non-cohabiting partner in the last 12 months) among B) women (annual increase of 1.1%, C) men (annual increase 2.3%).

Additional data: Complementary literature search also suggested upward trends for countries not covered by the DHSs. For example, one study in Brazil found a 2% yearly increase in condom use between 1998 and 2005, one study conducted in the USA found a 0.5% yearly increase in condom use between 1982 and 1995,[111] another study in the USA found an increase in condom use among 15-44 years old from 12.0% of in 1982 to 20.4% in 1995.[112] Similarly, a study conducted among high school students in the USA reported substantial increases in condom use between 1991 and 2001: 38% women reported condom use at last sex in 1991 compared to 51.3% in 2001, men reported 54.5% and 65.1%, respectively.[113] The National Health Statistics Report in the US reported that between 2011 and 2015, 23.8% of women aged 15-44 used a condom at last sexual intercourse in the past 12 months, this was 33.7% for men which had increased from 29.5% since 2002.[114]

Condom use amongst FSW and clients of FSW

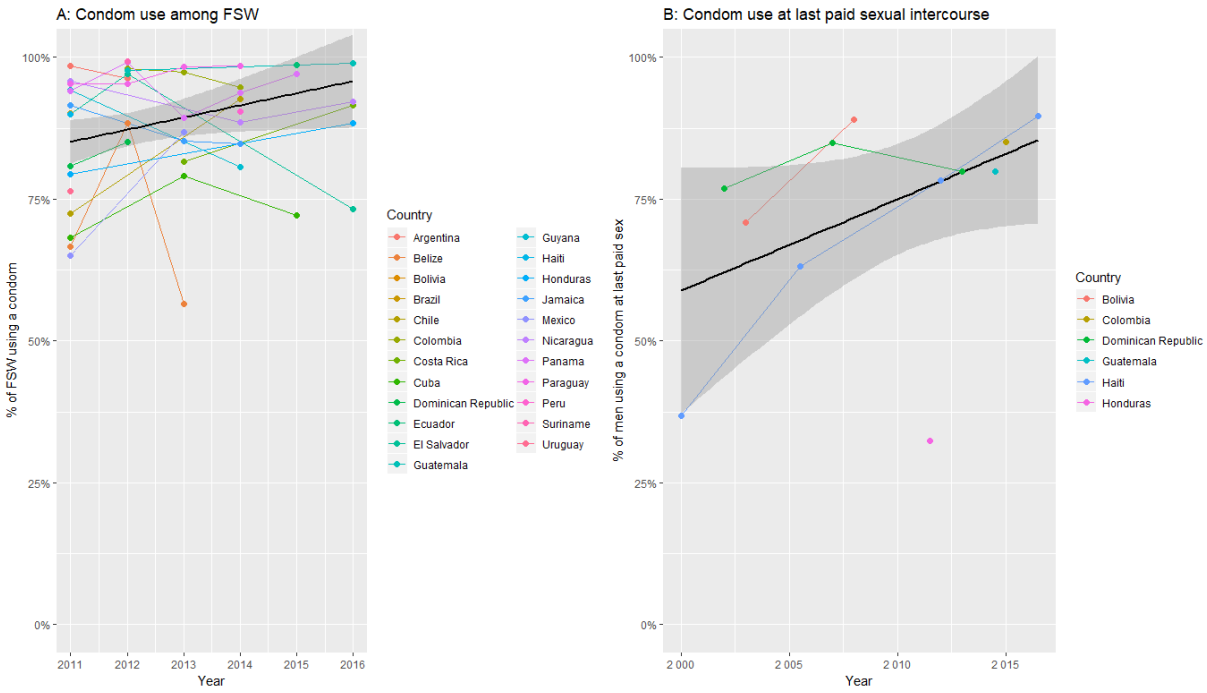


Figure S13: Percentage of FSW reporting using a condom during their last commercial act (A, annual increase2.14%) and condom use during last paid sex (amongst men who paid for sex in the last 12 months) (B, annual increase 1.61%) in WHO America region from the UNAIDS Key Population Atlas and DHS, respectively

Circumcision

DHS data on circumcision over time was only available for the Dominican Republic and Haiti, two countries with relatively small population sizes, compare to countries such as Brazil or the USA. Nevertheless, overall circumcision rates in the Americas region are relatively low compared to other regions (about 27%).[107] Less than 2% of men in Brazil are circumcised [105] whereas the USA is the only country with higher coverage (80% in 2010) following an slight overall 2.5% increase between 1999 and 2010.[115]

3.6. European region

Data availability: The DHS provided some but limited information on the same three condom and circumcision indicators as for other regions. Therefore, a literature search was conducted to confirm whether the trends found on the basis of the DHS data were representative of the rest of this WHO region. We did not find direct estimates of condom use amongst clients of FSW in Europe.

Condom use

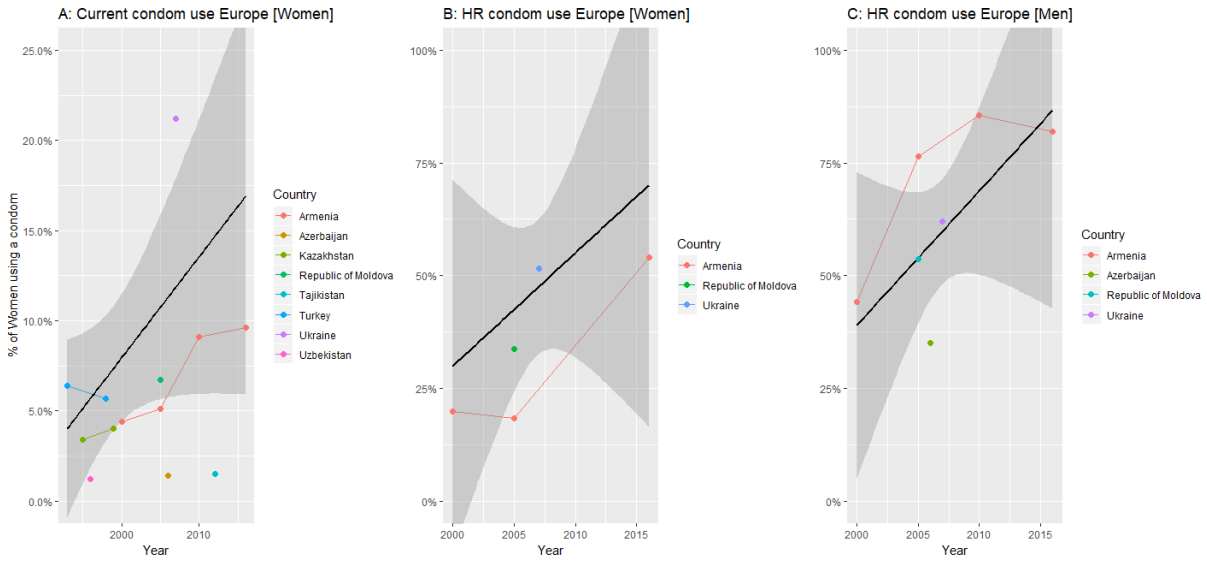


Figure S14: Summary of condom use in the Europe region from DHS data for : A) women who are currently using a condom (annual increase of 0.%); Summary of condom use in the European region from DHS data for : A) women who are currently using a condom (annual increase of 0.10%); Proportion reporting condom use at last high-risk sex (non-marital, non-cohabiting partner in the last 12 months) among B) women (annual increase of %, C) men (annual increase %). *Note that the upward trends largely based on the data points available for Armenia.*

Additional data: As the DHS does not include data on Western European countries, we searched the literature. A UN report showed that 69.2% of women in the European region, who were married or in-union between the ages of 15 and 49, reported using a contraception method, 16.7% of whom reported using condoms in 2015 compared to 9.7% in 1994, suggesting an average annual increase of 0.2%.[104] This increase was slightly more for Eastern and Southern Europe (from 10% and 13.9% in 1994 to 16.7% and 20.6% in 2015, respectively).[104]

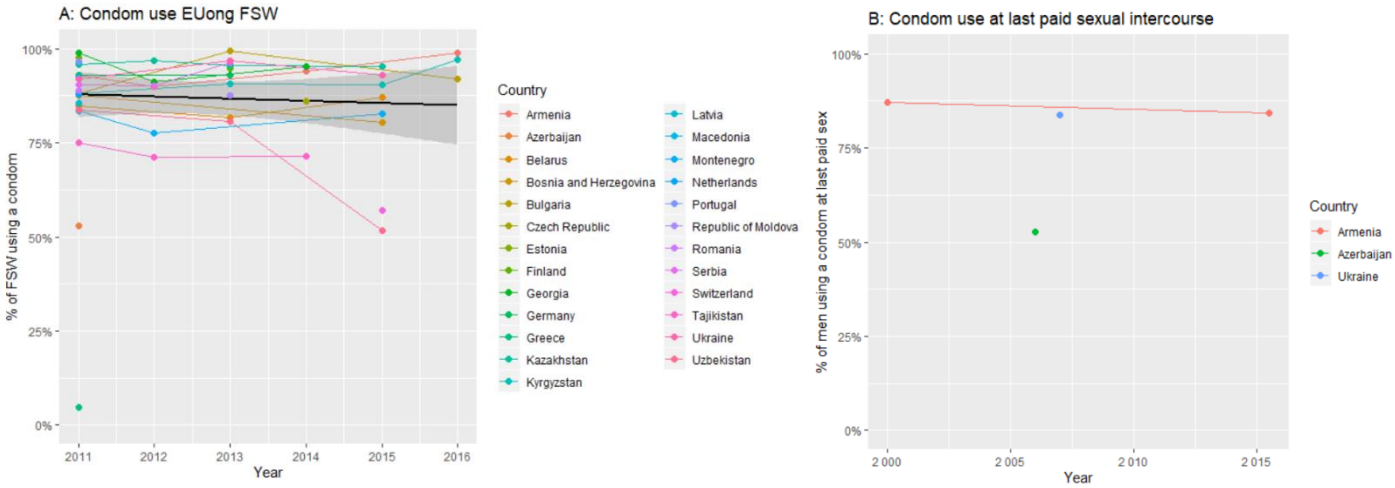


Figure S15: Percentage of FSW reporting using a condom during their last commercial act (A, high and essentially constant[116]) and condom use amongst men who paid for sex in the last 12 months at their last paid sexual intercourse (B, limited data) in WHO Europe region from the UNAIDS Key Population Atlas and DHS, respectively.

Circumcision

The DHS provided data male circumcision for only three European countries: 96.6% for Azerbaijan (2006), 1% for Moldova (2005) and 2.3% for Ukraine (2007). Overall, the region has a weighted average of approximately 24% prevalence of circumcision among the male population.[105]

Circumcision is thought to have decreased in the UK, from 20–30% in the 1940s to 15.8% of men in 2000,[116] which is assumed to be representative of trends for most of Europe as circumcision rates are thought to have fallen.[117]

3.7. Western Pacific region

Data availability: The little data on condom use as well as circumcision available from the DHS was completed with a literature search. Again, information on condom use amongst clients of FSW in the DHS was limited and not available from other sources for the Western Pacific region.

Condom use

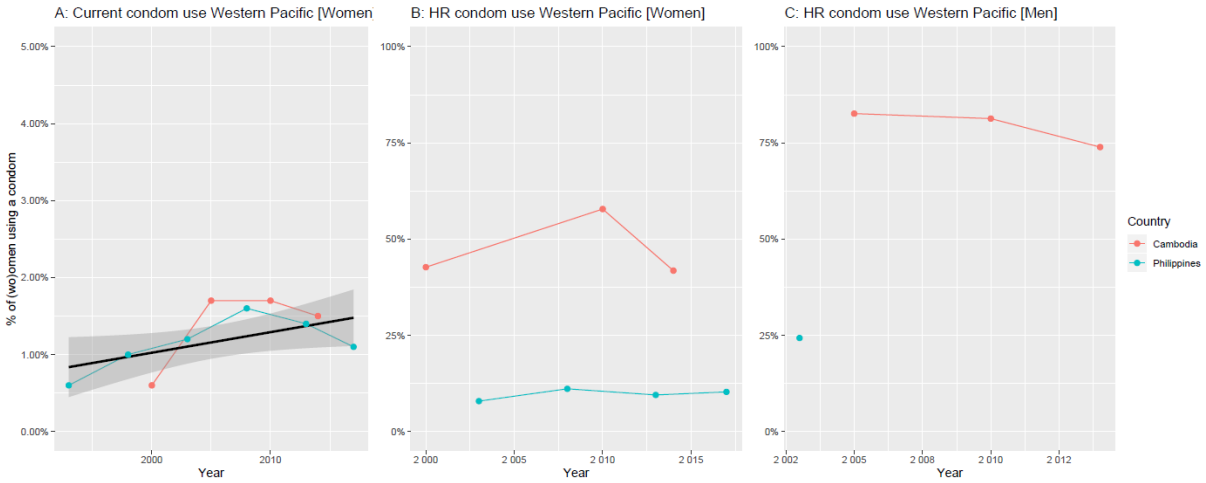


Figure S16: Summary of condom use in the Western Pacific region from DHS data for : A) women who are currently using a condom; Proportion reporting condom use at last high-risk sex (non-marital, non-cohabiting partner in the last 12 months) among B) women, C) men

Additional data: Though data through the DHS is sparse for the Western Pacific region, the UN provides estimates for condom use trends for the Southern Asia and South East Asia regions, which overlap with WHO definition of the Western Pacific and South East Asia region (Figure S16). According to UN both regions have seen a yearly increase in condom use of 0.1% and 0.2% for the South East Asia and Southern Asia region respectively.[104] They also provide estimates for Australia which saw an increase from 12.1% to 14.0% between 1994 and 2015.

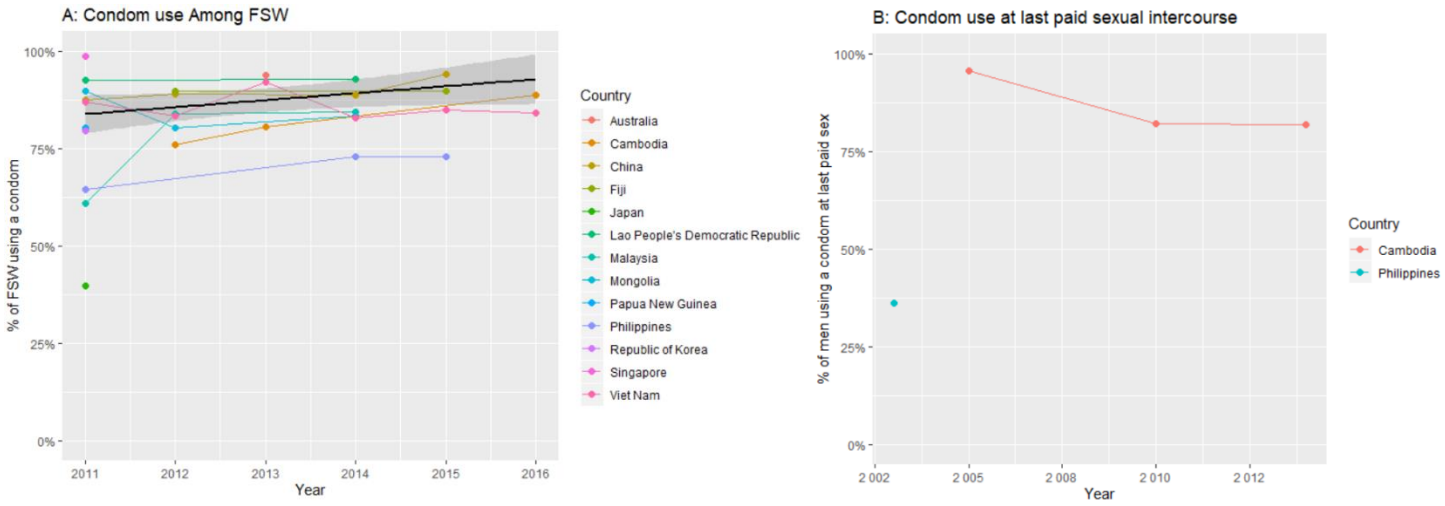


Figure S17 Percentage of FSW reporting using a condom with their most recent client (A, annual increase 4.78%), and condom use amongst men who paid for sex in the last 12 months at their last paid sexual intercourse (B, limited data) in WHO Western Pacific region from the UNAIDS Key Population Atlas and DHS, respectively

Circumcision

The DHS only provided the prevalence of circumcision among Cambodian males (2.1%, 2005). However, circumcision is routinely performed in both the Philippines and the Republic of Korea. The reported weighted average for the region is approximately 20% currently.[105] In Korea, circumcision prevalence has increased from essentially 0 % prior to the 1950s to 90% in 2000.[116] In Australia the prevalence of circumcision has declined. For example, between 2010 and 2016 the circumcision among boys under 6 months old fell with approximately 30%.[118] Apart from these exceptions, there appears to be no evidence for stark increases or declines in the region.

3.8. South-East Asian region

Data availability: Data on condom use in the DHS was quite sparse, however as presented below, some data points were available for India and Indonesia, which are two of the largest countries in the region. Unfortunately, the data on condom use during high-risk sex was not stratified by sex.

Condom Use

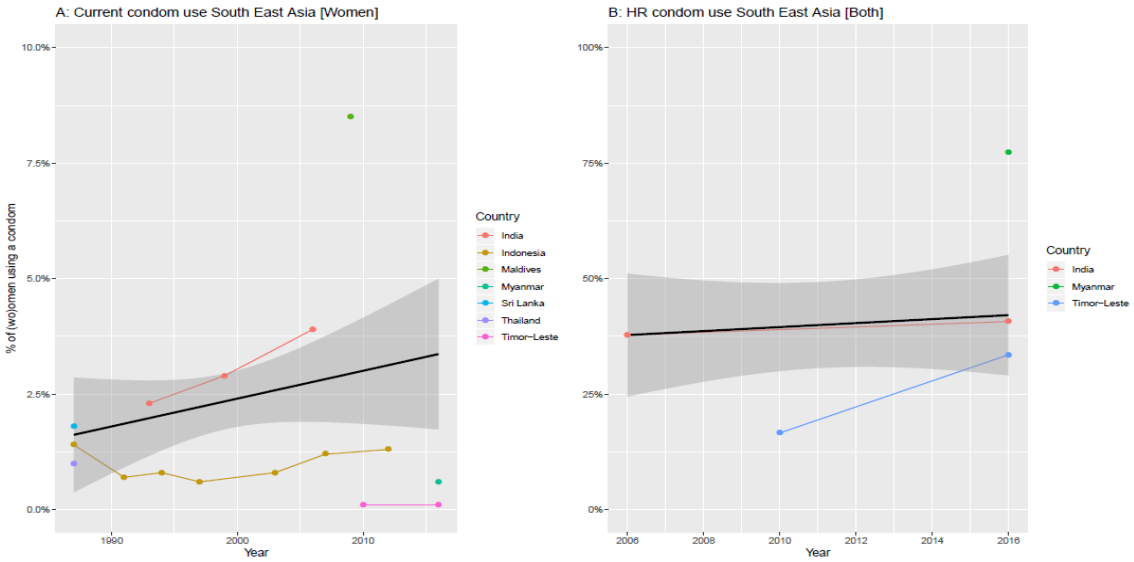


Figure S18: Summary of condom use in the South-East Asia region from DHS data for : A) women who are currently using a condom (annual increase of 0.06%); B) Proportion reporting condom use at last high-risk sex (non-marital, non-cohabiting partner in the last 12 months) among both men and women (annual increase of 0.43%).

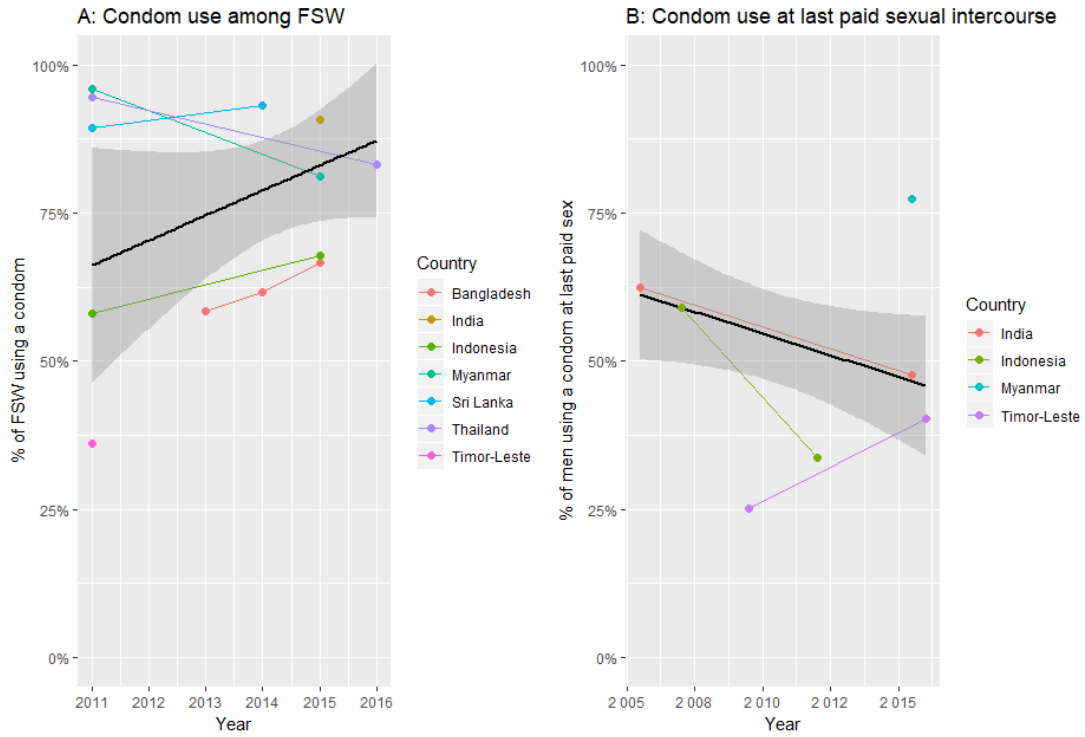


Figure S19: Percentage of FSW reporting using a condom at last commercial act (A, annual increase of 4.22%) and condom use amongst men who paid for sex in the last 12 months at their last paid sexual intercourse (B, annual suggested decrease -1.46%) in WHO South East Asian region based on data taken from the UNAIDS Key Population Atlas and DHS, respectively. *Note that this trend is primarily based on data from India.*

Circumcision

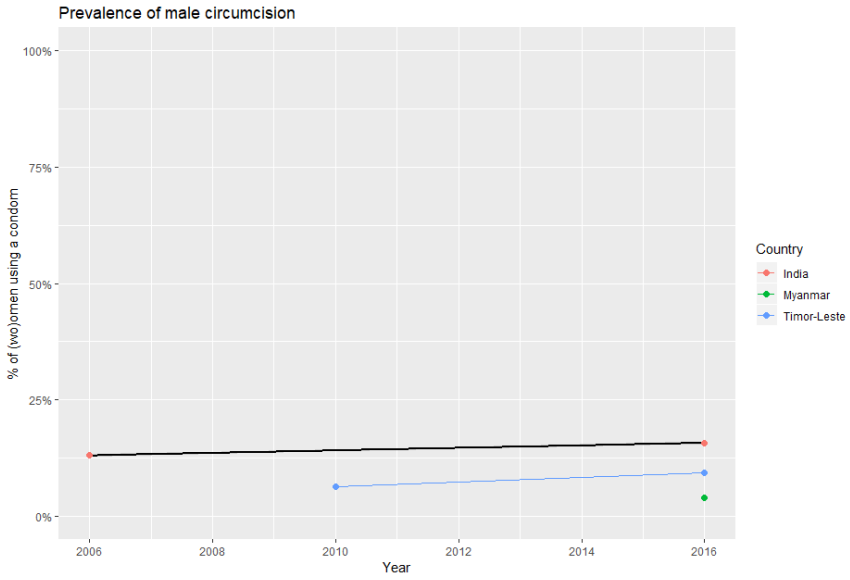


Figure S20: Summary of male circumcision coverage in the South East Asia region from the DHS.

Similarly, little data was available on circumcision prevalence in the WHO South East Asia region apart from time trend data for India and Timor-Leste (Figure S20), which showed a small increase (average 0.27% per year between 2006 and 2016). Overall, around 30% of the male population is circumcised in the region.[105] Two important exceptions to these low circumcision prevalence rates are Bangladesh and Indonesia where circumcision prevalence is > 90%.[105]

3.9. Eastern Mediterranean region

Data availability: Data on condom use was available on different indicators than presented for other regions as shown in Figure S21. No data was available on condom use amongst clients of sex workers, and a literature search provided no other data sources.

Condom use

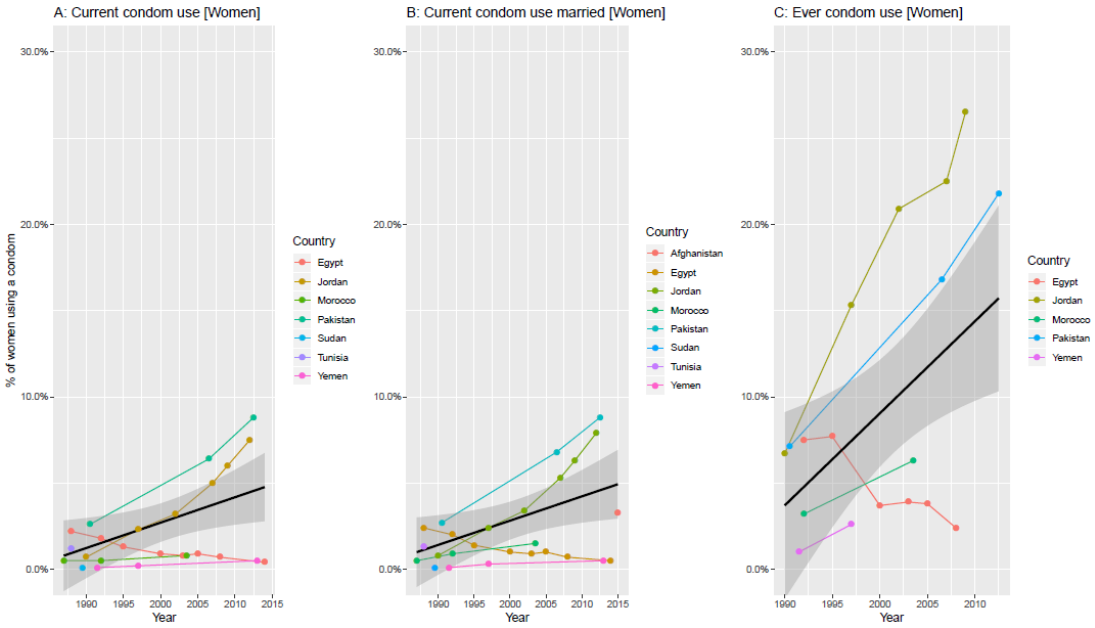


Figure S21: Current and ever condom use amongst women in the Eastern Mediterranean region based on data taken from DHS.

The indicators presented in Figure S21 all show an upward trend over time. Panel A, representing the percentage of women who report currently using a condom, shows a weighted yearly increase of 0.53%. The percentage of married women that report using a condom as depicted in panel B shows a weighted yearly increase of 0.14%. Lastly, the region appears to have seen a weighted yearly increase of 0.43% in women reporting ever having used a condom.

Condom use among FSW and their clients

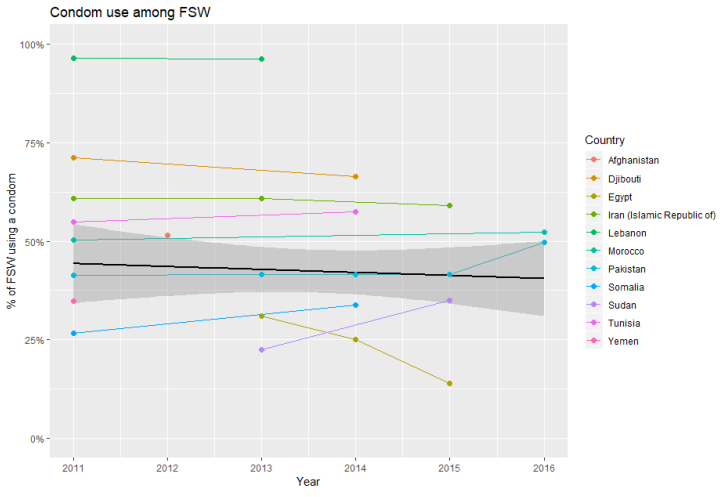


Figure S22: Condom use among FSW in the Eastern Mediterranean region based on data taken from UNAIDS Key Population Atlas.

Compared to other regions, condom use amongst FSW appears relatively low in the WHO Eastern Mediterranean region, the Figure S22 shows a weighted yearly trend of -0.76%. Unfortunately, no data was available for condom use among clients. The lack of region-specific

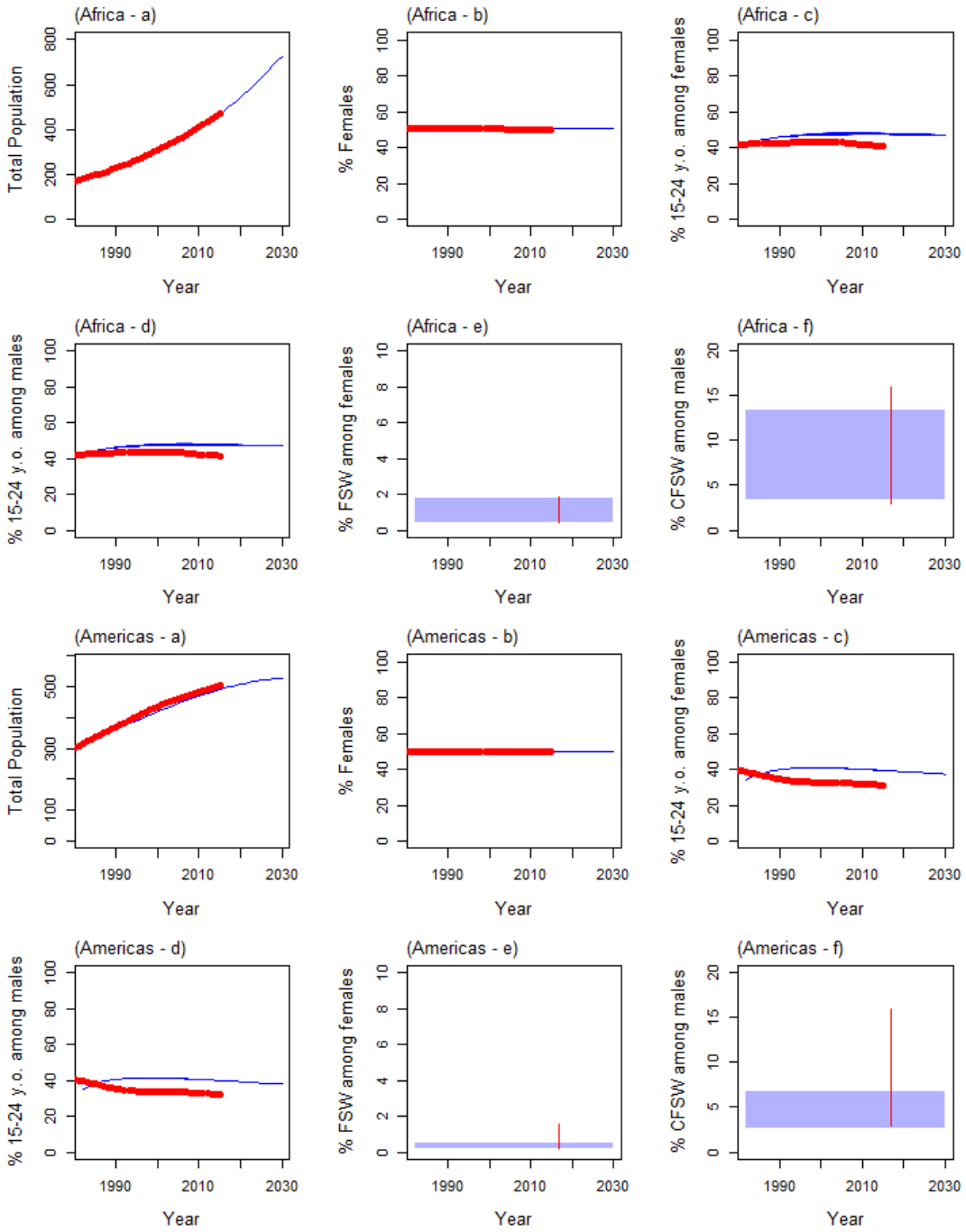
condom use data has been confirmed by a study producing regional estimates for the size of this population.[119]

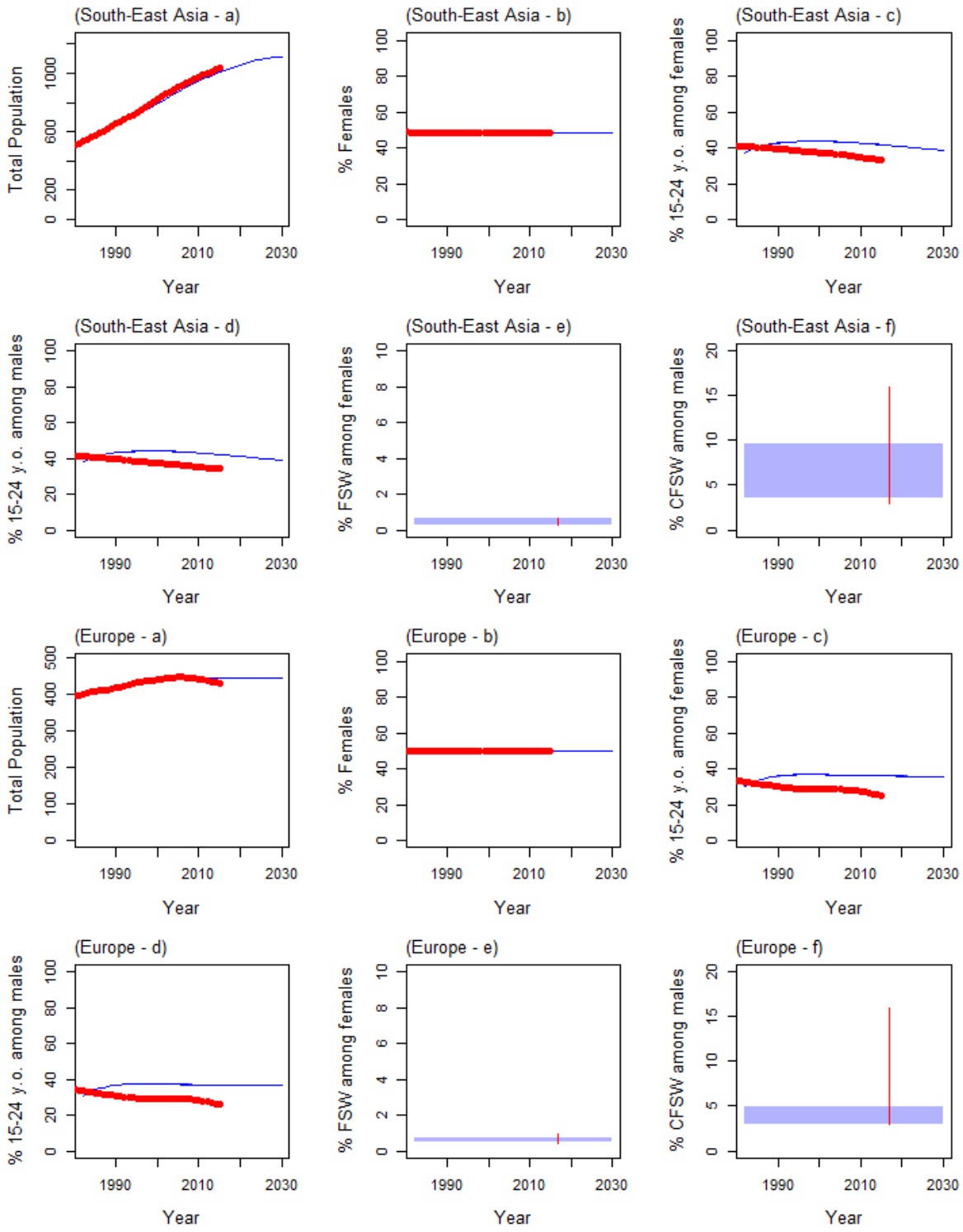
Circumcision

The average prevalence of male circumcision is relatively high (92%) in this region as many countries have a Muslim religion.[105] The DHS only reports data for Afghanistan (99.1% in 2015). As male circumcision is part of religious customs it can be assumed that the prevalence was relatively stable over the modelled epidemic period.

4. Supplementary results

4.1. Model fitting and comparison with other estimates


(Africa - a)
Total Population
Year
(Africa - b)
% Females
Year
(Africa - c)
% 15-24 y.o. among females
Year
(Africa - d)
% 15-24 y.o. among males
Year
(Africa - e)
% FSW among females
Year
(Africa - f)
% CFSW among males
Year
(Americas - a)
Total Population
Year
(Americas - b)
% Females
Year
(Americas - c)
% 15-24 y.o. among females
Year
(Americas - d)
% 15-24 y.o. among males
Year
(Americas - e)
% FSW among females
Year
(Americas - f)
% CFSW among males
Year


(South-East Asia - a)
Total Population
0 200 600 1000
1990 2010 2030
Year
(South-East Asia - b)
% Females
0 20 40 60 80 100
1990 2010 2030
Year
(South-East Asia - c)
% 15-24 y.o. among females
0 20 40 60 80 100
1990 2010 2030
Year
(South-East Asia - d)
% 15-24 y.o. among males
0 20 40 60 80 100
1990 2010 2030
Year
(South-East Asia - e)
% FSW among females
0 2 4 6 8 10
1990 2010 2030
Year
(South-East Asia - f)
% CFSW among males
0 5 10 15 20
1990 2010 2030
Year
(Europe - a)
Total Population
0 100 200 300 400 500
1990 2010 2030
Year
(Europe - b)
% Females
0 20 40 60 80 100
1990 2010 2030
Year
(Europe - c)
% 15-24 y.o. among females
0 20 40 60 80 100
1990 2010 2030
Year
(Europe - d)
% 15-24 y.o. among males
0 20 40 60 80 100
1990 2010 2030
Year
(Europe - e)
% FSW among females
0 2 4 6 8 10
1990 2010 2030
Year
(Europe - f)
% CFSW among males
0 5 10 15 20
1990 2010 2030
Year

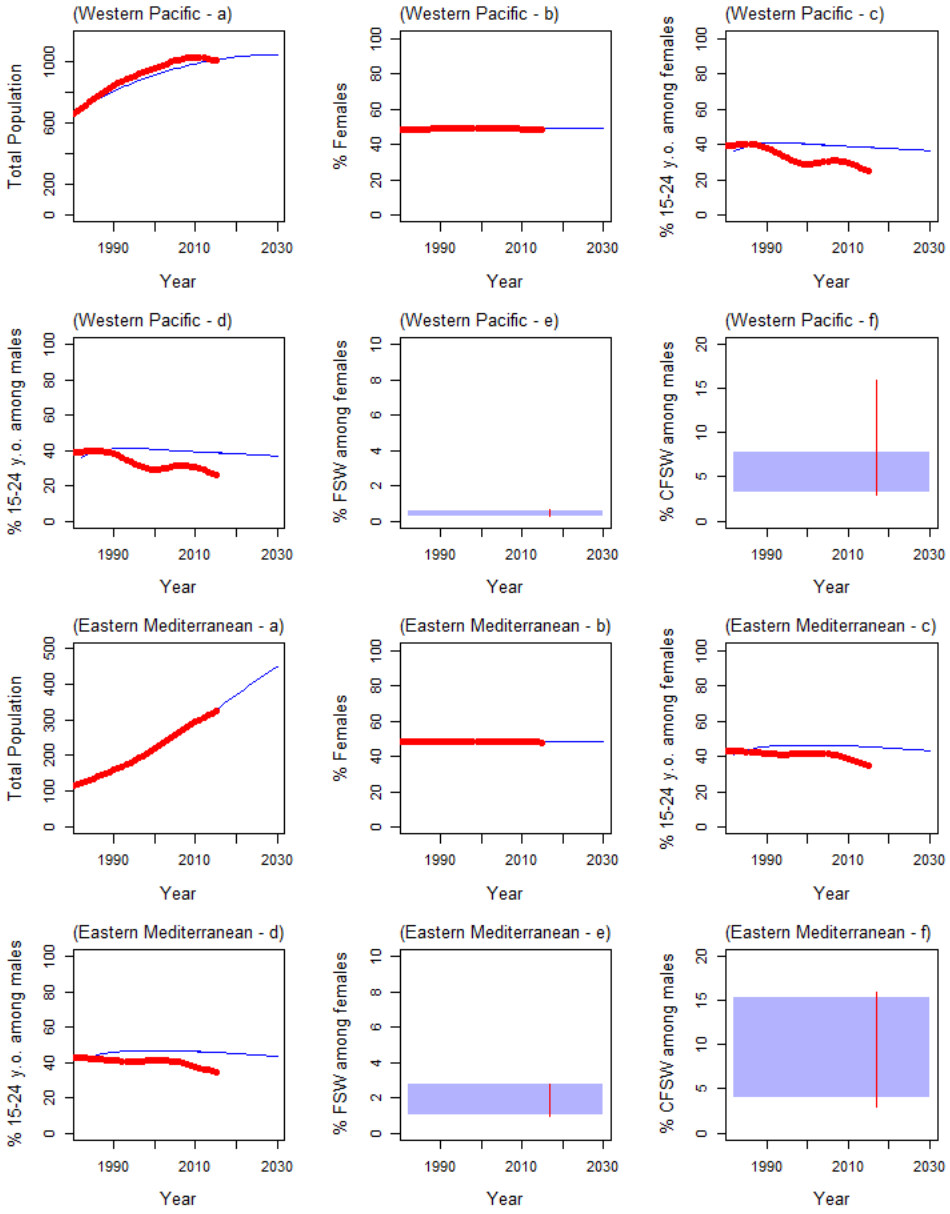
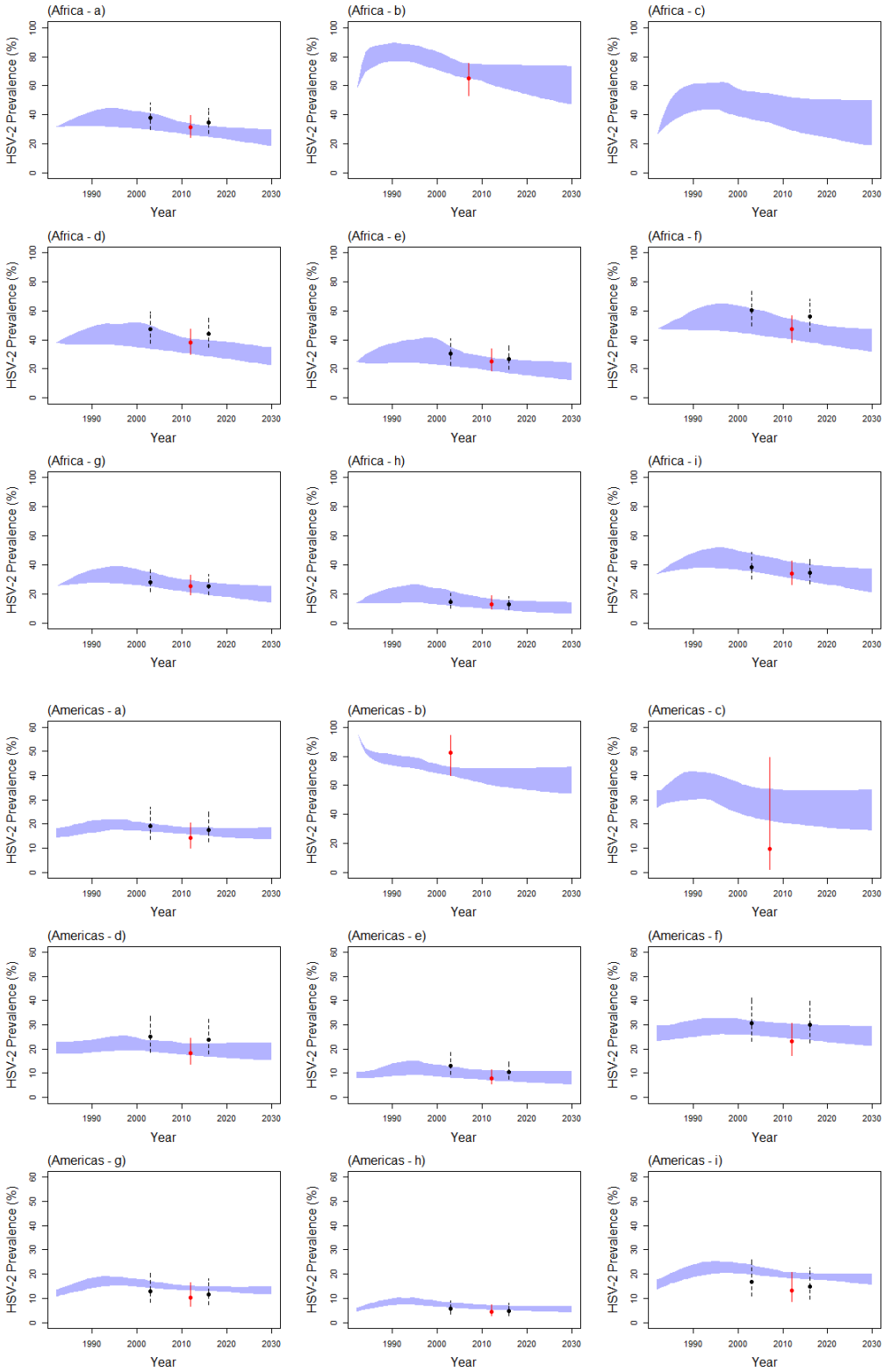
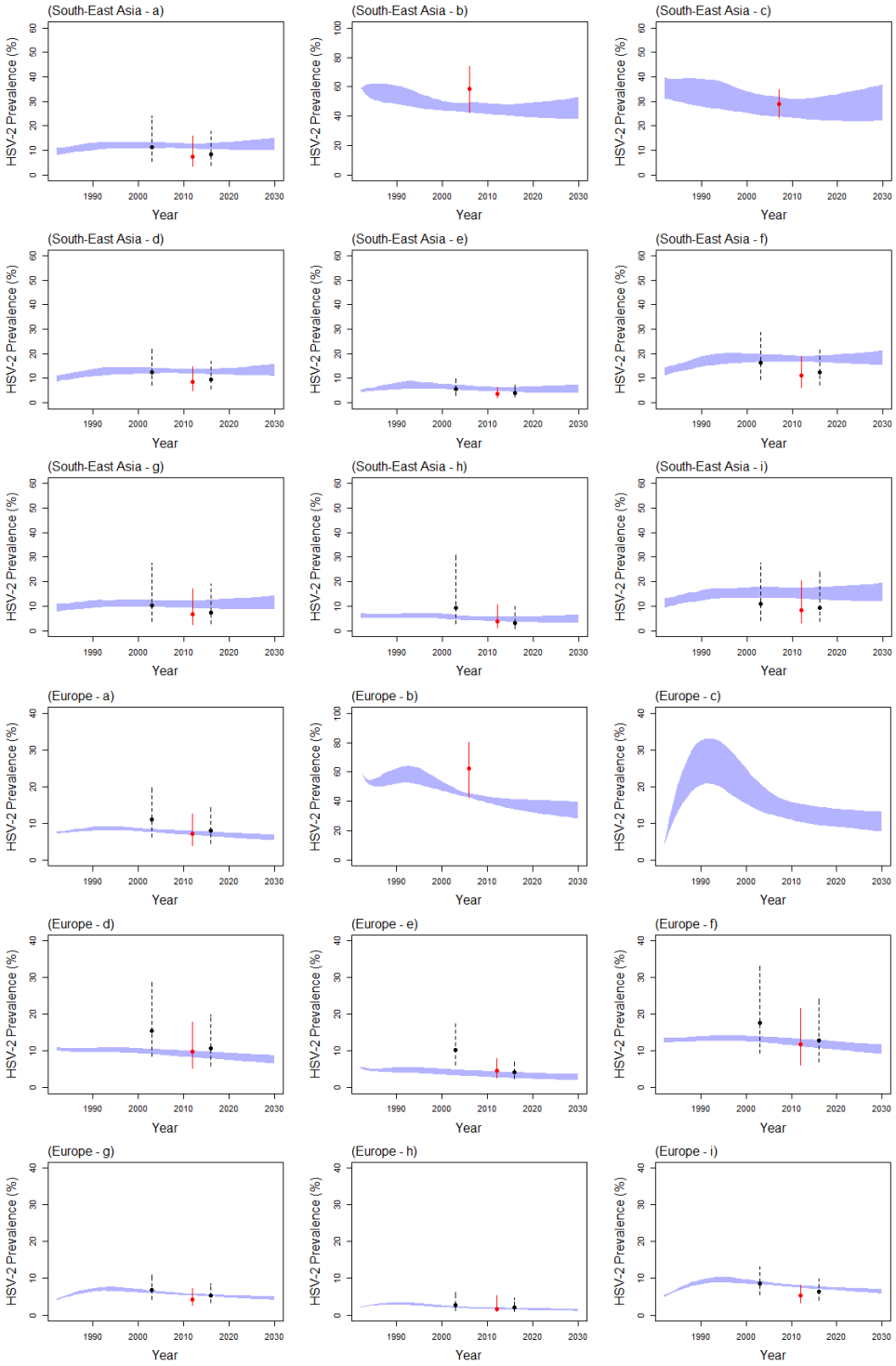


Figure S23: Model fits of sociodemographic outcomes in each WHO region over time under the conservative scenario: a) total 15-49 years old population size, b) proportion of females in the modelled population, c) fraction of younger (15-24 years old) females among all females d) fraction of younger (15-24 years old) males among all males, e) proportion of FSWs among all females, f) proportion of CFSWs among all males. Blue shades represent 95%UI of model outcomes. Red lines in the panels a-d represent UNDP estimates.[53]


(Africa - a)
(Africa - b)
(Africa - c)
(Africa - d)
(Africa - e)
(Africa - f)
(Africa - g)
(Africa - h)
(Africa - i)
(Americas - a)
(Americas - b)
(Americas - c)
(Americas - d)
(Americas - e)
(Americas - f)
(Americas - g)
(Americas - h)
(Americas - i)
HSV-2 Prevalence (%)
Year


(South-East Asia - a)
(South-East Asia - b)
(South-East Asia - c)
(South-East Asia - d)
(South-East Asia - e)
(South-East Asia - f)
(South-East Asia - g)
(South-East Asia - h)
(South-East Asia - i)
(Europe - a)
(Europe - b)
(Europe - c)
(Europe - d)
(Europe - e)
(Europe - f)
(Europe - g)
(Europe - h)
(Europe - i)
HSV-2 Prevalence (%)
Year

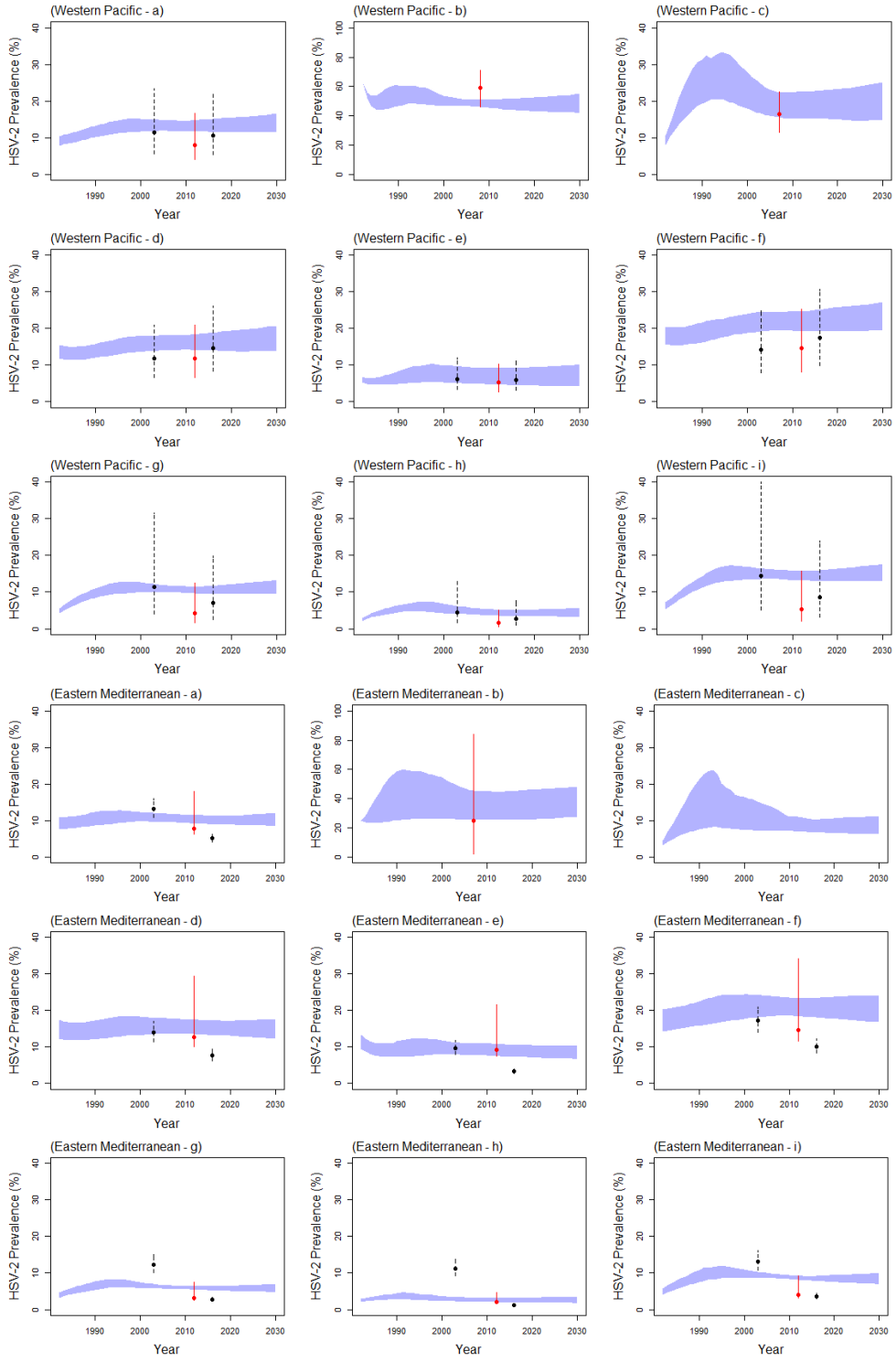
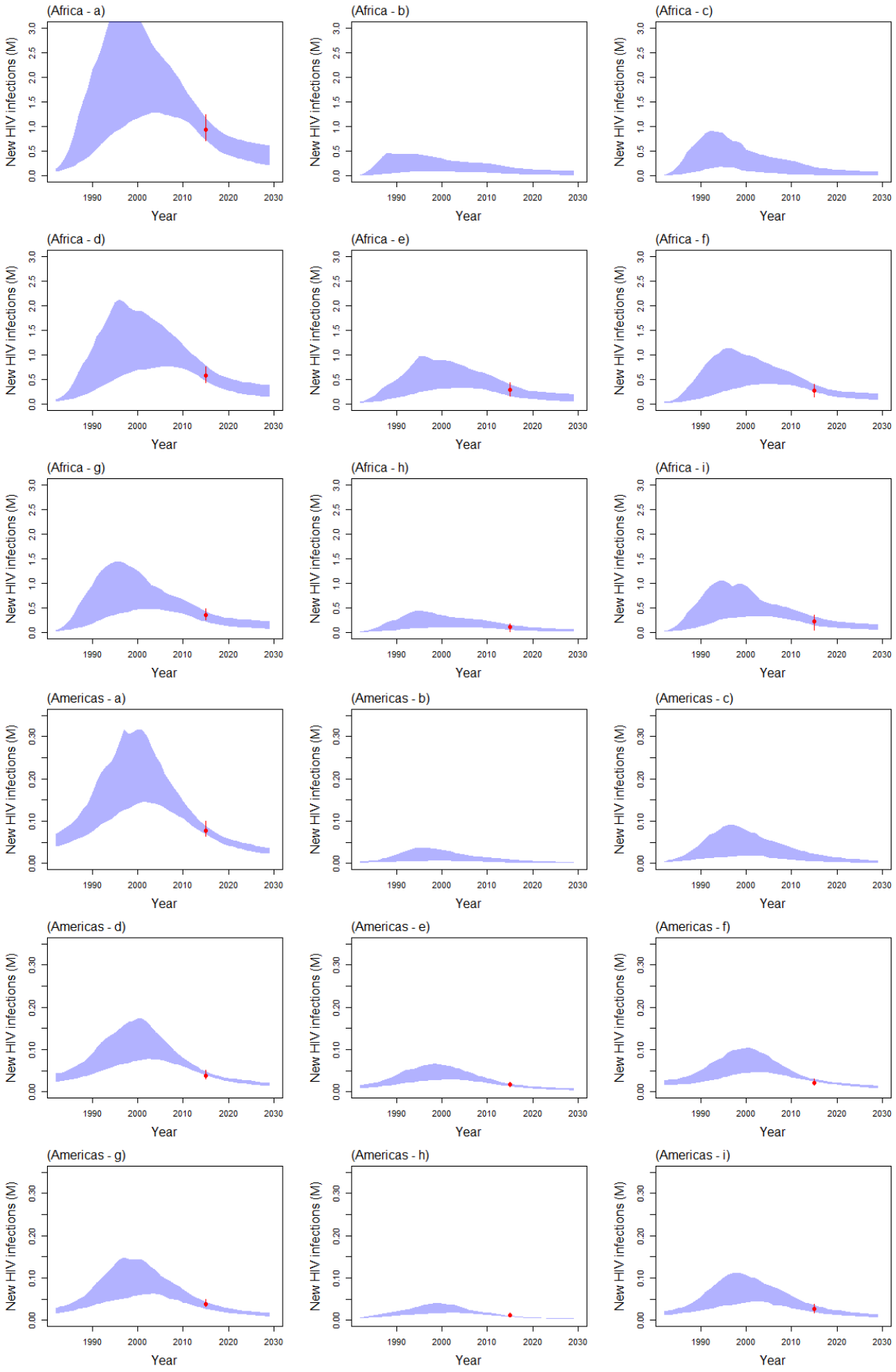
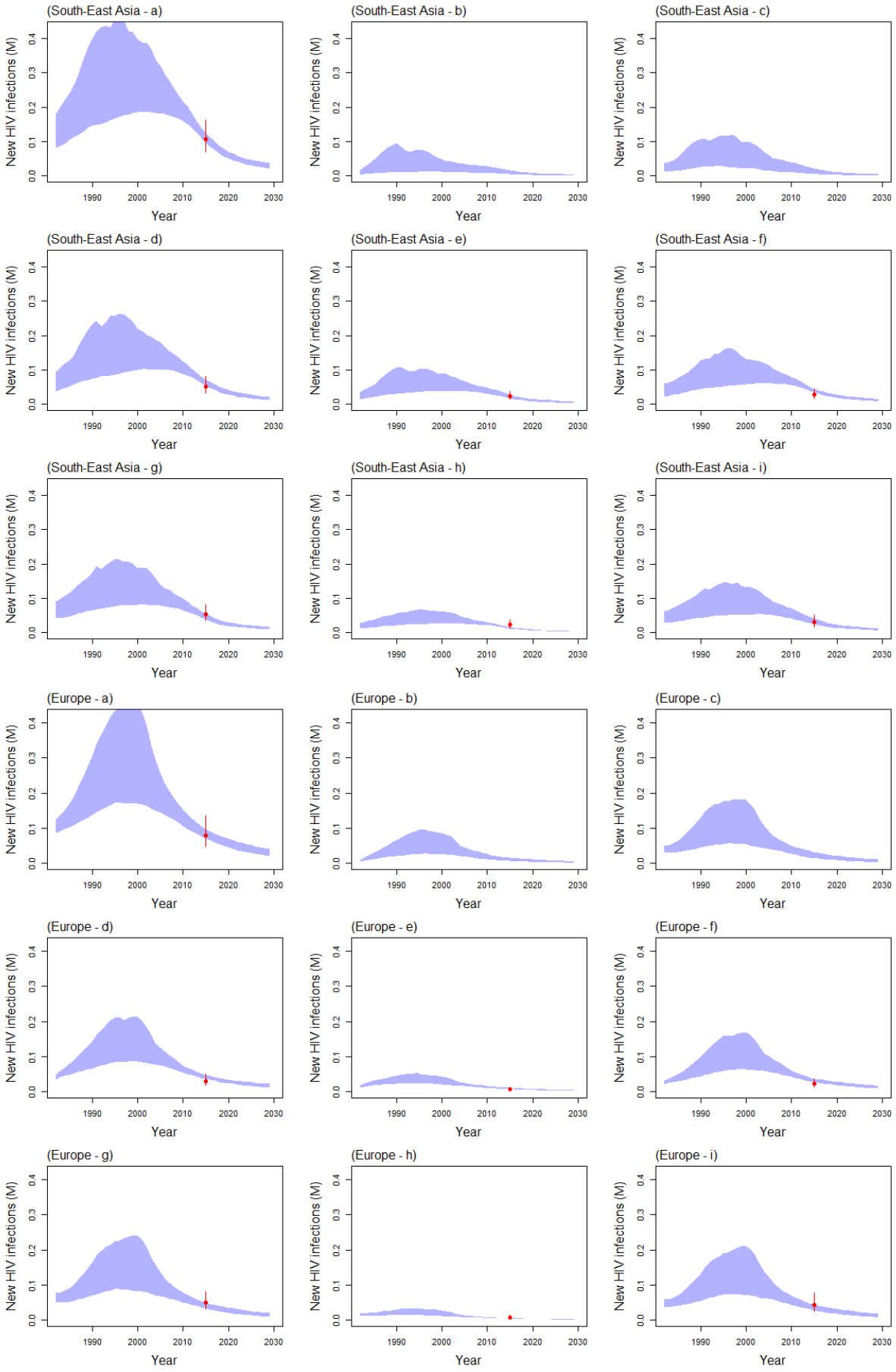


Figure S24: Model fits of HSV-2 prevalence under the conservative scenario: a) overall and among b) FSWs, c) CFSWs, d) all females, e) younger females (aged 15-24 years), f) older females (aged 25-49 years), g) all males, h) younger males (aged 15-24 years), i) older males (aged 25-49 years). Dots and intervals represent empirical HSV-2 prevalence estimates and 95% CI for 2012 used at the fitting stage (red)[3] and estimates for 2003 and 2016 only used for comparison.[1] Blue shades represent 95%UI of model predictions across all parameter sets.


(Africa - a)
(Africa - b)
(Africa - c)
(Africa - d)
(Africa - e)
(Africa - f)
(Africa - g)
(Africa - h)
(Africa - i)
(Americas - a)
(Americas - b)
(Americas - c)
(Americas - d)
(Americas - e)
(Americas - f)
(Americas - g)
(Americas - h)
(Americas - i)
New HIV infections (M)
Year


(South-East Asia - a)
(South-East Asia - b)
(South-East Asia - c)
(South-East Asia - d)
(South-East Asia - e)
(South-East Asia - f)
(South-East Asia - g)
(South-East Asia - h)
(South-East Asia - i)
(Europe - a)
(Europe - b)
(Europe - c)
(Europe - d)
(Europe - e)
(Europe - f)
(Europe - g)
(Europe - h)
(Europe - i)
New HIV infections (M)
Year
0.0
0.1
0.2
0.3
0.4
1990
2000
2010
2020
2030

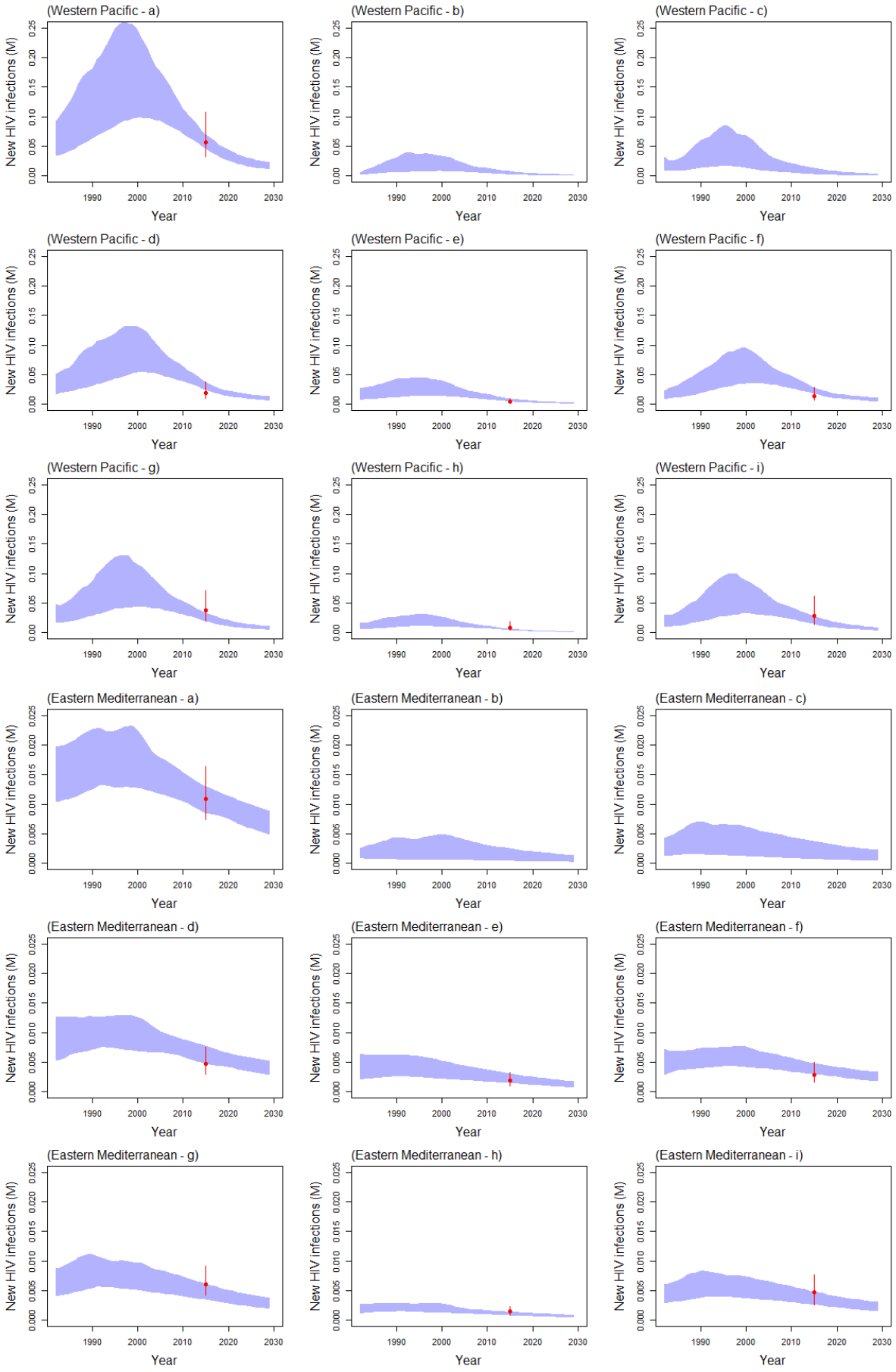

(Western Pacific - a)
(Western Pacific - b)
(Western Pacific - c)
(Western Pacific - d)
(Western Pacific - e)
(Western Pacific - f)
(Western Pacific - g)
(Western Pacific - h)
(Western Pacific - i)
(Eastern Mediterranean - a)
(Eastern Mediterranean - b)
(Eastern Mediterranean - c)
(Eastern Mediterranean - d)
(Eastern Mediterranean - e)
(Eastern Mediterranean - f)
(Eastern Mediterranean - g)
(Eastern Mediterranean - h)
(Eastern Mediterranean - i)
New HIV infections (M)
Year

Figure S25: Model fits under the conservative scenario to 2015 UNAIDS estimates of annual number of incident HIV infections among 15-49 years old non-PWID heterosexual individuals[4,9] (red dots and bars) a) overall and among b) FSWs, c) Clients of FSW (CFSWs), d) all females, e) younger females, f) older females, g) all males, h) younger males, i) older males. Blue shades represent 95%UI of model outcomes.

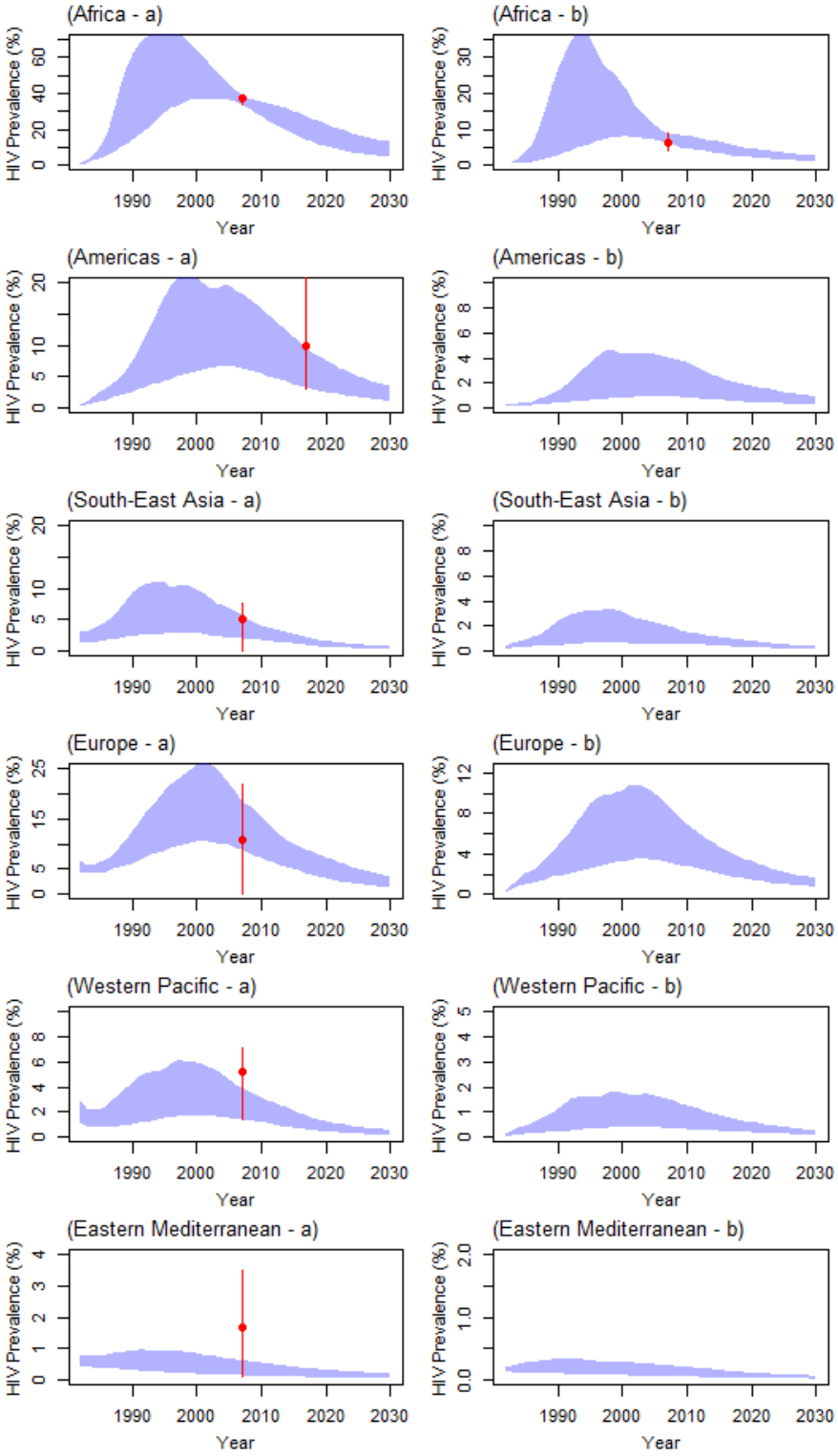


Figure S26: Model fits under the conservative scenario to HIV prevalence estimates among a) FSWs, and b) CFSWs in each WHO region over time. Blue shades represent 95%UI of model outcomes. Red dots and intervals represent estimates adapted from[11] for FSWs in all regions, and[6] for CFSWs in Africa.

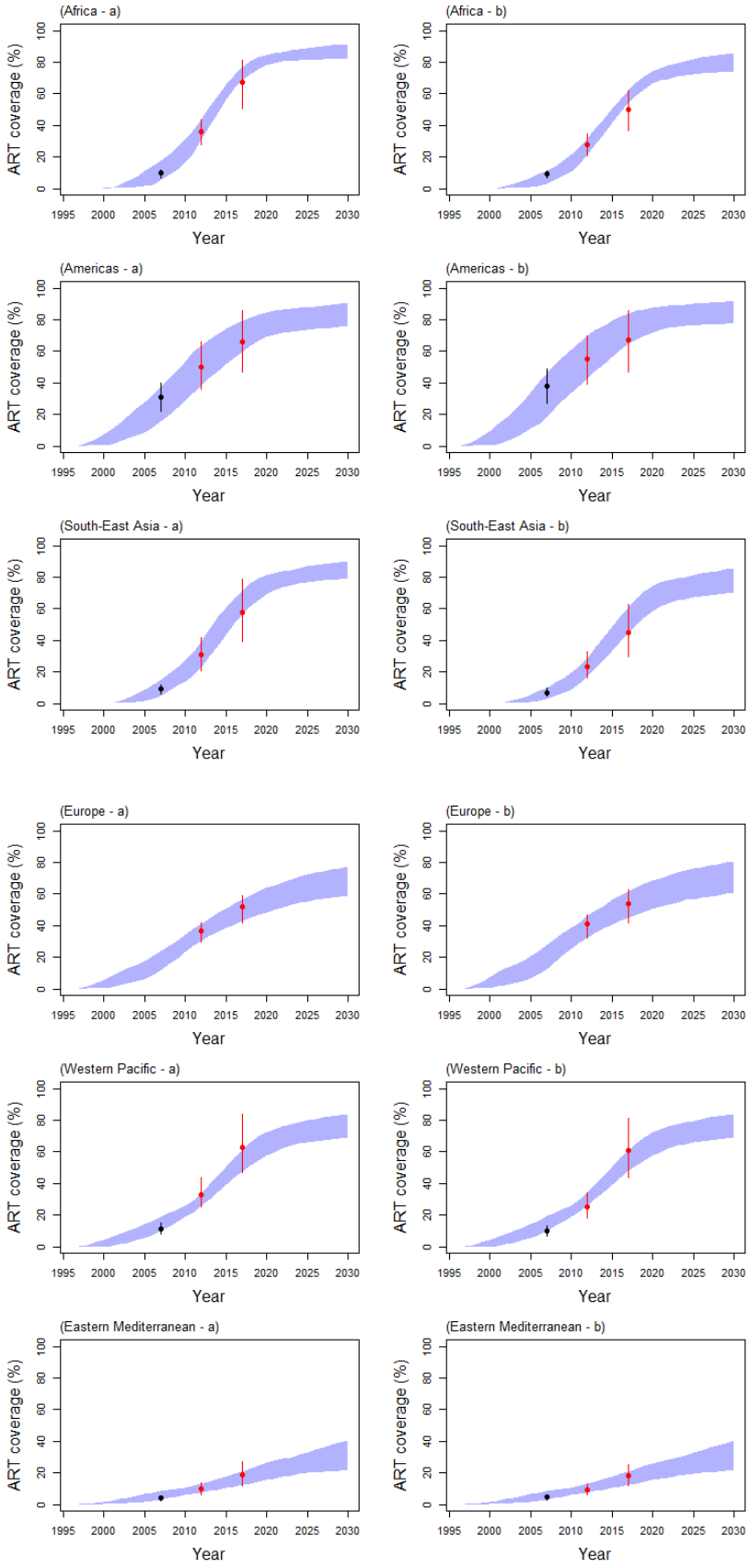
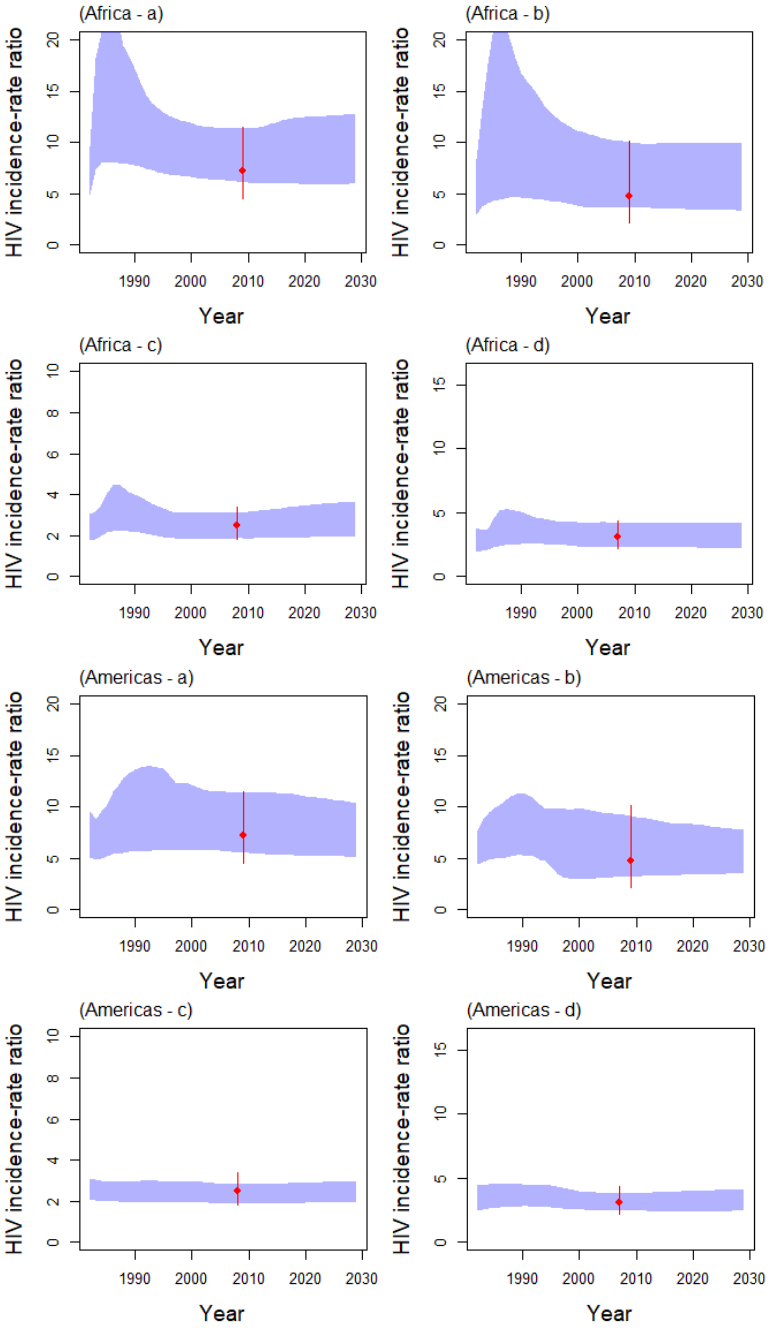
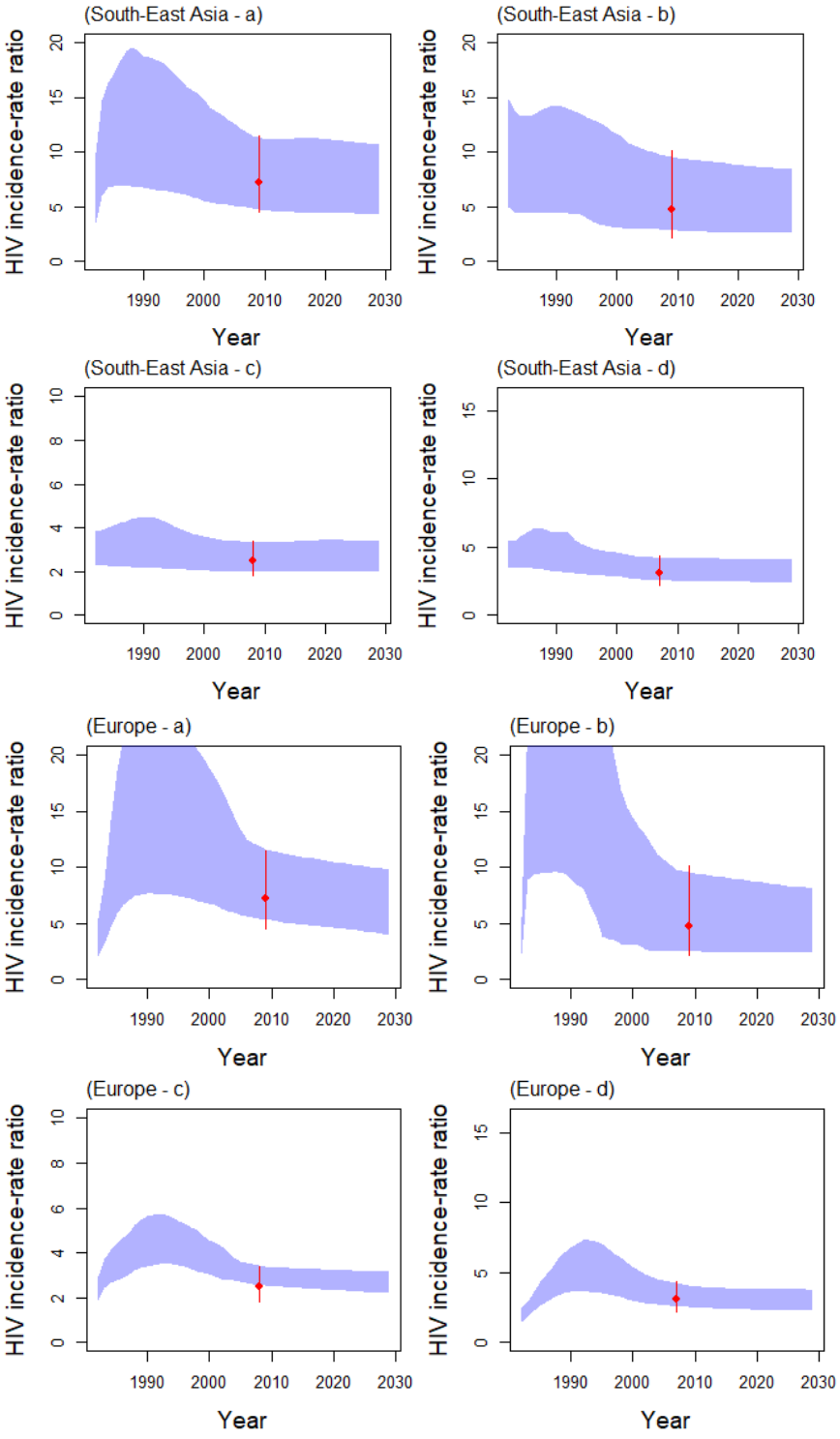


Figure S27: Model fits of ART coverage under the conservative scenario among all HIV-infected a) females, and b) males in each WHO region over time. Blue shades represent 95%UI of model outcomes. Red dots and intervals represent coverage estimates among 15-49 years

old from UNAIDS[9] used to fit the model, whereas dark dots and intervals represent UNAIDS estimates for 2007 which were only used for comparison.


(Africa - a)
(Africa - b)
(Africa - c)
(Africa - d)
(Americas - a)
(Americas - b)
(Americas - c)
(Americas - d)
HIV incidence-rate ratio
Year
1990
2000
2010
2020
2030


(South-East Asia - a)
(South-East Asia - b)
(South-East Asia - c)
(South-East Asia - d)
(Europe - a)
(Europe - b)
(Europe - c)
(Europe - d)
HIV incidence-rate ratio
Year
1990
2000
2010
2020
2030

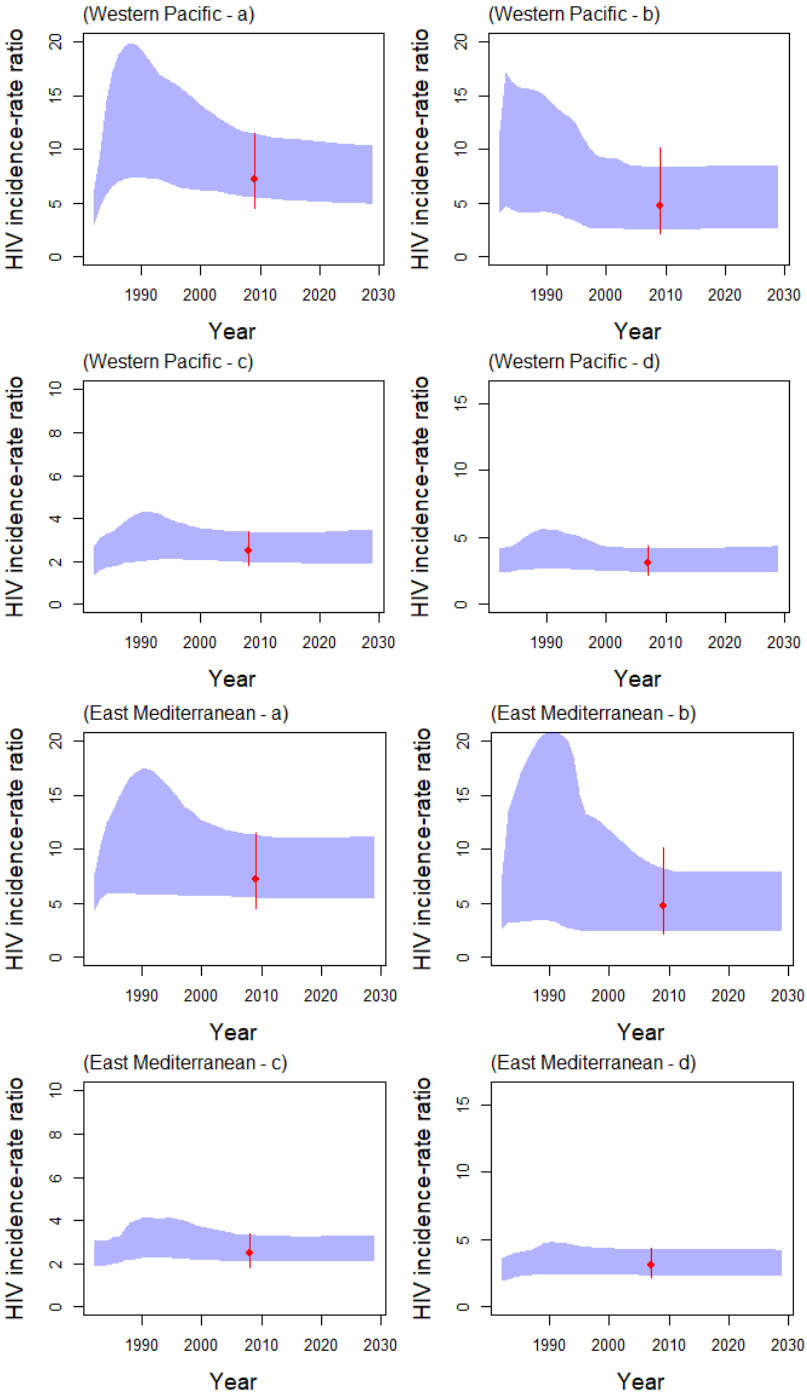
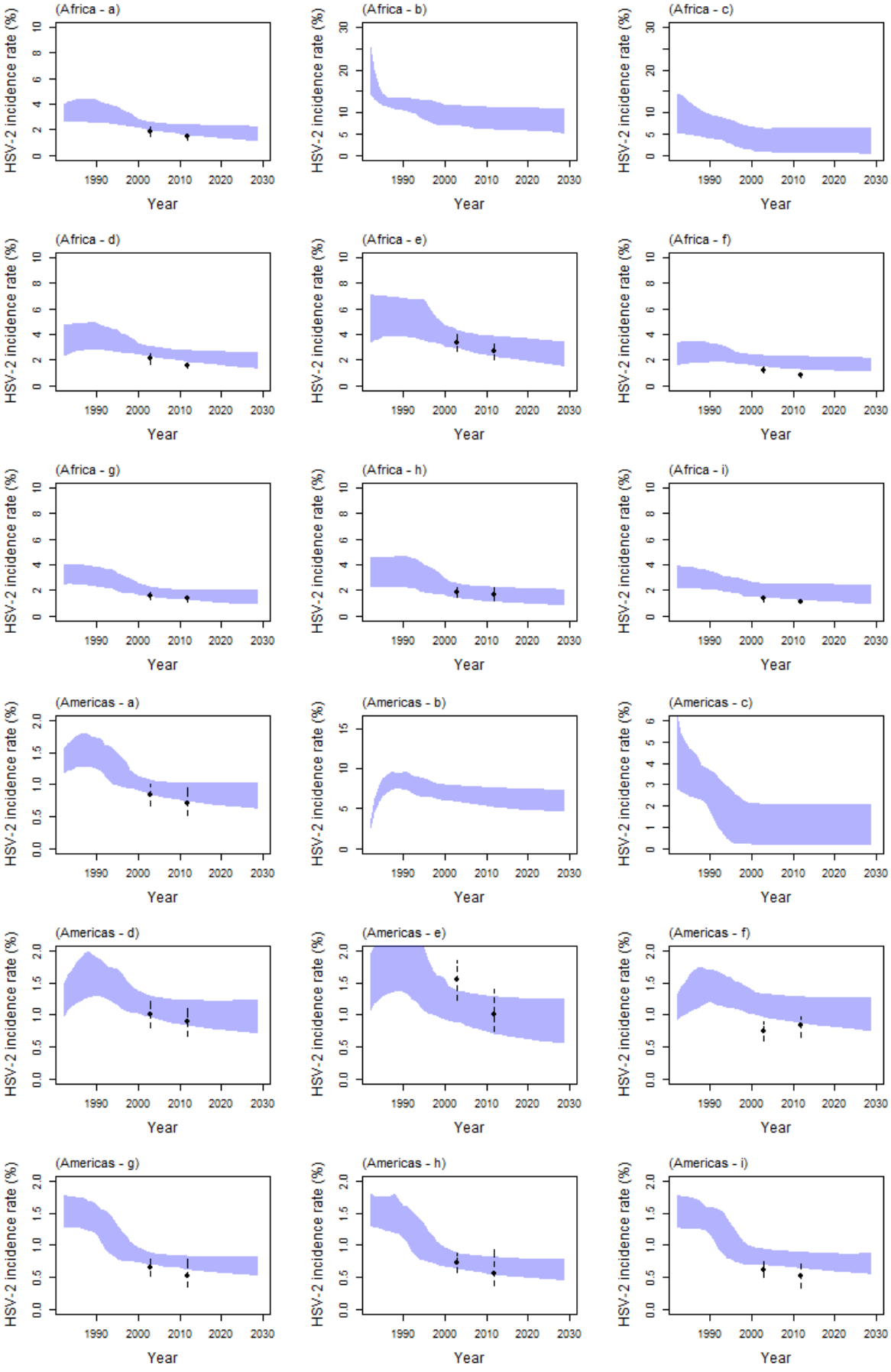
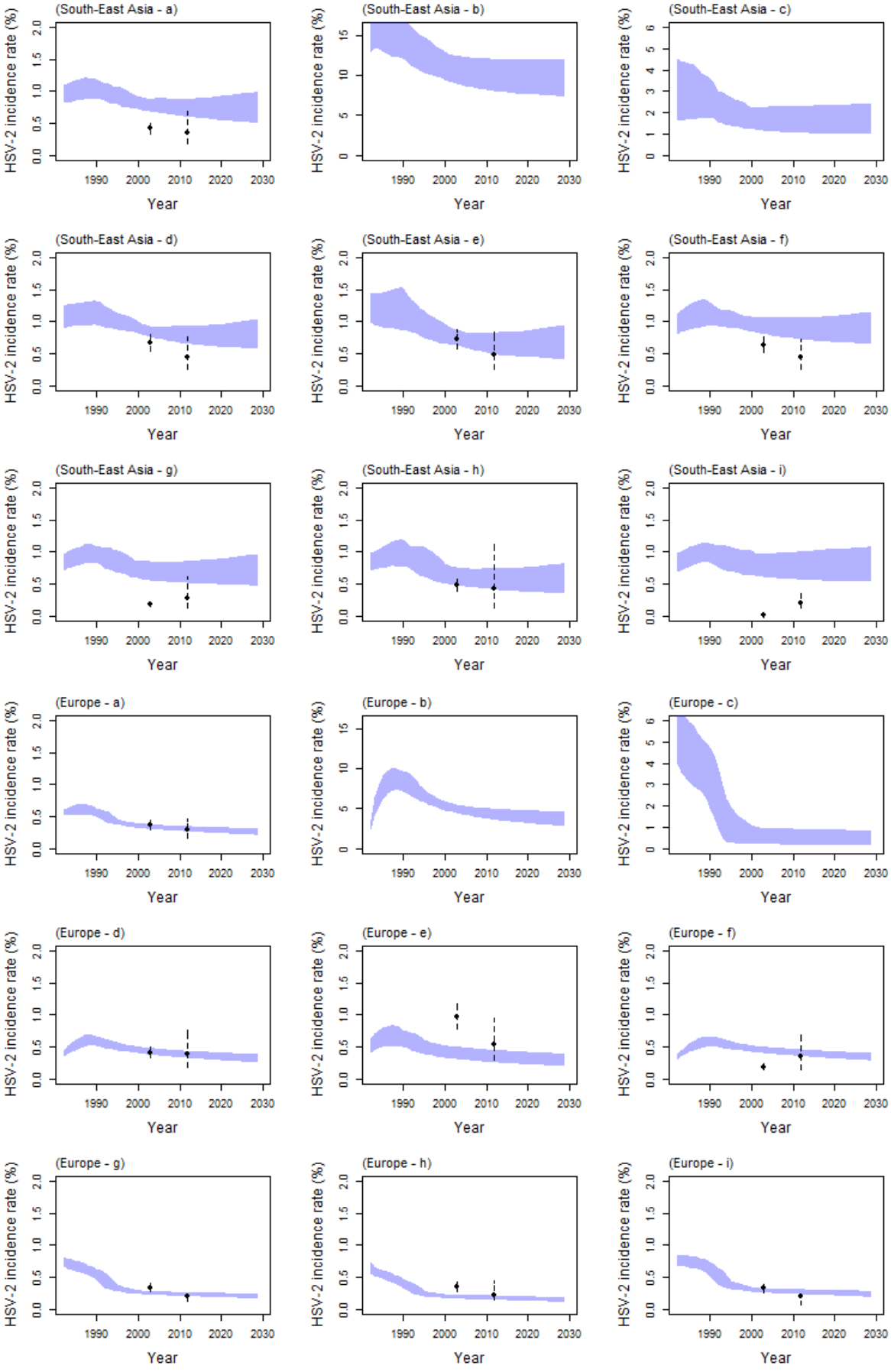


Figure S28: Model fits of HIV incidence rate ratio by HSV-2 infection status under the conservative scenario calculated among a) all females with recent HSV-2 infection vs HSV-2-uninfected, b) all males with recent HSV-2 infection vs HSV-2-uninfected, c) all females with established HSV-2 infection vs HSV-2-uninfected, d) all males with established HSV-2 infection vs HSV-2-uninfected, for each WHO region over time. Blue shades represent 95%UI of model outcomes. Red dots and intervals represent pooled estimates of empirical estimates from[8].


(Africa - a)
(Africa - b)
(Africa - c)
(Africa - d)
(Africa - e)
(Africa - f)
(Africa - g)
(Africa - h)
(Africa - i)
(Americas - a)
(Americas - b)
(Americas - c)
(Americas - d)
(Americas - e)
(Americas - f)
(Americas - g)
(Americas - h)
(Americas - i)
HSV-2 incidence rate (%)
Year


(South-East Asia - a)
(South-East Asia - b)
(South-East Asia - c)
(South-East Asia - d)
(South-East Asia - e)
(South-East Asia - f)
(South-East Asia - g)
(South-East Asia - h)
(South-East Asia - i)
(Europe - a)
(Europe - b)
(Europe - c)
(Europe - d)
(Europe - e)
(Europe - f)
(Europe - g)
(Europe - h)
(Europe - i)
HSV-2 incidence rate (%)
Year
1990
2000
2010
2020
2030

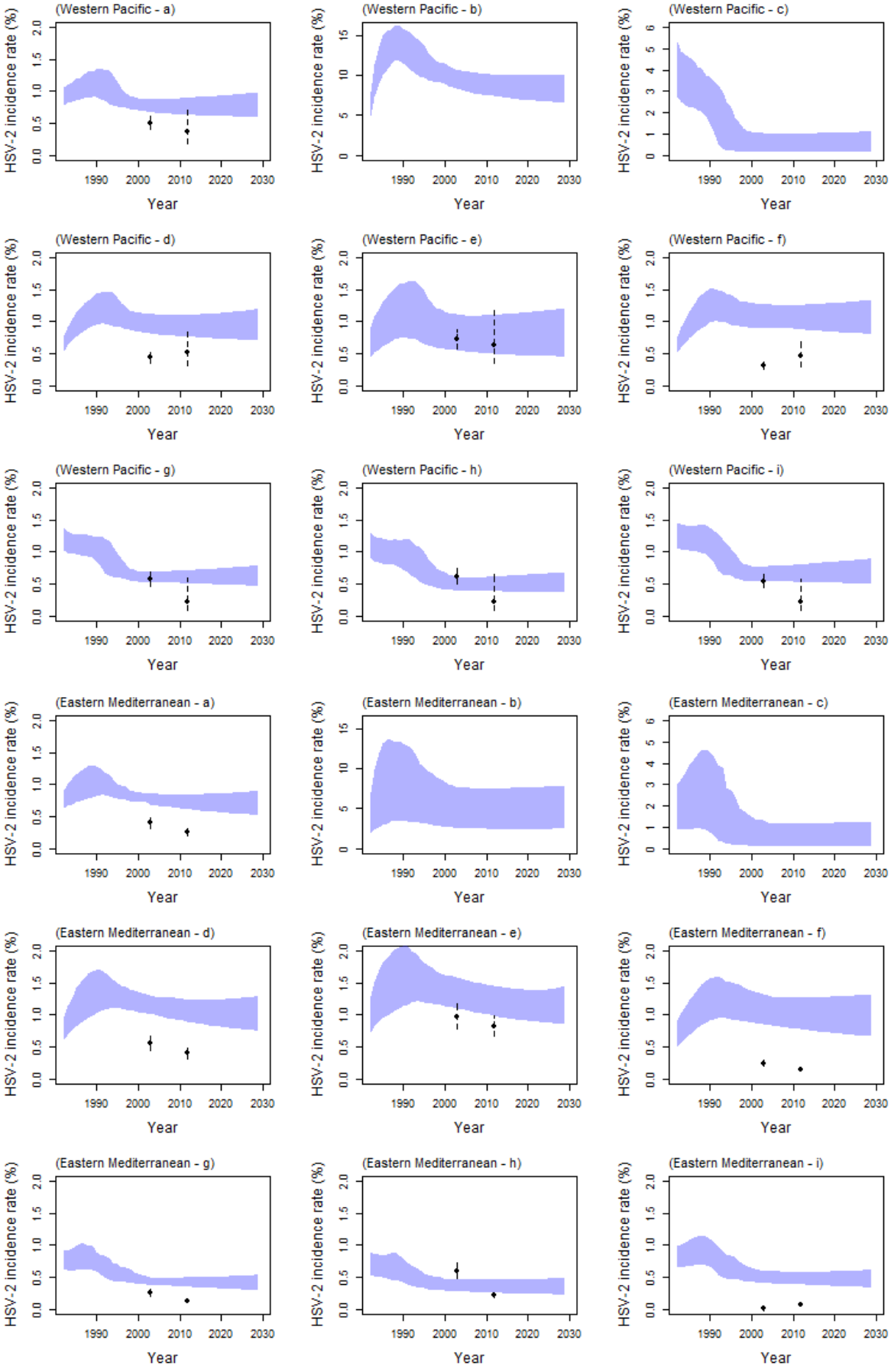

(Western Pacific - a)
(Western Pacific - b)
(Western Pacific - c)
(Western Pacific - d)
(Western Pacific - e)
(Western Pacific - f)
(Western Pacific - g)
(Western Pacific - h)
(Western Pacific - i)
(Eastern Mediterranean - a)
(Eastern Mediterranean - b)
(Eastern Mediterranean - c)
(Eastern Mediterranean - d)
(Eastern Mediterranean - e)
(Eastern Mediterranean - f)
(Eastern Mediterranean - g)
(Eastern Mediterranean - h)
(Eastern Mediterranean - i)
HSV-2 incidence rate (%)
Year

Figure S29: Estimated HSV-2 incidence rate (calculated among all individuals, including HSV-2-infected) under the conservative scenario. Blue shades represent 95%UI of model outcomes. Dark dots and interval show model-based estimates from [1,3] which were only used for comparison.

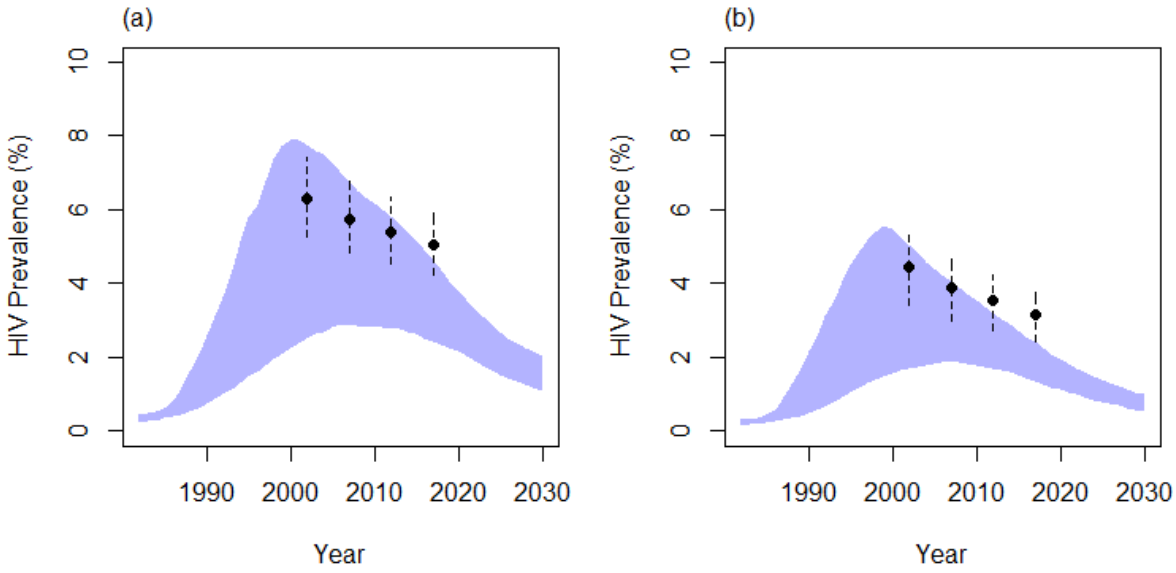


Figure S30: Estimated HIV prevalence among all 15-49 years old a) females, and 2) males in the WHO African region under the conservative scenario. Blue shades represent 95%UI of model outcomes. Dark dots and intervals show estimates from UNAIDS only used for comparison.

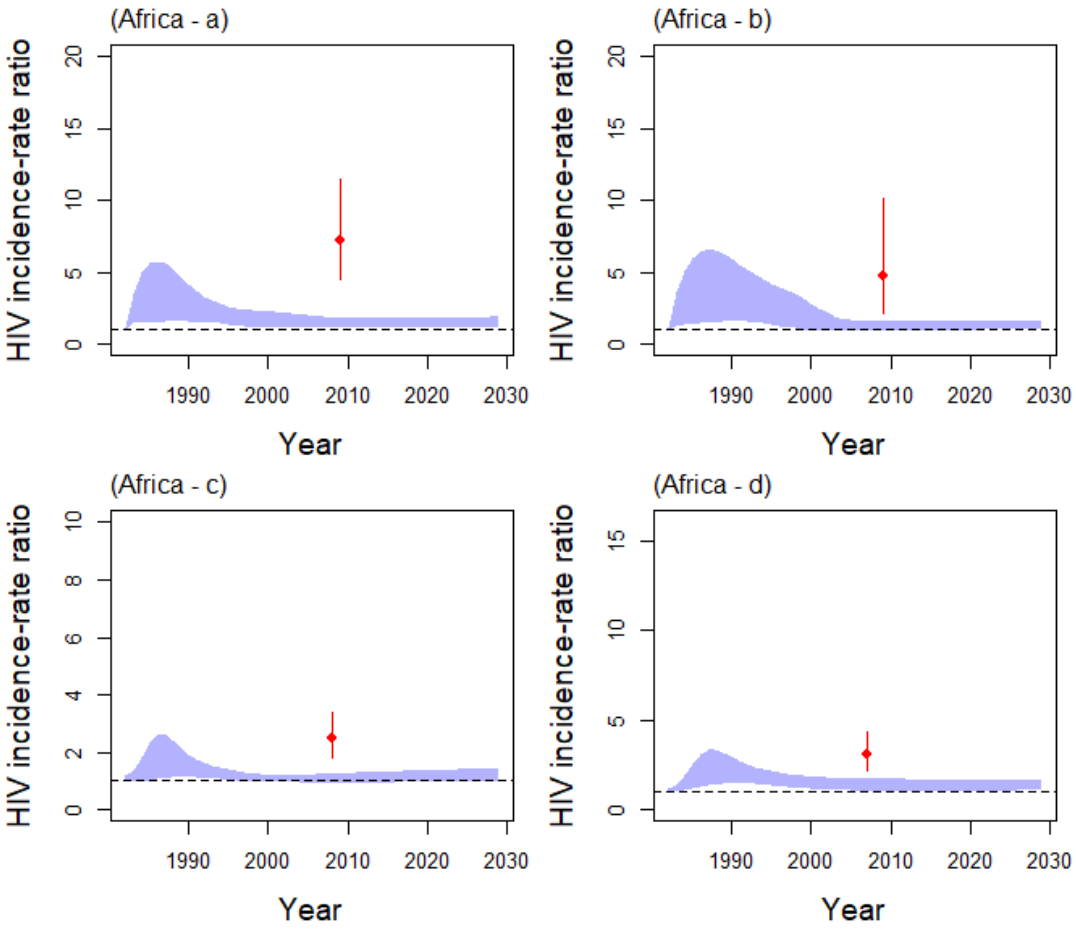


Figure S31: Specific scenario assuming no HSV-2/HIV interactions. HIV incidence rate ratio by HSV-2 infection status in a scenario assuming no interaction between HSV-2 and HIV (estimating a tPAF of 0%) calculated among a) all females with recent HSV-2 infection vs HSV-2-uninfected, b) all males with recent HSV-2 infection vs HSV-2-uninfected, c) all females with established HSV-2 infection vs HSV-2-uninfected, d) all males with established HSV-2 infection vs HSV-2-uninfected. Blue shades represent 95%UI of model outcomes. Red dots and intervals represent pooled estimates of empirical estimates from[8].

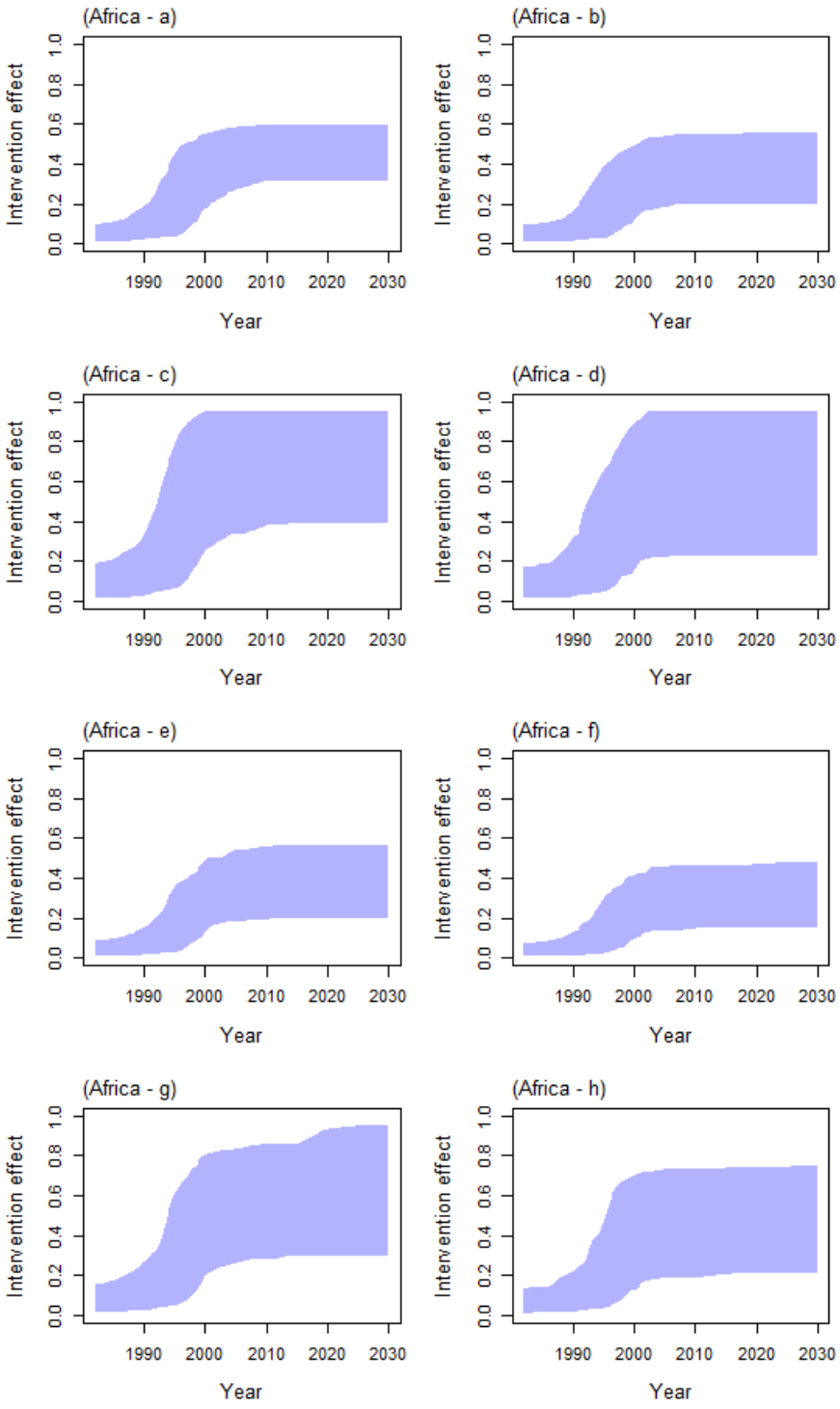


Figure S32: Model fitting for WHO Africa region, intervention coverage and efficacy against HSV-2 under the conservative scenario. Shaded areas are the modelled 95%UIs (2.5th and 97.5th percentile of the distribution) for the time-varying sigmoidal meta-parameter reflecting coverage and efficacy of interventions (primarily male circumcision and condom use) against HSV-2 among a) younger and b) older lower-risk males, c) younger and d) older CFSWs, e) younger and f) older lower-risk females, g) younger and h) older FSWs, under the conservative scenario.

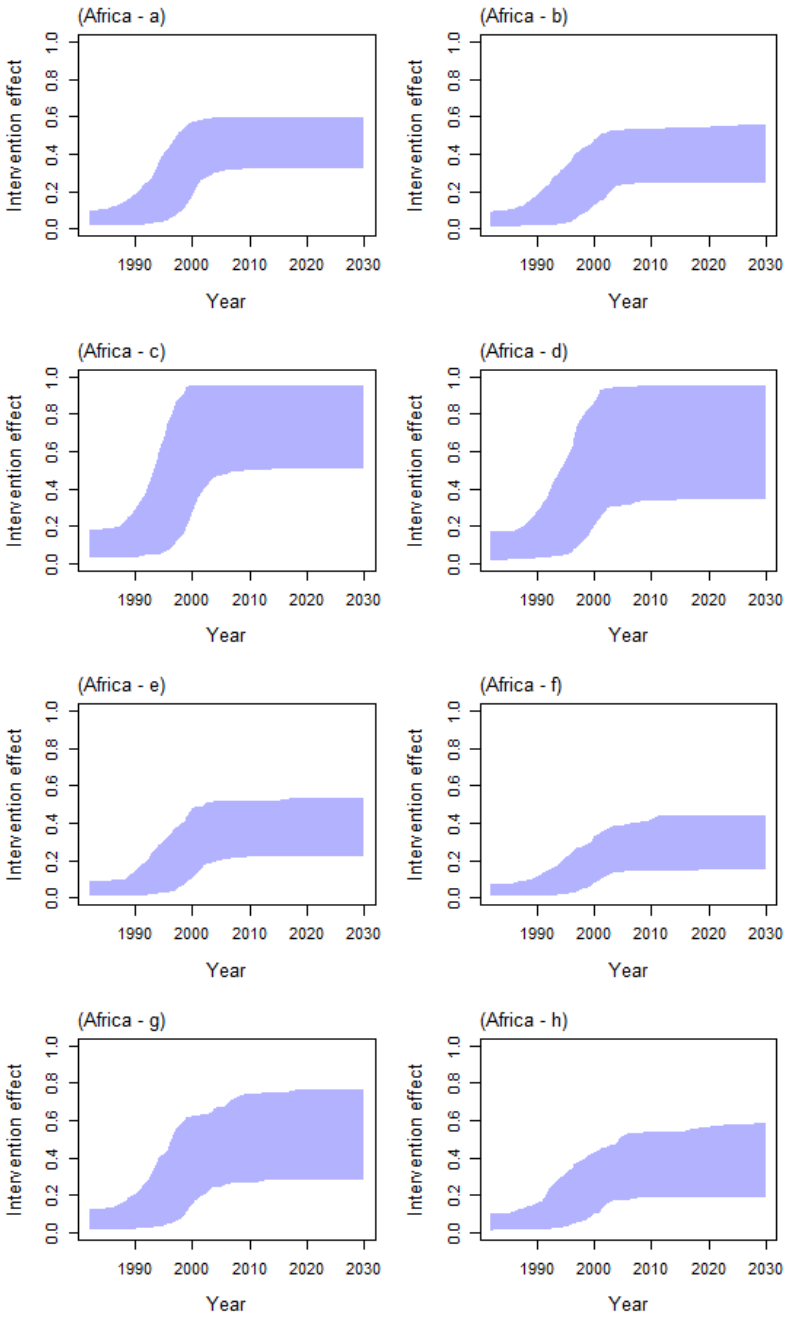


Figure S33: Model fitting for WHO Africa region, levels of intervention (reflecting coverage and efficacy of male circumcision and condom use) against HIV under the conservative scenario. Shaded areas are the modelled 95%UIs (2.5th and 97.5th percentile of the distribution) for the time-varying sigmoidal meta-parameter reflecting intervention levels against HIV among a) younger and b) older lower-risk males, c) younger and d) older CFSWs, e) younger and f) older lower-risk females, g) younger and h) older FSWs, under the conservative scenario.

Table S9a: Posterior distributions (median and 95% uncertainty interval) of the varying parameters under the conservative scenario						
	Africa	**Americas**	**South-East Asia**	**Europe**	**Western Pacific**	**Eastern Mediterranean**
Proportion of FSWs among all females	0.9% (0.5-1.7)	0.2% (0.2-0.5)	0.4% (0.3-0.7)	0.6% (0.5-0.8)	0.4% (0.3-0.5)	1.7% (1.0-2.7)
Proportion of CFSWs among all 15-49 years old males	6.7% (3.5-13.1)	4.5% (2.6-6.6)	5.9% (3.5-9.3)	3.9% (3.1-4.9)	5.3% (3.3-7.7)	9.4% (3.9-15.0)
Average duration of sex work in years	5.7 (5.0-6.0)	11.2 (10.1-11.9)	3.6 (3.0-4.0)	9.4 (8.5- 10.0)	3.7 (3.1-4.0)	5.5 (5.1-5.9)
Average duration as a CFSW in years	5.9 (2.6-9.4)	14.6 (10.7-19.5)	30.0 (20.6-38.7)	15.8 (11.2-19.4)	30.0 (20.6-38.9)	6.3 (2.5-9.6)
Annual number of sex acts of FSWs	898.3 (704.8-991.3)	899.1 (735.4-997.7)	893.1 (672.2-994.9)	942.0 (835.5-997.1)	934.6 (760.9-997.8)	733.6 (285.9-991.2)
Per-act infection risk for HIV (younger, lower-risk males partnered with younger lower-risk females)	0.00074 (0.00056-0.0009)	0.00081 (0.00073-0.00091)	0.00083 (0.00072-0.00098)	0.00061 (0.00056-0.00067)	0.00086 (0.00073-0.00098)	0.00060 (0.00052-0.00074)
RR of per-act HIV infection risk for older female (cf male)	1.80 (1.41-1.97)	1.67 (1.22-1.98)	1.38 (1.08-1.89)	1.32 (1.14-1.39)	1.32 (1.02-1.48)	1.77 (1.10-1.98)
RR of per-act HIV infection risk for younger female (cf older female)	2.08 (1.63-2.48)	2.42 (2.25-2.50)	2.31 (1.91-2.48)	2.36 (2.06-2.50)	2.13 (1.54-2.49)	1.63 (1.07-1.98)
RR which multiplies the infection risk for HIV to obtain the infection probability for established HSV-2 infection (for males)	1.23 (1.02-1.87)	1.05 (1.00-1.13)	1.05 (1.00-1.14)	1.03 (1.00-1.08)	1.07 (1.00-1.19)	1.05 (1.00-1.17)
RR of per-act HSV-2 infection risk for older female (cf male)	1.28 (1.02-1.93)	1.28 (1.06-1.47)	1.13 (1.01-1.28)	1.23 (1.11-1.30)	1.38 (1.07-1.49)	2.50 (2.02-2.98)
RR of per-act HSV-2 infection risk for younger female (cf older female)	2.17 (1.57-2.47)	1.83 (1.56-2.42)	1.70 (1.52-2.07)	1.90 (1.59-2.39)	1.51 (1.03-1.97)	1.67 (1.16-1.95)
RR of HSV-2 transmission risk during recent HSV-2 infection stage (cf established infection)	1.28 (1.21-1.39)	1.28 (1.20-1.40)	1.30 (1.21-1.39)	1.31 (1.20-1.40)	1.30 (1.21-1.40)	1.28 (1.21-1.39)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all females)	6.71 (4.91-8.79)	5.48 (3.93-7.35)	4.13 (2.06-6.32)	2.20 (1.34-3.37)	4.44 (2.93-5.92)	5.15 (3.72-7.09)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all males)	5.24 (2.84-7.49)	4.61 (3.75-6.16)	4.58 (2.26-6.82)	3.71 (2.26-5.34)	4.78 (2.65-7.53)	4.37 (2.44-7.14)

Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$(lower-risk females)	2.14 (1.68-2.85)	1.97 (1.60-2.58)	2.19 (1.40-2.97)	1.74 (1.24-2.24)	2.24 (1.37-2.78)	2.33 (1.47-3.23)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (lower-risk males)	2.51 (1.59-3.37)	3.13 (2.15-4.14)	2.97 (1.72-3.96)	2.50 (1.56-3.55)	2.99 (1.97-4.00)	2.85 (1.62-4.01)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (FSWs)	2.18 (1.44-2.69)	1.40 (1.14-2.04)	1.63 (1.19-2.46)	1.31 (1.16-1.58)	1.81 (1.26-2.48)	1.58 (1.14-2.50)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (CFSWs)	1.89 (1.41-2.60)	1.51 (1.27-2.07)	1.86 (1.30-2.35)	1.37 (1.14-1.66)	1.81 (1.21-2.37)	1.90 (1.25-2.88)
Increase in HIV transmission risk due to HSV-2 $RR^{HIV-T,\bar{s}}$	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Increased in HSV-2 transmission probability due to HIV $RR^{HSV-T,\bar{\imath}}$	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Effect of HSV-2 on the efficacy of ART in reducing per-act HIV transmission risk $RR_{HSV/ART-T}^{HIV}$	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Efficacy of ART in reducing the per-act increase in HSV-2 transmission risk due to HIV RR_{ART-T}^{HSV}	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HIV	0.05 (0.02-0.10)	0.05 (0.01-0.10)	0.05 (0.01-0.10)	0.05 (0.01-0.10)	0.08 (0.05-0.10)	0.26 (0.21-0.39)
End value of the HIV meta-parameter above	0.50 (0.32-0.60)	0.34 (0.30-0.39)	0.36 (0.30-0.48)	0.35 (0.30-0.44)	0.46 (0.40-0.54)	0.44 (0.40-0.50)
Time at which HIV meta-parameter value is halfway between start and end value	1998.1 (1993.0-2001.8)	1998.5 (1990.5-2004.8)	1997.9 (1990.5-2004.5)	2001.4 (1994.0-2004.7)	1999.4 (1990.4-2004.3)	1998.2 (1990.5-2004.3)
HIV meta-parameter shape gradient	0.51 (0.14-0.89)	0.49 (0.06-0.89)	0.56 (0.15-0.89)	0.48 (0.06-0.88)	0.50 (0.07-0.86)	0.54 (0.16-0.87)
RR of intervention levels for HIV among female (cf male)	0.67 (0.51-0.98)	0.70 (0.51-0.97)	0.84 (0.56-0.97)	0.84 (0.61-0.99)	0.61 (0.51-0.73)	0.61 (0.52-0.75)
RR of intervention levels for HIV among older female (cf younger female)	0.77 (0.52-0.99)	0.88 (0.57-0.99)	0.89 (0.73-0.99)	0.90 (0.63-0.99)	0.79 (0.51-0.99)	0.75 (0.54-0.98)

RR of intervention levels for HIV among older male (cf younger male)	0.88 (0.54-0.99)	0.85 (0.54-0.99)	0.88 (0.56-1.00)	0.79 (0.61-0.97)	0.79 (0.53-0.99)	0.64 (0.51-0.97)
RR of intervention levels for HIV among FSWs (cf lower-risk female)	1.26 (1.02-1.92)	1.67 (1.10-1.99)	1.63 (1.05-1.99)	1.74 (1.05-1.99)	1.53 (1.04-1.97)	1.56 (1.05-1.97)
RR of intervention levels for HIV among CFSWs (cf lower-risk female)	1.68 (1.10-1.97)	1.59 (1.03-1.98)	1.63 (1.06-1.99)	1.53 (1.05-1.99)	1.46 (1.11-1.96)	1.28 (1.01-1.80)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HSV-2	0.052 (0.012-0.097)	0.06 (0.012-0.098)	0.063 (0.012-0.097)	0.063 (0.014-0.097)	0.057 (0.011-0.097)	0.25 (0.11-0.30)
End value of the HSV-2 meta-parameter above	0.47 (0.32-0.60)	0.56 (0.47-0.60)	0.42 (0.31-0.59)	0.58 (0.54-0.60)	0.56 (0.51-0.60)	0.56 (0.50-0.60)
Time at which HSV-2 meta-parameter value is halfway between start and end value	1996.4 (1992.2-2001.3)	1993.2 (1990.2-1997.8)	1993.6 (1990.4-1998.8)	1991.5 (1990.2-1994.5)	1993.2 (1990.0-1996.7)	1992.5 (1990.2-2000.7)
HSV-2 meta-parameter shape gradient	0.46 (0.078-0.87)	0.55 (0.16-0.88)	0.48 (0.11-0.84)	0.57 (0.22-0.89)	0.61 (0.22-0.89)	0.66 (0.21-0.89)
RR of intervention levels for HSV-2 among female (cf male)	0.82 (0.53-0.98)	0.66 (0.52-0.94)	0.77 (0.52-0.97)	0.57 (0.50-0.69)	0.59 (0.50-0.86)	0.36 (0.27-0.48)
RR of intervention levels for HSV-2 among older female (cf younger female)	0.75 (0.53-0.99)	0.64 (0.50-0.92)	0.74 (0.51-0.99)	0.64 (0.50-0.86)	0.61 (0.50-0.88)	0.78 (0.55-0.99)
RR of intervention levels for HSV-2 among older male (cf younger male)	0.82 (0.51-0.99)	0.93 (0.75-0.99)	0.75 (0.51-0.99)	0.97 (0.91-1.00)	0.93 (0.81-1.00)	0.96 (0.84-1.00)
RR of intervention levels for HSV-2 among FSWs (cf lower-risk female)	1.59 (1.08-1.96)	1.15 (1.01-1.66)	1.17 (1.02-1.65)	1.12 (1.00-1.50)	1.18 (1.01-1.74)	1.50 (1.05-1.98)
RR of intervention levels for HSV-2 among CFSWs (cf lower-risk female)	1.54 (1.08-1.99)	1.48 (1.03-1.95)	1.20 (1.01-1.67)	1.63 (1.42-1.98)	1.69 (1.42-1.98)	1.75 (1.36-1.99)
RR for the average number of years an individual is HIV-infected and on ART before death (vs not on ART)	0.38 (0.26-0.50)	0.39 (0.26-0.48)	0.37 (0.25-0.48)	0.37 (0.26-0.48)	0.38 (0.26-0.49)	0.37 (0.26-0.49)

Proportion of population on ART who are virally supressed	0.77 (0.74-0.80)	0.82 (0.80-0.85)	0.85 (0.85-0.85)	0.76 (0.69-0.83)	0.85 (0.85-0.85)	0.76 (0.76-0.76)
Efficacy of ART in reducing per-act HIV transmission risk for those who are virally supressed	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
RR of ART initiation over 1996-2000 (cf 2010-2018)	0.0006 (0.0001-0.0009)	0.042 (0.005-0.096)	0.00057 (0.0001-0.001)	0.10 (0.018-0.19)	0.039 (0.0021-0.095)	0.11 (0.0099-0.19)
RR of ART initiation over 2000-2005 (cf 2010-2018)	0.059 (0.012-0.099)	0.20 (0.11-0.30)	0.065 (0.016-0.098)	0.27 (0.15-0.35)	0.15 (0.11-0.20)	0.25 (0.12-0.38)
RR of ART initiation over 2005-2010 (cf 2010-2018)	0.20 (0.11-0.29)	0.43 (0.32-0.67)	0.19 (0.12-0.25)	0.60 (0.46-0.74)	0.28 (0.21-0.44)	0.56 (0.40-0.76)
RR of ART initiation over 2010-2018 (cf 2010-2018)	1.62 (1.01-1.98)	1.51 (1.04-1.98)	1.57 (1.02-1.98)	1.53 (1.03-1.97)	1.53 (1.07-1.96)	1.46 (1.07-1.96)
Yearly rate of ART initiation among HIV+ females over 2010-2018	0.57 (0.51-0.68)	0.37 (0.30-0.60)	0.43 (0.31-0.53)	0.17 (0.13-0.23)	0.26 (0.20-0.34)	0.045 (0.033-0.065)
RR of ART initiation among HIV+ males (cf HIV+ females)	0.65 (0.61-0.69)	1.15 (1.03-1.30)	0.71 (0.62-0.79)	1.12 (1.01-1.28)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

Table S9b: Posterior distributions (median and 95% uncertainty interval) of the varying parameters under the liberal scenario						
	Africa	**Americas**	**South-East Asia**	**Europe**	**Western Pacific**	**Eastern Mediterranean**
Proportion of FSWs among all females	0.9% (0.5-1.7)	0.2% (0.1-0.4)	0.4% (0.3-0.6)	0.6% (0.5-0.7)	0.4% (0.3-0.5)	1.8% (1.0-2.7)
Proportion of CFSWs among all 15-49 years old males	6.7% (3.5-13.0)	5% (2.6-6.8)	6.2% (3.2-9.5)	3.6% (3-4.8)	5.7% (3.6-7.8)	9.0% (3.6-15.0)
Average duration of sex work in years	5.65 (5.04-5.95)	11.09 (10.20-11.98)	3.60 (2.88-3.97)	9.60 (8.47- 9.99)	3.76 (3.12-3.99)	5.46 (5.03-5.95)
Average duration as a CFSW in years	5.86 (2.64-9.44)	15.58 (11.34-19.87)	29.87 (20.57-39.50)	15.19 (10.50-19.64)	30.07 (21.57-39.33)	5.63 (2.27-9.30)
Annual number of sex acts of FSWs	898.33 (704.84-991.33)	904.41 (659.59-995.35)	908.99 (713.77-996.17)	929.33 (818.76-997.31)	933.23 (779.99-994.72)	620.91 (289.20-958.26)
Per-act infection risk for HIV (younger, lower-risk males partnered with younger lower-risk females)	0.0007 (0.0006-0.0009)	0.0007 (0.0006-0.0009)	0.0008 (0.0007-0.0009)	0.0006 (0.0005-0.0007)	0.0008 (0.0007-0.001)	0.0005 (0.0004-0.0007)
RR of per-act HIV infection risk for older female (cf male)	1.80 (1.41-1.97)	1.41 (1.02-1.94)	1.25 (1.01-1.85)	1.29 (1.11-1.38)	1.21 (1.00-1.48)	1.70 (1.21-1.99)
RR of per-act HIV infection risk for younger female (cf older female)	2.08 (1.63-2.48)	2.40 (2.22-2.49)	2.24 (1.86-2.47)	2.37 (2.02-2.50)	2.13 (1.53-2.47)	1.70 (1.05-1.98)
RR which multiplies the infection risk for HIV to obtain the infection probability for established HSV-2 infection (for males)	1.23 (1.02-1.87)	1.06 (1.01-1.14)	1.07 (1.01-1.14)	1.04 (1.00-1.09)	1.10 (1.02-1.19)	1.05 (1.00-1.19)
RR of per-act HSV-2 infection risk for older female (cf male)	1.28 (1.02-1.93)	1.32 (1.06-1.49)	1.13 (1.01-1.28)	1.24 (1.13-1.30)	1.40 (1.13-1.50)	2.51 (2.06-2.93)
RR of per-act HSV-2 infection risk for younger female (cf older female)	2.17 (1.57-2.47)	1.89 (1.53-2.46)	1.70 (1.51-2.08)	2.03 (1.60-2.42)	1.58 (1.04-1.97)	1.75 (1.33-1.99)
RR of HSV-2 transmission risk during recent HSV-2 infection stage (cf established infection)	1.28 (1.21-1.39)	1.29 (1.21-1.40)	1.29 (1.21-1.39)	1.27 (1.21-1.39)	1.30 (1.21-1.39)	1.29 (1.21-1.39)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all females)	6.71 (4.91-8.79)	5.53 (3.93-7.01)	4.24 (2.16-7.02)	2.38 (1.28-3.14)	4.58 (2.83-6.27)	4.91 (3.54-7.12)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all males)	5.24 (2.84-7.49)	4.75 (3.71-6.63)	5.20 (2.19-7.62)	3.48 (2.32-4.95)	5.08 (2.73-8.47)	4.20 (2.78-6.91)
Increase in HIV acquisition risk due to established HSV-2	2.14 (1.68-2.85)	2.06 (1.58-2.60)	2.15 (1.46-2.83)	1.99 (1.41-2.43)	2.08 (1.47-2.77)	2.31 (1.58-3.24)

infection $RR_{ra}^{HIV-A,s=3}$(lower-risk females)						
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (lower-risk males)	2.51 (1.59-3.37)	3.20 (2.24-4.18)	2.91 (1.66-4.04)	2.39 (1.79-3.39)	2.98 (1.84-4.12)	2.81 (1.41-3.93)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (FSWs)	2.18 (1.44-2.69)	1.45 (1.10-1.94)	1.64 (1.12-2.26)	1.29 (1.14-1.47)	1.67 (1.25-2.54)	1.76 (1.15-2.46)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (CFSWs)	1.89 (1.41-2.60)	1.49 (1.27-2.01)	1.79 (1.14-2.35)	1.37 (1.17-1.64)	1.77 (1.29-2.45)	1.92 (1.20-2.78)
Increase in HIV transmission risk due to HSV-2 $RR^{HIV-T,\tilde{s}}$	1.35 (1.11-1.72)	1.43 (1.09-1.77)	1.38 (1.10-1.81)	1.46 (1.12-1.80)	1.36 (1.08-1.73)	1.59 (1.19-1.80)
Increased in HSV-2 transmission probability due to HIV $RR^{HSV-T,\tilde{\imath}}$	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Effect of HSV-2 on the efficacy of ART in reducing per-act HIV transmission risk $RR_{HSV/ART-T}^{HIV}$	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
Efficacy of ART in reducing the per-act increase in HSV-2 transmission risk due to HIV RR_{ART-T}^{HSV}	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HIV	0.054 (0.017-0.096)	0.055 (0.012-0.095)	0.055 (0.021-0.097)	0.048 (0.012-0.096)	0.074 (0.051-0.098)	0.29 (0.21-0.40)
End value of the HIV meta-parameter above	0.50 (0.32-0.60)	0.34 (0.30-0.40)	0.40 (0.31-0.49)	0.39 (0.30-0.44)	0.47 (0.41-0.55)	0.45 (0.40-0.50)
Time at which HIV meta-parameter value is halfway between start and end value	1998.1 (1993.0-2001.8)	1997.9 (1991.0-2004.8)	1996.6 (1990.5-2004.3)	1999.7 (1992.5-2004.3)	1996.8 (1990.1-2004.5)	1997.9 (1991.0-2004.9)
HIV meta-parameter shape gradient	0.51 (0.14-0.89)	0.39 (0.061-0.86)	0.43 (0.077-0.87)	0.48 (0.13-0.86)	0.45 (0.081-0.88)	0.46 (0.066-0.88)
RR of intervention levels for HIV among female (cf male)	0.67 (0.51-0.98)	0.74 (0.51-0.98)	0.84 (0.52-0.99)	0.89 (0.67-0.99)	0.78 (0.52-0.99)	0.60 (0.50-0.72)
RR of intervention levels for HIV among older female (cf younger female)	0.77 (0.52-0.99)	0.84 (0.57-0.99)	0.90 (0.74-1.00)	0.90 (0.72-0.99)	0.83 (0.52-1.00)	0.72 (0.51-0.99)

RR of intervention levels for HIV among older male (cf younger male)	0.88 (0.54-0.99)	0.85 (0.58-1.00)	0.89 (0.53-0.99)	0.85 (0.61-0.98)	0.80 (0.52-0.98)	0.65 (0.51-0.97)
RR of intervention levels for HIV among FSWs (cf lower-risk female)	1.26 (1.02-1.92)	1.63 (1.07-1.99)	1.73 (1.05-1.99)	1.78 (1.22-1.99)	1.61 (1.05-1.99)	1.50 (1.05-1.90)
RR of intervention levels for HIV among CFSWs (cf lower-risk female)	1.68 (1.10-1.97)	1.58 (1.04-1.96)	1.71 (1.04-1.99)	1.62 (1.05-1.99)	1.57 (1.02-1.99)	1.40 (1.03-1.95)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HSV-2	0.052 (0.012-0.097)	0.062 (0.015-0.096)	0.061 (0.013-0.098)	0.059 (0.014-0.099)	0.06 (0.014-0.098)	0.21 (0.11-0.30)
End value of the HSV-2 meta-parameter above	0.47 (0.32-0.60)	0.56 (0.46-0.60)	0.42 (0.30-0.58)	0.58 (0.51-0.60)	0.55 (0.51-0.60)	0.56 (0.40-0.59)
Time at which HSV-2 meta-parameter value is halfway between start and end value	1996.4 (1992.2-2001.3)	1994.3 (1990.1-1997.9)	1994.6 (1990.1-1999.9)	1992.9 (1990.3-1994.9)	1993.1 (1990.1-1996.7)	1993.3 (1990.2-2001.8)
HSV-2 meta-parameter shape gradient	0.46 (0.078-0.87)	0.53 (0.079-0.88)	0.41 (0.061-0.88)	0.44 (0.21-0.80)	0.54 (0.22-0.86)	0.60 (0.11-0.88)
RR of intervention levels for HSV-2 among female (cf male)	0.82 (0.53-0.98)	0.64 (0.51-0.93)	0.72 (0.51-0.99)	0.57 (0.51-0.68)	0.61 (0.51-0.82)	0.35 (0.26-0.49)
RR of intervention levels for HSV-2 among older female (cf younger female)	0.75 (0.53-0.99)	0.64 (0.51-0.97)	0.75 (0.52-0.98)	0.59 (0.51-0.74)	0.63 (0.51-0.85)	0.79 (0.52-0.99)
RR of intervention levels for HSV-2 among older male (cf younger male)	0.82 (0.51-0.99)	0.90 (0.74-0.99)	0.75 (0.52-0.97)	0.96 (0.86-1.00)	0.92 (0.81-0.99)	0.93 (0.79-1.00)
RR of intervention levels for HSV-2 among FSWs (cf lower-risk female)	1.59 (1.08-1.96)	1.19 (1.02-1.79)	1.25 (1.01-1.98)	1.16 (1.00-1.40)	1.17 (1.01-1.66)	1.47 (1.06-1.94)
RR of intervention levels for HSV-2 among CFSWs (cf lower-risk female)	1.54 (1.08-1.99)	1.41 (1.03-1.94)	1.33 (1.03-1.67)	1.63 (1.45-1.95)	1.70 (1.41-1.95)	1.78 (1.18-1.98)
RR for the average number of years an individual is HIV-infected and on ART before death (vs not on ART)	0.38 (0.26-0.50)	0.37 (0.25-0.49)	0.36 (0.26-0.49)	0.37 (0.27-0.49)	0.38 (0.27-0.49)	0.36 (0.25-0.49)

Proportion of population on ART who are virally supressed	0.77 (0.74-0.80)	0.83 (0.80-0.85)	0.85 (0.85-0.85)	0.76 (0.70-0.82)	0.85 (0.85-0.85)	0.76 (0.76-0.76)
Efficacy of ART in reducing per-act HIV transmission risk for those who are virally supressed	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
RR of ART initiation over 1996-2000 (cf 2010-2018)	0.0006 (0.0001-0.001)	0.046 (0.0016-0.098)	0.0005 (0.0001-0.0009)	0.088 (0.011-0.19)	0.052 (0.0039-0.097)	0.09 (0.011-0.20)
RR of ART initiation over 2000-2005 (cf 2010-2018)	0.059 (0.012-0.099)	0.20 (0.11-0.30)	0.06 (0.02-0.098)	0.24 (0.16-0.34)	0.14 (0.10-0.19)	0.20 (0.11-0.38)
RR of ART initiation over 2005-2010 (cf 2010-2018)	0.20 (0.11-0.29)	0.44 (0.31-0.67)	0.19 (0.11-0.24)	0.57 (0.47-0.73)	0.30 (0.20-0.43)	0.55 (0.42-0.78)
RR of ART initiation over 2010-2018 (cf 2010-2018)	1.62 (1.01-1.98)	1.51 (1.06-1.98)	1.48 (1.02-1.93)	1.44 (1.02-1.94)	1.52 (1.06-1.97)	1.48 (1.04-1.97)
Yearly rate of ART initiation among HIV+ females over 2010-2018	0.57 (0.51-0.68)	0.42 (0.31-0.60)	0.44 (0.32-0.54)	0.17 (0.13-0.24)	0.25 (0.20-0.34)	0.044 (0.031-0.065)
RR of ART initiation among HIV+ males (cf HIV+ females)	0.65 (0.61-0.69)	1.17 (1.02-1.29)	0.74 (0.61-0.80)	1.15 (1.01-1.29)	1.00 (1.00-1.00)	1.00 (1.00-1.00)

Table S9c: Posterior distributions (median and 95% uncertainty interval) of the varying parameters under the fully liberal scenario.

	Africa	**Americas**
Proportion of FSWs among all females	0.7% (0.4-1.5)	0.2% (0.16-0.44)
Proportion of CFSWs among all 15-49 years old males	6.3% (3.4-12.0)	4.2% (2.5-6.9)
Average duration of sex work in years	5.57 (5.05-5.98)	11.29 (10.12-11.95)
Average duration as a CFSW in years	6.25 (2.80-9.62)	14.48 (10.20-19.52)
Annual number of sex acts of FSWs	857.4 (655.2-987.5)	870.6 (618.7-995.6)
Per-act infection risk for HIV (younger, lower-risk males partnered with younger lower-risk females)	0.0006 (0.0005-0.0008)	0.0008 (0.0006-0.0009)
RR of per-act HIV infection risk for older female (cf male)	1.73 (1.19-1.99)	1.42 (1.02-1.93)
RR of per-act HIV infection risk for younger female (cf older female)	2.20 (1.59-2.48)	2.42 (2.22-2.49)
RR which multiplies the infection risk for HIV to obtain the infection probability for established HSV-2 infection (for males)	1.21 (1.03-1.48)	1.05 (1.00-1.14)
RR of per-act HSV-2 infection risk for older female (cf male)	1.54 (1.05-1.98)	1.32 (1.03-1.49)
RR of per-act HSV-2 infection risk for younger female (cf older female)	2.16 (1.58-2.48)	1.91 (1.52-2.46)
RR of HSV-2 transmission risk during recent HSV-2 infection stage (cf established infection)	1.31 (1.20-1.39)	1.27 (1.20-1.39)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all females)	7.32 (4.66-9.46)	5.71 (4.26-7.27)
Increase in HIV acquisition risk due to recent HSV-2 infection $RR_{ra}^{HIV-A,s=2}$ (all males)	4.99 (2.39-7.68)	4.63 (3.73-6.46)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$(lower-risk females)	2.38 (1.76-3.14)	2.04 (1.59-2.54)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (lower-risk males)	2.73 (1.62-3.77)	2.99 (2.02-4.25)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (FSWs)	2.22 (1.42-2.89)	1.46 (1.11-1.89)
Increase in HIV acquisition risk due to established HSV-2 infection $RR_{ra}^{HIV-A,s=3}$ (CFSWs)	1.90 (1.42-2.77)	1.49 (1.29-1.91)
Increase in HIV transmission risk due to HSV-2 $RR^{HIV-T,\tilde{s}}$	1.41 (1.18-1.75)	1.39 (1.14-1.78)
Increased in HSV-2 transmission probability due to HIV $RR^{HSV-T,\tilde{\imath}}$	2.54 (1.65-4.37)	2.91 (1.88-4.01)
Effect of HSV-2 on the efficacy of ART in reducing per-act HIV transmission risk $RR_{HSV/ART-T}^{HIV}$	0.97 (0.95-1.00)	0.97 (0.95-1.00)
Efficacy of ART in reducing the per-act increase in HSV-2 transmission risk due to HIV RR_{ART-T}^{HSV}	0.59 (0.43-0.81)	0.64 (0.45-0.81)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HIV	0.055 (0.015-0.094)	0.039 (0.013-0.094)
End value of the HIV meta-parameter above	0.52 (0.36-0.59)	0.33 (0.30-0.39)
Time at which HIV meta-parameter value is halfway between start and end value	1997.4 (1992.4-2001.7)	1998.4 (1990.6-2004.5)
HIV meta-parameter shape gradient	0.52 (0.13-0.86)	0.45 (0.074-0.85)
RR of intervention levels for HIV among female (cf male)	0.68 (0.52-0.97)	0.77 (0.51-0.98)
RR of intervention levels for HIV among older female (cf younger female)	0.74 (0.51-0.98)	0.88 (0.53-1.00)
RR of intervention levels for HIV among older male (cf younger male)	0.88 (0.55-0.99)	0.87 (0.56-1.00)

RR of intervention levels for HIV among FSWs (cf lower-risk female)	1.29 (1.01-1.94)	1.69 (1.10-1.98)
RR of intervention levels for HIV among CFSWs (cf lower-risk female)	1.63 (1.04-1.98)	1.66 (1.07-1.99)
Starting value of the time-varying sigmoidal meta-parameter representing intervention levels for HSV-2	0.061 (0.016-0.096)	0.051 (0.014-0.098)
End value of the HSV-2 meta-parameter above	0.45 (0.31-0.57)	0.55 (0.46-0.60)
Time at which HSV-2 meta-parameter value is halfway between start and end value	1997.1 (1992.1-2001.8)	1993.2 (1990.3-1997.8)
HSV-2 meta-parameter shape gradient	0.49 (0.084-0.88)	0.48 (0.13-0.89)
RR of intervention levels for HSV-2 among female (cf male)	0.78 (0.51-0.97)	0.67 (0.51-0.94)
RR of intervention levels for HSV-2 among older female (cf younger female)	0.80 (0.53-0.98)	0.60 (0.50-0.94)
RR of intervention levels for HSV-2 among older male (cf younger male)	0.80 (0.53-0.99)	0.91 (0.71-1.00)
RR of intervention levels for HSV-2 among FSWs (cf lower-risk female)	1.65 (1.09-1.98)	1.21 (1.00-1.64)
RR of intervention levels for HSV-2 among CFSWs (cf lower-risk female)	1.59 (1.08-1.99)	1.49 (1.04-1.94)
RR for the average number of years an individual is HIV-infected and on ART before death (vs not on ART)	0.37 (0.27-0.49)	0.37 (0.26-0.50)
Proportion of population on ART who are virally supressed	0.77 (0.74-0.80)	0.83 (0.80-0.85)
Efficacy of ART in reducing per-act HIV transmission risk for those who are virally supressed	0.98 (0.96-1.00)	0.98 (0.96-1.00)
RR of ART initiation over 1996-2000 (cf 2010-2018)	0.0006 (0.0002-0.0009)	0.049 (0.0047-0.096)
RR of ART initiation over 2000-2005 (cf 2010-2018)	0.05 (0.01-0.095)	0.20 (0.10-0.28)
RR of ART initiation over 2005-2010 (cf 2010-2018)	0.20 (0.10-0.29)	0.44 (0.31-0.67)
RR of ART initiation over 2010-2018 (cf 2010-2018)	1.53 (1.02-1.98)	1.50 (1.02-1.98)
Yearly rate of ART initiation among HIV+ females over 2010-2018	0.57 (0.51-0.68)	0.42 (0.31-0.63)
RR of ART initiation among HIV+ males (cf HIV+ females)	0.65 (0.60-0.70)	1.19 (1.01-1.29)

4.2. tPAF estimates

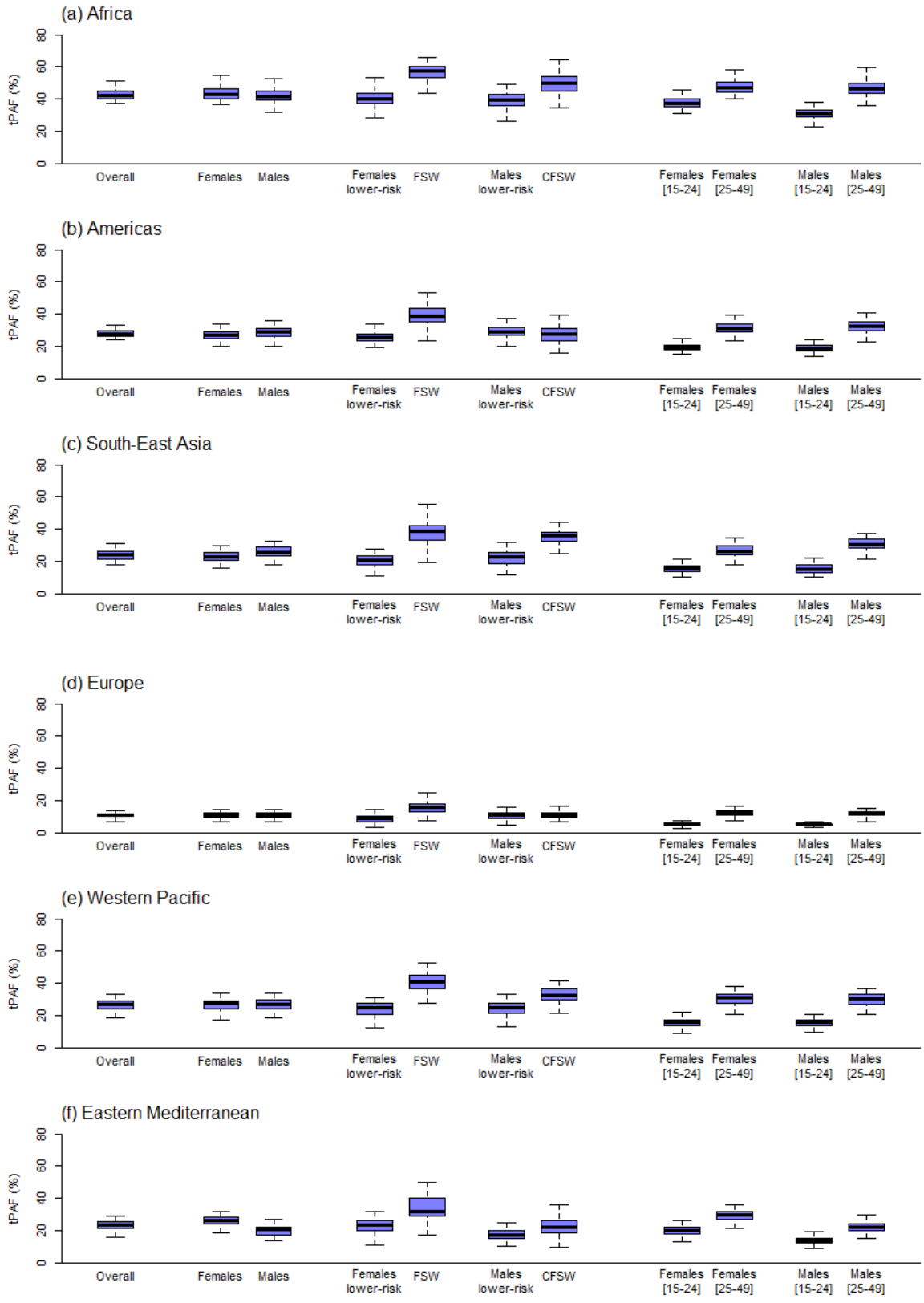


Figure S34: tPAF of HSV-2 on incident HIV infections under the conservative scenario over 2009-2018 for the WHO a) Africa, b) Americas, c) South-East Asia, d) Europe, e) Western Pacific, f) Eastern Mediterranean regions, calculated overall and stratified by gender, risk level and age. Boxplots represent median, interquartile range and 95%UI.

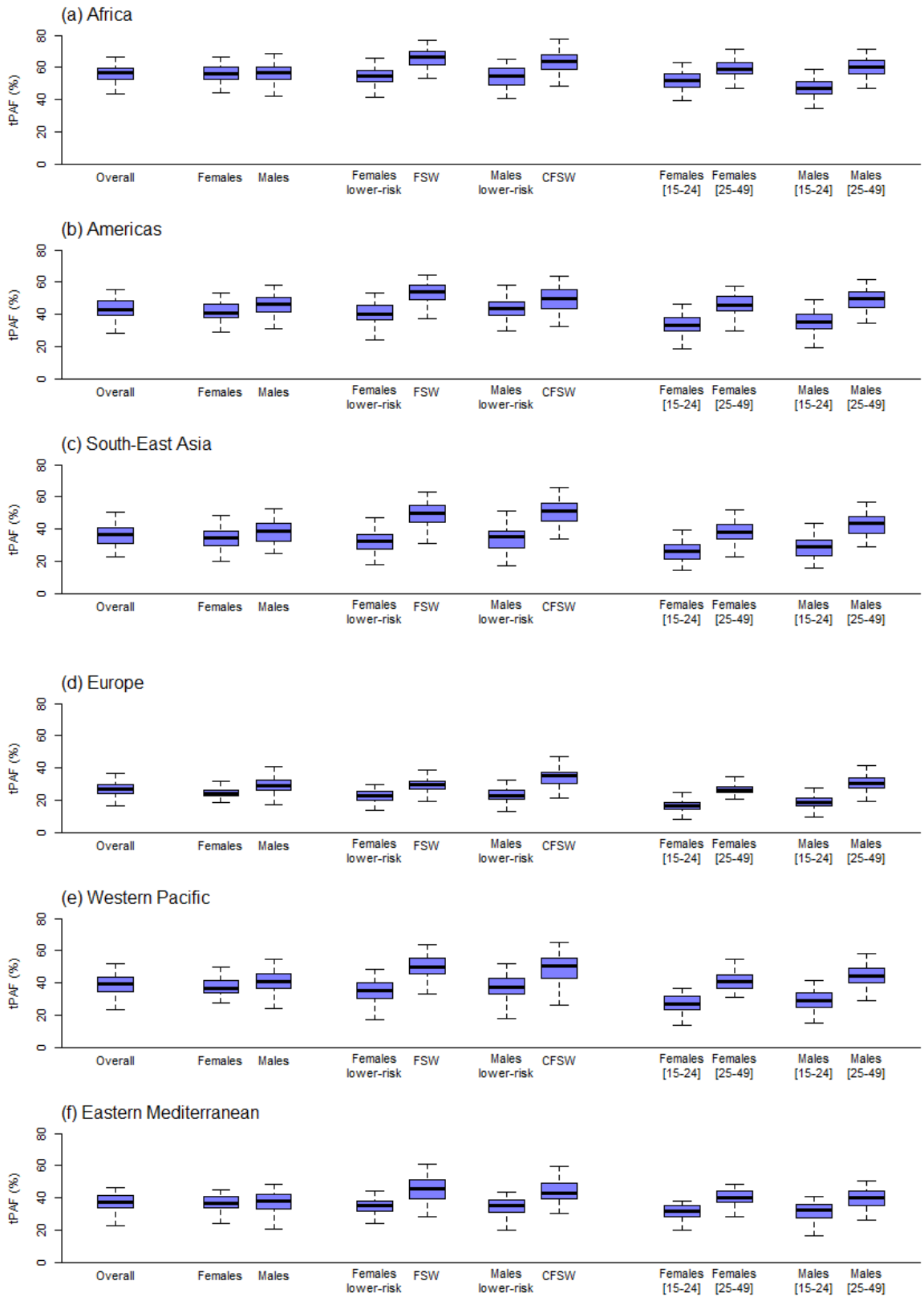
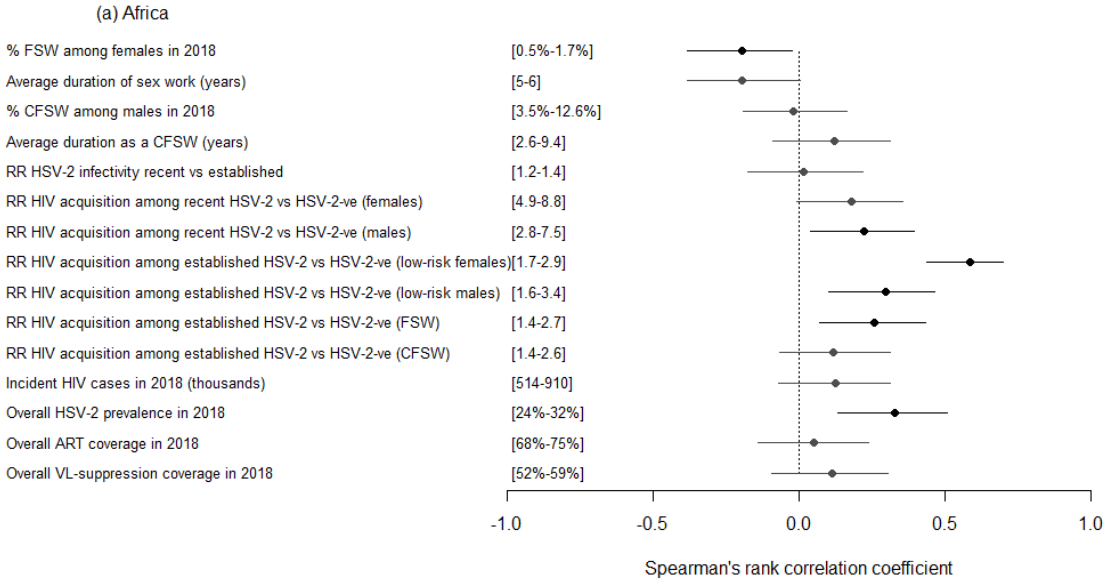


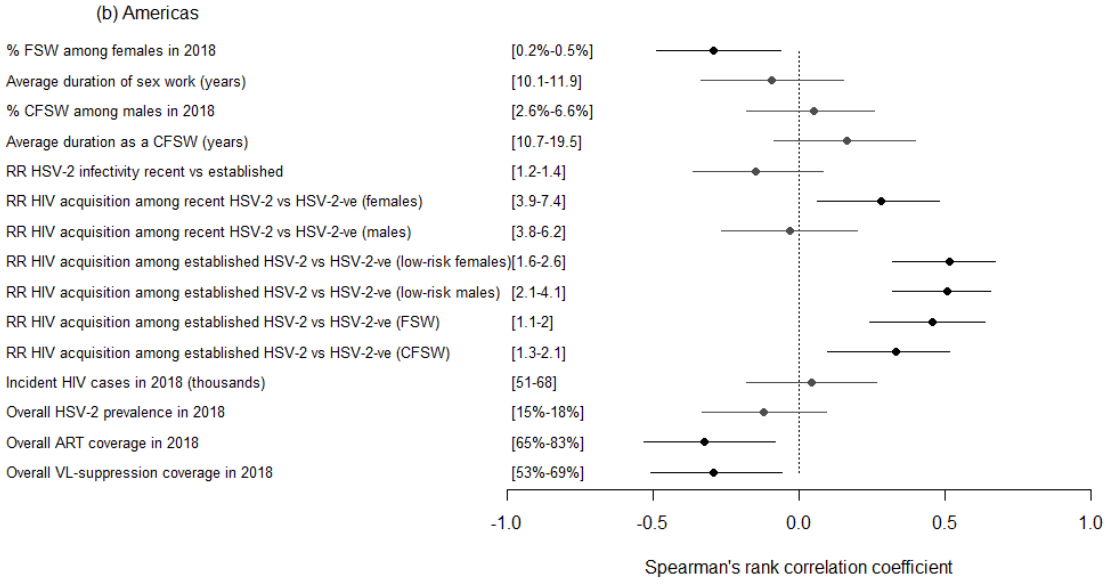
Figure S35: Boxplot of tPAF of HSV-2 on incident HIV infections under the liberal scenario over 2009-2018 for the WHO a) Africa, b) Americas, c) South-East Asia, d) Europe, e) Western Pacific, f) Eastern Mediterranean regions, calculated overall and stratified by gender, risk level and age. Boxplots represent median, interquartile range and 95%UI.

Table S10: Overall tPAF estimates for the different WHO regions (median and 95% UI), under the conservative and liberal scenarios: A) over 2009-2018 and B) for 2016 only.

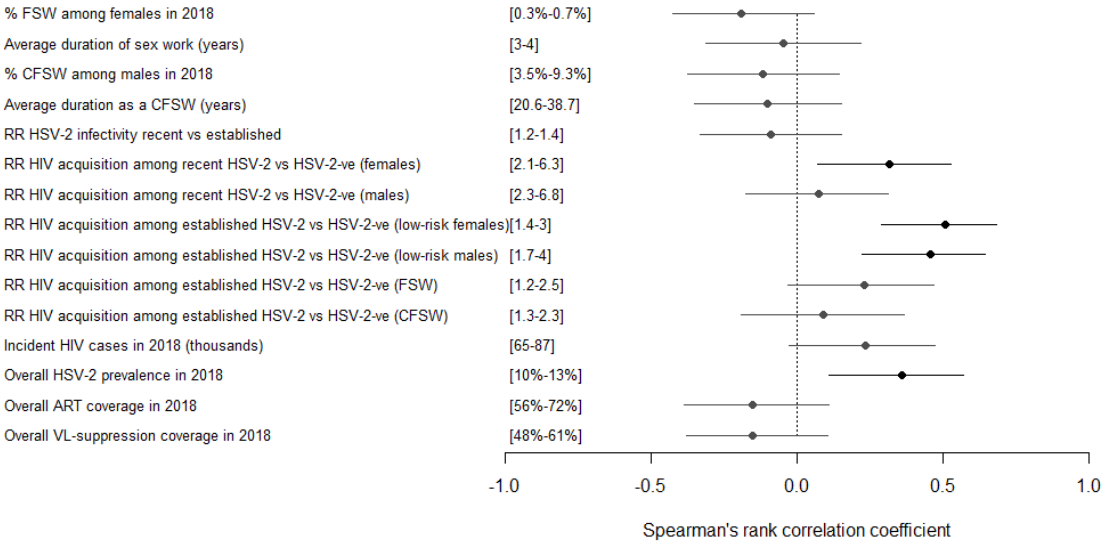
	Africa	Americas	South-East Asia	Europe	Western Pacific	Eastern Mediterranean
A) Calculated over 2009-2018						
Conservative scenario (increase in HIV acquisition risk due to HSV-2)	42.6% (38.0-51.2)	27.9% (23.6-33.6)	24.0% (18.6-29.7)	11.2% (7.9-13.8)	27.3% (20.0-32.1)	23.7% (17.8-27.9)
Liberal scenario (increase in HIV acquisition and transmission risk due to HSV-2)	56.5% (46.7-65.2)	43.2% (31.8-53.3)	36.5% (25.0-47.2)	26.8% (16.2-35.8)	39.2% (28.0-49.1)	37.3% (29.6-45.0)
Liberal scenario (separate effect of increase in HIV acquisition risk due to HSV-2)	43.7% (36.5-49.5)	30.1% (23.3-36.0)	24.8% (18.4-30.0)	11.6% (9.8-14.3)	27.8% (21.5-35.4)	24.6% (17.5-29.3)
Liberal scenario (separate effect of increase in HIV transmission risk due to HSV-2)	24.9% (9.9-41.4)	23.0% (5.6-35.6)	17.9% (5.5-32.5)	18.4% (5.9-28.8)	17.9% (4.8-31.8)	22.0% (8.6-29.5)
B) Calculated over 2016 only (for comparison with Looker et al. estimates [7])						
Conservative scenario (increase in HIV acquisition risk due to HSV-2)	33.6% (27.8-40.2)	20.9% (17.2-26.2)	18.4% (13.4-23.0)	7.7% (5.5- 9.6)	20.9% (14.6-24.6)	17.2% (12.4-20.7)
Liberal scenario	46.7% (37.3-56.7)	34.4% (24.4-44.2)	28.4% (18.5-38.2)	20.1% (11.9-27.7)	31.2% (21.6-39.8)	28.4% (20.7-34.5)
Liberal scenario (separate effect of increase in HIV acquisition risk due to HSV-2)	34.2% (28.3-39.7)	21.9% (16.7-26.9)	17.9% (12.8-22.4)	7.8% (6.0-10.3)	20.3% (15.8-26.0)	16.6% (11.9-20.5)
Liberal scenario (separate effect of increase in HIV transmission risk due to HSV-2)	19.2% (7.1-33.8)	16.5% (4.0-27.4)	13.0% (3.9-25.1)	13.6% (4.2-22.0)	13.3% (3.4-23.0)	15.5% (5.6-20.8)

4.3. Uncertainty analysis

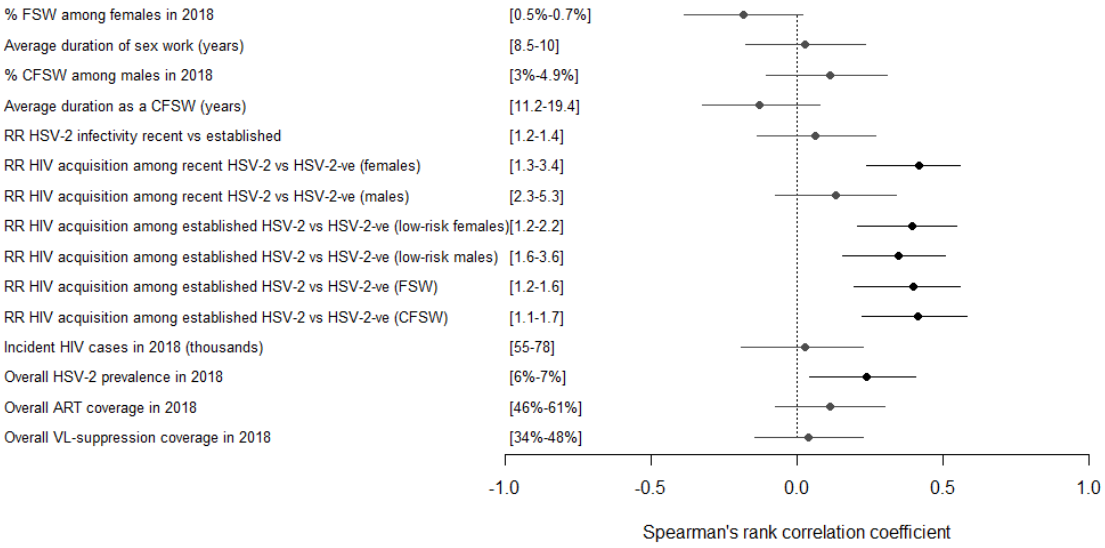


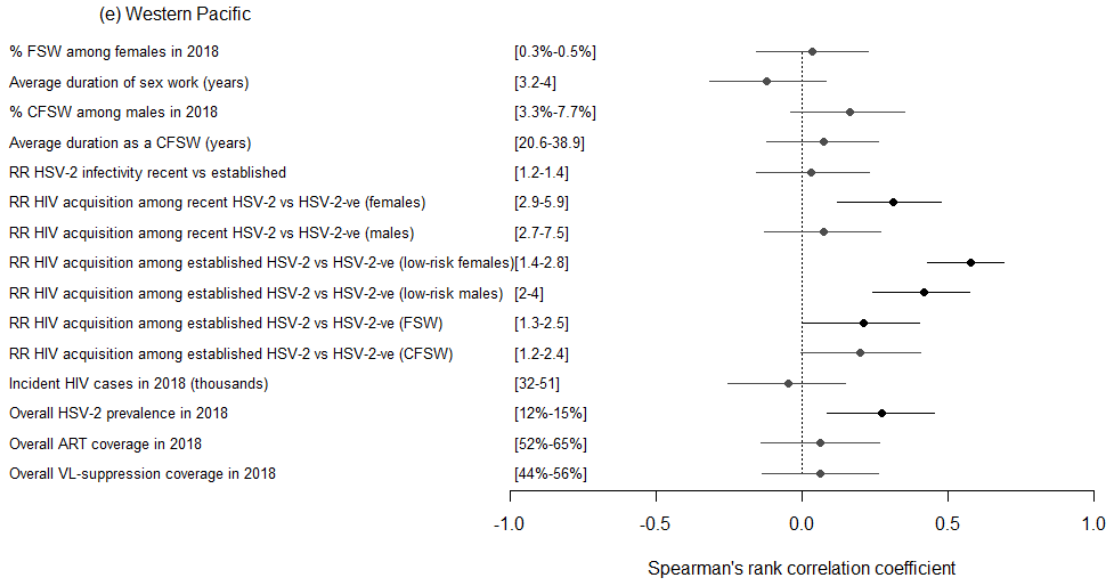


(c) South-East Asia



(d) Europe





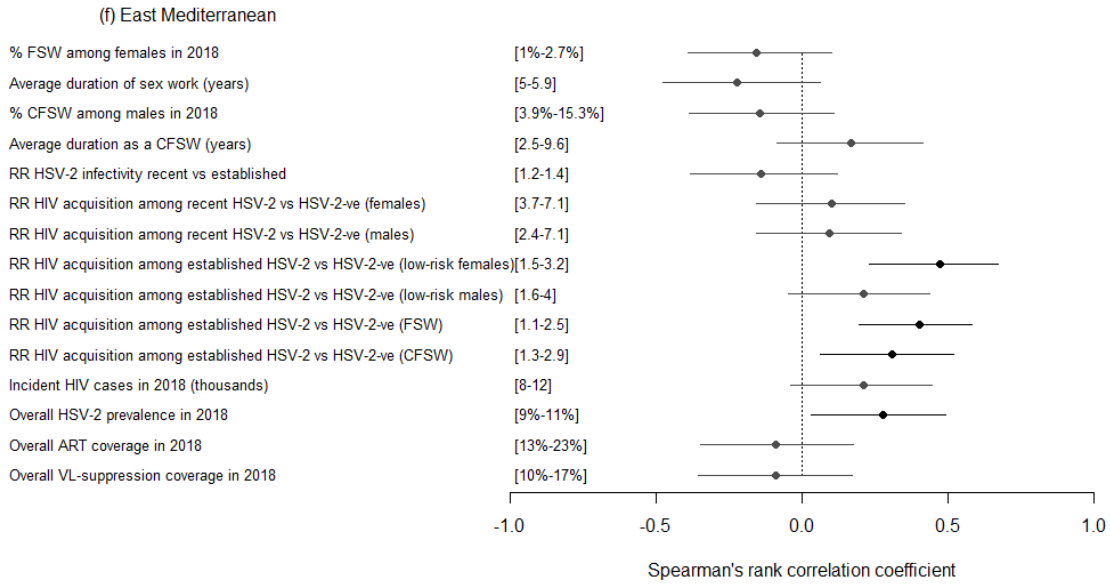


Figure S36: Model uncertainty analysis of the tPAF of HSV-2 on incident HIV infections for the WHO a) Africa, b) Americas, c) South-East Asia, d) Europe, e) Western Pacific, f) Eastern Mediterranean regions region, for the period 2009-2018, under the conservative scenario.

Points and lines represent estimates and 95% CI of Spearman's rank correlation coefficient assessing how the tPAF estimate is affected by changes in each of the listed model parameters, over the range of values shown in square brackets (posterior 95% UI). ART – antiretroviral therapy; FSWs – female sex worker; CFSWs – client of female sex worker; HSV-2 -ve – HSV-2 negative (i.e. HSV-2 uninfected); RR – relative risk (=cofactor effects); VL – viral load.

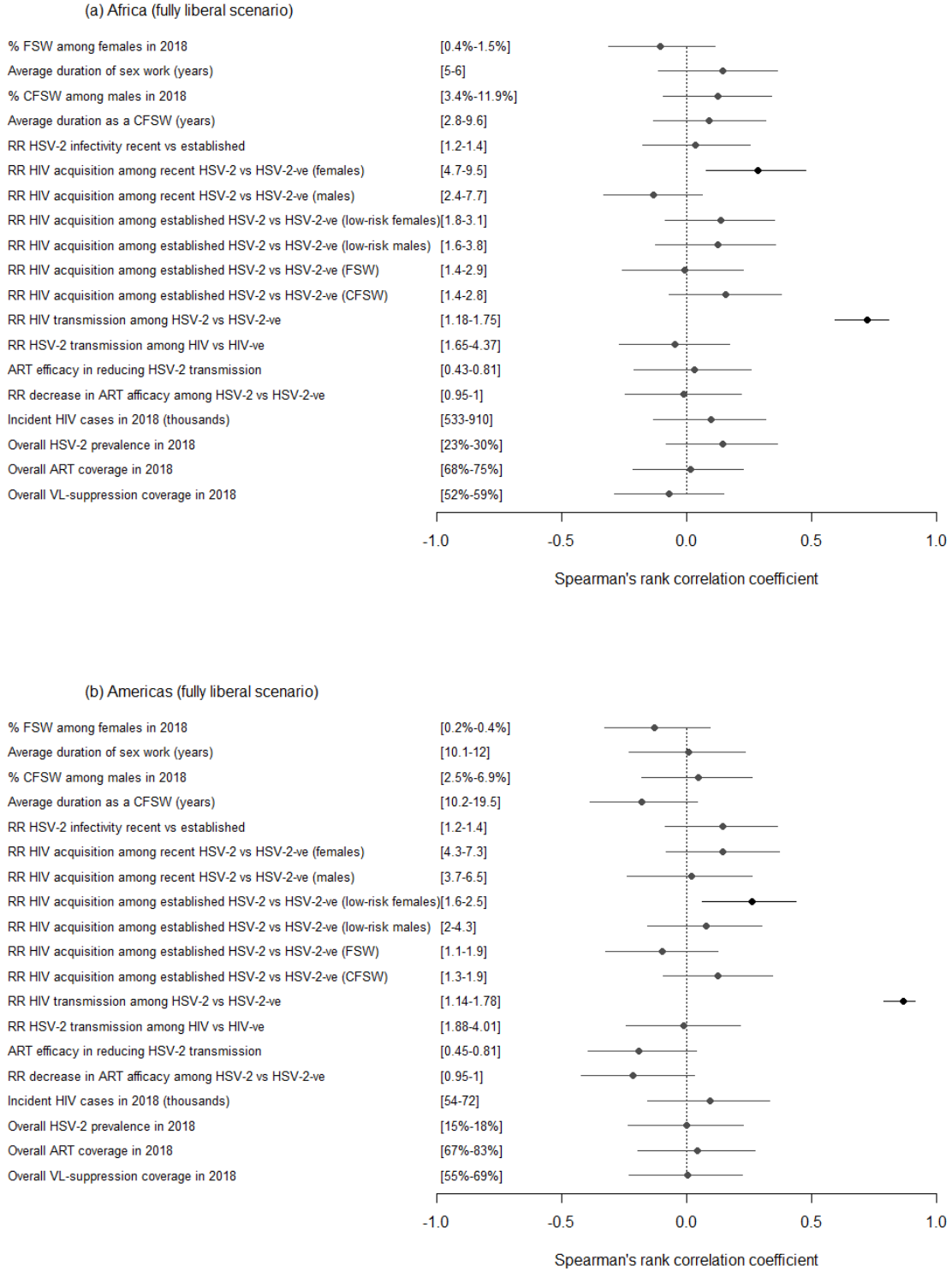
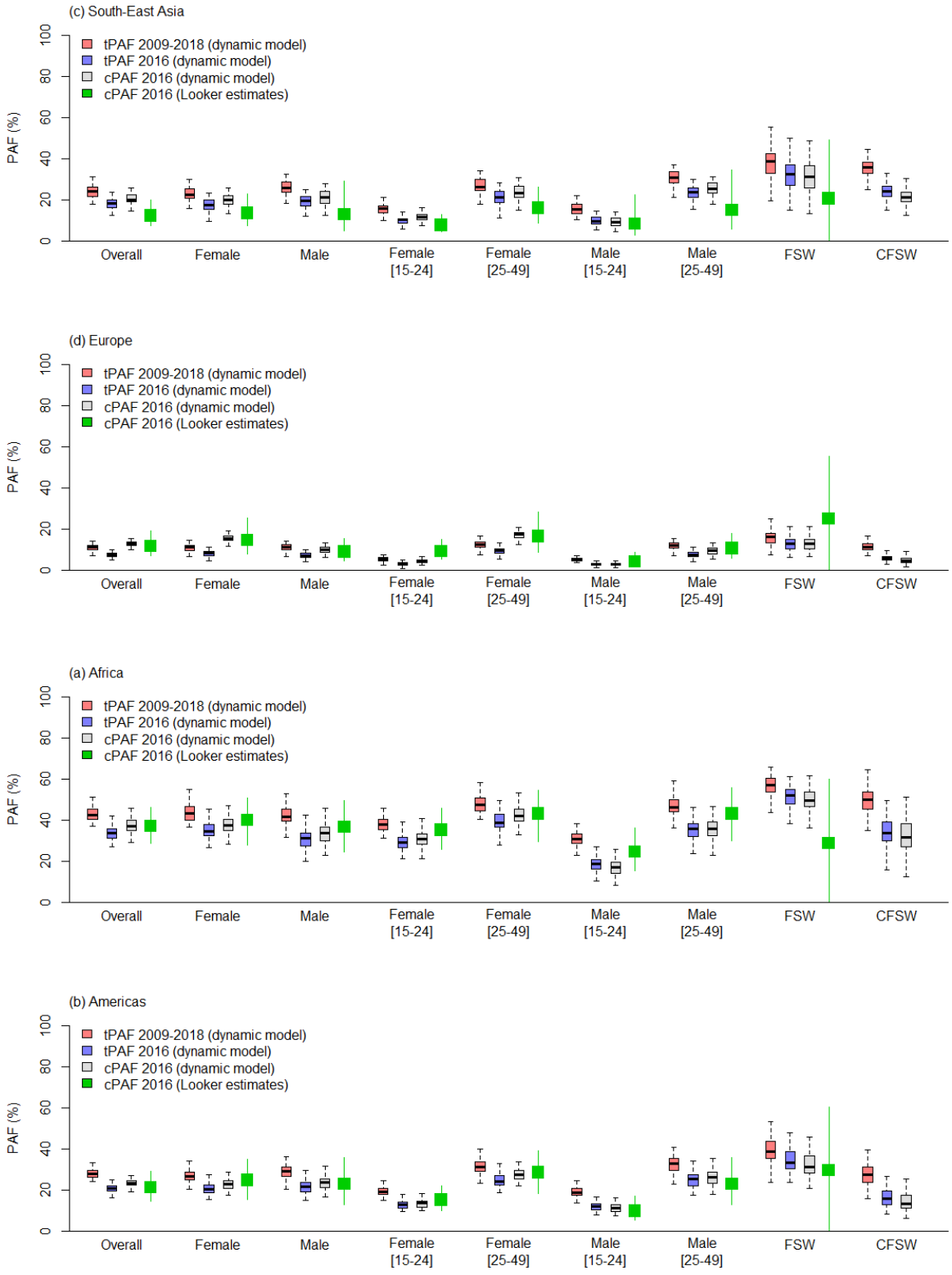


Figure S37: Model uncertainty analysis of the tPAF of HSV-2 on incident HIV infections in the a) African and 2) Americas regions, for the period 2009-2018, under the fully liberal scenario.

Points and lines represent estimates and 95% CI of Spearman's rank correlation coefficient assessing how the tPAF estimate is affected by changes in each of the listed model parameters, over the range of values shown in square brackets (posterior 95% UI). ART – antiretroviral

therapy; FSWs – female sex worker; CFSWs – client of female sex worker; HSV-2 -ve – HSV-2 negative (i.e. HSV-2 uninfected); RR – relative risk; VL – viral load.

4.4. Comparison with 1-year tPAF and cPAF estimates



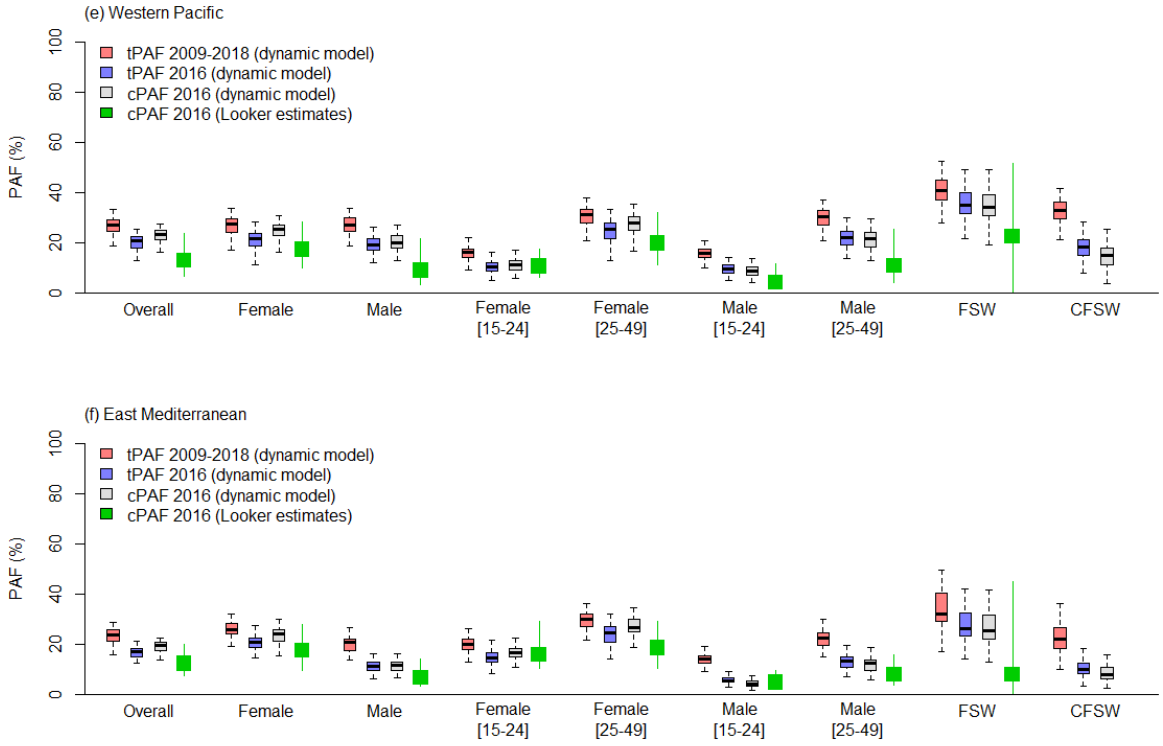


Figure S38: Boxplot of model tPAF estimates (red boxes for 2009-2018, blue boxes for the year 2016 only), model cPAF estimates (grey boxes), and Looker et al. [7] static cPAF estimates (for 2016, green boxes), for the WHO a) South-East, b) Americas, c) South-East Asia, d) Europe, e) Western Pacific, and f) East Mediterranean regions for the overall model population and stratified by sex, age and population risk level. Boxplots represent median, interquartile range and 95%UI. FSWs – female sex workers; CFSWs – clients of FSWs.

Table S11: Published classical PAF (cPAF) and transmission (tPAF) estimates of the effect of HSV-2 on incident HIV infections. Table highlights the HSV-2 cofactor assumptions made for each analysis: conservative (HSV-2 increases HIV susceptibility only), liberal (additionally assuming that HSV-2 can increase HIV transmissibility).

Model	Setting (year)	Estimate (95%CI)	cPAF/tPAF calculation	HSV-2 prevalence	Cofactor assumptions (measures of association with HIV risk, compared to HSV-2 uninfected individuals)[a]	Comments
Classical PAF (cPAF) estimates						
Looker et al. 2019[7]	Each WHO region (2016)	Africa: 37.1% (28.7-46.3) Americas: 21.3% (14.7-29.4) Eastern Mediterranean: 12.3% (7.5-20.1) Europe: 11.6% (7.0-19.4) South-East Asia: 12.4% (6.2-22.1) Western Pacific: 13.0% (6.5-23.7)	cPAF	Africa: ~32% Americas: ~14% Eastern Mediterranean: ~8% Europe: ~7% South-East Asia: ~8% Western Pacific: ~8%	**Conservative assumptions** HSV-2 increases HIV acquisition risk: IRR=7.2 (4.5-11.5) females, recent HSV-2 IRR=4.7 (2.2-10.1) males, recent HSV-2 IRR=2.5 (1.8-3.4) lower-risk females, established HSV-2 IRR=3.1 (2.2-4.3) lower-risk males, established HSV-2 IRR=1.5 (0.8-2.7) FSW, established HSV-2 IRR=1.7 (1.4-2.1) MSM, established HSV-2	cPAF only considers the direct effect of an increase in HIV susceptibility due to HSV-2
Todd et al. 2006[120]	Rural Tanzania (1991-1994)	Females: 58.7% (-2.5-83.3) Males: 64.9% (18.2-85.0)	cPAF	~59%	**Conservative assumptions** HSV-2 increases HIV acquisition risk: OR= 4.8 (1.2-18.8) females, incident HSV-2 OR= 2.9 (0.9–9.0) females, established HSV-2 OR= 5.6 (1.7-18.8) males, incident HSV-2	As above. Same study population as in[121].

					OR= 3.7 (1.3-10.4) males, established HSV-2	
Biraro et al. 2013[122]	Uganda (1990-2007)	Females: ~70% Males: ~60%	cPAF	Female: ~54% Male: ~35%	**Conservative assumptions** HSV-2 increases HIV acquisition risk: IRR= 7.3 (3.8-14.0) females, recent HSV-2 IRR = 3.7 (2.2-6.2) females, established HSV-2 IRR = 4.0 (1.7–9.5) males, recent HSV-2 IRR = 3.0 (1.8-4.9) females, established HSV-2	
Masese et al. 2015[123]	Kenya (1993-2012)	High-risk females: 52.8%	cPAF	High-risk females: 87%	**Conservative assumptions** HSV-2 increases HIV acquisition risk: HR= 3.0 (1.6-5.3) females, recent HSV-2 HR = 2.5 (1.5-4.1) females, established HSV-2	
van de Wijgert et al. 2009[124]	Zimbabwe and Uganda (1999-2004)	Females: 58.3%	cPAF	Females: ~69%	**Conservative assumptions** HSV-2 increases HIV acquisition risk: HR= 5.4 (3.1-9.4) females, incident HSV-2 HR = 3.7 (2.5-5.6) females, established HSV-2	
Venkatesh et al. 2011[125]	South Africa and Zimbabwe (2003-2005)	Females: ~31%	cPAF	Females: ~63%	HSV-2 increases HIV acquisition risk: OR= 3.7 (1.6-8.3); females, incident HSV-2 OR = 1.6 (1.2-2.0) females, established HSV-2	
Transmission dynamic model-based estimates						
African settings						

Abu-Raddad et al. 2008[126]	Kisumu, Kenya (1997)	25-35%, depending on cofactor assumptions	instantaneous tPAF	~50%	**Liberal assumptions** HSV-2 increases HIV acquisition risk during HSV-2 shedding by RR=4 or 9 HSV-2 increases HIV transmission risk during HSV-2 reactivations by RR=3	This tPAF estimate only captures direct effect of HSV-2 on HIV. Enhanced HIV susceptibility due to HSV-2 had slightly higher contribution to HIV than the enhanced HIV transmission risk due to HSV-2.
Freeman et al. 2007[127]	Four African cities (1997)	Kisumu (Kenya): 37.5% Ndola (Zambia): 36.1% Cotonou (Benin): 47.9% Yaoundé (Cameroon): 37.5%	2-year tPAF	Kisumu: ~ 60% Ndola: ~55% Cotonou: ~20% Yaoundé: ~50%	**Liberal assumptions** HSV-2 increases HIV acquisition and transmission risk: RR=25 for periods with primary herpetic ulcers RR= 10 for periods with recurrent herpetic ulcers In sensitivity analysis, HSV-2 increases HIV acquisition and transmission risk between ulcerative episodes by RR= 2 or 5.	In the sensitivity analysis, the tPAF estimates were 42.2-54.1% for Kisumu, 39.1-51.1% for Ndola, 53.4-62.7% for Cotonou, 43.7-58.1% for Yaoundé. Enhanced HIV transmission risk due to HSV-2 had contributed more to HIV than the enhanced HIV acquisition risk due to HSV-2.
Orroth et al. 2006[128]	Mwanza, Tanzania (1993) and Rakai,	Mwanza: 11.9% Rakai: 23.4%	2-year tPAF	~50% in both cities	**Liberal assumptions** Same as Freeman et al 2007, except that in the sensitivity analysis, HSV-2 increases HIV acquisition and	Same model as Freeman et al. When assumed that HSV-2 also affect

	Uganda (1995)				transmission risk between ulcerative episodes by RR= 5.	HIV between HSV-2 ulcerative episodes: 32% for Mwanza and 53% for Rakai.
South East Asian settings						
Foss et al. 2011[129]	Mysore, Karnataka, India (2004)	35.5% (22.2-62.5)	1-year tPAF	60-70%	**Liberal assumptions** HSV-2 alters HIV acquisition risk: RR=6.8 (1-8) for symptomatic HSV-2 RR=3.8 (0.5-5) for asymptomatic HSV-2 HSV-2 alters HIV transmission risk: RR=2.7 (0.3-5) for symptomatic HSV-2 RR=0.2 (0-4) for asymptomatic HSV-2	Only represented commercial partnerships of FSW. Altered HIV acquisition risk due to HSV-2 contributed more to HIV incidence than an altered HIV transmission risk due to HSV-2.

[a] Measures of association: "IRR"= incidence-rate ratio, "RR"= relative risk, "OR"=odds ratio, "HR"= Hazard ratio; measures in brackets denote uncertainty ranges (95%CI)
"Recent infection" defined as <1 year by Looker, et al., and Biraro, et al. "Incident infection" defined as those becoming infected during the 2-year follow-up by Todd, et al., van de Wijgert, et al., and those infected during follow-up by Venkatesh, et al., and Masese, et al. "Established infection" represents being infected at baseline for Todd et al., van de Wijgert, et al., Masese, et al., and Venkatesh, et al., and it represents >1 year by Looker, et al., and Biraro, et al.

95%CI=95% confidence or credible interval, FSW=female sex worker, MSM=men who have sex with men

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