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Modelling the interactions between Herpes simplex virus type-2 (HSV-2) and HIV: implications for the HIV epidemic in Southern India

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KEY MESSAGES

1. This is the first model exploring the role of HSV-2 in a concentrated HIV epidemic within an Asian setting.
2. The modelling suggests that HSV-2 plays an important role in the transmission and acquisition of HIV in Mysore, mostly through asymptomatic HSV-2 shedding.
3. Even in the best-case scenario, HSV-2 suppressive therapy is unlikely to reduce HIV transmission or acquisition by >50%, as aimed for in recent trials.
4. Modelling analyses can help guide trial design for expected power and sample size calculations, and retrospectively inform the interpretation of trial results.

ABSTRACT

Background

The role of HSV-2 in the HIV epidemic, and the potential impact of HSV-2 suppressive therapy, have been previously explored only within the context of sub-Saharan Africa. In this analysis, modelling is used to estimate: (1) the contribution of herpes simplex virus type-2 (HSV-2) to HIV transmission from clients to female sex workers (FSWs) in a Southern Indian setting; and (2) the maximum potential impact of 'perfect' HSV-2 suppressive therapy on HIV incidence.

Methods

A dynamic HSV-2/HIV model was developed, parameterised and fitted to Mysore data. The model estimated the attributable fractions (AFs) of HIV infections due to HSV-2. Multivariate sensitivity analyses and regression analyses were conducted.

Results

The model suggests that 36% (95% CI: 22-62%) of FSW HIV infections were due to HSV-2, mostly through HSV-2 asymptomatic shedding. Even if HSV-2 suppressive therapy could eliminate the effect of HSV-2 on HIV infectivity among all coinfecting clients, only 15% (95% CI: 3-41%) of HIV infections among FSWs would have been averted. 36% (95% CI: 18-61%) of HIV infections among HSV-2-infected FSWs could have been averted if suppressive therapy reduced their risk of HIV acquisition to that of the HSV-2-uninfected FSWs.

Conclusions

HSV-2 contributes substantially to HIV in this Southern Indian context. However, even in the best case scenario, HSV-2 suppressive therapy is unlikely to reduce HIV transmission or acquisition by more than 50% (as aimed for in recent trials), because of the limited strength of the interaction effect between HSV-2 and HIV.

Keywords

HIV; Herpes simplex virus type-2; mathematical modelling; India; female sex work.

INTRODUCTION

Herpes simplex virus type-2 (HSV-2) is highly prevalent in regions with high HIV prevalence and among groups at high risk of HIV.¹⁻² These associations are partly due to both infections being sexually transmitted, but several lines of biological evidence support bidirectional synergistic interactions between the two viruses.³⁻⁵ In HIV-uninfected individuals, HSV-2 infection increases susceptibility to HIV through clinical and subclinical recurrences which disrupt the genital epithelium and increase the density of HIV target cells in the genital submucosa.⁵⁻⁷ In accord with this evidence, a systematic meta-analysis of longitudinal studies of the effect of HSV-2 on HIV acquisition showed that, after adjusting for confounding by age and at least one measure of sexual behaviour, 38-60% of new HIV infections may be attributable to prevalent HSV-2 infection in women and 8-49% in men, in the general populations reviewed.⁸

In HIV-infected individuals, co-infection with HSV-2 may increase HIV infectivity by upregulating the replication of HIV through different interactions, potentially resulting in increased rates of HIV transmission from these coinfecting individuals.⁵ In fact, several cross-sectional studies have observed increased HIV genital shedding and plasma viral loads in the presence of HSV genital shedding or clinical recurrences.⁹⁻¹²

However, two recent randomised controlled trials evaluating the impact of HSV-2 suppressive therapy (HSVST) on HIV acquisition have shown that acyclovir 400mg twice daily had no significant effect on HIV incidence.¹³⁻¹⁴ These disappointing results may be related to the lack of effectiveness of the intervention, or the possibility that,

although the treatment reduced the HSV-2 virus, it did not cause a reduction in the density of cells which enhance susceptibility to HIV in HSV-2 infected individuals.^{7 13-}

¹⁶ In contrast, results of randomised controlled trials conducted among dually infected individuals have suggested that HSV-2 enhances HIV infectivity through demonstrating that HSVST reduces HIV shedding,¹⁷⁻²² although perhaps not sufficiently to actually reduce HIV transmission from coinfecting individuals²³.

Lastly, HSV-2 may also accelerate HIV disease progression by increasing HIV plasma viral load,²⁴ and HIV could potentially increase HSV-2 infectivity through increased genital shedding of HSV-2 among coinfecting individuals.^{10 25} The latest trial results support this hypothesis since HSVST used by those coinfecting significantly reduced HIV disease progression.²⁶

Only four models (albeit applied to several different research questions) have incorporated both HSV-2 and HIV, and their interactions.²⁷⁻³⁴ We build on these African and US focussed analyses, and our previous work³⁵, by using a model to explore the contribution of HSV-2 to HIV transmission for a female sex worker (FSW) population in Southern India, where the HIV epidemic is concentrated among high-risk groups. The relative importance of symptomatic versus asymptomatic HSV-2 genital shedding is explored. The implications of the findings for the maximum potential impact of HSVST are discussed.

METHODS

Dynamic deterministic models of HSV-2 and HIV were coupled to simulate the transmission of HIV and HSV-2 among FSWs and their clients. The HSV-2 model is described elsewhere,³⁵ and includes separate compartments for initial infection (which may be symptomatic or asymptomatic), the long ‘latent’ phase with infectious asymptomatic shedding, and periodic short recurrences of infectious symptoms. The HIV model incorporates the initial short phase of high viral load, followed by the long asymptomatic phase in which viral load is low. This coupled model was programmed in C and solved numerically. Further details are supplied in the supplemental online appendix.

The FSWs were modelled as a cohort, with the HSV-2, HIV and coinfection prevalences being modelled dynamically over the duration of sex work, whereas the client prevalences were assumed to remain constant over the short timeframe of five years considered. Clients were assumed to randomly contact FSWs regardless of the duration for which each had sold/bought sex.

Enhanced transmission of HIV or HSV-2 in the presence of the other infection was modelled through the use of ‘direct cofactors’ that directly increase the probability of transmission during each (penile-vaginal) sex act. Additionally, among coinfecting individuals, the symptomatic recurrence rate, proportion shedding asymptotically, and rate of progression to AIDS were all assumed to be increased compared with those

singly infected. The effect of other STIs facilitating HIV transmission was included as a constant cofactor.

Steps in analysis

Parameterisation

The parameter definitions and values used are shown in Table S1 in the supplemental online appendix, along with further details about the parameterisation process.

The model was parameterised and fitted using detailed behavioural and epidemiological data from FSWs in Mysore, Karnataka, and data on clients from Mysore when available, or elsewhere in Karnataka or other Indian states otherwise.³⁶⁻³⁷ Data came mostly from two unpublished surveys undertaken amongst FSWs (2004) and the general population (2005-6) in Mysore by the Karnataka Health Promotion Trust (KHPT), collected within the monitoring and evaluation of Avahan, the Bill and Melinda Gates Foundation funded India AIDS Initiative. The study was approved by the Ethics Review Boards of St Johns Medical College, Bangalore, India, Centre hospitalier affilié universitaire de Québec, Canada, and the University of Manitoba, Canada. The cohort model was fitted to HIV, HSV-2 and coinfection prevalences among FSWs by duration of sex work.

Uncertainty analysis and model fitting

First the model input parameter ranges were developed, distributions defined and correlations set (Table S1 in the online appendix). Latin Hypercube Sampling (LHS)

was then used to randomly sample 10,000 parameter sets from these uncertainty ranges. Those simulations that were rejected in our previous analysis,³⁵ are discarded here also, along with those predicting too low a prevalence at the start of sex work, leaving 7,536 simulations.

Any simulation that lay within the 95% confidence intervals (CIs) of the HSV-2, HIV and HSV-2/HIV coinfection prevalence data among FSWs, by duration of sex work up to five years, was accepted as a model fit. ‘Least chi-squared’ error was used to identify the best-fit. However, in addition to using prevalence data among FSWs, the mean values for the HSV-2 and HIV prevalence among the small number of men reporting visiting FSWs (42) in the unpublished general population survey from Mysore were also used to identify the best-fit.

Calculating attributable fractions

To investigate the contribution HSV-2 makes to HIV incidence, the model estimates of annual HIV incidence among FSWs after one to five years of sex work were compared with and without specific interaction cofactors included, for each model fit. These incidence values were used to calculate the attributable fraction (AF) of a specific interaction cofactor for increasing HIV transmission by using the following formula:

$$(1) \quad AF = \frac{(\text{Incidence with interaction}) - (\text{Incidence without interaction})}{(\text{Incidence with interaction})}.$$

An average AF was calculated after weighting the AFs at each year of sex work by the proportion having worked in sex work for each equivalent duration. Confidence bounds

were estimated by calculating the AFs for all the model fits and reporting the range spanned by 95% of the fits.

The model fits were also used to estimate the maximum potential impact that a hypothetical 'perfect' HSVST could have on HIV transmission in this FSW population, where 'perfect' refers here to completely removing the effect of HSV-2 on either HIV infectivity or HIV acquisition.

Sensitivity analysis

Multivariate sensitivity analysis using the best-fit simulation was used to identify which interaction inputs have the greatest effect on the predictions and to investigate the robustness of the model predictions to key assumptions. Each interaction model input was given the same relative uncertainty bounds ($\pm 20\%$), and 10,000 parameter sets were randomly sampled within these bounds using LHS. For each parameter set, the model was used to produce estimates of the percentage of incident HIV due to HSV-2. The relative importance of each non-correlated interaction parameter for the model prediction of the AFs was assessed using multilinear regression.

RESULTS

Selecting the best-fit and description of fits and correlations

Four hundred and one of the 7,536 model simulations fit within the 95% CIs of the observed HSV-2, HIV and coinfection prevalence data among FSWs. If, as in other similar analyses,^{27 34 38} we had only fitted to HSV-2 and HIV prevalences, 688 model fits would have been identified, leading to wider CIs on the model predictions and lower predictive power.

The model best-fit and the epidemiological data used to fit the model are shown in Figure 1. The input values used in the best-fit are given in Table S1 in the online appendix. The best-fit predicted an HSV-2 prevalence of 20% and HIV prevalence of 6% among clients (data estimates were 19% and 5%, respectively).

[INSERT Figure 1]

Attributable fractions

The AFs of all interaction effects of HSV-2 for HIV transmission among FSW are shown in Table 1, averaged over the first five years of sex work.

[INSERT Table 1]

Table 1 suggests that 35.5% (95% CI: 22.2-62.5%) of HIV infections among FSWs in Mysore are due to HSV-2, with the frequent infectious shedding of HSV-2 in the absence of symptoms contributing much more to HIV incidence than the less frequent recurrences of infectious symptoms (AF: 32.4% versus 3.0%).

If HSVST reduces the HIV infectivity of all coinfecting clients to the same level as singly HIV-infected clients, then the model projects that 14.6% (95% CI: 3.3-41.2%) of HIV infections among FSWs would have been averted.

If an average cofactor is calculated that quantifies the overall effect of HSV-2 on HIV infectivity among coinfecting individuals (see supplemental online appendix for details and figures), then Figure S2a suggests the impact projections are highly correlated to this average cofactor (linear regression $R^2=0.880$). Indeed, if HSV-2 increases HIV infectivity 3-fold (up from 1.9-fold in the best-fit) then the linear regression implies that the maximum impact of 'perfect' HSVST for the coinfecting clients would be a 34% decrease in HIV incidence in the FSWs. However, if this cofactor is between 1.25 and 1.43, coinciding with the shedding data from the trials^{17-20 22-23}, and what their translated effect³⁹ means for the average cofactor, then the regression suggests 7-10% of HIV infections could have been averted. This projection is in close agreement with the Partners in Prevention trial results of an 8% reduction in HIV incidence.²³

If instead it is assumed that HSVST used by all FSWs singly infected with HSV-2 reduces their risk of acquiring HIV to that of the HSV-2-uninfected FSWs, the model

projects that 36.0% (95% CI: 17.6-60.8%) of HIV infections among HSV-2-infected FSW could have been averted.

Again, if an average multiplicative cofactor for the effect of HSV-2 on increasing susceptibility to HIV among individuals singly-infected with HSV-2, is calculated in a similar way to that described above, then Figure S2b shows the impact projections are highly correlated to this average cofactor (linear regression $R^2=0.774$). If HSV-2 increases a FSW's susceptibility to HIV 5-fold (up from 3.6-fold in the best-fit) then the linear regression implies that the maximum impact of 'perfect' suppressive treatment for the HSV-2-infected FSWs would be a 55% decrease in HIV incidence among these FSWs. A lower average cofactor of 2, results in a lower impact estimate of 24%.

Sensitivity analysis

Table 2 shows that the AFs for HIV incidence change by at most 8% in relative terms for a 20% relative change in the interaction input parameters. The AFs are most sensitive to changes in the direct cofactors, i.e. those that increase the probability of HIV transmission per sex act in the presence of HSV-2. Other regression coefficients are very small. Table 2 presents the results when the largest cofactors from each correlated pair are entered into the multilinear regression.

[INSERT Table 2]

DISCUSSION

The limitations of the HSV-2 model have been discussed previously,³⁵ mainly that the model does not allow for sexual behaviour differences during symptomatic versus asymptomatic shedding.

Since the focus of this study is on the biological interactions between HIV and HSV-2, sexual behaviour among FSWs is assumed to be homogeneous (and similarly for clients), and HSV-2 is the only STI that is modelled dynamically. Non-commercial partnerships of FSWs and clients, or transmission to the general population are ignored, as is the population of men who have sex with men. Using the model as a cohort model, due to lack of data on clients, limited the use of the interaction parameters, potentially leading to underestimates in the attributable fractions.

The model suggests that approximately 36% of HIV infections among FSWs in Mysore are due to HSV-2. Similarly, another modelling analysis, by Abu-Raddad *et al.* (2008), predicted that 35% of HIV infections in Kisumu, Kenya, were attributable to HSV-2.²⁷ Freeman *et al.* (2007), also used African data in a modelling analysis which found that the population attributable fraction of HIV due to HSV-2 increases with the maturity of the epidemic.⁴⁰

Our model findings emphasise the greater contribution to the HIV epidemic of HSV-2 shedding in the absence of symptoms, than in the presence of symptoms. This is biologically plausible since, although symptomatic recurrences may be more important per shedding episode,⁴¹ asymptomatic shedding is much more frequent⁴².

Our analysis suggests that HSVST, used by either FSWs singly-infected with HSV-2 or clients coinfecting with HIV and HSV-2, may reduce HIV incidence among FSWs, but not to any great extent (by 36% or 15%, respectively). These findings are in close agreement with White *et al.* (2008) for a concentrated African epidemic³⁴ and Baggaley *et al.* (2009) for two generalised HIV epidemics in sub-Saharan Africa²⁸.

For the main analysis, the values used for the cofactor effect of HSV-2 on susceptibility to HIV were calculated from reviews and pre-HSVST trial data (e.g. see references 7, 42 and 47 in the online appendix).⁴ These cofactor values remain valid, despite the lack of significant impact observed in the HSVST trial of HIV acquisition¹³⁻¹⁴, since the trial results do not negate the good biological plausibility and observational data that HSV-2 increases HIV susceptibility.^{3-6 8 43-44} The disappointing results from the HIV acquisition trials compared to the successful HIV shedding trials could be due to many reasons, including factors relating to the drug choice, dosage strategy and adherence levels¹³⁻¹⁴, different effects of the drug in coinfecting individuals versus those singly infected with HSV-2¹⁵⁻¹⁶, and/or the possible persistence of activated CD8+ T cells which enhance susceptibility to HIV in HSV-2 infected individuals but are not shut down by HSVST⁷.

Observing an impact of HSVST in a trial setting may also be difficult because of limited statistical power. The Partners in Prevention trial was powered to detect a 50% decrease in HIV incidence,²³ yet our modelling suggests that this would have required HSV-2 to increase the per sex act HIV infectivity, among those coinfecting, at least 4-fold. The HIV acquisition trials were powered at a similar level and our results suggest that an

effect of HSVST would only have been observed if HSV-2 increased HIV susceptibility more than 4.5-fold. For these reasons, it is plausible that the trials observed no impact of HSVST on HIV incidence simply because the interaction between these viruses is not large enough to enable a significant impact to be observed for the statistical power set in the trials. The model strongly supports this premise for the impact of HSVST on HIV transmission (more so than acquisition), since even the upper bound on the model-predicted decrease in HIV incidence is 41% in this case, which is below the 50% that the trials were powered for. The broader scientific literature suggests that the values of these cofactors are likely to be lower than what the model suggests is required to observe a statistically significant impact in these trials (e.g. see references 7, 28, 42, 47, 58-59, 61-65 in the online appendix).⁴⁵ The Partners in Prevention trial results also support these model findings since the upper bound on the impact estimate was 40%,²³ implying that there may have been a small impact of acyclovir which could not achieve the statistical significance required in the trial. Any imperfections in the effect of HSVST or adherence issues in a trial would require even higher cofactors in order to observe a statistical significant result.

Given this, the modelling analyses suggest that, although HSV-2 may play an important role in both concentrated and generalised HIV epidemics, this interaction is likely too weak to warrant the promotion of HSVST specifically for HIV prevention, given the lack of effect noted in the trials. However, HSVST is an important intervention for those who are infected with HSV-2, and may offer broader benefits since it has been demonstrated in a trial to delay progression to AIDS among those coinfecting.²⁶ It also remains possible that HSVST could have a weak effect on reducing HIV acquisition or

transmission by less than 50%. Larger trials may be able to observe a weak effect of HSVST on HIV incidence but the importance of conducting such a trial would need to be weighed alongside the costs and relevance of identifying a low impact product.

Conclusions

This is the first model that has been used to explore the importance of HSV-2 to a concentrated HIV epidemic in an Asian setting. The modelling suggests that HSV-2 plays a critical role in the transmission and acquisition of HIV in Mysore, and that this may be mostly due to infectious shedding of HSV-2 in the absence of symptoms.

Given the successful trial of once-daily valacyclovir to reduce the risk of transmission of genital herpes⁴⁶, continuous suppressive treatment of HSV-2 could be an effective strategy among FSWs and their clients in India, for reducing the transmission of HSV-2. Over time, the HIV epidemic may be curtailed indirectly through the use of HSV-2 suppressive therapy, since a lower prevalence of HSV-2 could result in fewer HIV infections.

Increasing the potency of current HSV-2 antiviral drugs may help in further reducing HSV-2 incidence. However, the model suggests that even in the best case scenario, in which HSV-2 suppressive therapy completely removes the effect of HSV-2 on either HIV infectivity or HIV acquisition, this hypothetical 'perfect' therapy is unlikely to lead to a 50% reduction in HIV incidence, because of the limited strength of the interaction effect between HSV-2 and HIV.

Modelling analyses such as these should be repeated or adapted and used to explore the potential impact of other HIV/STI prevention interventions, helping to guide trial design for expected power and sample size calculations, and to retrospectively inform the interpretation of trial results.

AUTHOR CONTRIBUTIONS

AMF developed, programmed, parameterised and fit the model, conducted the modelling analyses, and wrote the manuscript (incorporating comments from coauthors). PTV input into the model development, parameterisation and fitting, and helped to guide the analyses, interpret the results and write the manuscript. PM participated in the planning of the project and analyses, helped interpret the findings and relate to other HSV-2/HIV research, and provided substantive edits and comments on drafts of the manuscript. HAW helped interpret the findings and relate to other HSV-2/HIV research, and provided substantive edits and comments on drafts of the manuscript. BMR, SR-P and RW were involved in the Mysore behavioural and epidemiological data collection and analysis required for model input and fitting parameters. JB, SM and CML helped contextualise the data collected and interpret for modelling. SM, CML and MA coordinated the data collection and analysis. CHW helped guide the analyses, interpret the findings, and provided substantive edits and comments on drafts of the manuscript.

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Due to printing space restrictions, references 31-46 are detailed in the supplemental online appendix.

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Competing Interest: None declared.

TABLES AND FIGURES

Table 1: Average attributable fractions due to specific interactions (percentage of annual HIV incidence among female sex workers (FSWs) due to interactions with HSV-2)

Specific interaction	Best-fit attributable fraction (95% confidence intervals from all fits) <i>% of HIV incidence among FSW due to specific interaction with HSV-2</i>
All interactions combined	35.5 (22.2-62.5)
Increased susceptibility and infectivity of HIV in the presence of <i>asymptomatic</i> HSV-2 shedding alone	32.4 (20.4-59.5)
Increased susceptibility and infectivity of HIV in the presence of <i>symptomatic</i> HSV-2 recurrences alone*	3.0 (1.4-4.3)
Increased <i>susceptibility</i> to HIV among HSV-2-infected FSWs	24.6 (11.2-46.7)
Increased <i>infectivity</i> of HIV from coinfecting clients*	10.4 (2.3-32.5)

* Includes implicitly the static effect on HIV transmission of the increased HSV-2 symptomatic recurrence rate among coinfecting clients

Table 2: Sensitivity analysis on the effect of a 20% change in model interaction inputs on the model best-fit attributable fraction of HIV due to HSV-2 among female sex workers (FSWs)

Model input parameters (values used for best-fit simulation in parentheses, derived from Table S1 in the supplemental online appendix)	Relative % change in attributable fraction of HIV incidence among FSW due to HSV-2 from best-fit value of 35.54% (absolute value)**	
	-20% relative change in parameter	+20% relative change in parameter
Cofactor for increased transmission of HIV to person symptomatically shedding HSV-2 (4.5)	-8.10% (32.66%)	+8.10% (38.42%)
Cofactor for increased transmission of HIV from coinfecting partner symptomatically shedding HSV-2 (2.7)	-3.70% (34.22%)	+3.70% (36.85%)
Cofactor for increased transmission of HSV-2 from a coinfecting partner with high HIV viraemia (0.76)	-1.15% (35.13%)	+1.15% (35.95%)
Cofactor for increased symptomatic HSV-2 shedding rate in those with HIV (1.4)	-0.66% (35.30%)	+0.66% (35.77%)
Cofactor for increased asymptomatic HSV-2 shedding in those with HIV (2.4)	-0.24% (35.45%)	+0.24% (35.62%)
Cofactor for increased transmission of HSV-2 to a person with high HIV viraemia (1.7)	+0.14% (35.59%)	-0.14% (35.49%)

** R^2 value over 0.98 in the multilinear regression

Figure 1: A comparison of the model best-fit with HSV-2 and HIV prevalence and coinfection prevalence data against the duration of sex work

Figure 1a. Comparison with HSV-2 and HIV prevalence data

Figure 1b: Comparison with HIV/HSV-2 coinfection prevalence data

Figure 1a. Comparison with HSV-2 and HIV prevalence data

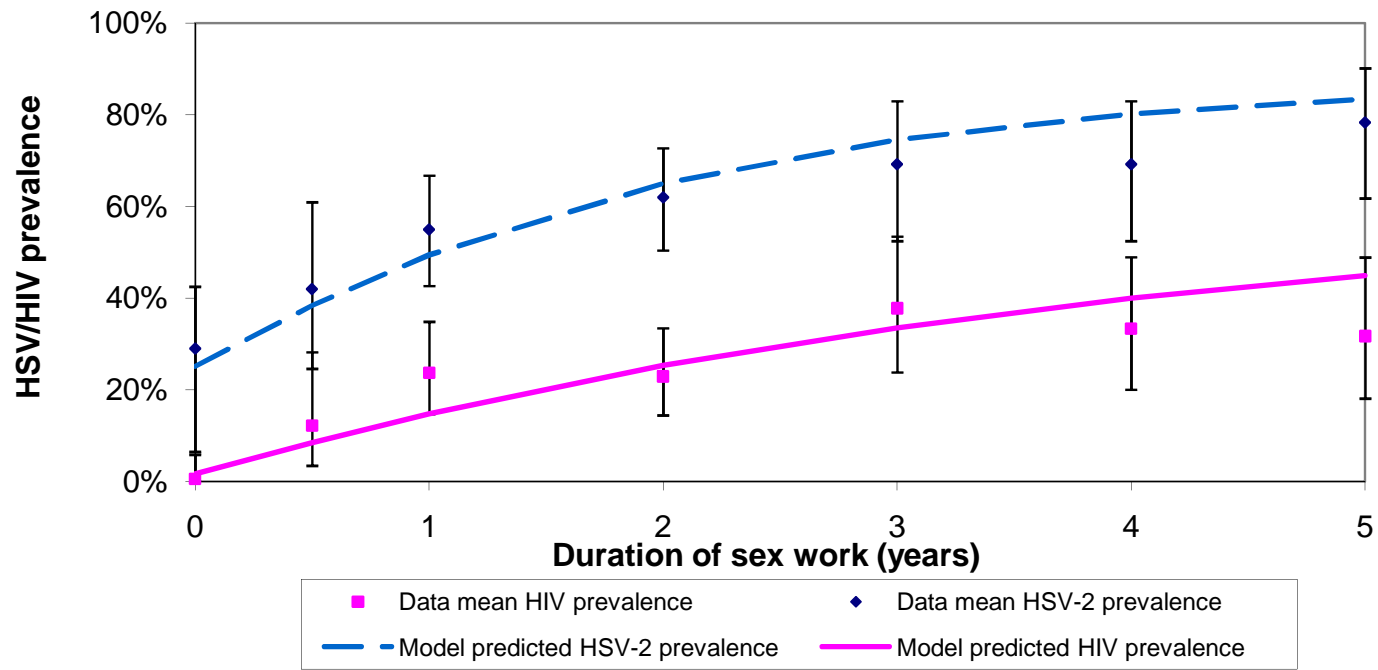


Figure 1b: Comparison with HIV/HSV-2 coinfection prevalence data

