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AN AGE-STRUCTURED MODEL FOR THE COUPLED DYNAMICS OF HIV AND HSV-2

Georgi Kapitanov and Christina Alvey

Department of Mathematics, Purdue University
150 N. University Street
West Lafayette, IN 47907-2067, USA

Katia Vogt-Geisse

Department of Mathematics, Purdue University
150 N. University Street
West Lafayette, IN 47907-2067, USA
and
Profesor Asociado a la Facultad de Ingeniería y Ciencias
de la Universidad Adolfo Ibáñez, Santiago, Chile

Zhilan Feng

Department of Mathematics, Purdue University
150 N. University Street
West Lafayette, IN 47907-2067, USA

Abstract. Evidence suggests a strong correlation between the prevalence of HSV-2 (genital herpes) and the perseverance of the HIV epidemic. HSV-2 is an incurable viral infection, characterized by periodic reactivation. We construct a model of the co-infection dynamics between the two diseases by incorporating a time-since-infection variable to track the alternating periods of infectiousness of HSV-2. The model considers only heterosexual relationships and distinguishes three population groups: males, general population females, and female sex workers. We calculate the basic reproduction numbers for each disease that provide threshold conditions, which determine whether a disease dies out or becomes endemic in the absence of the other disease. We also derive the invasion reproduction numbers that determine whether or not a disease can invade into a population in which the other disease is endemic. The calculations of the invasion reproduction numbers suggest a new aspect in their interpretation - the class from which the initial disease carrier arises is important for understanding the invasion dynamics and biological interpretation of the expressions of the reproduction numbers. Sensitivity analysis is conducted to examine the role of model parameters in influencing the model outcomes. The results are discussed in the last section.

1. **Introduction.** Few are unaware of the dangers of Human Immunodeficiency Virus (HIV) - a sexually transmitted disease (STD) that causes Acquired Immunodeficiency Syndrome (AIDS). AIDS allows for gradual failure of the immune system, leaving humans vulnerable to a variety of pathogen-caused infections. While many

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advancements have been made in preventing and treating HIV/AIDS, with close to 50,000 new cases every year in the United States [39], and 2.5 million worldwide [53] more education and development of strategies are necessary for further reducing the numbers.

Herpes Simplex Virus-2 (HSV-2) is a life-long, incurable viral STD, which is characterized by periods of latency (low or no infectiousness) and viral shedding (high infectiousness). An outbreak of HSV-2 can be either symptomatic or asymptomatic. The main symptom is genital ulcers [4, 24, 49]. There is mounting evidence of the correlation between HSV-2 and the transmission and acquisition of HIV. Studies show that the risk of HIV infection in HSV-2 seropositive individuals is significantly increased, even when controlling for sexual behavior. Genital ulcers increase the number of target cells available for HIV attachment and entry into the genital tract. Some HSV-2 proteins increase the expression of HIV, hence HIV can be found in the genital ulcers themselves. HSV-2 reactivation has also been shown to stimulate HIV replication, however even latent HSV-2 has been associated with higher risk of HIV acquisition. Further, HIV-positive individuals have a higher chance to acquire HSV-2 and, in fact, a large portion of the HIV-positive individuals (40%-80% in the US, e.g.) are co-infected with HSV-2 [1, 5, 11, 14, 15, 20, 33, 46].

HIV, as an important infectious disease, has gathered attention from mathematical epidemiologists throughout the years. Different aspects have been studied: antiviral therapy - strategy and drug resistance at the population level [12, 21], at the individual level (cell-to-cell viral transmission) [32, 42, 43], or sexual behavior in [30]. In [43], Roy et al. consider a time delay in the disease infection term, relating their results to a model without delay. In [21], Granich et al. make a prediction of reduction of incidence based on strategies of early detection and widely available antiviral therapy, through both deterministic and stochastic models. In [12], Chibaya et al. explore a model of vertical HIV transmission (mother-to-offspring), including treatment and drug-resistance. In [42], Rong et al. construct two age-of-infection models of HIV at the cellular level, exploring two strategies of treatment. In [30], Johnson et al. explore a model of sexual behavior (extramarital relationships, condom use, concurrent relationships, etc.) and its effect on the spread of HIV in South Africa. In [32], Kirschner et al. present a system of ordinary differential equations that explores drug sensitive and drug resistant viral cells dynamics.

Several mathematical models have dealt with HSV-2, [18, 19, 44] to name a few. In [19], Foss et al. give a nice review of the mathematical models of HSV-2 up to 2009 and are critical of the models that exclude some of the important aspects of the disease: latency, symptomatic and asymptomatic infectivity, reduction of shedding since initial infection, type of initial infection (symptomatic or asymptomatic), and the possibility for the disease to develop differently from the way it started (asymptomatic initial outbreak can turn into symptomatic recurrent outbreaks and vice versa). The system of ordinary differential equations proposed in [19] incorporates all these aspects, and explores the differences between an initial, complex system, and a simplified version. In [44], Schiffer et al. present a stochastic model of mucosal HSV-2 pathogenesis to mimic the pattern of HSV-2 genital shedding frequency, recurrences, peak copy number during episodes, duration of shedding episodes, and lesion diameter in particular patients. They conclude, corroborating their results with data, that HSV-2 expression has a high variability among patients, and even within a single patient as time progresses.

The model presented in the current paper is based on [18]. In [18], Feng et

al. present an ODE model that incorporates HSV-2 latency as a separate class of the population. Since we are focused on the effect of HSV-2 on HIV, we model HIV as a system of ordinary differential equations. In the current article, HSV-2 is modeled by partial differential equations with respect to chronological time and time-since-infection (age-of-infection). There are advantages to incorporating age-of-infection dependent functions for several of our parameters. One is reduction of the number of population classes while still incorporating latency. Even though we do not consider it in the current paper, another advantage would be incorporating both, reduction of shedding since the initial outbreak and reduction of the frequency of outbreaks as the disease progresses. Asymptomatic shedding can be included implicitly in the construction of the age-of-infection dependent transmission function. The disadvantage is in the increased mathematical complexity of the model. We have several goals. First, to identify the key aspects of the coupled dynamics of the two STDs and, more importantly, the parameters associated with HSV-2 that drive the HIV epidemics. Second, we divide our population in three groups: males, general population females, and female sex workers (FSWs). Considering only heterosexual relationships, we want to explore the effect of FSWs on the disease dynamics. Third, to explain the role of the age-of-infection variable on the calculation of the reproduction numbers of the STDs.

The paper is organized in the following manner: Section 2 introduces the model, Section 3 presents the basic reproduction numbers for each disease. The invasion reproduction numbers for each disease and their biological interpretations are shown in Section 4. Section 5 deals with numerical simulations and sensitivity analysis, and Section 6 contains a discussion of our results. The calculation of the invasion reproduction numbers is outlined in Appendices A and B. Appendix C contains biological interpretations or the terms in the invasion reproduction numbers and Appendix D explains how we chose the parameters for our numerical simulations and sensitivity analysis.

2. **Model formulation.** In this section we present a model that describes the interaction and transmission dynamics of HSV-2 and HIV among a heterosexual population. We consider three basic population groups: males (denoted m), low-risk females (f_1, members of the general population), and high-risk females (f_2, generally sex workers). We only consider transmission due to sexual encounters. Since we focus on the influence of HSV-2 on HIV prevalence, we use ordinary differential equations to describe the transmission dynamics of HIV in a simplified manner.

The population structure is compartmentalized at time t into the following classes of individuals: susceptible ($S_i(t)$), HIV-positive ($H_i(t)$), HSV-2-positive ($V_i(t,a)$, time-since-infection dependent), and co-infected ($P_i(t,a)$, time-since-infection dependent), $i = m, f_1, f_2$. Note that for each population group i, $S_i(t) + H_i(t) + \int_0^\infty V_i(t,a)da + \int_0^\infty P_i(t,a)da = N_i(t)$, the total population size of the group.

In our model there is a constant population recruitment rate Λ_i, which represents the influx of sexually active susceptible individuals. The exit rates $\mu_i^S, \mu_i^H, \mu_i^V(a)$, and $\mu_i^P(a)$ represent a combination of mortality and sexual inactivity (due to age or acquisition of AIDS). The force-of-infection terms are $\lambda_i^H(t)$ and $\lambda_i^V(t)$ for HIV and HSV-2 respectively. The expression for these terms is in (3). The terms δ_i^H and $\delta_i^V(a)$ refer to the higher susceptibility of people with one STD to the other, i.e. individuals with HIV have an enhanced chance of acquiring HSV-2 and individuals with HSV-2 have a higher probability of getting HIV. $\delta_i^V(a)$ is dependent on the time

since infection because whether a person with HSV-2 is latent or shedding may have an effect on their immune system and probability of being infected. The following two describe the boundary conditions: susceptibles infected with HSV-2 become HSV-2-positive with time-since-infection 0 and HIV-positive individuals infected with HSV-2 become co-infected with time-since-infection 0. We also assume some initial values/distributions at time 0 for each class, $S_i^0, H_i^0, V_i^0(a), P_i^0(a)$. Equation (1) presents the system, Table 1 explains each term, and for a visual representation of the dynamics described in (1), refer to Figure 1.

$$\begin{cases} \dfrac{dS_i}{dt} = \Lambda_i - (\lambda_i^V(t) + \lambda_i^H(t))S_i(t) - \mu_i^S S_i(t) \\ \dfrac{dH_i}{dt} = \lambda_i^H(t)S_i(t) - \delta_i^H \lambda_i^V(t)H_i(t) - \mu_i^H H_i(t) \\ \dfrac{\partial V_i}{\partial t} + \dfrac{\partial V_i}{\partial a} = -\delta_i^V(a)\lambda_i^H(t)V_i(t,a) - \mu_i^V(a)V_i(t,a) \\ \dfrac{\partial P_i}{\partial t} + \dfrac{\partial P_i}{\partial a} = \delta_i^V(a)\lambda_i^H(t)V_i(t,a) - \mu_i^P(a)P_i(t,a) \\ S_i(0) = S_i^0; H_i(0) = H_i^0 \\ V_i(0,a) = V_i^0(a); P_i(0,a) = P_i^0(a) \\ V_i(t,0) = \lambda_i^V(t)S_i(t) \\ P_i(t,0) = \delta_i^H \lambda_i^V(t)H_i(t), \quad i = m, f_1, f_2. \end{cases} \tag{1}$$

Let b_i be the number of partnerships an individual of group i has per unit time. Also, let c_1 and c_2 be the fraction of those partnerships a male individual has with a low-risk and a high-risk female partner, respectively. Note that $c_2 = 1 - c_1$. A male has the same number of partnerships with low-risk females as a low-risk female with males. The same holds true for males and high-risk females. Therefore, the following balance conditions emerge:

$$\begin{aligned} b_m c_1 N_m &= b_{f_1} N_{f_1} \\ b_m c_2 N_m &= b_{f_2} N_{f_2}. \end{aligned} \tag{2}$$

The force of infection functions appearing in (1) are derived in the following way:

$$\begin{aligned} \lambda_m^H(t) &= \sum_{j=1}^{2} b_{f_j} \beta_{f_j,m}^H \frac{H_{f_j}(t) + \int_0^\infty \delta_{f_j}^P(a) P_{f_j}(t,a) da}{N_m(t)}, \\ \lambda_{f_j}^H(t) &= b_m c_j \beta_{m,f_j}^H \frac{H_m(t) + \int_0^\infty \delta_m^P(a) P_m(t,a) da}{N_{f_j}(t)}, \quad j = 1, 2, \\ \lambda_m^V(t) &= \sum_{j=1}^{2} b_{f_j} \frac{\int_0^\infty \beta_{f_j,m}^V(a)[V_{f_j}(t,a) + \sigma_{f_j}^P(a) P_{f_j}(t,a)] da}{N_m(t)}, \\ \lambda_{f_j}^V(t) &= b_m c_j \frac{\int_0^\infty \beta_{m,f_j}^V(a)[V_m(t,a) + \sigma_m^P(a) P_m(t,a)] da}{N_{f_j}(t)}, \quad j = 1, 2. \end{aligned} \tag{3}$$

We assume that all our parameters are non-negative, with the following assumptions also applied:
$V_i(t,.), P_i(t,.) \in L^1[0,\infty), \forall t \geq 0, i \in \{m, f_1, f_2\}$;
$\lim_{a\to\infty} V_i(t,a) = \lim_{a\to\infty} P_i(t,a) = 0, \forall t \geq 0, i \in \{m, f_1, f_2\}$;

TABLE 1. Description of Model Parameters

Symbol	Description
$i = m, f_1, f_2$	Male, low-risk female, high-risk female sub-index.
$N_i(t)$	Total population of group i at time t.
$S_i(t)$	Number of susceptible individuals of group i at time t.
$H_i(t)$	Number of HIV-positive individuals of group i at time t.
$V_i(t,a)$	Number of individuals of group i who have been infected with HSV-2 for a months, at chronological time t.
$P_i(t,a)$	Number of individuals of group i who have both HIV and HSV-2 and have been infected with HSV-2 for a months, at chronological time t.
μ_i	Rate of exiting sexual activity for group i.
Λ_i	Total recruitment rate of group i.
$\delta_i^V(a)$	Enhanced susceptibility of individuals with HSV-2 to HIV.
δ_i^H	Enhanced susceptibility of individuals with HIV to HSV-2.
$\sigma_i^P(a)$	Enhanced infectivity of individuals with both STDs when transmitting HSV-2.
$\delta_i^P(a)$	Enhanced infectivity of individuals with both STDs when transmitting HIV.
b_m	Rate of male sexual partnerships with females.
b_{f_1}	Rate of sexual partnerships of group 1 females with males.
b_{f_2}	Rate of sexual partnerships of group 2 females with males.
$c_1, c_2 = 1 - c_1$	Fraction of m partnerships with f_1, f_2.
$\beta^H_{m,f_1}, \beta^H_{m,f_2}$	Probability of HIV transmission by an HIV-positive individual of group m to an f_j partner, per partnership, $j = 1, 2$.
$\beta^H_{f_1,m}, \beta^H_{f_2,m}$	Probability of HIV transmission by an HIV-positive individual of group f_j to an m partner, per partnership, $j = 1, 2$.
$\beta^V_{m,f_j}(a)$	Probability of HSV-2 transmission by an HSV-2-positive individual of group m with time-since-infection a to an f_j partner, per partnership, $j = 1, 2$.
$\beta^V_{f_j,m}(a)$	Probability of HSV-2 transmission by an HSV-2-positive individual of group f_j with time-since-infection a to an m partner, per partnership, $j = 1, 2$.
$\lambda^H_m(t)$	Rate of infection of male individuals with HIV at time t.
$\lambda^H_{f_j}(t)$	Rate of infection of f_j individuals with HIV at time t, $j = 1, 2$.
$\lambda^V_m(t)$	Rate of infection of male individuals with HSV-2 at time t.
$\lambda^V_{f_j}(t)$	Rate of infection of f_j individuals with HSV-2 at time t, $j = 1, 2$.

$\delta_i^V(.), \delta_i^P(.), \sigma_i^P(.) \in L^\infty[0,\infty)$;
$\mu_i^V(.), \mu_i^P(.) \in L^\infty[0,\infty), i \in \{m, f_1, f_2\}$;
$\beta^V_{m,f_j}(.), \beta^V_{f_j,m}(.) \in L^\infty[0,\infty), j = 1, 2.$
$\exists \mu_0 > 0$, such that $\mu_i^S, \mu_i^H, \mu_i^V(a), \mu_i^P(a) \geq \mu_0$;
$\delta_i^V(a), \delta_i^P(a), \sigma_i^P(.), \delta_i^H \geq 1, \forall a \geq 0$.

Positivity of solutions and well-posedness of the problem can be shown. Using the method of characteristics, we have the following solutions for $V_i(t,a)$ and $P_i(t,a), i = m, f_1, f_2$:

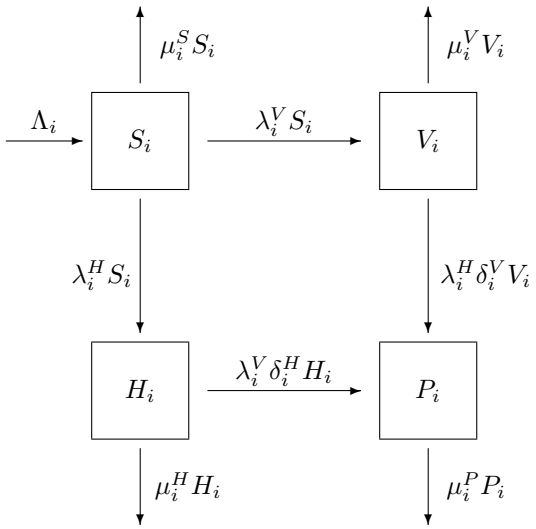

FIGURE 1. Model dynamics in a diagram form.

$$V_i(t,a) = \begin{cases} V_i^0(a-t)e^{-\int_0^t \delta_i^V(\tau-t+a)\lambda_i^H(\tau)+\mu_i^V(\tau-t+a)d\tau}, a > t \\ \lambda_i^V(t-a)S_i(t-a)e^{-\int_0^a \delta_i^V(\tau)\lambda_i^H(\tau+t-a)+\mu_i^V(\tau)d\tau}, t > a \end{cases} \tag{4}$$

$$P_i(t,a) = \begin{cases} P_i^0(a-t)e^{-\int_{a-t}^a \mu_i^P(\tau)d\tau} + \\ \int_0^t e^{-\int_{x-t+a}^a \mu_i^P(\tau)d\tau}\delta_i(x-t+a)\lambda_i^H(x)V_i(x,a)dx, a > t \\ \delta_i^H\lambda_i^V(t-a)H_i(t-a)L_i^P(a) + \\ \int_0^a \dfrac{L_i^P(a)}{L_i^P(x)}\delta_i^V(x)\lambda_i^H(x+t-a)V_i(x,x+t-a)dx, t > a, \end{cases} \tag{5}$$

where $L_i^P(a) := e^{-\int_0^a \mu_i^P(\tau)d\tau}$ is the probability that an individual in class P_i will survive until time-since-HSV-2-infection a. Note that it can be shown that the first parts of (4) and (5) decay to 0 in L^1 norm with respect to a as time goes to infinity. Since we will be examining the behavior of the system at equilibria, we will only consider the second parts of (4) and (5), namely the cases when $t > a$.

3. **The basic reproduction numbers.** The following sections deal with finding the basic reproduction number of each disease, i.e. R_0^H for HIV and R_0^V for HSV-2 when each disease is introduced in a population that is at the disease free equilibrium (DFE). The DFE is $(S_i^0 := \Lambda_i/\mu_i^S, 0, 0, 0)$, $i = m, f_1, f_2$. In our analysis we want to consider constant population size for each group $i = m, f_1, f_2$, therefore we assume that $\mu_i^S = \mu_i^H = \mu_i^V(a) = \mu_i^P(a)$. We will keep the notation with the superscripts in each class for interpretation purposes.

3.1. **Basic reproduction number for HIV (R_0^H).** We derive first the basic reproduction number for HIV. Suppose that the number of people with HSV-2 infection is and remains at the disease free equilibrium $V_i(t,a) = 0$, $P_i(t,a) = 0$.

Then the force of infection terms reduce to:

$$\begin{aligned}\lambda_i^V &= 0,\ i = m, f_1, f_2,\\ \lambda_m^H(t) &= \sum_{j=1}^{2} b_{f_j}\beta_{f_j,m}^H \frac{H_{f_j}(t)}{N_m(t)},\\ \lambda_{f_j}^H(t) &= b_m c_j \beta_{m,f_j}^H \frac{H_m(t)}{N_{f_j}(t)}, \quad j = 1, 2\end{aligned}$$

and the system to analyze is

$$\begin{cases}\dfrac{dS_i}{dt} = \Lambda_i - \lambda_i^H(t)S_i(t) - \mu_i^S S_i(t)\\ \dfrac{dH_i}{dt} = \lambda_i^H(t)S_i(t) - \mu_i^H H_i(t)\\ S_i(0) = S_i^0; H_i(0) = H_i^0.\end{cases} \tag{6}$$

System (6) has three infected variables with HIV, namely H_i, $i = m, f_1, f_2$. Using the notation from [48], we construct the matrices $\mathcal{F}$, F and $\mathcal{V}$, V. $\mathcal{F}$ is a vector of rates of appearances of new infections in the infectious compartments (H_m, H_{f_1}, and H_{f_2}), while $\mathcal{V}$ is a vector of rates of transfer of individuals in the infectious compartments by any other means. F and V are the Jacobian matrices of $\mathcal{F}$ and $\mathcal{V}$, respectively, with respect to the infectious classes, evaluated at the DFE.

$$\mathcal{F} = \begin{pmatrix}\displaystyle\sum_{j=1}^{2} b_{f_j}\beta_{f_j,m}^H \frac{S_m(t)}{N_m(t)} H_{f_j}(t)\\ b_m c_1 \beta_{m,f_1}^H \dfrac{S_{f_1}(t)}{N_{f_1}(t)} H_m(t)\\ b_m c_2 \beta_{m,f_2}^H \dfrac{S_{f_2}(t)}{N_{f_2}(t)} H_m(t)\end{pmatrix}, \quad \mathcal{V} = \begin{pmatrix}\mu_m^H H_m(t)\\ \mu_{f_1}^H H_{f_1}(t)\\ \mu_{f_2}^H H_{f_2}(t)\end{pmatrix}.$$

Evaluating at the DFE (noting that $S_i^0 = N_i^0$), we get:

$$F = \begin{pmatrix}0 & b_{f_1}\beta_{f_1,m}^H & b_{f_2}\beta_{f_2,m}^H\\ b_m c_1 \beta_{m,f_1}^H & 0 & 0\\ b_m c_2 \beta_{m,f_2}^H & 0 & 0\end{pmatrix}, \quad V = \begin{pmatrix}\mu_m^H & 0 & 0\\ 0 & \mu_{f_1}^H & 0\\ 0 & 0 & \mu_{f_2}^H\end{pmatrix},$$

$$V^{-1} = \begin{pmatrix}\dfrac{1}{\mu_m^H} & 0 & 0\\ 0 & \dfrac{1}{\mu_{f_1}^H} & 0\\ 0 & 0 & \dfrac{1}{\mu_{f_2}^H}\end{pmatrix} \quad \text{and} \quad FV^{-1} = \begin{pmatrix}0 & \dfrac{b_{f_1}\beta_{f_1,m}^H}{\mu_{f_1}^H} & \dfrac{b_{f_2}\beta_{f_2,m}^H}{\mu_{f_2}^H}\\ \dfrac{b_m c_1 \beta_{m,f_1}^H}{\mu_m^H} & 0 & 0\\ \dfrac{b_m c_2 \beta_{m,f_2}^H}{\mu_m^H} & 0 & 0\end{pmatrix}.$$

FV^{-1} is a rank 2 matrix, and therefore the basic reproduction number is given by:

$$R_0^H = \sqrt{\frac{b_m c_1 \beta_{m,f_1}^H}{\mu_m^H}\frac{b_{f_1}\beta_{f_1,m}^H}{\mu_{f_1}^H} + \frac{b_m c_2 \beta_{m,f_2}^H}{\mu_m^H}\frac{b_{f_2}\beta_{f_2,m}^H}{\mu_{f_2}^H}} \tag{7}$$

For $j = 1, 2$, $b_m c_j \beta_{m,f_j}^H$ is the rate with which HIV-positive males infect f_j females, while $1/\mu_m^H$ is the length of time a male stays in the H_m class. Therefore, $b_m c_j \beta_{m,f_j}^H/\mu_m^H$ is the total number of f_j females one HIV-positive male individual will infect within his life-time of sexual activity. Similarly, $b_{f_j}\beta_{f_j,m}^H/\mu_{f_j}^H$ is the number of males an HIV-positive f_j individual will infect in her life-time of sexual

activity. Therefore, (7) is the average number of secondary male infections produced by one HIV-positive male through partnerships with f_j individuals.

3.2. Basic reproduction number for HSV-2 (R_0^V).

Assume HIV is and remains at the disease free equilibrium, i.e $H_i^0 = 0$, $P_i^0(a) = 0$. The force of infection terms are then as follows,

$$\begin{aligned}
\lambda_i^H(t) &= 0, \ \ i = m, f_1, f_2, \\
\lambda_m^V(t) &= \sum_{j=1}^{2} b_{f_j} \frac{\int_0^\infty \beta_{f_j,m}^V(a) V_{f_j}(t,a)da}{N_m(t)}, \\
\lambda_{f_j}^V(t) &= b_m c_j \frac{\int_0^\infty \beta_{m,f_j}^V(a) V_m(t,a)da}{N_{f_j}(t)}, \quad j = 1, 2.
\end{aligned} \tag{8}$$

Then, the system to consider is

$$\begin{cases}
\dfrac{dS_i}{dt} = \Lambda_i - \lambda_i^V(t) S_i(t) - \mu_i^S S_i(t) \\
\dfrac{\partial V_i}{\partial t} + \dfrac{\partial V_i}{\partial a} = -\mu_i^V V_i(t,a) \\
S_i(0) = S_i^0; V_i(0,a) = V_i^0(a); V_i(t,0) = \lambda_i^V(t) S_i(t), \quad i = m, f_1, f_2.
\end{cases} \tag{9}$$

For simplification of notation we will define $L_i^V(a) := e^{-\int_0^a \mu_i^V(\tau)d\tau}$, which represents the probability that an individual is still sexually active at time-since-HSV-2-infection a. We will also call

$$\begin{aligned}
A_{f_j,m}^V(a) &:= \beta_{f_j,m}^V(a) L_{f_j}^V(a) \\
A_{m,f_j}^V(a) &:= \beta_{m,f_j}^V(a) L_m^V(a), \quad j = 1, 2.
\end{aligned} \tag{10}$$

Substituting the second part of (4), i.e.

$$V_i(t,a) = \lambda_i^V(t-a) S_i(t-a) e^{-\int_0^a \mu_i^V(\tau)d\tau}, \quad a < t$$

into (8), integrating over a and adding the classes in order to get an expression for the total population $N_i(t)$, and using (10), we obtain the following system of equations:

$$\begin{cases}
\dfrac{dS_i}{dt} = \Lambda_i - \lambda_i^V(t) S_i(t) - \mu_i^S S_i(t) \\
\dfrac{dN_i}{dt} = \Lambda_i - \mu_i^N N_i(t) \\
\lambda_m^V(t) = \displaystyle\sum_{j=1}^{2} b_{f_j} \frac{\int_0^\infty \lambda_{f_j}^V(t-a) S_{f_j}(t-a) A_{f_j,m}^V(a)da}{N_m(t)} \\
\lambda_{f_j}^V(t) = b_m c_j \dfrac{\int_0^\infty \lambda_m^V(t-a) S_m(t-a) A_{m,f_j}^V(a)da}{N_{f_j}(t)}, \quad j = 1, 2,
\end{cases} \tag{11}$$

where $\mu_i^N = \mu_i^S = \mu_i^V, i = m, f_1, f_2$.

Analyzing the previous system is equivalent to analyzing system (9), since the number of infectious individuals V_i can be obtained from $S_i(t), N_i(t), \lambda_i^V(t)$, $i = m, f_1, f_2$.

Next, we linearize system (11) around the DFE and by assuming constant population size we reduce the system to only the disease-related variables $\lambda_i^V, i = m, f_1, f_2$,

in order to find R_0^V:

$$\begin{cases} \lambda_m^V(t) &= \sum_{j=1}^{2} b_{f_j} \dfrac{\int_0^\infty \lambda_{f_j}^V(t-a) S_{f_j}^0 A_{f_j,m}^V(a) da}{S_m^0} \\ \lambda_{f_j}^V(t) &= b_m c_j \dfrac{\int_0^\infty \lambda_m^V(t-a) S_m^0 A_{m,f_j}^V(a) da}{S_{f_j}^0}, \quad j = 1,2. \end{cases} \tag{12}$$

In the next step we look for eigenvalues of the linear operator , i.e. we look for solutions of the form $\lambda_i^V(t) = \bar{\lambda}_i^V e^{\omega t}$, $i = m, f_1, f_2$, where $\bar{\lambda}_i$ is positive for each i and ω is the eigenvalue. By substituting these solutions into system (12) we obtain

$$\begin{cases} \bar{\lambda}_m^V &= \sum_{j=1}^{2} b_{f_j} \int_0^\infty \bar{\lambda}_{f_j}^V e^{-\omega a} A_{f_j,m}^V(a) da \ \dfrac{S_{f_j}^0}{S_m^0} \\ \bar{\lambda}_{f_j}^V &= b_m c_j \int_0^\infty \bar{\lambda}_m^V e^{-\omega a} A_{m,f_j}^V(a) da \ \dfrac{S_m^0}{S_{f_j}^0}, \quad j = 1,2. \end{cases}$$

Then the characteristic equation is as follows:

$$det \begin{pmatrix} -1 & b_{f_1} \hat{A}_{f_1,m} \dfrac{S_{f_1}^0}{S_m^0} & b_{f_2} \hat{A}_{f_2,m} \dfrac{S_{f_2}^0}{S_m^0} \\ b_m c_1 \hat{A}_{m,f_1} \dfrac{S_m^0}{S_{f_1}^0} & -1 & 0 \\ b_m c_2 \hat{A}_{m,f_2} \dfrac{S_m^0}{S_{f_2}^0} & 0 & -1 \end{pmatrix} = 0,$$

where

$$\hat{A}_{m,f_j}^V(\omega) := \int_0^\infty e^{-a\omega} A_{m,f_j}^V(a) da$$
$$\hat{A}_{f_j,m}^V(\omega) := \int_0^\infty e^{-a\omega} A_{f_j,m}^V(a) da, \quad j = 1,2.$$

The characteristic equation reduces to

$$G(\omega) := b_m c_1 \hat{A}_{m,f_1}^V(\omega) b_{f_1} \hat{A}_{f_1,m}^V(\omega) + b_m c_2 \hat{A}_{m,f_2}^V(\omega) b_{f_2} \hat{A}_{f_2,m}^V(\omega) = 1$$

and it is easy to see that for real ω, $\lim_{\omega\to\infty} G(\omega) = 0$ and $\lim_{\omega\to-\infty} G(\omega) = \infty$ and that $G(\omega)$ is a decreasing function. Also, by standard techniques, it is easy to show that the real root of the equation $G(\omega) = 1$ is the leading root, i.e. if ω_0 is the real root and ω is any complex root, then $Re(\omega) < \omega_0$.

We define the basic reproduction number as $R_0^V := \sqrt{G(0)}$, i.e.

$$\left(R_0^V\right)^2 := \left(R_{m,f_1,m}^V\right)^2 + \left(R_{m,f_2,m}^V\right)^2,$$

where

$$\begin{aligned} \left(R_{m,f_j,m}^V\right)^2 &:= b_m c_j \hat{A}_{m,f_j}^V(0) \cdot b_{f_j} \hat{A}_{f_j,m}^V(0) \\ &= b_m c_j \int_0^\infty \beta_{m,f_j}^V(a) L_m^V(a) da \cdot b_{f_j} \int_0^\infty \beta_{f_j,m}^V(a) L_{f_j}^V(a) da, \quad j = 1,2. \end{aligned}$$

The factor $\int_0^\infty b_m c_j \beta_{m,f_j}^V(a) L_m^V(a) da$ represents the number of f_j individuals infected by one HSV-2 positive male individual. Each of these infected females generate $b_{f_j} \int_0^\infty \beta_{f_j,m}^V(a) L_{f_j}^V(a) da$ male infections with HSV-2 during their entire period of infection. Thus, the product of these two factors represents the average

number of secondary male infections produced by one infected male individual via females of group j, $j = 1, 2$.

4. **Invasion reproduction numbers.** In this section we describe and explain the invasion reproduction number for each STD, i.e. the reproduction number of one of the diseases when the other STD is in an endemic state. Again, we will assume $\mu_i^S = \mu_i^H = \mu_i^V(a) = \mu_i^P(a), i = m, f_1, f_2$. We will keep the different notation for easier interpretation of the results.

4.1. **Invasion HIV reproduction number (R_V^H).** In this section we will present a biological interpretation of the invasion reproduction number for HIV, R_V^H, when invading an HSV-2 endemic population. The HSV-2 endemic equilibrium is given by $(S_i^0, 0, V_i^0(a), 0)$. The invasion HIV reproduction number is defined by

$$R_V^H := \sqrt{G_V^H(0)}, \tag{13}$$

where the detailed expression for $G_V^H(0)$ can be found in Appendix A(22).

We will rewrite (13) in a way that is easier to interpret biologically, but first we introduce the following notations for ease of presentation: $T_i^H := 1/E_i^H(0)$ is the average time an individual spends in class H_i, for $i = m, f_1, f_2$, where the definition of $E_i^H(0), i = m, f_1, f_2$ can be found in Appendix A(23). Further, the rate at which an HIV male (H_m) infects susceptible females (S_{f_j}, $j = 1, 2$) and HSV-2 only females (with time-since-infection x) ($V_{f_j}(x)$, $j = 1, 2$) with HIV are

$$\pi_{m,f_j}^H := b_m c_j \beta_{m,f_j}^H \qquad \text{and} \qquad \delta_{f_j}^V(x)\pi_{m,f_j}^H \qquad j = 1, 2$$

respectively. Also, $\delta_m^P(a)\pi_{m,f_j}^H$ is the rate at which a co-infected male $P_m(a)$, with time-since-HSV-2-infection a, infects a female with HIV where $\delta_m^P(a)$ is the enhanced HIV infectivity of a male with co-infection and time-since-HSV-2-infection equal to a.

In an analogous way, the rates of HIV infection from female to male are given by

$$\pi_{f_j,m}^H := b_{f_j}\beta_{f_j,m}^H, \qquad \delta_m^V(x)\pi_{f_j,m}^H \qquad \text{and} \qquad \delta_{f_j}^P(a)\pi_{f_j,m}^H \qquad j = 1, 2.$$

The probability that an HIV female individual ($H_{f_j}, j = 1, 2$) becomes co-infected ($P_{f_j}, j = 1, 2$), via an HSV-2 male (V_m) is

$$q_{H_{f_j},P_{f_j}}^{V_m} := \delta_{f_j}^H b_m c_j \frac{\phi_{m,f_j}^0}{N_{f_j}^0} T_{f_j}^H, \qquad j = 1, 2.$$

Analogously, the probability that an HIV male individual (H_m) becomes co-infected (P_m), via an HSV-2 female ($V_{f_j}, j = 1, 2$) is given by

$$q_{H_m,P_m}^{V_{f_j}} := \delta_m^H b_{f_j} \frac{\phi_{f_j,m}^0}{N_m^0} T_m^H, \qquad j = 1, 2.$$

Expression (13) can then be rewritten in the following form:

$$(R_V^H)^2 = (R_V^H(m, f_1, m))^2 + (R_V^H(m, f_2, m))^2, \tag{14}$$

where

$$\begin{aligned}\left(R_V^H(m, f_j, m)\right)^2 &= \mathcal{H}_{f_j}^{H_m}(S_{f_j}^0)\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0} \\ &+ \int_0^\infty [\mathcal{P}_m(H_m)](a)\delta_m^P(a)\pi_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0} da\end{aligned}$$

$$
\begin{aligned}
&+ \int_0^\infty \mathcal{H}_{f_j}^{H_m}(S_{f_j}^0) q_{H_{f_j},P_{f_j}}^{V_m} L_{f_j}^P(a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{H}_{f_j}^{\mathcal{P}_m(H_m)}(S_{f_j}^0) q_{H_{f_j},P_{f_j}}^{V_m} L_{f_j}^P(a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \\
&+ \int_0^\infty [\mathcal{P}_{f_j}^{H_m}(V_{f_j}^0)](a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \\
&+ \int_0^\infty [\mathcal{P}_{f_j}^{\mathcal{P}_m(H_m)}(V_{f_j}^0)](a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \\
&+ (\mathcal{H}_{f_j}^{P_m}(S_{f_j}^0))\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0} \\
&+ \int_0^\infty \mathcal{H}_{f_j}^{P_m}(S_{f_j}^0) q_{H_{f_j},P_{f_j}}^{V_m} L_{f_j}^P(a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \\
&+ \int_0^\infty [\mathcal{P}_{f_j}^{P_m}(V_{f_j}^0)](a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0} da \qquad (15)
\end{aligned}
$$

and $W_m^{0,V} := S_m^0 + \int_0^\infty \delta_m^V(a)V_m^0(a)da$ represents the weighted HIV susceptible population. Table 5 in Appendix C summarizes the other abbreviations appearing in (15). Each term on the right hand side of (14) represents the infection cycle from male (m) to female (f_1, f_2) back to male.

The remainder of this section describes biologically the terms in equation (15) and each term corresponds to one of the paths in Figure 2.

The invasion reproduction number R_V^H is a measure of how many secondary cases one HIV infectious individual will produce on average during his/her infectious period, when introduced into an HIV susceptible but HSV-2 endemic population. We understand by secondary infection the average number of new HIV cases that arise in one of the population groups to which the initial infectious individual belonged.

Our model considers an enhanced susceptibility for HSV-2 only individuals to HIV, measured by the parameters $\delta_m^V(a), \delta_{f_j}^V(a), j = 1, 2; 0 < a < \infty$. Therefore, one has to be cautious when introducing/choosing the initial HIV infectious individual, for this individual might be infected with HSV-2 before acquiring HIV. In the biological interpretation we present in this section, we choose to start by introducing an infected male individual into the HIV susceptible population. Hence, this first HIV infected male individual can be chosen either from the susceptible male population S_m^0 with a probability $S_m^0/W_m^{0,V}$, which makes this individual part of the H_m class, or from the HSV-2 infected male population with time-since-HSV-2-infection x, $V_m^0(x)$, with probability $\delta_m^V(x)V_m^0(x)/W_m^{0,V}$, which makes this individual part of the P_m class (entering the co-infection class at time-since-HSV-2-infection x).

The first six terms in (15) correspond to secondary HIV cases due to the initial HIV case being a male individual in the H_m class and the last three terms in (15) correspond to secondary HIV infections traced back to an initial co-infected P_m individual. Table 5 shows detailed interpretations of abbreviations appearing in each of the terms of equation (15). Each of the expressions listed in Table 5 is of the form $\mathcal{X}^{Z(U)}(Y)$ or $\mathcal{P}_m(U)$ for $\mathcal{X} = \mathcal{H}_{f_j}, \mathcal{P}_{f_j}$; $Z = H_m, \mathcal{P}_m, P_m$; $U = H_m, V_m^0$; $Y = S_{f_j}^0, V_{f_j}^0$; $j = 1, 2$. $\mathcal{X}$ represents number of people in the X class, for $X = H_{f_j}, P_{f_j}$ and $\mathcal{P}_m(U)$ represent the probability that a person in class U moves to class P_m. Also, $\mathcal{X}^{Z(U)}(Y)$ describes the following disease dynamics: a

person in class U moves to class Z infects people in class Y, who due to that infection end up in class X. Then, what follows explains the terms of equation (15).

The first term in (15) reads,

$$\mathcal{H}_{f_j}^{H_m}(S_{f_j}^0)\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0}.$$

$\mathcal{H}_{f_j}^{H_m}(S_{f_j}^0)$ represents the number of HIV females that got infected when being susceptible by one HIV male, throughout his sexual lifetime (see Table 5). This term corresponds to the following disease dynamics pictured in Figure 2,

$$S_m \xrightarrow{initial} H_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{infect} N_m.$$

Then the interpretation is as follows. As can be seen in Table 5, the initial HIV infected male is a male in the H_m class with probability $S_m^0/W_m^{0,V}$. This male infects susceptible females ($\mathcal{H}_{f_j}^{H_m}(S_{f_j}^0)$), who then as H_{f_j} females, infect either susceptible males or HSV-2 only infected males ($W_m^{0,V}/N_m^0$), at a rate $\pi_{f_j,m}^H$, throughout their time spent in the HIV class ($T_{f_j}^H$).

For brevity, the other terms are explained in detail in Appendix C. Here we will only present the arrows in Figure 2 that correspond to the dynamics of those terms, in the order presented in equation (15):

$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} H_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} H_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{infect} N_m,$$
$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m.$$

4.2. **Invasion HSV-2 reproduction number (R_H^V).** In this section we will present a biological interpretation for the invasion reproduction number for HSV-2, R_H^V, invading a susceptible and HIV endemic population. The equilibrium reached by the population is given by $(S_i^0, H_i^0, 0, 0)$. The full calculation of this invasion reproduction number can be found in Appendix B.

For $j = 1, 2$, let

$$L_i^V(a) := e^{-\int_0^a \mu_i^V(\tau)d\tau}, i = m, f_1, f_2,$$
$$lp_m^V(a) := e^{-\int_0^a \mathcal{F}_m^V(\tau)d\tau} \quad \left(\text{with } \mathcal{F}_m^V(\tau) = \delta_m^V(\tau)\sum_{j=1}^{2} b_m c_j \beta_{f_j,m}^H \frac{H_{f_j}^0}{N_{f_j}^0}\right),$$
$$-\dot{p}_m^V(x) = \mathcal{F}_m^V(x)p_m^V(x),$$
$$p_{f_j}^V(a) = e^{-\int_0^a \mathcal{F}_{f_j}^V(\tau)d\tau} \quad \left(\text{with } \mathcal{F}_{f_j}^V(\tau) = \delta_{f_j}^V(\tau) b_{f_j} \beta_{m,f_j}^H \frac{H_m^0}{N_m^0}\right),$$
$$-\dot{p}_{f_j}^V(x) = \mathcal{F}_{f_j}^V(x)p_{f_j}^V(x).$$

Here, $L_i^V(a) := e^{-\int_0^a \mu_i^V(x)dx}$ is the probability that an individual in the $V_i, i = m, f_1, f_2$ class is still sexually active at time-since-infection a, $p_i^V(a)$ represents the probability that an individual in the $V_i, i = m, f_1, f_2$ class remains in the HSV-2 only

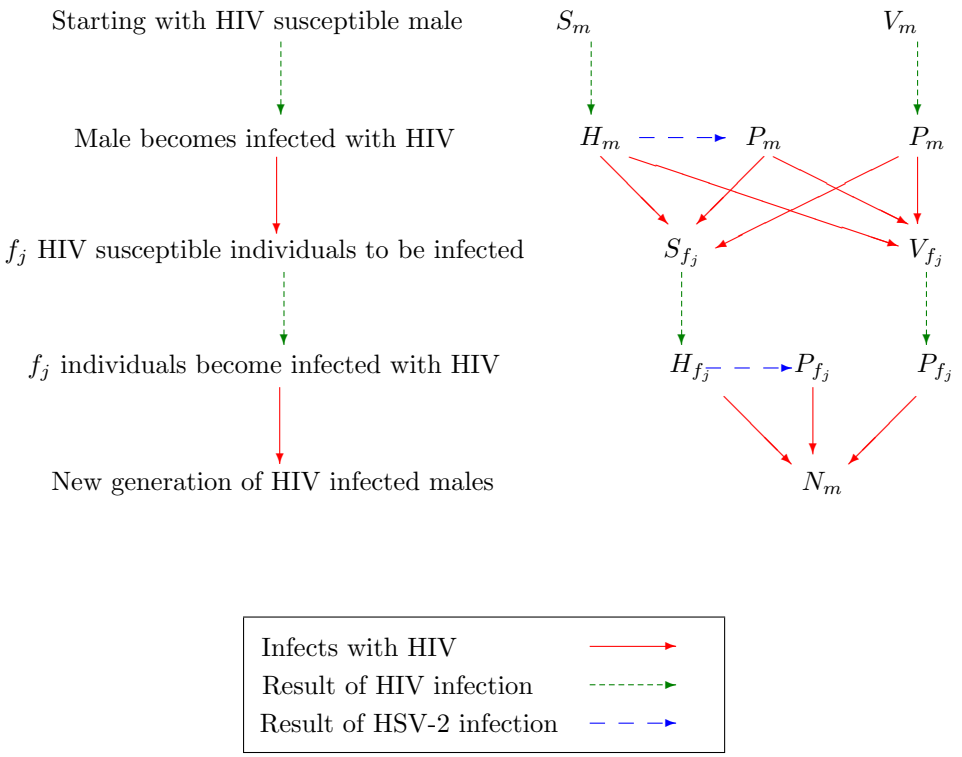

FIGURE 2. Transmission dynamics of HIV between classes m and f_j.

class when time-since-infection equal to a has been reached without acquiring HIV. The quantity $-\dot{p}_i^V(x)$ represents the rate at which a person in the $V_i, i = m, f_1, f_2$ class becomes infected with HIV at time-since-HSV-2-infection x.

Further, let us define

$$\pi^V_{m,f_j}(a) := b_m c_j \beta^V_{m,f_j}(a), \qquad j = 1, 2$$

the rate at which an HSV-2 only infected male of time-since-infection a infects susceptible females. Then, the rates $\delta^H_{f_j}\pi^V_{m,f_j}(a)$ and $\sigma^P_m(a)\pi^V_{m,f_j}(a)$ represent, respectively, the rate at which an HSV-2 only infected male infects an HIV female with enhanced susceptibility to HSV-2 $\delta^H_{f_j}$ and the rate at which a co-infected male with time-since-HSV-2-infection a and enhanced infectivity $\sigma^P_m(a)$ infects susceptible females. Also, $\sigma^P_m(a)\delta^H_{f_j}\pi^V_{m,f_j}(a)$ is the rate at which a co-infected male with time-since-HSV-2-infection a infects an HIV infected female.

We define analogously the rates of female to male infection in the respective cases as above by

$$\pi^V_{f_j,m}(a) := b_{f_j}\beta^V_{f_j,m}(a), \qquad j = 1, 2$$

and

$$\delta^H_m\pi^V_{f_j,m}(a), \quad \sigma^P_{f_j}(a)\pi^V_{f_j,m}(a), \quad \sigma^P_{f_j}(a)\delta^H_m\pi^V_{f_j,m}(a).$$

The invasion reproduction number for HSV-2 measures, on average, the secondary HSV-2 cases traced back to one HSV-2 individual introduced into a susceptible and HIV endemic population, throughout his/her HSV-2 infectious period.

Under secondary infection we understand a new HSV-2 infection of a person of the same population group as the initial introduced HSV-2 case.

We obtain from Appendix B the expression $R_H^V := \sqrt{G_H^V(0)}$ for the HSV-2 invasion reproduction number, which can be written as follows:

$$\left(R_H^V\right)^2 := \left(R_H^V(m, f_1, m)\right)^2 + \left(R_H^V(m, f_2, m)\right)^2. \tag{16}$$

Each term on the right hand side of equation (16) represents the infection cycle from one infected male individual, to one of the female classes ($f_j, j = 1, 2$) and back to males. For $j = 1, 2$ we have:

$$\begin{aligned}
&\left(R_H^V(m, f_j, m)\right)^2 \\
&= \int_0^\infty \mathcal{V}_{f_j}^{V_m}(S_{f_j}^0) L_{f_j}^V(a) p_{f_j}^V(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \left(\int_0^a \mathcal{V}_{f_j}^{V_m}(S_{f_j}^0) L_{f_j}^V(x) (-\dot{p}_{f_j}^V(x)) \frac{L_{f_j}^P(a)}{L_{f_j}^P(x)} dx \right) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{V}_{f_j}^{\mathcal{P}_m(V_m)}(S_{f_j}^0) L_{f_j}^V(a) p_{f_j}^V(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \left(\int_0^a \mathcal{V}_{f_j}^{\mathcal{P}_m(V_m)}(S_{f_j}^0) L_{f_j}^V(x) (-\dot{p}_{f_j}^V(x)) \frac{L_{f_j}^P(a)}{L_{f_j}^P(x)} dx \right) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{P}_{f_j}^{V_m}(H_{f_j}^0) L_{f_j}^P(a) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{P}_{f_j}^{\mathcal{P}_m(V_m)}(H_{f_j}^0) L_{f_j}^P(a) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{V}_{f_j}^{P_m}(S_{f_j}^0) L_{f_j}^V(a) p_{f_j}^V(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \left(\int_0^a \mathcal{V}_{f_j}^{P_m}(S_{f_j}^0) L_{f_j}^V(x) (-\dot{p}_{f_j}^V(x)) \frac{L_{f_j}^P(a)}{L_{f_j}^P(x)} dx \right) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da \\
&+ \int_0^\infty \mathcal{P}_{f_j}^{P_m}(H_{f_j}^0) L_{f_j}^P(a) \sigma_{f_j}^P(a) \pi_{f_j,m}^V(a) \frac{W_m^{0,H}}{N_m^0} da.
\end{aligned} \tag{17}$$

and $W_m^{0,H} := S_m^0 + \delta_m^H H_m^0$ is the weighted HSV-2 susceptible population.

Table 6 in Appendix C gives the expressions and the biological interpretation of the abbreviated terms in (17). Each term has the form $\mathcal{X}^Z(Y)$ or $[\mathcal{P}_m(V_m)](a)$. The later is described in the table and $\mathcal{X} = \mathcal{V}_{f_j}, \mathcal{P}_{f_j}$; $Z = V_m, P_m, \mathcal{P}_m(V_m)$, $Y = S_{f_1}, H_{f_1}$. The disease dynamics described by $\mathcal{X}^Z(Y)$ follows the path $Z \xrightarrow{infects} Y \xrightarrow{becomes} X$, where $\mathcal{X}$ represents the number of people in class X.

The biological meaning of the terms in equation (17) can be explained in a similar manner to what was shown for the HIV invasion reproduction number in the previous section. The first six terms in equation (17) are traced back to infections by an initial HSV-2 only male and the last three to infections by an initial co-infected male individual.

Each term corresponds to the following paths, each one being one of the nine paths shown in Figure 3. The first six terms in equation (17) follow the paths

$$S_m \xrightarrow{initial} V_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} V_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} V_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} V_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{become} Pf_j \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} V_m \xrightarrow{infects} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m,$$
$$S_m \xrightarrow{initial} V_m \xrightarrow{becomes} P_m \xrightarrow{infects} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m.$$

The last three terms in equation (17) follow the paths

$$H_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{infect} N_m,$$
$$H_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} V_{f_j} \xrightarrow{become} Pf_j \xrightarrow{infect} N_m \text{ and}$$
$$H_m \xrightarrow{initial} P_m \xrightarrow{infects} H_{f_j} \xrightarrow{become} Pf_j \xrightarrow{infect} N_m.$$

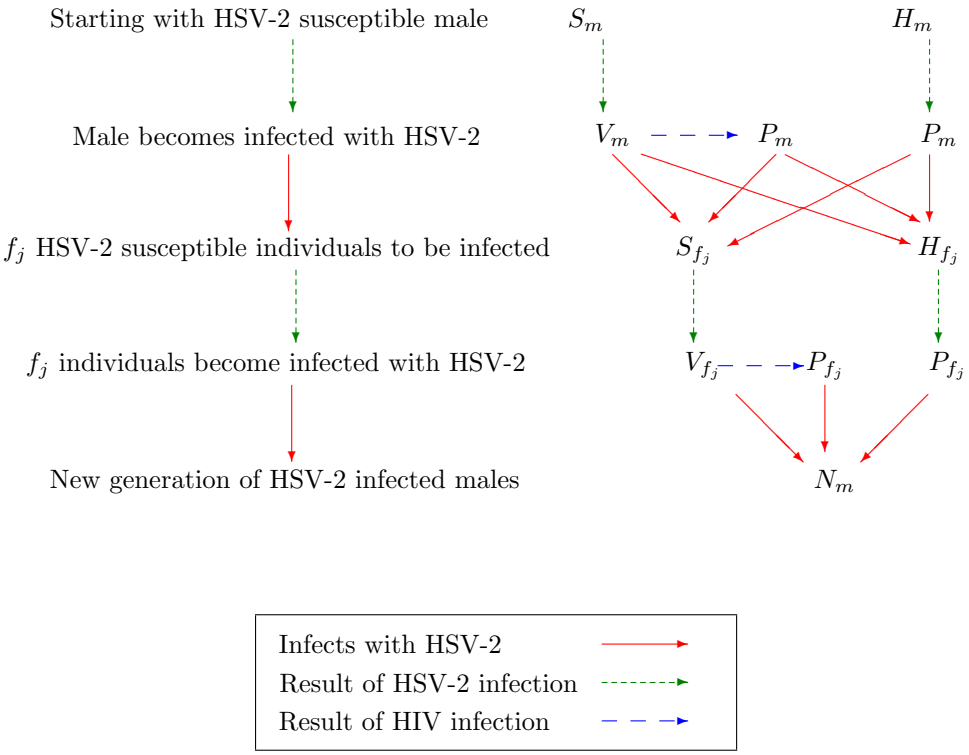

FIGURE 3. Transmission dynamics of HSV-2 between classes m and f_j.

5. **Numerical simulations.** The current section represents our numerical results associated with the given model - a representation of the total population dynamics using parameter values taken from literature (consult Appendix D) and sensitivity analysis on the reproduction numbers. For the total population dynamics we used an ODE model, constructed by integrating the population classes over the time-since-infection variable and assuming that all our parameters dependent on time-since-infection are constants. To verify the analytic results, we carried out simulations

of the model for the special case when the age-dependent parameter functions are constant. Because of the complexity of the full model, numerical simulations of the model with age-dependent parameters have been omitted in this paper. We plan to publish our numerical results for the more general case elsewhere.

5.1. **Total population dynamics - ODE model.** We performed a numerical simulation for the simplified ODE model to determine the prevalence of HIV and HSV-2, as well as the co-infection obtained from our model parameters (see Table 2). We then used these baseline values in conducting a sensitivity analysis for the basic and invasion reproduction numbers of the PDE system. The analysis can be found in Section 5.2. Note that we did not assume there is any difference in the transmission probabilities from males to either female group. Therefore, the infection probabilities per partner satisfy: $\beta^V_{m,f_1} = \beta^V_{m,f_2}$ and $\beta^H_{m,f_1} = \beta^H_{m,f_2}$. This assumption is valid both for the ODE plots and the sensitivity analysis. Four of the parameters in Table 2 have not appeared in the article so far: r, ρ^H, ρ^V_m, and ρ^V_f. They are auxiliary parameters and are only used in the calculations of other parameters, as evident from the same table. These parameters and their meanings are discussed in Appendix D.

In Figures 4 and 5, 35.8% of the male population, 34.3% of the general female population, and 46.6% of the FSW population will eventually have HIV (including co-infected). Considering this model does not include treatment or prevention, these numbers are consistent with HIV prevalence in South Africa, which is a country that only recently started strongly implementing policies in their goal to limit the

TABLE 2. ODE Parameter Values.

Parameter	Value	Unit	Parameter	Value	Unit
μ_m, μ_{f_1}, μ_{f_2}	$\frac{1}{360}, \frac{1}{360}, \frac{1}{60}$	$\frac{1}{\text{mo}}$	ρ^H	.0017	$\frac{\text{prob}}{\text{act}}$
Λ_i	$= \mu_i N_i$	$\frac{\text{ind}}{\text{mo}}$	r	2	$\frac{\text{act}}{\text{part}\times\text{yr}}$
b_m	$\frac{9}{365}$	$\frac{\text{part}}{\text{mo}}$	β^H_{m,f_j}	$= \frac{2.5\rho^H}{b_m}, j = 1,2$	$\frac{\text{prob}}{\text{part}}$
b_{f_1}	$= b_m c_1 \frac{N_m}{N_{f_1}}$	$\frac{\text{part}}{\text{mo}}$	$\beta^H_{f_1,m}$	$= \frac{2.5\rho^H}{b_{f_1}}$	$\frac{\text{prob}}{\text{part}}$
b_{f_2}	$= 10 b_{f_1}$	$\frac{\text{part}}{\text{mo}}$	$\beta^H_{f_2,m}$	$= \frac{r\rho^H}{12\mu^S_{f_2}}$	$\frac{\text{prob}}{\text{part}}$
δ^V_i	1	untls	ρ^V_m	.08	$\frac{\text{prob}}{\text{yr}}$
δ^H_i	1	untls	ρ^V_f	.04	$\frac{\text{prob}}{\text{yr}}$
σ^P_i	1	untls	β^V_{m,f_j}	$= \frac{\rho^V_m}{12 b_m}, j = 1,2$	$\frac{\text{prob}}{\text{part}}$
δ^P_i	1.1	untls	$\beta^V_{f_1,m}$	$= \frac{\rho^V_f}{12 b_{f_1}}$	$\frac{\text{prob}}{\text{part}}$
c_1	.9	untls	$\beta^V_{f_2,m}$	$= \frac{\rho^V_f}{12 b_{f_2}}$	$\frac{\text{prob}}{\text{part}}$

Abbreviations: mo = month, yr = year, ind = individual, act = sex act, part = partnership, untls = unitless

spread of the disease [40]. The HSV-2 prevalence levels (including co-infected) are, respectively, 33.9%, 42.5%, and 55.2%, which are again, consistent with findings [38, 51]. We observe an overall higher prevalence of HSV-2 than HIV, with co-infection largely in the FSW population. This high risk female class also contracts both diseases at a much faster rate than the male or general female populations, as evident from Figures 4 and 5. This may be due to the high number of partnerships for this population, but may also be caused by their shorter sexual lifespan.

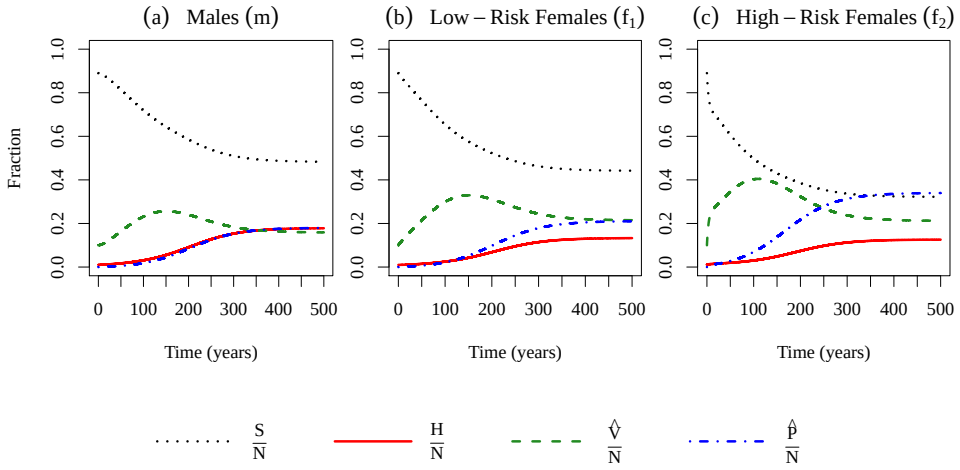

FIGURE 4. Prevalence of HIV, HSV-2, and co-infection among the three population groups, based on the total population dynamics. $\hat{V}(t) = \int_0^\infty V(t,a)da, \hat{P}(t) = \int_0^\infty P(t,a)da$.

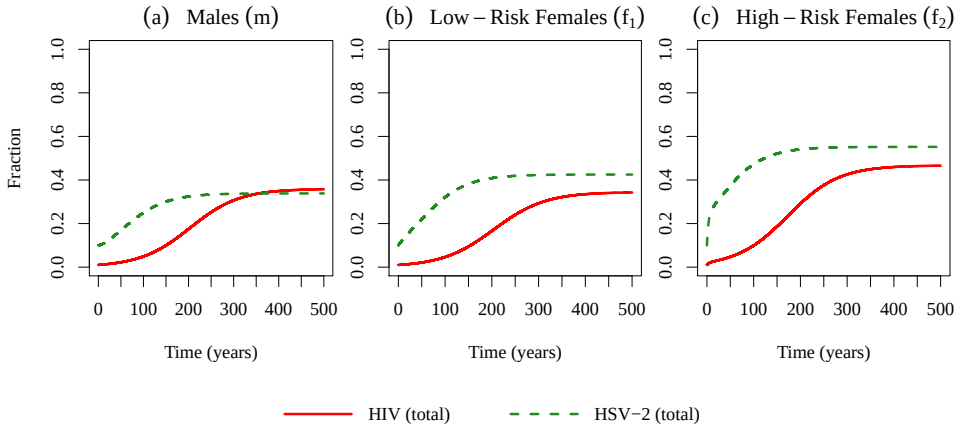

FIGURE 5. Total HIV and HSV-2 (including co-infection) prevalence among the three population groups, based on the total population dynamics.

The male and general female populations exhibit very similar HIV prevalence, taking into account the co-infection with HSV-2. The general female population, however, has a higher HSV-2 prevalence than the male population, which is consistent with observed data [51]. The shape of the HSV-2 curves is due to the appearance of a co-infected population with enhanced infectivity for HIV.

Figure 6 gives a numerical verification for the properties of the HIV-invasion reproduction number, R_V^H. If $R_0^H < 1$ and HSV-2 is not present among the population, HIV cannot persist. However, if HSV-2 is endemic and $R_V^H > 1$, an HIV epidemic is apparent, even though R_0^H is still less than one. The values used are: $R_0^H = 0.86, R_H^V = 1.62$.

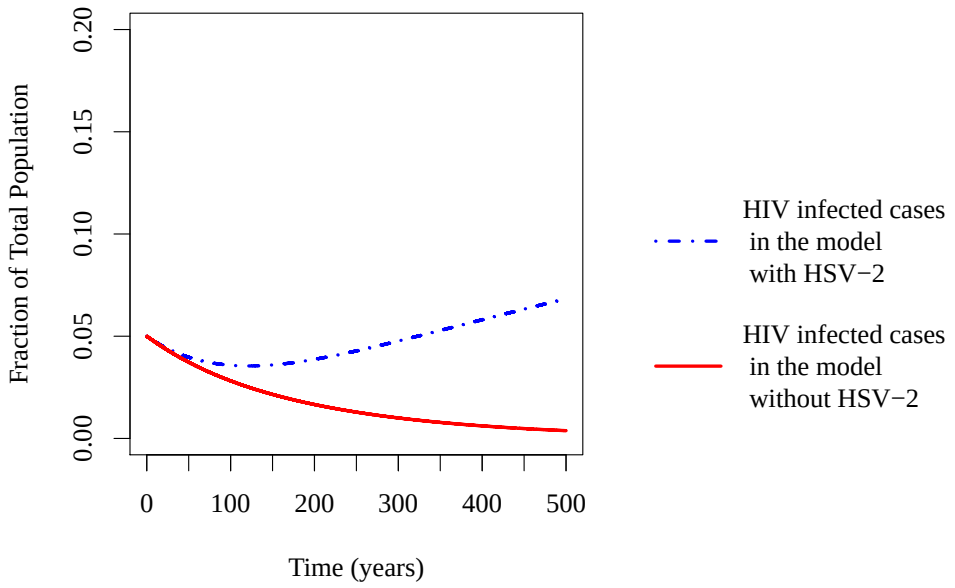

FIGURE 6. Total number of HIV cases among all population groups when $R_0^H < 1$. When HSV-2 is not present, HIV cannot persist. When HSV-2 is present and $R_V^H > 1$, HIV epidemics occurs. For this figure, $R_0^H = 0.86, R_H^V = 1.62$.

5.2. **Sensitivity analysis of the PDE system.** To explore the sensitivity of the basic and invasion reproduction numbers to the chosen model parameters, we performed an analysis using a method based on Latin Hypercube Sampling [6, 26] and calculated partial rank correlation coefficients (PRCC) [7, 25]. To use this method, it is necessary to obtain a range of values for each parameter (see Table 3), as well as determine a probability density function (pdf) for each parameter. It is important to note that the infection transmission enhancement parameters δ_i^V, δ_i^H, and σ_i^P were set at 1, $i = m, f_1, f_2$. For the purposes of this sensitivity analysis we only varied the infectivity enhancement of co-infected individuals when transmitting HIV, δ_i^P, and made it equal for $i = m, f_1, f_2$, hence only including δ_m^P in the sensitivity analysis (more information in Appendix D). Furthermore, we chose the HSV-2 infectivity probabilities $\beta_{i,k}^V(a), i, k = m, f_1, f_2, i \neq k$ to be step

TABLE 3. Parameter Ranges.

Parameter	Lower Bound	Upper Bound	Distribution
c	.7	1	U
μ_m	1/480	1/240	T
μ_{f_1}	1/480	1/240	T
μ_{f_2}	1/120	1/36	T
b_m	$5 \cdot \mu_m$	$12 \cdot \mu_m$	T
b_{f_2}	$5 \cdot b_{f_1}$	$10 \cdot b_{f_1}$	U
N_m	$.5 \cdot 10^5$	$1.5 \cdot 10^5$	T
ρ^H	.001	.002	T
r	1	3	U
ρ_f^V	.03	.12	T
ρ_m^V	.07	.24	T
δ_m^P	1.0	1.3	T

T indicates a triangular distribution, with peak at the fixed value from Table 1.
U indicates a uniform distribution.

functions. Appendix D contains more information on the function itself. $\beta_{i,k}^V$ in Figures 7 and 8 refers to the height of the step function. All other time-since-infection variables were chosen to be constant. In the Latin Hypercube Sampling, we chose either a uniform (U) or triangular (T) pdf with peak at the fixed ODE parameter value (see Tables 1 and 3). The Latin Hypercube is then created by sampling equally probable regions exactly once for each simulation [6,7,25]. A total of 3,000 simulations, and hence 3,000 sets of parameter values were obtained and consistently produced the results.

Using these sets of parameter values, we calculated PRCC indices by a method that determines the effect of varying each parameter individually on the reproduction numbers [6,7,25]. The PRCC indices that are obtained have a value between -1 and 1, with a positive (negative) PRCC value signifying the relationship between the parameter and reproduction number as a positive (negative) relationship. PRCC indices may also indicate which parameters have the most influence on the reproduction numbers, with indices of magnitude closer to 1 having the most influence and closer to 0 having almost no influence [6,7].

Figure 7 gives the PRCC indices for the basic reproduction numbers, R_0^H and R_0^V. The corresponding values for the indices can be found in Table 4. R_0^H seems significantly dependent on several factors: the length of the sexual activity period of males and the females of the general population (inverse proportion of μ_m and μ_{f_1}), males' sexual partnerships per month (b_m), and the transmission probability between a male and a general population female, β_{m,f_1}^H, and to a lesser extent between a male and a FSW, $\beta_{f_2,m}^H$. The length of sexual activity reflects that once an individual has a disease, the longer they are sexually active, the more individuals they will infect. It is interesting to note that the majority of the influential parameters for the HIV basic reproduction number are all related to the male population, with the probability of men infecting women with HIV being more important than the probabilities of women infecting men. c_1, the preference of men for women from the general population, seems to be another important factor in the value of R_0^H, which may be correlated to the length of the f_1 versus f_2 periods of sexual activity. Beyond the sexual active time for m and f_1, whose importance was discussed

TABLE 4. PRCC Values.

	PRCC value with respect to:			
Parameter	R_0^H	R_0^V	R_V^H	R_H^V
c	0.22301403	0.10190679	0.2602452853	0.098150824
b_m	0.28370741	0.10612063	0.2680427498	0.085017149
b_{f_1}	0.10567752	0.02932268	0.0995221633	0.004226425
b_{f_2}	0.08588136	0.12217032	0.0889434116	0.121739335
μ_m	-0.72321671	-0.32687223	-0.7110994875	-0.316704407
μ_{f_1}	-0.80320335	-0.39569917	-0.8073834092	-0.401428781
μ_{f_2}	-0.01708556	-0.04316572	-0.0248582479	-0.036844353
β^H_{m,f_1}	0.31556204	NA	0.2625038294	0.012115165
$\beta^H_{f_1,m}$	0.09022262	NA	0.1110768711	-0.017815740
$\beta^H_{f_2,m}$	0.16093696	NA	0.1513616342	-0.012076605
β^V_{m,f_1}	NA	0.66185297	0.2436370753	0.660516281
$\beta^V_{f_1,m}$	NA	0.13333530	-0.0000301969	0.135995528
$\beta^V_{f_2,m}$	NA	0.11782067	0.0719251663	0.117135153
δ^P_m	NA	NA	0.3808355572	0.004695554

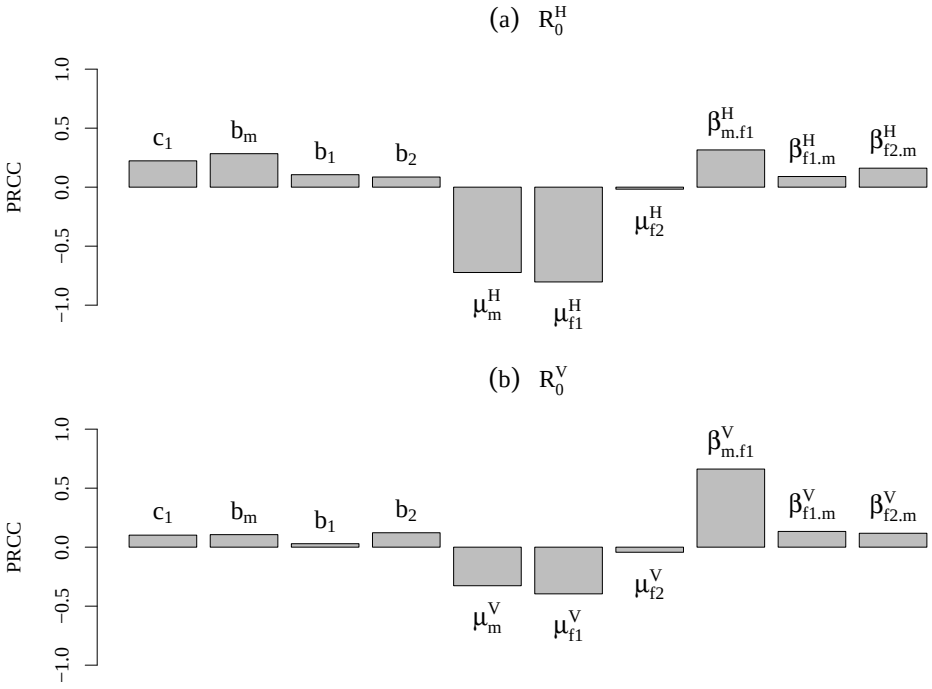

FIGURE 7. Effect of model parameters on the basic reproduction numbers, based on PRCC.

above, R_0^V seems to have only one significant factor: β^V_{m,f_1}, the probability of men infecting women with HSV-2. This is not surprising, considering men are almost twice as infectious.

As evident from Figure 8, the same parameters are most influential for the invasion reproduction numbers with one notable addition: δ_m^P, the enhanced infectivity co-infected individuals have when transmitting HIV, has a strong effect on R_V^H. This signifies the importance of HSV-2, and specifically the effect of co-infection, on the HIV prevalence. In Figure 8 it can also be observed that, in general, the transmission of HSV-2 probabilities, β^Vs, influence R_V^H but, on the contrary, the transmission of HIV probabilities, β^Hs, do not have a significant effect on R_H^V. Also the transmission from FSW to a male, $\beta_{f_2,m}^V$ has a greater impact on R_V^H than the transmission probability from general population female to male, $\beta_{f_1,m}$. The implications of these results are discussed in the next section.

6. **Discussion.** We present a model of the co-infection between HIV and HSV-2, prompted by the reported influence HSV-2 has on the HIV epidemic, and without considering methods of prevention or treatment. The model has several goals. One is to evaluate the effect of the co-infection of HIV and HSV-2 on HIV prevalence. The second is to explore the role of female sex workers on the HIV epidemic. The third goal is the introduction of a time-since-infection parameter that allows for more flexibility in modeling the interchanging acute and latent stages of HSV-2 and more flexibility when considering treatment and control of the disease. We calculate the basic and invasion reproduction numbers and perform sensitivity analysis (Figures 7 and 8). We also plot the total population dynamics based on a simplified version of our model, reducing our original system of partial differential equations to a system of ordinary differential equations by integrating over the time-since-infection variable a (Figure 4). Consider the reproduction numbers' sensitivity analysis in Figures 7 and 8. The following observations and implications are based on the given parameter values and ranges. Parameters may be different in different scenarios and countries, so if one is to implement the recommended strategies, it is important to run the model with appropriate parameters. It is possible different outcomes and hence different strategies would be more effective under different parameter values.

We observe that co-infection is very important in the disease dynamics. This can be seen by the effect of the enhancement δ^P on the HIV invasion reproduction number, indicating that the increased infectivity of co-infected individuals when transmitting HIV has a strong influence on R_V^H (see Figure 8). Thus, introducing a control measure on the HSV-2 populations, which would also affect the co-infected individuals, may be beneficial for reducing HIV prevalence. To support this hypothesis, we see that the transmission of HSV-2 probability β^V has a positive impact on R_V^H, while the transmission of HIV probability β^H has almost no influence on R_H^V. This suggests that treating individuals with HSV-2 could be effective in lowering HIV prevalence.

The fact that the infection probabilities from males to females, β_{m,f_j}^H and β_{m,f_j}^V, are more influential than those of the other two groups, suggests that treatment and control should be focused on the male population. This would prompt us to investigate the effect of condoms, circumcision, and viral treatment for HSV-2, among other strategies.

The parameters that inversely influence the reproduction numbers are the mortality rates, μ. Therefore, the length of the period of sexual activity seems to have a strong positive correlation with the spread of either disease. This parameter is only important for the general populations, m and f_1, while the high turnover of

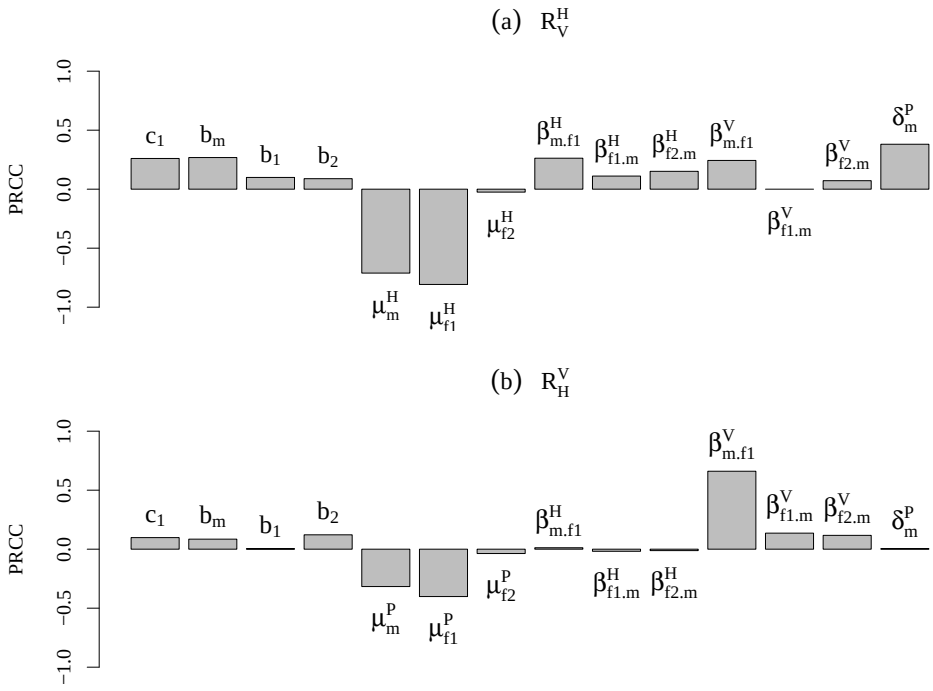

FIGURE 8. Effect of model parameters on the invasion reproduction numbers, based on PRCC.

FSWs seems to have no influence. Hence, education and early detection for STDs in the general population may be useful strategies for reducing the spread of both HIV and HSV-2.

The effect of female sex workers on the reproduction numbers is smaller than expected or often believed. There may be several reasons for this: high turnover (reflected in high μ_{f_2}), the tendency for men to choose women from the general population as sexual partners (reflected in high c_1 to c_2 ratio), the low infectious probability per partnership (because of the relatively infrequent encounters with the same partner), and the fact that the model does not consider what happens to these women after they leave the class. Improvements upon the model to consider the effect of these aspects will be explored in future work. However, this does not suggest that looking at FSWs as a separate population is not useful. Based on the sensitivity analysis, there are different modes through which the two female groups influence the reproduction numbers. The HSV-2 transmission probability from FSW to male per partnership, $\beta^V_{f_2,m}$, is more influential on R_V^H than the transmission probability from general population female to male, $\beta^V_{f_1,m}$. This suggests that strategies for reducing HSV-2 in the FSWs may be an effective control measure against the spread of HIV. On the other hand, since the general population female exit rate, μ_{f_1}, has so much more influence than the FSW exit rate, μ_{f_2}, early detection would be a more appropriate tactic when considering non-sex workers. These different strategies are to be explored.

There are several shortcomings of the model that would have to be discussed.

The exclusion of homosexual encounters may be a factor in its validity. Further, the model does not include other modes of transmitting HIV, more importantly vertical transmission and drug use. Also, we do not track the fate of women who leave the FSW group. These remain topics for future work.

Our model can be used to further include several more realistic characteristics concerning the two diseases. First, in this paper the transmission probabilities for HSV-2 are only modeled using a step function. In future work several functions that can model transition between latent and acute stages will be explored. These functions would include more aspects of the disease progression: different acute and latent periods, different levels of infectivity, depending on the time since infection, and the effect of symptomatic versus asymptomatic breakouts on an individual's infectiousness and prevention strategy. Second, the sensitivity analysis results can be used to study how implementing different control strategies, perturbing in our model the parameters affected by the control measure, may affect the disease prevalence. And third, including time-since-infection dependent enhancement parameters, may give insight into the importance of infectivity and/or susceptibility enhancement as a topic of future biological research, since as of now the direct influence of these enhancements is uncertain.

However, the model does a good job in estimating trends in disease progression in the lack of treatment. Furthermore, it gives an expression and a biological interpretation for its invasion reproduction numbers, adding an interesting aspect - the importance of the class from which the initial patient arises. Therefore, where the disease originates within the population and which group of people is more susceptible to this disease have an important role in reproduction number calculations and add another layer of information when wanting to implement control measures. This, as well, will be explored in future work.

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Appendix A. **Invasion HIV reproduction number (R_V^H).** In this section the invasion reproduction number for HIV, R_V^H, will be calculated. We assume the HIV disease invades an endemic HSV-2 population. We will analyze system (1), where the variables H_i, P_i will be assumed to be disease variables and S_i, V_i non-disease variables. We then linearize system (1) around the HIV disease free and HSV-2 endemic equilibrium $(S_i^0, 0, V_i^0(a), 0)$, look for eigenvalues for the linear operator and derive a characteristic equation,in order to define R_V^H.

First, we define the following:

$$\begin{aligned} \phi_{f_j,m}(t) &:= \int_0^\infty \beta_{f_j,m}^V(a) V_{f_j}(t,a)da, \\ \phi_{m,f_j}(t) &:= \int_0^\infty \beta_{m,f_j}^V(a) V_m(t,a)da, \quad j=1,2. \end{aligned} \tag{18}$$

$$\begin{aligned} \gamma_m(t) &:= \int_0^\infty \delta_m^P(a) P_m(t,a)da, \\ \gamma_{f_j}(t) &:= \int_0^\infty \delta_{f_j}^P(a) P_{f_j}(t,a)da, \quad j=1,2. \end{aligned} \tag{19}$$

$$\begin{aligned} \eta_{m,f_j}(t) &:= \int_0^\infty \beta_{m,f_j}^V(a)\sigma_m^P(a) P_m(t,a)da, \\ \eta_{f_j,m}(t) &:= \int_0^\infty \beta_{f_j,m}^V(a)\sigma_{f_j}^P(a) P_{f_j}(t,a)da, \quad j=1,2. \end{aligned} \tag{20}$$

Using (18), (19), and (20), the new expressions for the forces of infection become:

$$\begin{aligned} \lambda_m^H(t) &= \sum_{j=1}^2 b_{f_j}\beta_{f_j,m}^H \left(\frac{H_{f_j}(t)}{N_m(t)} + \frac{\gamma_{f_j}(t)}{N_m(t)}\right), \\ \lambda_{f_j}^H(t) &= b_m c_j \beta_{m,f_j}^H \left(\frac{H_m(t)}{N_{f_j}(t)} + \frac{\gamma_m(t)}{N_{f_j}(t)}\right), \quad j=1,2. \end{aligned}$$

$$\lambda_m^V(t) = \sum_{j=1}^{2} b_{f_j}\left(\frac{\phi_{f_j,m}(t)}{N_m(t)} + \frac{\eta_{f_j,m}(t)}{N_m(t)}\right),$$
$$\lambda_{f_j}^V(t) = b_m c_j\left(\frac{\phi_{m,f_j}(t)}{N_{f_j}(t)} + \frac{\eta_{m,f_j}(t)}{N_{f_j}(t)}\right), \quad j = 1, 2.$$

We will use (18) and (19) extensively in our calculations. Since we will linearize around the HIV disease free equilibrium, we also define $\phi^0_{f_j,m} := \int_0^\infty \beta^V_{f_j,m}(a)V^0_{f_j}(a)\,da$, $\phi^0_{m,f_j} := \int_0^\infty \beta^V_{m,f_j}(a)V^0_m(a)da$, for $j = 1, 2$.

When linearizing system (1) around the HIV disease free equilibrium $(S_i^0, 0, V_i^0(a), 0)$ and considering only the equations for the disease variables H_i and P_i, we obtain the following linear system equivalent to the linear system of equations with the disease variables H_i and P_i:

$$\begin{cases} \dfrac{dH_i}{dt} &= \tilde{\lambda}_i^H(t)S_i^0 - \delta_i^H\tilde{\lambda}_i^{0V}(t)H_i - \mu_i^H H_i(t), \quad i = m, f_1, f_2 \\ \gamma_m(t) &= \displaystyle\int_0^\infty \delta_m^P(a)\tilde{P}_m(t,a)da \\ \gamma_{f_j}(t) &= \displaystyle\int_0^\infty \delta_{f_j}^P(a)\tilde{P}_{f_j}(t,a)da, \quad j = 1, 2, \end{cases} \tag{21}$$

where

$$\tilde{\lambda}_m^H(t) = \sum_{j=1}^{2}\frac{b_{f_j}\beta^H_{f_j,m}}{N_m^0}(H_{f_j}(t) + \gamma_{f_j}(t)), \quad \tilde{\lambda}_{f_j}^H(t) = \frac{b_m c_j \beta^H_{m,f_j}}{N^0_{f_j}}(H_m(t) + \gamma_m(t)),$$
$$\tilde{\lambda}_m^{0V}(t) = \sum_{j=1}^{2} b_{f_j}\frac{\phi^0_{f_j,m}}{N_m^0}, \quad \tilde{\lambda}_{f_j}^{0V}(t) = b_m c_j\frac{\phi^0_{m,f_j}}{N^0_{f_j}},$$

and from linearizing the case $t > a$ in equation (5) of $P_i(t,a)$, $i = m, f_1, f_2$ we obtain

$$\begin{aligned}\tilde{P}_m(t,a) &= \sum_{j=1}^{2}\delta_m^H b_{f_j}\frac{\phi^0_{f_j,m}}{N_m^0}H_m(t-a)L_m^P(a) \\ &\quad + \sum_{j=1}^{2}\int_0^a \frac{L_m^P(a)}{L_m^P(x)}\delta_m^V(x)b_{f_j}\beta^H_{f_j,m}\frac{V_m^0(x)}{N_m^0}[H_{f_j}(x+t-a) + \gamma_{f_k}(x+t-a)]dx \\ \tilde{P}_{f_j}(t,a) &= \delta_{f_j}^H b_m c_j\frac{\phi^0_{m,f_j}}{N^0_{f_j}}H_{f_j}(t-a)L^P_{f_j}(a) \\ &\quad + \int_0^a \frac{L^P_{f_j}(a)}{L^P_{f_j}(x)}\delta^V_{f_j}(x)b_m c_j\beta^H_{m,f_j}\frac{V^0_{f_j}(x)}{N^0_{f_j}}[H_m(x+t-a) + \gamma_m(x+t-a)]dx, \\ &\quad j = 1, 2.\end{aligned}$$

In the next step we look for eigenvalues for the linear operator, i.e. for solutions of the form $H_i(t) = \bar{H}_i e^{\omega t}, \lambda_i(t) = \bar{\lambda}_i e^{\omega t}$, $i = m, f_1, f_2$. Substituting in (21) we obtain:

$$\omega\bar{H}_m = \sum_{j=1}^{2} b_{f_j}\beta^H_{f_j,m}\frac{S_m^0}{N_m^0}(\bar{H}_{f_j} + \bar{\gamma}_{f_j}) - \delta_m^H\sum_{j=1}^{2} b_{f_j}\frac{\phi^0_{f_j,m}}{N_m^0}\bar{H}_m - \mu_m^H\bar{H}_m,$$

$$\omega\bar{H}_{f_j} = b_m c_j \beta^H_{m,f_j} \frac{S^0_{f_j}}{N^0_{f_j}}(\bar{H}_m + \bar{\gamma}_m) - \delta^H_{f_j} b_m c_j \frac{\phi^0_{m,f_j}}{N^0_{f_j}} \bar{H}_{f_j} - \mu^H_{f_j} \bar{H}_{f_j}, \quad j = 1, 2,$$

$$\bar{\gamma}_m = \sum_{j=1}^{2} K_{1,f_j,m}(\omega)\bar{H}_m + \sum_{j=1}^{2} K_{2,f_j,m}(\omega)(\bar{H}_{f_j} + \bar{\gamma}_{f_j}),$$

$$\bar{\gamma}_{f_j} = K_{1,m,f_j}(\omega)\bar{H}_{f_j} + K_{2,m,f_j}(\omega)(\bar{H}_m + \bar{\gamma}_m), \quad j = 1, 2,$$

where

$$K_{1,f_j,m}(\omega) := \int_0^\infty \delta^P_m(a)\delta^H_m b_{f_j} \frac{\phi^0_{f_j,m}}{N^0_m} e^{-\omega a} L^P_m(a) da$$

$$K_{2,f_j,m}(\omega) := \int_0^\infty \delta^P_m(a) \int_0^a \frac{L^P_m(a)}{L^P_m(x)} \delta^V_m(x) b_{f_j} \beta^H_{f_j,m} \frac{V^0_m(x)}{N^0_m} e^{\omega(x-a)} dx da$$

and

$$K_{1,m,f_j}(\omega) := \int_0^\infty \delta^P_{f_j}(a)\delta^H_{f_j} b_m c_j \frac{\phi^0_{m,f_j}}{N^0_{f_j}} e^{-\omega a} L^P_{f_j}(a) da$$

$$K_{2,m,f_j}(\omega) := \int_0^\infty \delta^P_{f_j}(a) \int_0^a \frac{L^P_{f_j}(a)}{L^P_{f_j}(x)} \delta^V_{f_j}(x) b_m c_j \beta^H_{m,f_j} \frac{V^0_{f_j}(x)}{N^0_{f_j}} e^{\omega(x-a)} dx da.$$

The characteristic equation is then given by

$$det \begin{pmatrix} A & B \\ C & D \end{pmatrix} = 0,$$

where

$$A := \begin{pmatrix} -E^H_m(\omega) & b_{f_1}\beta^H_{f_1,m}\frac{S^0_m}{N^0_m} & b_{f_2}\beta^H_{f_2,m}\frac{S^0_m}{N^0_m} \\ b_m c_1 \beta^H_{m,f_1}\frac{S^0_{f_1}}{N^0_{f_1}} & -E^H_{f_1}(\omega) & 0 \\ b_m c_2 \beta^H_{m,f_2}\frac{S^0_{f_2}}{N^0_{f_2}} & 0 & -E^H_{f_2}(\omega) \end{pmatrix},$$

$$B := \begin{pmatrix} 0 & b_{f_1}\beta^H_{f_1,m}\frac{S^0_m}{N^0_m} & b_{f_2}\beta^H_{f_2,m}\frac{S^0_m}{N^0_m} \\ b_m c_1 \beta^H_{m,f_1}\frac{S^0_{f_1}}{N^0_{f_1}} & 0 & 0 \\ b_m c_2 \beta^H_{m,f_2}\frac{S^0_{f_2}}{N^0_{f_2}} & 0 & 0 \end{pmatrix},$$

$$C := \begin{pmatrix} \sum_{j=1}^2 K_{1,f_j,m}(\omega) & K_{2,f_1,m}(\omega) & K_{2,f_2,m}(\omega) \\ K_{2,m,f_1}(\omega) & K_{1,m,f_1}(\omega) & 0 \\ K_{2,m,f_2}(\omega) & 0 & K_{1,m,f_2}(\omega) \end{pmatrix},$$

$$D := \begin{pmatrix} -1 & K_{2,f_1,m}(\omega) & K_{2,f_2,m}(\omega) \\ K_{2,m,f_1}(\omega) & -1 & 0 \\ K_{2,m,f_2}(\omega) & 0 & -1 \end{pmatrix},$$

and

$$E_m^H(\omega) := \omega + \delta_m^H \sum_{j=1}^{2} b_{f_j} \frac{\phi_{f_j,m}^0}{N_m^0} + \mu_m^H$$

$$E_{f_j}^H(\omega) := \omega + \delta_{f_j}^H b_m c_j \frac{\phi_{m,f_j}^0}{N_{f_j}^0} + \mu_{f_j}^H.$$

After computing the determinant, the characteristic equation reads as follows:

$$\begin{aligned} 1 = &\sum_{j=1}^{2} \left[\frac{K_{2,f_j,m}(\omega)(1+K_{1,m,f_j}(\omega)) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(\omega)} \right] + \sum_{j=1}^{2} K_{2,f_j,m}(\omega) K_{2,m,f_j}(\omega) \\ &+ \sum_{j=1}^{2} \left[\frac{b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0} (1+K_{1,m,f_j}(\omega)) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(\omega)} \right] \frac{(1+\sum_{j=1}^{2} K_{1,f_j,m}(\omega))}{E_m^H(\omega)} \\ &+ \frac{\sum_{j=1}^{2} K_{2,m,f_j}(\omega) b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0}}{E_m^H(\omega)} (1 + \sum_{j=1}^{2} K_{1,f_j,m}) =: G_V^H(w). \end{aligned}$$

We can then define the invasion HIV reproduction number as $R_V^H := \sqrt{G_V^H(0)}$. This expression can be rewritten as

$$\begin{aligned} \left(R_V^H\right)^2 = \sum_{j=1}^{2} \Bigg\{ &\frac{b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0} b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(0) E_m^H(0)} + \frac{b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0} K_{1,m,f_j}(0) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(0) E_m^H(0)} \\ &+ \frac{b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0} b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0} (\sum_{j=1}^{2} K_{1,f_j,m}(0))}{E_{f_j}^H(0) E_m^H(0)} \\ &+ \frac{b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0} K_{1,m,f_j}(0) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0} (\sum_{j=1}^{2} K_{1,f_j,m}(0))}{E_{f_j}^H(0) E_m^H(0)} \\ &+ \frac{K_{2,m,f_j}(0) b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0}}{E_m^H(0)} + \frac{K_{2,m,f_j}(0) b_{f_j} \beta_{f_j,m}^H \frac{S_m^0}{N_m^0}}{E_m^H(0)} \sum_{j=1}^{2} K_{1,f_j,m} \\ &+ \frac{K_{2,f_j,m}(0) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(0)} + \frac{K_{2,f_j,m}(0) K_{1,m,f_j}(0) b_m c_j \beta_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}}{E_{f_j}^H(0)} \\ &+ K_{2,f_j,m}(0) K_{2,m,f_j}(0) \Bigg\} = G_V^H(0), \end{aligned} \tag{22}$$

where

$$\begin{aligned} E_m^H(0) &:= \delta_m^H b_{f_1} \frac{\phi_{f_1,m}^0}{N_m} + \delta_m^H b_{f_2} \frac{\phi_{f_2,m}^0}{N_m} + \mu_m^H, \\ E_{f_j}^H(0) &:= \delta_{f_j}^H b_m c_j \frac{\phi_{m,f_j}^0}{N_{f_1}^0} + \mu_{f_j}^H \end{aligned} \tag{23}$$

are the rates at which male m and female f_j, $j = 1, 2$ individuals exit the H_m and H_{f_j} classes respectively, either because of acquiring HSV-2 or because of ceasing sexual activity. A detailed biological interpretation can be found in Section 4.1.

Appendix B. **Invasion HSV-2 reproduction number (R_H^V).** In this section we will show the derivation of the HSV-2 invasion reproduction number R_H^V. We will proceed in a similar way as we did in order to find the HIV invasion reproduction number (see Appendix A). In this case we will consider that in system (1), the HSV-2 variables V_i, P_i are disease variables and S_i, H_i are non-disease variables. We will then linearize system (1) around the HSV-2 disease free but HIV endemic (H_i^0) equilibrium $(S_i^0, H_i^0, 0, 0)$, and then derive a characteristic equation in order to define R_H^V.

We first define the following for $j = 1, 2$

$$\hat{D}_{m,f_j}(\omega) := \frac{S_m^0}{N_{f_j}^0} \int_0^\infty b_m c_j \beta_{m,f_j}^V(a) L_m^V(a) p_m^V(a) e^{-a\omega} da$$

$$\hat{D}_{f_j,m}(\omega) := \frac{S_{f_j}^0}{N_m^0} \int_0^\infty b_{f_j} \beta_{f_j,m}^V(a) L_{f_j}^V(a) p_{f_j}^V(a) e^{-a\omega} da,$$

and

$$\begin{aligned}\hat{F}_{m,f_j}(\omega) :=& H_m^0 \int_0^\infty \beta_{m,f_j}^V(a) \sigma_m^P(a) \delta_m^H L_m^P(a) e^{-\omega a} da \\ &+ S_m^0 \int_0^\infty \int_0^a \beta_{m,f_j}(a) \sigma_m^P(a) L_m^V(x) \big(- \dot{p}_m^V(x) \big) \frac{L_m^P(a)}{L_m^P(x)} dx \; e^{-\omega a} da,\end{aligned}$$

$$\begin{aligned}\hat{F}_{f_j,m}(0) :=& H_{f_j}^0 \int_0^\infty \beta_{f_j,m}^V(a) \sigma_{f_j}^P(a) \delta_{f_j}^H L_{f_j}^P(a) e^{-\omega a} da \\ &+ S_{f_j}^0 \int_0^\infty \int_0^a \beta_{f_j,m}(a) \sigma_{f_j}^P L_{f_j}^V(x) \big(- \dot{p}_{f_j}^V(x) \big) \frac{L_{f_j}^P(a)}{L_{f_j}^P(x)} dx \; e^{-\omega a} da,\end{aligned}$$

where

$$L_i^V(a) := e^{-\int_0^a \mu_i^V(\tau) d\tau}, \quad i = m, f_1, f_2,$$

$$p_m^V(a) := e^{-\int_0^a \mathcal{F}_m^V(\tau) d\tau} \quad \Big(\text{with } \mathcal{F}_m^V(\tau) := \delta_m^V(\tau) \sum_{j=1}^2 b_m c_j \beta_{f_j,m}^H \frac{H_{f_j}^0}{N_{f_j}^0} \Big),$$

$$-\dot{p}_m^V(x) = \mathcal{F}_m^V(x) p_m^V(x),$$

$$p_{f_j}^V(a) := e^{-\int_0^a \mathcal{F}_{f_j}^V(\tau) d\tau} \quad \Big(\text{with } \mathcal{F}_{f_j}^V(\tau) := \delta_{f_j}^V(\tau) b_{f_j} \beta_{m,f_j}^H \frac{H_m^0}{N_m^0} \Big),$$

$$-\dot{p}_{f_j}^V(x) = \mathcal{F}_{f_j}^V(x) p_{f_j}^V(x), \quad j = 1, 2.$$

In the following, consider $\lambda_i^V(t), i = m, f_1, f_2$, $\eta_{m,f_j}(t), \eta_{f_j,m}(t)$, $j = 1, 2$, as defined in (20).

After linearizing system (1) around the HSV-2 disease free equilibrium $(S_i^0, H_i^0, 0, 0)$, $i = m, f_1, f_2$, reducing the system to only consider the HSV-2 disease variables, V_i and P_i, and substituting into the linear system solutions of the form

$$\lambda_i^V(t) = \bar{\lambda}_i^V e^{\omega t}, \eta_{m,f_j}(t) = \bar{\eta}_{m,f_j} e^{\omega t}, \eta_{f_j,m}(t) = \bar{\eta}_{f_j,m} e^{\omega t}$$

in order to find the eigenvalues of the linear operator, the linearized system can be rewritten in the form:

$$\begin{cases} \bar{\lambda}_m^V = \sum_{j=1}^{2} \hat{D}_{f_j,m}(\omega)\bar{\lambda}_{f_j}^V + \dfrac{b_{f_j}}{N_m^0}\bar{\eta}_{f_j,m} \\ \bar{\lambda}_{f_j}^V = \hat{D}_{m,f_j}(\omega)\bar{\lambda}_m^V + \dfrac{b_m c_j}{N_{f_j}^0}\bar{\eta}_{m,f_j} \\ \bar{\eta}_{m,f_j} = \hat{F}_{m,f_j}(\omega)\bar{\lambda}_m^V \\ \bar{\eta}_{f_j,m} = \hat{F}_{f_j,m}(\omega)\bar{\lambda}_{f_j}^V, \quad j = 1, 2. \end{cases} \tag{24}$$

Let us define

$$\hat{E}_{f_j,m}(\omega) := \hat{D}_{f_j,m}(\omega) + \frac{b_{f_j}}{N_m^0}\hat{F}_{f_j,m}(\omega),$$
$$\hat{E}_{m,f_j}(\omega) := \hat{D}_{m,f_j}(\omega) + \frac{b_m c_j}{N_{f_j}^0}\hat{F}_{m,f_j}(\omega), \quad j = 1, 2.$$

Then system (24) can be reduced to

$$\begin{cases} \bar{\lambda}_m^V = \sum_{j=1}^{2} \hat{E}_{f_j,m}(\omega)\bar{\lambda}_{f_j}^V \\ \bar{\lambda}_{f_j}^V = \hat{E}_{m,f_j}(\omega)\bar{\lambda}_m^V, \quad j = 1, 2, \end{cases} \tag{25}$$

and the characteristic equation of system (25) becomes

$$det \begin{pmatrix} -1 & \hat{E}_{f_1,m} & \hat{E}_{f_2,m} \\ \hat{E}_{m,f_1} & -1 & 0 \\ \hat{E}_{m,f_2} & 0 & -1 \end{pmatrix} = 0. \tag{26}$$

Computing the determinant, (26) is equivalent to the following equation

$$G_H^V(\omega) := \hat{E}_{f_1,m}(\omega)\hat{E}_{m,f_1}(\omega) + \hat{E}_{f_2,m}(\omega)\hat{E}_{m,f_2}(\omega) = 1.$$

We then can define the HSV-2 invasion reproduction number as $R_H^V := \sqrt{G_H^V(0)}$. For a biological interpretation refer to Section 4.2.

Appendix C. Biological interpretation of the terms of R_V^H. This Appendix describes biologically the remaining terms in equation (15). The first term was explained in Section 4.1.

The second term in (15) is as follows

$$\int_0^\infty [\mathcal{P}_m(H_m)](a)\delta_m^P(a)\pi_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0} da$$

where $[\mathcal{P}_m(H_m)](a)$ represents the number of co-infected males of time-since-HSV-2-infection a, that were HIV only males before (see Table 5). This case represents the path

$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{infect} N_m$$

in Figure 2. Here the initial HIV infected male becomes co-infected and is still sexually active at time-since-co-infection a, $([\mathcal{P}_m(H_m)](a))$. Then, at time-since-infection a, this male infects susceptible females at a rate $\delta^P_m(a)\pi^H_{m,f_j}$, who then as $H_{f_j}, j = 1, 2$ females infect males at a rate $\pi^H_{f_j,m}$, throughout their permanence in the HIV class $T^H_{f_j}$. We integrate to consider all individuals in P_m, of all times-since-HSV-2-infection, that infected susceptible females.

The third term in (15) is given by

$$\int_0^\infty \mathcal{H}^{H_m}_{f_j}(S^0_{f_j}) q^{V_m}_{H_{f_j},P_{f_j}} L^P_{f_j}(a)\delta^P_{f_j}(a)\pi^H_{f_j,m}\frac{W^{0,V}_m}{N^0_m}da$$

where $\mathcal{H}^{H_m}_{f_j}(S^0_{f_j})$ is as in the first term. The path

$$S_m \xrightarrow{initial} H_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m$$

in Figure 2 represents this scenario. This case is explained in the following way: the initial HIV-positive male is in H_m, infects susceptible females, who as H_{f_j} females, with probability $q^{V_m}_{H_{f_j},P_{f_j}}$, get infected with HSV-2 and are still sexually active at time-since-co-infection a with probability $L^P_{f_j}(a)$. These co-infected females then infect males at time-since-infection a, at a rate $\delta^P_{f_j}(a)\pi^H_{f_j,m}$. Finally, by integrating we consider infections due to co-infected females with all possible times-since-HSV-2-infection.

The fourth term reads,

$$\int_0^\infty \mathcal{H}^{\mathcal{P}_m(H_m)}_{f_j}(S^0_{f_j}) q^{V_m}_{H_{f_j},P_{f_j}} L^P_{f_j}(a)\delta^P_{f_j}(a)\pi^H_{f_j,m}\frac{W^{0,V}_m}{N^0_m}da,$$

where $(\mathcal{H}^{\mathcal{P}_m(H_m)}_{f_j}(S^0_{f_j}))(a)$ is the number of HIV females, who initially were in the susceptible class, got infected with HIV by a co-infected male who was initially an H_m male (see Table 5). The path corresponding to this term is

$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m$$

in Figure 2. The interpretation is as in the previous case, only that the initial HIV male individual becomes co-infected before infecting susceptible females.

The fifth term is

$$\int_0^\infty [\mathcal{P}^{H_m}_{f_j}(V^0_{f_j})](a)\delta^P_{f_j}(a)\pi^H_{f_j,m}\frac{W^{0,V}_m}{N^0_m}da,$$

where $[\mathcal{P}^{H_m}_{f_j}(V^0_{f_j})](a)$ represents the number of co-infected females (with time-since-infection a) who got infected with HIV while being in the HSV-2 only class, by the initial HIV male (who is in H_m) (see Table 5). This case follows the path

$$S_m \xrightarrow{initial} H_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m.$$

The situation is as follows, the first HIV male case infects $V^0_{f_j}(x)$ females during his sexual lifetime, who as P_{f_j} females remain sexually active at time-since-infection a $\left([\mathcal{P}^{H_m}_{f_j}(V^0_{f_j})](a)\right)$. These female individuals then infect males with HIV at a rate $\delta^P_{f_j}(a)\pi^H_{f_j,m}$. We integrate to consider infection by females with co-infection of all

possible times-since-infection.

The sixth term is

$$\int_0^\infty [\mathcal{P}_{f_j}^{\mathcal{P}_m(H_m)}(V_{f_j}^0)](a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0}da,$$

where $[\mathcal{P}_{f_j}^{\mathcal{P}_m(H_m)}(V_{f_j}^0)](a)$ is similar to $[\mathcal{P}_{f_j}^{H_m}(V_{f_j}^0)](a)$, with the only difference being that the females got the infection from the initial HIV male after he was co-infected with HSV-2 (see Table 5). This case follows the path

$$S_m \xrightarrow{initial} H_m \xrightarrow{becomes} P_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m.$$

The interpretation is as in term five, only that, as stated above, the initial HIV male individual becomes co-infected before infecting HSV-2 only females with HIV.

The last three terms correspond to the case when the initial HIV case is a male who was already infected with HSV-2.

The seventh term is as follows

$$(\mathcal{H}_{f_j}^{P_m}(S_{f_j}^0))\pi_{f_j,m}^H T_{f_j}^H \frac{W_m^{0,V}}{N_m^0},$$

where $\mathcal{H}_{f_j}^{P_m}(S_{f_j}^0)$ corresponds to the number of HIV females that acquired HIV, while susceptible, by the initial co-infected HIV male (see Table 5). These females then infect males at a rate $\pi_{f_j,m}^H$, throughout their permanence in the HIV class, $T_{f_j}^H$. Observe that this term follows the path

$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{infect} N_m.$$

The eighth term is the following

$$\int_0^\infty \mathcal{H}_{f_j}^{P_m}(S_{f_j}^0) q_{H_{f_j},P_{f_j}}^{V_m} L_{f_j}^P(a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0}da,$$

where $\mathcal{H}_{f_j}^{P_m}(S_{f_j}^0)$ is as in the previous case. This case describes the path

$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} S_{f_j} \xrightarrow{become} H_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m$$

in Figure 2. The interpretation is similar to the previous case, only that the females infected by the initial male, before infecting males, become co-infected with probability $q_{H_{f_j},P_{f_j}}^{V_m}$, and then infect males when their time-since-HSV-2-infection is a. We integrate to account for male infections from all times-since-infection of those co-infected females.

The last term reads

$$\int_0^\infty [\mathcal{P}_{f_j}^{P_m}(V_{f_j}^0)](a)\delta_{f_j}^P(a)\pi_{f_j,m}^H \frac{W_m^{0,V}}{N_m^0}da,$$

where $[\mathcal{P}_{f_j}^{P_m}(V_{f_j}^0)](a)$ is as in the previous case, with the only difference being that now $V_{f_j}^0$ females are being infected by P_m males, instead of susceptible females. The path followed by this term is the following,

$$V_m \xrightarrow{initial} P_m \xrightarrow{infects} V_{f_j} \xrightarrow{become} P_{f_j} \xrightarrow{infect} N_m.$$

TABLE 5. Description/Interpretation of terms appearing in equation (15).

Symbol	Definition	Description/Interpretation
$\mathcal{H}_{f_j}^{H_m}(S_{f_j}^0)$	$\frac{S_m^0}{W_m^{0,V}}\pi_{m,f_j}^H \mathcal{T}_m^H \frac{S_{f_j}^0}{N_{f_j}^0}$	# of HIV females, that were infected with HIV while in S_{f_j} by the initial H_m male throughout his sexual lifetime as an H_m male.
$[\mathcal{P}_m(H_m)](a)$	$\frac{S_m^0}{W_m^{0,V}}\left(\sum_{j=1}^2 q_{H_m,P_m}^{V_{f_j}}\right) L_m^P(a)$	Probability that the initial HIV male is in the H_m class, becomes co-infected, and is sexually active at time-since-infection a.
$\mathcal{H}_{f_j}^{\mathcal{P}_m(H_m)}(S_{f_j}^0)$	$\int_0^\infty [\mathcal{P}_m(H_m)](a)\delta_m^P(a)\pi_{m,f_j}^H da \frac{S_{f_j}^0}{N_{f_j}^0}$	# of HIV females, that were infected with HIV while in S_{f_j} by the initial HIV male when that male got co-infected and had time-since-infection $0 < a < \infty$.
$[\mathcal{P}_{f_j}^{H_m}(V_{f_j}^0)](a)$	$\int_0^a \frac{S_n^0}{W_m^{0,V}}\left(\pi_{m,f_j}^H \mathcal{T}_m^H \frac{\delta_{f_j}^V(x)V_{f_j}^0(x)}{N_{f_j}^0}\right)\frac{L_{f_j}^P(a)}{L_{f_j}^P(x)}dx$	# of co-infected females still sexually active at time-since-infection a, who got infected with HIV while already infected with HSV-2 with time since infection $x < a$. They became infected by the initial H_m male during his sexual lifetime.
$[\mathcal{P}_{f_j}^{\mathcal{P}_m(H_m)}(V_{f_j}^0)](a)$	$\int_0^a\int_0^\infty [\mathcal{P}_m(H_m)](b)\delta_m^P(b)\pi_{m,f_j}^H db\frac{\delta_{f_j}^V(x)V_{f_j}^0(x)}{N_{f_j}^0}\frac{L_{f_j}^P(a)}{L_{f_j}^P(x)}dx$	# of co-infected females still sexually active at time-since-infection a, who got infected with HIV while already infected with HSV-2 with time since infection $x < a$. They got infected by the initial HIV male when that male got co-infected and had time-since-infection $0 < b < \infty$.
$[\mathcal{P}_m(V_m^0)](a)$	$\int_0^a \frac{\delta_m^V(x)V_m^0(x)}{W_m^{0,V}}\frac{L_m^P(a)}{L_m^P(x)}dx$	Probability that the initial HIV case is co-infected and still sexually active at time-since-HSV-2-infection a.
$\mathcal{H}_{f_j}^{P_m}(S_{f_j}^0)$	$\int_0^\infty [\mathcal{P}_m(V_m^0)](a)\delta_m^P(a)\pi_{m,f_j}^H \frac{S_{f_j}^0}{N_{f_j}^0}da$	# of HIV females, who got infected with HIV while in S_{f_j}. They got the HIV infection by the initial co-infected male, that had time-since-HSV-2-infection $0 < a < \infty$.
$[\mathcal{P}_{f_j}^{P_m}(V_{f_j}^0)](a)$	$\int_0^a \frac{L_{f_j}^P(a)}{L_{f_j}^P(x)}\int_0^\infty [\mathcal{P}_m(V_m^0)](b)\delta_m^P(b)\pi_{m,f_j}^H \frac{\delta_{f_j}^V(x)V_{f_j}^0(x)}{N_{f_j}^0}dbdx$	# of co-infected females still sexually active at time-since-infection a. They acquired HIV while already infected with HSV-2 and having time-since-infection $x < a$. They got the HIV infection by the initial co-infected male, that had time-since-HSV-2 infection $0 < a < \infty$.

For this table, $j = 1, 2$.

TABLE 6. Description/Interpretation of terms appearing in equation (17).

Symbol	Definition	Description/Interpretation
$\mathcal{V}_{f_j}^{V_m}(S_{f_j}^0)$	$\int_0^\infty \frac{S_m^0}{W_m^{0,H}} L_m^V(a) p_m^V(a) \pi_{m,f_j}^V(a) \frac{S_{f_j}^0}{N_{f_j}^0} da$	# HSV-2 only females, who were infected with HSV-2 while in $S_{f_j}^0$ by the initial HSV-2 only male, throughout his sexual life-span as an HSV-2 only male ($0 < a < \infty$).
$[\mathcal{P}_m(V_m)](a)$	$\int_0^a \frac{S_m^0}{W_m^{0,H}} L_m^V(x)(-\dot{p}_m^V(x)) \frac{L_m^P(a)}{L_m^P(x)} dx$	Probability for the initial HSV-2 infected male to become co-infected at time-since-HSV-2-infection $0 < x < a$ and to remain co-infected at time-since-infection a.
$\mathcal{V}_{f_j}^{\mathcal{P}_m(V_m)}(S_{f_j}^0)$	$\int_0^\infty [\mathcal{P}_m(V_m)](a) \sigma_m^P(a) \pi_{m,f_j}^V(a) \frac{S_{f_j}^0}{N_{f_j}^0} da$	# HSV-2 only females, who were infected with HSV-2 while in $S_{f_j}^0$ by the initial HSV-2 only infected male after him acquiring co-infection, throughout all times since HSV-2 infection $0 < a < \infty$.
$\mathcal{P}_{f_j}^{V_m}(H_{f_j}^0)$	$\int_0^\infty \frac{S_m^0}{W_m^{0,H}} L_m^V(a) p_m^V(a) \pi_{m,f_j}^V(a) \frac{\delta_{f_j}^H H_{f_j}^0}{N_{f_j}^0} da$	# co-infected females, who were infected with HSV-2 while in $H_{f_j}^0$ by the initial HSV-2 only male, throughout his sexual life-span as an HSV-2 only male.
$\mathcal{P}_{f_j}^{\mathcal{P}_m(V_m)}(H_{f_j}^0)$	$\int_0^\infty [\mathcal{P}_m(V_m)](a) \sigma_m^P(a) \pi_{m,f_j}^V(a) \frac{\delta_{f_j}^H H_{f_j}^0}{N_{f_j}^0} da$	# co-infected females, who were infected with HSV-2 while in $H_{f_j}^0$ by the initial HSV-2 only male, after him acquiring co-infection, throughout all times since HSV-2 infection $0 < a < \infty$.
$\mathcal{V}_{f_j}^{P_m}(S_{f_j}^0)$	$\int_0^\infty \frac{\delta_m^H H_m^0}{W_m^{0,H}} L_m^P(a) \sigma_m^P(a) \pi_{m,f_j}^V(a) \frac{S_{f_j}^0}{N_{f_j}^0} da$	# HSV-2 only females, who were infected with HSV-2 while in $S_{f_j}^0$ by the initial co-infected male, throughout all times since HSV-2 infection $0 < a < \infty$.
$\mathcal{P}_{f_j}^{P_m}(H_{f_j}^0)$	$\int_0^\infty \frac{\delta_m^H H_m^0}{W_m^{0,H}} L_m^P(a) \sigma_m^P(a) \pi_{m,f_j}^V(a) \frac{\delta_{f_j}^H H_{f_j}^0}{N_{f_j}^0} da$	# co-infected females, who were infected with HSV-2 while in $H_{f_j}^0$ by the initial co-infected male, throughout all times since HSV-2 infection $0 < a < \infty$.

For this table, $j = 1, 2$.

Appendix D. **Choosing parameters.** This section justifies our choices for mean values of the parameters. For a full list of parameters, consult Table 1. In what follows, $i = m, f_1, f_2$.

D.1. μ_i**.** Recall that the analysis required a constant population size for each population group (m, f_1, f_2). Therefore, we considered the same exiting parameter μ_i for each class (S, H, V, P). This is not simply the mortality rate, it is the rate with which individuals cease sexual activity. We assume that the average sexual lifespan for individuals from the general population is 30 years. For high-risk women, class f_2, we assumed 4 years. It is hard to determine how long FSWs work on average - migration to different place of work, periods of working in and out of the sex industry, and disparity within the type of partners (client, relationship, etc.) make such a calculation unreliable. Furthermore, in our model we do not consider movement between groups. Still, the length of working in the sexual industry can be approximated to be around 4 years, considering the high turn over [31]. Therefore, our mean value for μ_m and μ_{f_1} is 1/360 and for μ_{f_2} is 1/48 per month.

D.2. b_i, N_i**.** Several of these parameters were found in the literature, while others were calculated using the balance equations (2).

Studies on African men agree that the average number of lifetime sexual partnerships for men are 8-10 [45], therefore, we chose 9 as our mean. Then, b_m is 9/360 partnerships per month.

The number of lifetime sexual partnerships for the general female population is not that concrete: [45] estimates this number to be around 2 for South Africa, while [29] estimates them at 6.8. The reasons for the vast disparities between female numbers in different areas and especially between male and female numbers that are often discussed are: overreporting in males, underreporting in females, low reliability of recollection, matters of how the questions on the survey are worded, and sampling bias that leaves sex workers out of the surveys [8, 29, 41, 45]. The average number of sexual partners for FSWs also varies: [31] estimates it at 22 per week, [41] gives a range of 13-22 per week, depending on how they are reported, and according to [47], it varies between 60 and 160 partners per year.

Given the great disparity between the data, we calculated b_{f_1} and b_{f_2} from b_m and our assumptions for the ratio between b_{f_2} and b_{f_1} and the preference men give to f_1 women when choosing a sexual partner, c_1. b_{f_2}/b_{f_1} was estimated at 10. The ratio may seem small considering the numbers above, however beyond the unreliability of the data discussed above, another cultural issue would have to be considered. In South Africa for example, it is common for individuals to enter casual relationships in exchange for money or gifts [16, 17, 28, 52]. We believe women with that behavior would have to be considered in the f_2 category. If they are, this would add another level of uncertainty about the parameters. Hence our estimation is conservative.

The proportion of partners of males who are f_1, c_1, was chosen to be 0.9. Adding to the discussion about difficulty in estimating parameters, [10] gives an overview of global studies that calculate the percentage of men who paid for sexual services. The figures differ greatly, depending on how the surveys were conducted. However, if "paying" for sex is considered exchanging money, gifts, or favors in return for sexual favors, then around 10% of men have engaged in such activity. Hence our assumption. $c_2 = 1 - c_1$. N_m is chosen at 10^7. We further assumed that $N_m = N_{f_1} + N_{f_2}$. Therefore, given b_m, c_1, N_m, and b_{f_2}/b_{f_1}, we calculate $b_{f_1}, b_{f_2}, c_2, N_{f_1}$, and N_{f_2} using the balance equation (2).

D.3. β^H. Note that the units of our values are probability of transmission per partnership. Therefore, if an individual has a lot of partnerships, the average transmission is low for each partnership. If a person has only a few partnerships, the average probability of transmission is high because a lot of time is spent per partnership. We assume that there is no difference between male and female transmissions per act. No significant difference has been found in lower income countries, while the usual assumption that men as inserters are more infectious has been shown for higher income countries [22]. The average infectivity is reported per coital act. In Africa the average probability per act varies greatly, depending on region, way of approximation, viral load, circumcision of males, and HIV stage [2,22,23,27,36,50]. The mean values of probabilities of transmission per act range between 0.0007 and 0.0082 [50]. HIV-positive individuals spend most of their time in the latent stage, so we assumed a more conservative 0.0017 per coital act. Therefore, in Table 2, ρ^H is the probability of HIV transmission per act and is set at 0.0017. Average acts per month vary [9]. However, we believe that 2.5 acts per month is within the average per lifetime [34]. For sex workers, we assumed the number of acts per partnership per year to be 2 because of the relatively high turnover of clients. Therefore, in Table 2, r is the number of sexual acts per partnership per year for FSWs and is estimated at 2. $\beta^H_{m,f_1}, \beta^H_{m,f_2}, \beta^H_{f_1,m}$, and $\beta^H_{f_2,m}$ were calculated accordingly.

D.4. β^V. We decided to use a simple step function describing $\beta^V_{i,k}, k = m, f_1, f_2, k \neq i$ for this paper. The step functions alternates periods of infectivity (nonzero value) and latency (zero). Different studies find different rates of transmission. [35] gives a great disparity between ethnicities for transmission rates. The average is 6.8% per year of male-to-female transmission risk (5.8 for white women, 11.2 for black women) and 4.4% per year risk for female-to-male contacts (2.6 for white, 8.1 for black males). The participants were instructed in safe sexual practices but the role of different sexual behaviors is not mentioned in the results. In [37] male-to-female probability of transmission is 16.9% (9.1% to 31%, depending on whether women had HSV-1 antibodies) and female-to-male is 3.8% per 11 months. 9 of the infections were asymptomatic, 4 were in early symptoms, which leads us to suspect that either the participants were instructed not to have sex during outbreaks or were aware of the risks before entering the survey. Based on these data, we assumed 8% male-to-female risk per year and 4% female-to-male. Therefore, in Table 2, ρ^V_m is the probability of transmission of HSV-2 by a male individual per year, and is set at 0.08. ρ^V_f is the probability of transmission of HSV-2 by a female individual, and is set at 0.04.

For the reproduction numbers sensitivity analysis, using some available data about the periods of latency, we constructed a step function for $\beta^V_{m,f_1}(a)$ by alternating periods of infectiousness of length two weeks with periods of latency (no infectivity) of 2.5 months [3,13,24,24]. The value of the step function at the non-zero intervals was constructed, so the average of $\beta^V_{m,f_1}(a)$ matched the 8% male-to-female infectious probability per year, converting it to probability per partnership. The other β^Vs were calculated similarly. The parameter $\beta^V_{i,k}, i, k = m, f_1, f_2, i \neq k$ used in the sensitivity analysis, figures 7 and 8 refers to the height of the step function.

D.5. δ^V **and** δ^P. In [14], the authors claim that the increased susceptibility of an individual with HSV-2 to HIV is 2-4 times higher than that of a healthy person. According to [20], the risk of acquisition of HIV if one already has HSV-2 is increased 3-fold. In [23], it was found that the probability per act of someone with both HSV-2

and HIV to transmit HIV increases 4-fold in comparison with an individual who only has HIV. However, our parameters are in probabilities per partnership. Therefore, an enhancement of 2 to 4 would make our probabilities greater than 1, which is not realistic. Therefore, we were conservative in our assumption that $\delta^P = 1.1$ and $\delta^V = 1$ regardless of gender.

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E-mail address: georgi.i.kapitanov@gmail.com
E-mail address: clorenzo@math.purdue.edu
E-mail address: kvogtgei@math.purdue.edu
E-mail address: zfeng@math.purdue.edu