HIV transmissions by stage under dynamic sexual partnerships

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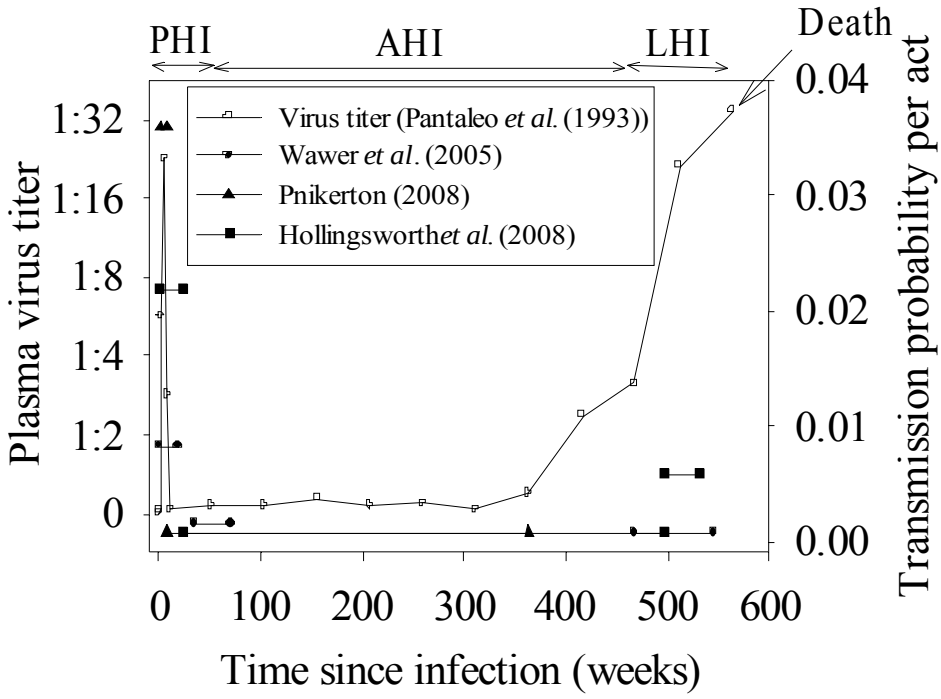
Abstract

Most models that assess the relative number of transmissions during different stages of human immunodeficiency virus (HIV) infection assume that the transmission occurs through instantaneous sexual contacts. In the real world, however, human sexual interactions occur in the context of a complex social system, and HIV is likely to transmit through repeated sexual acts during partnerships formed and broken over time that last for varying lengths of time. We sought to understand how dynamic sexual partnerships would influence transmission dynamics during different stages of HIV infection: primary HIV infection (PHI) and asymptomatic HIV infection (AHI). Using a pair approximation technique, we developed a dynamic model of HIV transmission in a homogeneous population that includes the formation and dissolution of sexual partnerships of varying duration. The fraction of transmissions during PHI is a U-shaped function of increasing partnership duration, such that the fraction decreases as partnership duration increases up to a few years, but rises again as partnerships are further lengthened. Our results show that the dynamics of sexual partnerships strongly influence HIV transmissions by stage and models that assume instantaneous contacts will likely overestimate transmissions during PHI for real, dynamic sexual partnerships with varying (non-zero) durations.

Introduction

Human immunodeficiency virus (HIV) represents a continuing threat to global health. Currently no vaccine exists to prevent HIV infection and no treatments exist to cure those who get infected. Characterization of HIV infections typically includes the stages shown in Figure 1: primary HIV infection (PHI), asymptomatic HIV infection (AHI) and late HIV infection (LHI) [1]. Figure 1 demonstrates the average timing of the various stages, provides estimates of average viral titers (open circles, scale on left axis), and shows estimates about transmission probability per act (closed symbols, scale on right axis) based on the data from several studies. Plasma virus titer estimates come from serial dilution tests (in this case, two-fold serial dilution) and they indicate the lowest concentration of virus that still infects cells (e.g., 1:256 indicates that virus infected cells at the first 8 serial two-fold dilutions of plasma). The transmission probability estimates do not cover the entire period of infection due to missing data over the entire range. Wawer et al. [2] provide the data for transmission rates for different stages of HIV infection in a Ugandan population. Pinkerton [3] re-analyzed the Wawer et al. [2] data and estimated transmission probability per act for PHI and AHI under varying durations of incubation stage and PHI, and the estimates included in Figure 1 assume baseline conditions (7 days of incubation period, 49 days of PHI). Hollingsworth et al. [4] also re-analyzed the same data and provide relative risk estimates, but not absolute values, and consequently to provide the comparison in Figure 1, we set the transmission probability during AHI to be similar to Pinkerton data. As shown in Figure 1, although PHI occurs relatively quickly and goes unrecognized, it represents a highly-infectious state with high viral titers. By contrast, AHI represents a phase of low infectivity, but it can last more than a decade. Patients who do not receive get treatment, primarily in developing countries, may experience high viral load before death in LHI.

Figure 1. A typical course of HIV infection. Open circles indicate virus titer (left Y-axis). Filled symbols indicate transmission probability per act (right Y-axis), where circles, triangles, and squares are based on the data from Wawer et al. [2], Pinkerton [3], Hollingsworth et al. [4], respectively.



Given the current lack of a vaccine or cure, disease control programs for HIV must target human behavior, testing, and disease treatment strategies. Different types of control programs target individuals in different stages. For example, public health prevention strategies currently focus on encouraging the use of condoms and on screening efforts to identify HIV-positive individuals followed by counseling to try to get them to receive treatment and to change their sexual behaviors, which may slow transmissions from them. However, screening efforts typically miss transmissions from HIV-infected individuals during PHI, because HIV individuals generally get screened after PHI. If a substantial number of transmissions occur during PHI, then routine case

detection programs might not be effective at reducing population levels of infection, and this further motivates the need for prevention activities.

Several prior models explored the role of normally-undetected PHI transmissions in the context of the overall risk of HIV transmission [5-8]. To capture the complexity of HIV transmission, these models disaggregate the population into several subgroups and assume complex mixing patterns among those subgroups. However, one limitation of these models is that they still retain the assumption that infection transmits through an instantaneous sexual contact such that: (1) an infected individual has an equal probability to infect any other susceptible individuals in the population and (2) the probability of two or more sexual contacts between the same people is negligibly small. This assumption is particularly unrealistic for sexually transmitted diseases such as HIV, because in reality people form relationships and HIV is likely to transmit through repeated sexual acts during sexual partnerships. Real sexual partnerships form and dissolve over time, and the complexity of the partnership patterns may significantly impact HIV transmission risks for individuals and within a population.

In this study we address the problem of how sexual partnership patterns influence transmission dynamics during different stages of HIV infection. To that end, we constructed a system dynamics model of the transmission of HIV in a population in which sexual partnerships form and dissolve. This model builds on the simple SI (susceptible-infected) model described by Sterman [9]. Sterman mentions many dimensions of the complex system of HIV transmission, including consideration of the social dynamics, stigma, multiple modes of transmission, behavioral changes made after infected people realize they are infected, etc [9]. However, Sterman does not consider the complexity of the partnership formations and their impact on transmissions. For this analysis, we focus on exploring the partnership formations and how they may impact transmission, and we use a highly-simplified homogeneous population model to demonstrate the interaction between infection and partnership dynamics. We refer readers to Sterman [9] for consideration of other complexities related to modeling HIV, and we offer this analysis as a potential modification of the assumption that infection transmits simply through instantaneous sexual contact.

In the Methods section, we describe a potential SI model of HIV transmission in a homogeneous population that ignores dynamic partnerships (Figure 2). Then we illustrate how we modify the SI model to incorporate partnership dynamics (Figure 3). We describe such processes as pair formation and dissolution and transmission in discordant pairs. We introduce a method called pair approximation to simplify complex processes in individuals who have multiple partners. Then we introduce the SI_1I_2 model in which the infectious period is represented as two separate stages. We also explain model inputs regarding our SI and SI_1I_2 models. In the Results section, we compare the standard SI model and our SI model with partnerships. Using SI_1I_2 model, we show how transmission dynamics during PHI and AHI interact differentially with partnership dynamics. Finally in the Discussion section, we present the implications and limitations of our results and opportunities for future work.

Methods

As shown in Figure 1 and discussed above, the course of HIV infection occurs typically in three distinct stages of varying duration and infectivity. In this study we only include PHI and AHI (i.e., we ignore LHI and use an SI_1I_2 model), because in the US and other developed countries HIV-infected patients receive treatment after infection and they cease sexual activity before they experience LHI. Using only two stages simplifies our model analyses while providing insights into how transmissions during different stages of HIV infection interact with partnership dynamics, and future models could extend the concepts presented here to include LHI for developing country models.

To develop the SI_1I_2 model we start with a SI model that represents the infectious period as a single stage. Figure 2 shows a schematic of an SI model for HIV transmissions in a homogeneous population without partnerships, in which infection transmits through an instantaneous sexual contact, represented by contact rate parameter. We assume that new

susceptible people enter the population and provide a continuing new pool available to initiate sexual activity and potentially become infected. We assume that susceptible people are recruited at the same rate that infected people die, which keeps the population size constant. The duration of infection and infectivity varies to mimic either PHI or AHI, or some average of the two.

Figure 2. Schematic of a potential SI model for HIV transmission in a homogeneous population in which infection transmits through an instantaneous sexual contact.

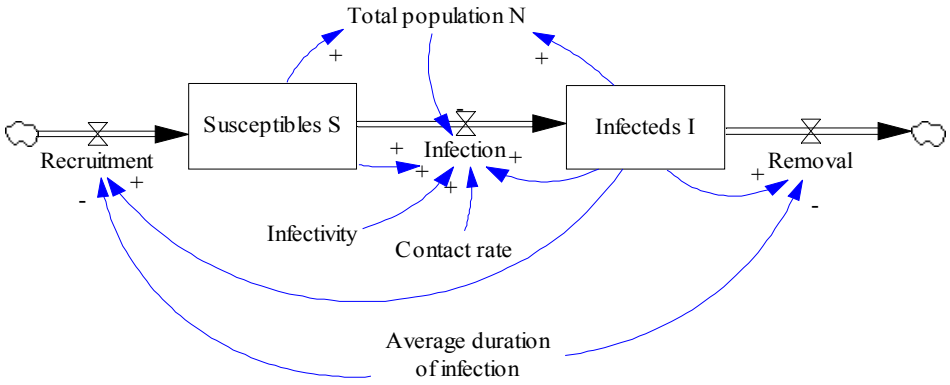
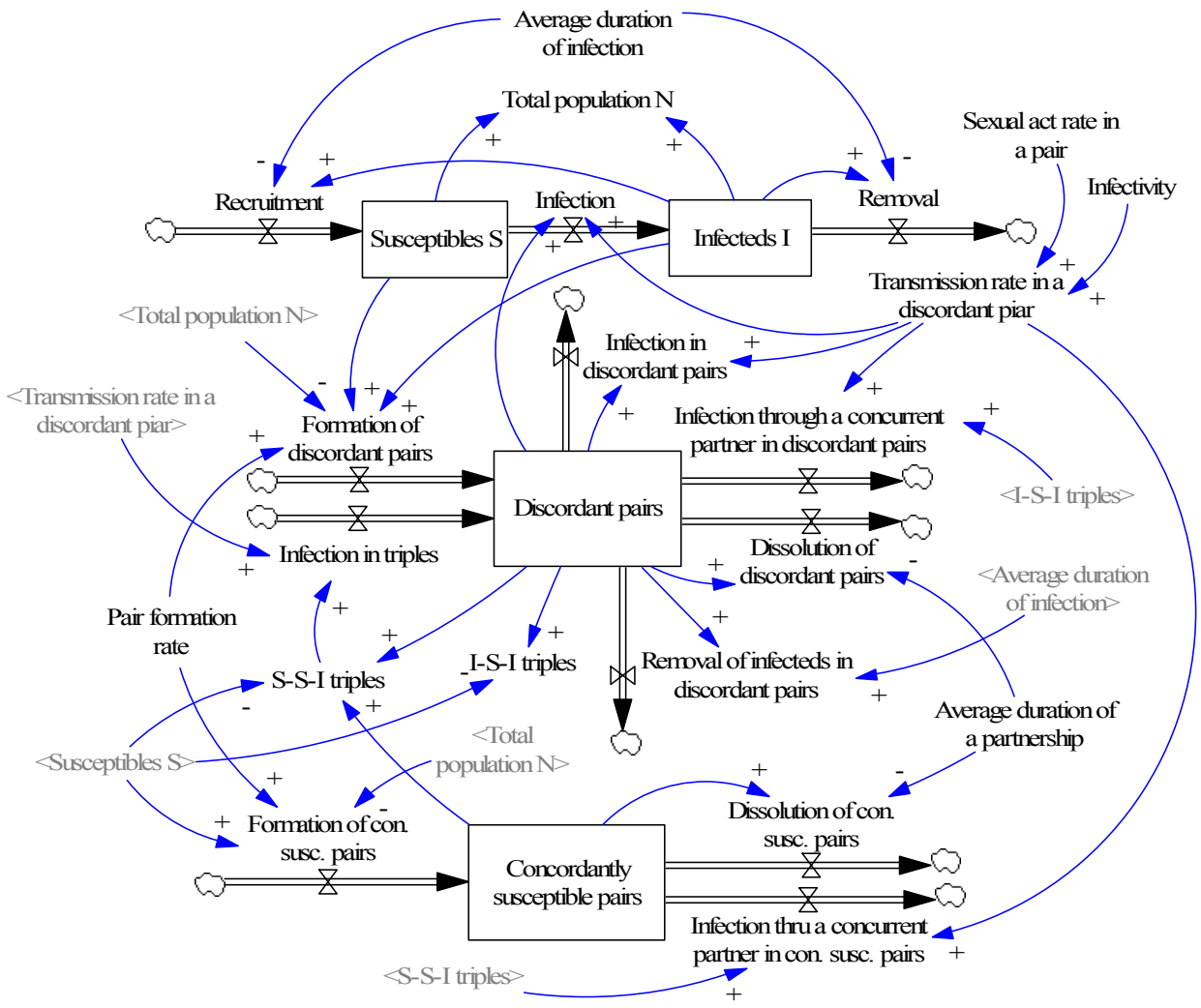


Figure 3 shows how we modify the SI model such that infection transmits through dynamic partnerships. In the SI model with partnerships, we divide the contact rate used in the SI model without partnerships into partnership formation and dissolution rates and *sexual act rate in a pair* terms. Thus, main difference between a standard SI model (Figure 2) and our SI model with partnerships (Figure 3) is that we explicitly model pairs of individuals, of which discordant pairs (i.e., pairs of susceptible and infected individuals) are the most critical. We also use an intermediate variable, *transmission rate in a discordant pair*, which represents the product between *sexual act rate in a pair* and *infectivity*. New infections arise only from discordant pairs, which form and dissolve with complex dynamics. If partnerships dissolve fast (i.e., instantaneously), then the SI model with partnerships reduces to a standard SI model. However, if we assume a non-negligible duration for the partnership, the two models diverge and the standard SI model yields higher infection levels than in the SI model with partnerships.

Figure 3. A diagram for SI model with partnerships.



The number of discordant pairs can increase through pair formation between susceptibles and infecteds or through infection of susceptibles with at least one infected partner, because in reality people can concurrently have more than one sexual partner. This implies the need to consider multiple partnerships, such as triples, because infection may occur for susceptibles at the center of S-S-I or I-S-I triples. To be precise, this transmission does not increase the number of discordant pairs because, by definition, transmissions decrease the number of existing discordant

pairs. However, we later separately capture the decrease of discordant pairs through transmission. The number of discordant pairs can decrease in four ways: (1) transmission changing a susceptible person into an infected person, (2) dissolution of a discordant pair, (3) removal of an infected person from a discordant pair, and/or (4) infection from a concurrent partner can decrease the number of discordant pairs.

Correctly modeling the impact of relationships on HIV transmission implies that we must know the number of S-S-I and I-S-I triples to model the dynamics of discordant pairs. Dynamics of these triples are more complex than those of discordant pairs and they are influenced by the dynamics of quadruples. In turn, dynamic of quadruples are influenced by quintuples and this can go on until the whole set of connected individuals get incorporated into the model. However, instead of keeping track of dynamics of higher-order terms (i.e., triples, quadruples, etc.), we approximate the number of triples using lower-order terms (i.e., pairs and individuals); hence, using pair approximation [10]. Various approximation methods exist and the simplest one assumes random dynamic partnerships: $[ijk] \approx [ij][jk]/[j]$ such that the number of partners in state k of individuals in state j is independent of whether those in state j have partners in state i or not. Thus, to approximate the number of S-S-I, we need to keep track of concordantly susceptible pairs (i.e., S-S pairs), because $[SSI] \approx [SS][SI]/[S]$. The number of S-S pairs increases only by pair formation between susceptibles, but decreases via pair dissolution or infection of either susceptible partner. For transmissions to occur, the susceptible needs at least one infected partner, which is captured by infection of susceptibles at the center of S-S-I triples.

Although our model includes two stages for infected (PHI and AHI), we do not show the figure for SI_1I_2 model with partnerships due to its complexity and the fact that it is a simple extension of SI model with partnerships shown in Figure 3. Table 1 summarizes the model inputs that we used to compare the results of the SI model with partnerships to an SI model without partnerships and to explore the SI_1I_2 model. In the SI_1I_2 model, we ignore the removal rate from infection, by assuming that all individuals cease sexually activity after on average 25 years (i.e.,

at a constant rate μ). All the equations of SI and SI_1I_2 models appear in the Appendix.

Table 1. Model inputs.

Symbol	Values	Description	Source
c	1	The number of sexual act in a partnership per day (i.e., contact rate in the standard SI model).	
$^*\beta_i$	$\{\beta_1, \beta_2\}$= {0.0036, 0.0008} per act	Infectivity (i.e., transmission probability per sexual act) during stage i for i = 1, 2 (1=PHI, 2=AHI).	[3-4]
γ	1/49 or 1/3650 days	Average rate of removal from infection (or progression from PHI to AHI in SI_1I_2 model).	[3-4]
σ	0.0001-20 per day	Pair dissolution rate per day.	
ρ	0.0001-20 per day	Pair formation rate per day.	
μ	1/(25*365) per day	The rate at which people cease their sexual activity.	
N	10000	Initial population size.	

* In the *SI* model, β_i is used without the subscript.

Results

In Figure 4, we compare the SI model with partnerships and the standard SI model. We adjust the model input values to maintain a constant number of sexual acts per unit time per person regardless of the duration of the partnership for purposes of comparison. The number of infected people in the SI model without partnerships grows exponentially until it comes to equilibrium (black solid line). The infection does not die out because susceptibles get continually recruited and provide a source for new infection. Infection dynamics in the SI model with partnerships

approach those of the SI model without partnerships if partnership duration is negligibly small (blue dashed line). However, if partnerships have non-negligible duration infection level is much lower (blue solid line). This occurs because, if infection has already occurred in prolonged partnerships, sexual acts of infecteds are with infecteds and they do not generate new infections, which could happen if partnerships change rapidly.

Figure 4. The number of infected people over time from the SI model without partnerships and the SI model with partnerships. Sexual act rate in a pair per day (or contact rate in the SI model without partnerships) (c) = 1, infectivity per act (β) = 0.036, duration of infection ($1/\gamma$) = 49, σ = 20 (i.e., on average 0.05 day of partnerships) or 0.03333 (i.e., on average 30 days of partnerships). ρ varies to keep ρ/σ at 1, which gives the average number of partners is roughly one. Initial (and equilibrium) population size N = 10000.

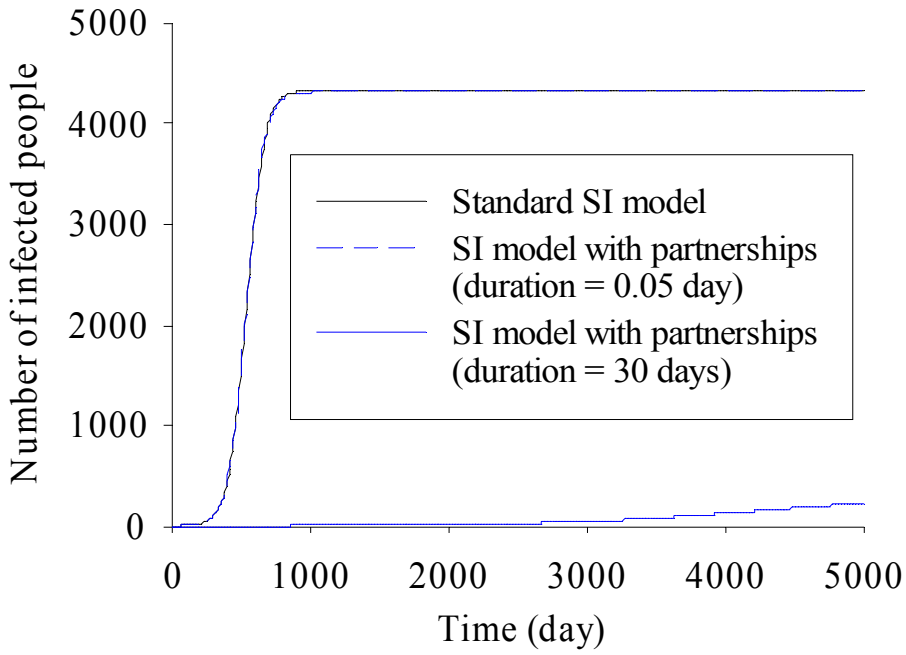
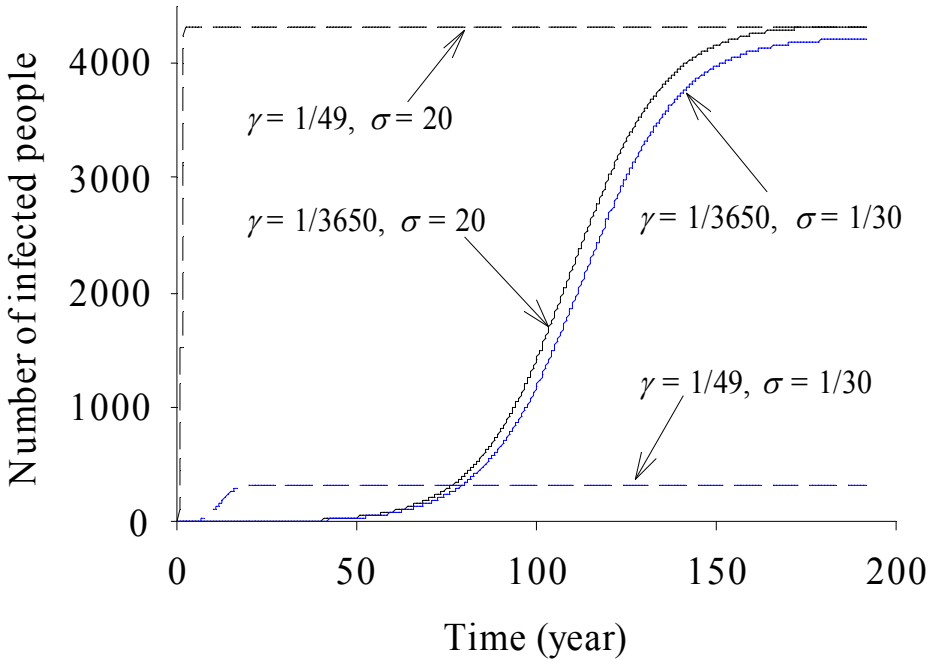


Figure 5 illustrates the interaction among duration of infection, infectivity, and partnership dynamics. As in Figure 4, people engage in the same number of sex acts per unit time regardless of the duration of the partnership. We set the duration of infection ($1/\gamma$) to be either 49 or 3650 days to mimic the duration of PHI and AHI, respectively. Infectivity (β) is 0.036 per act if $\gamma=1/49$ and 0.0004832877 if $\gamma=1/3650$ to keep the transmission potential (β/γ) constant. Decreasing the infectivity obviously slows the growth of infection. However, equilibrium infection levels are the same in the standard SI model as long as the transmission potential is kept constant. We next examine whether that relationship still holds in the SI model with partnerships.

Figure 5. Number of infected people over time in SI model with partnerships. $\sigma = 20$ (0.05 day of partnerships) or 0.03333 (30 days of partnerships). ρ varies to keep σ/ρ at 1. $c = 1$, $\beta = 0.0004832877$ if $\gamma = 1/3650$ and 0.036 if $\gamma = 1/49$.

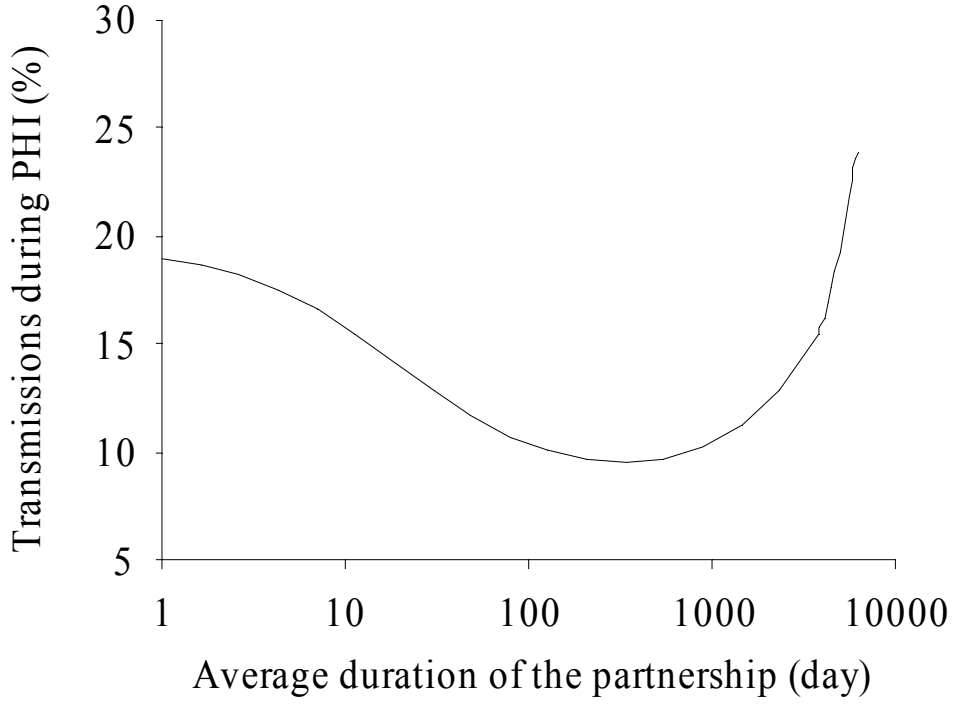


If partnerships change rapidly (black lines, average duration of the partnership = 0.05 day), endemic infection levels do not change as we change the duration of infection as long as we keep the transmission potential constant. If partnerships are lengthened (blue lines, average duration of the partnership = 30 days), infection levels are much higher for lower infectivity over a longer period ($\beta = 0.0004832877$, $\gamma = 1/3650$,) than for higher infectivity over a shorter period ($\beta = 0.036$, $\gamma = 1/49$). This happens because transmission occurs faster for higher infectivity and so more sexual acts are between infecteds in prolonged partnerships for higher infectivity than lower infectivity. This indicates that the relative number of transmissions at equilibrium may increase during AHI if partnerships are lengthened.

Figure 6 shows how transmissions during PHI and AHI at equilibrium change across varying durations of partnerships. The fraction of transmissions during PHI decreases as the average duration of the partnership increases up to a few hundred days, but it increases again as partnerships are further lengthened. As we have shown in Figure 5, in prolonged partnerships, transmissions during a stage with higher infectivity decreases more than those during a stage with lower infectivity. Thus, the fraction of transmissions during PHI decreases with increasing partnership duration.

Increases in the fraction of transmissions during PHI with the continued increase in the duration of the partnership occur because infecteds progress from PHI to AHI in SI_1I_2 model. Infecteds keep their partners as they progress from PHI to AHI unless the partnerships dissolve. This means infected partners during PHI are not replaced by other susceptibles and so infecteds may not have partners that are still susceptible as they have progressed to AHI. The relative fraction of transmissions during PHI increases accordingly, which makes prevention activities an increasingly important focus for intervention.

Figure 6. Fraction of transmissions during PHI SI_1I_2 model with partnerships. $\sigma = 0.0001 - 1$. ρ varies to keep σ/ρ at 1. $c = 1$, $\beta_1 = 0.036$, $\beta_2 = 0.0008$, $1/\gamma = 49$ days, $1/\mu = 25$ years.



Discussion

This paper demonstrates that the dynamics of sexual partnerships strongly influence the fraction of transmissions during PHI as well as equilibrium prevalence. These influences are strong enough that prior model analyses[5-8, 10-11] assuming instantaneous sexual contacts are inadequate for estimating the fraction of transmissions by stage of infection. Future analyses of

control programs that affect different stage of HIV differentially should consider interaction between infection and partnership dynamics.

Dynamic sexual partnerships have often been explored using agent-based models (ABM) [12-15]. Although ABMs are easier to include real-world details, they also have disadvantages. Analyzing ABMs takes more time than analyzing standard dynamic models and it is often hard to decide whether a new behavior from the ABM is really a new phenomenon or an artifact. Our model with partnerships bypasses these difficulties of ABM while still modeling dynamic partnerships. By adding only a couple of stocks in the model we successfully captured interesting and important interactions between infection and partnership dynamics. Although this simple model would require much expansion to include other real-world specifics of HIV transmission as noted in the introduction, it clearly demonstrates that some existing models missed important dynamics related to partnerships. As noted above, Sterman [9] describes many other dimensions of HIV transmission that may influence our inferences. We also note that we ignored multiple modes of transmission, even though transmission probabilities vary by direction of sex acts: transmission probability is higher for male-to-female transmission than for female-to-male transmission [16]. We suggest that future modeling efforts might find it worthwhile to examine how transmissions during different stages of HIV infection will be influenced by different combinations of homosexual and heterosexual partnerships.

We hope that this paper provides useful context related to considering the role of partnerships in the context of current and future system dynamics models related to the transmission of HIV, other sexually transmitted diseases, and other systems that depend on the formation of partnerships.

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Appendix

The SI model with partnerships

In the SI model with partnerships following notations are used. The state of individuals is represented as i, where $i = S, I$ indicates infection category. The number of individuals in state i is denoted by $[i]$. For example, $[S]$ indicates the number of susceptibles regardless of the number of partners. Similar rules apply to the number of pairs. Pairs of susceptible and infected persons is labeled as S-I pairs and their number is indicated by $[SI]$. By convention, the number of pairs is counted in both directions. Thus $[SI] = [IS]$, and $[SS]$ indicates twice the number of S-S pairs. The following set of differential equations describes the SI model with partnerships.

$$\left.\begin{aligned}
[\dot{S}] &= -\beta c[SI] + \gamma[I], \\
[\dot{I}] &= \beta c[SI] - \gamma[I], \\
[\dot{SI}] &= \rho[S][I]/N - (\gamma + \sigma)[SI] + \beta c(-[SI] - [ISI] + [SSI]), \\
[\dot{SS}] &= \rho[S][S]/N - 2\beta c[SSI] - \sigma[SS].
\end{aligned}\right\} \tag{1}$$

The SI_1I_2 model with partnerships

In the SI_1I_2 model, following notations are used. The state of individuals is represented as i_j, where $i = S, I$ and $j = 1, 2$ indicate infection category and the stage of infection, respectively. The number of individuals in state i_j is denoted by $[i_j]$. Similarly, β_j denotes the infectivity of infecteds in stage j. The following set of differential equations describes the SI_1I_2model.

$$
\left.
\begin{aligned}
[\dot{S}] &= -c\left(\beta_1[SI_1] - \beta_2[SI_2]\right) - \mu[S], \\
[\dot{I_1}] &= c(\beta_1[SI_1] + \beta_2[SI_2]) - (\gamma + \mu)[I_1], \\
[\dot{I_2}] &= \gamma[I_1] - \mu[I_2], \\
[\dot{SS}] &= \rho[S][S]/N - 2c(\beta_1[SSI_1] + \beta_2[SSI_2]) - (\sigma + 2\mu)[SS], \\
[\dot{SI_1}] &= \rho[S][I_1]/N + c\beta_1([SSI_1] - [I_1SI_1] - [SI_1]) \\
&\quad + c\beta_2([SSI_2] - [I_2SI_1]) - (\gamma + \sigma + 2\mu)[SI_1], \\
[\dot{SI_2}] &= \rho[S][I_2]/N + \gamma[SI_1] - c\beta_1[I_1SI_2] - c\beta_2([I_2SI_2] + [SI_2]) \\
&\quad - (\sigma + 2\mu)[SI_2].
\end{aligned}
\right\} \quad (2)
$$