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HIV Transmissions by Stage in Dynamic Sexual Partnerships

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Abstract

Most models assessing relative transmissions during different progressive stages of human immunodeficiency virus (HIV) infection assume that infections are transmitted through instantaneous sexual contacts. In reality, however, HIV will often be transmitted through repeated sex acts during partnerships that form and dissolve at varying rates. We sought to understand how dynamic sexual partnerships would influence transmissions during different progression stages of HIV infection: primary HIV infection (PHI) and chronic stage. Using a system of ordinary differential equations with a pair approximation technique, we constructed a model of HIV transmission in a homogeneous population in which sexual partnerships form and dissolve. We derived analytical expressions for useful epidemiological quantities such as basic reproduction number and also did simulation runs of the model. Partnership dynamics strongly influence transmissions during progressive stages of HIV infection. The fraction of transmissions during PHI has a U-shaped relationship with respect to the rate of partnership change, where the minimum and maximum occur given partnerships of about 100 days and fixed partnerships, respectively. Models that assume instantaneous contacts may overestimate transmissions during PHI for real, dynamic sexual partnerships with varying (non-zero) durations.

Keywords

primary HIV infection; transmission model; network; pair approximation

1. Introduction

Despite its decreasing incidence since late 1990s (Joint United Nations Programme on HIV/AIDS, 2010), human immunodeficiency virus (HIV) infection causes a major burden in global health (5th leading cause of the burden of disease globally in 2004) (World Health Organization, 2008). The number of people living with HIV continues to grow reaching an estimated 33.3 million in 2009 and 2.6 million people became newly infected with HIV in 2009 alone (Joint United Nations Programme on HIV/AIDS, 2010). Characterization of HIV

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infection in the individual typically includes three stages (which we will call primary, latent, and late stages) with significantly different serum viral load (Cohen et al., 2011; Fiebig et al., 2003; Pantaleo et al., 1993). The probability of transmission correlates with the serum viral load (Gray et al., 2001; Quinn et al., 2000) and thus varies over the course of HIV infection (Hollingsworth et al., 2008; Pinkerton, 2008; Wawer et al., 2005).

Since the identification of HIV as the etiological agent of AIDS in 1984 (Gallo, 2002; Montagnier, 2002), analyses of mathematical and computer models of HIV transmission have provided insights on the importance of various issues of HIV transmission including the rate of acquiring new sexual partners (Anderson and May, 1988; May and Anderson, 1987), social mixing patterns (Anderson et al., 1990; Anderson et al., 1989; Gupta et al., 1989; Hyman and Stanley, 1988; Hyman and Stanley, 1989; Jacquez et al., 1988; Koopman et al., 1988; Stigum et al., 1994; Stigum et al., 1997), and concurrent sexual partnerships (Goodreau et al., 2010; Morris and Kretzschmar, 1997; Watts and May, 1992). Some studies focus on the relative role of the different stages of HIV infection. A couple of studies emphasize the importance of the primary stage of HIV infection (PHI) on the overall transmission of HIV in the early stages of the epidemic (Jacquez et al., 1994) and also at endemic state with certain assumptions on mixing patterns (Koopman et al., 1997). On the other hand, model fitting to San Francisco City Clinic Cohort data produced the highest probability of transmission during the late stage of HIV infection implying the late stage played a leading role (augmented by a longer duration of late stage of HIV infection compared to PHI), especially during the late period of the epidemic (Rapatski et al., 2005b). Another study suggests that no HIV stage is dominant with primary and late stages of HIV infection playing increased roles during the early and the later stages of the epidemic, respectively, using examples of African cities (Abu-Raddad and Longini, 2008). These analyses are potentially useful because effectiveness of some control programs for HIV transmission will vary by the relative contributions of different stages of HIV infection. For example, identifying HIV-positive people and reducing transmissions from them will miss transmissions during PHI since patients are usually detected after PHI has already passed (Pilcher et al., 2004a; Pilcher et al., 2004b). On the other hand, a partially effective vaccine that reduces virus level (and thus infectivity) mostly during PHI (Johnston and Fauci, 2007) will have little effect on reducing transmissions occurring after PHI.

This paper examines a similar issue of relative role of the different stages of HIV infection in the transmission of HIV in a homosexual population using a mathematical model, but assumes sexual partnerships can be long-term and concurrent. Prior studies (Abu-Raddad and Longini, 2008; Jacquez et al., 1994; Koopman et al., 1997; Rapatski et al., 2005b) assumed that HIV transmits through instantaneous sexual contacts although in reality, HIV will likely transmit through repeated sex acts during partnerships that form and dissolve over time. One study (Kretzschmar and Dietz, 1998) examined a similar issue, but assumed sexual partnerships are monogamous while several studies suggest that concurrent sexual partnership may play an important role in transmissions of HIV in the overall population (Morris and Kretzschmar, 1997; Morris et al., 2010; Morris et al., 2009) and, especially, in transmissions during PHI (Goodreau et al., 2010). Our prior work (Kim et al., 2010) also addressed a similar issue, but in the context of individual-based (IB) model. The present study uses a system of ordinary differential equations with a pair approximation technique (Rand, 1997) to bypass extensive simulations required for the IB model. In doing so, we can also provide analytical expressions for important epidemiological quantities such as basic reproduction number (R_0) and explore the relationship between dynamics of sexual partnerships and transmissions during different stages of HIV infection across a wide range of parameter values.

In the Methods section, we discuss model parameters and formulation including a pair approximation technique. In the Results section, we derive R_0 and also graphically show how the rate of partnership change influences the fraction of transmissions during PHI. Finally, in the Discussion section, we discuss the implications of our study and real-world complexities that may influence our inferences.

2. Methods

2.1. Compartmental flows

The typical compartmental model categorizes a population by disease status (e.g., susceptible or infected) and assigns a specific compartment to the population in each category. Then, one defines the flows into, out of, and between compartments using differential equations. Our model categorizes population by partnership status as well as disease status. Figure 1 illustrates the difference between the typical compartmental model and the one in this paper in the context of a simple susceptible (S) - infected (I) model. A box with a letter (S or I) within indicates the population in the state and arrows indicate the flows for each population. Figure 1(a) shows the typical compartmental model, where the flow from S to I indicating the new infection is determined by $\beta[S][I]/N$, where $[S]$ and $[I]$ indicates the number of susceptible and infected people, respectively, and β defines the transmission rate per infected person per unit of time. This formulation assumes that susceptible people may be infected from any infected person in the population with equal chance. On the other hand, Figure 1(b) shows that new infections arise through explicit partnerships between susceptible and infected people; $\lambda[SI]$. Here, $[SI]$ indicates the number of pairs (or partnerships) and λ defines the transmission rate of the infected person in the partnership per unit of time. This formulation assumes that a susceptible person may be infected only by infected people that are already connected to that susceptible person. In this model, infection may be constrained to one partnership unless the infected person is already connected with or forms new connections with other susceptible people.

We use two models to explore the effects of partnership dynamics on the transmissions during different stages of HIV infection in a homosexual population. One model assumes a single compartment for the infectious period (SI model) whereas the other model divides the infectious period into two compartments (SI_1I_2 model). Our model comprises parameters (see Table 1) indicating transmission between susceptible and infected people (β), death from infection (γ), partnership formation (ρ), and partnership dissolution (σ), where β and γ are used without subscripts in SI model and with subscripts in SI_1I_2 model. We provide our rationale for the parameter values in the following section.

2.2. Duration of infectiousness ($1/\gamma$) and transmission rate (β)

In the SI model, we arbitrarily choose the duration of infectiousness ($1/\gamma$) and the transmission rate (β) to illustrate the interaction among partnership dynamics, the transmission rate, and the duration of infectiousness whereas in the SI_1I_2 model, we choose them to reflect the course of HIV infection (i.e., PHI and latent stage). In the SI_1I_2 model, the durations of infection are 49 days ($1/\gamma_1$) and 10 years ($1/\gamma_2$) for PHI and latent stage, respectively. Transmission rates are 45 times higher during PHI ($\beta_1=0.036$) than latent stage ($\beta_2=0.00084$), based on analyses of a Rakai study (Pinkerton, 2007). We omitted the late peak in infectivity including AIDS because we assume that people get treatment and do not experience AIDS while they are sexually active. We assume that people have a fixed frequency of sex acts per unit of time independent of the number of partners, based on the sex budget argument (Blower and Boe, 1993). In this formulation the frequency of sex acts per partnership drops as the number of partnerships rises. At a given transmission rate per infected person per unit of time, β (or β_i for $i=1,2$ in SI_1I_2 model), we compute the

transmission rate per partnership, λ (or λ_i for $i=1,2$ in SI_1I_2 model) by dividing β with the expected number of partners per person, n (which we will call “mean degree”), i.e., $\lambda = \beta/n$. When partnerships are at equilibrium and transmission conditions are near threshold such that infection frequency is negligible, n is derived from $N\rho = 2P\sigma$, where N and P denote the number of people and partnerships, respectively. Then by definition $n=2P/N=\rho/\sigma$, the ratio of partnership formation to dissolution rates. In the case where the influence of infection dynamics on partnership dynamics becomes significant (because partnerships of people dying from infection dissolve), we can compute the mean degree by $([SS]+2[SI]+[II]) / N$.

2.3. The SI model

In the SI model, we use the following notations. We use $[X]$ to denote the number of people in a state X . For example, $[S]$ indicates the number of susceptible people regardless of whether or not they have partnerships. Similarly, $[SI]$ represents the number of partnerships between a susceptible and an infected person. By convention, we count the number of partnerships in both directions, which implies that $[SI]=[IS]$, and $[SS]$ indicates twice the number of SS partnerships.

We express the time evolution of the number of susceptible people, $d[S]/dt$, as

$$\dot{[S]} = -\lambda[SI] + \gamma[I]. \quad (1)$$

The first term on the right hand side of Equation (1) captures infection transmission in SI partnerships. The second term indicates that new susceptible people are recruited every time death from infection occurs, which keeps the population size constant. Although this assumption of a constant population size may be unrealistic, we retain this assumption to simplify model analyses.

Time evolution of the number of SI partnerships is

$$\dot{[SI]} = \rho[S][I]/N - (\gamma + \sigma)[SI] + \lambda(-[SI] - [ISI] + [SSI]), \quad (2)$$

where N represents the total population size (i.e., $N = [I] + [S]$). The first term on the right hand side captures partnership formation between the susceptible and infected people. The next term captures partnership dissolution and death of the infected people in SI partnerships. The last term captures infection transmissions. HIV transmission in an SI partnership is captured by $\lambda[SI]$. The case where the susceptible person is concurrently connected to another infected person is captured by $\lambda[ISI]$. Although two SI partnerships exist in an ISI triple, we do not need a factor of two because $[ISI]$ indicates twice the number of ISI triples. The term $\lambda[SSI]$, captures transmissions in the case where the susceptible person is connected to both infected and susceptible people. This transmission turns an SS into an SI partnership (i.e., increases the number of SI partnerships). It also turns an SI into an II partnership, which the earlier term, $\lambda[SI]$, already captures. In Equations (1) and (2), we assume that new susceptible people enter the population at risk as singles whereas dying people may have one or more partners. Therefore, the time evolution equation of SI partnerships does not include the inflow from II partnerships that comes from instantaneously replacing infected deaths with susceptible people.

To close the system, we express triples with lower-order terms by using the following approximation:

$$[XYZ] \approx [XY][YZ]/[Y]. \quad (3)$$

This approximation assumes that people in states X and Z have partnership formation and dissolution dynamics that are independent of their being partnered to people in state Y . Error associated with the approximation may be assessed by comparing the model of pair approximation with a stochastic IB model, which we show in Figure 2 as an example.

To express the $[SSI]$ with lower-order terms, we need $[SS]$, of which time evolution is given as

$$\dot{[SS]} = \rho[S][S]/N - \sigma[SS] - 2\lambda[SSI]. \quad (4)$$

Again, $[SS]$ means twice the number of SS partnerships and thus the equation has a factor of two in the term $-2\lambda[SSI]$. The SI_1I_2 model is a straightforward extension of the SI model. Time evolution equations for the SI_1I_2 model appear in the Appendix A2.

2.4. Correlation

The correlation measure is useful for understanding infection transmission in models of partnerships. We define the correlation between people in states X and Y (C_{XY}) as

$$C_{XY} \equiv \frac{[XY]}{[X][Y]n/N}, \quad (5)$$

where n indicates the mean degree (Rand, 1997). If $C_{XY} = 1$, then the expected number of XY partnerships under random mixing (denominator) and the observed number of XY partnerships (numerator) are the same. Since transmission occurs only in SI partnerships, we are only interested in the correlation between the susceptible and infected people; C_{SI} (C_{SI1} and C_{SI2} in the SI_1I_2 model). This correlation can also be thought of as the observed fraction of susceptible people surrounding infected people (by stage, in the SI_1I_2 model) relative to the expected fraction under random mixing;

$$C_{SI} = \frac{[SI]}{[S][I]n/N} = \frac{[SI]/(n[I])}{S/N}. \quad (6)$$

3. Results

Basic reproduction number (R_0) is a fundamental quantity in infection transmission (Anderson and May, 1992). In a homogeneously mixing population it is the expected number of secondary infections produced by a single infected person in an entirely susceptible population. It is also an epidemic threshold; an epidemic is impossible if $R_0 < 1$.

3.1. R_0 for SI model

Derivation of R_0 follows the procedure described elsewhere (Keeling, 1999). Briefly, from the time evolution equation of the number of infected people,

$$\dot{[I]} = \lambda[S I] - \gamma[I] = (n\lambda C_{SI} S/N - \gamma)I. \quad (7)$$

The condition that $d[I]/dt > 0$ gives $n\lambda C_{SI} - \gamma > 0$. This leads to $R_0 = nC_{SI}\lambda/\gamma > 1$ assuming $[S]$ equals N .

Figure 2 shows the dynamics of the number of infected people and the correlation between infected and susceptible people (C_{SI}) during the initial 2000 days. C_{SI} is initially at one, but quickly converges to a “quasi-equilibrium” while the number of infected people grows exponentially. Because of the fast time scale of the dynamics of C_{SI} , we assume that C_{SI} is at quasi-equilibrium instead of being equal to one during the initial stages of the epidemic as in prior studies (Bauch and Rand, 2000; Keeling, 1999).

We now determine the quasi-equilibrium value of C_{SI} (i.e., C_{SI}^*). Under the assumption of the initial period of the epidemic (i.e., $[S] \rightarrow N$ and $[I] \rightarrow 0$) and random mixing of the population (i.e., $C_{SS} \rightarrow 1$) (see Appendix A.1 for details),

$$\dot{C}_{SI} = n\lambda C_{SI}^2 + ((n-1)\lambda - \sigma)C_{SI} + \sigma. \quad (8)$$

Under the assumption of an equilibrium (i.e., $\dot{C}_{SI} = 0$),

$$C_{SI}^* = \frac{-\sigma + \lambda(n-1) + \sqrt{(\sigma + \lambda(1-n))^2 + 4\lambda\rho}}{2n\lambda} \quad (9)$$

given that $C_{SI}^* \geq 0$.

We examine C_{SI}^* in two limiting cases: instantaneous and fixed partnerships. We then explore how transmission rate and the rate of partnership change influence C_{SI}^* between the two extremes of partnership duration. For instantaneous partnerships, we consider the limit where σ goes to infinity. To keep the mean degree constant if we don't account for death (i.e., $\rho/\sigma = \text{some constant}$), we take ρ to infinity at the same rate. Replacing σ and ρ by $\varepsilon\sigma$ and $\varepsilon\rho$ and letting ε go to infinity gives

$$\lim_{\varepsilon \rightarrow \infty} C_{SI} = 1 \Rightarrow \lim_{\varepsilon \rightarrow \infty} R_0 = \beta/\gamma. \quad (10)$$

This shows, if partnerships change rapidly, R_0 in the model of partnerships is the same as in the model assuming mass action (Altmann, 1995).

For fixed partnerships, we consider the limit where σ goes to zero. Again, we keep the mean degree constant by replacing σ and ρ by $\varepsilon\sigma$ and $\varepsilon\rho$. Letting ε go to zero gives

$$\lim_{\varepsilon \rightarrow 0} C_{SI} = 1 - 1/n \Rightarrow \lim_{\varepsilon \rightarrow 0} R_0 = (1 - 1/n)\beta/\gamma. \quad (11)$$

This shows R_0 in the model of fixed partnerships is smaller than in the mass action model by a factor of $1 - 1/n$. This also shows in the limit of large mean degree (i.e., $n \rightarrow N \rightarrow \text{infinity}$), C_{SI}^* goes to one and so R_0 in the model with partnerships is again the same as in the mass action model. One study showed that R_0 is $(1 - 2/n)\beta/\gamma$ in the regular fixed networks

(Keeling, 1999). The difference— $(1-1/n)$ versus $(1-2/n)$ —comes from different assumptions regarding expressing the number of triples with lower order terms. The prior work (Keeling, 1999) used $[XYZ]=\zeta[XY][YZ]/[Y]$ for $\zeta=(n-1)/n$ whereas we use $[XYZ]=[XY][YZ]/[Y]$. The former is appropriate for a regular, fixed network, but our assumption is more suitable for a dynamic random network (Rand, 1997).

Figure 3 illustrates C_{SI}^* monotonically decreases as transmission rate (β) increases if partnerships are neither fixed nor instantaneous. For simplicity, we present partnership duration ($1/\sigma$) as a proxy for the rate of partnership change, but note that partnership formation rate decreases as partnership duration increases such that the mean degree (ρ/σ) remains constant. Figure 3 implies that R_0 will be lower for an infection with higher transmissibility and shorter duration of infectiousness compared to an infection with lower transmissibility and longer duration of infectiousness if partnerships are ongoing and dynamic even when both infections have the same R_0 under instantaneous or fixed partnerships.

To illustrate the effects of the rate of partnership change and transmission rate over the course of HIV infection on transmissions at endemic equilibrium, we simulate the following two scenarios by numerically solving the equations. In one scenario (labeled high β), $1/\gamma$ and β are set at 50 days and 0.036 per day, respectively. In the other (labeled low β), both β and γ is decreased by 45 fold each. Thus, the transmission potential (β/γ) is the same for both scenarios. We then vary σ and ρ such that partnership duration ($1/\sigma$) varies from 0.1 to 1000 days while the mean degree (ρ/σ) remains constant. Figure 4 shows endemic fraction of infected people is the same for both scenarios if $1/\sigma = 0.1$. As the rate of partnership change decreases, however, endemic fraction of infected people is markedly different between the two scenarios. As partnership duration increases, transmissions occur more from an infection with longer duration and lower transmission rate than an infection with shorter duration and higher transmission rate. For HIV infection, this implies dynamic, ongoing partnerships will likely reduce transmissions more during PHI with higher transmissibility than later infections with lower transmissibility at endemic equilibrium.

3.2. R_0 for SI_1I_2 model

The procedure for deriving R_0 for the SI_1I_2 model is the same as in the SI model. From the time-evolution equation of I_1 (see Appendix A.2 for details),

$$R_0 = C_{SI1} \beta_1 / \gamma_1 + C_{SI2} \beta_2 / \gamma_2 ([I_2] / [I_1]). \quad (12)$$

We now derive quasi-equilibrium values for C_{SI1} and C_{SI2} (i.e., C_{SI1}^* and C_{SI2}^*). At quasi-equilibrium, we also assume that $[I_1^*]\gamma_1 = [I_2^*]\gamma_2$, where $[X^*]$ indicate the number of people in state X at quasi-equilibrium. C_{SIi}^* are computed as in the SI model and letting $C_{SIi}^* = 0$ for $i=1,2$ gives two equations for two variables (see Appendix A.3 for details).

For instantaneous partnerships, we consider the limit where σ goes to infinity. As in the SI model, we keep the mean degree constant by taking ρ to infinity at the same rate as σ . Replacing ρ and σ by $\varepsilon\rho$ and $\varepsilon\sigma$ and letting ε go to infinity gives

$$\lim_{\varepsilon \rightarrow \infty} C_{SI} = 1 \text{ for } i=1,2 \quad (13)$$

This gives

$$R_0 = \beta_1 / \gamma_1 + \beta_2 / \gamma_2. \quad (14)$$

As in the *SI* model, if partnerships change rapidly, R_0 in the model with partnerships is the same as in the mass action model.

For fixed partnerships, we consider the limit where σ goes to zero. Replacing σ and ρ by $\varepsilon\sigma$ and $\varepsilon\rho$ and letting ε go to zero gives

$$\begin{aligned} \lim_{x \rightarrow \infty} C_{SI1}^* &= 1 - \frac{1}{n} \frac{\beta_1 \beta_2 / n + \beta_1 \gamma_2}{\beta_1 \beta_2 / n + \beta_1 \gamma_2 + \beta_2 \gamma_1}, \\ \lim_{x \rightarrow \infty} C_{SI2}^* &= \left(\frac{\gamma_2}{\beta_2 / n + \gamma_2} \right) C_{SI1}^*. \end{aligned} \quad (15)$$

We see that C_{SI2}^* is always less than C_{SI1}^* for a nonzero, finite n and β_2 in fixed partnerships. This means that the fraction of susceptible people surrounding the infected people with latent stage (I_2) is always smaller than the one for infected people with PHI (I_1). This is because, under fixed partnerships, some of the initially susceptible partners are infected during the index case's PHI, but are not replaced with susceptible people, which may happen if partnerships are dynamic.

Figure 5a shows how C_{SI1}^* and C_{SI2}^* change by the rate of partnership change between the two extremes of instantaneous and fixed partnerships. As the average duration of the partnership starts to increase, the fraction of susceptible partners becomes lower for the infected people with PHI than those with latent stage (i.e., $C_{SI1}^* < C_{SI2}^*$). This is mainly because transmission rate is higher during PHI than the latent stage. As the average duration of the partnership increases further, however, the fraction of susceptible partners becomes lower for infected people with latent stage than infected people with PHI (i.e., $C_{SI1}^* > C_{SI2}^*$). This reversion occurs mainly because as the rate of partnership change slows, infected partners are not replaced by new partners while infected people progress from PHI to the latent stage, as we have discussed for the case of fixed partnerships. Additional transmissions during the latent stage cause the fraction of susceptible partners to go even lower during I_2 than during I_1 . Figures 5(b) and 5(c) show that the fractional contribution to R_0 of PHI and the fraction of transmissions during PHI at endemic state reflect the change of C_{SI1}^* and C_{SI2}^* —they initially drop, but rise as partnership duration increases.

4. Discussion

We have derived analytical expressions for the correlation between susceptible and infected people and the R_0 for the transmission of HIV on networks of dynamic sexual partnerships. These expressions provide clear explanations for the interaction between partnership dynamics and the transmissions during different stages of HIV infection. Due to its simplicity and consequent explanatory power, this model assuming concurrent partnerships provides a valuable addition to the study done in the context of the IB model (Kim et al., 2010) and to the study that assumes monogamous partnerships (Kretzschmar and Dietz, 1998). The analytic framework used makes clear that there are contrasting forces affecting the role of acute (i.e., PHI) and chronic (i.e., latent) infection as the duration of the partnership rises. These forces affect both the contribution of acute infection to the basic reproduction number (R_0) and to the endemic level of infection. As partnership duration first rises through time periods in the same order of magnitude as the duration of acute infection, the contribution of acute infection decreases because higher transmission probability per act during acute infection leaves progressively more partnerships with dually infected individuals. But then as partnership duration becomes much longer than the duration of acute infection, the contributions from chronic infection decrease much more because acute

infections progress to chronic infections while keeping their partners that may have already been infected during acute infection. This increases the likelihood that the partners during chronic infection are already infected and thus decreases the chance of transmission during chronic infection. Our study implies that interactions between transmissions during the course of HIV infection and partnership dynamics are strong and thus models that assume instantaneous partnerships (Abu-Raddad and Longini Jr, 2008; Koopman et al., 1997; Rapatski et al., 2005a) may not be adequate for assessing the role of different stages of HIV infection.

The fixed network model (Keeling, 2005; Keeling, 1997; Meyers et al., 2005; Newman, 2002) has often been used to relax the assumption of instantaneous contacts of the typical compartmental model. Although these studies of fixed network models have produced valuable results and a recent work presents a framework that can account for the growth of the network (Guerra and Gómez-Gardeñes, 2010), they are usually suited for modeling short-lived epidemics. The transmission of HIV is better represented as endemic infection in a population with ongoing and dynamic partnerships. Our study could serve as an important starting point for future models of HIV transmission on dynamic networks.

One study (Kretzschmar and Dietz, 1998) showed that the relative contribution of the early stage of HIV infection to the spread of HIV would be smaller when sexual partnerships change slowly than when sexual partnerships change rapidly in the context of monogamous sexual partnerships. The present shows that if sexual partnerships are concurrent, the relative contribution of PHI may be even higher when sexual partnerships change very slowly than when partnerships change rapidly.

Volz and others (Volz, 2008; Volz and Meyers, 2007) have introduced a method that uses the predefined distribution of the number of partners across the population while partnerships are dynamic. Our model assumes random partnership formation and dissolution, which leads to Poisson-distributed partnerships. It would be worth examining how our inferences on the fraction of transmissions during PHI will be influenced by the distribution of partnerships, which may significantly influence infection levels (Eames and Keeling, 2002; Volz and Meyers, 2007).

We have assumed a homosexual population with equal contributions of insertive and receptive sex acts on both sides of the relation. This assumption keeps the model simple such that we can focus on the interaction between the partnership dynamics and varying transmissibility during progression stages of HIV infection. However, per-act relative risk for acquisition of HIV differs between insertive and receptive acts both for vaginal and anal sex (Varghese et al., 2002) and thus it would be of interest to see how the directional assumption of sex would change our inference. We are currently pursuing this question and our preliminary work shows that increasing difference in the insertive and receptive transmission rates decreases the contribution of transmissions during PHI, which is not observed unless partnerships are long-term. This implies that we need to account for both long-term, concurrent sexual partnerships, and directionality of sex acts at the same time to address the question of relative role of different stages of HIV infection. Likewise we have assumed homogenous mixing and homogeneous partnership formation dynamics. Another real world complexity that will influence the fraction of transmissions is that people have a combination of short term encounters and ongoing partnerships, which one prior work (Xiridou et al., 2004) addressed in the context of monogamous partnerships. While all these aspects of reality will further modify the relative contribution of different stages of HIV infection to the overall transmission, by isolating the effects of partnership duration on R_0 and endemic transmissions, we provide a basis for intuition about what will act in the real world. These intuitions will be important both in devising new methods to estimate

transmission rates by stage of HIV infection and for evaluating the potential effects of intervention programs.

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Appendix

A.1 Time evolution equations for the correlation between S and I (C_{SI})

$$\begin{aligned}\dot{C}_{SI} &= \frac{N}{n} \frac{d}{dt} \left(\frac{[SI]}{[S][I]} \right) = \frac{N}{n} \left(\frac{[S][I] \frac{d}{dt} [SI] - [SI] \frac{d}{dt} ([S][I])}{[S]^2 [I]^2} \right) \\ &= \frac{N}{n} \left(\frac{[S]\dot{I}}{[S][I]} - \frac{[\dot{S}][S]}{[S]^2 [I]} - \frac{[I]\dot{S}}{[S][I]^2} \right) = C_{SI} \left(\frac{[\dot{S}I]}{[SI]} - \frac{[\dot{S}]}{[S]} - \frac{[\dot{I}]}{[I]} \right)\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{1)} \end{matrix}$$

$$\begin{aligned}\frac{\dot{[SI]}}{[SI]} &= \frac{\rho[S][I]}{N[SI]} + \lambda \left(\frac{[SS]}{[S]} - \frac{[SI]}{[S]} - 1 \right) - (\gamma + \sigma) \\ &\rightarrow \sigma/C_{SI} + \lambda(n-1) - (\gamma + \sigma) \\ \text{as } [S]/N \rightarrow 1, C_{SS} \rightarrow 1, [I]/N \rightarrow 0, \text{ and } C_{SI} < 1.\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{2)} \end{matrix}$$

$$\begin{aligned}\frac{\dot{[S]}}{[S]} &= \lambda[SI]/[S] - \gamma[I]/[S] - (\gamma + \sigma) \\ &\rightarrow \sigma/C_{SI} + \lambda(n-1) - (\gamma + \sigma) \\ \text{as } [S]/N \rightarrow 1, C_{SS} \rightarrow 1, [I]/N \rightarrow 0, \text{ and } C_{SI} < 1.\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{3)} \end{matrix}$$

$$\begin{aligned}\frac{\dot{[I]}}{[I]} &= \lambda[SI]/[I] - \gamma = \lambda n C_{SI} S/N - \gamma \\ &\rightarrow \lambda n C_{SI} - \gamma \text{ as } S/N \rightarrow 1.\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{4)} \end{matrix}$$

Plugging Equations (A.2)-(A.4) to Equation (A.1) gives

$$\sigma + ((n-1)\lambda - \sigma)C_{SI} - \lambda n C_{SI}^2.$$

A.2 Equations for SI_1I_2 model

In the SI_1I_2 model, the state of people is represented as X_j , where $X = S, I$ and $j = 1, 2$ indicate infection category and the stage of infection, respectively. The number of people in state X_j is denoted by $[X_j]$. Similarly, λ_j denotes the transmission rate per unit of time of the infected person in stage j in a partnership. The following equations describes the SI_1I_2 model:

$$\begin{aligned}\dot{[S]} &= -\lambda_1[SI_1] - \lambda_2[SI_2] + \gamma_2[I_2] \\ \dot{[I_1]} &= \lambda_1[SI_1] + \lambda_2[SI_2] - \gamma_1[I_1] \\ \dot{[I_2]} &= \gamma_1[I_1] - \gamma_2[I_2] \\ \dot{[SS]} &= \rho[S][S]/N - 2(\lambda_1[SSI_1] + \lambda_2[SSI_2]) - \sigma[SS] \\ \dot{[SI_1]} &= \rho[S][I_1]/N + \lambda_1([SSI_1] - [I_1SI_1] - [SI_1I_1]) + \lambda_2([SSI_2] - [I_2SI_1]) - (\gamma_1 + \sigma)[SI_1] \\ \dot{[SI_2]} &= \rho[S][I_2]/N + \gamma_1[SI_1] - \lambda_1([I_1SI_2] - \lambda_2([I_2SI_2] + [SI_2I_2]) - (\gamma_2 + \sigma)[SI_2])\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{5)} \end{matrix}$$

A.3 Time evolution equations for C_{SI1} and C_{SI2}

$$\begin{aligned}\dot{C}_{SI_1} &= \frac{N}{n} \frac{d}{dt} \left(\frac{[SI_1]}{[S][I_1]} \right) = C_{SI_1} \left(\frac{\dot{[SI_1]}}{[SI_1]} - \frac{\dot{[I_1]}}{[I_1]} - \frac{\dot{[S]}}{[S]} \right) \rightarrow a_1 C_{SI_1}^2 + a_2 C_{SI_1} + a_3, \text{ where} \\ a_1 &= -n\lambda_1, a_2 = -(n-1)\lambda_1 - \sigma - C_{SI_2}^2 n\lambda_2\gamma_1/\gamma_2, a_3 = \sigma + C_{SI_2} n\lambda_2\gamma_1/\gamma_2.\end{aligned}\quad \begin{matrix} \text{(A.} \\ \text{6)} \end{matrix}$$

$$\dot{C}_{SI_2} = \frac{N}{n} \frac{d}{dt} \left(\frac{[SI_2]}{[S][I_2]} \right) = C_{SI_1} \left(\frac{\dot{[SI_2]}}{[SI_2]} - \frac{\dot{[I_2]}}{[I_2]} - \frac{\dot{[S]}}{[S]} \right) \rightarrow \sigma + \gamma_2 C_{SI_1} - C_{SI_2}(\lambda_2 + \gamma_2 + \sigma).\quad \begin{matrix} \text{(A.} \\ \text{7)} \end{matrix}$$

Letting both Equations (A.6) and (A.7) equal zero gives two equations for two variables.

Highlights

- We model HIV transmissions in a population where sexual partnerships form and dissolve over time.
- We use a combination of analytical and numerical methods.
- The role of primary HIV infection is lowest when sexual partnerships last around 100 days.
- Standard models of HIV transmission may not be adequate to study the role of primary HIV infection.

Figure 1.
Comparison of the typical compartmental model (a) and our partnership model (b).

Fig. 2a

Fig. 2b

Figure 2.

Results from pair approximation (solid line) and the average and one standard deviation of 100 stochastic simulation runs (triangle with error bar). (a) shows the fraction of population infected, (b) shows the correlation between susceptible and infected people (C_{SI}) over time. $\beta=0.04$, $1/\gamma=100$, $\rho=0.02$, $\sigma=0.01$, $N=10000$.

Figure 3. Correlation at quasi-equilibrium (C_{SI}^*) across transmission rate at instantaneous, fixed, and ongoing/dynamic partnerships. $\rho/\sigma = 2$.

Figure 4.

Fraction of population infected over time. $\rho/\sigma=2$. For “high β ”, $\beta=0.036$, $1/\gamma=50$ and for “low β ”, $\beta=0.0008$, $1/\gamma=2250$.

Figure 5.

(a) Quasi-equilibrium values of the correlation with susceptible people during PHI, (C_{SI1}^*) or latent stage (C_{SI2}^*). (b) fractional contribution to R_0 of PHI across partnership duration. (c) fraction of transmissions during PHI at endemic state across partnership duration. $\beta_1=0.036$, $\beta_2=0.00084$, $1/\gamma_1=49$, $1/\gamma_2=3650$, $\rho/\sigma=2$.

Table 1

Model parameters.

Symbol	Description
β_i^*	Transmission rate per infected person per day during stage i for $i = 1, 2$ (1=primary HIV infection (PHI), 2=latent stage)
γ_i^*	Death rate per day from infection. In SI_1I_2 model, γ_1 represents the progression rate from PHI to the latent stage
σ	Partnership dissolution rate per day
ρ	Partnership formation rate per day

* In the SI model, β and γ are used without the subscript.