Published in final edited form as:

Stat Commun Infect Dis. ; 4(1): . doi:10.1515/1948-4690.1041.

Episodic HIV Risk Behavior Can Greatly Amplify HIV Prevalence and the Fraction of Transmissions from Acute HIV Infection

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Abstract

A deterministic compartmental model was explored that relaxed the unrealistic assumption in most HIV transmission models that behaviors of individuals are constant over time. A simple model was formulated to better explain the effects observed. Individuals had a high and a low contact rate and went back and forth between them. This episodic risk behavior interacted with the short period of high transmissibility during acute HIV infection to cause dramatic increases in prevalence as the differences between high and low contact rates increased and as the duration of high risk better matched the duration of acute HIV infection. These same changes caused a considerable increase in the fraction of all transmissions that occurred during acute infection. These strong changes occurred despite a constant total number of contacts and a constant total transmission potential from acute infection. Two phenomena played a strong role in generating these effects. First, people were infected more often during their high contact rate phase and they remained with high contact rates during the highly contagious acute infection stage. Second, when individuals with previously low contact rates moved into an episodic high-risk period, they were more likely to be susceptible and thus provided more high contact rate susceptible individuals who could get infected. These phenomena make test and treat control strategies less effective and could cause some behavioral interventions to increase transmission. Signature effects on genetic patterns between HIV strains could make it possible to determine whether these episodic risk effects are acting in a population.

Keywords

HIV; mathematical modeling; risk behavior; MSM

Introduction

In the decades from its emergence, great strides have been made in controlling HIV. Antiretroviral treatment has greatly improved and has saved millions of lives. Neonatal transmission and transmission via needles among injecting drug users have been markedly reduced (Hall et al. 2008). On the other hand, HIV incidence among men who have sex with men (MSM) continues to rise with increasing rates of treatment having little effect on controlling transmission in this group (Hall et al. 2008; Prejean et al. 2011). There are diverse speculations as to why this might be the case including rapid evolution of the virus itself, safe-sex exhaustion, or emergence of versatility in terms of insertive or receptive sex

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roles among MSM (Blower et al. 1992; Blower et al. 1995; Goodreau and Golden 2007; Vittinghoff et al. 1999). Nonetheless, convincing evidence and arguments as to how different factors contribute to our failure to control HIV transmission among MSM are lacking. The formulations we present here constitute a theory expressing one mechanism through which biological and social factors interact to maintain high infection levels in MSM populations.

Our ability to understand HIV transmission dynamics is hindered by the fact that we cannot observe HIV transmission patterns directly. In part, this is due to most infections not being detected until long after transmission. That makes it impossible to trace all sexual partners and count directly how many transmissions are occurring during the highly infectious but brief acute HIV infection stage (AHI). It also makes it rare that AHI outbreaks are detected and investigated at the time they are occurring. Currently the existence of such outbreaks is detected through genetic clustering (c.f. Brenner et al. 2007; 2011) and phylogenetic relationships (Hughes et al. 2009; Lewis et al. 2008). As many as 64% of infections detected in the first 6–24 months after infection can be identified as part of genetic clusters (Brenner and Moodie 2012; Brenner et al. 2007). Quite possibly most clustering involves transmission during AHI but inferring AHI transmission fractions from genetic data require better theory. This paper takes a step in that direction by developing a model that elucidates an important mechanism by which acute infections are linked into outbreaks.

The ability to use genetic data to test transmission theory has recently been advanced by new methods for incorporating transmission models into coalescent models (Rasmussen et al. 2011; Volz et al. 2009; Volz 2012). Being able to fit different models to genetic data creates the potential to assess the robustness of inferences about the fraction of transmissions from AHI by realistically relaxing diverse aspects of transmission models (Koopman 2005). These include partnership formation and duration patterns (Kim et al. 2010), specific behaviors such as anal or oral sex with or without protection, insertive and receptive behavior patterns (Alam et al. 2010), different sexual mixing sites (Koopman et al. 2005), and heterogeneous sexual behavior in the population (Anderson et al. 1992; Hethcote and Van Ark 1987). In this paper, we focus on elaboration of a particular model aspect that has especially strong effects: episodic risk behavior. Another paper in this symposium illustrated short-term temporal heterogeneity in sexual contact rates in a prospective risk behavior study designed to estimate transmission risks for different types of sexual contacts between MSM (Romero-Severson et al. from this edition).

Episodic risk is defined by brief periods of higher risk behavior possibly precipitated by random events such as a change in relationship status, drug use, or as an endogenous aspect of sexual behavior in general. We modeled episodic risk with flows back and forth between high and low contact rate states. The first paper to do this was Koopman et al. (1997). However, the predominant feeling has been that previous demonstration of high AHI transmission (Jacquez et al. 1994; Koopman et al. 1997) was only applicable during the early stages of the epidemic (Rapatski et al. 2005). That is, once infection levels reach an endemic equilibrium, the fraction of transmissions is a simple function of the times one spends in different stages and the transmission probabilities during those stages (Abu-Raddad and Longini 2008; Hollingsworth et al. 2008).

In this paper, we show how episodic risk can amplify AHI transmissions even after endemic equilibrium has been reached. Specifically, we show how behavioral changes in individuals over time can amplify transmission at the population level by amplifying transmission from acute HIV infection. The mechanisms include both increasing the contact rates of recently infected individuals and increasing the number of high risk susceptible individuals with whom high risk infected individuals can make contact.

Methods

Model Formulation

We developed a deterministic compartmental model of HIV transmission in men who have sex with men that integrates episodic risk behavior, non-random mixing, and multiple stages of infection. The model has only two risk phases with different contact rates (high and low), two infection stages (acute and chronic), and two sexual mixing sites. There is a common mixing site where individuals in the high and low risk phases mix proportionally and a high-risk mixing site where only the high-risk individuals make contacts. Contacts are modeled as instantaneous and symmetrical partnerships with an undefined number of sex acts having no specified direction or pattern (such as insertive or receptive, anal or oral).

The deterministic compartmental model is specified as a system of six differential equations for a MSM population, one for each compartment in the model. A schematic of the model is shown in Figure 1. The characters S , A and C for each compartment refer to the susceptible, acute HIV and chronic HIV stages respectively. The subscripts H and L refer to the high and low contact rate for each subpopulation respectively. The grey area in Figure 1 depicts the high-risk mixing site where individuals with high contact rate make a proportion of their contacts ( ) exclusively with each other. The dotted area designated as the common mixing site represents the site where individuals with high contact rate make the remaining fraction of their contacts ($1 -$) with individuals with low contact rate proportionally. The parameters that govern the rate of each flow are shown in Figure 1 near the arrow depicting that flow. The values of β_H and β_L are given in Table 1.

Arrows between subpopulations with identical infection status represent the flow of individuals between these subpopulations due to the movement between high and low-risk phases. β_H represents the rate of turnover from high to low contact rate while β_L refers to the flow in the opposite direction. We assume a constant birth rate indicated by the arrows in Figure 1 pointing into S_L and S_H . Individuals leave the system either by a process of ‘natural removal’ that accounts for cessation for sexual activity for any reason (horizontal arrows pointing out of each compartment in Figure 1) or by death of chronically infected individuals due to AIDS (vertical arrows pointing out of the C_L and C_H compartments). Table 1 presents a complete list of the model’s parameters.

We model episodic risk as movement between phases of high and low sexual activity. The magnitude of difference between the high and low risk phases is parameterized by the ratio of contact rates in the high and low risk phases. Average contact rates in the whole system are held constant such that an increase in this ratio or the proportion of individuals in the high-risk phase implies a decrease in the low risk contact rate to maintain a constant average contact rate. The default value for the average contact rate ( ) was selected so the system is just above the epidemic threshold under the homogenous risk setting without episodic dynamics.

The natural history of HIV infection is modeled with acute and chronic stages of infection. Contagiousness is abstracted as a higher transmissibility per act during a relatively short acute stage and a lower transmissibility during a much longer chronic stage with first order flows between stages and out of the last stage. As a simplifying assumption, we ignore the rise of contagiousness that has been demonstrated in late infection. This assumption is reasonable in a population with widespread access to antiretroviral treatments that have greatly reduced the prevalence of AIDS and the concomitant rise in viral titer associated with end-stage HIV infection. Simulations also suggested that assuming three rather than two infections stages does not fundamentally alter the phenomenon that we illustrate. In our model, we assume the average duration of the acute stage to be 2 months and that of the

chronic stage to be 10 years (Pilcher et al. 2004). On average, uninfected individuals will remain sexually active for 40 years.

The contagiousness parameters were adapted from an analysis of the Rakai data (Wawer et al. 2005) by Pinkerton (2008). In our model, we set the baseline transmission probability (β) across the entire course of infection to be 0.003, which is consistent with overall average transmission probabilities across all homosexual sex acts (c.f. Vittinghoff et al. 1999). The possible underestimate of the baseline transmission probability per partnership is compensated for by the fact that we adjusted the average contact rate to be near threshold for the given baseline transmission probability.

Formulation of Transmission Probabilities and Fraction of Transmission Potential from Acute Stage

The increased contagiousness in the acute stage is governed in the model by the fraction of *transmission potential* from the acute stage (X), which is the expected fraction of transmissions from acute HIV occurring in a homogeneous population at equilibrium. The following presents how we derived the formulation of transmission probability per contact during acute HIV infection, β_1 , and during chronic HIV infection, β_2 , based on baseline transmission probability, β , and X .

The average time an infected individual spends in acute infection, denoted as T_1 , is

calculated as $T_1 = \frac{1}{\gamma_1 + \mu}$ (1). Given that the probability for an acutely infected individual to

progress to the chronic stage rather than being removed due to other reasons is $\frac{\gamma_1}{\gamma_1 + \mu}$, the average time an infected individual spends in the chronic stage, denoted as T_2 , can be

expressed as $T_2 = (\frac{\gamma_1}{\gamma_1 + \mu})(\frac{1}{\gamma_2 + \mu})$ (2).

If the rate of sexual contact in the homogeneous population is denoted as χ , the average number of secondary cases generated by an infected individual during acute infection is $\beta_1 T_1$, and the average number of secondary cases generated by an infector during chronic infection is $\beta_2 T_2$, while the average number of secondary cases generated by an infector during the entire period of infection is $\beta \chi (T_1 + T_2)$. As a result, the fraction of transmission

potential from acute infection is $X = \frac{\beta_1 \chi T_1}{\beta \chi (T_1 + T_2)} = \frac{\beta_1 T_1}{\beta (T_1 + T_2)}$ (3), and the fraction of

transmission potential from chronic infection is $1 - X = \frac{\beta_2 \chi T_2}{\beta \chi (T_1 + T_2)} = \frac{\beta_2 T_2}{\beta (T_1 + T_2)}$ (4). After

substituting equations (1) and (2) into (3), $\beta_1 = X(1 + \frac{\gamma_1}{\gamma_2 + \mu})\beta$. Using the same logic, we find

that $\beta_2 = (1 - X)(1 + \frac{\gamma_2 + \mu}{\gamma_1})\beta$.

Parameterizing the system in this way, we can easily determine the effect of episodic risk on acute stage transmission rates compared to a homogeneous null model. Transmissibility per contact is assumed constant during each infection stage. This is determined by the above-mentioned model parameters (see Table 1).

Model elaboration for dynamic system analysis

To better clarify what flows from what stages of infection and what contact rates were sustaining transmission, we divided each of the four compartments of the infected population (A_H , A_L , C_H , C_L) from the episodic risk model (Table 2) into six compartments.

By doing this, we track the information of location of transmission, contact rate phase and stage of HIV infection of the source infectors. Thus, in this elaborated model, infected individuals now have a 3-letter superscript that refer to the state of the individual who infected them and where they went on to transmit. The first character in the superscripts refers to the site where they became infected, with R being the high-risk mixing site and G being the common mixing site. The middle letter refer to the contact rate phase of the source infector, with H being the high contact rate phase and L being the low contact rate phase. The last character represents the stage of HIV infection of the source infector, with A being the acute stage and C being the chronic stage. The set of differential equations for the dynamic system analysis of the elaborated model is provided in Table 3.

Results

Exploring joint effects of high-risk turnover rate and between-risk-group contact rate ratio at the population-level

We numerically solved equations out to equilibrium. The rate of turnover in the high-risk group had strong effects on both the endemic prevalence and fraction of transmission during acute stage.

As the turnover rate of the high-risk group slows from 10 times per month (once every 0.008 years) to once per 1000 months (once every 83.3 years), both the endemic prevalence and the acute transmission rate show an inverted U shape, peaking between turnover rates of 1 per month and 1 per year (Figure 2). At the extremes of fast or slow turnover, the fraction of acute transmissions is the same as in a homogeneous population. As the ratios of contact rates between high and low risk groups increase, the peak effects of turnover rates increase as well and occur at faster turnover rates.

Increasing the fraction of transmission potential during acute stage while keeping the total transmission potential constant increases both the endemic fraction of transmissions during acute stage and the endemic prevalence (compare panels A and B). Furthermore, the endemic prevalence peaks at a faster turnover rate because given an increased transmission rate during the acute stage; individuals need to spend shorter time at high-risk phase to lift the endemic prevalence to peak. These observed effects hold at all values of the contact rate ratio as shown in Figure 2.

As the fraction of time that each individual spends at high risk (ρ_H) increases, both the endemic fraction of transmission during the acute stage and the endemic prevalence decrease at each value of the contact rate ratio (compare panels C and D in Figure 2). Given our assumption of constant average contact rate, for any given contact rate ratio greater than 1, increasing ρ_H causes a decrease in contact rates for both risk levels and hence decreases the overall force of infection. When the turnover rate is low enough and the contact rate ratio is high enough, the endemic prevalence starts to decrease as the contact rate ratio increases. Given a slow turnover, high-risk susceptible individuals are infected much faster as compared to the low risk susceptible individuals due to their elevated contact rates causing infection saturation in the high-risk phase. Higher turnover rates supplement the pool of high-risk susceptible individuals with new high-risk susceptible individuals. As ρ_H increases, each individual spends more time in the high-risk phase. This increases the proportion of contacts between infected individuals causing saturation of infection in the high-risk phase.

Effect of separate mixing on the endemic prevalence and fraction of transmission by acute stage

Overall, the fraction of contacts made by high-risk infectors at the high-risk site ( ) showed little impact either on the endemic prevalence or on fraction of transmission during acute stage or on the dynamics of these two outcomes (data not shown). This is unlike the observations in Koopman et al. (2005). Only at lower overall contact rates and very slow turnover between contact rate groups do we see the effects of α as noted in Koopman et al. (2005). At any other contact rates, a higher fraction of high contact rate group's contacts made at a high risk mixing site increases the rate of exponential growth in the early epidemic.

Exploration of dynamics underlying high contact rate group turnover effects

We now look into the dynamics of prevalence and the fraction of transmissions from acute HIV (AHI) over a period of 150 years. In Figure 3 (A and B), we explore these dynamics for the duration of time spent in the high-risk state for ranges from 0.01 to 80 years. In Figure 3 (C and D), we explore the dynamics by varying the ratio of contact rates from 1 to 41.

Figure 3 (A and B) shows that episodic risk increases the contribution of acute HIV early in the epidemic and later at the endemic equilibrium. Faster risk turnover results in the faster replenishment of the susceptible population in the high-risk phase. At the same time, it increases the risk of a low-risk susceptible contacting an infected individual who is still in the highly contagious acute stage. For slower turnover rates, the fraction of the transmissions from AHI decreases. This is because of the decrease in the inflow of susceptibles in the high-risk phase. It also increases the duration of the time spent in the high-risk phase by high-risk individuals. Thus, high-risk individuals are likely to progress to the chronic stage by the time they switch to the low-risk phase.

Overall, the prevalence and the fraction of transmissions during the acute stage increase with the ratio of contact rates (see Figure 3; panels C and D). Increasing contact rate ratios result in increasing high-risk contact rates that in turn increase transmission from high-risk infectors. For high contact rate ratios, the fraction of transmission from acute stage reaches a higher peak level, indicating a greater effect when the high-risk contact rate increases.

Higher peak levels of acute stage transmissions reflect the potential of the acute HIV population to build the epidemic together with the replenishment of the susceptible population. This explains why the fraction of transmissions during acute stage with a higher peak level also has a larger rebound as shown in Figure 3 (B and D).

Effect of risk turnover and contact rate ratios on the contact rate of acute HIV stage population

In Figure 4, we examine the effects of high-risk group turnover rate on the endemic prevalence, the average contact rates of the acute stage population and that of the susceptibles at equilibrium. We explore for a range of the duration of time spent in the high-risk phase from 0.008 years to 83 years and the ratio of contact rates from 1 to 41. As Figure 4B shows, the turnover rate of the high-risk population has a clear effect on the average contact rates of acute stage infected individuals at equilibrium. Higher turnover rate brings more susceptibles into the high contact rate phase. At higher contact rate ratios, the new susceptible at high contact rate are more likely to be infected and thus faster turnover in the high contact rate phase has even greater effects.

The endemic prevalence reaches its peak at a faster turnover rate than the average contact rate of acutely infected individuals (Figure 4A). This is due to the combined effect of the

overall force of infection and average contact rate among the susceptibles (Figure 4B). Given the high contagiousness of the acute stage infectors, the interaction of high transmissibility and increased contact rates during acute stage drives the overall force of infection.

Tracking sources of infections

By breaking the compartments of infections in our original model into different subgroups, we were able to track the source of infection and mixing site where the transmissions occurred. Figure 5A and 5C illustrate the fraction of transmissions during acute stage and chronic stage HIV infection. Figures 5B and 5D focus on the contributions of high-risk infectors and low risk infectors. From B and D, although the high contact rate group only comprises of 5% of the total population, they account for 50% or more of all transmissions at contact rate ratios as low as 7. Although there is an effect of the turnover rate on the fraction of infections by individuals in the high-risk phase, the effect is small. The role of the high versus low-risk infectors is controlled primarily by the contact rate ratio.

From panels A and C in Figure 5, we see a different role for the contact rate ratio and the turnover rate in determining the fraction of transmission from acute stage infectors. The contact rate ratio has little effect on the fraction of infections from acute infectors at extreme values of the turnover rate. However, at intermediate values of the turnover rate, the contact rates ratio can nearly double the contribution of acute stage infectors. This interaction is caused by the increased prevalence of high-risk, acutely infected individuals. The flow of new susceptibles into the high-risk phase generates an increased incidence and therefore an increased prevalence of acute stage, high-risk infectors. Because the dynamics are assumed to be mass action, the increased prevalence of acute high-risk infectors means increased contact between susceptibles and acutely infected individuals. The effect diminishes at extremely short average durations of the high risk phase because the system becomes essentially homogeneous. In that case, the system is controlled by the average contact rate rather than the contact rate ratio. At extremely long average durations, on the other hand, any newly infected individual is highly unlikely to change risk groups prior to leaving the system. He will, therefore, with high probability, have the same contact rate for the duration of his infection, and the fraction of his expected cumulative contribution to the force of infection over time that occurs during his acute infection will be essentially the same as in a homogeneous system. Because this is true for all infected individuals, it will also be true for the system as a whole. In this limit, the contact rate ratio still matters for determining the total incidence, but does not affect the fraction of that incidence that comes from transmissions by acutely or chronically infected individuals.

In Figure 6, we further divide the source of infection based on their contact rate phase, stage of infection and location. When the turnover rate is low, neither acute nor chronic individuals are generating many new infections at the high-risk site (panels A and D). This is due to the fact that without turnover to replenish susceptibles in the high-risk phase, the high-risk individuals rapidly become infected. Therefore, at the high-risk site almost all contacts are among already infected individuals. However, at the low-risk site, susceptibles with low contact rates are much more likely to contact either an acute (panel B) or a chronic (panel E) high risk infected individual resulting in elevated incidence rates from those classes in the absence of turnover. Also, by assumption, most individuals entering the model are susceptibles with low contact rates, which provides a greater supply of susceptibles to the low risk mixing site.

Discussion

Explaining the major effects we observed

We have shown that episodic periods of high-risk behavior interspersed with longer periods of lower risk have large effects on the endemic level of HIV infection and the fraction of transmissions from acute HIV infection. We see that prevalence can vary from near zero to very high levels and the fraction of transmissions from acute infection can nearly double as the turnover rate from low-to-high contact rate phases increase and as the time spent with high rates varies. This is despite the fact that the total contacts in the population and the transmission potential for each individual are kept constant during each stage of infection.

Two important elements explain the strong effects mentioned above. The first has to do with the average total contagiousness of individuals during acute and chronic infection. That contagiousness is determined jointly by the number of contacts made and transmission probabilities per contact. Episodic risk increases the association between high contact rates and the high transmissibility of acute infection because an individual is more likely to get infected during a high contact rate period and is more likely to still be in that high contact rate period during their acute HIV infection (AHI). Then, as they progress to the less contagious chronic infection stage, they also pass into a lower contact rate phase. The more strongly that the high transmission stage of infection is correlated with the high contact rate state, the higher will be the average contagiousness across the course of infection. This is reflected in the part of Figure 4 that presents the average contact rates during the acute infection stage.

The second part of the explanation for these big effects has to do with the average contact rates of susceptible individuals. When individuals spend a long time in the high contact rate state, they become infected and a sexual contact by them with other infected individuals no longer presents an opportunity to transmit infection. If individuals stay in a low contact rate state, they are more likely to avoid infection. Then when they transit to a high contact rate state, they provide a new source of high contact rate susceptible individuals that the individuals with high contact rates in the acute infection stage can infect. This is seen in the contact rates of susceptible individuals in Figure 4. The average contact rate of susceptible individuals is seen to increase considerably as the turnover increases. When the turnover rate is slow, high contact rate individuals are infected and are not replaced by new susceptible individuals. This lowers the average contact rate of susceptible individuals.

Our previous work on when to focus control on high risk groups (Koopman et al. 2005) led us to believe that a third element would also act to generate episodic risk effects on prevalence and AHI transmissions. That previous work modeled SIR infections. For SIR infections, we saw that when high-risk individuals mixed separately from low risk individuals, it allowed them to build up higher levels of infection so that they then disseminated more infection when they made contact with lower risk individuals. However, that was not the case for the HIV infections modeled here. Whether high contact individuals mixed at a high-risk or a common mixing site, the prevalence and the fraction of transmissions from acute infection were barely changed at all. The difference was not that in the previous work we allowed transmission probabilities rather than contact rates to define high risk. In fact, we saw the same effects of separate high risk mixing in that previous work when we defined high risks by contact. In further support of the cause of high risk (contact rates vs. transmission probabilities), we have observed that mixing makes little difference when high risk is caused by higher transmission probabilities (data not presented). The reasons for this are complex: under some conditions, separate mixing at a high-risk site can lead to a greater dissemination of infection. However, discussion of this effect is beyond the scope of this paper.

The real-world importance of the described theoretical effects

If the episodic risk effects that we have described occur in the real world to the extent that we suspect they do, then previous model analyses using fixed behaviors for subgroups (Cohen et al. 2011; Rapatski et al. 2005) have underestimated the fraction of transmissions from acute HIV. Nevertheless, a key question is how we can assess the extent to which these episodic risk effects are occurring in any particular population. Fluctuation of contact rates was observed in the CDC cohort studied to assess HIV transmission risks from different acts (Romero-Severson et al. this edition). That study included diverse geographic areas. The existence of episodic risk behavior is less formally supported by experiences of HIV counselors where most people with high-risk behaviors report that they have had longer periods of low risk behaviors.

Our results may be compared to recent modeling studies that have focused on the role of acute infection (Eaton et al. 2011; Powers et al. 2011). Eaton et al. (2011) analyze an important phenomenon that, like episodic risk, augments the importance of acute infection. In some sense, entering a high contact rate phase may be akin to entering a concurrent partnership phase, although in our model, we assume instantaneous contacts. On the other hand, the study by Powers et al. (2011) assume fixed risk, which corresponds to our results when the duration of stay in high risk is very long such that there is virtually no risk turnover. The Bayesian melding approach to model fitting used by Powers et al. (2011) means that the effects of the phenomenon of episodic risk could be absorbed partially into the transmission by stage parameter estimates. It seems that their results would have estimated a larger fraction of transmissions from acute infection if they had included episodic risk in their model. However, this is hard to assess.

Broader evidence should be sought regarding whether there are real world effects of episodic risk corresponding to the theoretical effects we have demonstrated. One approach could be to do more behavioral studies that ask the needed questions. So far, few studies have documented episodic risk behavior. Another approach is to find signatures of episodic risk in both HIV surveillance data and in HIV genetic sequences (Brenner et al. 2011). When the model in this paper is simulated as a stochastic discrete individual-based model, we observe that infection trees of acute HIV transmissions are interspersed among more isolated chronic infection transmissions and have size distributions that are roughly comparable to those observed in Montreal (Brenner et al. 2007). Our initial results show that episodic risk dynamics influence both the size and duration of acute HIV outbreaks providing a possible link between genetic cluster size distributions and episodic risk dynamics. More sophisticated methods that are currently being developed can be used to calculate the likelihood of the genetic data given a transmission model allowing for direct evaluation of the evidence for episodic risk in the genetic data (Rasmussen et al. 2011; Volz et al. 2009; Volz 2012). Parameter ranges should be further constricted by fitting models to observed patterns of HIV infection over time using surveillance data.

More thorough model explorations may be needed to assess the real world importance of episodic risk effects. More surprises regarding dynamic effects may arise as we analyze the interactions of episodic risk effects with contact pattern effects, partnership duration, insertive-receptive behavior effects, and oral, anal, protected, and unprotected risk pattern effects. To strengthen our inferences that episodic risk behavior greatly increases HIV prevalence and acute HIV transmissions, a thorough exploration of the effects of relaxing the simplifying assumptions in the model presented is called for. For example, realistic distributions for the duration of acute stage and the distribution of virus levels across that time should be explored. In reality, there is a high narrow peak of virus levels a few weeks into infection and then a long period of falling levels before the set point of chronic infection is reached (Pilcher et al. 2007). We hypothesize that the effects we have observed will be

just as strong or stronger under more realistically detailed acute infection timing and contagiousness. Likewise, our initial explorations indicate that a more realistic description of episodic risk behavior in a population will not significantly diminish the effects we have illustrated in this paper.

The infection control implications of our findings suggest that some HIV transmission control activities may be misdirected. For example, the test and treat strategy by default detects mostly cases after acute infection. Our results indicate that greater focusing on acute infection transmission clusters (Brenner et al. 2011) will be needed to detect more acute infections. Second, behavior modification messages may be similarly misdirected. In our model, we did not incorporate change in sexual behavior over an individual's lifetime because of, e.g. HIV awareness programs. This is because our aim in this paper is to understand the dynamics of episodic risk behavior under theoretical settings. Nevertheless, if suggestions to decrease risk only work for a period but are overwhelmed by situational pressures, then our model indicates that such suggestions could not only fail to decrease transmission, but might in fact increase transmission.

The broader context of this work and future directions

The analyses presented in this paper are a needed step toward improving our understanding of HIV transmission dynamics. All perception comes from a combination of data and theory. We do not see patterns when our minds are not prepared to see them. To an extent our ignorance of HIV transmission patterns in MSM is attributable to a dearth of well-structured theory about how different hypothetical transmission system conformations lead to specific transmission patterns and what mechanisms underlie these effects. A body of HIV transmission system theory is growing and thousands of modeling studies of HIV transmission have been published (Akpa and Oyejola 2010). Still, theory and data are barely beginning to come together in a way that allows us to see clearly how and why acute HIV transmissions cluster, and how this could explain the failure to control the spread of HIV infection in the MSM population.

By relaxing some of the unrealistic assumptions in our model and incorporating realistic details such as oral and anal acts, insertive and receptive behavior, partnership duration, and mixing patterns, we will begin to identify characteristics of both surveillance data and genetic sequence data that indicate what is affecting transmission dynamics. This, we believe, will clarify the role acute infection transmissions plays in the MSM HIV transmission system.

Acknowledgments

All authors were supported by a subcontract to the University of Michigan from NIH grant R01AI078752; EMV was also supported by NIAID 5-K01-AI-091440-03.

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Figure 1.
Conceptual episodic risk model with contact structure and population composition

FIGURE 2.

Endemic prevalence and fraction of transmission during acute stage of Infection as function of log scale of duration of stay at high risk level as the contact Rate ratio (r) is raised from 1 to 41 by increments of 2 and showed in different colors. The left y axis is for the endemic prevalence and the right y axis is for the fraction of transmission during the acute stage of infection. Parameters values not specified in this figure are consistent with those in Table 1.

FIGURE 3.

Model runs showing the endemic prevalence (Panels A and C) and the fraction of transmissions from the acute stage (Panels B and D) for 150 years. Above: average time spent at high contact rate phase is raised from 0.1 to 80 years. Below: the ratio of high over low contact rate from 1 to 41.

Parameter values not specified in this figure are the same as given in Table 1.

FIGURE 4.

Endemic prevalence (A) and average contact rate of acutely infected individuals (solid lines in B) or average contact rate of susceptibles (dashed lines in B) at equilibrium as average time spent at high contact rate phase is varied from 0.01 to 100 years.

Parameter values not specified in this figure are the same as given in Table 1.

FIGURE 5.

Proportion of transmissions at endemic equilibrium generated by acutely infected individuals (A), infected individuals in high contact rate phase (B), chronically infected individuals (C) or infected individuals in low contact rate phase (D). In each panel, the ratio of high over low contact rate is raised from 1 to 41 by increments of 2. Parameter values not specified in this figure are the same as given in Table 1.

FIGURE 6.

Proportion of transmissions at endemic equilibrium generated by different types of infected individuals. In each panel, the ratio of high over low contact rate is raised from 1 to 41 by increments of 2. Parameter values not specified in this figure are the same as given in Table 1.

Table 1

List of the episodic risk model parameters and their default values

Parameter	Value	Unit	Definition
U	$1/(40 \times 12)$	/month	Flow of new individuals into sexually active population
μ	$1/(40 \times 12)$	/month	Rate of leaving the sexually active population
γ_1	$1/2$	/month	Rate of transitioning from acute to chronic infection
γ_2	$1/120$	/month	Rate of death from AIDS during chronic infection
	0.003	/contact	Average transmission probability across stages
X	variable	-	Fraction of transmission potential from acute stage
β_1	$X\beta \left(1 + \frac{\gamma_1}{\gamma_2 + \mu}\right)$	/contact	Transmission probability during acute stage
β_2	$(1-X)\beta \left(1 + \frac{\gamma_2 + \mu}{\gamma_1}\right)$	/contact	Transmission probability during chronic stage
H	variable	-	Average fraction of population with high contact rate in the absence of HIV
	3.4114	/month	Average contact rate in the entire population
	variable	-	Ratio of high contact rate over low contact rate
H	L	/month	Contact rate for the high-risk population
L	$\frac{\chi}{(1 - \pi_H + \rho\pi_H)}$	/month	Contact rate for the low risk population
	0.3	-	Fraction of contacts of individuals with high contact rate at the high-risk site
H	variable	/month	Rate of transitioning from high contact rate state to low contact rate state
L	$\varphi_H \left(\frac{\pi_H}{(1 - \pi_H)} \right)$	/month	Rate of transitioning from low contact rate state to high contact rate state
H	$\frac{A_H\beta_1 + C_H\beta_2}{S_H + A_H + C_H}$	-	Force of infection per contact at the high risk mixing site
L	$\frac{(A_L + (1 - \nu)A_H\rho)\beta_1 + (C_L + (1 - \nu)C_H\rho)\beta_2}{S_L + A_L + C_L + (S_H + A_H + C_H)\rho(1 - \nu)}$	-	Force of infection per contact at the general mixing site

Table 2

Differential equations for the deterministic episodic risk compartmental model

$$\begin{aligned}
\frac{dS_H}{dt} &= U\pi_H - S_H\chi_H(\nu\lambda_H + (1-\nu)\lambda_L) - \varphi_H S_H + \varphi_L S_L - \mu S_H \\
\frac{dS_L}{dt} &= U(1-\pi_H) - S_L\chi_L\lambda_L + \varphi_H S_H - \varphi_L S_L - \mu S_L \\
\frac{dA_H}{dt} &= S_H\chi_H(\nu\lambda_H + (1-\nu)\lambda_L) - A_H\gamma_1 - \varphi_H A_H + \varphi_L A_L - \mu A_H \\
\frac{dC_H}{dt} &= A_H\gamma_1 - C_H\gamma_2 - \varphi_H C_H + \varphi_L C_L - \mu C_H \\
\frac{dA_L}{dt} &= S_L\chi_L\lambda_L - A_L\gamma_1 - \varphi_L A_L + \varphi_H A_H - \mu A_L \\
\frac{dC_L}{dt} &= A_L\gamma_1 - C_L\gamma_2 - \varphi_L C_L + \varphi_H C_H - \mu C_L
\end{aligned}$$

Table 3

Equations for the elaborated deterministic compartmental model focusing on the source and site of infection

$$\begin{aligned}
\frac{dA_H^{RHA}}{dt} &= S_H \chi_H \nu \frac{A_H \beta_1}{S_H + A_H + C_H} - A_H^{RHA} \gamma_1 - \varphi_H A_H^{RHA} + \varphi_L A_L^{RHA} - \mu A_H^{RHA} \\
\frac{dA_H^{RHC}}{dt} &= S_H \chi_H \nu \frac{C_H \beta_2}{S_H + A_H + C_H} - A_H^{RHC} \gamma_1 - \varphi_H A_H^{RHC} + \varphi_L A_L^{RHC} - \mu A_H^{RHC} \\
\frac{dA_H^{GHA}}{dt} &= S_H \chi_H (1-\nu) \frac{A_H (1-\nu) \rho \beta_1}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_H^{GHA} \gamma_1 - \varphi_H A_H^{GHA} + \varphi_L A_L^{GHA} - \mu A_H^{GHA} \\
\frac{dA_H^{GHC}}{dt} &= S_H \chi_H (1-\nu) \frac{C_H (1-\nu) \rho \beta_2}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_H^{GHC} \gamma_1 - \varphi_H A_H^{GHC} + \varphi_L A_L^{GHC} - \mu A_H^{GHC} \\
\frac{dA_H^{GLA}}{dt} &= S_H \chi_H (1-\nu) \frac{A_L \beta_1}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_H^{GLA} \gamma_1 - \varphi_H A_H^{GLA} + \varphi_L A_L^{GLA} - \mu A_H^{GLA} \\
\frac{dA_H^{GLC}}{dt} &= S_H \chi_H (1-\nu) \frac{C_L \beta_2}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_H^{GLC} \gamma_1 - \varphi_H A_H^{GLC} + \varphi_L A_L^{GLC} - \mu A_H^{GLC} \\
\frac{dC_H^{RHA}}{dt} &= A_H^{RHA} \gamma_1 - C_H^{RHA} \gamma_2 - \varphi_H C_H^{RHA} + \varphi_L C_L^{RHA} - \mu C_H^{RHA} \\
\frac{dC_H^{RHC}}{dt} &= A_H^{RHC} \gamma_1 - C_H^{RHC} \gamma_2 - \varphi_H C_H^{RHC} + \varphi_L C_L^{RHC} - \mu C_H^{RHC} \\
\frac{dC_H^{GHA}}{dt} &= A_H^{GHA} \gamma_1 - C_H^{GHA} \gamma_2 - \varphi_H C_H^{GHA} + \varphi_L C_L^{GHA} - \mu C_H^{GHA} \\
\frac{dC_H^{GHC}}{dt} &= A_H^{GHC} \gamma_1 - C_H^{GHC} \gamma_2 - \varphi_H C_H^{GHC} + \varphi_L C_L^{GHC} - \mu C_H^{GHC} \\
\frac{dC_H^{GLA}}{dt} &= A_H^{GLA} \gamma_1 - C_H^{GLA} \gamma_2 - \varphi_H C_H^{GLA} + \varphi_L C_L^{GLA} - \mu C_H^{GLA} \\
\frac{dC_H^{GLC}}{dt} &= A_H^{GLC} \gamma_1 - C_H^{GLC} \gamma_2 - \varphi_H C_H^{GLC} + \varphi_L C_L^{GLC} - \mu C_H^{GLC} \\
\frac{dA_L^{RHA}}{dt} &= -A_L^{RHA} \gamma_1 + \varphi_H A_H^{RHA} - \varphi_L A_L^{RHA} - \mu A_L^{RHA} \\
\frac{dA_L^{RHC}}{dt} &= -A_L^{RHC} \gamma_1 + \varphi_H A_H^{RHC} - \varphi_L A_L^{RHC} - \mu A_L^{RHC} \\
\frac{dA_L^{GHA}}{dt} &= S_L \chi_L \frac{A_H \beta_1 (1-\nu) \rho}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_L^{GHA} \gamma_1 + \varphi_H A_H^{GHA} - \varphi_L A_L^{GHA} - \mu A_L^{GHA} \\
\frac{dA_L^{GHC}}{dt} &= S_L \chi_L \frac{C_H \beta_2 (1-\nu) \rho}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_L^{GHC} \gamma_1 + \varphi_H A_H^{GHC} - \varphi_L A_L^{GHC} - \mu A_L^{GHC} \\
\frac{dA_L^{GLA}}{dt} &= S_L \chi_L \frac{A_L \beta_1}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_L^{GLA} \gamma_1 + \varphi_H A_H^{GLA} - \varphi_L A_L^{GLA} - \mu A_L^{GLA} \\
\frac{dA_L^{GLC}}{dt} &= S_L \chi_L \frac{C_L \beta_2}{(S_H + A_H + C_H)(1-\nu) \rho + S_L + A_L + C_L} - A_L^{GLC} \gamma_1 + \varphi_H A_H^{GLC} - \varphi_L A_L^{GLC} - \mu A_L^{GLC} \\
\frac{dC_L^{RHA}}{dt} &= A_H^{RHA} \gamma_1 - C_L^{RHA} \gamma_2 - \varphi_L C_L^{RHA} + \varphi_H C_H^{RHA} - \mu C_L^{RHA} \\
\frac{dC_L^{RHC}}{dt} &= A_H^{RHC} \gamma_1 - C_L^{RHC} \gamma_2 - \varphi_L C_L^{RHC} + \varphi_H C_H^{RHC} - \mu C_L^{RHC} \\
\frac{dC_L^{GHA}}{dt} &= A_H^{GHA} \gamma_1 - C_L^{GHA} \gamma_2 - \varphi_L C_L^{GHA} + \varphi_H C_H^{GHA} - \mu C_L^{GHA} \\
\frac{dC_L^{GHC}}{dt} &= A_H^{GHC} \gamma_1 - C_L^{GHC} \gamma_2 - \varphi_L C_L^{GHC} + \varphi_H C_H^{GHC} - \mu C_L^{GHC} \\
\frac{dC_L^{GLA}}{dt} &= A_H^{GLA} \gamma_1 - C_L^{GLA} \gamma_2 - \varphi_L C_L^{GLA} + \varphi_H C_H^{GLA} - \mu C_L^{GLA} \\
\frac{dC_L^{GLC}}{dt} &= A_H^{GLC} \gamma_1 - C_L^{GLC} \gamma_2 - \varphi_L C_L^{GLC} + \varphi_H C_H^{GLC} - \mu C_L^{GLC}
\end{aligned}$$