Calculating the Contribution of Herpes Simplex Virus Type 2 Epidemics to Increasing HIV Incidence: Treatment Implications

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Herpes simplex virus type 2 (HSV-2) is the most prevalent sexually transmitted pathogen worldwide. There is considerable biological and epidemiological evidence that HSV-2 infection increases the risk of acquiring HIV infection and may also increase the risk of transmitting HIV. Here, we use a mathematical model to predict the effect of a high-prevalence HSV-2 epidemic on HIV incidence. Our results show that HSV-2 epidemics can more than double the peak HIV incidence; that the biological heterogeneity in susceptibility and transmission induced by an HSV-2 epidemic causes HIV incidence to rise, fall, and then rise again; and that HSV-2 epidemics concentrate HIV epidemics, creating a “core group” of HIV transmitters. Our modeling results imply that findings from HSV-2 intervention trials aimed at reduction of HIV incidence will be variable and that positive findings will be obtained only from trials in communities in which HIV incidence is steeply rising.

Recent studies have highlighted the role of sexually transmitted diseases (STDs) in the spread of HIV infection. Several epidemiological studies have found that STDs appear to facilitate HIV transmission, even after sexual behavior is controlled for. The association is particularly strong for genital ulcer disease [1]. Herpes simplex virus type 2 (HSV-2) infections are the most common cause of genital ulcer disease in the United States (where the prevalence in the general population is 22%) [2] and in developing countries [3, 4]. In the United States, HSV-2 prevalence is especially high in 2 communities that have experienced high HIV incidence: men who have sex with men (among whom HSV-2 prevalence is 30%–60% [5, 6]) and African Americans (among whom prevalence in adults is 35%–55% [7]). It has been suggested that controlling high-prevalence HSV-2 epidemics could potentially decrease HIV transmission; however, no empirical or theoretical studies have yet investigated this hypothesis. To determine the potential impact that the control of HSV-2 epidemics (with antiviral therapy) could have on HIV transmission, it is first necessary to determine the magnitude of the effect of HSV-2 epidemics on HIV incidence. Thus, we used a mathematical model (coupled with uncertainty analyses) to predict the temporal dynamics of an HIV epidemic moving through a community in which there is a high prevalence of HSV-2 infection. We conducted 2 uncertainty analyses to quantify the potential impact of HSV-2 on HIV incidence. For one uncertainty analysis, we assumed that HSV-2 infection could increase the risk only of acquiring HIV, and for the other uncertainty analysis we assumed that HSV-2 infection could increase the risk of transmitting HIV. In the light of our results, we discuss whether the treatment of HSV-2 infections with antiviral therapy could substantially decrease HIV transmission.

To predict the temporal dynamics of an HIV epidemic, we used a transmission model that specifies the transmission dynamics of both viruses: HIV and HSV-2. Transmission models are mathematical models that consist of a series of equations formulated on the basis...
of specific biological assumptions about the specific pathogens that are being modeled [8, 9]. These mathematical models are developed to track the number of individuals at risk of infection and the number of people who become infected and diseased. The processes of infection, disease progression, and death determine the rate of change of the size of each population group; these processes are represented by dynamic equations that constitute the model. Transmission models are useful tools for understanding epidemic dynamics, because epidemics are complex nonlinear systems [8, 9]. These types of mathematical models can also be used as health policy tools to evaluate medical and behavioral interventions [10, 11]. Understanding and predicting the interactions between 2 epidemics generated by 2 different pathogens is particularly complex, because it is necessary to model the transmission dynamics of each pathogen separately and of both jointly [12–17]. Thus, by using a mathematical model of the transmission processes, we are able to keep track of the HIV epidemic, the HSV-2 epidemic, and the epidemiological overlap of the 2 epidemics generated by the group of persons coinfected with HSV-2 and HIV. Hence, we are able to model the synergistic interactions between the HSV-2 and the HIV epidemics [18].

The presence of genital ulcers has been suggested as a potential risk factor for HIV acquisition since the beginning of the HIV epidemic [6, 19]. Numerous epidemiological studies have supported the association of genital ulcers in general—and genital herpes in particular—with acquisition of HIV infection [2–4, 20–25]. Herpes simplex viruses are the most common cause of genital ulcers in both developed and developing countries [21–23]. A recent meta-analysis of the literature on coinfection with HIV and HSV-2 reported that the risk of HIV acquisition is increased ~2-fold in HSV-2–seropositive persons [26], with a summary relative risk (RR) estimate of 2.1 (95% CI, 1.4–3.2) and a summary OR of 3.9 (95% CI, 3.1–5.1). This meta-analysis found that slightly higher risk estimates were reported by studies conducted in the developing parts of the world (OR, 4.6; 95% CI, 3.5–5.9) than those in the developed parts of the world (OR, 2.9; 95% CI, 1.7–4.7). An increased risk of HIV acquisition (because of prior HSV-2 infection) was found for women (OR, 3.9; 95% CI, 2.7–5.5), heterosexual men (OR, 4.1; 95% CI, 2.9–5.8), and men who have sex with men (OR, 4.3; 95% CI, 2.4–7.6) [26]. Results from these studies can be explained by the biology of genital herpesvirus infections. Mucosal disruption (due to genital ulceration) occurs during a symptomatic episode of genital herpes; this mucosal disruption provides a direct portal for HIV entry. In addition, because herpetic ulcerations are associated with influx of CD4-bearing lymphocytes [27, 28], a larger number of target cells for HIV attachment and entry are present in the genital tracts of persons with HSV-2 infection. Hence, both the mucosal disruption and the presence of increased numbers of activated CD4+ cells in HSV-2–infected persons increase the likelihood that an exposure to HIV will result in infection. It is also possible that microlesions that can occur during the asymptomatic stage of HSV-2 infection may be important in facilitating the entry of HIV. Thus, these biological processes cause HSV-2–infected persons to be at increased risk for acquisition of HIV infection. However, it is unclear what impact this increased individual-level risk of HIV acquisition has on HIV incidence.

The assessment of HSV-2 as a risk factor for HIV transmission (rather than as a risk factor for HIV acquisition) is methodologically much more difficult, and hence the importance of HSV-2 as a risk factor for HIV transmission is still relatively uncertain. However, both biological and epidemiological evidence suggests that HSV-2 infection may increase the risk of transmitting HIV, and a variety of biological mechanisms have been suggested. HIV has often been found in genital ulcers caused by HSV-2 [29, 30] and in cervicovaginal secretions during HSV-2 reactivation [31]. Among persons with HIV infection, migration of activated lymphocytes to genital herpes lesions has been shown to result in increased local HIV replication on mucosal surfaces, and hence increased HIV titer [32]. Furthermore, HIV and HSV-2 have been shown to coinfect lymphocytes in vitro and in vivo, and HSV-2 regulatory proteins can increase HIV replication. HIV-infected persons often experience more episodes of reactivation of HSV-2 [33] and longer episodes of HSV-2 shedding. Together, these biological mechanisms could lead to a significantly higher efficiency of sexual transmission of HIV from persons coinfected with HIV and HSV-2. The magnitude of the increase in the risk of HIV transmission due to HSV-2 coinfection remains to be determined definitively, because relatively few epidemiological studies have been conducted. A study of HIV-discordant couples found an RR of 1.9 for HIV seropositivity in women whose husbands have genital herpes [34], and another study found acquisition of HIV to be 4.7-fold higher among men who acquired a genital ulcer from a sex worker [35]. Finally, a recent study in Rakai, Uganda [36], has shown that a history of genital ulcer disease was associated with a 5-fold increase in risk of HIV transmission per sex act. Thus, there is a considerable body of evidence that strongly indicates that HSV-2 is a risk factor for HIV acquisition, but the evidence that HSV-2 is a risk factor for HIV transmission is currently less compelling.

**METHODS**

We determined the magnitude of the effect that HSV-2 epidemics could have on HIV incidence by using a mathematical model to predict (with a degree of uncertainty) the HIV incidence in a very sexually active community in which there is initially a high prevalence of HSV-2 infection. To make these predictions, we coupled an HSV-2 epidemic model [37–39] with an HIV epidemic model [10, 40, 41] to form a trans-
mission model of HIV and HSV-2 coepidemic dynamics; both models are described by a series of ordinary differential equations and have been presented in detail elsewhere [10, 37–41]. The coupled model allows us to track susceptible persons (i.e., persons uninfected with either HSV-2 or HIV), persons infected with only HIV, persons infected with only HSV-2, and persons coinfected with HSV-2 and HIV. The ordinary differential equations that specify this 2-epidemic interactive system reflect the rate of change of the number of persons in each state of infection. The coupled model, therefore, reflects the transmission dynamics of an HIV epidemic in the presence of an HSV-2 epidemic.

An HSV-2 epidemic induces biological heterogeneity in a community by generating individual differences in susceptibility to HIV and in transmission risk. To carefully analyze the epidemiological impact of these biological heterogeneities in susceptibility to HIV and in transmission risk, we modeled the impact of HSV-2 epidemics on HIV epidemics in behaviorally homogeneous communities. HSV-2 epidemics will have the greatest impact on HIV epidemics in very sexually active communities that are heavily infected with HSV-2. Thus, we modeled a very sexually active community in which the prevalence of infection with HSV-2 was 50% when the first case of HIV infection was introduced. Because the HSV-2 and HIV epidemics dynamically interact, the prevalence of HSV-2 does not remain stable but increases over time after HSV-2 has been introduced. Thus, the conditions that we modeled closely resemble those of either a community of men who have sex with men (among whom HSV-2 prevalence is 30%–60% [5, 6]) or an inner-city urban African American community (among whom prevalence in adults is 35%–55% [7]).

To use the coupled model to make predictions, we used time-dependent uncertainty analysis; this methodology has been described in detail elsewhere [10, 37, 39–42]. To conduct the uncertainty analysis, we specified a probability-distribution function for each of the uncertain model parameters. We used a stratified Monte Carlo sampling scheme (based on Latin hypercube sampling) to sample the parameter space. We then seeded the HIV epidemic with one HIV-infected person and numerically simulated the coupled transmission model 1000 times, using parameter values generated by the Latin hypercube sampling. We predicted HIV incidence and prevalence for these 1000 HIV epidemics over a 50-year period. For each analysis, we began with 50% of the population infected with HSV-2. We used uncertainty analysis to predict the HSV-2–driven dynamics of an HIV epidemic, under 2 different assumptions: that HSV-2 infection increases the risk only of acquiring HIV infection and that HSV-2 infection increases the risk both of acquiring and of transmitting HIV. Thus, we performed 2 uncertainty analyses.

For the first uncertainty analysis, we assumed that HSV-2 infection increases the risk only of acquiring HIV infection but that the exact magnitude of the increased risk is uncertain. We assumed that HSV-2–infected persons would be more susceptible, to some degree, to HIV infection during an episode of viral shedding (and that the viral shedding episode could be symptomatic or asymptomatic). To operationalize this assumption, we varied the HIV susceptibility factor (one of the parameters in the coupled model) over the range of 1 (no increase in HIV susceptibility due to HSV-2 infection) to a maximum of a 7-fold increase in HIV susceptibility due to HSV-2; this corresponds to the range of increase in risk calculated by Wald and Link [26]. For the second uncertainty analysis, we assumed that HSV-2 infection could increase the risk both of acquiring and of transmitting HIV. Transmission risk of HIV from HSV-2–infected persons could be increased by a variety of mechanisms. Hence, to conduct this analysis, we increased (with a degree of uncertainty) both the HIV susceptibility factor (as in the first analysis) and the values of 3 other model parameters that increased the risk of HIV transmission from coinfected persons. Thus, in coinfected persons, we increased the probability of HIV transmission during an HSV-2 shedding episode, the average length of an HSV-2 shedding episode, and the average number of HSV-2 shedding episodes per year. We modeled the probability of HSV-2 transmission per partnership, but transmission was possible only during an HSV-2 shedding episode; thus, the HSV-2 transmission probability per partnership specified the probability of transmission over the cumulative sum of viral shedding episodes that occurred during the partnership. We varied the 3 uncertain parameters by specifying upper and lower bounds and by assuming a uniform distribution. We varied the probability of HIV transmission per partnership from a baseline of 0.15 (which was equal to the probability of HIV transmission from an HSV-2–uninfected person) to a maximum of 1. We modeled the length of a viral shedding episode in an HIV-negative person as an exponential function with an average of 3.5 days. We varied the average length of an HSV-2 shedding episode in an HIV-positive person from 25% to 200% longer than the average length of an HSV-2 shedding episode in an HIV-negative person (i.e., from an average of 4.4 days to an average of 7 days). We modeled the average number of viral shedding episodes in an HIV-negative person as an exponential function with an average of 12 viral shedding episodes per year. We varied the average number of HSV-2 shedding episodes per year in an HIV-positive person from 50% to 200% of the number in an HIV-negative person. We then sampled each range of parameter estimates independently by use of Latin hypercube sampling. Our assumptions resulted in the average HIV-negative person spending 12% of days shedding HSV-2 and in the average HIV-positive person spending anywhere from 22%
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RESULTS

We compared the 2 uncertainty analyses to evaluate the effect of the different assumptions that HSV-2 could have on HIV acquisition and transmission. We had assumed either that HSV-2 infection increased the risk only of acquiring HIV infection or that HSV-2 infection increased the risk both of acquiring and of transmitting HIV. Given the current state of knowledge of the precise degree to which HSV-2 infection increases the risk of acquisition and transmission of HIV, the qualitative patterns generated by the model are more important than the quantitative predictions. We obtained qualitatively similar results for the 2 uncertainty analyses; thus, our results appear robust. The results of our 2 uncertainty analyses are as follows.

In our uncertainty analyses, we varied parameter values for the risk of HSV-2–infected persons acquiring and transmitting HIV over a fairly wide range that is biologically plausible [26]. Thus, the predictions (with a degree of uncertainty) generated by our model reflected the range in the variability of these parameters that we had assumed (see Methods). As the values of these parameters increased, HIV incidence increased (figure 1). Predictions of HIV incidence, given that HSV-2 infection increases the risk only of HIV acquisition by increasing the susceptibility of HSV-2–infected persons to HIV, are shown in figure 1A. Predictions of HIV incidence, given that HSV-2 infection can increase the risk both of acquiring and of transmitting HIV, are shown in figure 1B. Our results show that a high-prevalence HSV-2 epidemic in a sexually active community can substantially increase the severity of an HIV epidemic (figure 1); if HSV-2 can increase the risk both of acquiring and of transmitting HIV, then the effect of HSV-2 can more than double the peak HIV incidence (interquartile range at 15 years, 8.6%–21.3%) (figure 1B).

HIV epidemics that occur in sexually active communities in which there is a high prevalence of HSV-2 infection exhibit a complex HIV incidence pattern composed of 2 phases: HIV incidence rises and falls (phase I) and then begins to rise again (phase II) (figure 1). This complex pattern of HIV incidence occurs even though there is no behavioral heterogeneity included in the model and simply reflects the HSV-2–generated biological heterogeneity. If HSV-2 infection increases the risk only of HIV acquisition, the second phase of increasing HIV incidence is only gradual (figure 1A); however, if HSV-2 infection increases the risk of both acquisition and transmission of HIV, the second phase of increasing HIV incidence is more substantial (figure 1B). This 2-phase HIV incidence pattern is due to the heterogeneity in HIV susceptibility and transmission risk that is induced by the HSV-2 epidemic.

To understand the 2-phase HIV incidence curve, we determined (for the 2 uncertainty analyses) the transmission dynamics of the HIV epidemic in the HSV-2–infected (figure 2A and 2B) and the HSV-2–uninfected groups (figure 2C and 2D) separately, under the assumption that HSV-2 increases the risk only of acquiring HIV (figure 2A and 2C) or that HSV-2 increases both the acquisition and transmission risks of HIV (figure 2B and 2D). Both uncertainty analyses show that the HIV epidemic first swept through the HSV-2–infected community (figure 2A and 2B); hence, the HIV incidence rose, fell, and then (after 20–30 years) stabilized in this group (figure 2A and 2B). In contrast, HIV incidence in the HSV-2–uninfected group was still increasing after 50 years (figure 2C and 2D). Thus, the percentage of HIV incident cases from the HSV-2 group was initially high (~60%) for the first 15–20 years of an HIV ep-
Figure 2. Predicted data, as shown in figure 1. Median (solid line) and interquartile range (shaded lines) are shown. A and C, HIV incidence curve, under the assumption that herpes simplex virus type 2 (HSV-2) infection increases the risk only of acquiring HIV infection; B and D, HIV incidence, under the assumption that HSV-2 infection increases the risk both of acquiring and of transmitting HIV. A and B show the HIV incidence curve in the HSV-2–infected group; C and D show the HIV incidence curve in the HSV-2–uninfected group.

Our results shed light on certain key features of HIV epidemiology. Heterosexual spread of HIV has been particularly rapid in the African American community in the United States, although most studies have shown that rates of change in sex partners are not substantially different between whites and Af-
Figure 3. Predicted data, as shown in figure 1, except that data are shown as the percentage of the HIV incident cases in persons who had a prior herpes simplex virus type 2 (HSV-2) infection before they become infected with HIV. Median (solid line) and interquartile range (shaded lines) are shown. A, HIV incidence curve, under the assumption that HSV-2 infection increases the risk only of acquiring HIV infection; B, HIV incidence, under the assumption that HSV-2 infection increases the risk both of acquiring and of transmitting HIV.

Figure 4. Predicted HIV prevalence using the same parameter estimates that generated the predicted incidence data in figure 1. Median (solid line) and interquartile range (shaded lines) are shown. A, Percentage of prevalent HIV cases in persons who are coinfected with HIV and herpes simplex virus type 2 (HSV-2), under the assumption that HSV-2 infection increases the risk only of acquiring HIV infection; B, Percentage of prevalent HIV cases in persons who are coinfected with HIV and HSV-2, under the assumption that HSV-2 infection increases the risk both of acquiring and of transmitting HIV.
has begun to rise again after having sharply decreased [44]. This increase in HIV incidence reflects, in large part, increases in risk behaviors, as was predicted by earlier theoretical analyses [40, 41]. However, by simultaneously modeling HSV-2 and HIV epidemics, our current results suggest that certain increases in HIV incidence are to be expected (even in the absence of any increases in risk behaviors) because of HSV-2–driven dynamics.

To first understand the complex interactions between HSV-2 and HIV epidemics, we did not include the effects of either HSV-2 or HIV treatment. However, in our uncertainty analyses, we varied HIV risk acquisition (by increasing susceptibility in HSV-2–infected persons), and varied HIV transmission risk (by increasing the length of the HSV-2 shedding episode, the average number of HSV-2 shedding episodes, and the HIV load in persons coinfected with HSV-2 and HIV). Therefore, our results can be used to shed light on the potential for HSV-2 treatment to reduce HIV incidence. Type-specific serological tests for HSV-2 [45, 46] are now commercially available so that undiagnosed carriers of HSV-2 can be identified, antiviral therapy has been shown to suppress HSV-2 shedding [32, 47], and a clinical trial has recently shown that an antiviral drug (valacyclovir) can reduce sexual transmission of HSV-2 [48]. However, it is not yet clear how these tests and therapies could be effectively used to benefit public health. Our modeling results suggest that at this stage in the HIV pandemic, after HIV epidemics have been progressing for several decades, treating HSV-2–infected persons may reduce their susceptibility to HIV infection (and therefore would prevent a few persons from becoming HIV-infected) but would probably have very little population-level impact in terms of reducing HIV incidence. Thus, in many environments, targeting HSV-2 as a modifiable risk factor in reducing HIV acquisition is not likely to be an effective population prevention strategy. However, our results imply that at this stage in the epidemic, targeting persons coinfected with both HSV-2 and HIV and treating both their HIV and HSV-2 infections could potentially be an effective public health intervention for reduction of HIV incidence; this intervention strategy deserves further exploration. For this strategy to be implemented, HIV-positive persons would need to be tested for HSV-2 infection, and anti-HSV therapy could be added to combination antiretroviral therapies for coinfected persons to significantly decrease levels of both HIV and HSV-2 [49]. It is also necessary to perform intervention trials to definitively ascertain whether treatment of HSV-2 could significantly reduce HIV incidence. However, our modeling suggests that results from these HSV-2 intervention trials will be variable and that positive results are likely to be obtained only from trials in communities in which HIV incidence is steeply rising.

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References


