Targeting Virological Core Groups: A New Paradigm for Controlling Herpes Simplex Virus Type 2 Epidemics

Sally Blower,1 Anna Wald,4 Hayley Gershengorn,3 Fei Wang,2 and Larry Corey4

1Department of Biomathematics, David Geffen School of Medicine, University of California, Los Angeles (UCLA), and 2Department of Computer Science, UCLA, Westwood; 3Department of Medicine, New York Presbyterian Hospital, Weill-Cornell Medical College, New York, New York; 4Departments of Medicine, Epidemiology, and Laboratory Medicine, University of Washington and Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle

Background. Classic modeling of sexually transmitted diseases has focused on modeling behavioral heterogeneity and designing epidemic control strategies targeted at behavioral core groups.

Methods. We analyzed a new mathematical model of herpes simplex virus type 2 (HSV-2) epidemics that includes virological core groups (i.e., groups of individuals with high rates of viral reactivation) and suggest a new paradigm for epidemic control. We used our model, in conjunction with virological data, to determine the potential role of virological core groups in contributing to transmission and the effect that daily antiviral therapy (DAT) could have on reducing transmission if virological core groups were targeted.

Results. We estimated that a virological core group (11% of infected individuals) can cause a disproportionately large percentage (44%) of new infections and that a median of only 6.4 person-years of DAT would be necessary to prevent 1 HSV-2 infection. We determined that relatively few individuals would need to receive DAT to substantially reduce the incidence of HSV-2 infection.

Conclusion. Identifying and targeting individuals in the virological core group could be an effective and practical public health strategy for reducing transmission. Treating individuals who are high-frequency viral shedders should be evaluated as a strategy for reducing HSV-2 transmission.

Approximately 1 in 4 individuals in the United States is infected with herpes simplex virus (HSV) type 2 [1]; however, most infected individuals are asymptomatic and unaware that they are infected [1–3]. Both symptomatic and asymptomatic individuals shed virus in genital secretions, but virus is shed only intermittently, and transmission can occur only when individuals are shedding virus. Most transmissions occur during subclinical episodes of viral reactivation. There is great heterogeneity in the frequency of reactivation; some infected individuals experience frequent viral reactivation events, whereas others experience viral reactivation only rarely [4–8]. Daily antiviral therapy (DAT) has been shown to markedly reduce the frequency of HSV-2 reactivation among both men and women [6, 7, 9]. More recently, in HSV-2–infected individuals, DAT with valacyclovir has been shown to reduce transmission of HSV-2 among monogamous sex partners by ∼50% [10]. Although valacyclovir has received approval from the US Food and Drug Administration for its use in preventing the transmission of genital herpes, it is unclear what public health effect DAT could have on reducing incidence rates of HSV-2, because the majority of HSV-2–infected individuals are asymptomatic [1–3] and are therefore unlikely to have the infection diagnosed and to be offered DAT.

Classic modeling of sexually transmitted diseases has
focused on modeling behavioral heterogeneity and on designing epidemic control strategies targeted at behavioral core groups [11, 12]. This modeling approach is sensible when there is little biological heterogeneity in disease pathogenesis. Under these conditions, high-frequency transmitters are characterized by their high numbers of new sex partners, and behavioral core groups contribute disproportionately to the transmission rate [11, 12]. Because there is no cure for HSV-2 infection, all individuals infected with HSV-2 remain infected for life, but, because of the variation in reactivation rates over time in any 1 individual and because of the heterogeneity in reactivation rates between individuals, there is considerable variability in the amount of time that an individual will be infectious. Infected individuals with a high frequency of reactivation shed virus on a high proportion of days and hence have the potential to cause substantially more HSV-2 infections than infected individuals with a low frequency of reactivation. Hence, the high-frequency transmitters in HSV-2 epidemics are likely to be individuals with high rates of viral reactivation. Thus, we hypothesized that targeting virological core groups (i.e., individuals with high rates of viral reactivation) would be an effective new strategy for controlling HSV-2 epidemics. Here, we present a novel mathematical model of HSV-2 epidemics that includes virological core groups. We used this model in conjunction with virological data to address 2 questions: first, what is the role of virological core groups in contributing to HSV-2 transmission? and, second, if virological core groups were targeted for treatment, what effect would suppressive antiviral therapy have on reducing transmission?

We quantified the role of virological core groups in contributing to HSV-2 transmission by using data to estimate the value of the basic reproduction number of HSV-2 ($R_0$), where $R_0$ is defined as the average number of secondary infectious cases of HSV-2 that are produced by 1 infectious individual introduced into a population in which everyone is susceptible and no treatment is available [13, 14]. We then predicted the potential public health effect of targeting virological core groups, by estimating both the potential population- and individual-level effectiveness of DAT in reducing transmission. We determined population-level effectiveness by using data to estimate the value of $R$, where $R$ is defined as the case reproduction number of HSV-2 when treatment is available [13, 14], and by calculating the average number of HSV-2 infections prevented by DAT over time. We determined individual-level effectiveness by calculating the number of person-years of DAT that would be necessary to prevent 1 HSV-2 infection. Finally, we discuss the implications of our results for designing new and effective epidemic control strategies.

**METHODS**

**Virological core group model.** Our virological core group model depicts the transmission dynamics of HSV-2 in a sexually active population and builds on our earlier models of HSV-2 epidemics [14–15]. A flow diagram of the model is shown in figure 1. The model contains 7 different subgroups: susceptible individuals ($X$), individuals who are infected with HSV-2 and are shedding virus ($H^H$, $H^L$, and $Q^H$), and individuals who are infected with HSV-2 and are quiescent ($Q^Q$, $Q^L$, and $Q^S$), where the superscript modifier signifies the viral reactivation rate of the infected individual ($H$, high viral reactivation rate; $L$, low viral reactivation rate; and $S$, suppressed viral reactivation rate due to DAT). Infected individuals oscillate between 2 states: viral shedding, when they are infectious but can be either asymptomatic or symptomatic, and quiescent, when the virus is latent, and, hence, infected individuals are noninfectious. The viral reactivation rate ($r$) is the rate per capita at which viruses re-activate from the quiescent state (when they are sequestered in the dorsal ganglia), travel via neurons to the genital mucosa, and begin shedding. The average length of the viral shedding episode is specified by $1/q$ and is exponentially distributed. Thus, the average length of time during which an individual is infectious and has the potential to transmit HSV-2 can be calculated by multiplying $1/q$ by the total number of viral reactivation episodes that occur during the individual’s sexual life span, which is defined as the time over which an individual acquires new sex partners [13, 14].

To model heterogeneity in rates of viral reactivation, we modeled 3 types of infected individuals and also included temporal waning in rates of viral reactivation. We modeled “high-frequency shedders” (who always have high rates of viral reactivation during their sexual life span), “low-frequency shedders” (who always have low rates of viral reactivation during their sexual life span), and “high-to-low–frequency shedders” (who have high rates of viral reactivation when they are first infected

![Figure 1. Flow chart of mathematical model that includes virological core group and noncore group; model equations are given and described in Methods.](image-url)
with HSV-2 but wane to lower rates of viral reactivation during their sexual life span at rate $\omega$ [i.e., the number of days that they are infectious per year decreases over time]) (figure 1). At any particular time, high-frequency shedders and high-to-low–frequency shedders (when they have high reactivation rates) constitute the virological core group (figure 1). Low-frequency shedders and high-to-low–frequency shedders (when they have low reactivation rates) constitute the virological noncore group (figure 1). It is important to note that the virological core group is the minority group and is not simply the group of newly infected symptomatic persons who have high shedding rates for the first year after acquiring infection. The equations that specify our mathematical model are as follows:

$$\frac{dX}{dt} = \pi - Xc\lambda - X\mu$$

(1)

$$\frac{dH^t}{dt} = pXc\lambda + Q_0^t + Q_1^t r^t - H^t(\tau + \sigma_1 + q^{t^1} + \mu)$$

(2)

$$\frac{dH^r}{dt} = (1 - p)Xc\lambda + Q_0^t w + Q_1^t r^t - H^r(q^t + \mu + \sigma^t)$$

(3)

$$\frac{dH^s}{dt} = Q^s r^s - H^s(q^s + \mu)$$

(4)

$$\frac{dQ^t}{dt} = H^t(\sigma^t + q^t) - Q^t(r^t + \mu)$$

(5)

$$\frac{dQ^s}{dt} = H^s(\sigma^s + q^s) - Q^s(r^s + \mu)$$

(6)

and

$$\frac{dQ^x}{dt} = H^x(\tau + H^s q^x - Q^x(d + r^s + \mu))$$

(7)

where $NN = X + H^t + H^s + Q^t + Q^s$ and $\lambda = (\beta^t H^t + \beta^s H^s + \beta^x H^x)/NN$.

We modeled different treatment strategies using current medical guidelines for antiviral therapy; hence, we allowed high-frequency shedders to receive either episodic therapy (i.e., they could receive treatment only during a viral shedding episode) or DAT (figure 1). Individuals receiving DAT continued to receive therapy for a specified duration; during this time, their viral reactivation rate was reduced, but episodic outbreaks could occur infrequently (figure 1). Low-frequency shedders were eligible only for episodic therapy, and high-to-low–frequency shedders could receive episodic therapy or DAT (when they were high-frequency shedders), but only episodic therapy once their viral reactivation rate waned and they became low-frequency shedders (figure 1). Therefore, individuals in the virological core group were eligible for either episodic therapy or DAT, and individuals in the virological noncore group were eligible only for episodic therapy. The model structure also allowed HSV-2–infected individuals to start and stop receiving episodic therapy and DAT at any time and individuals with both prevalent and incident cases to receive either therapy.

Monte Carlo estimates of $R_0$, $R$, and cumulative infections prevented. We analyzed our model to derive an analytical expression for $R_0$ and $R$ [13, 14]. $R_0$ and $R$ are threshold conditions used to evaluate both the severity of an epidemic and the control measures that are necessary to reduce $(R_0 > R)$ and/or eradicate $(R < 1)$ the pathogen; thus, the ratio $(R_0 - R)/R_0$ indicates the degree to which treatment would reduce the severity of the epidemic. During an ongoing HSV-2 epidemic, persons infected with HSV-2 are at risk of reinfection; thus, another reproduction number can also be calculated ($R$, the effective reproduction number). $R$ is defined as the average number of secondary infectious cases of HSV-2 that are produced by 1 infectious individual over time; hence, $R = R_x(x(t))$, if no treatment is available, or $R = Rx(t)$, if treatment is available, where $x(t)$ specifies the fraction of the population who are susceptible at time $t$. At the start of an epidemic, everyone is susceptible; hence, $x(t) = 1$, and $R = R_0$, if no treatment is available, or $R = R$, if treatment is available. As the epidemic progresses and prevalence increases, $x(t)$ and $R$ decrease until a steady-state equilibrium is reached, at which point $R = 1$, and $R_0 = 1/x$, if no treatment is available, or $R = 1/x$, if treatment is available. If treatment levels are sufficient to cause $R < 1$, then $R$ will decrease to 0. It is important to note that all of the reproduction numbers are related to each other; however, $R_0$ and $R$ are time independent, whereas $R$ is time dependent because it varies as a function of $x(t)$. Thus, $R_0$ and $R$ are often more useful measures than $R$.

We estimated the values of $R_0$ and $R$ by using parameter estimates obtained from virological data and stochastic simulations based on Monte Carlo methodology [16, 17]. We also used Monte Carlo methods to conduct a time-dependent uncertainty and multivariate sensitivity analysis of the cumulative number of infections prevented over time (a time-dependent measure related to $R'$) [16, 18] and the number of person-years of DAT that would be necessary to prevent 1 HSV-2 infection. By use of a Monte Carlo sampling technique, we were able to simultaneously vary the values of all of the input parameters, each of which was specified by a probability density function (pdf). To conduct the time-dependent uncertainty analysis, we numerically simulated the model 1000 times by...
Table 1. Parameter ranges for uncertainty and multivariate sensitivity analysis.

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter description</th>
<th>Unit</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/(q)</td>
<td>Average length of an infectious VSE</td>
<td>Days</td>
<td>2</td>
<td>4</td>
<td>[19, 20]</td>
</tr>
<tr>
<td>(N_{HF}^c)</td>
<td>Average no. of VSEs/year for high-frequency shedders</td>
<td>No. of episodes</td>
<td>10</td>
<td>24</td>
<td>[4–8]</td>
</tr>
<tr>
<td>(N_{LF}^c)</td>
<td>Average no. of VSEs/year for low-frequency shedders</td>
<td>No. of episodes</td>
<td>4</td>
<td>10</td>
<td>[4–8]</td>
</tr>
<tr>
<td>(\rho)</td>
<td>Probability of being a high-frequency shedder after initial acquisition of HSV-2</td>
<td>…</td>
<td>0.2</td>
<td>0.5</td>
<td>[21, 22]</td>
</tr>
<tr>
<td>1/(\nu)</td>
<td>Average duration in the high-frequency shedding state before waning to the low-frequency shedding state</td>
<td>Years</td>
<td>3</td>
<td>9</td>
<td>[22]</td>
</tr>
<tr>
<td>(\beta)</td>
<td>Average transmission probability/sex partnership</td>
<td>…</td>
<td>0.1</td>
<td>0.5</td>
<td>[23–25]</td>
</tr>
<tr>
<td>1/(\mu)</td>
<td>Average time of sexual life span (i.e., time span during which selecting new sex partners)</td>
<td>Years</td>
<td>10</td>
<td>20</td>
<td>[13, 14]</td>
</tr>
</tbody>
</table>

**NOTE.** HSV-2, herpes simplex virus type 2; VSE, viral-shedding episode.

use of a Latin hypercube sample of the parameter space; computer programs were written in C. We conducted multivariate sensitivity analysis of all outcome variables and calculated sensitivity coefficients in terms of partial rank correlation coefficients (PRCCCs) [16–18]. We used virological data sets to estimate the pdfs for each model parameter and then used Monte Carlo sampling to sample from these pdfs (table 1). We used data on the average number of viral-shedding episodes per year and on the average length of an infectious episode (pdfs given in table 1) to estimate average rates of viral reactivation for both the high-frequency shedders and the low-frequency shedders [13, 14].

We predicted the potential public health effect of increased usage of DAT by using Monte Carlo methods to conduct a time-dependent uncertainty analysis [16, 18, 26]. Treatment parameters in the model were used as exploratory variables by specifying pdfs [18, 26]. We assumed that, at any point in time, 10%–90% (with a likely value of 50%) of the virological core group could receive DAT, individuals would receive DAT for 6 months to 5 years (with a likely value of 2 years), and DAT would be 70%–95% effective in suppressing viral reactivation in high-frequency shedders. These latter figures are based on published data on the effectiveness of DAT [27], as measured by detection of mucosal HSV DNA by use of polymerase chain reaction and by data from pharmaceutical companies on the average duration of DAT once it is initiated. In addition, we assumed that a median of 3% (interquartile range [IQR], 1%–5%) of high-frequency shedders and 9% (IQR, 4%–15%) of low-frequency shedders would receive episodic therapy.

**RESULTS**

Our 1000-sample Monte Carlo data-sampling procedure generated parameter values for both virological core groups and noncore groups; the relative sizes of the groups varied in each of the 1000 simulations, but the core group always contained the fewest individuals. We calculated the average number of days that an individual shed virus per year in each group (figure 2A). Infected individuals in the core group with the highest reactivation rate had an average of 94 (25.8%) viral shedding days (VSDs)/year, and infected individuals in the core group with the lowest reactivation rate had an average of only 20 (5.5%) VSDs/year (figure 2A). In contrast, infected individuals in the noncore group with the highest reactivation rate had an average of 39 (10.7%) VSDs/year, and infected individuals in
the noncore group with the lowest reactivation rate had an average of only 8 (2.2%) VSDs/year (figure 2A). We used the viral-shedding data and the derived analytical expression for $R_0$ to calculate Monte Carlo estimates of $R_0$. Mathematical analyses of our model equations revealed that $R_0 = R_{0HR} + R_{0HLR} + (1 - p) R_{0LR}$, where $R_{0HR}$ is the basic reproduction number in the high-frequency shedders, $R_{0HLR}$ is the basic reproduction number in the high-to-low–frequency shedders, and $R_{0LR}$ is the basic reproduction number in the low-frequency shedders. The detailed expression for $R_0$ (derived from our model) is as follows:

$$R_0 = \frac{(1 - p)c\beta^H}{\mu - \frac{q^H}{\gamma + \mu} + \frac{pc}{\mu}} + \frac{q^H + \mu - \frac{q^H}{\gamma + \mu}}{\mu} + \frac{p}{\mu}
$$

We used our data to estimate that the value of $R_0$ (as calculated with equation 8) was 1.3–2.0; these values give a population prevalence of HSV-2 infection of 22%–50%, a figure supported by several serological surveys of HSV-2 seroprevalence in North America and Europe [1, 3].

We used our model to calculate the relative contributions of the virological core and the noncore groups to the value of $R_0$. An average individual in the virological core group generates more secondary HSV-2 infections than does an average individual in the noncore group (figure 2B). If 22% of the population is infected with HSV-2 (as in the general population in the United States [1]), then our model predicts that an individual in the virological core group generates a median of 1.6 secondary infections (IQR, 1.5–1.7 secondary infections) and that an individual in the noncore group generates a median of only 1.1 secondary infections (IQR, 1.0–1.2 secondary infections) (figure 2B, blue data). At higher HSV-2 prevalence rates (e.g., 50%, such as in certain African American and gay communities in the United States [1, 3]), the difference in $R_0$ between the core and the noncore groups is more substantial; under these conditions, an average individual in the core group generates a median of 2.5 secondary infections (IQR, 2.3–2.7 secondary infections), whereas an average individual in the noncore group generates a median of 1.7 secondary infections (IQR, 1.6–1.8 secondary infections) (figure 2B, red data). In terms of the overall contribution to $R_0$, we calculated that individuals from the virological core group cause a median of 44% of new HSV-2 infections (IQR, 36%–52% of new HSV-2 infections), even though the core group constitutes only a small proportion (median, 11%; IQR, 8%–14%) of the infected population; thus, individuals in the virological core group have a disproportionate effect in driving the epidemic.

We used our model to examine the potential effects of DAT on transmission dynamics. We determined the effect of DAT on reducing $R$ and on preventing HSV-2 infections. We used virological data (see Methods) to obtain Monte Carlo estimates of $R$. For an epidemic with a prevalence of 22%, we calculated that
Our results imply that any strategy directed at interrupting transmission would be more effective to have a larger fraction of the virological core group receiving DAT for a short time than to have a smaller fraction of the virological core group receiving DAT for a long time. This is because the reduction in transmission is determined by the total number of individuals receiving DAT at any point in time; thus, the coverage rate of the virological core group is more important than the duration of DAT.

The disproportionate population-level effect of targeting the virological core group is readily apparent. By treating only a relatively small percentage of individuals, it would be possible to prevent a substantial number of new HSV-2 infections (figure 4A). After only 1 year, a median of 25% (IQR, 19%–32%; minimum, 7%; maximum, 56%) of HSV-2 infections would be prevented (figure 4A). Population-level effectiveness will be variable and will depend on the degree of coverage of DAT; the greater the coverage of DAT, the greater the number of HSV-2 infections prevented (figure 4A). High-prevalence HSV-2 epidemics (50% prevalence) will likely require substantially higher coverage than will moderate-prevalence epidemics (22% prevalence), to achieve a comparable reduction in incidence (figure 4A), because DAT reduces R to <1 if the initial HSV-2 prevalence is 22%, but R remains >1 if the initial HSV-2 prevalence is 50%. Finally, we determined the potential individual-level effectiveness of DAT by calculating the number of person-years of DAT that would be necessary to prevent 1 HSV-2 infection (figure 4B). Our results show that 1 HSV-2 infection would be prevented for every 6.4 person-years (IQR, 5.1–8.1 person-years) of DAT. Therefore, even if DAT is not widely used, it would not be hard to prevent HSV-2 infections if individuals in the core group with high viral shedding rates are targeted.

**DISCUSSION**

Our modeling results provide several novel insights into the transmission dynamics of HSV-2 epidemics. By analyzing virological data with our new theoretical framework, we have found that the biological variability in the viral-shedding patterns (between and within individuals) markedly influences the
transmission dynamics of genital herpes. Although we are not suggesting that shedding frequency is the sole determinant in influencing transmission dynamics (obviously, other host genetic and virological factors are also important), we do suggest that patterns of viral shedding are likely to explain some of the varied prevalence rates in HSV-2 seen in populations worldwide. Our results indicate that the majority of new HSV-2 infections that occur may be attributable to a relatively small percentage of persons who are high-frequency shedders. The model that we formulated allows a single individual to move from the virological core group (high-frequency shedders) to the noncore group (low-frequency shedders) over time. Thus, our model reflects data from many empirical studies showing that individuals with recently acquired genital herpes almost always shed virus at high rates (>25% of days) for the first few months after acquisition of infection, whereas only a small fraction of persons who have longstanding genital herpes (>10 years) shed HSV-2 at such rates. Our results suggest that identifying persons with incident genital herpes and utilizing DAT may be a new strategy to consider for public health control. Our results indicate the importance of implementing effective control programs before prevalence increases to >50%. Of interest, our results demonstrate that identifying and treating (for a short period of time) a high percentage of high-frequency shedders would be more effective in reducing transmission than would treating fewer persons for a long period of time.

Valacyclovir has recently been shown to reduce the transmission of HSV-2 among sex partners and is a new case-management tool for physicians [10]. Valacyclovir could also potentially act as a public health prevention tool. Our modeling analyses suggest that HSV-2 could be reduced by concentrating on identifying and treating persons who have high-frequency HSV-2 reactivation. We have shown both that virological core groups are extremely important in transmission and that targeting virological core groups could be effective in reducing transmission. Conventional control strategies for sexually transmitted diseases are based on targeting behavioral core groups [11, 12]. Because HSV-2 is very prevalent (>20% in the general population), targeting behavioral core groups will be ineffective in controlling genital herpes. We suggest that virological core groups should be targeted for treatment; the virological core group that we have defined includes people who are high-frequency shedders. Unfortunately, to date, only frequent sampling of mucosal sites can identify (on an individual basis) high-frequency shedders. Automated methods to detect HSV shedding from frequent sampling are now available, and it is possible that technological breakthroughs may afford even more cost-effective approaches. At present, the best epidemiological determinant of a high-frequency shedder is recent acquisition of genital herpes (i.e., persons infected during the last 12–18 months) [4, 28]. In the United States and Europe, the majority of the virological core group members are therefore likely to be sexually active adults in their mid-20s.

Recent theoretical analyses have shown that antiretrovirals could decrease transmission of HIV [18, 26, 29, 30]; however, to achieve a significant reduction in incidence rates, a large percentage of HIV-infected individuals need to receive treatment [18, 26, 29, 30]. In contrast, one of the attractive features of our proposed new strategy for HSV-2 epidemics is that only a relatively small fraction of HSV-2–infected individuals would need to be treated to substantially reduce HSV-2 transmission. Clinical studies have indicated that almost all high-frequency shedders are symptomatic [31–33]. Although many of these individuals have unrecognized disease because of nonspecific symptoms or previous misdiagnosis of genital herpes, recent studies have shown that serological assays can accurately identify such persons [34, 35]. Applying Bayesian statistical analyses to virological data can be used to quantify the rate of waning of rates of viral reactivation of high-frequency shedders [36]. The feasibility of identifying members of the virological core group needs to be examined, and their adherence to antiviral therapy assessed. However, because of their symptoms, many members of the virological core group are likely to seek and comply with treatment. Studies have shown that compliance with anti–herpes virus therapy among persons with recognized symptomatic diseases is high [37, 38]. Individuals who are most in need of the therapeutic benefits of DAT are also those whom it is most important to target for prevention (i.e., “super shedders” are likely to be “super spreaders”). In summary, targeting virological core groups would be both a potentially effective and practical novel public health strategy for interrupting the transmission of genital herpes with current therapeutic tools. Because HSV-2 epidemics fuel HIV epidemics [39], our proposed strategy for reducing HSV-2 epidemics could also potentially reduce HIV transmission in certain locations.

Acknowledgment

We thank Erin Bodine for editorial assistance.

References


