Use of antiviral treatment and prophylaxis is unlikely to have a major impact on the prevalence of herpes simplex virus type 2

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Background: Genital infection with herpes simplex virus (HSV) is common and can cause severe morbidity, over many years in some cases. Aciclovir provides suppressive therapy but there is debate over the effects of its use on the spread of infection.

Objectives: To explore the influence of the natural history of genital HSV and the impact of antiviral therapy.

Methods: A simple mathematical model of HSV-2 transmission dynamics was developed, and parameter values estimated from published data.

Results: The relative durations of the risk of transmitting HSV-2 and the duration of therapy generate a non-linear relation between the duration of antiviral therapy and the reduction in prevalenceof infection. If there is a wide distribution of risk of HSV-2 transmission over the course of an infection then practicable aciclovir use is unlikely to have any great impact on disease transmission dynamics.

Conclusions: There are still many uncertainties in the transmission dynamics of HSV-2. In particular, infectiousness over the course of an infection requires more detailed exploration. To have a significant impact on the prevalence of HSV-2 aciclovir use would have to be widespread and for a long duration.

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Introduction

Herpes simplex virus type 2 (HSV-2) can cause painful recurring ulcers, which could be important in enhancing the transmission of human immunodeficiency virus (HIV).[1–4] The current treatment options of aciclovir (and the prodrug, valaciclovir) and penciclovir (generated by famiciclovir), while not curing infection, successfully suppress symptoms.[5–10] This raises issues about the ability of treatment and disease prophylaxis to reduce the incidence and prevalence of infection.[11–13] As well as reducing the severity of symptoms, frequent oral doses of aciclovir, valaciclovir, or famiciclovir over a period of months or years reduce both the frequency and duration of viral shedding during treatment.[2 5 14 15] This provides a potential means of controlling the spread of infection within a population, and there is debate over whether the use of suppressive therapy and easier access to treatment (for example, "over the counter" without prescription) should be encouraged.[11–13 16–18] In order to explore the potential impact of such aciclovir use, we developed a very simple mathematical model of the transmission dynamics of HSV-2 which included the impact of treatment altering transmission probabilities, and reviewed the parameter values available in published literature.

Methods

A compartmental model of the type discussed by Anderson[19] and Brunham and Plummer[20] (that is, a model where the population divided according to infection status), was developed to describe the heterosexual spread of genital HSV infection throughout the most sexually active age group of a typical Western population—those aged 16–35 years. This group has the highest rates of sexual partner change both for males and females,[21] and the peak incidence for HSV-2 infection.[22–25] Three compartments were used describe infection in the population: susceptible, S_i, recently infected, T_i, and long term infected, I_i. As in the models of Hethcote and Yorke[26] for gonorrhoea, the model population was divided in two groups ($i=1$ and $i=2$), with different rates of sexual partner change, c_i and frequency of sexual intercourse within the partnership. The different frequency of sexual acts is reflected in different transmission probabilities per sexual partnership between a susceptible from group i and an infected from group j, β_{ij}. The activity classes corresponded to Williams *et al*'s[27] activity classes 1–3 and 4–6, respectively. The proportion of sexual partners chosen from each activity group was described by mixing coefficient, ρ_{ij}, controlled by a coefficient ε.[28] The rates of flow between the compartments are described by a set of ordinary differential equations:

$$\frac{dS_i}{dt} = \mu N_i - S_i c_i \sum_j \left[\rho_{ij} \frac{(\beta_{ij}(I_j + (1-f)T_j) + f\beta_{ij}^T T_j)}{N_j} \right] - \mu S_i$$

$$\frac{dT_i}{dt} = S_i c_i \sum_j \left[\rho_{ij} \frac{(\beta_{ij}(I_j + (1-f)T_j) + f\beta_{ij}^T T_j)}{N_j} \right] - \left(\mu + \frac{1}{TD} \right) T_i$$

$$\frac{dI_i}{dt} = \frac{1}{TD} T_i - \mu I_i$$

Table 1   Values given to the parameters

Parameter	Symbol	Estimate
Rate of entry into, and exit from the sexually active age group	μ	1/19 per year
Proportion of the population in high activity group		0.14
HSV-2 transmission probability per high activity partnership	β_{11}	5.1%
HSV-2 transmission probability per low activity partnership	β_{22}	17.4%
Rate of partner change: low and high activity groups	c_1, c_2	0.48, 3.5 per year
Degree of interaction between low- and high-activity groups	ε	0.7
Transmission probability, during treatment: low- and high-activity groups	$\beta_{11}^T, \beta_{22}^T$	0%, 0% or 31.7%, 9.9%
Proportion treated	f	0.3, 1.0
Mean treatment duration	TD	1-50 years

After infection individuals enter the "recently infected" compartment T_i, where a fraction f are treated and have a modified value for the transmission probability β_{ij}^T. In the absence of treatment the fraction treated, f, is set to zero. Those not being treated are as infectious as those in the "long term infected" compartment, I_i, which those in the "recently infected" compartment enter at a rate $1/TD$ and remain in until they leave the model population. The pattern of mixing ranges from fully assortative to random determined by the value ε where

$$\rho_{ij} = (1-\varepsilon)\delta_{ij} + \varepsilon\left(\frac{c_i N_i}{\Sigma c_s N_s}\right)$$

Here δ_{ij} is the identity matrix and s a dummy variable describing each of the sexual activity groups. Each activity group consists of N_i people ($N_i = S_i + T_i + I_i$). The rate of entry into the sexually active population is the same as the rate of leaving, μ, so that the population remains constant. This means that all individual have a negative exponential distributed sexually active lifespan with a mean duration of 19 years.

The values given to the parameters are described in table 1. Numerical solutions (4th order Runge-Kutta method) were obtained using the Model Maker v2.0 software package.

The pattern of transmission of an infectious disease depends upon the biological properties of the host-pathogen interaction (for example, the frequency of symptomatic and asymptomatic shedding of virus at infectious doses) and the behaviour of the host (for example, the frequency of sexual intercourse and whether it occurs while the infected partner is symptomatically, as well as asymptomatically, shedding virus).[19][29] The transmission probability, β_{ij}, used in the model is defined per sexual partnership. Assuming there is a fixed chance of transmission for each sex act (β_a) then the transmission probability for each sexual partnership (β_p) is a function of the number of sex acts within the partnership (Na):

$$\beta_p = 1-(1-\beta_a)^{Na}$$

This relation was observed empirically for gonorrhoea,[30][31] where the duration of infectiousness is short enough for a simple model in which transmission occurs on partner change. Data on the likelihood of HSV-2 transmission were taken from a prospective study in which one partner had a recurrent symptomatic infection and the other was initially seronegative for HSV-2.[32] Infection risk was assessed typically over 1 year in this sample, which was biased to stable partnerships and to those who had symptomatic infection. For transmission from men to women, prior exposure of the female partner to HSV-1 appears to offer protection against HSV-2 infection, reducing the rate of transmission from 31.8% per year of partnership to 9.1%. Assuming that around 65% of the population exposed to HSV-2 has already experienced infection with HSV-1[25] gives a weighted mean value of 17% for the transmission probability. The estimated transmission probability per year from women to men was 4.5%. The number of men in the study who were infected was too small to analyse the effect of their HSV-1 serological status, although they are expected to have similar protection.[32] The average transmission probability from men to women and from women to men is the geometric mean of the separate values (8.76%) and is the appropriate value for our model where we do not distinguish between the sexes.[19] We do though make allowance for the different duration of high and low activity partnerships and the frequency of sex that occurs per unit time within the partnership. If the average duration of partnerships is the inverse of the rate of partner change, then high activity partnerships last on average for 0.28 years and low activity partnerships for 2.08 years.[27] If we assume, based on reported behaviours,[21] that those with high numbers of partners have twice as many sex acts per partner, per unit of time, as others, then we can recalculate from the transmission probability estimated for stable partnerships over 1 year (8.76%), the transmission probability per partnership lasting for 2.08 years (17.4%) and that for partnerships of 0.28 years with twice as many sex acts per unit time (5.1%). In the results we varied which partnerships these values applied to and, because these estimates are subject to many biases, we used a range of values by reducing the initial estimates by 50% and 25% and increasing them by 25%.

To explore the impact of suppressive therapy we need to estimate how it alters the transmission probability. Although the duration of infectiousness is very long, infected individuals are not *continuously* infectious. Rather, there are episodic outbreaks of viral shedding from the site of infection.[3] Some of these are accompanied by recognised symptoms, but most are asymptomatic.[29][32][33] It is likely that the level of infectiousness during an outbreak depends upon the viral titre at the site of shedding,[29] and that symptoms appear during the highest titre outbreaks. If this is true then the viral titre required to cause symptoms is greater than that required for transmission (between 50% and 70% of transmission events occur during an asymptomatic episode.[32] Aciclovir is known to reduce the frequency both of recurrent symptoms[16] and of viral shedding events detectable by cell culture and DNA polymerase chain reaction (PCR) assays.[2][15] Some asymptomatic shedding can be below the detection limit for cell culture methods, but be detectable by PCR assays.[15] It is possible that aciclovir may suppress symptoms without eliminating the potential for transmission. The presence of
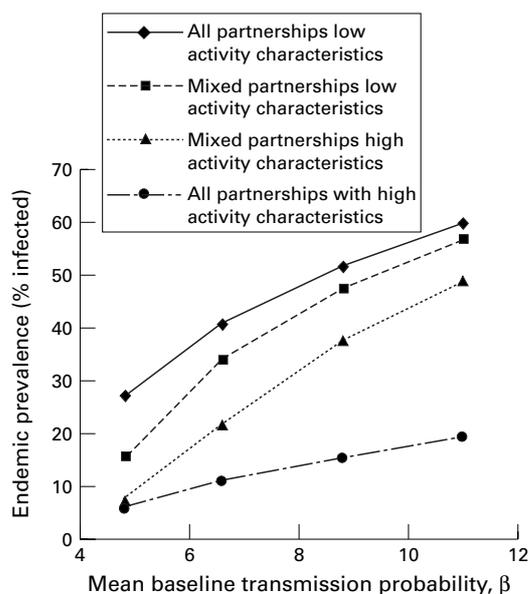
Figure 1   The influence of transmission probabilities per partnership on the endemic (steady state) prevalence of infection in a mathematical model of HSV-2 transmission. The transmission probabilities are varied to illustrate the sensitivity of solutions to the estimated value, which is likely to depend upon both the length of the partnership and the frequency of sex acts per unit time within the partnership. The calculation of transmission probabilities is described in the text. Each line represents a different assumption about the duration of partnerships and frequency of sex. At two extremes every partnership is long with a low frequency of sex (low activity characteristics) or every partnership is short with a high frequency of sex (high activity characteristics). In between these extremes where every partnership has the same characteristics, we illustrate the results where partnerships within the high activity group and within the low activity group have the characteristics appropriate to their activity. We then have lines which compare the prevalence when partnerships between low and high activity (mixed partnerships) are similar to within low activity or, intuitively more likely, within high activity.

painful lesions is likely to deter contact, and so symptomatic outbreaks are probably *less likely* to lead to transmission events than asympto-

matic ones, despite their higher viral titre.[1][34] Thus, if it prevented symptoms but not the shedding of virus in transmissible quantities, suppressive therapy could increase the rate of transmission of the disease.[12] Among patients with symptomatic infection, in the absence treatment, it was reported that approximately 50% of viral shedding episodes are asymptomatic.[2] Thus, if treatment suppresses symptoms completely, whilst not altering the frequency of infectious level viral shedding then the number of asymptomatic potential transmission events per partnership would be doubled. However, the use of more sensitive PCR assays has suggested that asymptomatic viral shedding is actually more common than this,[15] which would limit the potential increased risk due to preventing symptoms. In addition, the observed 80% median reduction in the frequency of viral detection by PCR in treated subjects suggests that transmission probabilities are more likely to decrease than increase.[15] In the "best case", the transmission probability for treated individuals was zero (that is, transmission is prevented), and in the "worst case" the frequency of "infectious" sex acts was taken to be doubled.

Results

The endemic prevalence of HSV-2 depends upon the transmission probability of the virus (fig 1). Realistic prevalences of infection below 40% of the sexually active population occur either when the transmission probability used is lower than that estimated, or when partnerships which involve those with many partners have a lower than average transmission probability. However, our model is too simple to use observed prevalences of HSV-2 to estimate patterns of sexual behaviour or parameter values with any confidence. We therefore used a range of prevalences in the absence of suppressive therapy as a baseline to explore the impact of its introduction. Most STDs, such gonorrhoea, syphilis, and chancroid, have a relatively short duration of infectiousness and depend upon a "core group" of individuals with high rates of sexual partner change in order to persist.[19][35][36] There is usually a high transmission probability, which facilitates rapid transmission within and from this core group, who tend to have many short partnerships. Such STDs do not usually infect many individuals outside of the core group because infection chains rapidly break down among less sexually active individuals. In contrast, genital HSV-2 has a relatively low transmission probability, but a very long duration of infectiousness—perhaps lifelong. Thus, HSV-2 infection will be more widespread in the sexually active population.

To determine the impact of suppressive therapy on this widespread infection a fraction of the population is assumed to receive therapy throughout the "recently infected" stage the duration of which was varied (fig 2). Once therapy is withdrawn, individuals are assumed to be as infectious as those who had not received aciclovir.[37] To predict the maximum effect of aciclovir usage, it was assumed that *all*
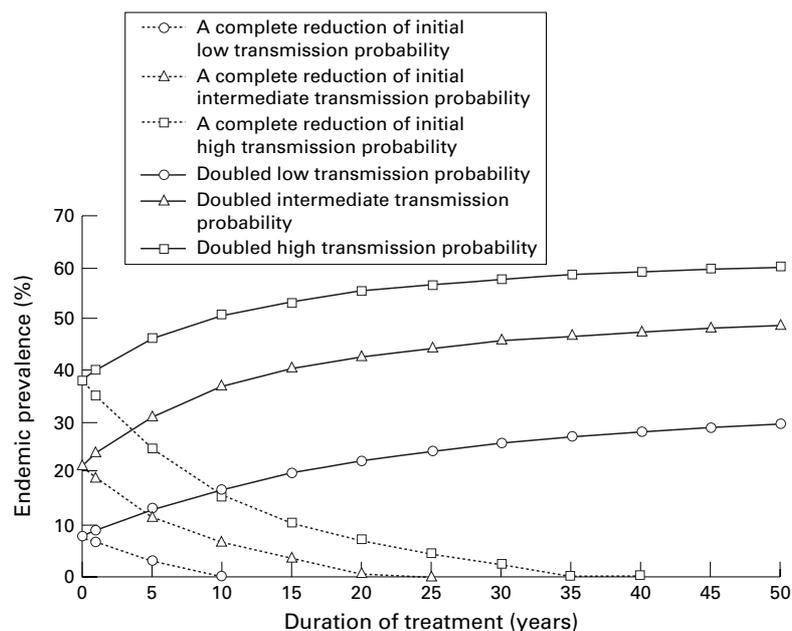

Figure 2   The modelled relation between the endemic (steady state) prevalence and the mean duration of suppressive therapy with aciclovir when 30% of those infected are treated. The model parameters are those in table 1 except that three sets of transmission probability in the absence of treatment (50%, 75%, and 100% of the estimated values) were used. The impact of two extreme influences of suppressive therapy: a 100% reduction in transmission probability and a doubling of transmission probability are illustrated.
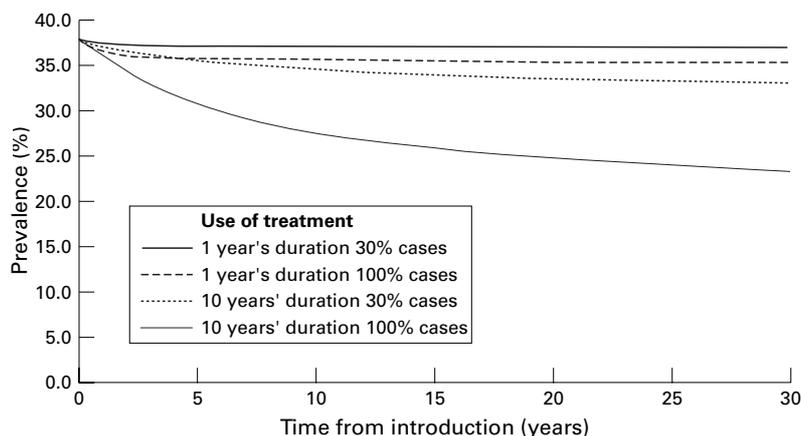
Figure 3 The change in prevalence over time after the introduction of suppressive therapy that prevents all transmission from those receiving treatment. Both the fraction of those infected who receive suppressive therapy (30% and 100%) and the length of time for which it is given (1 year and 10 years) is varied. Other parameter values were those in table 1. The reduction is only significant if all those infected are given therapy for a long period.

infected individuals regardless of symptoms received treatment upon becoming infected. As the duration of treatment is increased, the prevalence of HSV-2 declines in the "best case" and increases in the "worst" (fig 2). The change in prevalence is related to the treatment duration in a non-linear fashion, with changes becoming smaller as the duration increases. This is because as people age they reduce their rates of sexual partner change (in our model leaving the sexually active model population) and their risk of transmitting the infection declines. Thus, as the duration of treatment increases fewer individuals are still influential in viral transmission. The impact of treatment is modest in either direction. Even in the best case, elimination still requires that individuals be treated for many years, whereas suppressive therapy is normally used for just 2 years.[5] [38] Many of those infected are asymptomatic, or have unrecognised symptoms, and would not receive such treatment.[39] Only about 30% have recognised symptoms,[39] which is the maximum proportion likely to receive aciclovir without screening for infection. We explored the situa-

tions where everyone and where 30% of those infected are treated and looked at the time it takes for the intervention to have an effect (fig 3). The effects of such an intervention would be slow to be seen, taking decades for any substantial change to occur. The results of treating all infected individuals were modest, and the effects of treating the much more realistic 30% were correspondingly even less dramatic.

The widespread use of suppressive therapy depends on being able to identify asymptomatic infections. This would be more manageable if screening were restricted to groups, such as STD clinic patients, who have a high risk of acquiring and transmitting infection. We explore the impact of therapy restricted to the high activity group (fig 4). It is only when suppressive therapy is used beyond the core group that there are substantial declines in the steady state prevalence.

Discussion

Our results highlight two important concerns about the use of aciclovir as a population level intervention to control HSV-2 transmission. Currently we need to know more about the relation between disease symptoms, viral shedding, and the likelihood of HSV-2 transmission.[12] [18] [29] Because we are uncertain of how the suppression of symptoms will influence the probability of sexual contact and how much virus has to be shed for transmission to be possible, we are uncertain of the decrease in the transmission probability of HSV-2 with aciclovir.[12] In the case of gonorrhoea, patients often deny having sex while symptomatic.[40] If this is also true of HSV-2 then suppressing symptoms without preventing transmissible levels of viral shedding could increase the transmission of infection. Evidence that the reduced shedding of detectable virus will reduce the transmission probability would be reassuring. However, it is made less important by the second result that all but the most extensive use of antivirals has little impact on a system that is dominated by the long duration of infectiousness.

The epidemiology of most other sexually transmitted infections is dominated by a number of individuals who for generally short durations have a very high risk of acquiring and transmitting infection.[41] Under such circumstances the targeted prevention of transmission can have wide ranging impact. In contrast HSV-2 has a low transmissibility for a long duration and hence a more "core group" (see Garnett and Anderson[36]). It is much less sensitive to a short term reduction in the transmission probability. Aciclovir is likely to have little impact on HSV epidemiology, whether it increases or decreases transmission probabilities, because of the relatively short duration of treatment.

Only about one third of those infected have recognised symptoms[39] and many of these will not report those symptoms or receive treatment. This means that unless there is screening for infection mass prophylaxis would be restricted to a small fraction of those infectious individuals. Such mass long term screening
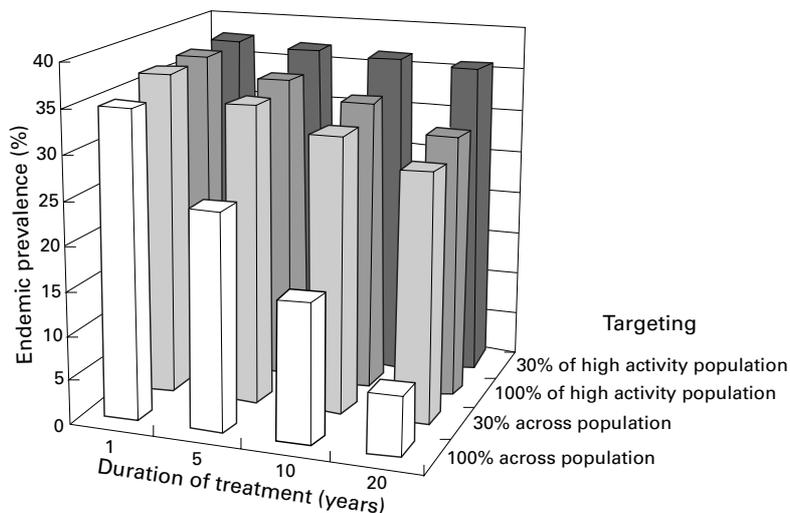

Figure 4 The impact of targeted use of suppressive therapy, which prevents transmission. The impact of the duration of therapy on the model steady state prevalence is illustrated for different proportions of the infected population receiving suppressive therapy. Parameter values were those in table 1. Either 30% or 100% of those infected receive therapy, both across the population, or in the high activity (core) group. The impact on prevalence is much less if therapy is restricted to those with high activity.

and treatment would be expensive, logistically complex, and possibly unwelcome, because those asymptomatically infected may not wish to know of their infection. The degree of patient compliance required and the cost of treatment are high, whether funded publicly or by individuals privately purchasing aciclovir. The widespread use of aciclovir to prevent transmission would only be worth considering if it were to have a major impact. This would require therapy for a long period. Aciclovir is safe and efficacious for a long period and the introduction of drugs with better bioavailablity such as valaciclovir and famciclovir could make treatment schedules more acceptable.[16] None the less, it would be a major undertaking.

At present, genital HSV-2 epidemiology is too poorly understood for reliable quantitative projections. The model presented here is deliberately simple in order to generate qualitative insight. Despite this simplicity, the findings with respect to the impact of aciclovir are reasonably robust to model assumptions, owing to the exaggeration of both the numbers of people treated, and reductions in transmission probability possible. However, our assumptions about changes in the transmission probability with time from infection (that is, that it does not change), the relative transmissibility of symptomatic and asymptomatic infection, and the duration of sexual activity within the at risk population, influence the success of aciclovir use as a population level intervention. For example, the severity and frequency of symptoms declines with time since infection.[1–3 33] If most infectious viral shedding occurs early in infection, then the use of suppressive therapy over this period would be more beneficial than if virus is shed equally throughout an infection.

In light of the likely ineffectiveness of aciclovir in reducing HSV-2 prevalence, we believe that it is necessary for other strategies to be pursued, such as education. Unfortunately, while an awareness of symptoms could help if some events thought to be asymptomatic include unrecognised symptoms,[39] truly asymptomatic shedding is likely to maintain transmission rates. Condoms are not totally effective in preventing transmission,[32] and the most sexually active individuals tend to use them the least.[14 21] Thus, it appears that there is no easy answer to controlling the spread of HSV-2.

It is important to note that our results only apply to the use of aciclovir as a public health tool aimed at reducing the incidence of infection. The decision of whether to prescribe aciclovir requires a number of factors to be considered including cost, convenience, the potential spread of resistant strains, and the patient's quality of life.[5 39 16 18] In light of the minimal likely epidemiological impact, even if suppressive therapy increases transmission rates,[38 39] there will be little population level cost to be weighed against the personal cost of morbidity. The likely decline in drug costs with the expiry of the aciclovir patent[13] is likely to increase its use. Whether oral aciclovir should be made available without prescription, however, is not clear. For example, one of the effects of this may be to increase the incidence of other STDs, as individuals may misdiagnose an infection as HSV, and so fail to have the true cause treated appropriately.[13]

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