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## Once-Daily Valacyclovir to Reduce the Risk of Transmission of Genital Herpes

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### ABSTRACT

#### BACKGROUND

Nucleoside analogues against herpes simplex virus (HSV) have been shown to suppress shedding of HSV type 2 (HSV-2) on genital mucosal surfaces and may prevent sexual transmission of HSV.

#### METHODS

We followed 1484 immunocompetent, heterosexual, monogamous couples: one with clinically symptomatic genital HSV-2 and one susceptible to HSV-2. The partners with HSV-2 infection were randomly assigned to receive either 500 mg of valacyclovir once daily or placebo for eight months. The susceptible partner was evaluated monthly for clinical signs and symptoms of genital herpes. Source partners were followed for recurrences of genital herpes; 89 were enrolled in a substudy of HSV-2 mucosal shedding. Both partners were counseled on safer sex and were offered condoms at each visit. The predefined primary end point was the reduction in transmission of symptomatic genital herpes.

#### RESULTS

Clinically symptomatic HSV-2 infection developed in 4 of 743 susceptible partners who were given valacyclovir, as compared with 16 of 741 who were given placebo (hazard ratio, 0.25; 95 percent confidence interval, 0.08 to 0.75;  $P=0.008$ ). Overall, acquisition of HSV-2 was observed in 14 of the susceptible partners who received valacyclovir (1.9 percent), as compared with 27 (3.6 percent) who received placebo (hazard ratio, 0.52; 95 percent confidence interval, 0.27 to 0.99;  $P=0.04$ ). HSV DNA was detected in samples of genital secretions on 2.9 percent of the days among the HSV-2–infected (source) partners who received valacyclovir, as compared with 10.8 percent of the days among those who received placebo ( $P<0.001$ ). The mean rates of recurrence were 0.11 per month and 0.40 per month, respectively ( $P<0.001$ ).

#### CONCLUSIONS

Once-daily suppressive therapy with valacyclovir significantly reduces the risk of transmission of genital herpes among heterosexual, HSV-2–discordant couples.

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**H**ERPES SIMPLEX VIRUS TYPE 2 (HSV-2) causes a chronic genital viral infection characterized by high rates of clinical and subclinical reactivation in the genital mucosa and the attendant risk of sexual transmission.<sup>1-4</sup> Both symptomatic and asymptomatic reactivations of HSV infection have been shown to result in sexual transmission.<sup>5-8</sup> Population-based studies in the United States indicate that 22 percent of adults have antibodies to HSV-2 and that an estimated 1.6 million new cases of HSV-2 infection are acquired yearly.<sup>9,10</sup> HSV-2 has become the most frequent cause of genital ulcer disease in all regions of the world.<sup>11-14</sup>

Transmission of genital herpes to others is the chief concern in persons with known genital herpes.<sup>15-17</sup> Although antiviral agents have been shown for nearly two decades to reduce the frequency of clinical reactivation of genital herpes,<sup>18,19</sup> only more recently has it been shown that daily antiviral therapy also reduces the frequency and amount of HSV that is shed subclinically on genital mucosal surfaces, the principal source of transmitted infections.<sup>20-22</sup> This reduction in subclinical shedding provided the rationale for our randomized, placebo-controlled trial, which was designed to determine whether once-daily valacyclovir could reduce the risk of sexual transmission of genital herpes.

## METHODS

### STUDY POPULATION

We enrolled heterosexual couples who were serologically discordant for HSV-2 infection from 96 study sites. The inclusion criteria for the HSV-2–seropositive source partner were an age of 18 years or older, presence of recurrent genital herpes with fewer than 10 episodes per year, and nonuse of any daily antiviral therapy. The inclusion criteria for the susceptible partner were an age of 18 years or older and HSV-2 seronegativity on Western blot analysis. The relationship between the source partner and the susceptible partner was required to be monogamous. Both partners were required to be immunocompetent and in good health and the couple to be using effective contraception.

### STUDY DESIGN

The partners signed separate informed-consent forms that had been approved by local institutional review boards. The partners were seen together at the screening visit, separately at randomization, and at monthly intervals during the eight-month study

period. The HSV-2–seropositive partners were randomly assigned, in a 1:1 ratio, to 500 mg of valacyclovir once daily or to matching placebo.<sup>23</sup> At each visit, safer sex practices, including the use of condoms during sexual intercourse, were discussed with each partner, and standardized counseling was provided when signs and symptoms of genital herpes were recognized.<sup>24</sup> Condoms were provided free of charge to all participants in the trial throughout the study period. For the source partner, adverse experiences and recurrences of genital herpes were recorded on diary cards and reviewed at each clinic visit. The source partners were asked to come to the clinic during recurrences for which episodic therapy with valacyclovir (500 mg twice a day) for five days was offered.<sup>25</sup> After the five-day course of valacyclovir had been completed, the source partner resumed taking the randomly assigned medication.

Source partners at four centers were invited to participate in a substudy to define the frequency of reactivation of HSV-2 infection in the genital region. Participants in this substudy were instructed on how to swab the genital secretions every day for two months. Women swabbed the cervicovaginal, vulvar, and perianal regions, and men swabbed the penile skin and perianal area.<sup>4,20-22,26</sup> The participants placed the swabs in polymerase-chain-reaction (PCR) buffer and delivered them to the clinic at the next scheduled visit.

During monthly visits by the susceptible partner, serum samples were collected for HSV analysis, and diaries were reviewed for notes concerning sexual activity, condom use, and symptoms suggestive of incident genital herpes during the preceding month.<sup>5</sup> The susceptible partners were instructed to visit the clinic if they observed symptoms or lesions compatible with genital herpes. Separate swabs of genital secretions were obtained for HSV culture and HSV DNA detection by PCR and were shipped to the central laboratory at the University of Washington.<sup>27,28</sup> If new genital herpes was clinically diagnosed, patients were offered treatment with a licensed dose of valacyclovir.<sup>29</sup>

### STUDY END POINTS

Acquisition of HSV-2 infection was defined as the isolation of HSV-2 in culture, the detection of HSV-2 DNA, or HSV-2 seroconversion in the susceptible partner during the course of the trial.<sup>2,5,8,15,16</sup> Clinically symptomatic genital herpes was defined according to the presence of clinical signs and symptoms and was confirmed by isolation of HSV-2 in

culture, detection of HSV-2 DNA by PCR, or HSV-2 seroconversion. An end-points committee, whose members were blinded to the treatment assignment, reviewed all cases of genital herpes clinically diagnosed during the study. This committee also reviewed all cases in which the susceptible partner had an abnormal genital symptom or sign during the study, as well as all cases of genital herpes confirmed by laboratory analysis.

#### LABORATORY ANALYSES

All serum was sent to the central laboratory. Serum samples obtained at the time of screening, at the time of randomization, and at one month and eight months were run in parallel on Western blots. Seroconversion was defined according to previously published criteria — namely, the development of one to four new bands, including bands corresponding to HSV-2 glycoprotein G type 2 (gG2) or to HSV type 1 (HSV-1) glycoproteins, such as glycoprotein G type 1 (gG1).<sup>5,8,15</sup> Cultures and PCR analyses for HSV were performed as previously described.<sup>4,26-28</sup> All isolates from susceptible partners who acquired HSV-2 were tested for their susceptibility to acyclovir by the plaque-reduction assay.<sup>30</sup>

#### STATISTICAL ANALYSIS

The predefined primary end point was a laboratory-confirmed, clinically symptomatic first episode of genital HSV-2 infection in the susceptible partner. Secondary end points included the time to overall HSV-2 acquisition (i.e., the occurrence of the primary end point, HSV-2 seroconversion in the susceptible partner, or both) and the time to a first recurrence of genital HSV-2 in the source partner. A 3 percent rate of clinically symptomatic genital herpes (annualized rate, 5 percent) was assumed for placebo.<sup>15</sup> Because this study was designed to detect a 75 percent difference between valacyclovir and placebo in the rates of clinically symptomatic disease, we estimated that 28 confirmed cases of genital HSV-2 infection were required for 90 percent power with a two-tailed test of proportions at the 5 percent significance level.<sup>31</sup> It was estimated that random assignment of 750 couples to each treatment group would achieve these assumptions. Randomization was performed at a central site in blocks of 10 to ensure balance between the groups. Randomization was stratified according to the sex and HSV-1 status of the susceptible partners.

The two study groups were compared with respect to the primary end point with use of the strat-

ified version of Fisher's exact test.<sup>32</sup> Analyses included data from all the subjects who had been randomly assigned to a study group and who took at least one dose of medication. No interim analyses were planned or conducted. The study groups were compared with respect to time-to-event end points with use of the log-rank test, with stratification according to the susceptible partner's sex and HSV-1 status on screening. Hazard ratios were calculated by means of the Cox proportional-hazards model, with covariates defined according to stratum and treatment. Data for subjects who did not reach an end point were censored as event-free periods ending on the last day that the absence of the end point was confirmed. Interaction tests were used to determine whether there was evidence of a differential effect of valacyclovir treatment across subgroups.<sup>33</sup> All reported P values are two-sided. Analysis of the data was performed at GlaxoSmithKline, the sponsor of the study. The authors had access to the primary data, directed the analyses, and made all decisions pertaining to the manuscript and its submission for publication.

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## RESULTS

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#### DEMOGRAPHICS

The trial was initiated in February 1998, and the last couple was enrolled in July 2001. Of the 4034 screened couples, 1385 of the susceptible partners (34.3 percent) were HSV-2-positive at the time of screening and hence were ineligible, 799 of the source partners (19.8 percent) were not HSV-2-positive and hence were ineligible, and 352 couples (8.7 percent) declined to take part; hence, 1498 couples (37.1 percent), from 96 sites, proceeded to randomization. Fourteen persons (7 assigned to the valacyclovir group and 7 to the placebo group) elected not to take the study medication, leaving 1484 participating couples. Our analyses were based on data from the 1484 source partners (743 in the valacyclovir group and 741 in the placebo group) who took their assigned study medication. The number of couples at each study center varied from 1 to 141 (median, 8). Of the 1484 participating couples, 803 were in the United States, 118 in Canada, 462 in Europe, 43 in Latin America, and 58 in Australia.

Of the 1484 participating couples, 1159 (78.1 percent) completed the study. Reasons for withdrawal among the remaining 325 couples were based on the source partner's reason and included 82 who withdrew voluntarily (28 assigned to valacy-

clovir and 54 to placebo), 99 who were lost to follow-up (53 and 46, respectively), 66 whose relationship was dissolved (33 and 33, respectively), 16 who had an adverse event (11 and 5, respectively), 16 for whom there were protocol violations (8 and 8, respectively), 13 who decided to attempt pregnancy (6 and 7, respectively), 9 who reported frequent recurrences while taking the study medication (1 and 8, respectively), and 24 who withdrew for other reasons (18 and 6, respectively). The total number of withdrawals and the reasons for withdrawal were similar for the couples whose source partner was assigned to take valacyclovir (21 percent) and those whose source partner was assigned to take placebo (23 percent). However, voluntary withdrawal was more frequent among source partners who were randomly assigned to placebo than among those who were randomly assigned to valacyclovir (54 vs. 28,  $P=0.003$ ), probably because of the frequent recurrences among the placebo-treated source partners.

Among the 1484 HSV-2-susceptible subjects, 488 (32.9 percent) were the female partners of men with HSV-2 infection (Table 1). Of these women, 383 were seropositive for HSV-1 (78.5 percent). Of

the 996 susceptible partners who were men, 641 were HSV-1-seropositive (64.4 percent).

Compliance with the medication regimen was high. Overall, 1042 of the 1484 source partners (70.2 percent) reported taking at least 95 percent of the prescribed doses.

#### ACQUISITION OF HSV INFECTION AND DISEASE

The end-points committee reviewed data from 71 susceptible partners in whom genitourinary signs and symptoms compatible with new genital herpes developed during the course of the study. Twenty had clinical and laboratory evidence of genital HSV-2 infection associated with these symptoms: in 15 (2 taking valacyclovir and 13 taking placebo) HSV-2 seroconversion (with or without detection of virus) confirmed the diagnosis, and in 5 (2 valacyclovir and 3 placebo) the diagnosis was confirmed by viral culture or HSV PCR only. Of the remaining 51 susceptible partners with genitourinary symptoms, 3 (2 valacyclovir and 1 placebo) had seroconversion to HSV-2 positivity during the study; however, the seroconversion predated the reported symptoms, and hence the new infection was believed to be asymptomatic. In the remaining 48 susceptible partners with genitourinary symptoms, the symptoms were rejected as end points because none of the susceptible partners had laboratory evidence of genital herpes. The source partners of these 48 subjects were almost equally divided between the placebo group (with 25) and the valacyclovir group (with 23). Of the 1413 susceptible partners who did not have symptoms, 18 had seroconversion to HSV-2 and 4 had seroconversion to HSV-1. Thus, a total of 41 HSV-2 infections and 4 HSV-1 infections were detected during the study period. Of these 45 documented infections, 14 were acquired by the sexual partners of subjects who were taking valacyclovir, as compared with 31 partners of subjects who were taking placebo (Table 2 and Fig. 1A).

Of the 41 HSV-2 infections, 20 were associated with symptomatic new genital herpes (the primary end point of the study) and 21 with seroconversion only (Table 2). Of the 20 symptomatic acquisitions of HSV-2, 16 occurred among the 741 partners of placebo recipients (2.2 percent), as compared with 4 among the 743 partners of valacyclovir recipients (0.5 percent) (relative risk, 0.25; 95 percent confidence interval, 0.08 to 0.74;  $P=0.01$ ). The time to development of a symptomatic first episode of genital herpes was significantly longer among the partners of valacyclovir recipients than among the partners

**Table 1. Demographic and Clinical Characteristics of the HSV-2-Infected (Source) Partners and the HSV-2-Seronegative Susceptible Partners, According to the Source Partner's Treatment Assignment.**

Characteristic	Valacyclovir (N=743)	Placebo (N=741)
<b>Source partners</b>		
Age — yr		
Median	35	34
Range	18–75	19–65
Female sex — no. (%)	499 (67.2)	497 (67.1)
White race — no. (%)	666 (89.6)	672 (90.7)
Seropositive for HSV-1 and HSV-2 — no. (%)	380 (51.1)	397 (53.6)
Duration of genital HSV infection — yr		
Median	8	7
Range	0–37	0–51
<b>Susceptible partners</b>		
Age — yr		
Median	35	34
Range	18–74	18–76
Female sex — no. (%)	244 (32.8)	244 (32.9)
White race — no. (%)	664 (89.4)	666 (89.9)
Seronegative for HSV-1 and HSV-2 — no. (%)	225 (30.3)	226 (30.5)
Duration of current sexual relationship — yr		
Median	2	2
Range	0–52	0–41

of placebo recipients (Fig. 1B). When we evaluated all 41 cases of HSV-2 acquisition, we found that HSV-2 had been acquired by 27 of the susceptible partners of placebo recipients (3.6 percent) as compared with 14 of the susceptible partners of valacyclovir recipients (1.9 percent) (hazard ratio, 0.52; 95 percent confidence interval, 0.27 to 0.99;  $P=0.04$ ) (Table 2 and Fig. 1C). More female partners than male partners of placebo-treated subjects acquired HSV-2 infection (7.4 percent vs. 1.8 percent) (Table 3 and Fig. 1D). Time-to-event analysis revealed no evidence of a significant difference in treatment effect between susceptible female and male partners ( $P=0.73$  by the interaction test) (Fig. 1D).

#### HSV REACTIVATION AND SHEDDING AMONG SOURCE PARTNERS

Among the 741 source partners assigned to take placebo, 573 reported a genital recurrence during the study (77.3 percent), as compared with 288 of the 743 assigned to take valacyclovir (38.8 percent) ( $P<0.001$ ). Valacyclovir significantly prolonged the time to a first recurrence (hazard ratio, 0.30; 95 percent confidence interval, 0.26 to 0.35;  $P<0.001$ ). The mean rate of recurrence was 0.40 per month among the source partners taking placebo as compared with 0.11 per month among those taking valacyclovir ( $P<0.001$ ).

The 89 source partners participating in the shedding substudy (68 women and 21 men) collected daily samples of genital secretions for a median of 58 days. Overall, HSV was detected by PCR on 2.9 percent of the days among the 39 source partners taking valacyclovir as compared with 10.8 percent of the days among the 50 source partners taking placebo ( $P<0.001$ ). Shedding was detected in 19 of 39 valacyclovir-treated partners (48.7 percent), as compared with 41 of 50 placebo-treated partners (82.0 percent) (relative risk, 0.60; 95 percent confi-

dence interval, 0.43 to 0.83;  $P=0.002$ ). The difference in shedding was seen in both men and women. In only 3 of 39 valacyclovir-treated source partners (7.7 percent) was HSV DNA detected on at least 10 percent of the days, as compared with 25 of 50 placebo-treated source partners (50.0 percent,  $P<0.001$ ) (Fig. 2A). Shedding occurred on 3.3 percent and 0.9 percent of the days among the valacyclovir-treated women and men, respectively, as compared with 11.4 percent and 9.2 percent of the days among placebo-treated women and men. The median number of genome copies of HSV DNA from positive mucosal-swab specimens was  $1 \times 10^{3.1}$  in the valacyclovir group and  $1 \times 10^{5.4}$  in the placebo group ( $P<0.001$ ) (Fig. 2B).

#### SEXUAL ACTIVITY, CONDOM USE, AND COVARIATES OF TRANSMISSION

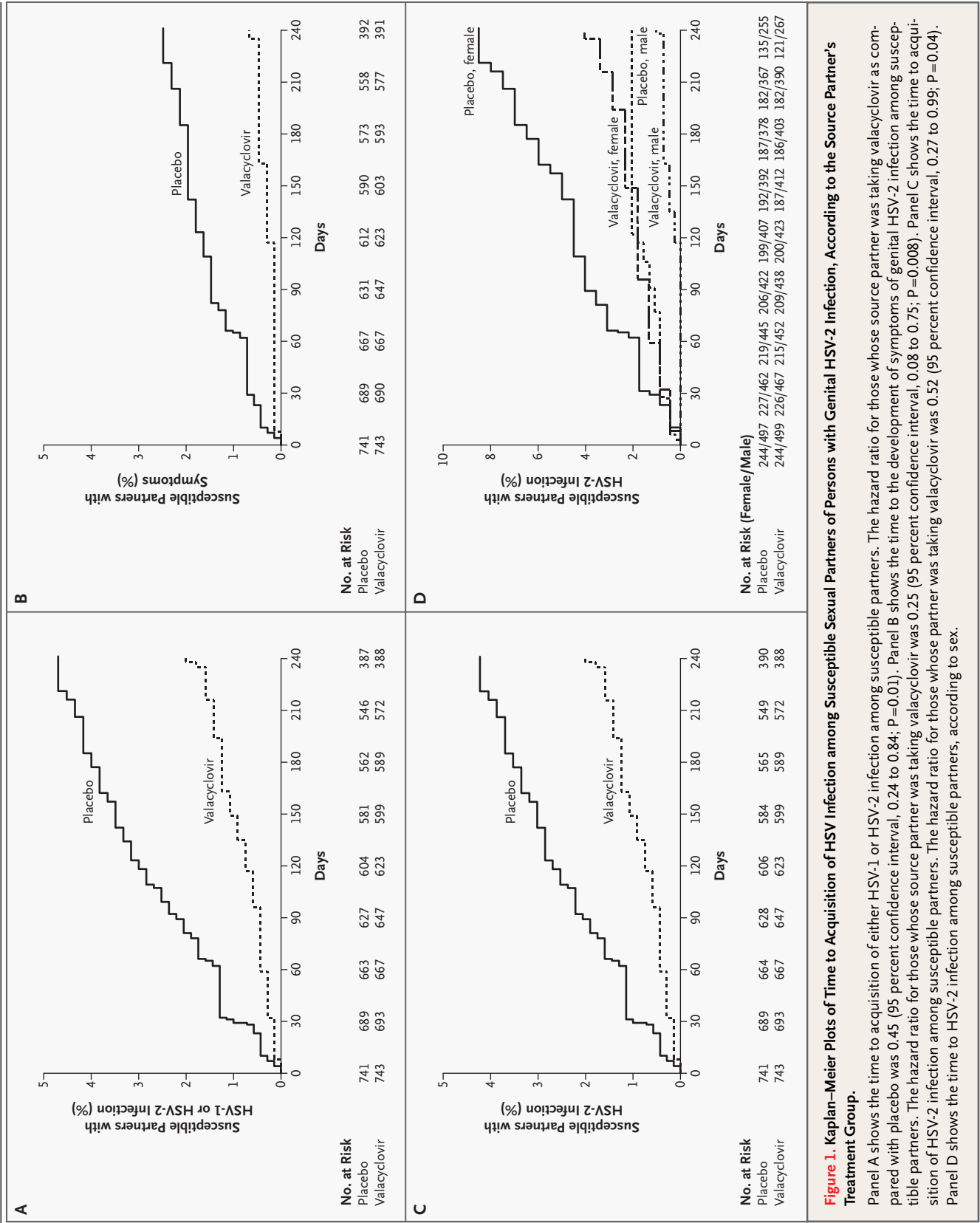
The median number of sexual contacts per couple during the study was 49 in the valacyclovir group and 46 in the placebo group (range, 0 to 482). The frequency of genital HSV-2 acquisition increased with the reported frequency of sexual activity and was 0.35 per 1000 sexual contacts among the susceptible partners of valacyclovir recipients, as compared with 0.68 per 1000 sexual contacts among the susceptible partners of placebo recipients. The respective rates of acquisition among susceptible women were 0.60 and 1.27 per 1000 sexual contacts and, among susceptible men, 0.23 and 0.35 per 1000 sexual contacts.

Despite counseling, 37 percent of the couples reported at each monthly visit that they never used condoms for vaginal or anal intercourse at all during the study, 20 percent reported that they used condoms more than 90 percent of the time, and 43 percent reported that they used them between 1 and 90 percent of the time. Although rates of transmission of HSV-2 were lower in the valacyclovir group

**Table 2.** Acquisition of HSV Infection among the Susceptible Partners, According to the Source Partner's Treatment Assignment.\*

Variable	Valacyclovir (N=743) no. (%)	Placebo (N=741) no. (%)	Total No.	Hazard Ratio (95% CI)	P Value
Acquisition of symptomatic HSV-2 infection	4 (0.5)	16 (2.2)	20	0.25 (0.08–0.75)	0.008
Overall acquisition of HSV-2 infection	14 (1.9)	27 (3.6)	41	0.52 (0.27–0.99)	0.04
Acquisition of HSV-1 or HSV-2 infection	14 (1.9)	31 (4.2)	45	0.45 (0.24–0.84)	0.01

\* P values were calculated with the log-rank test. CI denotes confidence interval.



**Figure 1. Kaplan-Meier Plots of Time to Acquisition of HSV Infection among Susceptible Sexual Partners of Persons with Genital HSV-2 Infection, According to the Source Partner's Treatment Group.**

Panel A shows the time to acquisition of either HSV-1 or HSV-2 infection among susceptible partners. The hazard ratio for those whose source partner was taking valacyclovir as compared with placebo was 0.45 (95 percent confidence interval, 0.24 to 0.84;  $P=0.01$ ). Panel B shows the time to the development of symptoms of genital HSV-2 infection among susceptible partners. The hazard ratio for those whose source partner was taking valacyclovir was 0.25 (95 percent confidence interval, 0.08 to 0.75;  $P=0.008$ ). Panel C shows the time to acquisition of HSV-2 infection among susceptible partners. The hazard ratio for those whose partner was taking valacyclovir was 0.52 (95 percent confidence interval, 0.27 to 0.99;  $P=0.04$ ). Panel D shows the time to HSV-2 infection among susceptible partners, according to sex.

than in the placebo group for all levels of condom use (Table 3), there was considerable overlap between the groups in the rates of acquisition (see Supplementary Appendix 1, available with the full text of this article at [www.nejm.org](http://www.nejm.org)).

Exploratory covariate analyses were performed for both clinical and overall HSV-2 acquisition. Condom use was defined as a time-dependent covariate. In these multivariate analyses, factors found to influence the risk of HSV-2 transmission significantly were female sex of the susceptible partner, greater number of sexual contacts, and shorter duration of genital herpes in the source partner (Tables 3 and 4). There was no evidence that valacyclovir had a reduced therapeutic effect when efficacy was examined among subgroups defined by these covariates.

#### ADVERSE EFFECTS AND SUSCEPTIBILITY OF ISOLATES FROM CASES OF ACQUISITION

The frequency of adverse effects was similar in the placebo and valacyclovir groups and was similar to those reported in studies of valacyclovir in immunocompetent persons with genital herpes.<sup>23,25,29</sup> No serious adverse events were considered by the investigators to be related to use of the study medication. HSV-2 isolates were available for sensitivity testing from 11 of the 20 cases of symptomatic new infection. All 11 isolates were sensitive to acyclovir, with plaque-neutralization titers of less than 0.2 µg per milliliter.<sup>30</sup>

#### DISCUSSION

Our study demonstrates that oral valacyclovir taken by immunocompetent persons with recurrent genital HSV-2 infection significantly reduces the rates of HSV reactivation, subclinical shedding, and transmission of genital herpes to a susceptible partner. A 500-mg dose of valacyclovir taken once daily reduced the risks of acquisition of symptomatic genital herpes and acquisition of HSV-2 infection overall by susceptible, HSV-2-seronegative heterosexual partners. The results of the trial demonstrate the effectiveness of treating the source partner with an antiviral agent to reduce the risk of transmission of a sexually transmitted viral disease. The results were in addition to any effects that may have been attributable to counseling or safer-sex practices used by the study population.

People with genital herpes and their sexual partners consider the transmission of this infection their chief concern.<sup>17</sup> Adding to this concern are data

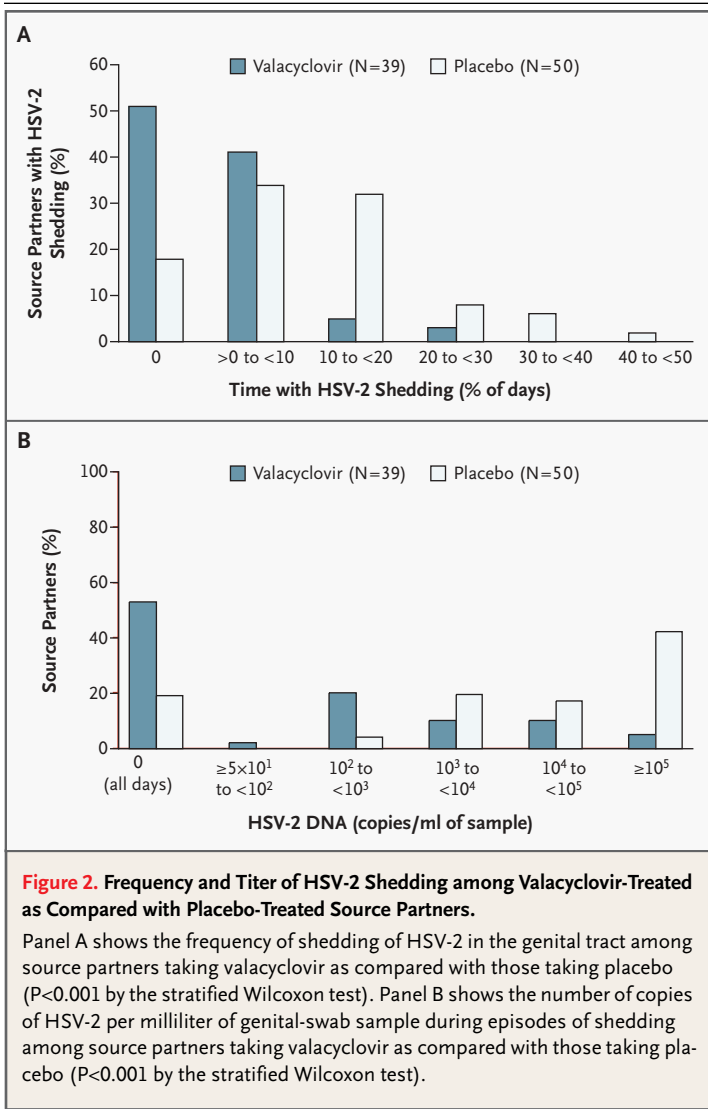
**Table 3. Rates of Transmission of HSV-2 Infection to Susceptible Partners, According to Risk Stratum.**

Variable	Valacyclovir (N=743)	Placebo (N=741)
	<i>no. who acquired HSV-2/ total no. (%)</i>	
Overall	14/743 (1.9)	27/741 (3.6)
Sex of susceptible partner		
Female	8/244 (3.3)	18/244 (7.4)
Male	6/499 (1.2)	9/497 (1.8)
HSV-1 status of susceptible partner		
Positive	10/517 (1.9)	19/514 (3.7)
Negative	4/226 (1.8)	8/227 (3.5)
Duration of genital HSV-2 infection in source partner*		
<2 yr	4/127 (3.1)	8/137 (5.8)
≥2 yr	10/613 (1.6)	19/602 (3.2)
Duration of relationship*		
<2.5 yr	10/401 (2.5)	21/409 (5.1)
≥2.5 yr	4/336 (1.2)	6/326 (1.8)
Frequency of condom use*†		
Never	4/274 (1.5)	11/250 (4.4)
Sometimes	7/288 (2.4)	12/313 (3.8)
Nearly always	3/141 (2.1)	4/140 (2.9)
Sexual contacts per month*		
≤5	1/225 (0.4)	6/257 (2.3)
>5 to 10	6/310 (1.9)	8/261 (3.1)
>10	7/176 (4.0)	13/191 (6.8)

\* The percentages are based on the number of couples for whom data were available.

† The categories represent combined monthly reported use during the eight-month study period; "sometimes" means 1 to 90 percent of the time and "nearly always" more than 90 percent of the time.

showing that HSV-2-seropositive persons have an increased risk of infection with the human immunodeficiency virus<sup>11-14,34</sup> and that new HSV-2 infection during late pregnancy poses a high risk of transmission of HSV-2 to the neonate.<sup>35</sup> Condoms are partially effective in reducing HSV-2 transmission and, along with abstinence during outbreaks, should continue to be recommended.<sup>36</sup> Our trial was conducted among couples who received monthly counseling about the use of condoms for reducing the risk of transmission of HSV-2 infection and other sexually transmitted infections and who were offered free condoms. Yet, 37 percent of the couples reported no condom use during the trial. Covariate analyses accounting for reported condom use indicated that valacyclovir use continued to be associated with reduced rates of transmission. The lowest observed rates of transmission were among couples who reported that they almost always used condoms and in whom the source partner was taking valacy-



clovir. However, our study does not allow us to define what levels of condom use in combination with valacyclovir therapy provide optimal or suboptimal protection.

We studied persons with recurrent genital herpes who were already candidates for antiviral suppression. Prevention of transmission of HSV infection is an added benefit to the relief of clinically symptomatic disease in such persons. According to the overall rate of HSV-2 acquisition that we observed and the 48 percent reduction in risk with valacyclovir, one would expect to treat 38 persons with recurrent genital herpes for a year to prevent one case of HSV-2 infection in a susceptible partner. However, this number varies according to the sex of the sus-

ceptible partner, frequency of condom use, duration of the relationship, and other variables that influence the likelihood of transmission. Thus, in our study, the annualized number needed to treat is 11 for couples in which the susceptible woman's partner will not use condoms and 24 for couples with the highest level of sexual activity.

The frequency of acquisition of HSV-2 infection in our trial was lower than in trials of HSV-2 acquisition conducted in observational cohorts and other discordant partnerships, probably because of the low biologic risk of infection among long-standing couples, the high proportion of susceptible male participants, and the extensive counseling we performed.<sup>7,15,16,37,38</sup> If one used the annualized incidence of 11.4 percent, derived from a recent trial of vaccination to prevent HSV infection in seronegative subjects,<sup>16</sup> the overall number of persons needed to treat would be 18 to prevent one transmission. If one used data from an observational cohort study of susceptible pregnant women with HSV-2–seropositive partners, the number needed to treat would be 11.<sup>37</sup> The lower rate of transmission from HSV-2–infected women to men makes this figure two to three times higher in discordant couples in which the susceptible partner is female.

To what extent can we extrapolate both the biologic and cost-effectiveness aspects of the data in this study to other settings? It is likely that the transmission effects we found are applicable to nonmonogamous heterosexual couples. Valacyclovir is effective in suppressing genital herpes in men who have sex with men.<sup>39</sup> However, as shown in the trial, sexual transmission is influenced by sexual behavior and biologic factors. Most instances of HSV-2 transmission occur with source partners who do not have a history of genital herpes,<sup>5,15,38</sup> and few studies describing daily antiviral medication in such persons are available. Additional studies to evaluate whether suppressive therapy will prevent transmission among couples with a source partner with subclinical HSV-2 infection, couples in whom the susceptible partner is immunocompromised, and homosexual couples should be undertaken. Studies in which the susceptible partner is pregnant are of special importance because of the high risk of acquisition of HSV-1 or HSV-2 infection in this setting. The few cases of asymptomatic HSV-1 acquisition in this study were not sufficient to allow us to determine whether valacyclovir would reduce the risk of HSV-1 transmission.

**Table 4. Covariate Analyses of Factors Influencing the Transmission of Genital Herpes.\***

Covariate	Acquisition of Symptomatic HSV-2 Infection		Overall Acquisition of HSV-2 Infection	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Valacyclovir (vs. placebo)	0.25 (0.08–0.75)	0.01	0.52 (0.27–0.99)	0.05
Susceptible partner female	3.30 (1.31–8.28)	0.01	3.50 (1.82–6.73)	<0.001
Susceptible partner HSV-1–negative	1.64 (0.64–4.17)	0.30	1.31 (0.66–2.61)	0.44
Less frequent condom use at time of acquisition†	1.70 (0.95–3.05)	0.08	1.18 (0.82–1.69)	0.38
More frequent sexual contacts during study‡	1.83 (0.97–3.43)	0.06	1.73 (1.12–2.67)	0.01
Duration of HSV-2 infection in source partner <2 yr (vs. ≥2 yr)	2.89 (1.12–7.49)	0.03	2.06 (1.03–4.12)	0.04
Duration of relationship <2.5 yr (vs. ≥2.5 yr)	3.18 (0.89–11.33)	0.08	1.87 (0.89–3.93)	0.10

\* CI denotes confidence interval.

† The categories were “never,” “sometimes,” and “nearly always”; the hazard ratio is for the comparison with the next category (more frequent condom use).

‡ The categories were ≤5, >5 to 10, and >10 contacts per month; the hazard ratio is for the comparison with the next category (less frequent sexual contacts).

Because the observed reduction in the rate of transmission of genital herpes with valacyclovir is clinically relevant but not complete, it is important that disclosure of genital herpes to the susceptible partner and the practice of safer sex continue, since both may reduce the risk of transmission of genital herpes.

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#### APPENDIX

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