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# Effect of Condoms on Reducing the Transmission of Herpes Simplex Virus Type 2 From Men to Women

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RECENT ESTIMATES INDICATE that 22% of persons who are older than 12 years in the United States are infected with herpes simplex virus type 2 (HSV-2).<sup>1</sup> Except for rare perinatal acquisition, HSV-2 infections are acquired by contact with infected secretions during sexual encounters.<sup>2</sup> No prospective studies have been done on the effect of condoms on reducing HSV-2 transmission. As HSV can be shed from both mucosal and skin surfaces, concern has been raised regarding the ability of condoms to reduce sexual transmission of the virus.<sup>3</sup>

A recent study of an investigational vaccine for prevention of HSV-2 infection failed to show protection from HSV-2 acquisition among vaccinated susceptible persons in sexually active couples in which 1 partner had HSV-2 infection and 1 did not.<sup>4</sup> We used the demographic and behavioral data ob-

**Context** Herpes simplex virus type 2 (HSV-2) is one of the most common sexually transmitted infections in the United States. No prospective study has shown the ability of condoms to reduce transmission of HSV-2.

**Objective** To evaluate risk factors for HSV-2 acquisition and efficacy of condoms in prevention of HSV-2 transmission.

**Design** Analysis of data from a randomized, double-blind, placebo-controlled trial conducted December 13, 1993, to June 28, 1996, of an ineffective candidate HSV-2 vaccine with 18 months of follow-up.

**Setting** Eighteen clinical trial centers in the United States.

**Participants** A total of 528 monogamous couples discordant for HSV-2 infection, including an HSV-2-susceptible population of 261 men and 267 women.

**Main Outcome Measure** Acquisition of HSV-2 infection by susceptible partners, compared with those remaining free of HSV-2 with regard to demographic characteristics, sexual activity, and condom use.

**Results** Twenty-six women (9.7%) vs 5 men (1.9%) acquired HSV-2, for a rate per 10000 sex acts (episodes of sexual intercourse) of 8.9 vs 1.5, respectively ( $P < .001$ ). In multivariable analysis, younger age (adjusted hazard ratio [HR] per 5 years, 1.57; 95% confidence interval [CI], 1.22-2.04), seropositivity for HSV-1 and HSV-2 vs HSV-2 alone in the source partner (adjusted HR, 2.34; 95% CI, 1.14-4.82), and more frequent sexual activity (adjusted HR per additional sex act per week, 1.10; 95% CI, 1.01-1.19) were associated with higher risk of HSV-2 acquisition. Condom use during more than 25% of sex acts was associated with protection against HSV-2 acquisition for women (adjusted HR, 0.085; 95% CI, 0.01-0.67) but not for men (adjusted HR, 2.02; 95% CI, 0.32-12.50). Risk of HSV-2 transmission declined from 8.5 per 100 person-years in the initial 150-day interval to 0.9 per 100 person-years in the final 150-day interval ( $P = .002$  for trend), concurrent with a decrease in sexual activity and proportion of sex acts occurring when the source partner had genital lesions.

**Conclusions** Condom use offers significant protection against HSV-2 infection in susceptible women. Changes in sexual behavior, correlated with counseling about avoiding sex when a partner has lesions, were associated with reduction in HSV-2 acquisition over time. These data suggest that identification of discordant couples can reduce transmission of HSV-2, especially for heterosexual couples in which the male partner has HSV-2 infection.

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See also Patient Page.

tained from that study to examine risk factors for HSV-2 acquisition among 528 HSV-2 seronegative vaccine or placebo recipients who were monoga-

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mous partners of persons with recurrent symptomatic genital HSV-2 infection. As a longitudinal study of HSV-2 discordant couples, the trial was a good model to examine the effectiveness of other prevention methods.

## METHODS

### Study Population

The subjects of this study were participants in 1 of 2 concurrent double-blind, randomized, placebo-controlled efficacy trials of a recombinant HSV subunit vaccine (containing HSV-2 glycoproteins D and B) for protection against HSV-2 acquisition.<sup>5</sup> Briefly, the study participants were recruited by advertising at 18 clinical trial centers; median recruitment of 19 participants per center, with 2 centers recruiting 41% of participants. Institutional review board approval was obtained by each center, and all participants gave written informed consent.

Healthy, HSV-2 seronegative, and human immunodeficiency virus (HIV) seronegative adults were eligible for participation if in a monogamous relationship for at least 6 months with an HSV-2 seropositive person with recurrent genital herpes. Initial serologies were performed at the screening visit. The potential source partners were seen once to document the history of genital herpes and serologic status. The susceptible partners had 11 routinely scheduled visits during the 18-month study. Enrollment into the study and the first immunization were scheduled within a month of the screening visit. Procedures during visits included immunizations (month 0, 1, and 6), and safety and immunogenicity assessments. Serum samples were obtained for HSV antibody testing at each visit. The enrollment criteria required that 25% of susceptible partners were women seronegative for HSV-1 as well as HSV-2, as previous studies had suggested that their risk of HSV-2 acquisition was particularly high.<sup>6</sup>

Standard demographic and sexual history information was collected from susceptible partners at study entry. For the duration of the study, the sus-

ceptible partner maintained a daily log of sexual contact with the source partner and any other partners, which was used to summarize sexual activity between visits. The information gathered included number of times the subject had sexual intercourse termed *sex acts* (defined as penile-vaginal or penile-rectal contact), whether condoms were used, number of times the subject had sex when the source partner had lesions, use of acyclovir by the source partner, and number of new partners. Diaries were reviewed with the subjects at each clinic visit and the entries were summarized in the case report forms. At each visit, clinicians counseled the participants to abstain from sex if the source partner had a genital herpes recurrence and to use condoms at all other times. However, consistent condom use by the male source or male susceptible partner was not required for study participation. Episodic antiviral therapy for treatment of recurrences in the source partner was allowed. Chronic daily antiviral therapy by the source partner was an exclusion criterion for study entry, and only 18 (3.4%) participants reported such use by their partners during the study. These subjects were retained in the analysis.

Susceptible partners were evaluated in clinic for all genital complaints. If genital herpes was suspected, viral cultures were obtained and serologies were drawn at that visit and approximately 6 weeks later. Acquisition of genital herpes was the end point of the study.

### Laboratory Methods

Western blot was used to establish initial HSV serostatus at entry into the study and to document seroconversion.<sup>7,8</sup> The serum samples from HSV-2 seronegative subjects were preabsorbed using Sepharose 4B beads (Sigma, St Louis, Mo) containing glycoproteins B<sub>2</sub> and D<sub>2</sub> to remove antibodies against the vaccine proteins, as previously described.<sup>4,9</sup> All serologic tests were performed at the University of Washington, Seattle. Viral cultures,

with typing, were done as needed at local laboratories of participating sites, using standard techniques.<sup>10,11</sup>

### Statistical Methods

Time of acquisition of HSV-2 was defined as the date of the first positive culture or the estimated date of seroconversion by Western blot, calculated as the midpoint between the date of the last negative Western blot results and the first positive Western blot results. For this study, we evaluated all HSV-2 acquisitions from the time of screening to study termination, regardless of whether the subject received any immunizations. Thus, this article includes 16 persons not included in the vaccine efficacy analysis<sup>4</sup> who had HSV-2 infection at entry (n=9) or lacked any follow-up (n=7), but excludes 3 people who were not monogamous at study entry. For select analyses, we subdivided the observation time into 4 intervals of 150 days: days 0 to 150, days 151 to 300, days 301 to 450, and day 451 to study termination. The person followed up longest was seen on day 641; however, 98% of the participants were last seen by day 604, thus the time intervals were all similar in duration.

Reported frequency of sex acts was used to calculate average sexual exposures per week for each 150-day interval that the person was in the study. As contact with an active genital sore has been hypothesized as a risk factor for transmission, we classified each time interval in the study as to whether there was sexual activity when genital lesions were present. Condom use during each time interval was categorized as more than 25% vs 25% or less. This value was chosen as it was close to the median reported condom use and few subjects reported condom use between 25% and 100%. The source partner's use of acyclovir, as reported by the susceptible partner, was categorized as yes or no for each time interval. As suggested by prior analysis,<sup>4</sup> receipt of vaccine vs placebo did not influence the variables of interest ( $P=.53$ ) and was not included in the models shown.

Kaplan-Meier plots and log-rank tests were used to investigate the influence of baseline variables on time to acquisition of HSV-2. Participants who did not acquire HSV-2 and remained in a monogamous sexual relationship with the source partner were censored at the date of last follow-up. Susceptible persons who changed or added partners, or discontinued the original relationship, were censored at the time of the resolution of the original monogamous relationship, even if the new partner also had genital herpes. This was done because new partners were not asked to come to the clinic for serologic testing. A proportional hazards model was used to investigate both the effects of baseline data and of the time-dependent covariates that changed at each 150-day interval on HSV-2 acquisition. Models were stratified by gender, as the assumption of proportional hazards was not justified for this variable. Poisson regression for grouped survival data was used to examine the decreasing trend in rate of acquisition over time. Confidence intervals (CIs)

given are Wald 95% CIs and *P* values are based on likelihood ratio (LR) tests. Statistical analyses were computed using S-PLUS statistical software (Version 4.5, MathSoft Inc, Seattle, Wash). All reported *P* values are 2-tailed.

**RESULTS**

Five hundred twenty-eight monogamous couples were enrolled in the study. The HSV-2-susceptible population included 261 men and 267 women. The median age of the HSV-2-susceptible partners was 36 years; most were white (92%) and most were currently in heterosexual relationships (98%). Forty-one percent of susceptible participants were HSV seronegative and 59% had antibody to HSV-1. As the study required monogamy for 6 months prior to enrollment, most patients were in long-term relationships with a median duration of 18 months. At baseline, the subjects reported a median frequency of sex acts of twice per week in the month prior to enrollment. When asked to estimate the percentage of time condoms were used

during the subject's lifetime, half reported condom use of 10% or less.

Among the source partners, 329 (62%) had HSV-2 infection only and 199 (38%) had both HSV-1 and HSV-2 infection documented by serologic testing. The median number of HSV-2 recurrences was 3 (range, 0-26) in the year prior to study entry. Over the course of the study, 100 (19%) participants ended the relationship with the source partner or acquired other partners prior to the final visit. Of the 428 (81%) couples who remained monogamous, 90% completed 12 months of the study and 85% completed 18 months of the study.

**Incidence of HSV-2 Infection**

Thirty-one persons (5.9%) acquired HSV-2 infection during the observation period. As reported previously,<sup>6,12</sup> acquisition rates for women were higher than for men as 26 (9.7%) women vs 5 (1.9%) men acquired HSV-2 infection (*P*<.001)(TABLE 1). Female and male susceptible partners reported similar frequency of sexual activity during the course of the trial, with a mean of 2 sex acts per week during the study period. On a per sex act basis, the rate of HSV-2 acquisition was nearly 6 times higher for women than for men, 8.9 vs 1.5 per 10000 sex acts, respectively (Table 1).

**Baseline Characteristics Associated With Risk for HSV-2 Acquisition**

Risk factors for HSV-2 acquisition were examined in univariate and multivariable models. In univariate analyses of baseline characteristics, women were at higher risk of HSV-2 acquisition than men with a hazard ratio (HR) of 5.51 (95% CI, 2.12-14.4) (TABLE 2). Younger age was associated with higher risk of acquisition (HR, 1.48; 95% CI, 1.17-1.88 for each 5 years younger). Race other than white conferred higher risk of HSV-2 acquisition (HR, 2.68; 95% CI, 1.03-6.99). Source partners with HSV-1 and HSV-2 were more likely to transmit HSV-2 than source partners with HSV-2 alone (HR, 2.38; 95% CI, 1.17-4.86). Report of more frequent sex acts in the month prior to study entry

**Table 1.** Incidence of HSV-2 Infection in Susceptible Partners\*

	No. Infected/No. of Total (%)	HSV-2 Rate	
		100 Person-Years	10 000 Sex Acts
Women	26/267 (9.74)	8.6	8.9
Men	5/261 (1.92)	1.5	1.5
<b>Total</b>	<b>31/528 (5.87)</b>	<b>4.9</b>	<b>5.0</b>

\*HSV-2 indicates herpes simplex virus type 2.

**Table 2.** Influence of Baseline Characteristics on HSV-2 Acquisition\*

Comparison Characteristic	HR (95% CI)	
	Univariate	Adjusted†
Women vs men	5.51 (2.12-14.4)	...
Risk for each age 5 years younger	1.48 (1.17-1.88)	1.57 (1.22-2.04)
Nonwhite vs white	2.68 (1.03-6.99)	...
Susceptible person is HSV-1 seronegative vs HSV-1 seropositive	1.52 (0.75-3.08)	...
Partner is HSV-1 and HSV-2 seropositive vs HSV-2 seropositive only	2.38 (1.17-4.86)	2.34 (1.14-4.82)
Recurrence of HSV in partner ≥4 vs ≤3 times during year prior to study entry	1.83 (0.90-3.73)	...
Baseline lifetime condom use >50% vs ≤50% of sex acts	0.18 (0.02-1.32)	0.08 (0.01-0.60)
Risk for each additional sex act per week during month prior to study	1.12 (1.03-1.21)	1.10 (1.01-1.19)

\*HSV-1 indicates herpes simplex virus type 1; HSV-2, HSV type 2; HR, hazard ratio; and CI, confidence interval.

†Adjusted estimates are from a model stratified by sex, and adjusted for age, partner's serostatus, and sex acts per week. Ellipses indicate estimates for predictors that were not included in the model.

was associated with higher risk of HSV-2 acquisition (HR, 1.12; 95% CI, 1.03-1.21) for each additional sex act. More frequent genital herpes recurrences in the source partner, lower reported lifetime condom use (FIGURE), and HSV seronegativity of the susceptible partner also appeared to predict higher risk of HSV-2 acquisition but these associations did not reach statistical significance. In a multivariable analysis stratified for gender, the source partner's serostatus, age, and frequency of sex acts remained statistically significant predictors of HSV-2 acquisition. In addition, higher frequency of lifetime condom use was predictive of lower HSV-2 acquisition (HR, 0.08; 95% CI, 0.01-0.60) for participants reporting condom use for more than 50% of sex acts vs less.

**Sexual Behavior During the Study**

Information about frequency of sex acts, sex with lesions present, condom use, and antiviral therapy in the potential source partner was collected from the susceptible partner at each visit after enrollment. Of the 528 enrollees, this information was available for 502 (95%) participants. Data were not available for 9 participants who acquired HSV-2 between the screening and the enrollment visit and for 17 participants who did not return for a follow-up visit. Several sexual behavior variables changed over the course of the study. The frequency of sexual activity declined during the study period, from a mean of 2.3 sex acts per week reported during the initial 150 days of the study to a mean of 2.0, 1.7, and 1.5 per week during the subsequent 150-day intervals. Furthermore, the proportion of participants having sex when the source partner had genital lesions declined from 20% to 13% over the study period (P=.001, McNemar test). While sex when lesions were present was rare, it was reported in the interval preceding acquisition of HSV-2 by 23% of the subjects who seroconverted.

Condom use was low throughout the study, as only 61% of couples reported ever using condoms during follow-up, despite counseling at each

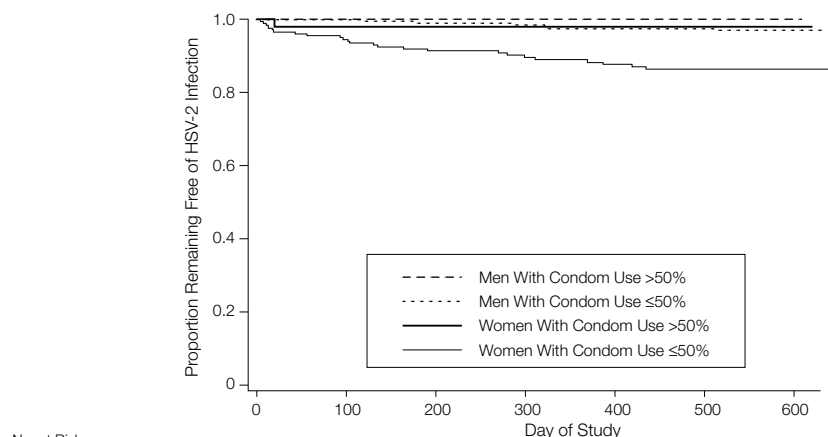
clinic visit (TABLE 3). Of 304 couples who reported condom use, 13% used condoms for each sex act, 26% used condoms for 51% to 99% of sex acts, 12% used condoms for 26% to 50% of sex acts, and 49% used condoms for 25% or fewer sex acts. Among 118 persons reporting condom use for more than 50% of sex acts, only 2 persons acquired HSV-2 infection. One man reported 100% condom use throughout the study, and another man reported 57% condom use overall, but did not use condoms in the interval preceding HSV-2 acquisition. Of the remaining 20 cases of HSV-2 acquisition on whom condom use data were available, 10 (46%) reported no condom use. Over-

all, the use of condoms declined from 27% to 21% of sex acts over the course of the study. Women at risk for HSV-2 acquisition were more likely to report condom use by their partners than were men at risk, with mean condom use during follow-up of 30% of sex acts for women vs 20% for men.

**Use of Acyclovir by the Source Partners**

Acyclovir use was reported as *episodic*, defined as use for recurrences for a period of at most 10 days, or as *suppressive*, defined as regular use independent of recurrences for a longer period of time. Episodic acyclovir was used at least once during the study by

**Figure.** Acquisition of Herpes Simplex Virus Type 2 (HSV-2) Infection



No. at Risk		0	100	200	300	400	500	600
Men	Condom Use >50%	31	25	25	24	24	22	1
	Condom Use ≤50%	230	213	196	183	175	168	5
Women	Condom Use >50%	54	47	40	36	33	31	1
	Condom Use ≤50%	213	182	171	148	137	128	5

Results are stratified by sex and are based on reported lifetime condom use at study entry.

**Table 3.** Use of Condoms by the Study Participants\*

Frequency of Condom Use	Acquisition of HSV-2		Total†
	Yes (n = 22)	No (n = 480)	
Never	10 (45.5)	188 (39.2)	198 (39.4)
Sex acts, %			
1-25	8 (36.4)	142 (29.6)	150 (29.9)
26-50	2 (9.1)	34 (7.1)	36 (7.2)
51-99	1 (4.6)	77 (16.0)	78 (15.5)
Always	1 (4.6)	39 (8.1)	40 (8.0)

\*Values expressed as number (percentage). HSV-2 indicates herpes simplex virus type 2.

†Condom use data were available on 22 of 31 persons who acquired HSV-2 during the study and 480 of 497 who did not.

232 source partners (44%). While data on the use of acyclovir for each recurrence in the source partner were not collected, acyclovir use and sex when lesions were present in the same time interval were reported at 3% of all visits. Acyclovir use was twice as frequent in time intervals when participants had sex when lesions were present vs no sex when lesions were present (38% vs 17%;  $P < .001$ ). This may reflect use of acyclovir for episodic therapy for recurrences and suggests that some patients who treat recurrences may be less likely to abstain from sex during lesional episodes.

**Effect of Condoms on Reducing HSV-2 Acquisition**

In a model stratified by gender, more frequent sexual activity conferred a significantly higher risk of HSV-2 acquisition (HR, 1.16; 95% CI, 1.05-1.28) for each additional sex act per week (TABLE 4). In a univariate analysis, sex when lesions were present increased the risk of HSV-2 acquisition but the increase did not reach statistical significance. Protection offered by the use of condoms more than 25% of the time or by the source partner's episodic acyclovir use was also not statistically sig-

nificant (HR, 0.38; 95% CI, 0.11-1.30 and HR, 0.64; 95% CI, 0.24-1.73, respectively).

In multivariable analysis, frequent sexual activity was significantly associated with higher risk of HSV-2 acquisition (HR, 1.16; 95% CI, 1.03-1.30) for each additional sex act per week, and condom use was protective (HR, 0.25; 95% CI, 0.07-0.88) for condom use more than 25% of the time. However, when the genders were examined separately, condoms appeared highly protective for women (adjusted HR, 0.085; 95% CI, 0.011-0.67) but not for men (HR, 2.02; 95% CI, 0.32-12.5). These analyses were only adjusted for age and frequency of sexual activity, as the partner's HSV-1 serostatus was no longer a significant predictor in this subset of patients.

**Declining Risk of HSV-2 Infection Over Time**

Because sexual behavior changed over the course of the study, we investigated the influence of these changes on the rate of HSV-2 acquisition at different time intervals. The rate of HSV-2 acquisition declined significantly during the study period, both when the rate was defined per each 150-day inter-

val, and when defined per sex act (TABLE 5). The acquisition rate was 8.5 per 100 person-years in the initial 150 days of the study, decreasing to 4.1 and 3.9 per 100 person-years in the middle periods, and 0.9 per 100 person-years during the final study period ( $P = .002$  for trend). The highest risk for acquisition, 26 per 100 person-years, was observed during the month between screening and initial immunization when 9 participants acquired HSV-2.

To explore the possible reasons for the decrease in HSV-2 acquisition over time, we examined the data using Poisson regression that included the same potential risk factors as well as a variable for time categorized into 150-day intervals. In a univariate model, the time interval was significantly associated with a declining risk of HSV-2 acquisition (RR, 0.57; 95% CI, 0.39-0.84;  $P = .002$ ). Estimates for other risk factors were similar to those found using Cox regression (data not shown). However, in a multivariable analysis adjusted for sexual activity during follow-up as well as age and sex, time interval became less important and borderline significant (RR, 0.69; 95% CI, 0.47-1.02;  $P = .049$ ). This indicates that at least a portion of the observed decline in the risk of HSV-2 acquisition over the course of the study can be explained by behavioral changes that occurred during the study period, specifically, by a decrease in sexual activity. These changes may have resulted from counseling messages at each visit to use condoms and avoid sexual contact when the HSV-2-seropositive partner had genital lesions.

**COMMENT**

Our study revealed several new findings about the frequency and prevention of transmission of HSV-2 infection to sexual partners. Among monogamous couples with 1 partner who had known symptomatic genital herpes and 1 who was susceptible, we showed that the rate of transmission from men to women is 8.9/10 000 sex acts. This rate is similar to that seen with sexually acquired HIV.<sup>13-15</sup> One novel aspect of our

**Table 4.** Risks During Study for HSV-2 Acquisition\*

Risk	HR (95% CI)	
	Univariate	Adjusted†
Risk for each additional sex act per week	1.16 (1.05-1.28)	1.16 (1.03-1.30)
Condom use >25% vs ≤25%	0.38 (0.11-1.30)	0.25 (0.07-0.88)
Sex when lesions present vs no sex when lesions present	2.01 (0.78-5.18)	...
Acyclovir use by source partner vs no acyclovir use	0.64 (0.24-1.73)	...

\*HSV-2 indicates herpes simplex virus type 2; HR, hazard ratio; and CI, confidence interval.  
 †Adjusted estimates are from a model stratified by sex, and adjusted for age, condom use, and sex acts per week.  
 Ellipses indicate estimates for predictors that were not included in the model.

**Table 5.** Changes in Risk of HSV-2 Acquisition During the Study\*

	Days			
	0-150	150-300	300-450	450-641†
No. of cases/No. at risk	17/528	7/446	6/391	1/363
Rate of acquisition/100 person-years	8.5	4.1	3.9	0.9
Rate of acquisition/10 000 sex acts	8.5	4.3	5.2	0.7

\*HSV-2 indicates herpes simplex virus type 2.  
 †Represents the last day of visit; 98% of participants completed the study by day 604.

study was the finding that the risk of transmission can be affected by sexual behavior. The risk increased with more frequent sexual activity, but condom use offered significant protection, at least for susceptible women.

This study is the first to document protection against HSV-2 acquisition with condom use. While recommendation for consistent condom use has been included in the Centers for Disease Control and Prevention Sexually Transmitted Disease treatment guidelines, the recommendation was based on a policy for sexually transmitted diseases in general, rather than specific data for HSV-2.<sup>16</sup> Because HSV can be shed over a large area of the genital region, it has not been clear whether condom use protects against transmission of HSV-2 as well as it protects against other sexually transmitted diseases. Our data indicate that condoms markedly reduce the risk of acquisition of HSV-2 in women, but not in men. The significant protection with condom use observed for women is in accord with shedding studies that indicate that penile skin is the most common site of HSV shedding in heterosexual men.<sup>17</sup> Thus, sheathing of the penis with a condom may effectively reduce transmission from penile skin. The lack of protection with condom use among men may reflect more likely exposure of men to female genital sites from which the virus is shed. Contact with vulvar or perianal areas, the most common sites of viral shedding in women, may be a factor in the lower effectiveness of condoms in transmission from women to men.<sup>3,17</sup> Alternatively, men may be more likely to limit condom use to situations with higher risk of acquisition, such as lesions in the source partner. This practice may obscure any benefit of condoms.

Our data allow us to estimate how many cases of HSV-2 could be averted with consistent condom use in discordant couples. In the United States, an estimated 500 000 persons acquire HSV-2 infection each year, of whom an estimated 350 000 are women.<sup>18</sup> Assuming a relative risk for HSV-2 infec-

tion of 10 for women who use condoms 25% of the time or less, more consistent condom use may avert up to 315 000 new cases of HSV-2 infection among women. Unfortunately, condom use remains infrequent in the general population.<sup>19-21</sup>

One of the unpredicted findings in our study was the reduction of HSV-2 acquisition over the time of follow-up. This reduction appears to be partly explained by alterations in sexual behavior among the study participants, and may be related to the persistent counseling messages given during the course of the study. Condom use and less frequent sexual activity were associated with reduced acquisition rates of HSV-2 infection. A reduction in sexual activity in the presence of genital lesions may also have reduced HSV-2 transmission rates over the course of the study, although these findings were inconclusive. The role of suppressive antiviral therapy in reducing the risk of sexual transmission is currently under investigation.

While changes in sexual activity and practices over the course of the study may account for alterations in acquisition rates, biological explanations of declining risk of infection are also possible. Genetic differences in the likelihood of acquisition of HSV may be present. While receptors for HSV have recently been found,<sup>22-24</sup> alleles that confer high or low susceptibility to HSV infection have not yet been identified. Furthermore, repeated mucosal exposure to HSV-2 may result in "immunization" of the person that offers at least partial protection from the infection. This form of acquired resistance has been described in HIV-uninfected persons with repeated exposure to HIV-infected partners.<sup>25-27</sup> Recently, HSV seronegative persons with T-cell responses to HSV have been reported (L.C., unpublished data, December 2000). Finally, the infectivity of the source partner is likely to wane over time, as clinical and subclinical viral shedding from the genital area declines with time from acquisition of HSV infection.<sup>3,28</sup>

Our study population differs from most HSV-2 discordant couples in several important aspects. First, in this clinical trial both partners knew that one had genital herpes and one was at risk. This knowledge of being at risk, and sufficient concern for transmission to enroll in a vaccine study, were likely to be associated with a lower risk of transmission. Second, eligibility for the study required that couples had been together for at least 6 months. A previous study has shown that the median duration of relationship prior to acquisition of genital herpes is 3 months.<sup>29</sup> Thus, the period in a relationship of highest risk for transmission was not included in this study. Our finding that the rate of acquisition was highest in the first month of follow-up supports this observation. Finally, other than condom use, these analyses do not indicate that the risk factors differ between women and men. Because few incident cases were in men, the analyses of risk factors are weighted toward women, and the estimates are less reliable for men.

In summary, our study is the first to show that use of condoms and changes in sexual behavior can reduce the transmission of genital herpes. While condom efficacy has been previously demonstrated for HIV infection,<sup>30</sup> prevention of genital herpes can now be added to reasons to use condoms for the general population. Whether this knowledge will lead to increased use of condoms is unknown. A recent survey showed that while most people correctly identify genital herpes as a common infection, few perceive themselves at risk for HSV-2 acquisition.<sup>31</sup> The availability of accurate, type-specific serologic tests for HSV-2 is likely to identify many people with previously unrecognized infection.<sup>32,33</sup> Counseling to encourage consistent condom use is appropriate for these patients, especially for men with HSV-2 infection.

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