

Knowledge of Partners' Genital Herpes Protects against Herpes Simplex Virus Type 2 Acquisition

Anna Wald,^{1,2,3,5} Elizabeth Krantz,² Stacy Selke,² Ellen Lairson,² Rhoda Ashley Morrow,² and Judy Zeh⁴

Departments of ¹Medicine, ²Laboratory Medicine, ³Epidemiology, and ⁴Statistics, University of Washington, and ⁵Program in Infectious Diseases, Fred Hutchinson Cancer Research Center, Seattle, Washington

(See the editorial commentary by Hook and Leone, on pages 6–7.)

Background. Prospective studies of herpes simplex virus type 2 (HSV-2) infection in discordant couples have shown a low rate of transmission. However, unlike partners with genital herpes in prospectively monitored couples, most persons who transmit genital herpes are not aware of having the infection.

Methods. Because HSV has a short incubation period and most persons who acquire genital herpes can identify the transmitting partner, a time-to-event design was used to assess risks of HSV acquisition among patients with newly acquired genital herpes.

Results. Among 199 persons with laboratory-documented newly acquired genital herpes, the median duration of the sexual relationship with the transmitting partner was 3.5 months, and the median number of sex acts before transmission was 40. The median time to HSV-2 acquisition was greater among participants whose partners disclosed that they had genital herpes, compared with participants whose partners did not disclose their status (270 vs. 60 days; $P = .03$). In multivariate models, having a partner who disclosed that he or she had genital herpes remained a strong protective factor against genital HSV-2 acquisition (hazard ratio, 0.48 [95% confidence interval, 0.25–0.91]).

Conclusion. These findings suggest that testing persons with HSV type-specific serologic assays and encouraging disclosure may result in a decreased risk of HSV-2 transmission to sex partners.

Although the prevalence of herpes simplex virus type 2 (HSV-2) infection has increased in the past 2 decades [1, 2], little is known about the dynamics of HSV-1 and HSV-2 transmission. Retrospective studies that evaluated source partners of persons with a first episode of genital herpes have suggested a short time between the initiation of sexual activity and infection [3]. In contrast, among stable, monogamous couples, the risk of transmission appears to be low [4, 5]. To provide a potential explanation for these apparently disparate data, we hypothesized that persons who know their HSV-2 status and disclose it to their sex partners are less likely to transmit HSV-2 than are persons who do not know their HSV-2 status. To address this question, we enrolled persons with

documented newly acquired genital herpes and assessed the characteristics of the relationship that resulted in transmission. Because HSV has a short incubation period (2–12 days), most persons with newly acquired HSV infection can accurately identify the person who transmitted the infection to them [6, 7].

PATIENTS, MATERIALS, AND METHODS

Study participants and procedures. Patients presenting to the University of Washington Virology Research Clinic or Sexually Transmitted Disease (STD) clinic in Seattle with a first episode of genital lesions consistent with herpes were invited to participate. The participants underwent clinical examination and collection of swabs (for HSV culture and polymerase chain reaction [PCR]) and blood (for detection of antibodies against HSV-1 and HSV-2). Using a standardized questionnaire, the participants were asked about the number of sex partners they had during the 4 weeks preceding the development of genital lesions and specific questions about relationships with up to the 3 most recent sex partners. Treatment with antiviral therapy and counseling were provided as recommended elsewhere [8], and blood was

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Reprints or correspondence: Dr. Anna Wald, University of Washington Virology Research Clinic, 600 Broadway, Ste. 400, Seattle, WA (annawald@u.washington.edu).

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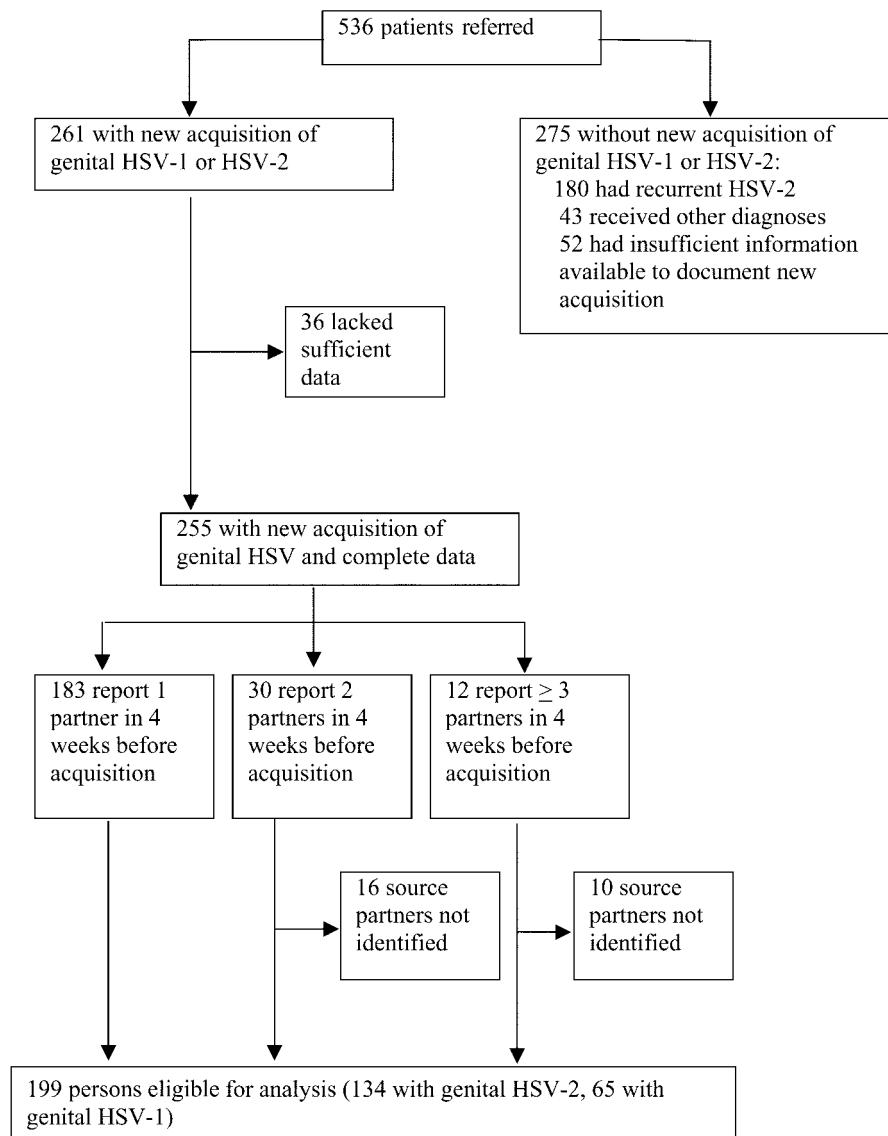


Figure 1. Study profile. HSV, herpes simplex virus.

drawn at 3 months for the detection of seroconversion to HSV [9]. None of the participants reported being HIV positive, and most had tested HIV negative in the past. The University of Washington institutional review board approved the protocol, and all participants signed a consent form.

Newly acquired genital HSV infection was defined as clinically diagnosed genital herpes with laboratory documentation of new HSV-1 or HSV-2 infection. The laboratory documentation included detection of HSV in a person who lacked antibodies to the HSV type found in genital secretions or demonstration of seroconversion to HSV-1 or HSV-2. Inclusion or exclusion of partnerships from analysis was based on a definition of transmitting partners that was specified before analysis. Sex partners were defined as transmitting partners if they were the only sex partner during the 4 weeks preceding the

development of genital herpes. Patients reporting >1 partner during that 4-week interval were included only if (1) all partners were evaluated and only 1 had virologic or serologic evidence of the infection that was transmitted or (2) all but 1 partner was evaluated and none of the partners who were evaluated had laboratory evidence of the infection that was transmitted. In that case, the single partner who was not evaluated was identified as the transmitting partner.

Laboratory methods. HSV Western blot was used to identify type-specific antibodies to HSV-1 and HSV-2 [10]. Seroconversion was identified as the acquisition of antibodies in paired serum samples. HSV culture, typing of the isolates, HSV DNA PCR, and restriction endonuclease analysis were performed as described elsewhere [11–14].

Statistical analyses. The acquisition of HSV-1 and HSV-2

Table 1. Demographic and clinical characteristics of the participants with newly acquired genital herpes simplex virus (HSV) infection.

Patient characteristic	HSV-2		HSV-1		Total (n = 199)
	Men (n = 47)	Women (n = 87)	Men (n = 25)	Women (n = 40)	
Age, median (range), years	28 (18–58)	25 (15–58)	30 (15–41)	23 (17–46)	26 (15–58)
Sexual preference					
Heterosexual	47 (100)	82 (94)	22 (88)	39 (98)	190 (95)
Homosexual or bisexual	0	4 (5)	3 (12)	1 (2)	8 (4)
Race					
White	31 (66)	63 (72)	22 (88)	31 (78)	147 (74)
African American	6 (13)	6 (7)	1 (4)	1 (2)	14 (7)
Other	10 (21)	18 (21)	2 (8)	8 (20)	38 (19)
Highest level of education					
≤High school	14 (30)	16 (18)	7 (28)	9 (23)	46 (23)
Some college	13 (28)	34 (39)	6 (24)	14 (34)	67 (34)
≥4-year college	20 (42)	37 (43)	12 (48)	17 (43)	86 (43)
Current marital status					
Never married	33 (70)	62 (71)	13 (52)	29 (73)	137 (69)
Married or living with partner	9 (19)	6 (7)	6 (24)	6 (15)	27 (14)
Other	5 (11)	19 (22)	6 (24)	5 (12)	35 (18)
Age at first sexual intercourse, median (range) years	17 (12–29)	17 (10–32)	17 (10–34)	16 (13–23)	17 (10–34)
Lifetime sex partners, no.					
≥20	22 (47)	12 (14)	6 (24)	2 (5)	42 (21)
10–19	10 (21)	34 (39)	9 (36)	10 (25)	63 (32)
7–9	5 (11)	15 (17)	6 (24)	8 (20)	34 (17)
4–6	6 (13)	19 (22)	2 (8)	14 (35)	41 (21)
1–3	4 (8)	7 (8)	2 (8)	5 (13)	18 (9)
Partners in the past 12 months, no.					
≥7	3 (6)	8 (9)	1 (4)	0	12 (6)
4–6	8 (17)	20 (23)	3 (12)	4 (10)	35 (18)
3	8 (17)	11 (13)	5 (20)	6 (15)	30 (15)
2	12 (26)	28 (32)	6 (24)	13 (33)	59 (30)
1	14 (30)	19 (22)	10 (40)	17 (42)	60 (30)
Prior history of STD	16 (34)	34 (39)	8 (32)	14 (35)	72 (36)

NOTE. Data are the no. of subjects (% of total) unless otherwise indicated; nos. may not add up to the total in the case of missing data. STD, sexually transmitted disease.

was analyzed separately but with the same methodology. The outcome—the time to acquisition of genital herpes—was defined as the number of days from the beginning of the sexual relationship with the transmitting partner until acquisition [15]. Relationships lasting >1 year were censored at 1 year. The main predictor—whether the source told the participant that he or she had genital herpes—was modeled as telling versus not telling. Kaplan-Meier curves, log-rank tests, and proportional-hazards models were used to assess relationships between the main predictor, as well as other patient characteristics, and the time to acquisition of genital herpes. Because of the study design, the main predictor was ascertained at the time of the outcome. To allow for appropriate survival modeling, we assumed that this covariate information was indicative of the baseline status, defined at the beginning of the relationship. However, we also performed a sensitivity analysis for this variable in which we reclassified subjects by their true baseline

status. Therefore, persons whose partners told them that they had genital herpes after the first time they had sex were then categorized in sensitivity analyses as not having been told.

RESULTS

Of 536 patients referred for the study, 261 (49%) had documented newly acquired genital HSV-1 or HSV-2 infection. New acquisition of genital herpes was documented by detection of HSV from genital swabs in the absence of antibody to that type of virus in 97 patients (37%), by detection of HSV and seroconversion in 104 patients (40%), and by detection of seroconversion to HSV-1 or HSV-2 in the setting of clinically compatible lesions in 24 patients (9%). Thirty-six patients (14%) with newly acquired genital herpes were excluded because they did not provide data about sex partners. Among the remaining 275 patients, 180 had a first recognized recurrence of genital

Table 2. Sexual behavior with the partner who transmitted herpes simplex virus type 1 (HSV-1) or HSV-2.

Patient characteristic	HSV-2		HSV-1		Total (n = 199)
	Men (n = 47)	Women (n = 87)	Men (n = 25)	Women (n = 40)	
Type of relationship					
Steady	35 (74)	74 (85)	24 (96)	33 (82)	166 (83)
Casual	11 (23)	12 (14)	1 (4)	7 (18)	31 (16)
Age concordance ^a					
Same age as source	16 (34)	28 (32)	4 (16)	15 (37)	63 (32)
Younger than source	12 (26)	45 (52)	6 (24)	20 (50)	83 (42)
Older than source	18 (38)	12 (14)	15 (60)	5 (13)	50 (25)
Duration of partnership resulting in transmission, median (IQR), months	4 (1–10)	3 (1–8)	3.3 (2–9.5)	6 (2) ^b	3.5 (1.5–10)
Talk about STDs with source					
Before having sex	14 (30)	44 (51)	13 (52)	19 (47)	90 (45)
After having sex	13 (28)	21 (24)	3 (12)	13 (33)	50 (25)
Never	20 (42)	22 (25)	9 (36)	8 (20)	59 (30)
Talk about genital herpes with source					
Before having sex	3 (6)	21 (24)	4 (16)	4 (10)	32 (16)
After having sex	7 (15)	6 (7)	3 (12)	2 (5)	18 (9)
Never	36 (77)	60 (69)	18 (72)	34 (85)	148 (74)
Source told patient they had genital herpes					
Yes, before or after sex	2 (4)	16 (18)	3 (12)	1 (3)	22 (11)
No	45 (96)	71 (82)	22 (88)	39 (97)	177 (89)
Patient thought source knew they had genital herpes					
Yes	6 (13)	24 (28)	2 (8)	3 (8)	35 (18)
No	27 (57)	47 (54)	20 (80)	32 (80)	126 (63)
Did not think partner infected them	12 (26)	12 (14)	2 (8)	3 (8)	29 (15)
Patient thought partner had concurrent sexual relationships					
Yes	5 (11)	13 (15)	1 (4)	4 (16)	23 (12)
Not sure	19 (40)	22 (25)	4 (16)	11 (28)	56 (28)
No	23 (49)	50 (57)	20 (80)	24 (60)	117 (59)
Condom use during first sexual intercourse with this partner					
Yes	22 (47)	46 (53)	9 (36)	23 (58)	100 (50)
No	25 (53)	40 (46)	16 (64)	17 (42)	98 (49)
Condom use during last sexual intercourse with this partner					
Yes	14 (30)	14 (16)	3 (12)	8 (20)	39 (20)
No	32 (68)	72 (83)	22 (88)	31 (78)	157 (79)
Incidences of vaginal sex with partner during the 4 weeks before first signs of genital herpes, no.					
Several times a day	1 (2)	4 (5)	2 (8)	0	7 (4)
Every day (28 times)	0	7 (8)	1 (4)	0	8 (4)
10–20	10 (21)	30 (34)	11 (44)	16 (40)	67 (34)
5–9	10 (21)	19 (22)	5 (20)	7 (18)	41 (21)
2–4	15 (32)	12 (14)	5 (20)	11 (27)	43 (22)
1	10 (21)	11 (13)	1 (4)	6 (15)	28 (14)

NOTE. Data are the no. of subjects (% of total) unless otherwise indicated; nos. may not add up to totals in cases of missing data. IQR, interquartile range; STD, sexually transmitted disease.

^a Using 4-year age categories.

^b Only the 25th percentile; no 75th percentile is available here, because 38% of participants were censored in this subgroup.

herpes, as documented by the presence of fully developed antibodies on the Western blot at first evaluation; 43 had alternative diagnoses; and 52 provided information insufficient to document the acquisition of infection (figure 1).

Among 225 participants with newly acquired genital HSV-1 or HSV-2 infection, 183 (81%) reported only 1 partner, 30 (13%) reported 2 partners, and 12 (5%) reported ≥ 3 partners

in the 4 weeks preceding presentation. In 16 participants reporting ≥ 2 partners, laboratory evidence of concordant HSV infection in only 1 partner allowed for the identification of the transmitting partner. Thus, the analyses were conducted for 65 participants with genital HSV-1 infection and 134 participants with HSV-2 infection. Among these 199 participants with newly acquired HSV-1 or HSV-2 genital herpes, 127 (64%) were wom-

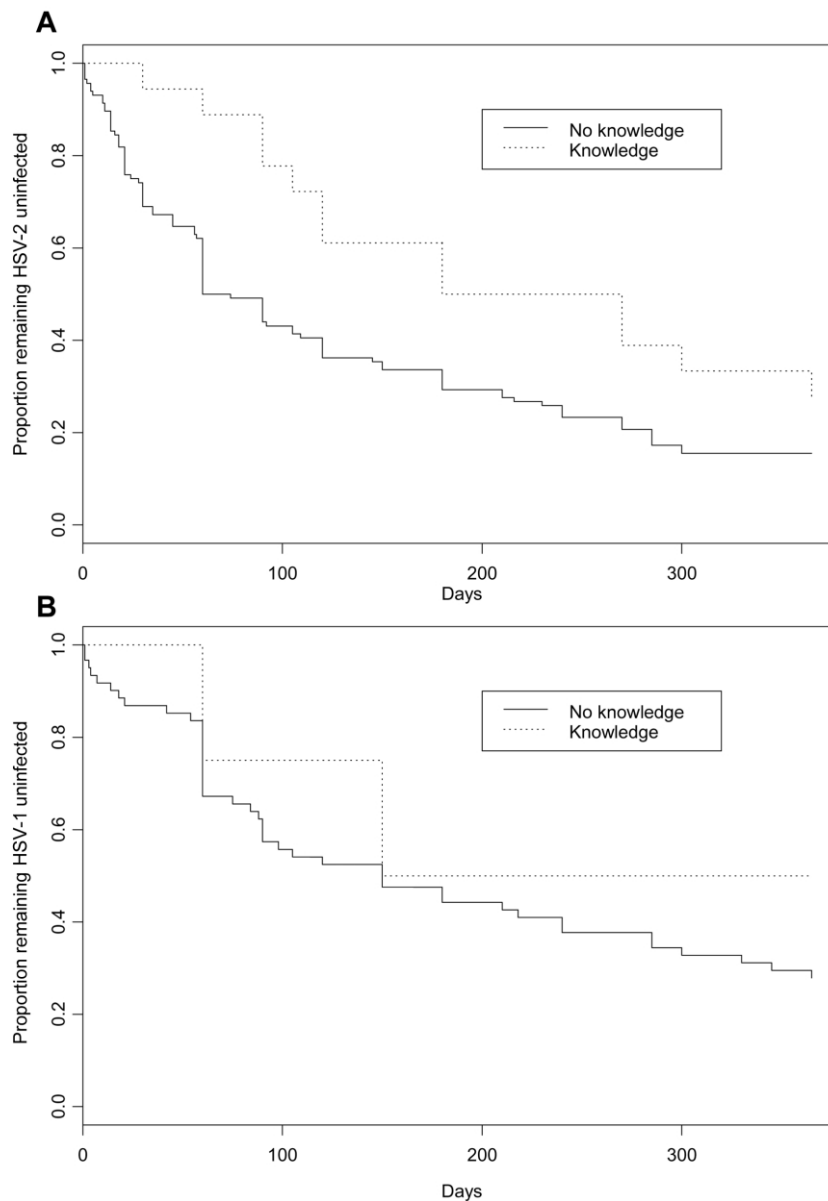


Figure 2. Kaplan-Meier survival curves, according to whether the index patient knew that the source partner had genital herpes. *A*, Herpes simplex virus type 2 (HSV-2). *B*, HSV-1.

en and 72 (36%) were men. The median age was 26 years; 74% were white, 7% were African American, and 19% were of another race/ethnicity (table 1).

Partnership characteristics. Most persons who acquired genital herpes were in relatively new relationships, with 7% reporting a relationship lasting ≤ 1 week, 16% reporting a relationship lasting 1 week–1 month, and 64% reporting a relationship lasting 1–6 months before HSV acquisition. Only 42 participants (21%) reported relationships lasting >1 year and, thus, were censored at 1 year. The median duration of sexual relationships was 3.5 months (interquartile range [IQR], 1.5–

10 months), and the median number of sex acts before HSV transmission was 40 (IQR, 15–75).

Despite the relatively short duration of the relationships, 166 participants (83%) characterized their relationship as steady (table 2). Condom use was infrequent, with 50% reporting condom use the first time they had sexual intercourse with the transmitting partner and 20% reporting condom use the last time they had sexual intercourse. Only 6% of persons with newly acquired genital HSV-1 infection and only 13% of persons with newly acquired HSV-2 infection reported that the partner disclosed to them that he or she had genital herpes.

Table 3. Risk factors for shorter time to acquisition of herpes simplex virus type 2 (HSV-2) infection.

Covariate	Median time to HSV-2 acquisition, days	Univariate HR (95% CI)	Adjusted HR ^a (95% CI)
Sex			
Male	120	1.0	1.0
Female	90	1.27 (0.85–1.88)	1.47 (0.97–2.23)
Age effect of each 10 years younger			
		1.47 (1.16–1.86)	1.44 (1.10–1.87)
Sexual preference			
Heterosexual	90	1.0	
Homosexual/bisexual	28	2.25 (0.82–6.16)	
Race			
White	105	1.0	
Nonwhite	90	1.34 (0.89–2.00)	
Education			
≤High school	57	1.0	1.0
Some college	120	0.46 (0.28–0.76)	0.45 (0.26–0.76)
≥4-year college	105	0.59 (0.37–0.94)	0.80 (0.46–1.39)
Age at first sexual intercourse			
≤15 years	60	1.0	
16–17 years	105	0.78 (0.49–1.24)	
≥18 years	180	0.54 (0.34–0.86)	
Age concordance			
Older than source	180	1.0	
Same age as source	120	1.23 (0.72–2.09)	
Younger than source	60	1.82 (1.10–3.02)	
Talk about STDs with source			
No	56	1.0	
Yes	120	0.61 (0.41–0.91)	
Talk about genital herpes with source			
No	60	1.0	
Yes	210	0.51 (0.33–0.79)	
Source told patient he/she had genital herpes			
No	60	1.0	1.0
Yes	270	0.55 (0.31–0.98)	0.48 (0.25–0.91)
Patient thought source had concurrent sexual relationships			
No	90	1.0	1.0
Not sure or yes	120	0.88 (0.60–1.29)	0.70 (0.47–1.06)
Condom use during first sexual intercourse with source			
Yes	90	1.0	
No	90	0.90 (0.62–1.30)	
Condom use during last sexual intercourse with source			
Yes	90	1.0	
No	105	0.92 (0.58–1.46)	

NOTE. CI, confidence interval; HR, hazard ratio; STD, sexually transmitted disease.

^a Adjusted for sex, age, education, suspicion of partner having concurrent relationships, and whether the source told the participant that he/she had genital herpes.

The median time to HSV-2 acquisition was greater in participants whose partners informed them that they had genital herpes than in those whose partners did not (270 vs. 60 days, respectively; $P = .03$, log-rank test). By contrast, the median time to HSV-1 acquisition was 150 days for both groups ($P = .41$, log-rank test) (figure 2). Among the 22 partners who

disclosed that they had genital herpes, 15 partners did so before having sex for the first time and 7 only did so after the initiation of sexual activity. Most participants with newly acquired genital herpes believed that the partner was truthful—only 9% of participants who acquired HSV thought that the partner knew that he or she had genital herpes but did not reveal it.

Table 4. Risk factors for shorter time to acquisition of herpes simplex virus type 1 (HSV-1) infection.

Covariate	Median time to HSV-1 acquisition, days	Univariate HR (95% CI)	Adjusted HR ^a (95% CI)
Sex			
Male	98	1.0	1.0
Female	180	0.64 (0.35–1.14)	0.48 (0.24–0.97)
Age			
>32 years	300	1.0	1.0
≤32 years	98	2.22 (1.03–4.78)	2.75 (1.13–6.68)
Sexual preference			
Heterosexual	180	1.0	
Homosexual/bisexual	60	3.15 (1.06–9.35)	
Race			
White	150	1.0	
Nonwhite	60	1.38 (0.66–2.86)	
Education			
≤High school	98	1.0	
Some college	180	0.74 (0.35–1.58)	
≥4-year college	150	0.72 (0.35–1.46)	
History of STD			
No	150	1.0	1.0
Yes	150	1.20 (0.66–2.19)	0.56 (0.28–1.11)
Lifetime sex partners, no.			
≤6	240	1.0	1.0
>6	105	1.48 (0.80–2.74)	1.52 (0.75–3.09)
Age at first sexual intercourse			
≤15 years	210	1.0	
16–17 years	120	1.57 (0.78–3.18)	
≥18 years	240	0.94 (0.45–1.97)	
Age concordance			
Same age as source	180	1.0	
Older than source	90	1.53 (0.72–3.23)	
Younger than source	240	1.12 (0.54–2.33)	
Talk about STDs with source			
No	60	1.0	
Yes	218	0.46 (0.24–0.87)	
Talk about genital herpes with source			
No	150	1.0	
Yes	285	0.68 (0.32–1.47)	
Source told patient he/she had genital herpes			
No	150	1.0	1.0
Yes	150	0.56 (0.14–2.33)	0.35 (0.07–1.70)
Patient thought source had concurrent sexual relationships			
No	180	1.0	1.0
Not sure	105	1.27 (0.64–2.52)	1.81 (0.86–3.82)
Yes	NA ^b	0.18 (0.02–1.32)	0.24 (0.03–1.86)
Condom use during first sexual intercourse with source			
Yes	150	1.0	
No	150	0.86 (0.48–1.54)	
Condom use during last sexual intercourse with source			
Yes	90	1.0	
No	150	0.71 (0.34–1.47)	

NOTE. CI, confidence interval; HR, hazard ratio; STD, sexually transmitted disease.

^a Adjusted for sex, age, history of STDs, no. of lifetime partners, suspicion of partner having concurrent relationships, and whether the source told the patient he/she had genital herpes.

^b Not applicable (NA): only 4 were in this group and 3 of 4 were censored, so no median time to acquisition is available.

To confirm the identity of transmitting couples, we obtained HSV-2 isolates from 13 pairs of partners. Restriction enzyme analysis revealed that the pairs were indistinguishable in 9 cases, differed by 1 restriction enzyme in 1 case, and differed by 2 restriction enzymes in 3 cases. However, among the pairs with variations, none differed by >2 bands with any 1 enzyme, which indicates that they were within 1 genetic change of each other and, thus, were closely related.

Risk factors for HSV-2 acquisition. When we examined risk factors for HSV-2 acquisition, participants who were younger (hazard ratio [HR], 1.47 [95% confidence interval {CI}, 1.16–1.86] for each 10 years younger) and those who were younger than their partner (HR, 1.82 [95% CI, 1.10–3.02]) were at a significantly increased risk of HSV-2 acquisition (table 3). Participants with more education (HR, 0.46 [95% CI, 0.28–0.76] for those with some college vs. a high school degree or less; HR, 0.59 [95% CI, 0.37–0.94] for those with a 4-year college degree or more vs. those with a high school degree or less), participants who discussed STDs or genital herpes with their partner (HR, 0.51 [95% CI, 0.33–0.79] for discussing genital herpes vs. not), and those who were told by their partner that he or she had genital herpes (HR, 0.55 [95% CI, 0.31–0.98]) were at a significantly lower risk of HSV-2 acquisition. Sex, race, and sexual preference were not associated with the risk of HSV-2 acquisition. Condom use was not found to be protective in any analyses.

In multivariate models, having a partner who disclosed that he or she had genital herpes remained a strong protective factor against genital HSV-2 acquisition (HR, 0.48 [95% CI, 0.25–0.91]). In addition, persons with more education and those who were older remained at a relatively lower risk of HSV-2 acquisition (table 3). After adjustment for other characteristics, women were at a somewhat increased risk for HSV-2 acquisition (HR, 1.47 [95% CI, 0.97–2.23]).

In a sensitivity analysis that reclassified participants who reported that their partner disclosed having genital herpes after the first time they had sex as not having been informed, the protective effect of having been told that the partner had genital herpes was greater than in the original analysis (adjusted HR, 0.34 [95% CI, 0.15–0.81]). Thus, having been told before engaging in sex was associated with a lower risk of HSV-2 acquisition than having been told at any time during the relationship, although the CIs overlapped.

Risk factors for HSV-1 acquisition. Similar to the analysis that examined risk factors for HSV-2 acquisition, we explored the factors that may be important for HSV-1 acquisition among 65 participants with genital HSV-1 infection. In univariate analysis, younger age (HR, 2.22 [95% CI, 1.03–4.78] for ≤ 32 vs. >32 years) and homosexual or bisexual preference (HR, 3.15 [95% CI, 1.06–9.35]) were significantly associated with a higher risk of HSV-1 acquisition (table 4). Talking about STDs with

their partner had a protective effect (HR, 0.46 [95% CI, 0.24–0.87]). Participants who were told that their partner had genital herpes had a decreased risk of HSV-1 acquisition, although this result was not significant (HR, 0.56 [95% CI, 0.14–2.33]). However, only 4 of 65 participants with HSV-1 infection reported that their partner said he or she had genital herpes. Other factors—including race, education, and condom use with the transmitting partner—were not significantly associated with risk of HSV-1 acquisition.

Multivariate analyses adjusting for sex, age, history of STDs, number of lifetime partners, and suspicion of partner engaging in concurrent relationships revealed a stronger point estimate for having been told that their partner had genital herpes, although this result was still not statistically significant (adjusted HR, 0.35 [95% CI, 0.07–1.70]). Younger age remained significantly associated with HSV-1 acquisition in the multivariate model (table 4). Women were at a lower risk of HSV-1 acquisition than were men (adjusted HR, 0.48 [95% CI, 0.24–0.97]); this was partially explained by the higher risk of HSV-1 acquisition among men who had sex with men. A history of STDs, number of lifetime partners, and suspicion of partners having concurrent relationships were not statistically significant; however, because they substantially influenced the estimate for being told that the partner had genital herpes, they were retained in the multivariate model.

DISCUSSION

Our study of newly acquired genital herpes revealed several novel insights into the sexual transmission of HSV. Among persons with newly acquired genital herpes, the median duration of relationships was 3.5 months, which suggests that HSV is transmitted quickly in new relationships. Most persons who transmitted HSV-2 infection did not know that they had genital herpes; lack of awareness of the infection is consistent with published data from HSV-2 serosurveys [1]. Importantly, the risk of HSV-2 transmission was approximately halved when the source partner knew that he or she had genital herpes and informed the participant. These observations suggest that identifying persons with unrecognized HSV-2 infection may result in a decreased risk of transmission from such persons to new sex partners. The change in sexual behavior that accompanies disclosure and protects against STD transmission is not clear; however, the disclosure of HIV serostatus is considered to be important in the prevention of HIV transmission, and studies have clearly documented the complex issues involved in whether disclosure occurs [16]. Finally, our results show that HSV transmission occurs most often among partners who are monogamous and who consider the relationship to be steady. As such, messages about STD prevention that focus on decreasing the number of partners and avoiding concurrency are unlikely to affect HSV acquisition.

Our study used a design that has become the standard approach in studies of factors influencing time to pregnancy [15, 17–22]. We chose to censor participants at 1 year, to allow for the possibility that the source partner had acquired HSV from concurrent partners after the initiation of the relationship of interest. In that case, the duration of the relationship would not equal the duration of risk for HSV acquisition. An advantage of this approach is that we were able to study people who were in new relationships and those who may not have known that they or their partner had genital herpes. Such persons cannot be studied prospectively, because it would not be ethical to test people for HSV-2 and withhold test results. However, the disadvantage of the design is that, because we did not have access to a population of couples who did not transmit HSV, we were unable to calculate incidence rates, which is similar to studies of time-to-pregnancy that have yielded relative risks but not incidence rates [15].

Another corollary of our study design is that only persons with symptomatic genital herpes were enrolled, because we relied on clinical presentation for the initial diagnosis. A minority of newly acquired genital HSV-2 and HSV-1 infections result in a diagnosis at the time of acquisition, and the factors that distinguish between persons with symptomatic and asymptomatic HSV acquisition are poorly understood [23]. However, the enrollment of persons identified as seroconverting to HSV without clinical evidence of infection would necessitate prospective monitoring, obviating the possibility of this study design.

Gender and condom use, both of which have been recognized as determinants of HSV-2 transmission in prospective studies [5, 24, 25], did not influence the risk of transmission in this cohort. However, the increase in risk for women, compared with men, has varied widely among studies. For example, in 2 parallel studies of the subunit candidate vaccine, the risk of HSV-2 acquisition was 6-fold higher for women than for men who had a partner with genital herpes but was only 1.2-fold higher for women than for men among persons enrolled from STD clinics [5, 26]. Similarly, although condoms were shown to be protective in the candidate vaccine study, they were only marginally protective in a trial of valacyclovir for the prevention of HSV-2 transmission [4, 5]. Consistent condom use was unusual among our participants, which potentially suggests that those persons who use condoms regularly are protected against HSV-2 acquisition and, thus, could not become participants. Recent studies have emphasized the methodologic difficulties involved in the assessment of condom efficacy, and these may explain the variability in study findings [27, 28].

Despite the difficulty in relying on self-reported information about sexual behavior, we collected information about a relatively short period of time, during which recall of events should have been accurate and representative of the baseline status. Because the patients did not have an ongoing relationship with

the clinician and were often distressed by their new diagnosis of genital herpes, social desirability bias was less likely to occur than in prospective studies that collect information on sexual activity and condom use after counseling about such activities.

The decrease in risk of transmission was noted in a previous study of HSV-2–discordant partners. In the 18-month trial of a candidate vaccine, the absolute risk of HSV-2 transmission decreased during follow-up, from 8.5 cases/100 person-years during the initial 150-day interval to 0.9 cases/100 person-years during the last 150-day interval [5]. Similarly, a relationship lasting >2.5 years before study entry and a duration of genital herpes lasting >2 years in the source partner were associated with a decreased risk of HSV-2 transmission in the valacyclovir clinical trial (although the former did not reach statistical significance) [4]. Of note, the median duration of relationships before study enrollment in these 2 trials was 18 and 24 months, respectively. In addition, the main reason for a lack of eligibility in the discordant-couple studies was the discovery that both partners were already infected with HSV-2, despite the clinical history of genital herpes in only 1 partner [4, 24, 29]. This serologic concordance at study entry suggests that transmission has already occurred, although it is also possible that the “susceptible” partner had acquired HSV-2 in a prior relationship. The present study demonstrates that most HSV-2 transmission events occur early in partnerships; thus, these couples are unlikely to participate in prospective studies.

That our study included fewer persons with genital HSV-1 infection limited its power to detect significant risks for HSV-1 transmission. However, the duration of the relationship before transmission was also short, and our results suggested that disclosing the presence of genital HSV-1 infection to partners may be protective. Of note, the source of newly acquired genital HSV-1 infections is usually unknown. Although, in some studies, a history of oral-genital contact appeared to be common among persons who acquired genital HSV-1 infection, studies of HSV transmission from women to neonates at delivery have shown that HSV-1 reactivation may be associated with a greater risk of transmission than HSV-2 reactivation [30–32]. As such, further studies are needed to define the risk of transmission from oral versus genital HSV-1 infection.

The time-to-event study design can yield a different type of insight than a prospective study, and, to our knowledge, it has not been used in the research of sexually transmitted pathogens or other infections. However, both a decrease in the rate of HIV transmission with the duration of relationship and a low frequency of HIV acquisition among persons in prospectively monitored HIV-discordant couples have been noted [33–37]. The low rate of observed transmission events results in difficulty in obtaining a firm understanding of important cofactors that may influence transmission. Couples who participate in such prospective studies may be fundamentally different from those

who do not participate—they may be more committed to each other and more interested in preventing transmission, whether of HIV or HSV-2. Host factors that influence acquisition are also likely to vary, and individuals with the highest susceptibility may already have acquired infection by the time when they are identified as potential study participants. Finally, the course of infection in the source partner may result in varying levels of infectiousness over time. For HSV-2, early disease is associated with high shedding rates, and this may contribute to higher rates of transmission in new relationships, which then wane as the reactivation frequency declines [38, 39].

Can transmission from HSV-2-seropositive persons be prevented by serologic testing only? Probably not, but serologic testing of persons with clinically silent infection, as well as those at risk, is likely to be the cornerstone of any prevention strategy for HSV-2 infection. Accurate type-specific HSV serologic tests are commercially available, although their use is still limited [40]. Prospective studies of persons with HSV-2 antibodies have demonstrated that they have clinically and virologically active infection: most recognize recurrences and shed virus in the genital area [41–43]. More importantly, the persons with unrecognized HSV-2 infection are the source of most new infections, and our results suggest that transmission may be delayed by awareness of the infection. There is an ongoing debate about whether a wider use of HSV serologic tests in the general population is appropriate [40, 44, 45]. Concerns range from issues surrounding the accuracy of the tests, to the burden on health-care practitioners of providing appropriate counseling, to the psychosocial distress that may accompany a new diagnosis of genital herpes [46, 47]. Recent studies addressing these concerns have been reassuring: no lasting distress was identified in persons receiving a serologic diagnosis of HSV-2 infection [48–50]. Physicians should encourage patients to disclose their genital herpes to partners before the initiation of sexual activity, as currently recommended [8].

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