

## CONCISE COMMUNICATION

## Herpes Simplex Virus Type 1 as a Cause of Genital Herpes: Impact on Surveillance and Prevention

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This study compared characteristics of patients who had herpes simplex virus (HSV) type 1 with characteristics of patients who had HSV-2, by use of data from a cross-sectional analysis. Data were collected in an urban sexually transmitted diseases clinic from patients who had positive genital HSV cultures. Overall, 17.1% (95% confidence interval [CI], 14.9%–19.3%) of 1145 genital HSV isolates obtained during 1993–1997 were HSV-1. The proportion of HSV-1 among initial genital herpes infections was higher among men who had sex with men (46.9%) than among women (21.4%) and was lowest among heterosexual men (14.6%). White race (odds ratio [OR], 3.7; 95% CI, 2.3–5.9) and receptive oral sex in the preceding 2 months (OR, 2.8; 95% CI, 1.9–4.3) significantly increased the odds that initial infections were HSV-1 rather than HSV-2. Genital HSV-1 may often be acquired through contact with a partner's mouth. These data suggest that seroprevalence studies based solely on HSV-2 type-specific assays underestimate overall prevalence of genital HSV infection.

Genital herpes is the most prevalent sexually transmitted disease (STD) in the United States [1]. The most accurate estimates derived from seroprevalence surveys show that 1 person in 5 in the United States is infected with herpes simplex virus (HSV) type 2 [2]; these data are widely purported to estimate the impact of genital HSV. However, the estimates ignore the contribution of sexually acquired HSV-1 to the epidemic of genital herpes. While infection with HSV-1 usually causes cold sores, whereas infection with HSV-2 most often results in genital lesions, either virus may infect oral or genital sites [3]. The specific sexual behaviors associated with transmission of HSV-1 have not been well delineated.

This study evaluated demographic and behavioral characteristics of patients with genital HSV-1 and compared them with those of patients with genital HSV-2 infection. We determined the relative frequency of genital HSV-1 as a cause of disease in low-income clients attending a public STD clinic and investigated risk factors associated with this diagnosis.

### Methods

The Harborview Medical Center STD Clinic offers diagnosis and treatment on a fee-scale that slides to no cost for low-income clients.

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Results of HSV cultures are available at no charge to the patient if the cultures are clinically indicated. Swabs of lesions are obtained for HSV isolation if a patient presents with new genital lesions or if the diagnosis of a recurrent lesion is in question.

*Study population.* From 1993 through 1997, the STD clinic averaged >10,000 unduplicated patients per year. The study population comprised patients with positive HSV isolates from genital or anal sites. Definitions of infections as initial or recurrent were based on patients' self-reports regarding presence or absence of previous outbreaks. Virus culture specimens were collected with Dacron swabs, placed in 2 mL of virus transport medium, and stored at 5°C until delivery to the laboratory the same day. Standard virus isolation methods were used; all isolates were confirmed and typed with the use of monoclonal antibodies [4].

The STD clinic uses standardized data collection instruments for all clinical encounters. The resulting information (~380 variables per visit) has been entered into an electronic database since 1993. Included in this data set are medical history, behavioral information, and findings of genital examinations and laboratory investigations. The presence or absence of 4 categories of sexual activity for the 2 months prior to clinic visit is coded. Activity types include receptive oral sex (i.e., partner's mouth on patient's genital area), vaginal intercourse, insertive anal intercourse (i.e., patient's penis in partner's anus), and receptive anal intercourse (partner's penis in patient's anus). In addition to recent sexual activity, gender and sexual orientation (categorized in this study as men who had sex with men [MSM], heterosexual men, and heterosexual women), race (white or nonwhite), and age were compared for persons diagnosed with genital HSV-1 and HSV-2 infections.

*Statistical analysis.* Six potential risk factors for genital HSV-1 infection were examined in univariate and multivariate logistic-regression models. Adjusted odds ratio (OR) estimates were derived from a multivariate model that included all 6 predictors. Two-sided 95% confidence intervals (CIs) were based on Wald's statistic, and

*P* values were based on the likelihood ratio statistic. Statistical significance was evaluated after application of the Bonferroni adjustment for 6 tests; *P* ≤ .008 provided an overall  $\alpha$  of .05.

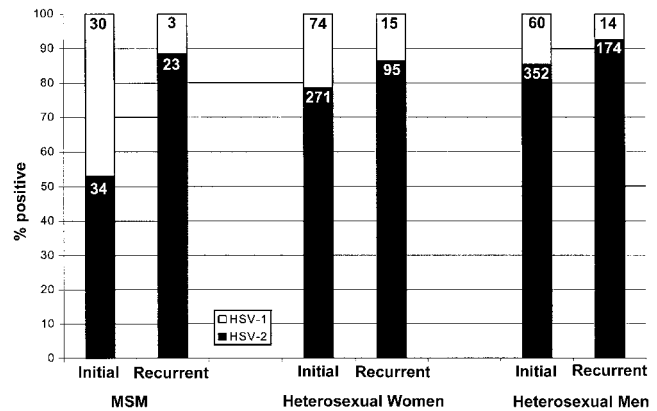
**Results**

HSV was isolated from 1145 unduplicated patients: 600 (52.4%) heterosexual men, 90 (7.9%) MSM, and 455 (39.7%) heterosexual women. The population was young (mean age ± SD, 28.2 ± 9.0 years), most were white (673, 58.8%), and all were sexually active. More than half (605, 52.8%) reported receptive oral sex during the last 2 months, 983 (85.9%) reported vaginal intercourse, 77 (6.7%) reported receptive anal sex, and 74 (6.5%) reported insertive anal sex.

Figure 1 shows the relative proportions of genital HSV-1 and HSV-2 isolates in initial and recurrent infections among heterosexual men, MSM, and heterosexual women. Overall, 196 cultures (17.1%; 95% CI, 14.9%–19.3%) were positive for HSV-1 and 949 (82.9%; 95% CI, 80.7%–85.1%) were positive for HSV-2. Of the 821 isolates from persons with initial genital HSV infections, 164 (20.0%; 95% CI, 17.2%–22.7%) were HSV-1. This compared with 32 (9.9%) of 324 isolates (95% CI, 6.6%–13.1%) from recurrent genital herpes. HSV-1 was found significantly more often in initial than in recurrent lesions (OR, 2.3; 95% CI, 1.5–3.5). The proportion of isolates from initial lesions that were HSV-1 was greater for MSM (46.9%) than for women (21.4%) and was lowest for heterosexual men (14.6%).

Table 1 shows the univariate and adjusted OR estimates for predictors of initial genital HSV-1 infection. There were significant positive univariate associations of HSV-1 with gender and sexual orientation, white race, receipt of oral sex, and participation and role in anal intercourse. There was a significant negative association with vaginal intercourse. In the multivariate analysis, white race (OR, 3.7; 95% CI, 2.3–5.9) and receptive oral sex (OR, 2.8; 95% CI, 1.9–4.3) retained statistical significance as risk factors for HSV-1, and the negative association between HSV-1 and vaginal sex (OR, 0.4; 95% CI, 0.2–0.8) approached significance (*P* = .009). Age was not significantly associated with HSV-1 versus HSV-2 isolation in either the univariate or multivariate model.

Although there were no statistically significant interactions among the 6 predictors in the adjusted model, multivariate analyses within the 3 gender-orientation categories produced substantially different OR estimates. Among the 412 heterosexual men, HSV-1 was significantly higher among whites than in other racial groups (OR, 4.5; *P* < .001). For the 345 heterosexual women, white race (OR, 3.9; *P* < .001) and receptive oral sex (OR, 4.4; *P* < .001) had significant positive associations, and vaginal sex (OR, 0.2; *P* = .007) had a significant negative association with HSV-1. No predictors were statistically significant for the small sample of 64 MSM.



**Figure 1.** Isolation of herpes simplex virus (HSV) type 1 and HSV-2 by stage of disease and sexual orientation.

**Discussion**

Studies outside the United States have indicated a substantial, and possibly increasing, proportion of HSV-1 in genital herpes infections [5–7]. Our data support these findings and suggest that seroprevalence studies that use HSV-2 type-specific assays significantly underestimate the incidence and prevalence of genital HSV infection and that the magnitude of underestimates is ≥15%. Our study results suggest that underestimation is particularly likely for initial infections, for whites, and for recipients of oral sex.

Although both initial and recurrent genital infections due to HSV-1 occur, HSV-1 is less likely than HSV-2 to reactivate in the genital tract either symptomatically or asymptotically [3, 8]. This probably explains the relative predominance of HSV-2 infections observed among patients with recurrent genital herpes.

In our study, initial genital infection with HSV-1 was relatively rare in nonwhites compared with whites. In part, this may reflect the lower incidence of oral sex reported by nonwhites (42.3% vs. 63.3% among whites), a pattern that is consistent with other sexual behavior surveys that found less oral sex among blacks [9]. However, even after adjusting for oral sexual activity, significant differences by race remained. A prior population-based seroprevalence study [10] found higher rates of HSV-1 infection among black and Hispanic populations. This suggests that low rates of initial HSV-1 genital infection among minorities in the current study may reflect high rates of early acquisition of oral HSV-1, rendering minorities relatively immune to genital HSV-1 infection by the time of adulthood.

The positive association of HSV-1 infection with receptive oral sex and the negative association with vaginal sex suggest that the partner’s mouth rather than genital area may be a common source of new HSV-1 infections. Shedding of HSV-1 from the oropharynx in the absence of lesions is well documented [11].

**Table 1.** Risk factors for genital herpes simplex virus type 1 in 821 patients with initial genital herpes infections.

Variable	No.	% HSV-1	Univariate model		Multivariate model		
			OR	95% CI	OR	P	95% CI
Age	821	NA	1.0	1.0–1.0	1.0	.383	1.0–1.0
Sexual orientation							
Heterosexual men	412	14.6	1.0		1.0	.232	
Heterosexual women	345	21.4	1.6	1.1–2.3	1.4		0.9–2.1
Men having sex with men	64	46.9	5.2	3.0–9.1	1.7		0.7–4.3
Race							
Nonwhite	333	8.1	1.0		1.0		
White	488	28.1	4.4	2.8–6.9	3.7	<.001	2.3–5.9
Received oral sex							
No	371	10.8	1.0		1.0		
Yes	450	27.6	3.1	2.1–4.6	2.8	<.001	1.9–4.3
Vaginal intercourse							
No	98	37.8	1.0		1.0		
Yes	723	17.6	0.4	0.2–0.6	0.4	.009	0.2–0.8
Anal sex							
None	723	18.1	1.0		1.0	.091	
Insertive only	37	16.2	0.9	0.4–2.1	0.4		0.2–1.2
Receptive only	42	33.3	2.3	1.2–4.4	1.1		0.5–2.4
Insertive + receptive	19	68.4	9.8	3.7–26.2	2.5		0.7–8.9

NOTE. HSV-1, herpes simplex virus type 1; OR, odds ratio; CI, confidence interval; NA, not applicable.

Among patients in this study, initial HSV-1 infections were disproportionately high among MSM. The finding that almost half of initial genital herpes among MSM was caused by HSV-1 infection was surprising, although a high rate of HSV-1 seroconversion among MSM has been noted in other studies [12]. The high rate for MSM in this sample appeared to be a function of at least 2 risk factors. A higher proportion of MSM than of heterosexuals were white (75% vs. 58%), and more MSM reported receiving oral sex (77% vs. 53%). In addition, MSM were less likely than heterosexuals to have participated in vaginal sex (19% vs. 94%), an activity strongly associated with HSV-2. The MSM sample was too small to allow confident generalization of this pattern to a larger MSM population. Future studies using a larger MSM sample to estimate the independent contributions of sexual activities and condom use on HSV-1 acquisition will be important.

In this study, more heterosexual women than heterosexual men had HSV-1 infection, and more of the women (66%) than men (52%) were white, the racial category with highest risk for HSV-1. Although both sexes participated almost equally in the sexual activities studied, OR estimates computed by sex suggest that heterosexual women may experience greater HSV-1 risk from receptive oral sex than men do. However, studies based on larger samples will be necessary for accurate identification of interactions between sex and risk factors for HSV-1 in heterosexuals.

Inexpensive, type-specific assays can determine whether clients are seropositive for HSV-1, HSV-2, or both. Because these tests are about to become available for clinical use [13], client counseling messages will need to be modified and, in some instances, made more complex. Persons who test negative for

HSV-1 must be counseled that receptive oral sex places them at risk for genital HSV-1 acquisition. This may be especially important for HSV-1-seronegative pregnant women, whose risk for transmitting HSV to the newborn is high if primary genital HSV-1 infection occurs late in pregnancy [14].

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