Prevalence and Correlates of Herpes Simplex Virus Type-2 Infection Among Men Who Have Sex With Men, San Francisco, 2008

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Background: Most herpes simplex virus type 2 (HSV-2) infections are asymptomatic or unrecognized, so periodic serological surveys are necessary in order to measure the true prevalence of infection, track trends over time, and identify correlates of infection, including coinfection with human immunodeficiency virus (HIV).

Methods: We conducted a community-based, cross-sectional, serological survey among 500 men who have sex with men (MSM) in San Francisco during 2008.

Results: The seroprevalence of HSV-2 infection was 26.1% (95% confidence interval [CI], 18.3–33.9), of HIV infection was 18.6% (95% CI, 13.0–24.4), and of HSV-2/HIV coinfection was 12.0% (95% CI, 7.3–16.8; categories not mutually exclusive). HSV-2 prevalence was 3.7 (95% CI, 2.3–5.9) times as high among HIV-infected MSM as among HIV-uninfected MSM. Strong predictors of HSV-2 infection among both HIV-infected and HIV-uninfected MSM were older age and black race.

Conclusions: The prevalence of HSV-2 infection among MSM in San Francisco is similar to that among MSM nationwide and is higher than that among all men nationwide. Prevalence rates are highly disparate among subpopulations of MSM in San Francisco, with the strongest predictors of infection being HIV-positive serostatus, older age, and black race. Primary prevention of HSV-2, particularly among populations at the highest risk for infection with HSV-2 or HIV, should remain a major public health goal to reduce the substantial morbidity caused by both of these infections.

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Herpes simplex virus Type 2 (HSV-2) infection is one of the most common sexually transmitted diseases (STDs) worldwide, and is also the cause of most genital ulcer disease and neonatal herpes.[1] Moreover, HSV-2 infection has been strongly associated with transmission and acquisition of human immunodeficiency virus (HIV) infection.[2–6] Randomized controlled trials have not shown that suppressive therapy for HSV-2 infection can prevent HIV transmission or acquisition,[7,8] although suppressive therapy might slow down the progression of HIV disease.[5–7]

HSV-2 infection is not a nationally reportable disease, although reporting of certain HSV-2 infections is legally mandated in some states.[9] Moreover, because most HSV-2 infections are asymptomatic or unrecognized, case reporting may severely underestimate the true burden of infection. Therefore, periodic serosurveys, even in states with HSV-2 reporting, are the best ways to assess the true extent of infection, track trends in prevalence over time, and identify disparities in infection. A national cross-sectional study of households, conducted during 2005–2008 through the National Health and Nutrition Examination Survey (NHANES), found that HSV-2 seroprevalence among persons aged 14 to 49 years was 16.2% (95% confidence interval [CI], 14.6–17.9) overall, 11.5% (95% CI, 9.8–13.3) among men, and 20.9% (95% CI, 18.9–23.1) among women.[10] Using NHANES data collected during 2001–2006, a study of men aged 18 to 59 years who reported of ever having sex with men found that HSV-2 seroprevalence was 18.4% (95% CI, 12.7–25.8).[11] These findings suggest that HSV-2 prevalence among men who have sex with men (MSM) may be higher than among other men. However, because such household surveys include few MSM overall, the CIs do not exclude similar prevalence of HSV-2 between MSM and heterosexual men. Moreover, male-male sexual behavior may be underreported in household surveys, further obscuring true differences in HSV-2 prevalence. Specific surveys of HSV-2 prevalence are therefore needed for MSM and other populations at high risk for infection.

We therefore capitalized on the US National HIV Behavioral Surveillance (NHBS) survey for MSM to more precisely measure the prevalence of HSV-2 among MSM. The overall objectives of the NHBS are to track HIV prevalence and related risk behavior. The objectives of the current study are to determine the seroprevalence of HSV-2 and to identify and compare the correlates of seroprevalent HSV-2 among HIV-uninfected and HIV-infected MSM in a community-based sample in San Francisco.

METHODS

We analyzed the data collected in San Francisco during 2008 as part of the Centers for Disease Control and Prevention-

TABLE 1. Characteristics of and HSV-2 Seroprevalence Among HIV-Uninfected Men Who Have Sex With Men, San Francisco, 2008

	No. Participants		Adjusted Prevalence		Bivariate Analysis			Final Multivariate Analysis		
	Total	HSV-2 Seropositive (%)	Prev.	95% CI	PR	95% CI	*P*	PR	95% CI	*P*
Overall	365	70 (19.2)	17.3	9.3–25.4						
Age (yr)										
18–29	142	7 (4.9)	1.6	0–3.5	Ref.		<0.01	Ref.		<0.01
30–39	108	22 (20.4)	17.4	9.2–25.6	10.7	3.4–33.7		14.8	4.6–47.4	
40–49	78	23 (29.5)	29.8	13.9–45.7	18.3	6.0–56.2		19.4	6.7–56.4	
≥50	37	18 (48.7)	56.6	29.0–84.1	34.8	11.2–108.0		42.3	15.4–116.4	
Race/ethnicity										
White	191	38 (20.0)	19.4	8.8–30.1	Ref.		<0.01	Ref.		<0.01
Asian/Pacific Islander	52	3 (5.8)	2.2	0–5.3	0.1	0.0–0.4		0.3	0.1–0.9	
Black	27	8 (30.0)	23.2	1.1–45.2	1.2	0.4–3.5		1.8	1.0–3.3	
Hispanic/Latino	93	21 (22.6)	20.8	7.9–33.6	1.1	0.6–1.9		1.3	0.7–2.5	
Education										
No college	49	16 (32.7)	16.8	2.1–31.6	Ref.		0.32	Ref.		0.06
Some college	112	22 (19.6)	17.4	7.0–27.8	1.0	0.4–2.7		0.6	0.3–1.1	
College degree	137	15 (11.0)	13.4	5.5–21.2	0.8	0.3–1.9		0.4	0.2–0.8	
Postgraduate	67	17 (25.4)	27.3	5.3–49.4	1.6	0.6–4.4		0.7	0.3–1.5	
Annual income										
$0–$19,999	81	13 (16.1)	12.2	0.5–23.9	Ref.		0.42	Exc.		
$20,000–$39,999	87	17 (19.5)	17.4	3.8–31.0	1.4	0.6–3.4				
$40,000–$74,999	84	14 (16.7)	14.5	4.7–24.2	1.2	0.4–3.2				
≥$75,000	109	25 (22.9)	24.5	11.0–38.0	2.0	0.8–4.9				
Ever injected drugs										
No	346	62 (17.9)	16.4	8.3–24.4	Ref.		0.20	Ref.		0.04
Yes	19	8 (42.1)	32.9	0–73.2	2.0	0.7–5.8		1.9	1.0–3.5	
Ever had sex with woman										
No	170	22 (12.9)	10.7	4.0–17.4	Ref.		0.02	Ref.		0.08
Yes	195	48 (24.6)	21.6	10.7–32.5	2.0	1.1–3.6		1.6	0.9–2.8	
Sex with man before age 18										
No	190	32 (16.8)	16.2	7.2–25.2	Ref.		0.68	Exc.		
Yes	175	38 (21.7)	18.5	8.0–29.1	1.1	0.6–2.1				
Sex with woman before age 18										
No	251	43 (17.1)	15.8	6.3–25.2	Ref.		0.48	Ref.		0.09
Yes	114	27 (23.7)	20.0	9.2–30.9	1.3	0.7–2.4		1.4	1.0–2.0	
Identify as hetero/bisexual										
No	321	63 (19.6)	18.0	10.1–30.0	Ref.		0.51	Exc.		
Yes	44	7 (15.9)	13.5	0–28.1	0.8	0.3–1.8				
≥5 partners during previous year										
No	191	31 (16.2)	15.8	7.7–24.0	Ref.		0.48	Ref.		0.13
Yes	174	39 (22.4)	19.2	8.4–30.0	1.2	0.7–2.1		1.5	0.9–2.6	
Uncircumcised										
No	296	56 (18.9)	16.6	8.90–24.4	Ref.		0.45	Exc.		
Yes	69	14 (20.3)	20.9	5.8–36.1	1.3	0.7–2.3				

Totals might not sum correctly because of missing data.
HSV indicates herpes simplex virus; HIV, human immunodeficiency virus; Prev., prevalence; CI, confidence interval; PR, prevalence ratio; Ref., reference; Exc., excluded from final multivariate analysis.

coordinated NHBS for MSM. NHBS methods are described in detail elsewhere.[12–15] In brief, NHBS tracks HIV prevalence and risk behaviors among US populations at high risk of HIV infection through serial cross-sectional surveys. During 2008, NHBS recruited MSM in 21 metropolitan areas through time-location sampling, a method developed to study hard-to-reach populations through venue-based recruitment. Time-location sampling in San Francisco began with formative research that identified venue-day-times, which were places where and times when MSM congregate. At randomly selected venue-day-times, research staff consecutively intercepted men entering a predetermined area, assessed eligibility, and invited eligible men to participate. Eligibility criteria included being male, age ≥18 years, a resident of a county in the San Francisco Metropolitan Statistical Area (i.e., San Francisco, Marin, or San Mateo), and approached by research staff.

Self-administered surveys on hand-held computers elicited information about demographic characteristics and

TABLE 2. Characteristics of and HSV-2 Seroprevalence Among HIV-Infected Men Who Have Sex With Men, San Francisco, 2008

	No. Participants		Adjusted Prevalence		Bivariate Analysis			Final Multivariate Analysis		
	Total	HSV-2 Seropositive (%)	Prev.	95% CI	PR	95% CI	*P*	PR	95% CI	*P*
Overall	95	59 (62.1)	64.5	53.0–76.1						
Age (yr)										
18–29	7	3 (42.9)	65.2	9.8–100.0	Ref.		<0.01	Ref.		<0.01
30–39	27	10 (37.0)	36.7	19.4–54.0	0.6	0.3–1.2		0.7	0.4–1.2	
40–49	41	30 (73.2)	75.0	57.2–92.8	1.1	0.6–2.2		1.3	0.9–2.0	
≥50	20	16 (80.0)	86.0	70.8–100.0	1.3	0.7–2.5		1.2	0.7–1.9	
Race/ethnicity										
White	53	33 (52.3)	59.9	42.3–77.6	Ref.		<0.01	Ref.		<0.01
Asian/Pacific Islander	3	0 (0)	0		Col.			Col.		
Black	11	10 (90.1)	96.3	86.5–100.0	1.6	1.2–2.2		1.4	1.1–1.8	
Hispanic/Latino	26	16 (61.5)	69.0	45.0–93.0	1.2	0.7–1.8		0.6	0.4–1.0	
Education										
No college	18	13 (72.2)	67.8	30.7–100.0	Ref.		0.21	Ref.		0.05
Some college	42	25 (59.5)	70.7	53.5–87.8	1.0	0.6–1.8		1.2	0.9–1.7	
College degree	25	18 (72.0)	65.3	41.1–89.4	1.0	0.5–1.9		1.4	0.9–2.2	
Postgraduate	10	3 (30.0)	20.6	0–47.8	0.3	0.1–1.0		0.5	0.2–1.2	
Annual income										
$0–$19,999	31	25 (80.7)	80.5	62.4–98.6	Ref.		0.02	Ref.		0.15
$20,000–$39,999	27	13 (48.2)	56.6	33.9–79.2	0.7	0.5–1.0		0.8	0.6–1.0	
$40,000–$74,999	15	7 (46.7)	41.9	2.3–81.5	0.5	0.2–1.2		0.7	0.3–1.6	
≥$75,000	22	14 (63.6)	58.4	35.0–81.9	0.7	0.5–1.1		0.9	0.6–1.4	
Ever injected drugs										
No	71	46 (64.8)	68.0	54.3–81.8	Ref.		0.43			0.04
Yes	24	13 (54.2)	52.0	18.2–85.8	0.8	0.4–1.5		0.7	0.4–1.0	
Ever had sex with woman										
No	32	17 (53.1)	50.8	31.1–70.6	Ref.		0.09			<0.01
Yes	63	42 (66.7)	71.6	57.9–85.3	1.4	0.9–2.1		1.5	1.1–2.0	
Sex with man before age 18										
No	32	17 (53.1)	56.8	36.5–77.0	Ref.		0.42			0.01
Yes	63	42 (66.7)	67.5	52.5–82.5	1.2	0.8–1.8		1.5	1.1–2.0	
Sex with woman before age 18										
No	56	34 (60.7)	61.3	45.1–77.6	Ref.		0.60	Exc.		
Yes	39	25 (64.1)	67.8	49.7–85.8	1.1	0.8–1.6				
Identify as hetero/bisexual										
No	85	51 (60.0)	61.2	50.0–72.8	Ref.		0.03	Exc.		
Yes	10	8 (80.0)	84.3	55.9–100.0	1.4	1.0–1.8				
≥5 partners during previous year										
No	41	31 (75.6)	78.8	62.9–94.6	Ref.		0.03	Exc.		
Yes	54	28 (51.9)	51.9	35.9–68.0	0.7	0.5–1.0				
Uncircumcised										
No	71	43 (60.6)	57.5	42.9–72.1	Ref.		0.01			<0.01
Yes	24	16 (66.7)	84.2	70.2–98.3	1.5	1.1–2.0		1.9	1.3–2.8	

Totals might not sum correctly because of missing data.
HSV indicates herpes simplex virus; HIV, human immunodeficiency virus; Prev., prevalence; CI, confidence interval; PR, prevalence ratio; Ref., reference; Col., collinear; Exc., excluded from final multivariate analysis.

behaviors associated with HIV and STDs. Research staff collected serological specimens. We determined HSV-2 serostatus using HerpeSelect 2 ELISA IgG (Focus Diagnostics, Cypress, CA), with optical density values <0.90 classified as negative, 0.90 to 3.49 as intermediate, and ≥3.50 as positive.[8,16,17] We determined HIV serostatus using Genetic Systems HIV-1/HIV-2 Plus O EIA (Bio-Rad Laboratories, Redmond, WA), with EIA-positive specimens confirmed using Fluorognost HIV-1 IFA, (Sanochemia Pharmazeutika AG, Vienna, Austria). Participants received results and any necessary referrals within 2 weeks.

We conducted statistical analyses using STATA version 10.1 (StataCorp, LP, College Station, TX), with observations weighted by the inverse probability of being approached and standard errors adjusted for clustering by venue. We included only those persons who had a positive or negative result on both serological tests and who were classified as MSM (defined as either identifying as gay or bisexual or reporting ≥1 male anal or oral sex partner during the previous year). We used Poisson regression with robust error variance to assess potential correlates of HSV-2 seropositivity so that results could be reported as prevalence ratios, given the high prevalence of infection.[18] We constructed final multivariate models using a backwards stepwise process that initially included all potential correlates and sequentially excluded variables with the highest *P* value until only those with $P < 0.20$ remained. We consid-

TABLE 3. Prevalences of HSV-2 Infection, HIV Infection, and HSV-2/HIV Coinfection Among Men Who Have Sex With Men, San Francisco, 2008

	No. Participants		Adjusted Prevalence		Bivariate Analysis		
	Total	Seropositive (%)	Prev.	95% CI	PR	95% CI	*P*
HSV-2 infection	460	129 (28.0%)	26.1	18.3–33.9			
HIV infection	460	95 (20.7%)	18.6	13.0–24.4			
HSV-2/HIV coinfection	460	59 (12.8%)	12.0	7.3–16.8			
HSV-2 infection (stratified on HIV status)							
HIV-uninfected	365	70 (19.2)	17.3	9.3–25.4	Ref.		<0.01
HIV-infected	95	59 (62.1)	64.5	53.0–76.1	3.7	2.3–5.9	

HSV indicates herpes simplex virus; HIV, human immunodeficiency virus; Prev., prevalence; CI, confidence interval; PR, prevalence ratio; Ref., reference.

ered variables with $P < 0.05$ significantly associated with HSV-2 seropositivity.

RESULTS

Of 1520 persons approached at 56 randomly selected venues, 1121 were screened, 781 were eligible, and 590 were recruited. A total of 500 recruited persons completed the survey, received serological tests, and were classified as MSM. Of these, 129 (25.8%) tested positive for HSV-2, 331 (66.2%) tested negative, and 40 (8.0%) had indeterminate results. Characteristics of the 460 participants included in the analysis, by HIV serological status, are shown in Tables 1 and 2.

Overall, seroprevalence was 26.1% (95% CI, 18.3–33.9) for HSV-2 infection, 18.6% (95% CI, 13.0–24.4) for HIV infection, and 12.0% (95% CI, 7.3–16.8) for HSV-2/HIV coinfection (categories not mutually exclusive; Table 3). HSV-2 seroprevalence differed significantly between HIV-infected MSM (64.5% [95% CI, 53.0–76.1]) and HIV-uninfected MSM (17.3% [95% CI, 9.3–25.4]). The HSV-2 seroprevalence ratio of HIV-infected compared with HIV-uninfected MSM was 3.7 (95% CI, 2.3–5.9).

Among HIV-uninfected MSM, HSV-2 infection was significantly associated in bivariate models with older age, race/ethnicity (lowest among Asian/Pacific Islanders, highest among blacks), and ever having had sex with a woman (Table 1). In the final multivariate model, HSV-2 infection was significantly associated with older age, race/ethnicity (lowest among Asian/Pacific Islanders, highest among blacks), and ever having injected drugs (Table 1).

Among HIV-infected MSM, HSV-2 infection was significantly associated in bivariate models with older age, race/ethnicity (lowest among Asian/Pacific Islanders, highest among blacks), lower income, heterosexual or bisexual identity, having had <5 partners during the previous year, and being uncircumcised (Table 2). In the final multivariate model, HSV-2 infection was associated with older age, race/ethnicity (lowest among Hispanics/Latinos [Asian/Pacific Islanders were excluded due to collinearity], highest among blacks), middle levels of education, never having injected drugs, ever having had sex with a woman, having had sex with a man before 18 years of age, and being uncircumcised (Table 2).

DISCUSSION

This study showed that 26.1% (95% CI, 18.3%–33.9%) of MSM in San Francisco are seropositive for HSV-2. Moreover, HSV-2 seroprevalence among subgroups of MSM is highly variable. One correlate strongly associated with HSV-2 seropositivity is HIV infection, with HIV-infected MSM nearly 4 times as likely as HIV-uninfected MSM to be seropositive for HSV-2. Other correlates strongly associated with HSV-2 seropositivity among HIV-infected and HIV-uninfected MSM included older age, which corresponds to the lifetime nature of HSV-2 infection, and black race/ethnicity.

The point estimate for HSV-2 seroprevalence among San Francisco MSM in this study is higher than the point estimate for HSV-2 seroprevalence among MSM nationally obtained through the NHANES study of 18.4% (95% CI, 12.7–25.8),[11] although the CIs overlap. The difference in point estimates might result from differences in geographic location, sampling technique, year of study, ages included in the analysis or definition of MSM, or from chance variation. Of note, the HSV-2 seroprevalence estimate in this study is higher than the HSV-2 seroprevalence estimate of 11.5% (95% CI, 9.8–13.3; CIs do not overlap) for US men overall.[10]

The higher seroprevalence among black MSM compared with other racial and ethnic groups in this study—23.2% (95% CI, 1.1–45.2) among HIV-uninfected and 96.3% (95% CI, 86.5–100.0) among HIV-infected black MSM—is, unfortunately, consistent with national NHANES data collected during 2005–2008.[10] Those data showed that HSV-2 seroprevalence among black men in the United States was 29.0% (95% CI, 26.3–31.9), about 3 times that of white and Mexican-American men. The racial disparity in HSV-2 seroprevalence parallels that observed for other STDs and HIV.[19,20]

This study is subject to several limitations. First, time-location sampling only approximates a true probability-based sample and would fail to capture, for example, MSM who do not congregate at venue-day-times identified during formative research. Second, the relatively small sample size resulted in some strata with minimal data and might have limited our ability to detect differences that truly exist. Third, there was substantial loss of participants among those initially identified as eligible. Unfortunately, we have no further information on the largest number who declined participation in the survey, from which likely bias or imputed estimates could be inferred. Finally, MSM of San Francisco might not be typical of other areas, limiting the study's generalizability.

Despite negative results in the RCTs of HSV-2 suppression to prevent HIV acquisition and transmission,[7,8] HSV-2 infection carries substantial clinical and public health importance. Because data suggest that HSV-2 may facilitate infection with HIV,[2–6] primary prevention of HSV-2 remains a major goal. Given the higher seroprevalence among MSM compared

with other men, this study underscores the clinical importance of ascertaining the gender of sex partners when evaluating a patient. Serologic screening for HSV-2 is generally not recommended for HIV-uninfected MSM, although some experts recommend HSV-2 serologic screening in all HIV-infected patients,[21] and others recommend serologic screening in HIV-uninfected patients at high risk of acquiring HIV.[22]

Importantly, effective episodic and suppressive therapies for HSV-2 exist, which can be useful clinically as well as from an HSV-2 prevention and control perspective. From a public health perspective, efforts to increase awareness among healthcare providers and the public of the high prevalence of HSV-2 infection, and of the behavioral and clinical connections between HSV-2 and HIV infection, might be useful first steps toward HSV-2 prevention and control, particularly in populations disproportionately affected by both infections. Finally, we highlight the need for conducting periodic HSV-2 prevalence surveys in populations at risk to track changes in the distribution and correlates of infection over time. We see strength in the current approach of including HSV-2 serology in the NHBS as it enables comparisons across multiple cities in the United States, across multiple time points, using identical methods.

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