

Herpes Simplex Virus Type 2 Infection as a Risk Factor for Human Immunodeficiency Virus Acquisition in Men Who Have Sex with Men

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The association of human immunodeficiency virus (HIV) acquisition with herpes simplex virus type 2 (HSV-2) was assessed among men who have sex with men (MSM) in a nested case-control study of 116 case subjects who seroconverted to HIV during follow-up and 342 control subjects who remained HIV seronegative, frequency-matched by follow-up duration and report of HIV-infected sex partner and unprotected anal sex. The baseline HSV-2 seroprevalence was higher among case (46%) than control (34%) subjects ($P = .03$); the HSV-2 seroincidence was 7% versus 4% ($P = .3$). Only 15% of HSV-2-infected MSM reported herpes outbreaks in the past year. HIV acquisition was associated with prior HSV-2 infection (odds ratio [OR], 1.8; 95% confidence interval [CI], 1.1–2.9), reporting >12 sex partners (OR, 2.9; 95% CI, 1.4–6.3), and reporting fewer herpes outbreaks in the past year (OR, 0.3; 95% CI, 0.1–0.8). HSV-2 increases the risk of HIV acquisition, independent of recognized herpes lesions and behaviors reflecting potential HIV exposure. HSV-2 suppression with antiviral therapy should be evaluated as an HIV prevention strategy among MSM.

Human immunodeficiency virus (HIV) prevalence and incidence in the United States is highest among men who have sex with men (MSM). Thus, the most effective prevention strategies should be directed toward

those factors associated with increased risk of HIV acquisition and transmission in that population. Observed heterogeneity in the per-contact risk of HIV acquisition via sexual exposure is most likely due to variability in biologic factors that alter susceptibility and infectivity [1]. Early studies focused primarily on increased HIV susceptibility and infectiousness that resulted from bacterial sexually transmitted diseases (STDs) [2–5]. In a recent multisite study among MSM, urethritis conferred a 2.3-fold increased risk of HIV acquisition [6]. Other factors associated with HIV acquisition among MSM include sex with an HIV-positive partner, injection drug use, unprotected receptive anal intercourse, condom failure, young age, and lack of circumcision [6–8].

Herpes simplex virus type 2 (HSV-2), the cause of genital herpes, is considered to be a major factor in geographic differences in HIV prevalence among heterosexual individuals in Africa [9]. A recent meta-analy-

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Written informed consent was obtained from all participants. The human experimentation guidelines of the US Department of Health and Human Services and the individual institutions were followed in conducting the clinical research.

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sis of studies primarily conducted among heterosexual populations reported that HSV-2 infection was associated with a 2.1-fold increased risk of HIV acquisition in 9 studies documenting HSV-2 infection before HIV acquisition [10]. However, among MSM, a group in which HSV-2 prevalence is as high as 80% among those with HIV [11] and as high as 50% among those without HIV [12], HSV-2 infection has been observed to be associated with an increased risk of HIV seroconversion in some [13, 14], but not all [15], studies. Differences in these findings may have been due to the limited number of individuals who converted from HIV seronegative to seropositive in prior studies and to challenges in controlling for exposure to HIV using behavioral variables.

Given recently observed increases in the rates of bacterial STDs [16–18] and HIV incidence [19] among MSM, as well as the high HSV-2 seroprevalence among MSM, there is a critical need to identify modifiable risk factors so that additional strategies to reduce sexual HIV transmission can be developed. We conducted a nested case-control study to examine the association between HSV-2 seropositivity and subsequent risk of HIV acquisition among MSM, to determine whether HSV-2 treatment could serve as a new HIV prevention target in this population.

METHODS

Study design and population. A case-control study was performed, nested within 2 multisite cohort studies: the Centers for Disease Control and Prevention Collaborative HIV Seroincidence Study (CHSS) in San Francisco, Denver, and Chicago (1993–1994) and the National Institute of Allergy and Infectious Diseases HIV Vaccine Preparedness Study (VPS) in San Francisco, Denver, Chicago, Boston, Seattle, and New York (1995–1997). HIV-seronegative MSM were eligible to participate if they had engaged in anal sex within the past year and were recruited through advertising, outreach activities, STD clinics, HIV testing sites, and referrals from other study participants. Subjects were followed up for 18 months with visits at 6-month intervals and completed semistructured interviews that included questions about risk behaviors and STD symptoms. Study protocols and questionnaires for the studies were similar; a common database was established that included variables assessed in both studies, such as demographic characteristics, sexual behaviors, STD diagnoses and symptoms (rectal, urethral, or pharyngeal gonorrhea or chlamydia or nonspecific urethritis), and injection and noninjection (amphetamines, barbiturates, cocaine, hallucinogens, marijuana, narcotics, and amyl nitrite) drug use in the previous 6 months. Participants were asked about anogenital sores and the anatomic location of any “outbreak of herpes in the last 6 months.” HSV serologic testing was performed on stored serum samples, and thus questions about herpes outbreaks were answered without specific

knowledge of subjects’ HSV serostatus and before any herpes counseling.

The HIV seroincidence was 2.3/100 person-years and 1.55/100 person-years among 2189 MSM enrolled in the CHSS cohort [6] and 3257 MSM enrolled in the VPS cohort [20], respectively. For our study, we defined “case subjects” as men who were HIV seronegative at baseline and seroconverted to HIV positive during the study, as determined by a positive ELISA result confirmed by a Western blot. Control subjects were selected from the group of men who remained HIV seronegative throughout the study and for whom adequate serum samples were available for HSV testing at the same visit “wave” as the case subjects (to provide a comparable follow-up period for case and control subjects). A total of 131 MSM acquired HIV (59 in the CHSS cohort and 72 in the VPS cohort), of whom 116 (88.5%) had sufficient serum samples stored and had provided consent for subsequent testing of stored serum. Three control subjects were selected for each case subject ($n = 348$), and complete behavioral and laboratory data were available for 342 of those. Because the number of available control subjects was large, and to avoid overmatching, frequency-matching was used; control subjects were frequency-matched to case subjects by duration of follow-up and report of sexual intercourse with an HIV-positive partner and unprotected receptive anal sex during the year before the last visit (these were identified as the 2 most important risk factors for HIV acquisition in the CHSS and VPS cohorts [6, 21]).

Laboratory methods. HSV-1 and HSV-2 serostatus was evaluated by type-specific HSV Western blot, which was performed as described elsewhere [22] by technologists at the University of Washington (Seattle) who were blinded to the subjects’ case-control status. If HSV-2 antibodies were detected in both the first and the last serum samples, a participant was considered to have prevalent HSV-2 infection. If the serum sample from the last visit was HSV-2 seropositive and the first sample was HSV-2 seronegative, a participant was considered to have incident HSV-2 infection. For these subjects, all interim samples were tested to determine the visit at which HSV-2 antibodies were first detected.

Statistical analysis. The primary exposure of interest was HSV-2 seropositivity (either prevalent or incident HSV-2 infection), defined by positive results of an HSV-2 Western blot before HIV seroconversion or, for control subjects, the last visit “wave.” Groups were compared using χ^2 statistics for categorical variables and Wilcoxon rank sum statistics for continuous variables. Logistic regression analyses were used to examine univariate associations between HIV seroconversion and demographic characteristics; injection and noninjection drug use; self-reported STD symptoms, diagnoses, and anogenital herpes outbreaks in the past 12 months; and HSV-1 and HSV-2 serostatus. Sexual risk behaviors included number of sexual partners

and frequency of receptive and insertive unprotected anal sex (continuous variables) and HIV-positive sexual partners, partners of unknown HIV status, and condom breakage (dichotomous variables) in the past 12 months. Information about sexual risk behaviors and STDs was collected at semiannual visits; an average measure was created for the 12-month period prior to HIV seroconversion among case subjects and the comparable period among control subjects, as was done in initial analyses from the CHSS [6].

Multivariable logistic regression analyses were performed to assess the association between HIV seroconversion and prior HSV-2 infection, controlling for factors potentially related to likelihood of HIV exposure (condom breakage, any HIV-positive partner or partner of unknown HIV status in the prior 12 months, number of sexual partners, and frequency of unprotected receptive anal intercourse); variables thought a priori to be potential confounders of the association between HIV infection and HSV-2 serostatus (age and bacterial STD or reported herpes outbreak in the past 12 months); race/ethnicity; health insurance (reflecting possible differences in access to health care or health care-seeking behaviors); city of recruitment; and year of HIV seroconversion (or last visit, for control subjects). Furthermore, to more directly assess the role of HSV-2 in sexual acquisition of HIV, we excluded from the analysis of this association 16 men who reported injection drug use in the previous 12 months. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using the regression coefficients and standard errors obtained from the logistic regression analyses.

RESULTS

Case subjects who acquired HIV during the study period were more likely than control subjects to be of a racial or ethnic minority, less likely to have health insurance coverage, and more likely to report injection drug use (table 1). For the 12-month period preceding seroconversion, case subjects also reported a higher number of sexual partners than did control subjects (median, 6.5 vs. 4.5 partners; $P = .008$) and a higher frequency of unprotected receptive anal sex (median, 3 vs. 1.5 episodes; $P = .004$) and any condom breakage (39% vs. 29%; $P = .05$). Whereas case and control subjects were similar with respect to HSV-1 seropositivity and self-reported bacterial STDs in the past 12 months (table 2), a higher proportion of case subjects were HSV-2 seropositive at the initial visit (41% vs. 31%). In addition, among subjects who were HSV-2 seronegative at baseline, 5 (7.4%) of 68 case subjects and 9 (3.8%) of 236 control subjects acquired HSV-2 during follow-up. Thus, in summary, 46% of case subjects were HSV-2 seropositive before HIV seroconversion, compared with 34% of control subjects before their last visits ($P = .03$).

Overall, 6.0% of case subjects and 11.4% of control subjects

reported herpes symptoms in the previous 12 months ($P = .1$; table 2), a trend that, although it was not statistically significant, was observed among both HSV-2-seropositive subjects (7.6% vs. 18.1%) and HSV-2-seronegative subjects (4.8% vs. 8.0%). Only 1 of the 14 subjects who seroconverted to HSV-2 during the study (a control subject) reported having symptoms consistent with genital herpes during the past 12 months. Eighteen of the 21 HSV-2-seronegative MSM who reported anogenital lesions or herpes symptoms were HSV-1 seropositive, which suggests that their symptoms may have been due to HSV-1 reactivation.

In a multivariable logistic regression analysis assessing the association of HIV seroconversion with prior HSV-2 infection, we found prior HSV-2 seropositivity to be associated with a 1.8-fold increased risk of HIV seroconversion (95% CI, 1.1–2.9; adjusted for age, lack of health insurance, and self-reported risk behaviors in the previous 12 months; table 3). Having >12 (compared with <3) sexual partners in the previous year (OR, 2.9; 95% CI, 1.4–6.3), lack of reported herpes outbreaks in the past 12 months (OR, 0.3; 95% CI, 0.1–0.8), and lack of health insurance (OR, 2.3; 95% CI, 1.4–3.8) were also independently associated with HIV acquisition. Although men who reported having herpes symptoms within the past 12 months had a higher median number of sexual partners than men who did not report such symptoms (9 vs. 4.5; $P < .001$), no significant differences in the proportion reporting any unprotected receptive or insertive anal intercourse were observed. Self-reported bacterial STDs within the past 12 months did not appear to increase the risk of HIV seroconversion. The association of HSV-2 seropositivity with HIV acquisition did not change when the 16 MSM who reported injection drug use in the previous year were included (OR, 1.8; 95% CI, 1.1–2.9). No interactions between HSV-2 infection and clinical, demographic, and behavioral variables were found.

To examine the association between HIV acquisition and subclinical HSV-2 infection, we performed a multivariable analysis among case and control subjects who did not report having anogenital herpes symptoms in the previous 12 months. These results were similar to the findings described above; previous HSV-2 seropositivity was associated with a 1.7-fold increased risk of HIV acquisition (95% CI, 1.0–2.9). Finally, to assess the association between recent HSV-2 infection and HIV acquisition among subjects who were HSV-2 seronegative at the initial visit, we compared the odds of HIV acquisition among men who did versus men who did not seroconvert to HSV-2 positive during follow-up (adjusted OR, 2.8; 95% CI, 0.8–10.1; $P = .11$).

DISCUSSION

In this nested case-control study of HIV-negative MSM in 6 US cities who were followed prospectively for 18 months, previous HSV-2 infection was associated with a 1.8-fold increased

Table 1. Sociodemographic characteristics and sexual and drug use behaviors among 116 men who have sex with men and who seroconverted to human immunodeficiency virus (HIV) positive during the study (case subjects) and 342 control subjects.

Variable	Case subjects	Control subjects	<i>P</i> ^a
Sociodemographic characteristic			
Age, median years (range)	30.5 (19–54)	31 (18–61)	.2
College education or higher	51 (44.0)	178 (52.0)	.1
White race	82 (70.7)	272 (79.5)	.05
Employed	95 (81.9)	291 (85.1)	.4
Health insurance coverage	58 (50.0)	236 (69.0)	<.001
City of enrollment			
San Francisco	44 (37.9)	139 (40.6)	.1
Denver	31 (26.7)	79 (23.1)	
Chicago	29 (25.0)	62 (18.1)	
Other ^b	12 (10.3)	62 (18.1)	
Sexual and drug use behaviors in the 12 months before the last study visit			
No. of sex partners ^c			
<3	28 (24.1)	109 (31.9)	.03
3–5	23 (19.8)	78 (22.8)	
6–12	25 (21.6)	84 (24.6)	
>12	40 (34.5)	69 (20.2)	
Any HIV-positive partner	65 (56.0)	182 (53.2)	.6
Any partner of unknown HIV status	85 (73.3)	244 (71.4)	.8
Unprotected receptive anal sex			
Any in the past year	73 (62.9)	217 (63.5)	.9
Frequency among those with ≥1 episode, median no. of episodes (range)	3 (1–126)	1.5 (1–87)	.004
Unprotected insertive anal sex			
Any in the past year	67 (57.8)	203 (59.4)	.7
Frequency among those with ≥1 episode, median no. of episodes (range)	3.5 (1–64)	3 (1–156)	.7
Condom breakage	45 (38.8)	99 (29.0)	.05
Noninjection drug use ^d	87 (75.0)	241 (70.5)	.4
Injection drug use	9 (7.8)	7 (2.1)	.01

NOTE. Data are no. (%) of subjects, unless otherwise indicated. Behavioral data for 2 control subjects were missing.

^a Wilcoxon rank sum test.

^b Seattle, Boston, and New York.

^c Quartiles of average nos. of sex partners during the 12 months before HIV seroconversion in case subjects.

^d Amphetamines, barbiturates, cocaine, hallucinogens, marijuana, narcotics, or amyl nitrite.

likelihood of HIV acquisition, independent of various socio-demographic characteristics, sexual behaviors, and self-reported bacterial STDs in the past 12 months, which is similar to recent findings among heterosexual men and women [10, 23–25] and MSM [13, 14, 26]. Because HSV-2 and HIV could conceivably be acquired from the same sexual exposure, we evaluated the risk of HIV acquisition after HSV-2 seroconversion to more accurately estimate the effect of HSV-2 reactivation on HIV susceptibility. Furthermore, the increased risk of HIV acquisition due to herpes infection was specific to HSV-2 and not to HSV-1 infection. A greater number of sexual partners, lack

of reported herpes outbreaks in the past 12 months, and lack of health insurance were also independently associated with HIV acquisition. Lack of health insurance could be associated with unmeasured socioeconomic or behavioral factors or with health care-seeking behaviors and access to health care, which might be associated with recognition of herpes symptoms or other STDs. Because case and control subjects were frequency-matched by report of unprotected receptive anal intercourse and HIV-positive partners in the prior 12 months, the association between these factors and HIV seroconversion could not be evaluated.

Table 2. Herpes simplex virus type 2 (HSV-2) and HSV-1 serostatus, bacterial sexually transmitted diseases (STDs), and herpes symptoms among 116 men who have sex with men and who seroconverted to human immunodeficiency virus (HIV) positive during the study (case subjects) and 342 control subjects.

Variable	Case subjects, n/N (%)	Control subjects, n/N (%)	P
Positive HSV-1 serostatus ^a	75/116 (64.7)	201/342 (58.8)	.3
Bacterial STD in the past 12 months ^b	19/116 (16.4)	40/342 (11.7)	.2
HSV-2 seropositive at the initial study visit	48/116 (41.4)	106/342 (30.9)	.05
Incident HSV-2 infection during follow-up ^c	5/68 (7.4)	9/236 (3.8)	.3
Positive HSV-2 serostatus ^a	53/116 (45.7)	116/342 (33.9)	.03
Herpes symptoms in the past 12 months ^d	7/116 (6.0)	39/342 (11.4)	.1
Among HSV-2-seropositive subjects	4/53 (7.6)	21/116 (18.1)	.1
Among HSV-2-seronegative subjects	3/63 (4.8)	18/226 (8.0)	.6

NOTE. n/N, no. of subjects with variable/total no. for whom data were available.

^a HSV serostatus before HIV seroconversion for case subjects and at a comparable study visit for control subjects.

^b Self-report of having been diagnosed or treated by a medical provider for rectal, urethral, or pharyngeal gonorrhea or chlamydia or nonspecific urethritis in the past 12 months.

^c Among subjects who were HSV-2 seronegative at the initial visit.

^d Self-report of a rectal, genital, or oral herpes outbreak or anogenital sores in the last 12 months, regardless of HSV-2 serostatus.

This study is, to our knowledge, the largest published analysis of HSV-2 infection and HIV acquisition among MSM; it included more than twice as many HIV seroconverters as previously published studies. We found an HSV-2 seroprevalence of 46% before HIV acquisition among subjects who seroconverted during the study, which is comparable to the seroprevalence reported in case-control studies conducted by Kingsley et al. [15] (43%) and Holmberg et al. [13] (45%) but somewhat lower than that reported by Keet et al. [14] (68%). HSV-2 seropositivity was significantly associated with HIV acquisition risk in the studies by Holmberg et al. [13] (OR, 2.6; 95% CI, 1.2–5.9) and Keet et al. [14] (OR, 4.0; 95% CI, 1.7–9.8), but no association was found in the Multicenter AIDS Cohort study (MACS; OR, 1.0; 95% CI, 0.3–2.9 [15]). Differences in these findings could be due to the inclusion of a smaller number of subjects who seroconverted or to confounding by unmeasured behavioral factors for which the analysis was not controlled.

The strengths of our study included our ability to document HSV-2 infection before HIV acquisition and to assess confounding by a number of important variables. Control subjects were frequency-matched to case subjects by report of sexual intercourse with an HIV-positive partner or unprotected receptive anal sex during the previous year (the 2 most important risk factors for HIV acquisition identified in the CHSS and VPS cohorts, the studies from which our subjects were drawn) and duration of follow-up (to ensure that case and control subjects had similar periods of follow-up in which acquisition of HIV might occur). In addition, we were able to control for other important factors, including age, race/ethnicity, access to health care, city of enrollment, condom breakage, having a partner of

unknown HIV status, number of sex partners, frequency of unprotected receptive anal intercourse, reported anogenital herpes symptoms, and self-reported bacterial STDs. However, the possibility that residual confounding due to unmeasured risk factors occurred cannot be excluded. Furthermore, because relatively few

Table 3. Likelihood of human immunodeficiency virus (HIV) seroconversion in association with previous herpes simplex virus type 2 (HSV-2) seropositivity among noninjection drug-using men who have sex with men.

Variable	Adjusted OR ^a (95% CI)	P
HSV-2 seropositivity prior to HIV seroconversion	1.8 (1.1–2.9)	.03
Any reported herpes symptoms in the past 12 months	0.3 (0.1–0.8)	.02
No. of sex partners in the past 12 months		
<3	Reference	
3–5	1.4 (0.7–3.0)	.3
6–12	1.5 (0.7–3.1)	.3
>12	2.9 (1.4–6.3)	.006
Bacterial STDs ^b	1.4 (0.7–2.8)	.3

NOTE. CI, confidence interval; OR, odds ratio; STD, sexually transmitted disease.

^a Adjusted for age, race/ethnicity, health insurance, city of enrollment, year of HIV seroconversion (or last visit, for control subjects), condom breakage, any HIV-positive partner or any partner of unknown HIV status in the prior 12 months, and frequency of unprotected receptive anal intercourse.

^b Self-report of having received a diagnosis of or having been treated by a medical provider for rectal, urethral, or pharyngeal gonorrhea or chlamydia or nonspecific urethritis in the past 12 months.

MSM acquired HSV-2 during follow-up, our study had limited power to compare HIV acquisition risk among those with incident HSV-2 infection with the risk among those with prevalent HSV-2 infection. However, our finding that there is a potentially greater risk of HIV acquisition associated with incident HSV-2 infection is similar to observations reported from a study of heterosexual individuals in Pune, India [27], and is consistent with the longer duration and higher frequency of HSV-2 reactivation that occurs in the first year after HSV-2 acquisition [28].

A minority of HSV-2-seropositive MSM in the present study (7.6% of case subjects and 18.1% of control subjects) reported herpes lesions or symptoms in the prior 12 months, which is similar to the proportions reported by Keet et al. [14] (22%) and Holmberg et al. [13] (15%) but higher than those observed in the MACS cohort (4% of HIV-positive and 2% of HIV-negative HSV-2-seropositive MSM) [15]. Low proportions of individuals reporting genital herpes symptoms are also observed in general populations (in studies done in the United States), in which up to 90% of HSV-2-seropositive persons fail to report a history of genital herpes [29–32]. Furthermore, the similar frequency of subclinical HSV-2 reactivation among persons with and without a history of genital herpes symptoms [33] suggests that HSV-2 likely increases HIV susceptibility, even among HSV-2-seropositive persons who do not recognize or report herpes episodes. Our finding of a 1.7-fold increased risk of HIV acquisition among MSM who did not report having herpes lesions or symptoms in the prior 12 months supports this hypothesis. Our observation of a lower risk of HIV seroconversion among individuals who reported recent herpes recurrences might result from men being less likely to engage in unprotected sexual intercourse when they recognize herpes symptoms or from use of suppressive antiviral therapy among MSM with recurrent herpes episodes. We were not able to directly assess these hypotheses, however, because of a lack of information about use of suppressive therapy and timing of HSV symptoms in relation to sexual intercourse. Thus, given the low proportion of HSV-2-seropositive MSM who reported a history of genital herpes symptoms and given the potential difficulty in recognizing perianal herpes reactivation, serologic testing may be an important component of prevention strategies aimed at identification of HSV-2-infected MSM.

We and others [10, 13, 14] have not found that the risk of HIV acquisition is increased among individuals infected with HSV-1, even though HSV-1 appears to account for an increasing proportion of initial anogenital HSV infections among MSM [34]. HSV-1 may be associated with a very modest increase in HIV susceptibility; ~86% of the HSV-2-seronegative MSM in the present study who reported having anogenital herpes symptoms in the prior 12 months were HSV-1 seropositive. However, the attributable risk of HIV acquisition associated with HSV-1

is likely less than that associated with HSV-2, because HSV-1 reactivates much less frequently than HSV-2.

HIV acquisition was associated with an increased number of partners but not with increased frequency of unprotected receptive anal sex. We did not find bacterial STDs to be an independent risk factor for HIV acquisition, which may be partly the result of the fact that bacterial STDs were ascertained by self-report and not by laboratory assay. Because anorectal gonococcal and chlamydial infections among MSM are often asymptomatic [18], self-reporting likely leads to underestimation of the true prevalence of bacterial STDs. However, it is important to note that a recent resurgence of bacterial STDs has been observed among MSM [16, 18], perhaps increasing the relative contribution of these STDs to HIV acquisition or transmission risk [19]. Clearly, given the limitations of self-reporting of sexual behaviors and STDs and the varying ability to adequately control for confounding in case-control studies, our findings support HIV prevention strategies aimed at reducing numbers of partners and occurrences of unprotected anal sex, as well as the diagnosis and treatment of bacterial STDs among MSM.

The finding of an almost 2-fold increased risk of HIV acquisition among HSV-2-seropositive MSM, independent of other sexual risk factors, underscores the need to evaluate, among high-risk MSM, the efficacy of interventions to reduce HSV-2 acquisition and suppress HSV-2 reactivation as potential HIV prevention strategies. HSV-2 seroprevalence is as high as 70% among MSM in Latin America and heterosexual women in sub-Saharan Africa [9, 23–25]. HSV-2 reactivates in the majority of infected persons, even in the absence of recognized lesions [12, 30, 31, 35, 36]. Moreover, epidemiologic studies suggest that, in populations with high HSV-2 seroprevalence rates, HSV-2 accounts for a substantial proportion of new HIV infections [10]. Given the low proportion of persons with HSV-2 infection who recognize lesions, more widespread use of type-specific HSV serologic tests should be recommended for populations at substantial risk of HIV acquisition. Acyclovir is relatively inexpensive, available in generic formulations, safe, and very well tolerated and suppresses asymptomatic as well as symptomatic HSV reactivation. Suppressive antiviral therapy among HSV-2-seropositive persons who are at high risk of HIV infection will be tested for efficacy in preventing HIV acquisition as a “proof of concept” in a National Institutes of Health–funded multicenter trial beginning in 2003. Although use of antiviral agents for episodic therapy would be less costly and easier to implement as an HIV prevention strategy, it is also likely to be less effective in preventing HIV acquisition than daily suppressive therapy, given the high proportion of subclinical HSV-2 reactivation. Both approaches to HSV-2 prevention warrant testing to determine relative efficacy and public health impact.

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References

- Vittinghoff E, Douglas JM Jr, Judson FN, McKirnan D, MacQueen K, Buchbinder SP. Per-contact risk of human immunodeficiency virus transmission between male sexual partners. *Am J Epidemiol* **1999**; 150:306–11.
- Craib KJP, Meddings DR, Strathdee SA, et al. Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. *Genitourin Med* **1995**; 71:150–4.
- Evans BG, Catchpole MA, Heptonstall J, et al. Sexually transmitted diseases and HIV-1 infection among homosexual men in England and Wales. *BMJ* **1993**; 306:426–8.
- Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *AIDSCAP Malawi Research Group. Lancet* **1997**; 349:1868–73.
- Cohen MS. Sexually transmitted diseases enhance HIV transmission: no longer a hypothesis. *Lancet* **1998**; 351:5–7.
- Buchbinder SP, Douglas JM Jr, McKirnan DJ, Judson FN, Katz MH, MacQueen KM. Feasibility of human immunodeficiency virus vaccine trials in homosexual men in the United States: risk behavior, seroconversion, and willingness to participate. *J Infect Dis* **1996**; 174:954–61.
- Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* **2000**; 342:921–9.
- Kreiss JK, Hopkins SG. The association between circumcision status and human immunodeficiency virus infection among homosexual men. *J Infect Dis* **1993**; 168:1404–8.
- Buve A, Carael M, Hayes RJ, et al. The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. *AIDS* **2001**; 15:S127–31.
- Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* **2002**; 185:45–52.
- Schacker T, Zeh J, Hu H-L, Hill E, Corey L. Frequency of symptomatic and asymptomatic herpes simplex virus type 2 reactivations among human immunodeficiency virus-infected men. *J Infect Dis* **1998**; 178: 1616–22.
- Krone MR, Wald A, Tabet SR, Paradise M, Corey L, Celum CL. Herpes simplex virus type 2 shedding in human immunodeficiency virus-negative men who have sex with men: frequency, patterns, and risk factors. *Clin Infect Dis* **2000**; 30:261–7.
- Holmberg SD, Stewart JA, Gerber AR, et al. Prior herpes simplex virus type 2 infection as a risk factor for HIV infection. *JAMA* **1988**; 259: 1048–50.
- Keet IP, Lee FK, van Griensven GJ, Lange JM, Nahmias A, Coutinho RA. Herpes simplex virus type 2 and other genital ulcerative infections as a risk factor for HIV-1 acquisition. *Genitourin Med* **1990**; 66:330–3.
- Kingsley LA, Armstrong J, Rahman A, Ho M, Rinaldo CR Jr. No association between herpes simplex virus type-2 seropositivity or anogenital lesions and HIV seroconversion among homosexual men. *J Acquir Immune Defic Syndr* **1990**; 3:773–9.
- Berglund T, Fredlund H, Giesecke J. Epidemiology of the reemergence of gonorrhoea in Sweden. *Sex Transm Dis* **2001**; 28:111–4.
- Stall RD, Hays RB, Waldo CR, Ekstrand M, McFarland W. The gay '90s: a review of research in the 1990s on sexual behavior and HIV risk among men who have sex with men. *AIDS* **2000**; 14:S101–14.
- Whittington WLH, Collis T, Dithmer-Schreck D, et al. Sexually transmitted diseases and human immunodeficiency virus-discordant partnerships among men who have sex with men. *Clin Infect Dis* **2002**; 35:1010–7.
- Katz MH, Schwarcz SK, Kellogg TA, et al. Impact of highly active antiretroviral treatment on HIV seroconversion among men who have sex with men: San Francisco. *Am J Public Health* **2002**; 92:388–94.
- Seage GR 3rd, Holte SE, Metzger DS, et al. Are US populations appropriate for trials of human immunodeficiency virus vaccine? The HIVNET Vaccine Preparedness Study. *Am J Epidemiol* **2001**; 153:619–27.
- Buchbinder SP, Heagerty PJ, Mayer KH, et al. Risk factors for HIV seroconversion in a contemporary cohort of high risk men who have sex with men (MSM) [abstract 23350]. In: Bridging the gap: conference record of the 12th World AIDS Conference (Geneva). Stockholm: International AIDS Society, **1998**:411.
- Ashley RL, Militoni J, Lee F, Nahmias A, Corey L. Comparison of Western blot (immunoblot) and glycoprotein G-specific immunodot enzyme assay for detecting antibodies to herpes simplex virus types 1 and 2 in human sera. *J Clin Microbiol* **1988**; 26:662–7.
- Gray RH, Wawer MJ, Serwadda D, et al. Serologic HSV-2 associated with HIV acquisition/transmission in discordant couples and the general population: Rakai, Uganda. *Int J STD AIDS* **2001**; 12(Suppl 2):64.
- del Mar Pujades Rodriguez M, Obasi A, Mosha F, et al. Herpes simplex virus type 2 infection increases HIV incidence: a prospective study in rural Tanzania. *AIDS* **2002**; 16:451–62.
- Auvert B, Ballard R, Campbell C, et al. HIV infection among youth in a South African mining town is associated with herpes simplex virus-2 seropositivity and sexual behaviour. *AIDS* **2001**; 15:885–98.
- Lucchetti A, Sanchez JL, Collis TK, et al. Bacterial STDs and HSV-2 acquisition among MSM HIV seroconverters in Peru [abstract 370]. In: Final programme and abstracts of the 1st International AIDS Society Conference on HIV Pathogenesis and Treatment (Buenos Aires). Stockholm: International AIDS Society, **2001**:187.
- Reynolds SJ, Risbud AR, Shepherd ME, et al. Recent herpes simplex virus type 2 infection and the risk of HIV acquisition in Pune, India [abstract MoOrC1012]. In: Knowledge and commitment for action: abstract book of the 14th International AIDS Conference (Barcelona, Spain), vol 1. Stockholm: International AIDS Society, **2002**:88.
- Koelle DM, Benedetti J, Langenberg A, Corey L. Asymptomatic reactivation of herpes simplex virus in women after the first episode of genital herpes. *Ann Intern Med* **1992**; 116:433–7.
- Fleming DT, McQuillan GM, Johnson RE, et al. Herpes simplex virus type 2 in the United States, 1976 to 1994. *N Engl J Med* **1997**; 337: 1105–11.
- Wald A, Zeh J, Selke SA, Ashley RL, Corey L. Virologic characteristics of subclinical and symptomatic genital herpes infections. *N Engl J Med* **1995**; 333:770–5.
- Wald A, Zeh J, Selke S, Warren T, Ashley R, Corey L. Genital shedding of herpes simplex virus among men. *J Infect Dis* **2002**; 186(Suppl 1): S34–9.
- Wald A, Corey L, Cone R, Hobson A, Davis G, Zeh J. Frequent genital herpes simplex virus 2 shedding in immunocompetent women: effect of acyclovir treatment. *J Clin Invest* **1997**; 99:1092–7.
- Wald A, Zeh J, Selke SA, et al. Reactivation of genital herpes simplex virus type 2 infection in asymptomatic seropositive persons. *N Engl J Med* **2000**; 342:844–50.
- Lafferty WE, Downey L, Celum C, Wald A. Herpes simplex virus type 1 as a cause of genital herpes: impact on surveillance and prevention. *J Infect Dis* **2000**; 181:1454–7.
- Koelle DM, Wald A. Herpes simplex virus: the importance of asymptomatic shedding. *J Antimicrob Chemother* **2000**; 45:1–8.
- Krone MR, Tabet SR, Paradise MA, Wald A, Corey L, Celum CL. Herpes simplex virus shedding among human immunodeficiency virus-negative men who have sex with men: site and frequency of shedding. *J Infect Dis* **1998**; 178:978–82.