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Predictors of Undiagnosed Herpes Simplex Virus Type 2 Seropositivity Among Persons Attending an HIV Care Clinic

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Abstract

We evaluated herpes simplex virus type 2 (HSV-2) seropositivity in an HIV clinic-based population with CD4 lymphocyte counts ≥ 250 cells/ μ L and no previous knowledge of HSV-2 infection by history of serology. We demonstrate that although the seroprevalence of HSV-2 is higher in this HIV-infected population, predictors of HSV-2 seropositivity are similar to those in the general population.

Herpes simplex virus type 2 (HSV-2) is common in persons with HIV.¹ Yet, the majority of HSV-2 infections in HIV-infected persons remain undiagnosed.² Despite the well-described complex bidirectional interplay of HIV and HSV-2 infections, little is known regarding factors associated with undiagnosed HSV-2 infection in HIV-infected populations and how HIV, an important risk factor itself, might interact with other factors in HSV-2 coinfection.³ We prospectively enrolled HIV-infected persons with no history of HSV-2 infection, receiving care at our university HIV clinic, and screened them serologically for HSV-2. Our goals were to determine the seroprevalence of detected HSV-2 in an HIV-infected population, and to identify variables associated with HSV-2 infection.

Between July 2009 and May 2011, 310 HIV-infected patients in care for at least 6 months at the University of Alabama at Birmingham HIV Clinic and with no known history of HSV-2 infection by previous serology or clinical diagnosis agreed to participate in HSV-2 screening. As part of a larger study, only patients with CD4 lymphocyte counts ≥ 250 cells/ μ L during the preceding 6 months were included. Participants provided informed consent and underwent a brief survey. Patient information was also collected from the medical record. This study was approved by the institutional review board of the University of Alabama at Birmingham.

Sera were tested in duplicate using Focus Diagnostics HerpeSelect HSV-2 ELISA IgG (Cypress, CA), and the results were averaged for interpretation. Manufacturer-recommended

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Conflict of interest

The other authors have nothing to declare.

cutoffs were used for interpretation of results. The Sure-Vue Rapid HSV-2 Test (Fischer Scientific, Pittsburgh, PA) was also performed on each sample. Test agreement was 96%. In cases of discordance, HSV-2-specific Western blot analysis was performed at the University of Washington (N = 13) and resolved all but 4 discrepant results.⁴

Independent variables were selected a priori for analysis in the context of HSV-2 serologic status. Using a cross-sectional approach, the presence of HSV-2 among HIV-seropositive individuals was estimated using the prevalence odds ratio (OR) and corresponding 95% confidence interval (CI) calculated from logistic regression. Estimates were adjusted for potential confounders (age, sex, race/ethnicity, and mean duration of HIV infection). Final models were selected by comparing the goodness-of-fit χ^2 for models that included selected additional potential confounders and interaction terms. Statistical significance, based on multivariate logistic models, was calculated using the maximum conditional likelihood and χ^2 tests. All statistical tests were 2 sided. All analyses were conducted using STATA version 10.0 (StataCorp, College Station, TX).

Of 306 HIV-infected participants with no previous history of HSV-2 infection, 188 (61%) were HSV-2 seropositive (Table 1). Women (OR = 2.65, 95% CI: 1.26–5.55; P = 0.01) and African Americans (OR = 2.25, 95% CI: 1.39–3.63; P = 0.001) were more often HSV-2 seropositive when compared with men and Caucasians, respectively. HSV-2-seropositive individuals were older (mean age, 43 vs. 40 years; OR = 1.03, 95% CI: 1.01–1.09; P = 0.007) and had known of their HIV infection longer (mean duration, 11.1 vs. 8.8 years; OR = 1.05, 95% CI: 1.02–1.09; P = 0.005). No differences were observed according to HIV risk factors, defined as a history of heterosexual sex, same-sex sex, or intravenous drug use. However, previous or current users of any illicit drug were significantly more likely to have HIV and HSV-2 coinfection than nonusers (OR = 1.86, 95% CI: 1.13–3.08; P = 0.02), and the magnitude of the effect was more pronounced in heroin/opiate users (OR = 4.73, 95% CI: 1.27–17.56; P = 0.02). Both cocaine users (OR = 1.69, 96% CI: 0.98–2.90; P = 0.06) and methamphetamine users (OR = 1.94, 95% CI: 0.92–4.12; P = 0.08) were also more likely to have HIV and HSV-2 coinfection, although not achieving significance at P = 0.05.

We also evaluated associations between HSV-2 seropositivity and a history of other sexually transmitted infections (STIs), hepatitis B (HBV) infection, or hepatitis C (HCV) infection. Participants with any STI (OR = 2.29, 95% CI: 1.35–3.88; P = 0.02) and specifically a history of gonorrhea (OR = 2.36, 95% CI: 1.03–5.36; P = 0.04) or syphilis (OR = 2.48, 95% CI: 1.27–2.85; P = 0.01) were significantly more likely to have HIV and HSV-2 coinfection compared with those without an STI history. Similarly, participants with HBV and HCV infections were more likely to have HIV and HSV-2 coinfection (HBV—OR = 2.65, 95% CI: 1.24–5.66, P = 0.01; and HCV—OR = 2.01, 95% CI: 0.91–4.45, P = 0.08), although not significantly for HCV-seropositive individuals.

Multivariate analyses largely confirmed univariate associations with HIV and HSV-2 coinfection. After adjusting for female sex, age, black race/ethnicity, and duration of HIV infection, a history of syphilis (OR = 2.05, 95% CI: 1.01–4.16; P = 0.05), HBV infection (OR = 2.26, 95% CI: 1.03–4.97; P = 0.04), and previous or current use of heroin/opiates (OR = 5.11, 95% CI: 1.33–19.61; P = 0.02) significantly contributed to the likelihood of having HSV-2 infection in HIV-seropositive persons.

In our HIV-infected population, the seroprevalence of undiagnosed HSV-2 infection was 61%. Predictors of HSV-2 seropositivity included female sex, black race, and older age. These findings mirror HSV-2-associated sociodemographic characteristics observed in the general population.^{5–7} Drug use and a history of an STI were highly associated with HSV-2 seroprevalence. These data suggest that although HSV-2 prevalence is markedly elevated in

HIV-infected patients, established predictors of HSV-2 seropositivity apply to this population as it does to other well-characterized groups.

A history of STI and specifically a history of either syphilis or HBV infection was independently associated with HSV-2 seropositivity. The associations between HSV-2 and either syphilis or HBV infection have been described in HIV-uninfected men who have sex with men (MSM).⁷ Similarly, in our HIV-infected population, the majority of HSV-2 coinfections with HBV infection or syphilis occurred in MSM (data not shown). Even with the localization of HBV infection and syphilis to MSM, we did not find an association between HSV-2 seroprevalence according to HIV risk category. Instead, HSV-2 seroprevalence was common in all subgroups. Even then, we suspect that correlates of HSV-2 infection may differ based on HIV risk category. Further work is needed to elucidate correlates of HSV-2 seroprevalence unique to each HIV risk category.

We acknowledge the limitations of this study. We did not have access to variables strongly associated with HSV-2 risk, including lifetime number of sexual partners. The participants had CD4 lymphocyte counts ≥ 250 cell/ μ L, excluding an important subpopulation of HIV-infected persons with low CD4 lymphocyte counts in which unique associations with HSV-2 may exist. A larger, yet similarly well-characterized, population would also facilitate an improved characterization of the relationship between HSV-2 seropositivity and variables approximating significance in this study (i.e., HCV infection, cocaine and methamphetamine use).

Despite the limitations, our findings offer new insight into predictors of HSV-2 coinfection in an HIV-infected population with good CD4 lymphocyte counts and undiagnosed HSV-2 infection. The high prevalence of HSV-2 in this HIV-infected population supports the suggestion by some experts to screen all HIV-infected persons for HSV-2.⁸ Knowledge of HSV-2 infection may allow for personalized prevention messages for both acquisition and transmission of HIV and HSV-2. Our findings may also help to target HSV-2 screening/treatment and prevention efforts among HIV-infected patients in environments in which HSV-2 screening is not a part of routine care.

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TABLE 1

Correlates of HSV-2 Seropositivity Among HIV-Infected Individuals*

Variable	HSV-2+ n = 188	HSV-2- n = 118	pOR (95% CI) [†]	P
Gender				
Male	151 (80)	108 (92)	Referent	Referent
Female	37 (20)	10 (8)	2.65 (1.26–5.55) **	0.01
Age (yr), mean (±SD)	43 (±9)	40 (±11)	1.03 (1.01–1.06)	0.007
Race/ethnicity				
Caucasian	90 (48)	80 (68)	Referent	Referent
African American	96 (51)	38 (32)	2.25 (1.39–3.63)	0.001
History of HIV-1 infection (yr), mean (±SD)	11.10 (±6.89)	8.77 (±0.61)	1.05 (1.02–1.09)	0.005
HIV risk factor				
Heterosexual	48 (26)	22 (19)	Referent	Referent
Men who have sex with men (MSM)	109 (59)	82 (70)	1.43 (0.66–3.10)	0.36
Intravenous drug use (IVDU)	9 (5)	4 (3)	1.72 (0.43–6.89)	0.45
MSM + IVDU	13 (7)	5 (4)	2.73 (0.74–10.04)	0.13
CD4 lymphocyte, cells/μL at enrollment [‡]	612 (±282)	559 (±196)	NS	0.25
CD4 lymphocytes, mean % (95% confidence interval) at enrollment	30 (29–31)	30 (28–32)	NS	0.51
Drug use, any	109 (60)	51 (45)	1.86 (1.13–3.08)	0.02
Marijuana	53 (28)	34 (29)	1.10 (0.64–1.90)	0.73
Cocaine	72 (39)	31 (26)	1.69 (0.98–2.90)	0.06
Methamphetamine	26 (14)	15 (13)	1.94 (0.92–4.12)	0.08
Heroin/opiates	17 (9)	3 (3)	4.73 (1.27–17.56)	0.02
IVDU	22 (12)	9 (8)	1.72 (0.72–4.10)	0.22
History of sexually transmitted infection, any	90 (48)	35 (30)	2.29 (1.35–3.88)	0.002
Chlamydia	8 (4)	3 (3)	2.22 (0.55–8.96)	0.26
Gonorrhea	30 (16)	9 (8)	2.36 (1.03–5.36)	0.04
Syphilis	48 (26)	15 (13)	2.48 (1.27–2.85)	0.01
Hepatitis B	34 (18)	11 (9)	2.65 (1.24–5.66)	0.01
Hepatitis C	35 (19)	10 (8)	2.01 (0.91–4.45)	0.08

* Data are presented as number (percent) unless otherwise designated. Missing data were not included in the analysis.

[†] P values were calculated for nondemographic parameters using logistic regression adjusted for male sex, age, European American ancestry, and years of HIV-1 infection.

[‡] Note that log(10)-transformed cell counts were used for CD4 lymphocytes.

** Bold indicates values reaching statistical significance (*P < 0.05).

HSV-2 indicates herpes simplex virus type 2; pOR, prevalence odds ratio; CI, confidence interval; SD, standard deviation; NS, not significant.