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Herpes simplex virus type 2 associated with HIV infection among New York heterosexuals living in high-risk areas

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Summary

Herpes simplex virus type 2 (HSV-2) has been shown to increase the risk of sexual human immunodeficiency virus (HIV) transmission. A matched case-control design was used to examine the association between HSV-2 and HIV infection among heterosexuals in 'high-risk areas' (HRAs) in New York City (NYC). We identified NYC HRAs using HIV surveillance data on heterosexual-related adult HIV diagnoses and USA census data on household poverty. Heterosexuals who were socially or geographically linked to an HRA were recruited using respondent-driven sampling. HIV prevalence was 8.6% and HSV-2 prevalence was 80.1%. Only 6% of HIV-positives knew they were infected. HIV-positive cases were matched to HIV-negative controls on gender, race/ethnicity and age, and tested for antibody to HSV-2. In a multivariate model, HIV infection was associated with HSV-2 infection (adjusted odds ratio [AOR] = 3.5, 95% confidence interval 1.1–11.7) and non-HSV-related sexually transmitted infection diagnosis in the previous year (AOR = 2.6, 1.1–6.2). Effective approaches to HIV risk reduction for individuals with HSV-2 remain uncertain, and these are urgently needed in high-risk communities where multiple social, behavioural and biological factors that facilitate HIV infection coexist.

Keywords

HIV; heterosexual; epidemiology; prevention; HSV-2

INTRODUCTION

A number of studies have shown that sexually transmitted infections (STIs) increase the risk of sexual human immunodeficiency virus (HIV) transmission.[1,2] Herpes simplex virus type 2 (HSV-2) infection appears to facilitate HIV transmission by creating portals of entry (lesions) and by causing an increase in CD4+ T-cells, the primary target cells for HIV infection in the genital mucosa.[3] HSV-2 has been shown to be associated with incident HIV infection in several observational studies of men who have sex with men (MSM) in the USA

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and Europe, heterosexual men and women in Africa and Asia, and illicit drug users in North America.[2,4–7]

In this paper, we describe a case-control study of the association between HSV-2 and HIV infection in heterosexuals in New York City (NYC) neighbourhoods where heterosexual HIV transmission is concentrated. NYC has experienced the largest local HIV/AIDS epidemic among high-income nations, with more than 200,000 cases reported since 1981. Twenty-three percent of the 3745 cases diagnosed in NYC in 2006 were attributed to heterosexual contact.[8] Heterosexual HIV transmission in NYC is concentrated in predominately African-American and Hispanic neighbourhoods – in particular, in Harlem, the South Bronx and central Brooklyn. Knowledge regarding the heterosexual HIV epidemic in the USA is still developing, and understanding the interaction of various social, behavioural and biological factors that promote HIV transmission among heterosexuals is essential to developing effective HIV prevention programmes.

METHODS

Data were drawn from the National HIV Behavioral Surveillance (NHBS) study, an ongoing cross-sectional, anonymous study of three populations at increased risk of HIV infection – MSM, injection drug users (IDUs) and high-risk heterosexuals.[9] Participants in the 2006–2007 survey of high-risk heterosexuals in NYC (NYC NHBS-HET) were the subject of this analysis. High-risk heterosexuals were sampled to account for the geographical and social clustering of heterosexual HIV and poverty. We identified the main NYC clusters using HIV surveillance data on heterosexual-related adult HIV diagnoses (2001–2006) and USA census data on household poverty (2000). A high-risk area (HRA) index was calculated for all NYC zip codes by summing the HIV and poverty rates and standardizing to the overall NYC rates. The 30 zip codes with the highest index values were classified as HRAs.

To be eligible for enrolment in the survey, individuals must have lived in one of the 30 HRAs or have been recruited into the survey by an eligible study participant who was a resident of an HRA. Additionally, participants must have been aged 18–50, have had vaginal or anal intercourse with an opposite-sex partner within the previous year, be English or Spanish-speaking and reside in NYC. MSM and current IDUs were eligible to participate in the survey (so long as they met other eligibility criteria), but were removed from this analysis. Respondent-driven sampling (RDS), a modified chain-referral method, was used to recruit eligible participants.[10] Chains of recruitment were initiated by ‘seeds’ – in this case, highly socially connected individuals identified by the study ethnographer. Seeds were given three coupons and instructions to distribute the coupons to other eligible persons. Each eligible participant who lived in an HRA was also offered the opportunity to recruit three other individuals. Incentives of US$10 for recruiting each eligible peer, US$20 for completing the survey and US$10 for an HIV test were paid to participants. Informed consent was obtained from those who were eligible, and willing to participate.

Data collection included completion of a questionnaire administered using hand-held computer-assisted personal interviewing technology and drawing of a venous blood specimen. Blood was screened for HIV antibody by HIV-1/2 + O enzyme immunoassay and

confirmed by HIV-1 Western blot (Bio-Rad Laboratories, Hercules, CA, USA). Remnant serum was tested for HSV-2 antibody by the HerpeSelect immunoblot assay (Focus Diagnostics, Cypress, CA, USA). Study procedures were reviewed and approved by the institutional review boards of the National Development and Research Institutes, New York City Department of Health and Mental Hygiene, and the Centers for Disease Control and Prevention.

A matched case-control design was used to examine the relationship between HIV and HSV-2 infection in this sample. Gender, race and age were chosen as matching criteria because they are potentially strong confounders of the association between HIV and HSV-2.[11] HIV-positive cases were gender-, race- and age-matched to three HIV-negative controls; age-matching ±two years was carried out.

Given the matched, case-control design of this study, the effects of exposure and potential confounders were estimated using a stratified conditional logistic regression analysis.[12] To determine which variables to include in the final conditional logistic regression model, each potential confounder (demographic characteristics, drug use and sexual risk behaviour) was added to a model with the exposure variable. If that addition changed the coefficient for the exposure variable by more than 10%, the variable was included in the final, multivariable model.

RESULTS

There were 850 eligible participants in NYC NHBS-HET, 23 of whom did not have an HIV test as part of the study. Of the remaining 827, 71 tested HIV positive (8.6%). Eleven current IDUs and six MSM were excluded from this analysis. Among the 54 HIV positives who remained, there were 39 with sufficient quantity of stored blood for HSV-2 testing. The 39 HIV-positive participants included in this analysis were matched to 111 HIV-negative controls. Fifty-nine percent of cases and controls were women, 84.6% were African-American and 15.4% Hispanic (see Table 1). Mean age was 43.4 years. Substantially fewer cases than controls had been homeless in the previous year, defined as living on the streets, in a shelter or single-room occupancy apartment (28.2% versus 54.7% of controls).

Age at sexual debut did not differ between cases and controls (mean age = 14.65). Cases reported a similar number of sex partners in the previous year (median 4 for cases versus 3 for controls, $P = 0.5$). A high proportion of participants reported exchanging sex for drugs or money in the previous year (41.0% of cases and 37.6% of controls). Unprotected sex with a casual or exchange partner was also reported by 58.3% of subjects. Crack smoking in the past year was reported by 45.3% of cases and 38.5% of controls ($P = 0.46$). A significantly higher proportion of cases reported being diagnosed with any STI in the past year (46.2% versus 26.5% of controls (odds ratio = 2.32, 95% confidence interval [CI] = 1.1–4.9).

HSV-2 prevalence was extremely high in this sample (81%); HSV-2 prevalence was higher among cases (89.7%) than controls (78.4%). In a multivariate model that adjusted for drug injection, homelessness and recent non-herpes STI diagnosis, HSV-2 infection was associated with HIV infection (adjusted odds ratio [AOR] = 3.48, 95% CI = 1.05–11.71).

Self-reported STI diagnosis in the previous year (excluding HSV-2) was also associated with HIV infection (AOR = 2.61, 95% CI = 1.10–6.19). Homelessness was inversely associated with HIV status (AOR = 0.23, 95% CI = 0.09–0.58). Lifetime history of drug injection was included in the model as it met data-based criteria for confounding.

DISCUSSION

HIV infection was associated with a 3.5-fold higher likelihood of HSV-2 infection in NYC high-risk heterosexuals, after controlling for demographic and behavioural factors that could lead to spurious associations. Several previous studies have found associations of similar magnitude in heterosexuals in developing countries and Europe, and among MSM.[2,5] In a recent cross-sectional study of heroin sniffers and smokers in NYC, there was a high prevalence of HSV-2 (60%) and HIV (19%), and HSV-2 infection was associated with a two-fold higher likelihood of HIV infection.[7] Thus, this report confirms the HIV–HSV-2 association in a population of sexually active heterosexuals living in HRAs within a city that has been characterized as an HIV epicentre.

The cross-sectional design of the NHBS-HET study precludes a causal interpretation of the HSV-2–HIV association. However, a longitudinal study would require 9000–23,000 person-years of follow-up, assuming an HIV seroconversion rate of 0.2/100 person-years and a relative risk in the range of 2.0–3.0. The biological evidence to support the hypothesis that HSV-2 increases sexual HIV transmission is quite convincing, but there is debate whether the relation is causal or an association arising from the fact that HSV-2 and HIV share behavioural risk factors.[3,13] For this reason, we used a matched design and adjusted for relevant risk behaviours to exert control for confounding. The temporal sequence between HSV-2 and HIV infection cannot be determined using cross-sectional data, but research has demonstrated that HSV-2 is typically acquired before HIV.[10] Age matching in this study may have removed some of the confounding effect of time-at-risk on the relation between HSV-2 and HIV. The relatively small sample may have reduced our ability to identify other confounding factors, and there may be important confounders that we did not measure.

We did not test for other sexually transmitted diseases that could facilitate HIV infection, and there may have been some false-positive HSV-2 tests as a result of cross-reactivity with HSV-1. Recent STI diagnosis (principally gonorrhoea and chlamydia) was also associated with HIV infection in this study. The inverse association between homelessness and HIV infection was puzzling. The literature suggests that homelessness is associated with HIV infection and is associated with increased sexual and drug-related risk behaviour, so an explanation for this finding is not immediately apparent.[14] Such an association could be the result of increased access to social services including housing for HIV-positive persons, although none of the HIV-positive participants in this analysis were aware of their infection. Another potential explanation may be methodological. In the RDS-recruited sample for this study, HIV infection tended to occur in clusters along recruitment chains (data not shown). Thus, the association could have arisen as a result of natural recruitment biases among the homeless in our study. The nested case-control study design of this HSV-2 analysis precluded weighting the data to reduce the effects of this potential recruitment bias.

The prevalence of HSV-2 infection was greater than 75% in both cases and controls, and the prevalence of HIV infection in the NYC NHBS-HET sample was 8.6%. A large proportion reported HIV risk behaviours in the previous year, including exchange sex and crack smoking. As mentioned, none of the 39 HIV-positive participants in this sample were aware of their HIV infection; in the entire NYC NHBS-HET sample, only 6% of HIV positives knew they were infected. The fact that the recruitment strategy led to identification of a number of undiagnosed cases of HIV infection suggests that case finding should consider geographic clustering and social ties among HIV-positive individuals.

Schillinger *et al.*[15] recently showed that only 12% of HSV-2-positive New Yorkers were aware of their HSV-2 infection. Increasing awareness of the HIV–HSV-2 association may lead many to seek HSV-2 screening and also contribute to better-informed decisions related to safe sex practices. However, effective approaches to HIV risk reduction for individuals with HSV-2 infection remain uncertain. Two recent clinical trials have reported that treatment of HSV-2 did not lower the risk of HIV transmission.[16,17] Thus, strategies should also seek to prevent new HSV-2 infections, particularly in communities with excess rates of HIV. New research is needed to determine optimum approaches within high-risk communities where multiple social, behavioural and biological determinants of HIV transmission coexist.

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Table 1

Comparison of HIV-seropositive heterosexuals (cases) and age-, race- and gender-matched controls, New York 2006–2007, National HIV Behavioral Surveillance Study

	Cases *N* = 39 (%)	Controls *N* = 111 (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Gender				
Male	16 (41.0)	42 (37.8)		
Female	23 (59.0)	69 (62.2)		
Race				
African-American	33 (84.6)	94 (84.7)		
Hispanic	6 (15.4)	17 (15.3)		
Age at enrolment*	43.4 (4.61)	43.4 (4.52)		
Age at sexual debut	14.4 (3.91)	14.7 (2.77)	0.98 (0.86, 1.10)	
Ever inject drugs	7 (17.9)	14 (12.6)	1.45 (0.55, 3.85)	2.00 (0.65, 6.17)
In past year				
Homeless	11 (28.2)	60 (54.1)	**0.34 (0.16, 0.76)**	**0.23 (0.09, 0.58)**
Arrested	8 (20.5)	36 (32.4)	0.52 (0.21, 1.28)	
Mean number of sex partners (SD)*	13.8 (24.4)	9.6 (19.3)	1.01 (0.99, 1.03)	
Any exchange sex	16 (41.0)	40 (36.0)	1.30 (0.61, 2.78)	
Unprotected sex w/casual or exchange partner	23 (59.0)	65 (58.6)	1.07 (0.52, 2.22)	
Any non-injection crack use	15 (38.5)	51 (45.9)	0.79 (0.38, 1.63)	
Any STD diagnosis (excludes HSV-2)	16 (35.6)	29 (26.1)	1.97 (0.92, 4.20)	**2.61 (1.10, 6.19)**
HSV-2 seropositive: yes	35 (89.7)	87 (78.4)	2.74 (0.88, 8.65)	**3.48 (1.05, 11.71)**

* In the multivariate modelling, per-year increase in age at sexual debut and per-partner increase in number of sex partners were entered into the model

OR (CI) values that are significant are shown in **bold**