

## BLOOD-BORNE AND SEXUAL TRANSMISSION OF HUMAN HERPESVIRUS 8 IN WOMEN WITH OR AT RISK FOR HUMAN IMMUNODEFICIENCY VIRUS INFECTION

MICHAEL J. CANNON, PH.D., SHEILA C. DOLLARD, PH.D., DAWN K. SMITH, M.D., ROBERT S. KLEIN, M.D.,  
PAULA SCHUMAN, M.D., M.P.H., JOSIAH D. RICH, M.D., M.P.H., DAVID VLAHOV, PH.D., AND PHILIP E. PELLETT, PH.D.,  
FOR THE HIV EPIDEMIOLOGY RESEARCH STUDY GROUP\*

### ABSTRACT

**Background** Human herpesvirus 8 (HHV-8), the causal agent of Kaposi's sarcoma, is transmitted sexually among homosexual men, but little is known of its transmission among women. Although HHV-8 has been detected in blood, there has been no clear evidence of blood-borne transmission.

**Methods** We identified risk factors for HHV-8 infection in 1295 women in Baltimore, Detroit, New York, and Providence, Rhode Island, who reported high-risk sexual behavior or drug use. HHV-8 serologic studies were performed with two enzyme-linked immunosorbent assays.

**Results** In univariate analyses, HHV-8 was associated with black race, Hispanic ethnic background, a lower level of education, and infection with syphilis, the human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). The risk of seropositivity for HHV-8 increased with the frequency of injection-drug use ( $P < 0.001$ ); HHV-8 seroprevalence among the women who used drugs daily was three times that among women who never injected drugs. Among the women with a low risk of sexual transmission, HHV-8 seroprevalence was 0 percent in those who had never injected drugs and 36 percent in those who had injected drugs ( $P < 0.001$ ). However, injection-drug use was linked less strongly to HHV-8 infection than to infection with HBV or HCV. In a multivariate analysis, independent predictors of HHV-8 seropositivity included HIV infection (odds ratio, 1.6; 95 percent confidence interval, 1.1 to 2.2), syphilis infection (odds ratio, 1.8; 95 percent confidence interval, 1.1 to 2.8), and daily injection-drug use (odds ratio, 3.2; 95 percent confidence interval, 1.4 to 7.6).

**Conclusions** Both injection-drug use and correlates of sexual activity were risk factors for HHV-8 infection in the women studied. The independent association of HHV-8 infection with injection-drug use suggests that HHV-8 is transmitted through needle sharing, albeit less efficiently than HBV, HCV, or HIV. (N Engl J Med 2001;344:637-43.)

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**H**UMAN herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus, appears to have a causal role in several diseases, including Kaposi's sarcoma, primary-effusion lymphoma, and multicentric Castleman's disease.<sup>1</sup> Kaposi's sarcoma is the most common cancer related to the acquired immunode-

fiency syndrome (AIDS), the most common cancer in some African countries, and a common cancer in transplant recipients.<sup>2-4</sup> HHV-8 can be found in a number of body tissues and fluids, indicating the potential for multiple routes of transmission.

HHV-8 DNA has been detected by the polymerase chain reaction (PCR) in peripheral-blood specimens from 50 percent of persons with Kaposi's sarcoma and from 20 percent of men who are seropositive for the human immunodeficiency virus (HIV) and who have sex with men.<sup>5</sup> HHV-8 can be detected in saliva samples from about 30 percent of HHV-8-seropositive men who have sex with men.<sup>6</sup> The virus is also present in saliva samples from up to 75 percent of HIV-positive patients with Kaposi's sarcoma,<sup>7</sup> but it is detected infrequently in semen<sup>8</sup> and in any tissue or fluid from persons at low risk for Kaposi's sarcoma.<sup>5</sup> Consequently, serologic studies have been used to identify the modes of transmission of HHV-8. For example, among men who have sex with men, the seroprevalence of HHV-8 has been strongly linked to the number of homosexual partners.<sup>9,10</sup> Heterosexual sex, on the other hand, has not been clearly established as a mode of transmission,<sup>11-13</sup> and little is known about transmission in women. In Africa, HHV-8 seroprevalence in preadolescent children is similar to that in adults, suggesting that nonsexual routes of transmission predominate.<sup>14-16</sup>

Although viral DNA and even infectious virus have been detected in blood, including blood from a blood donor,<sup>17</sup> evidence of the blood-borne transmission of HHV-8 among injection-drug users has been suggestive but inconclusive.<sup>9,18,19</sup> There has been no evidence of HHV-8 infection in recipients of transfused blood from HHV-8-seropositive donors, but the number of recipients studied has been small.<sup>20,21</sup>

The goal of our study was to evaluate exposure to

From the Centers for Disease Control and Prevention, Atlanta (M.J.C., S.C.D., D.K.S., P.E.P.); Rollins School of Public Health, Emory University, Atlanta (M.J.C.); the Division of Infectious Diseases, Department of Medicine, and the Department of Epidemiology and Social Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, N.Y. (R.S.K.); the Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit (P.S.); Brown University, Providence, R.I. (J.D.R.); and the Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, and the New York Academy of Medicine, New York (D.V.). Address reprint requests to Dr. Pellett at the Centers for Disease Control and Prevention, 1600 Clifton Rd., Mailstop G18, Atlanta, GA 30333, or at ppellett@cdc.gov.

\*Other members of the HIV Epidemiology Research Study Group are listed in the Appendix.

infected blood and heterosexual sex as modes of HHV-8 transmission in women. We assessed risk factors for HHV-8 seropositivity among women in the HIV Epidemiology Research Study, a prospective study of HIV infection in women. Since the predominant route of HHV-8 transmission, male homosexual sex, does not apply in this population, this study is well suited for determining whether HHV-8 is transmitted through exposure to infected blood or through heterosexual sex.

## METHODS

### Study Population

The HIV Epidemiology Research Study is a prospective, multisite study of HIV infection in women.<sup>22</sup> Between 1993 and 1995, 871 HIV-positive women and 439 demographically matched, HIV-negative women who engaged in behavior that increases the risk of HIV infection were enrolled in four cities: Detroit, Baltimore, New York, and Providence, Rhode Island. To be eligible for the study, each woman had to have engaged in one or more of the following types of high-risk behavior: using injection drugs at some time since 1985, having sex with at least five partners in the previous five years, having sex with a male injection-drug user, exchanging sex for money or drugs (hereafter referred to as commercial sex), or having sex with a man known or suspected to be infected with HIV. Follow-up visits took place at six-month intervals. By December 31, 1998, more than two thirds of the women had completed at least 9 study visits, and some had completed as many as 12 visits.

### Demographic, Behavioral, and Laboratory Variables

At enrollment, the women provided information on age, race or ethnic group, level of education, and level of income. At every visit, the women were asked a wide range of questions regarding drug use. To assess the risk related to injection-drug use, we defined five categories of risk: never used injection drugs, used injection drugs but not during the course of the study, used injection drugs during some but not all of the six-month periods between visits, used injection drugs during all the six-month periods between visits but not daily during every period, and used injection drugs daily during every six-month period between visits. Similar categories were defined for the smoking of "crack" cocaine, but the last two categories were combined because of the small numbers of daily crack smokers. At each visit, women were asked about their sex partners during the previous six months and the types of sexual behavior in which they had engaged with those partners. At the second visit, women were also asked about their lifetime male sex partners, any history of commercial sex, and their age at the time they first had sexual intercourse.

Blood specimens were obtained at the first visit, and serologic tests were performed for HIV, antibody to hepatitis B virus (HBV) core antigen, hepatitis C virus (HCV), herpes simplex virus type 1 (HSV-1, formally recognized as human herpesvirus 1), and herpes simplex virus type 2 (HSV-2, formally recognized as human herpesvirus 2). Serologic tests for syphilis and cultures for gonorrhea were performed at each of the first five visits. A positive result at any of these visits was considered to be positive in the analyses. We used the measurement of HIV viral load (if any) and the CD4 count that were obtained from the last visit.

### Serologic Tests for HHV-8

Banked samples of serum from the last visit were available for 1295 of the 1310 women enrolled in the study (99 percent); 65 percent of these samples came from the ninth visit (four years after enrollment) or later. The two serologic assays targeted peptides from open reading frames 65 and K8.1.<sup>23,24</sup> We used methods for the

coating of microtiter plates and for the enzyme-linked immunosorbent assays that have been described elsewhere,<sup>25</sup> with the following modifications: coated plates were stored at  $-20^{\circ}\text{C}$ ; serum specimens were diluted at a ratio of 1:100; the mean optical density at a wavelength of 450 nm was determined from duplicate test wells; and for each assay, the cutoff value was the mean corrected optical density for 20 control specimens plus 5 SD. Serum samples that were reactive in either assay were retested for confirmation. Samples that were negative on retesting were reported as negative for that assay. Seropositivity was defined as a positive result of either assay. Using this definition of seropositivity, we calculated that in earlier studies, 92 percent of patients with Kaposi's sarcoma (37 of 40) (unpublished data), 3 percent of U.S. blood donors (30 of 1000) (unpublished data), and 55 percent of HIV-positive men who had sex with men (21 of 38)<sup>24</sup> were seropositive for HHV-8.

### Statistical Analysis

Significant univariate associations with HHV-8 seropositivity were identified using the chi-square test of independence. A two-sided test for linear trends in proportions was used for variables with more than two ordered categories.<sup>26,27</sup> Variables independently associated with HHV-8 infection were identified by means of multivariate logistic regression. We used two regression models in which HHV-8 seropositivity was the outcome; the exposure variable was self-reported injection-drug use in one model and HCV seropositivity, a marker for injection-drug use, in the other model. No covariate was an influential confounder (i.e., changed the estimated odds ratio by more than 10 percent) when included individually in the two models. Nevertheless, in both models we included all covariates that had a significant univariate association with HHV-8 seropositivity, except for HBV seropositivity, which was excluded because it was closely correlated with both self-reported injection-drug use and HCV seropositivity.

## RESULTS

### Demographic Characteristics

Of the 1295 women tested, 16.1 percent were seropositive for HHV-8. Seroprevalence was highest in Baltimore and New York and was higher among blacks and Hispanics than among non-Hispanic whites (Table 1). Lower educational level was associated with HHV-8 seropositivity, and there was a nonsignificant increase in HHV-8 seropositivity with increasing age. The one woman with Kaposi's sarcoma was seropositive according to both assays.

### Injection-Drug Use and High-Risk Sexual Activity

In the univariate analysis, HHV-8 seropositivity was significantly associated with self-reported injection-drug use, and the HHV-8 seroprevalence increased with the frequency of injection-drug use (Table 1). Women who injected drugs daily throughout their participation in the study had an HHV-8 seroprevalence that was three times as high as that among women who never used injection drugs. In contrast, the frequency of crack smoking was not related to HHV-8 serologic status.

There was some evidence that HHV-8 seropositivity was associated with the type of injection drug used. Among the 132 women who injected drugs during the six-month period preceding every visit, HHV-8 seroprevalence was higher among those who injected cocaine (26.1 percent) than among those who

**TABLE 1.** HHV-8 SEROPREVALENCE ACCORDING TO DEMOGRAPHIC VARIABLES AND SELF-REPORTED BEHAVIOR (UNIVARIATE ANALYSIS).\*

VARIABLE	No. OF WOMEN†	HHV-8 SEROPOSITIVE no. (%)	ODDS RATIO (95% CI)	P VALUE
Study site				
Detroit	300	35 (11.7)	1	
Providence, R.I.	338	45 (13.3)	1.2 (0.7–1.9)	0.53
Baltimore	322	62 (19.3)	1.8 (1.2–2.8)	0.009
New York	335	66 (19.7)	1.9 (1.2–2.9)	0.006
Race or ethnic group				
White	313	36 (11.5)	1	
Black	757	133 (17.6)	1.6 (1.1–2.4)	0.01
Hispanic	209	37 (17.7)	1.7 (1.0–2.7)	0.05
Age				0.07‡
<26 yr	40	5 (12.5)	1	
26–30 yr	127	14 (11.0)	0.9 (0.3–2.6)	
31–35 yr	260	41 (15.8)	1.3 (0.5–3.5)	
36–40 yr	355	56 (15.8)	1.3 (0.5–3.5)	
41–45 yr	268	47 (17.5)	1.5 (0.6–4.0)	
46–50 yr	169	31 (18.3)	1.6 (0.6–4.3)	
>50 yr	76	14 (18.4)	1.6 (0.5–4.8)	
More than high-school education				0.02
No	991	172 (17.4)	1	
Yes	302	36 (11.9)	0.6 (0.4–0.9)	
Injection-drug use				<0.001‡
Never	523	67 (12.8)	1	
Never during study	345	58 (16.8)	1.4 (0.9–2.0)	
Sometimes during study	294	50 (17.0)	1.4 (0.9–2.1)	
During 6 mo before every visit but not daily	104	23 (22.1)	1.9 (1.1–3.3)	
Daily during 6 mo before every visit	28	10 (35.7)	3.8 (1.7–8.5)	
Crack smoking				0.83‡
Never	518	83 (16.0)	1	
Never during study	302	45 (14.9)	0.9 (0.6–1.4)	
Sometimes during study	416	70 (16.8)	1.1 (0.7–1.5)	
Before every visit	58	9 (15.5)	1.0 (0.5–2.0)	
Lifetime no. of male sex partners				0.39‡
0–5	301	47 (15.6)	1	
6–10	238	41 (17.2)	1.1 (0.7–1.8)	
11–20	147	21 (14.3)	0.9 (0.5–1.6)	
21–50	130	12 (9.2)	0.6 (0.3–1.1)	
>50	137	22 (16.1)	1.0 (0.6–1.8)	
Sex with bisexual man during study§				0.57
No	1075	168 (15.6)	1	
Yes	107	19 (17.8)	1.2 (0.7–2.0)	
Anal sex during study				0.61
No	991	162 (16.3)	1	
Yes	304	46 (15.1)	0.9 (0.6–1.3)	
Age at first intercourse				0.32
≥15 yr	662	111 (16.8)	1	
<15 yr	368	53 (14.4)	0.8 (0.6–1.2)	
Commercial sex				0.21
No	574	83 (14.5)	1	
Yes	596	102 (17.1)	1.2 (0.9–1.7)	

\*HHV-8 denotes human herpesvirus 8, and CI confidence interval.

†Data were not available for all women for all the variables.

‡The P value is for a test for linear trend in proportions.

§A bisexual man was defined as a man who had ever had homosexual sex.

injected heroin only (19.0 percent), although the difference was not statistically significant.

None of the self-reported markers of high-risk sexual activity, such as a high lifetime number of male sex partners, a history of commercial sex, or a young age at the time of first intercourse, were associated

with HHV-8 seropositivity in the univariate analysis (Table 1). HHV-8 seropositivity was not associated with sex with bisexual men or anal intercourse.

HHV-8 serologic status was significantly associated with a number of laboratory variables (Table 2). A positive test for HHV-8 was most strongly associ-

**TABLE 2.** HHV-8 SEROPREVALENCE ACCORDING TO LABORATORY MEASUREMENTS (UNIVARIATE ANALYSIS).\*

VARIABLE	NO. OF WOMEN†	HHV-8 SEROPOSITIVE no. (%)	ODDS RATIO (95% CI)	P VALUE
CD4+ cell count‡				0.13
<200/mm <sup>3</sup>	268	54 (20.1)	1	
200–499/mm <sup>3</sup>	399	58 (14.5)	0.7 (0.4–1.0)	
≥500/mm <sup>3</sup>	622	95 (15.3)	0.7 (0.5–1.0)	
HIV‡				0.002
Seronegative	421	49 (11.6)	1	
Seropositive	874	159 (18.2)	1.7 (1.2–2.4)	
HIV load‡				0.16§
<10 <sup>2</sup> copies/ml	178	29 (16.3)	1	
10 <sup>2</sup> to <10 <sup>3</sup> copies/ml	180	31 (17.2)	1.1 (0.6–1.9)	
10 <sup>3</sup> to <10 <sup>4</sup> copies/ml	240	41 (17.1)	1.1 (0.6–1.8)	
10 <sup>4</sup> to <10 <sup>5</sup> copies/ml	229	46 (20.1)	1.3 (0.8–2.2)	
≥10 <sup>5</sup> copies/ml	43	11 (25.6)	1.8 (0.8–3.9)	
Antibody to hepatitis B core antigen				0.04
Negative	583	78 (13.4)	1	
Positive	644	114 (17.7)	1.4 (1.0–1.9)	
HCV				0.002
Seronegative	540	65 (12.0)	1	
Seropositive	677	126 (18.6)	1.7 (1.2–2.3)	
HSV-1				0.08
Seronegative	314	39 (12.4)	1	
Seropositive	921	153 (16.6)	1.4 (1.0–2.0)	
HSV-2				0.49
Seronegative	445	65 (14.6)	1	
Seropositive	790	127 (16.1)	1.1 (0.8–1.5)	
Gonorrhea culture				0.58
Negative	1164	178 (15.3)	1	
Positive	26	5 (19.2)	1.3 (0.5–3.5)	
Syphilis				0.002
Seronegative	1172	176 (15.0)	1	
Seropositive	123	32 (26.0)	2.0 (1.3–3.1)	

\*HHV-8 denotes human herpesvirus 8, CI confidence interval, HIV human immunodeficiency virus, HCV hepatitis C virus, HSV-1 herpes simplex virus type 1, and HSV-2 herpes simplex virus type 2.

†Data were not available for all women for all the variables.

‡The measurement used was that obtained at the last visit.

§The P value is for a test for linear trend in proportions.

ated with a positive test for syphilis, HIV, or HCV; the association with HBV was weaker but still significant.

To determine whether injection-drug use was independently associated with HHV-8 seropositivity, we used multivariate logistic regression to control for potential confounders. After adjusting for race or ethnic group, study site, educational level, and HIV and syphilis serologic status, HHV-8 was still associated with injection-drug use (Table 3). In a regression model in which HCV seropositivity was substituted for injection-drug use, the association with HHV-8 positivity was also significant (odds ratio, 1.5; 95 percent confidence interval, 1.1 to 2.8).

To assess whether sexual risk factors were responsible for the observed association between injection-drug use and HHV-8 seropositivity, we analyzed data for women with a low risk of infection by sexual transmission. This risk status was defined on the basis of

**TABLE 3.** ADJUSTED ODDS RATIOS FOR HHV-8 SEROPOSITIVITY (MULTIVARIATE ANALYSIS).\*

VARIABLE	ADJUSTED ODDS RATIO (95% CI)	P VALUE
Injection-drug use		
Never	1	
Never during study	1.3 (0.9–2.0)	0.14
Sometimes during study	1.3 (0.8–2.0)	0.25
During 6 mo before every visit but not daily	1.8 (1.0–3.2)	0.05
Daily during 6 mo before every visit	3.2 (1.4–7.6)	0.007
Race or ethnic group		
White	1	
Black	1.5 (0.9–2.4)	0.09
Hispanic	1.2 (0.7–2.1)	0.52
Study site		
Detroit	1	
Providence, R.I.	1.5 (0.9–2.6)	0.11
Baltimore	1.5 (0.9–2.4)	0.14
New York	2.0 (1.2–3.3)	0.008
More than high-school education		
No	1	
Yes	0.8 (0.5–1.1)	0.17
HIV		
Seronegative	1	
Seropositive	1.6 (1.1–2.2)	0.01
Syphilis		
Seronegative	1	
Seropositive	1.8 (1.1–2.8)	0.01

\*The odds ratio for each variable was adjusted for all other variables in the table. HHV-8 denotes human herpesvirus 8, CI confidence interval, and HIV human immunodeficiency virus.

both self-reported criteria (no commercial sex and fewer than six lifetime male sex partners) and laboratory criteria (negative results of serologic tests for HSV-2 and syphilis). Among women who satisfied all these criteria, those who had ever injected drugs were more likely to be seropositive for HHV-8 than those who had never injected drugs (36 percent vs. 0 percent,  $P < 0.001$ ). HHV-8 seropositivity increased as the frequency of injection-drug use increased and was strongly associated with HCV seropositivity (Table 4).

#### Sexual Risk Factors in Women without Injection-Drug Use

In the overall study population, most markers for sexual risk were not associated with HHV-8 seropositivity (Tables 1 and 2). However, we found associations with sexual risk among women who did not use injection drugs (Table 5); these include associations between HHV-8 seropositivity and having had more than 50 male sex partners, having had sex with a bisexual man, HSV-2 seropositivity, commercial sex, and seropositivity for syphilis (although only the last two associations were statistically significant).

#### DISCUSSION

In this study of women with or at risk for HIV infection, we found evidence that HHV-8 is trans-

**TABLE 4.** HHV-8 SEROPREVALENCE AMONG WOMEN WITH A LOW RISK OF SEXUAL TRANSMISSION, ACCORDING TO INJECTION-DRUG USE AND HCV SEROSTATUS (UNIVARIATE ANALYSIS).\*

VARIABLE	NO. OF WOMEN†	HHV-8	ODDS RATIO (95% CI)	P VALUE
		SEROPOSITIVE		
		no. (%)		
Injection-drug use				0.001‡
Never	56	0		
Never during study	11	2 (18.2)	ND	
Sometimes during study	26	11 (42.3)	ND	
Before every visit	2	1 (50.0)	ND	
HCV				<0.001
Seronegative	57	1 (1.8)	1.0	
Seropositive	36	13 (36.1)	31.7 (3.9–256.2)	

\*A low risk of sexual transmission was defined as negative tests for herpes simplex virus type 2 (HSV-2) and syphilis, no history of commercial sex, and fewer than six lifetime male sex partners. HHV-8 denotes human herpesvirus 8, HCV hepatitis C virus, CI confidence interval, and ND not determined.

†Data for all variables were not available for all women with a low risk of sexual transmission.

‡The P value is for a test for linear trend in proportions.

missible through both exposure to infected blood and heterosexual sex. Blood-borne transmission was implicated by associations between HHV-8 and both self-reported injection-drug use and HCV seropositivity. Because HCV seropositivity is an objective surrogate marker of injection-drug use, its association with HHV-8 corroborates the association between injection-drug use and HHV-8. In addition, HHV-8 was associated with the frequency of injection-drug use in a dose-response fashion, but not with the frequency of crack smoking. The finding that the seroprevalence of HHV-8 was somewhat higher among regular users of cocaine than among regular users of heroin is also consistent with a relation between HHV-8 seropositivity and the frequency of drug injection, since cocaine users inject more frequently than heroin users.

The associations of HHV-8 seropositivity with injection-drug use and HCV seropositivity did not appear to be caused by confounding. A logistic-regression model that controlled for race or ethnic group, study site, educational level, and HIV and syphilis ser-

**TABLE 5.** SELECTED SEXUAL RISK FACTORS FOR HHV-8 SEROPOSITIVITY IN WOMEN WHO DID NOT USE INJECTION DRUGS (UNIVARIATE ANALYSIS).\*

VARIABLE	WOMEN WHO DID NOT USE INJECTION DRUGS				ODDS RATIO FOR ALL WOMEN†
	NO. OF WOMEN‡	HHV-8 SEROPOSITIVE	ODDS RATIO (95% CI)	P VALUE	
Lifetime no. of male sex partners					0.38§
0–5	129	13 (10.1)	1		1
6–10	98	16 (16.3)	1.7 (0.8–3.8)		1.1
11–20	61	5 (8.2)	0.8 (0.3–2.3)		0.9
21–50	52	6 (11.5)	1.2 (0.4–3.2)		0.6
>50	49	9 (18.4)	2.0 (0.8–5.1)		1.0
Sex with bisexual man during study					0.34
No	428	52 (12.1)	1		1
Yes	47	8 (17.0)	1.5 (0.7–3.4)		1.2
Age at first intercourse					0.61
≥15 yr	283	39 (13.8)	1		1
<15 yr	126	15 (11.9)	0.9 (0.4–1.7)		0.8
Commercial sex					0.005
No	311	30 (9.6)	1		1
Yes	160	30 (18.8)	2.2 (1.3–3.7)		1.2
HSV-2					0.13
Seronegative	191	19 (9.9)	1		1
Seropositive	307	45 (14.7)	1.6 (0.9–2.8)		1.1
Syphilis					0.01
Seronegative	479	56 (11.7)	1		1
Seropositive	44	11 (25.0)	2.5 (1.2–5.3)		2.0
HIV					0.17
Seronegative	188	19 (10.1)	1		
Seropositive	335	48 (14.3)	1.5 (0.8–2.6)		1.7

\*HHV-8 denotes human herpesvirus 8, CI confidence interval, HSV-2 herpes simplex virus type 2, and HIV human immunodeficiency virus.

†The odds ratios for all women are taken from Tables 1 and 2 and shown here for purposes of comparison.

‡Data for all variables were not available for women who did not use injection drugs.

§The P value is for a test for linear trend in proportions.

ologic status showed a significant association between HHV-8 seropositivity and injection-drug use. There was a similar association among women with a relatively low risk of sexual transmission; in this group, sexual risk factors were not likely to explain the large difference in HHV-8 seroprevalence between women who injected drugs and women who did not inject drugs.

Our results were not substantially affected by our definition of seropositivity as a positive result of either of the two assays. For each assay individually, we found a statistically significant trend toward higher HHV-8 seroprevalence with increasing use of injection drugs, as well as a significant association between HHV-8 seropositivity and HCV seropositivity (data not shown).

As with any study of seroprevalence, we cannot be certain that the women engaged in the types of behavior associated with seropositivity at the time when HHV-8 infection was acquired. A study of HHV-8 seroconversion over time would be required to determine whether HHV-8 infection coincides temporally with injection-drug use.

The observed association between injection-drug use and HHV-8 seropositivity is consistent with the findings of previous studies. After controlling for the number of homosexual partners, Martin et al.<sup>9</sup> found moderate but nonsignificant associations between HHV-8 infection and both needle sharing and blood transfusions, although few study participants reported these events. Rezza et al.<sup>19</sup> reported higher HHV-8 seroprevalence among injection-drug users than among sexually active persons who did not use injection drugs, but the authors did not determine whether the difference was attributable to injection-drug use. In a large cohort study in Amsterdam, HHV-8 seroconversion occurred in 31 injection-drug users,<sup>18</sup> but individual risk factors were not examined to determine whether HHV-8 was transmitted through sexual routes or through needle sharing.

Two findings suggest that although HHV-8 may be transmitted through needle sharing, it is likely that its transmission by blood is inefficient or occurs infrequently. First, HHV-8 seroprevalence was considerably lower among the women who used injection drugs in our study than it has been shown to be among HIV-positive homosexual men.<sup>24</sup> Second, injection-drug use was less strongly linked to HHV-8 than to the blood-borne viruses HBV and HCV. Seroprevalence among sometime users of injection drugs was 17 percent for HHV-8, as compared with 75 percent for HBV and 86 percent for HCV; among women who injected drugs during the six months before every visit, seroprevalence was 25 percent for HHV-8 but 80 percent for HBV and 95 percent for HCV. Such differences might be explained by the recent introduction of HHV-8 into this population. Nonetheless, the probabilities of exposure and of transmission

appear to be lower for women who use injection drugs than for men who engage in homosexual sex.

Two studies found no evidence of HHV-8 seroconversion among 32 recipients of transfused blood from HHV-8-seropositive donors,<sup>20,21</sup> perhaps because such donors do not usually have viremia<sup>5,17</sup> (and unpublished data). Another possibility is that HHV-8 circulates predominantly within B lymphocytes,<sup>17</sup> which are scarce in most types of transfusions. In addition, HHV-8 may have limited viability in stored blood and is likely to be susceptible to the routine methods of viral inactivation and sterilization that are used for plasma derivatives. Nevertheless, occasional transmission through transfusion cannot yet be ruled out. Blood-borne transmission of HHV-8 may occur more often in injection-drug users because they have repeated exposure to whole blood from persons who are more likely than blood donors to have HHV-8 viremia.

Blood-borne transmission of HHV-8 has been considered unlikely in part because among HIV-positive persons, Kaposi's sarcoma occurs less frequently in injection-drug users than in homosexual men; however, the difference is by a factor of only 5 to 10.<sup>2</sup> This difference is likely to be a function of HHV-8 seroprevalence in these populations and could be affected by the route of transmission, the amount of virus transmitted, and other unidentified factors. It is clear that some injection-drug users become infected with HHV-8. Because infectious HHV-8 can be found in blood<sup>17</sup> and because the incidence of Kaposi's sarcoma is higher among HIV-positive injection-drug users than in the general population,<sup>2</sup> needle sharing is a logical route of transmission. Our findings support this hypothesis.

We also found evidence of heterosexual transmission of HHV-8. In the overall study population, the only correlate of sexual activity significantly associated with HHV-8 was seropositivity for syphilis. However, among women who never injected drugs, both commercial sex and seropositivity for syphilis were significantly associated with HHV-8 seropositivity, and the odds ratios for HHV-8 seropositivity associated with HSV-2 seropositivity, sex with a bisexual man, and more than 50 lifetime male sex partners were substantially increased. Transmission through heterosexual sex is also suggested by the lower seroprevalence of HHV-8 among blood donors (3.0 percent, unpublished data) than among the women in this study who did not use injection drugs, all of whom had elevated levels of risk from sexual behavior (12.8 percent,  $P < 0.001$ ).

Our findings regarding sexual risk factors for HHV-8 among women are consistent with a previous finding of increased HHV-8 seroprevalence among commercial sex workers in Honduras.<sup>11</sup> However, in non-African, heterosexual persons attending sexually transmitted disease clinics in the United Kingdom,

HHV-8 seropositivity was not associated with sexual activity during the previous 12 months, although there were nonsignificant associations between HHV-8 seropositivity and gonorrhea, syphilis, and HSV-2 infection.<sup>12</sup> Our results may differ from the results of that study because the modes of transmission of HHV-8 differ in the two populations or because that study did not have adequate power to detect an association between HHV-8 seropositivity and sexual risk factors.

In conclusion, among the women in our study, both injection-drug use and sexual activity were risk factors for HHV-8 infection. The independent association of HHV-8 seropositivity with injection-drug use suggests that needle sharing leads to transmission of the virus, which in turn suggests that the virus can be transmitted through blood. Thus, it will be important to determine whether HHV-8 is transmitted by transfusions of blood or blood derivatives and whether such transmission is associated with disease.

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## APPENDIX

In addition to the authors, members of the HIV Epidemiology Research Study Group include R. Klein, E. Schoenbaum, J. Arnsten, R. Burk, C. Chang, P. Demas, and A. Howard (Montefiore Medical Center, Albert Einstein College of Medicine); P. Schuman and J. Sobel (Wayne State University School of Medicine); A. Rompalo, D. Vlahov, and D. Celentano (Johns Hopkins University School of Medicine); C. Carpenter, K. Mayer, S. Cu-Uvin, T. Flanagan, J. Hagan, V. Stone, K. Tashima, and J. Rich (Brown University School of Medicine); A. Duerr, L. Gardner, S. Holmberg, D. Jamieson, J. Moore, R. Phelps, D. Smith, and D. Warren (Centers for Disease Control and Prevention); and K. Davenny (National Institute of Drug Abuse).

## REFERENCES

- Ganem D. Human herpesvirus 8 and its role in the genesis of Kaposi's sarcoma. *Curr Clin Top Infect Dis* 1998;18:237-51.
- Jones JL, Hanson DL, Dworkin MS, et al. Surveillance for AIDS-defining opportunistic illnesses, 1992-1997. *MMWR CDC Surveill Summ* 1999;48(SS-2):1-22.
- Chokunonga E, Levy LM, Bassett MT, Mauchaza BG, Thomas DB, Parkin DM. Cancer incidence in the African population of Harare, Zimbabwe: second results from the cancer registry 1993-1995. *Int J Cancer* 2000;85:54-9.
- Penn I. Kaposi's sarcoma in transplant recipients. *Transplantation* 1997;64:669-73.
- Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *Lancet* 1995;346:799-802.
- Pauk J, Huang M-L, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med* 2000;343:1369-77.
- Koelle DM, Huang ML, Chandran B, Vieira J, Piepkorn M, Corey L. Frequent detection of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in saliva of human immunodeficiency virus-infected men: clinical and immunologic correlates. *J Infect Dis* 1997;176:94-102.
- Pellet PE, Spira TJ, Bagasra O, et al. Multicenter comparison of PCR assays for detection of human herpesvirus 8 DNA in semen. *J Clin Microbiol* 1999;37:1298-301.
- Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 1998;338:948-54.
- Melbye M, Cook PM, Hjalgrim H, et al. Risk factors of Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981-1996. *Int J Cancer* 1998;77:543-8.
- Sosa C, Klaskala W, Chandran B, et al. Human herpesvirus 8 as a potential sexually transmitted agent in Honduras. *J Infect Dis* 1998;178:547-51.
- Smith NA, Sabin CA, Gopal R, et al. Serologic evidence of human herpesvirus 8 transmission by homosexual but not heterosexual sex. *J Infect Dis* 1999;180:600-6.
- Kedes DH, Ganem D, Ameli N, Bacchetti P, Greenblatt R. The prevalence of serum antibody to human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) among HIV-seropositive and high-risk HIV-seronegative women. *JAMA* 1997;277:478-81.
- Mayama S, Cuevas LE, Sheldon J, et al. Prevalence and transmission of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. *Int J Cancer* 1998;77:817-20.
- Gessain A, Mauclere P, van Beveren M, et al. Human herpesvirus 8 primary infection occurs during childhood in Cameroon, Central Africa. *Int J Cancer* 1999;81:189-92.
- Andreoni M, El-Sawaf G, Rezza G, et al. High seroprevalence of antibodies to human herpesvirus-8 in Egyptian children: evidence of nonsexual transmission. *J Natl Cancer Inst* 1999;91:465-9.
- Blackbourn DJ, Ambroziak J, Lennette E, Adams M, Ramachandran B, Levy JA. Infectious human herpesvirus 8 in a healthy North American blood donor. *Lancet* 1997;349:609-11.
- Renwick N, Halaby T, Weverling GJ, et al. Seroconversion for human herpesvirus 8 during HIV infection is highly predictive of Kaposi's sarcoma. *AIDS* 1998;12:2481-8.
- Rezza G, Lennette ET, Giuliani M, et al. Prevalence and determinants of anti-lytic and anti-latent antibodies to human herpesvirus-8 among Italian individuals at risk of sexually and parenterally transmitted infections. *Int J Cancer* 1998;77:361-5.
- Operskalski EA, Busch MP, Mosley JW, Kedes DH. Blood donations and viruses. *Lancet* 1997;349:1327.
- Engels EA, Eastman H, Ablashi DV, Wilks RJ, Braham J, Manns A. Risk of transfusion-associated transmission of human herpesvirus 8. *J Natl Cancer Inst* 1999;91:1773-5.
- Smith DK, Warren DL, Vlahov D, et al. Design and baseline participant characteristics of Human Immunodeficiency Virus Epidemiology Research (HER) Study: a prospective cohort study of human immunodeficiency virus infection in US women. *Am J Epidemiol* 1997;146:459-69.
- Pau CP, Lam LL, Spira TJ, et al. Mapping and serodiagnostic application of a dominant epitope within herpesvirus 8 ORF 65-encoded protein. *J Clin Microbiol* 1998;36:1574-7.
- Spira TJ, Lam L, Dollard SC, et al. Comparison of serologic assays and PCR for diagnosis of human herpesvirus 8 infection. *J Clin Microbiol* 2000;38:2174-80.
- Pau CP, Lee-Thomas S, Auwanit W, et al. Highly specific V3 peptide enzyme immunoassay for serotyping HIV-1 specimens from Thailand. *AIDS* 1993;7:337-40.
- Armitage P. Tests for linear trends in proportions and frequencies. *Biometrics* 1955;11:375-86.
- Cochran WG. Some methods for strengthening the common  $\chi^2$  tests. *Biometrics* 1954;10:417-51.

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