Published in final edited form as:
Ann Epidemiol. 2008 July ; 18(7): 517–521. doi:10.1016/j.annepidem.2008.03.009.

Sexual activity and Kaposi's sarcoma among HIV-1 and HHV-8 coinfected men

Eric W. Nawar[1], **Stephen R. Cole**[1], **Homayoon Farzadegan**[1], **Mallory D. Witt**[2], **Frank J. Jenkins**[3], **Joseph B. Margolick**[4], **John P. Phair**[5], and **Lisa P. Jacobson**[1]

1 *Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

2 *David Geffen School of Medicine at UCLA, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Torrance, CA*

3 *Departments of Pathology and Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, PA*

4 *Department of Molecular Microbiology & Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD*

5 *Comprehensive AIDS Center, Northwestern University Medical School, Chicago, IL*

Abstract

Purpose—There is notable heterogeneity in the progression to Kaposi's Sarcoma (KS) among men coinfected with HIV-1 and HHV-8; additional determinants of KS likely exist. Here, we explore sexual activity as a proxy for a sexually transmitted determinant beyond HIV-1 and HHV-8.

Methods—The association between sexual activity and incident KS was estimated using data from 1,354 HIV-1 and HHV-8 coinfected homosexual men followed for up to 10 years in the Multicenter AIDS Cohort Study.

Results—As expected, white race, low CD4 cell count and acquiring HHV-8 after HIV-1 infection increased, while smoking decreased, the hazard of KS. The unadjusted hazard of KS among those with high sexual activity was 0.68 relative to the hazard of those with low sexual activity (95% confidence interval [CI]: 0.49, 0.93), and was somewhat muted after adjustment for characteristics measured at study entry (i.e. race, smoking, CD4 cell count, infection order, history of sexual activity, and sexually transmitted diseases). However, adjustment for time-varying covariates, particularly CD4 cell count, resulted in a nullification of the association (adjusted hazard ratio = 1.06; 95% CI: 0.77, 1.48).

Conclusion—Once HIV-1 and HHV-8 coinfection is established in homosexual men, progression to KS does not appear to be due to a third pathogen transmitted by sexual activity.

Keywords

HIV-1; HHV-8; Kaposi's sarcoma; sexual activity

Correspondence & Reprint Requests: Dr. Stephen R. Cole, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, E7640, Baltimore, MD 21205, Tel: 410-955-4342, Fax: 410-955-7587, scole@jhsph.edu.

Human herpesvirus type 8 (HHV-8) has been implicated as a causative agent in incident Kaposi's sarcoma (KS) among individuals infected with human immunodeficiency virus type 1 (HIV-1) [2–6]. As with other herpes viruses, in developed countries HHV-8 is transmitted primarily through sexual behaviors [7,8], although the risk factors of sexual transmission remain unclear [9–12]. There remains notable heterogeneity in the progression to KS among those coinfected with HIV-1 and HHV-8 [6,16,17], suggesting additional causes of KS.

Studies restricted to HHV-8 infected individuals have attempted to identify additional risk factors for KS [18], including HHV-8 viral load [19], HIV-1 and HHV-8 infection order [6, 17], and non-exposure to tobacco products [20]. A cross-sectional study of HHV-8 infected men with AIDS showed a decreased risk of KS among bisexual men as compared with men who were exclusively homosexual [21], which suggests an additional sexually transmitted pathogen more common among homosexual men (either superinfection with multiple subtypes of HHV-8, or a third pathogen other than HIV and HHV-8). As a prospective test of this third pathogen hypothesis, we measured the association of sexual activity with incident KS, among homosexual men coinfected with HIV-1 and HHV-8.

METHODS

Study Population

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective study of the natural and treated histories of HIV-1 infection and AIDS in homosexual and bisexual men in the US that began in 1984. Before 2001, a total of 5622 participants were enrolled from sites in Baltimore, Chicago, Pittsburgh, and Los Angeles, and have been seen at semiannual follow-up visits. All participants provided written consent and study protocols were approved by institutional review boards at each study site.

During each follow-up visit, an interviewer administered a detailed questionnaire including questions about sexual behavior. Blood samples were collected and stored in a central repository. HIV-1 seropositivity was ascertained using ELISA and confirmed by Western blot tests. Evidence of HHV-8 infection was determined by the presence of antibodies against lytic HHV-8 viral proteins. Detailed descriptions of the MACS [22,23], as well as the HHV-8 serological methods used [17], have been previously published.

The current study began in March 1985, the first study visit from which stored MACS samples were subsequently tested for HHV-8, and ended in November 1995 to preclude the overwhelming effects of highly active antiretroviral therapy on incident KS. Of the 5,622 MACS participants, 1,464 men were coinfected with HIV-1 and HHV-8 before the end of the study period. The study population comprised 1,354 of 1,464 or 92% of these HIV-1 and HHV-8 coinfected men who were free of KS at the start of the study period and had at least one follow-up visit.

Outcome Ascertainment

At each follow-up visit, participants were asked to report their medical history including KS diagnoses. 95% of reported KS cases were confirmed by medical records or registries; only confirmed KS cases are used in the present analyses.

Exposure Assessment

The primary exposure of interest was recent (i.e., prior six months) sexual activity reported at each semiannual visit. We ranked sexual activity using a time-varying composite score created using four sexual behavior variables, which asked the number of partners for: insertive oral sex, receptive oral sex, anal receptive intercourse, and anal insertive intercourse, all since the

last visit. If any of the four sexual activity reports were missing, data from the most recent of the previous three study visits was carried forward. Responses to the four sexual activity reports were categorized as low = 0, medium = 1 and high = 2, then combined into a composite score that ranged from 0 to 8, and demonstrated a high internal-consistency reliability of 0.86. Sexual activity was ranked as low, medium or high based on tertiles of the overall score. In addition, lifetime sexual activity was captured by recalling the lifetime number of male sexual partners at enrollment.

Statistical Analysis

The primary outcome was time from HIV-1 and HHV-8 coinfection to incident KS. The majority of the study population was coinfected at enrollment. Therefore, person-time accrued from age at the maximum of study entry or coinfection until the first of: a KS diagnosis, loss to follow-up, death, or administrative censoring on 30 November 1995.

CD4 cell count, smoking, and reported sexually transmitted diseases (i.e., syphilis, gonorrhea, or genital warts) were explored both as time-fixed (i.e., at study entry) and as time-varying variables. To estimate the total effect of sexual activity on incident KS rather than the direct effect of sexual activity not mediated through values of covariates affected by prior sexual activity, the time-varying variables were measured from the visit prior to the measurement of sexual activity. Infection with HIV-1 before HHV-8 and HHV-8 before HIV-1 were each compared to co-prevalent men. KS-free time was estimated using extended Kaplan-Meier curves, which all for late entries [24]. Cox regression analysis was used to determine the association of sexual activity with the hazard of developing KS [25], here we use incidence interchangeably with hazard. All models used the 292 incident KS cases in the final study population that comprised observations with no missing data for any of the analysis variables. Hazard ratios (HR) were used as a measure of association and 95% confidence intervals (CI) as a measure of precision.

RESULTS

The 1,354 coinfected men were followed for up to 10 years from study entry with a median (25^{th} percentile, 75^{th} percentile) follow-up time of 5.8 (3.0, 9.1) years. Table 1 provides descriptive characteristics of the study population at study entry. The median age of the cohort was 34 (30, 39) years at the start of follow-up, 85% of the cohort was white, 78% were co-prevalent with HIV-1 and HHV-8, and the median CD4 cell count at study entry was 541 cells/mm^3. 34% reported smoking at least half a pack of cigarettes per day at study entry, and this smoking proportion did not change appreciably during follow-up (data not shown). Table 1 also shows the associations between key factors and sexual activity reported at study entry: Infection order, CD4 cell count, reports of sexually transmitted disease, and the lifetime number of sexual partners were each notably associated with level of sexual activity reported at study entry as shown in Table 1.

292 of 1,354 men incurred KS during follow up. Being Caucasian carried a near 80% increase in KS incidence and acquiring HIV-1 prior to HHV-8 carried a 50% increase in the KS incidence (Table 2). Each increase of 50 CD4 cells/mm^3 decreased the KS incidence by 20% and smoking decreased the KS incidence in a dose-response fashion (p for trend = 0.03). Additionally, lifetime number of partners was associated with a moderate increased KS incidence for >99 partners, but was somewhat attenuated in the final model (Table 2).

The age-adjusted model suggests that the KS incidence for the moderate or high sexual activity groups is about 70% of the incidence for the low sexual activity group; similar results are observed for the model adjusting for time-fixed characteristics (Table 2). The model further

adjusting for time-varying CD4 cell count, smoking, and reported sexually transmitted disease yielded a null association between sexual activity and KS incidence (Table 2).

DISCUSSION

We explored whether sexual activity, as a proxy for a third sexually transmitted pathogen, was associated with incident KS among homosexual men coinfected with HIV-1 and HHV-8. After control for time-varying confounding, primarily by CD4 cell count, we found that sexual activity was not independently associated with incident KS.

Sexual activity was shown to be associated with KS prior to knowledge that HHV-8 was a causative factor [1,26,27]. The few studies investigating incident KS among HIV-1 and HHV-8 coinfected men have been primarily limited to laboratory measurements [18,19]. A recent cross-sectional study of HIV-1 and HHV-8 coinfected men [21] that observed an association between sexual activity and incident KS was unable to distinguish the temporal order of sexual activity and KS. While male homosexual behavior has been shown to be the primary risk factor for the transmission of HHV-8 [7] it is less clear what impact, if any, it may have on the risk of progression to KS beyond the acquisition of HHV-8. The age-adjusted analysis suggested an inverse association between moderate or high sexual activity and KS. However adjusting for time-varying CD4 cell counts nullified the association. Adjustment for the more recent time-varying CD4 cell count (compared to CD4 count measured at study entry) may better control for confounding due to CD4; time-varying CD4 cell count is a likely confounder of the sexual activity-KS relation since it was both associated with sexual activity and an important predictor of KS. The association between recent CD4 cell count and sexual activity is most likely not a direct causal effect, but rather indicative of sicker men engaging in less sexual activity than healthier men.

The associations of race, infection order, CD4 cell count, and smoking with KS were all in expected directions based on prior research. We observed a strong association between Caucasian race and KS. A potential explanation for this finding is that those with higher socioeconomic status have better access to medical care [28] and therefore get diagnosed with KS earlier than individuals with less access. An alternative explanation is that there may be difficulty in diagnosing KS in darkly pigmented skin [29]. We also observed a moderate association whereby acquiring HIV-1 before HHV-8 increased incident KS. While this finding is consistent with prior studies [6,17], ours results were limited by the fact that 78% of the study population was co-prevalent. Prior to our study, smoking had been associated with a decreased incident of both classic and AIDS-related KS [20,30]. Goedert *et al*. [20] observed that subjects with classic KS were only 25% as likely to be current or former smokers as compared to non-KS controls. Hoover *et al*. [30] examined incident KS without regard to HHV-8 serostatus and observed about 35% reduction in the incidence of AIDS-related KS among participants who smoked at least a half a pack of cigarettes per day compared to non-smokers.

There are three central limitations to this study. First, the method we used to define sexual activity was a composite score based on four questions asked during semiannual follow-up visits, and is a fallible measure of overall sexual activity. Specifically, not all types of sexual activity were represented by the questions used. For example neither deep wet kissing nor oral-anal activity were represented and therefore any independent effect of those activities on incident KS would be missed by this analysis, but only to the extent that they are not proxied well by the four questions used in the composite score. Second, serological assays used to determine HHV-8 serostatus have imperfect sensitivity and specificity [31] and therefore HHV-8 serostatus may be misclassified. Third, as with all observational analyses unmeasured confounding is a possible explanation for the findings.

In summary, we used a large well-characterized prospective cohort to estimate the association of sexual activity and incident KS for HIV-1 and HHV-8 coinfected homosexual men. This study showed no meaningful association between sexual activity and KS, but demonstrates the importance of adjusting for time-varying covariates. Further, this study adds to the accumulating literature by demonstrating: an increased KS incidence among Caucasians, an increased KS incidence among those infected with HIV-1 prior to HHV-8, and a decreased KS incidence among smokers. The remaining heterogeneity in incident KS among HIV-1 and HHV-8 coinfected men does not appear to be due to sexual activity. Further efforts are needed to elucidate remaining modifiable determinants of KS to assist in developing preventive measures.

Acknowledgements

Data in this manuscript were collected by the Multicenter AIDS Cohort Study (MACS) with centers (Principal Investigators) at The Johns Hopkins University Bloomberg School of Public Health (Joseph B. Margolick, Lisa Jacobson), Howard Brown Health Center and Northwestern University Medical School (John Phair), University of California, Los Angeles (Roger Detels, Beth Jamieson), and University of Pittsburgh (Charles Rinaldo). The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute. UO1-AI-35042, 5-MO1-RR-00722 (GCRC), UO1-AI-35043, UO1-AI-37984, UO1-AI-35039, UO1-AI-35040, UO1-AI-37613, UO1-AI-35041. Website located at http://www.statepi.jhsph.edu/macs/macs.html.

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TABLE 1

Characteristics of 1,354 HIV-1 and HHV-8 coinfected men at study entry

Characteristic: *	Total	Sexual Activity		
		Low	Moderate	High
	N = 1,354	N = 164	N = 645	N = 545
Age, yrs	34 (30,39)	37 (33,42)	34 (30,38)	34 (30,39)
Race, % (n):				
Caucasian	85% (1,158)	86% (141)	85% (549)	86% (468)
African-American	7% (88)	4% (6)	6% (37)	8% (45)
Hispanic	7% (91)	9% (15)	8% (51)	5% (25)
Other	1% (17)	1% (2)	1% (8)	1% (7)
Infection order:				
HIV-1 prior to HHV-8	14% (189)	35% (57)	11% (69)	12% (63)
HHV-8 prior to HIV-1	8% (107)	5% (8)	8% (51)	9% (48)
Co-prevalent	78% (1,058)	60% (99)	81% (525)	80% (434)
CD4 count, cells/mm^3	541 (376,737)	434 (246,693)	548 (400,751)	558 (381,718)
Sexually transmitted disease, % (n) †	13% (171)	6% (10)	9% (60)	19% (101)
Current packs/day smoking, % (n):				
None	66% (876)	68% (111)	64% (416)	64% (349)
>0 – 1	13% (170)	9% (15)	13% (81)	14% (74)
>1 – 2	14% (190)	18% (29)	14% (89)	13% (72)
>2	7% (89)	5% (9)	7% (44)	7% (36)
Lifetime male sexual partners, % (n):				
<100	22% (299)	34% (55)	26% (168)	14% (76)
100 – 299	24% (330)	26% (43)	25% (161)	23% (126)
300 – 999	28% (381)	22% (36)	27% (175)	31% (170)
>999	25% (338)	18% (29)	21% (138)	31% (171)

* median (interquartile range), unless otherwise noted

† syphilis, gonorrhea, or genital wart

TABLE 2

Association of sexual activity with incident Karposi's sarcoma in 1,354 HIV-1 and HHV-8 coinfected men

	Age-adjusted		Time-fixed Adjustment *		Time-varying Adjustment *	
	HR	95% CI	HR	95% CI	HR	95% CI
Sexual activity:						
Moderate vs. low	0.73	0.56, 0.95	0.79	0.61, 1.02	1.00	0.77, 1.30
High vs. low	0.68	0.49, 0.93	0.72	0.52, 1.00	1.06	0.77, 1.48
>99 lifetime male sexual partners	1.37	1.01, 1.86	1.28	0.94, 1.74	1.25	0.92, 1.70
Caucasian race			1.75	1.17, 2.61	1.78	1.19, 2.67
Infection order:						
HIV-1 prior to HHV-8 vs. co-prevalent			1.81	1.32, 2.48	1.50	1.10, 2.04
HHV-8 prior to HIV-1 vs. co-prevalent			1.05	0.59, 1.87	1.09	0.62, 1.92
CD4 count, 50 cells/mm^3			0.91	0.89, 0.94	0.80	0.77, 0.82
Sexually transmitted disease			1.12	0.81, 1.56	0.74	0.47, 1.15
Current packs/day smoking:						
>0 – 1 vs. none			1.10	0.79, 1.53	0.99	0.70, 1.41
>1 – 2 vs. none			0.81	0.56, 1.13	0.70	0.48, 1.03
>2 vs. none			0.51	0.27, 0.94	0.60	0.31, 1.18

* Time-fixed adjustment for values presented in Table, time-varying adjustment for CD4 count, sexually transmitted disease and smoking