Correlates of human herpesvirus 8 seropositivity among heterosexual men in Kenya

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Background: Several studies have suggested that sexual transmission of human herpesvirus 8 (HHV-8) occurs among homosexual men in developed countries. However, few studies have examined heterosexual HHV-8 transmission, especially among African populations in which HHV-8 is endemic.

Objectives: To determine the seroprevalence and correlates of HHV-8 infection among heterosexual African men.

Design: Cross-sectional study.

Methods: Participants were 1061 men enrolled in a prospective cohort study of risk factors for HIV-1 acquisition among trucking company employees in Mombasa, Kenya. Stored frozen sera from the study baseline visit were tested for antibodies to HHV-8 by whole-virus lysate ELISA.

Results: HHV-8 seroprevalence was 43%. In multivariate logistic regression analysis, HHV-8 infection was independently associated with older age [for men aged 30–39 years: odds ratio (OR), 1.5; 95% confidence interval (CI), 1.1–2.0; for men aged $\geq$ 40 years: OR, 1.7; 95% CI, 1.1–2.7, compared with men aged $<$ 30 years], Christian religion (OR, 1.6; 95% CI, 1.2–2.1), being uncircumcised (OR, 1.5; 95% CI, 1.0–2.2), and ever having syphilis (OR, 2.2; 95% CI, 1.4–3.5). Ever having used condoms was associated with decreased likelihood of infection (OR, 0.7; 95% CI, 0.6–1.0). Seropositivity was not significantly related to other sexual behaviors characterized or to HIV-1 status.

Conclusions: HHV-8 seropositivity is common in this population and increases with age, suggesting on-going transmission during adulthood. Infection was more common among men who were uncircumcised or who had ever had syphilis and was less common among those who had ever used condoms, suggesting that sexual factors may play a role in HHV-8 transmission. Prospective studies of HHV-8 acquisition in heterosexual African populations are needed to demonstrate whether safer sexual practices can reduce transmission.

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Introduction

Kaposi's sarcoma is the most frequently occurring cancer among men with AIDS in the USA [1], and has become the most common cancer among men overall in some African countries [2]. Epidemiologic and molecular studies have implicated human herpesvirus 8 (HHV-8) as the causal agent of Kaposi's sarcoma [3]. Identification of risk factors for HHV-8 may suggest intervention strategies to prevent transmission and malignancy.

Early studies of the epidemiology of AIDS-associated Kaposi's sarcoma suggested a relationship with sexual behavior [4]. HHV-8 infection has been associated with higher-risk sexual behavior among homosexual men [5,6], but evidence for sexual transmission among heterosexual populations has been inconsistent [7,8]. In African populations, HHV-8 infection is more common than in Western populations, and studies have found evidence for both sexual and non-sexual transmission [9,10].

From 1993 through 1997, we conducted a prospective study of risk factors for HIV-1 acquisition among male trucking company employees in Mombasa, Kenya [11]. Archived frozen sera from this study were available, affording us the opportunity to conduct a cross-sectional study of risk factors, including sexual factors, associated with HHV-8 infection among heterosexual African men.

Methods

The study protocol was approved by the institutional review boards of the University of Washington and the University of Nairobi. Participants provided informed consent. Study procedures have been described previously [11]. Briefly, a mobile research clinic visited each of six participating trucking companies weekly. After completing HIV-1 counseling, blood was obtained for HIV-1 and syphilis testing. Men returned for their results the following week. HIV-1 seronegative men were offered enrollment in the cohort. To protect confidentiality, seropositive men were also enrolled. A standard questionnaire, covering demographic characteristics and occupational and sexual history was administered and a physical examination was conducted, including determination of circumcision status. Stored sera were later tested for antibodies to HHV-8.

Laboratory procedures

HIV-1 testing was by ELISA (Detect-HIV, BioChem Immunosystems, Montreal, Canada). Positive results were confirmed with a second ELISA (Recombigen, Cambridge Biotech, Galway, Ireland). Syphilis serologic testing was by rapid plasma reagin (RPR, Becton Dickinson, Cockeysville, Maryland, USA) and *Treponema pallidum* hemagglutination assay (TPHA, Biotech Laboratories, Lightwater, UK). All men having a positive TPHA were defined as ever having syphilis. Those with a positive TPHA and a positive RPR were defined as having current syphilis. Antibodies to HHV-8 were detected by an in-house, whole-virus lysate ELISA [12].

Data analysis

Statistical analyses were conducted using SPSS 10.0 (SPSS, Chicago, Illinois, USA) and EpiInfo 2000 (Centers for Disease Control and Prevention, Atlanta, Georgia, USA). Comparisons of categorical variables were conducted using χ^2 and Fisher's exact tests and comparisons of continuous variables using Mann–Whitney U-tests and Spearman's correlation coefficient. Logistic regression was used for multivariate analyses.

Results

Study population

A total of 1175 men were enrolled, and samples for HHV-8 serologic testing were available for 1137 (97%). Of these, 76 (7%) had equivocal HHV-8 results and were excluded from this analysis. Of the remaining 1061 men, 460 (43%) were HHV-8 seropositive and 601 (57%) were HHV-8 seronegative. The median age was 30 years (range, 17–64 years) and the median number of years of education was 9 (range, 0–19 years). The median number of sexual partners during the year preceding enrollment was two (range, 0 to >100 sexual partners). Of the men, 693 (65%) were married, 630 (59%) had a history of sex with a prostitute, and only 584 (55%) had ever used a condom; 149 (14%) were uncircumcised, and 123 (12%) were HIV-1 seropositive; three ($<1\%$) reported a history of sex with another man.

Correlates of HHV-8 seropositivity

HHV-8 seropositive men were significantly older than seronegative men (median 31 years vs. 29 years; $P<0.001$), reflecting a strong association between age and increasing HHV-8 seroprevalence (Table 1). HHV-8 seropositive men were more likely to be married and Christian than HHV-8 seronegative men. Men with $\geqslant 13$ years of education were less likely to be infected with HHV-8 than men with <13 years of education (57/159, 36% versus 403/902, 45%; $P=0.04$). HHV-8 infection was also less common among men who smoked tobacco or who chewed miraa (an amphetamine-containing leaf). HHV-8 seropositivity increased steadily with years of sexual activity, though the number of years of sexual activity

Table 1. Univariate correlates of HHV-8 seropositivity.

Characteristic	n	HHV-8 seropositive [n (%)]	OR (95% CI)	*P*
Demographic characteristics				
Age (years)				0.001[a]
< 30	529	200 (38%)	1.0	
30–39	379	177 (47%)	1.4 (1.1–1.9)	0.008
⩾ 40	153	83 (54%)	2.0 (1.3–2.9)	< 0.001
Education (years)				0.2[a]
0–8	470	212 (45%)	1.0	
9–12	432	191 (44%)	1.0 (0.7–1.3)	0.8
⩾ 13	159	57 (36%)	0.7 (0.5–1.0)	0.04
Married				
No	368	141 (38%)	1.0	
Yes	693	319 (46%)	1.4 (1.1–1.8)	0.02
Religion				
Muslim	220	79 (36%)	1.0	
Protestant	426	192 (45%)	1.5 (1.0–2.1)	0.03
Catholic	343	163 (48%)	1.6 (1.1–2.3)	0.007
Other	72	26 (36%)	1.0 (0.6–1.8)	1.0
Smoke tobacco				
No	635	292 (46%)	1.0	
Yes	426	168 (39%)	0.8 (0.6–1.0)	0.03
Drink alcohol				
No	561	235 (42%)	1.0	
Yes	500	225 (45%)	1.1 (0.9–1.5)	0.3
Smoke marijuana				
No	1013	442 (44%)	1.0	
Yes	48	18 (38%)	0.8 (0.4–1.5)	0.4
Chew miraa				
No	911	411 (45%)	1.0	
Yes	149	48 (32%)	0.6 (0.4–0.9)	0.003
Occupational characteristics				
Occupation				
Driver	165	67 (41%)	1.0	
Driver's assistant	230	104 (45%)	1.2 (0.8–1.9)	0.4
Mechanic	264	112 (42%)	1.1 (0.7–1.6)	0.7
Other	402	177 (44%)	1.2 (0.8–1.7)	0.5
Travel, days per month				1.0[a]
0	596	258 (43%)	1.0	
1–14	206	90 (44%)	1.0 (0.7–1.4)	0.9
> 14	259	112 (43%)	1.0 (0.7–1.4)	1.0
Sexual characteristics				
Years of sexual activity				< 0.001[a]
0–4	55	16 (29%)	1.0	
5–9	240	92 (38%)	1.5 (0.8–3.0)	0.2
10–14	283	117 (41%)	1.7 (0.9–3.4)	0.09
15–19	237	108 (46%)	2.0 (1.0–4.1)	0.03
20–24	122	62 (51%)	2.5 (1.2–5.3)	0.007
⩾25	124	65 (52%)	2.7 (1.3–5.6)	0.004
Ever used condoms				
No	477	227 (48%)	1.0	
Yes	584	233 (40%)	0.7 (0.6–0.9)	0.01
Ever had sex with prostitute				
No	431	187 (43%)	1.0	
Yes	630	273 (43%)	1.0 (0.8–1.3)	1.0
Number of partners, past year				0.6[a]
0–1	419	182 (43%)	1.0	
2–4	470	207 (44%)	1.0 (0.8–1.4)	0.9
5–9	108	38 (35%)	0.7 (0.4–1.1)	0.1
⩾ 10	63	33 (52%)	1.4 (0.8–2.5)	0.2
Sex with prostitute, past year				
No	696	303 (44%)	1.0	
Yes	364	157 (43%)	1.0 (0.8–1.3)	0.9
Uncircumcised[b]				
No	901	374 (42%)	1.0	
Yes	149	80 (54%)	1.6 (1.1–2.4)	0.005

(continued overleaf)

Table 1. (continued).

Characteristic	n	HHV-8 seropositive [n (%)]	OR (95% CI)	*P*
Physical and serologic findings				
Urethral discharge				
No	1020	444 (44%)	1.0	
Yes	38	15 (40%)	0.9 (0.4–1.7)	0.6
Genital ulcer disease				
No	1047	455 (44%)	1.0	
Yes	11	4 (36%)	0.7 (0.2–3.0)	0.8
Current syphilis[c]				
No	993	414 (42%)	1.0	
Yes	40	30 (75%)	4.2 (1.9–9.3)	< 0.001
Ever syphilis[d]				
No	935	383 (41%)	1.0	
Yes	98	59 (60%)	2.2 (1.4–3.4)	< 0.001
HIV-1 antibody positive[e]				
No	926	398 (43%)	1.0	
Yes	123	56 (46%)	1.1 (0.8–1.7)	0.6

[a]χ^2 test for trend. [b]Circumcision status not available for three men. An additional eight partially circumcised men were excluded. [c]Defined as positive rapid plasma reagin and positive *Treponema pallidum* hemagglutination assay (TPHA) test results. [d]Defined as a positive TPHA test result. [e]Twelve men with discordant HIV-1 ELISA results were excluded from the analysis. OR, Odds ratio; CI, confidence interval.

was also strongly correlated with age (Spearman's correlation coefficient, 0.90; $P < 0.001$). A history of condom use was associated with a significantly decreased likelihood of HHV-8 seropositivity, and uncircumcised status and ever having syphilis were associated with significantly increased likelihoods of infection. There was no relationship between HHV-8 infection and occupation, days per month away from home, history of sex with a prostitute, number of sexual partners during the year preceding enrollment, signs of sexually transmitted disease, or HIV-1 status.

To evaluate independent risk factors for HHV-8 seropositivity, a multivariate logistic regression model was constructed, including those factors with statistically significant relationships with HHV-8 infection in univariate analysis. Because the aim of this study was to assess the relation between sexual behavior and HHV-8 infection, number of sexual partners and HIV-1 serostatus were also included. Years of sexual activity was not included because of collinearity with age. Ever having syphilis was included, rather than current syphilis, to better reflect lifetime sexual behavior. In multivariate analysis, age, Christian religion, uncircumcised status, and a history of syphilis were independently associated with an increased likelihood of HHV-8 infection, and ever having used condoms was associated with decreased risk (Table 2). No associations between HHV-8 infection and marital status, tobacco or miraa use were preserved in multivariate analysis. There remained no statistically significant relationship between number of sexual partners during the previous year or HIV-1 infection and HHV-8 seropositivity.

Table 2. Multivariate analysis of correlates of HHV-8 seropositivity

Characteristic	OR (95% CI)	P
Age (years)		
< 30	1.0	
30–39	1.5 (1.1–2.0)	0.02
⩾ 40	1.7 (1.1–2.7)	0.02
Education ⩾ 13 years	0.7 (0.5–1.1)	0.13
Currently married	1.0 (0.7–1.4)	0.9
Christian	1.6 (1.2–2.1)	0.003
Smoke tobacco	0.8 (0.6–1.1)	0.2
Chew miraa	0.7 (0.5–1.1)	0.13
Ever used condoms	0.7 (0.6–1.0)	0.03
Uncircumcised	1.5 (1.0–2.2)	0.04
Number of partners, past year		
0–1	1.0	
2–4	1.1 (0.8–1.4)	0.7
5–9	0.7 (0.4–1.2)	0.2
10+	1.7 (0.9–2.9)	0.08
Ever had syphilis	2.2 (1.4–3.5)	0.001
HIV-1	0.8 (0.5–1.2)	0.4

OR, Odds ratio; CI, confidence interval.

Discussion

In this large cross-sectional study of heterosexual Kenyan men, the seroprevalence of HHV-8 infection was 43%. Seropositivity increased with age, suggesting that some transmission occurs during adulthood in this population. Infection was associated with never having used condoms, with ever having syphilis, and with being uncircumcised, suggesting that sexual factors may play a role in HHV-8 acquisition. However, we found no statistically significant association between HHV-8 seropositivity and recent sexual behavior, a history of sexual encounters with prostitutes, or HIV-1 status.

Seroepidemiological studies have demonstrated that HHV-8 infection is common among African adults, with prevalences approaching 50% [9,13–15]. Studies among children have shown increasing HHV-8 seroprevalences with age and high prevalences among adolescents [10,16], suggesting that many infections are acquired prior to adulthood. Familial aggregation of HHV-8 seropositivity in endemic populations suggests that mother-to-child and sibling–sibling routes of transmission may predominate [17]. However, several studies have shown that HHV-8 seroprevalence continues to increase with age among adults in these populations [9,15], potentially due to sexual transmission.

Evidence for sexual transmission of HHV-8 largely comes from studies of homosexual men in industrialized countries, among whom HHV-8 seropositivity has been associated with greater numbers of sexual partners, a history of sexually transmitted diseases, and HIV-1 infection [5,6,18]. There has been only a small number of studies among heterosexual populations. Two from Italy showed higher HHV-8 seroprevalences among female prostitutes, men reporting sex with prostitutes, sexually transmitted disease clinic attendees, and sexual partners of men with Kaposi's sarcoma [19,20]. A study from Honduras found HHV-8 infection to be associated with HIV-1 infection and, among women, with commercial sex work [21]. Studies from Africa have demonstrated HHV-8 to be associated with a greater number of lifetime sexual partners [15] and with commercial sex work [9]. However, these associations were weak and similar findings have not been documented in all studies [7,16]. HHV-8 infection has not been consistently associated with HIV-1 infection in studies from Africa [9,14,15,22].

Lack of male circumcision has been repeatedly associated with increased risk of HIV-1 acquisition in African populations [23], including this cohort [24]. Possible mechanisms for this relation include increased trauma during sexual intercourse, better survival of viral agents within the preputial sac, and increased risk of genital ulcer disease [24,25]. Ecological studies have shown a strong relationship between the prevalence of male circumcision in African populations and the prevalence of HIV-1 [26], and it would be interesting to know if this relation is similar for HHV-8.

We found that a history of syphilis was independently associated with increased likelihood of HHV-8 infection. Serologic evidence of syphilis is a marker for higher risk sexual behavior [27], suggesting that sexual activity may play a role in HHV-8 transmission. A history of syphilis has been associated with HHV-8 infection among homosexual men [5,7].

We also found that a history of condom use was associated with decreased likelihood of HHV-8 infection. To our knowledge, this is the first study to demonstrate that condom use might protect from HHV-8 infection, and additional studies are needed to examine whether changing sexual behavior could reduce transmission. Finally, we found that Christian religion was associated with HHV-8 infection, which may reflect differences in sexual behavior or sexual mixing within this population.

One limitation of our study is that information on lifetime number of sexual partners was not available, though previous studies have shown this to be a risk factor for HHV-8 [15]. We collected data on sexual activity during the year prior to study enrollment, but this may inadequately reflect lifetime risk behavior. Similarly, data on history of sexually transmitted diseases were not available, though we used serologic testing to identify men who had ever had syphilis, for which we found an association with HHV-8 infection.

An important limitation of this study is its cross-sectional design. Cross-sectional studies among African populations may not have adequate sensitivity to identify risk factors for sexual transmission of HHV-8 infection [22], as the high baseline prevalence of infection in African populations due to prepubertal acquisition may obscure all but the strongest associations. This is because inclusion of individuals who acquired HHV-8 before sexual debut would result in misclassification of risk and bias towards the null. This may in part explain the absence of any significant association between HHV-8 infection and HIV-1 status or recent sexual behavior. Similar difficulties have been encountered in studies of sexual transmission of other infections that have multiple transmission routes, such as hepatitis B [28]. The pattern of HHV-8 spread before sexual debut in our population is unknown, but other studies from Africa have suggested that non-sexual routes are important, as most infections are acquired during childhood [10]. Recent studies have shown that HHV-8 is infrequently detectable in genital secretions of infected individuals but can be found in saliva [22,29,30], suggesting that sexual transmission may be inefficient and non-sexual transmission may occur among adults. Prospective studies that measure a variety of exposures are needed to establish temporality and causality of risk factors for HHV-8 acquisition among heterosexual populations.

This study provides new evidence that HHV-8 transmission occurs during adulthood in African heterosexual populations and may be associated with sexual activity. Our finding that being uncircumcised was independently associated with HHV-8 is novel and suggests possible mechanisms by which HHV-8 may be transmitted. Moreover, our data are the first to suggest that condom use may be protective for HHV-8 infec-

tion. Prospective studies are needed to document whether safer sexual practices are able to reduce HHV-8 acquisition.

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