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Population-Based Assessment of Kaposi Sarcoma-Associated Herpesvirus DNA in Plasma among Ugandans

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Abstract

Risk of Kaposi sarcoma (KS) is linked to detection of Kaposi sarcoma-associated herpesvirus (KSHV) DNA in plasma, but little is known about the prevalence and risk factors for plasma KSHV DNA detection among the general population where KS is endemic. Correlates of KSHV plasma detection were investigated in a population-based sample of adult Ugandans (15–59 years) who participated in an HIV/AIDS serobehavioral survey in 2004/2005. KSHV DNA was measured in plasma of 1,080 KSHV seropositive and 356 KSHV seronegative persons using polymerase chain reaction (PCR). KSHV DNA in plasma was detected in 157 (8.7%) persons; of these 149 (95%) were KSHV seropositive and 8 (5%) were seronegative. Detection of KSHV DNA in plasma was significantly associated with male sex ($P<0.001$), older age ($P=0.003$), residence in a rural versus urban area ($P=0.002$), geographic region ($P=0.02$), and being KSHV seropositive (13.8% seropositive versus 2.3% seronegative, $P<0.001$). In a multivariable model, KSHV DNA plasma quantity was significantly higher in men ($P=0.002$), inversely associated with age ($P=0.05$), and residing in an urban area ($P=0.01$). In Uganda, KSHV is detected more frequently in the plasma of adult males and residents of rural regions, potentially explaining the increased risk of KS in these subsets of the Ugandan population.

Keywords

Kaposi Sarcoma-Associated Herpesvirus; Kaposi Sarcoma; Plasma; Epidemiology; Uganda

INTRODUCTION

Kaposi sarcoma (KS) is a rare vascular multi-centric tumor of spindle cells first described by Moritz Kaposi in 1872 [Kaposi, 1872]. KS occurs worldwide, but with marked geographic variation [Oettle, 1962; Hutt and Burkitt, 1965]. It occurs as “classical KS” in Mediterranean Europe [Ronchese, 1958], and as endemic KS in parts of equatorial Africa

[Oettle, 1962; Hutt and Burkitt, 1965], including Uganda [Hutt, 1981], where it comprises up to 10% of cancers among adults in certain regions. In 1981, epidemic KS heralded the eruption of the human immunodeficiency virus (HIV) epidemic and focused attention on the acquired immunodeficiency syndrome (AIDS) [1981; Gottlieb et al., 1981; Hymes et al., 1981]. In 1994, a novel herpesvirus, KS-associated herpesvirus (KSHV, also called human herpesvirus 8 or HHV-8), was discovered in KS tissues from a person with AIDS [Chang et al., 1994; Martin, 2011]. KSHV is now accepted as the infectious cause of KS [IARC, 2012].

The distribution of KS may be accounted for by the prevalence of KSHV as evidenced by the strong geographic correlation between KSHV seropositivity and KS incidence. The highest rates of both are noted in equatorial Africa [Dedicoat and Newton, 2003; Dukers and Rezza, 2003], intermediate rates in Mediterranean Europe [Serraino et al., 2001], low rates in North America and Northern Europe [Engels et al., 2002; Engels et al., 2007]. In the West, circumscribed occurrence of high KS incidence is linked to pockets of high KSHV seropositivity in homosexual men [Mbulaiteye et al., 2006]. However, departures from a strong correlation of KSHV prevalence and KS incidence have been noted. For example, high KSHV seropositivity has been reported in studies conducted in the Gambia [Ariyoshi et al., 1998] and Botswana [Engels et al., 2000] in Africa, and among Amerindians [Biggar et al., 2000] and African-origin people living in Guyana in South America [Plancoulaine et al., 2000], but KS is rare in populations in these regions. In Uganda, where the majority of adults are KSHV seropositive [Biryahwaho et al., 2010; Shebl et al., 2011] and KS is endemic [Hutt, 1981], there are marked variations in KSHV prevalence [Biryahwaho et al., 2010] and KS incidence [Taylor et al., 1972] in different geographic regions of the country. Population-based KSHV seropositivity, based on results from a representative national survey of adult Ugandans aged 15–59 years conducted in 2004/2005 [Wabinga et al., 2000], ranged 47% in Kampala to 66% in West Nile region. Similar variation in KSHV seropositivity has been observed in other studies conducted in Uganda, ranging from 34% in a population-based study in Mukono district [Butler et al., 2011], located near Kampala, to nearly 88% of persons studied at the Uganda Cancer Institute in Kampala [de-The et al., 1999; Johnston et al., 2009]. Similarly, the crude incidence of KS, uncorrected for age, during 1964–1968, before the AIDS epidemic, was reported to range between 0 cases per 100,000 person-years in Mubende district, in central regions of Uganda and 19.8 cases per 100,000 person-years in Toro district [Taylor et al., 1972], in the West Nile regions of Uganda. Additional evidence for the disparity between KSHV prevalence and KS incidence is reflected in the differential incidence between genders, with endemic KS being ten-fold more common and epidemic KS three-fold more common among men than women, although the prevalence of KSHV in Ugandan women is only about 20% lower than that in men [Biryahwaho et al., 2010; Shebl et al., 2011]. The disparity in KS incidence relative to KSHV seropositivity suggests that additional co-factors that vary by geography and gender influence the risk for KS in KSHV seropositive individuals.

KSHV DNA in peripheral blood is associated with an increased risk of developing KS [Nsubuga et al., 2008], and is detected more frequently in persons with KS and with HIV infection [Johnston et al., 2009]. No work to date has examined the prevalence of KSHV DNA in peripheral blood in the general population where KS is endemic and/or epidemic. Here we report the first study to be conducted in Africa to investigate prevalence and risk factors of KSHV DNA in plasma in a well-characterized nationally-representative population-based sample in Uganda, where both KSHV and KS are endemic.

MATERIALS AND METHODS

Selection of study subjects

Samples for KSHV DNA and serologic testing were selected randomly from Uganda adults aged 15–59 years who participated in the Uganda HIV/AIDS serobehavioral survey (UHSBS) in 2004–2005 [Bunnell et al., 2008; Mermin et al., 2008]. The UHSBS was based on a two-stage cluster survey design and it was nationally-representative of the Ugandan adult population [Bunnell et al., 2008; Mermin et al., 2008]. KSHV serology on the selected samples was performed as previously described [Biryahwaho et al., 2010]. Briefly, enzyme immunoassays (EIAs) based on synthetic peptides encoded by K8.1 and orf65 viral genes [Pau et al., 1998; Spira et al., 2000] were run at the Uganda Virus Research Institute (UVRI). To provide background optical density (OD) readings, blank uncoated wells were run as negative controls adjacent to each plasma specimen. The raw EIA OD readings were adjusted by subtracting the mean of the OD readings of the negative wells. Samples were considered KSHV seropositive when the adjusted OD values were >0.7 on the K8.1 test or >2.5 on the orf65 test for samples with OD results of 0.5–0.7 on the K8.1 test [Biryahwaho et al., 2010]. Samples that did not meet these criteria were considered KSHV seronegative. We selected all KSHV seropositive participants and random sample of participants with a negative KSHV serology to measure the quantity of KSHV DNA in their serum using polymerase chain reaction (PCR).

Laboratory assays

DNA extraction and KSHV PCR—DNA extraction and KSHV PCR were performed at the Hutchinson Cancer Research Institute – Uganda Molecular Diagnostics Laboratory. DNA was extracted from 200 μ L of plasma using the QIAmap96 DNA blood kit (Qiagen) and was eluted with 100 μ L of AE buffer (Qiagen) [Casper et al., 2007]. Ten μ L of DNA was used to detect and quantify KSHV by real-time Taqman PCR using double primer / probe sets for ORF 73 (CCA GGA AGT CCC ACA GTG TTC /FAM- CAT CCG GGC TGC CAG CAT TTG-TAMRA /GCC ACC GGT AAA GTA GGA CTA GAC) and T07-K12 (TCCCCACCGAGTGCTT/FAM-AATGCGGAGAGGAATGMGB/GCACGCGGTGTCAACCA). Multiple negative controls and positive controls were included in each PCR run. An internal positive control was spiked into all reactions to monitor PCR interference [Spira et al., 2000]. Samples were considered positive if they had 50 copies of KSHV DNA/ml of sample.

Statistical methods

Descriptive analyses included summary tables and examination of univariate associations between KSHV and individuals characteristics such as age, sex, education, residence, wealth index and HIV status.

To accommodate the fact that we sampled our study subjects from a complex survey, we calculated the probability of a person being included in this study by multiplying the original probability of inclusion, obtained as the inverse of the survey weight, by the probability of being selected for KSHV PCR testing, and the probability that samples were tested using PCR. The sample weights of our study were calculated as the inverse of the study inclusion probabilities. We accounted for the sampling design that gave rise to our data, when assessing associations between KSHV PCR positivity and demographic, socioeconomic, and sexual behavioral characteristics by incorporating the weight information using PROC SURVEYMEANS and PROC SURVEYFREQ in SAS 9.2. Similarly, odds ratios (ORs) and 95% confidence intervals (95% CIs) of association of KSHV viremia with demographic, socioeconomic, and sexual variables were calculated using logistic regression models accounting for the design in PROC SURVEYLOGISTIC in SAS 9.2. Domain analysis with

the domain statement in PROC SURVEYLOGISTIC was used to obtain subpopulations estimates and variances [Rao and Scott, 1981]. Two-sided P values of <0.05 were considered to be statistically significant. All analyses were conducted with SAS (Version 9.2, SAS Institute Inc.; Cary, NC, USA).

Ethics statement

Ethical approval to conduct the Uganda HIV/AIDS serobehavioral survey (UHSBS) in 2004/2005 was obtained from the UVRI Science Ethics Committee and the National Council of Science and Technology in Uganda, and from the Centers for Disease Control and Prevention (CDC, Atlanta, Georgia, USA) [Bunnell et al., 2008; Mermin et al., 2008; Biryahwaho et al., 2010]. Written informed consent was obtained from the participant to answer a questionnaire and give a venous blood for HIV, syphilis, herpes simplex virus 2 (HSV2), hepatitis B virus (HBV) serology [Bunnell et al., 2008], and storage for future studies. Ethical approval to conduct the KSHV serology study was obtained from the Office of Human Subject Research at the National Institutes of Health. Only samples from participants who consented for their blood to be stored were included in the current study. Individual identifiers were not used in the current study.

RESULTS

Figure 1 shows how the 1,436 participants tested for KSHV DNA in this study (1,080 KSHV seropositive and 356 KSHV seronegative) were selected from the UHSBS participants. No differences were noted in the socio-demographic characteristics and HIV status of the subjects who were selected and tested versus those who were selected but not tested by PCR (1080 versus 425 in the KSHV seropositive and 356 versus 144 in the KSHV seronegative) (Supplemental Table I).

KSHV DNA in plasma was detected by PCR in 157 (8.7%) persons (Table I). Of these, 149 (95%) were among KSHV seropositive individuals and 8 (5%) were among KSHV seronegative individuals (Figure 1). The mean KSHV DNA quantity in plasma was 2.7 log copies per mL (inter-quartile range 2.4–3.0). The quantity of KSHV DNA in plasma was similar in KSHV seropositive and KSHV seronegative individuals (2.8 versus 2.7 log copies per mL, $P=0.35$), in men and women (2.8 versus 2.7 log copies per mL, $P=0.63$), and in rural and urban residents (2.8 versus 2.7 log copies per mL, $P=0.42$). However, KSHV DNA was detected more frequently in men than in the women (11.6% versus 6.2%, respectively, $P<0.001$).

Among men, the prevalence of KSHV DNA in plasma doubled from about 10% in men aged 15–19 years to approximately 20% among men aged 50 years or older ($P=0.06$) (Table I). KSHV DNA was detected about 2 times more frequently in men residing in rural local areas compared to men residing in urban local areas (12.8% versus 6.7%, $P=0.04$), and varied by geographic regions ($P=0.06$), with the lowest KSHV DNA prevalence observed in the Kampala region (5.7%), the capital city of Uganda, and the highest prevalence observed in the Western region (18.4%). KSHV DNA was detected more frequently in those who reported having ever been married compared to never married (13.3% versus 8.7%, $P=0.05$), and it was higher in those who reported lack of formal education compared to those who reported higher levels of education ($P=0.05$), but it was unrelated to wealth index among the men.

Similar to observations in the men, the prevalence of KSHV DNA detection in plasma doubled from about 6% among women aged 15–19 years to 11% among women aged 50 years or older ($P=0.06$) (Table I), but the trend was not statistically significant. Similarly, women residing in a rural area had 2.5 times the prevalence of KSHV DNA than those

residing in urban areas (7.0% versus 2.6%, $P=0.02$). In contrast to observations among men, KSHV DNA in plasma was related to religion ($P=0.01$), but not to geographic region ($P=0.316$), marital status ($P=0.26$), education ($P=0.65$), and wealth index ($P=0.57$).

In analyses for men and women combined, prevalence of KSHV DNA in plasma was significantly associated with older age ($P=0.003$), rural versus urban area ($P=0.002$), and geographic region ($P=0.02$), but it was unrelated to religion ($P=0.80$) or to formal education ($P=0.63$).

Among men, detection of KSHV DNA in plasma was unrelated to sexual characteristics, including ever use of a condom, a history of any sexually transmitted disease (STD), paying or receiving money for sex, number sexual unions, or to environmental characteristics, such as owning livestock among the men (Table II). Notably, detection of KSHV DNA in plasma was unrelated to being HSV2 or HIV seropositivity. Among men, KSHV DNA was detected 1.5 times more frequently in those who were uncircumcised compared to those who were not (15.9% versus 10.1%, $P=0.03$). Detection of KSHV DNA was associated strongly and positively with KSHV serostatus, and was detected 8 times more frequently in men who were KSHV seropositive than those who were KSHV seronegative (18.7% versus 2.4%, $P<0.001$).

The results were similar among women (Table II). Detection of KSHV DNA in plasma was unrelated to ever use of a condom, a history of any STD, number of sexual unions, HSV2 or HIV seropositive status. Unlike men, KSHV DNA was detected 2 times in women who reported owning livestock than those who did not (7.5% versus 3.4%, $P=0.01$). Similar to men, detection of KSHV DNA in plasma was associated strongly and positively with KSHV serostatus. KSHV DNA in plasma was detected 4.5 times more frequently in women who were KSHV seropositive than those who were KSHV seronegative (9.4% versus 2.1%, $P=0.001$).

In analyses combining men and women, detection of KSHV DNA in plasma was associated with KSHV seropositivity (seropositive versus seronegative 13.8% and 2.3% respectively, $P<0.001$). In multivariable models (Table III), detection of KSHV DNA in plasma was significantly higher in men ($P=0.002$), and inversely and significantly associated with age ($P=0.05$) and residing in an urban area ($P=0.01$). The association with male sex and with rural-urban residence was significant in analyses adjusting for KSHV antibody status, but the association with age, while not changed materially, it was no longer significant.

DISCUSSION

The first population-based assessment of the correlates of KSHV DNA detection that included both serologic and direct virologic assays was conducted in a region endemic for KS. In this large study, KSHV DNA in the plasma was found to be common (14%) in the general population in Uganda with antibodies to KSHV and uncommon (2.3%) among KSHV-seronegative individuals. Detection of KSHV DNA in plasma was associated with male gender and residence in a rural area.

One of the more interesting observations from this study was a heterogeneity in the prevalence of KSHV plasma DNA detection by region of the country, which corresponded closely to the geographic variance in KS observed prior to the HIV pandemic [Taylor et al., 1972] (Figure 2). These geographic regions are mostly populated by people of different tribes, which perhaps agrees with findings from Johnston et al. [2009], where an association was found between a study participant's self-identified ethnic tribe in Uganda and the frequency of KSHV detection in plasma. However, the geographic regions defined in the

serosurvey differ by more than simply the ethnicity of the population, and ultimately the reasons for the variations in KSHV DNA detection in plasma are unknown.

The findings of strong correlation between detection of KSHV DNA in plasma and male sex also agrees with Johnston et al. [2009], as well as the several-fold increased incidence of KS in men in Uganda. In contrast to the study by Johnston et al, we did not find significant correlations between detection of KSHV DNA in plasma and HIV infection and having multiple sex partners. Making direct comparisons of findings from this study and Johnston et al. however, is risky because we evaluated adults from a general population in Uganda, whereas Johnston et al. evaluated both healthy study volunteers and unwell persons who were attending a tertiary-level urban clinic that caters to persons with HIV infection and/or cancer.

It was found that the detection of KSHV DNA in plasma increased with increasing age in both men and women. This finding mirrors the increase in the incidence of KS with age in endemic and classic manifestations of the disease. KSHV DNA in peripheral blood might be due to KSHV reactivation due to age-related immunosenescence or immunodysregulated due to other age-related exposures, but careful studies of innate, humoral and cellular immunity to KSHV, and impact of other exposures such as parasites [Mbulaiteye et al., 2008; Fu et al., 2012], have not been performed.

A small percentage of individuals who were KSHV seronegative were KSHV DNA positive in plasma. KSHV DNA in adults who are seronegative might be due to recent acquisition of infection, or to reactivation of latent infection in individuals who have low antibody levels. The KSHV DNA quantities among these KSHV seronegative individuals were high, which suggests that the results likely represented real KSHV infection. KSHV DNA in KSHV seronegative individuals has been reported before in Uganda [Mbulaiteye et al., 2004] in the peripheral blood of children as well as their mothers. In these studies, sequence analysis performed in the K1 KSHV gene confirmed real and unique infections in the KSHV seronegative individuals. KSHV DNA was detected more frequently in children than their mothers, which is intuitive given that recent infection is more likely in children than adults. However, as infection was observed in the mothers, these results and our study suggest that KSHV transmission among adults living in KS endemic areas is not uncommon, although the mode of transmission is not clear.

Imperfect serological assays [Rabkin et al., 1998], as evidenced by the less than 100% positivity among subjects with KS and concerns about misclassification of serostatus, have tended to diminish impact of findings from serological studies. It was found that KSHV serostatus was the strongest predictor of detection of KSHV DNA in plasma is both reassuring and suggests that associations with KSHV seropositivity are valid for interpretation as markers KSHV infection, as indicated by detection of KSHV DNA in plasma. This study has some limitations. These include that not all samples selected were tested by PCR. Some samples from some subjects were exhausted, while samples from other subjects could not be traced. This reduced the effective sample size of the study. This limitation probably did not bias the associations because no differences were noted in subjects who were tested by PCR versus those who were selected but not tested. Another limitation is lack of complete knowledge of the health status of the persons in the cohort, other than sexually transmitted diseases. Even so, the subjects are likely to have been healthier than is normally found in hospital-based studies. The strengths of this study include using a large nationally-representative population-based sample with detailed demographical data from all regions in Uganda. This allowed us to provide a reasonable estimate of KSHV DNA prevalence in plasma and to investigate the association of KSHV DNA detection in relation to known risk factors for KS.

To summarize, detection of KSHV DNA in plasma was significantly associated with male sex, residing in a rural areas, and with having KSHV antibodies. These results suggest that KSHV DNA in plasma is common in the general population in Uganda, where KS is endemic, and detection is linked to male sex and rural residence, which are risk factors for KS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Figure 2.

Table 1

Association of KSHV Viremia With Socio-Demographic Characteristics in Uganda.

	Male persons			Female persons			Male and female persons		
Characteristic	KSHV +	% KSHV + (95% CI) ^a	<i>P</i> value ^b	KSHV +	% KSHV + (95% CI) ^a	<i>P</i> value ^b	KSHV +	% KSHV + (95% CI) ^a	<i>P</i> value ^b
All subjects	100	11.6 (9.1, 14.1)		57	6.2 (4.5, 7.9)		157	8.7 (7.2, 10.3)	
Age group, years									
15–19	21	9.9 (5.7, 14.0)	0.06	14	6.2 (2.8, 9.6)	0.06	35	8.0 (5.1, 10.8)	0.003
20–29	24	9.9 (6.0, 13.8)		10	3.2 (1.0, 5.4)		34	6.0 (3.9, 8.1)	
30–39	28	14.3 (8.9, 19.6)		15	7.3 (3.6, 11.1)		43	10.6 (7.4, 13.9)	
40–49	11	7.8 (3.3, 12.3)		11	9.2 (3.7, 14.7)		22	8.5 (5.0, 12.0)	
50–59	16	20.4 (8.7, 32.1)		7	11.1 (3.2, 19.0)		23	16.2 (8.9, 23.5)	
Residence									
Urban	12	6.7 (2.8, 10.7)	0.04	5	2.6 (0.5, 4.7)	0.02	17	4.6 (2.4, 6.7)	0.002
Rural	88	12.8 (9.9, 15.7)		52	7.0 (5.0, 9.0)		140	9.7 (7.9, 11.6)	
Region									
Central	14	16.5 (7.3, 25.7)	0.06	11	11.2 (4.2, 18.2)	0.32	25	13.6 (7.8, 19.4)	0.02
Kampala	6	5.7 (1.4, 9.9)		2	2.1 (0.0, 4.7)		8	4.0 (1.5, 6.4)	
East Central	10	8.7 (3.5, 13.9)		4	4.6 (0.0, 9.4)		14	6.6 (2.8, 10.5)	
Eastern	10	8.2 (2.7, 13.8)		8	6.5 (2.6, 10.3)		18	7.3 (3.6, 11.0)	
Northeastern	17	18.3 (9.2, 27.3)		6	5.6 (0.0, 11.5)		23	11.8 (6.2, 17.3)	
North Central	6	8.5 (1.5, 15.5)		4	5.0 (0.4, 9.5)		10	6.6 (2.8, 10.4)	
West Nile	11	11.2 (4.5, 17.8)		8	6.4 (2.1, 10.6)		19	8.5 (4.0, 13.0)	
Western	17	18.4 (10.3, 26.5)		9	8.6 (2.9, 14.3)		26	13.1 (8.0, 18.2)	
Southwestern	9	9.5 (2.0, 16.9)		5	4.2 (0.6, 7.8)		14	6.5 (2.1, 10.9)	
Marital status									
Never married	29	8.7 (5.5, 11.8)	0.05	11	4.5 (1.7, 7.3)	0.26	40	6.9 (4.6, 9.2)	0.10
Married	71	13.3 (10.0, 16.7)		46	6.7 (4.6, 8.8)		117	9.5 (7.6, 11.5)	
Religion									
Catholic	43	11.9 (8.1, 15.7)	0.49	22	5.7 (3.3, 8.1)	0.01	65	8.6 (6.5, 10.8)	0.81
Protestant/Anglican	32	10.3 (6.6, 14.0)		27	8.5 (5.4, 11.5)		59	9.3 (6.7, 11.9)	
Muslim	18	14.8 (7.6, 22.0)		2	1.5 (0.0, 3.4)		20	8.0 (4.2, 11.7)	
Education									
None	18	21.1 (11.6, 30.4)	0.05	14	7.0 (3.0, 11.0)	0.65	32	10.5 (6.7, 14.3)	0.64
Primary	60	11.3 (8.2, 14.5)		30	5.5 (3.4, 7.6)		90	8.4 (6.4, 10.4)	
Secondary	17	9.1 (4.7, 13.5)		11	7.6 (3.3, 11.9)		28	8.5 (5.3, 11.7)	
Higher Level	5	8.9 (0.9, 16.8)		1	2.9 (0.0, 8.6)		6	6.6 (1.2, 12.0)	
Wealth index									
Lowest	22	13.2 (7.6, 18.8)	0.12	13	6.6 (3.1, 10.0)	0.57	35	9.6 (6.4, 12.8)	0.07
Low	27	16.2 (10.2, 22.2)		12	7.3 (3.2, 11.5)		39	11.7 (8.0, 15.4)	

	Male persons			Female persons			Male and female persons		
Characteristic	KSHV +	% KSHV + (95% CI) ^a	<i>P value</i> ^b	KSHV +	% KSHV + (95% CI) ^a	<i>P value</i> ^b	KSHV +	% KSHV + (95% CI) ^a	<i>P value</i> ^b
Intermediate	13	9.2 (4.1, 14.2)		10	7.5 (2.6, 12.5)		23	8.3 (4.7, 12.0)	
High	19	13.1 (7.0, 19.3)		12	6.3 (2.9, 9.7)		31	9.4 (6.1, 12.6)	
Highest	19	7.9 (4.4, 11.4)		10	4.0 (1.7, 6.2)		29	5.9 (3.9, 7.9)	

^aWeighted percentage

^bP-value for heterogeneity

Table II

Associations of KSHV Viremia With Sexual and Environmental Risk Factors in Uganda.

	Males			Females			Males and females		
Characteristic	KSHV +	% KSHV+ (95% CI) ^a	P ^b	KSHV +	% KSHV + (95% CI) ^a	P ^b	KSHV +	% KSHV + (95% CI) ^a	P ^b
Ever used condom									
No	49	13.3 (9.2, 17.5)	0.48	35	6.4 (4.2, 8.6)	0.70	84	9.1 (6.9, 11.3)	0.87
Yes	17	10.8 (5.5, 16.1)		8	7.4(2.1, 12.8)		25	9.4 (5.6, 13.2)	
Missing	34			14			48		
Any STD									
No	83	11.7 (8.9, 14.4)	0.97	42	5.9 (4.1, 7.7)	0.57	125	8.8 (7.0, 10.5)	0.98
Yes	17	11.5 (6.1, 17.0)		15	7.0 (3.4, 10.5)		32	8.7 (5.6, 11.9)	
Number of Unions									
1	34	12.9 (8.4, 17.3)	0.58	34	6.8 (4.2, 9.4)	0.74	68	8.8 (6.3, 11.2)	0.46
2	24	15.2 (8.1, 22.2)		11	6.0 (2.6, 9.4)		35	10.5 (6.6, 14.5)	
Missing	42			12			54		
Paid/Received money for sex in last 12 months									
No	3	6.7 (0.0, 14.2)	0.18						
Yes	2	21.3 (0.0, 50.1)							
Missing	95								
Circumcised									
No	64	10.1 (7.5, 12.6)	0.03						
Yes	36	15.9 (10.5, 21.3)							
Missing	0								
Livestock									
No	33	12.6 (8.3, 16.9)	0.56	11	3.4 (1.5, 5.3)	0.01	44	7.8 (5.5, 10.1)	0.32
Yes	67	11.2 (8.5, 13.9)		46	7.5 (5.2, 9.8)		113	9.3 (7.3, 11.2)	
HSV2									
No	58	10.6 (7.6, 13.6)	0.28	29	5.5 (3.5, 7.6)	0.37	87	8.1 (6.1, 10.1)	0.30
Yes	42	13.4 (9.1, 17.7)		28	7.0 (4.3, 9.6)		70	9.7 (7.3, 12.0)	
HIV status									
Negative	92	11.1 (8.7, 13.5)	0.09	54	6.2 (4.5, 8.0)	0.84	146	8.5 (7.0, 10.1)	0.27
Positive	8	22.3 (5.5, 39.2)		3	5.5 (0.0, 11.7)		11	12.8 (4.0, 21.7)	
KSHV antibody status									
Negative	4	2.4 (0.1, 4.7)	<.0001	4	2.1 (0.1, 4.2)	0.001	8	2.3 (0.7, 3.8)	<.0001
Positive	96	18.7 (15.1, 22.3)		53	9.4 (7.0, 11.7)		149	13.8 (11.6, 16.0)	

Table notes: STD-sexually transmitted disease

^aWeighted percentage^bP-value for heterogeneity

Table III

Associations of KSHV Viremia With Demographic Variables in Uganda.

Characteristic	Males and females		Males and females	
	aOR* (95% CI)	P value	aOR [§] (95% CI)	P value
Sex				
Female	Ref		Ref	
Male	1.9 (1.4, 2.8)	0.0002	2.0 (1.4, 2.9)	0.0002
Age group, years		0.05 ^a		0.1231 ^a
15–19	0.5 (0.3, 1.0)		0.7 (0.3, 1.4)	
20–29	0.4 (0.2, 0.8)		0.5 (0.2, 0.9)	
30–39	0.7 (0.4, 1.3)		0.8 (0.4, 1.5)	
40–49	0.5 (0.3, 1.0)		0.6 (0.3, 1.2)	
50–59	Ref		Ref	
Residence				
Urban	0.5 (0.3, 0.8)	0.01	0.5 (0.3, 0.9)	0.02
Rural	Ref		Ref	
KSHV antibody status				
Negative			Ref	
Positive			6.7 (3.2, 13.9)	<.0001

* Not adjusted for KSHV antibody status

[§] Adjusted for KSHV antibody status^a P value for heterogeneity