Risk Factors for Kaposi's sarcoma among HIV-Positive Individuals in a Case Control Study in Cameroon

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Abstract

Background—Individuals co-infected with Kaposi's sarcoma herpesvirus (KSHV) and Human Immunodeficiency Virus (HIV) are at greatly increased risk of developing Kaposi's sarcoma (KS). The objective of the current analysis is to identify risk cofactors, for KS among HIV-positive individuals.

Methods—We conducted a case-control study of KS in Cameroon on 161 HIV-positive and 14 HIV-negative cases and 680 HIV-positive and 322 HIV-negative controls. Participants answered a physician-administered questionnaire and provided blood and saliva specimens. Antibodies against KSHV lytic, K8.1, and latent, ORF73, antigens were measured by ELISA to determine

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Conflicts of Interest
None to declare.

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KSHV serostatus. Conditional logistic regression was performed to determine multivariate odds ratios (OR) and 95% confidence intervals (CI) for risk factors associated with KS among HIV-positive cases and controls.

Results—Overall, 98% (158) of HIV-positive cases, 100% (14) of HIV-negative cases, 81% (550) of HIV-positive controls, and 80% (257) of HIV-negative controls were KSHV seropositive. Risk factors for KS among HIV-positive individuals included KSHV seropositivity (OR=9.6; 95% CI 2.9, 31.5), non-use of a mosquito bed net (OR 1.9; 95% CI 1.2, 2.9), minority ethnicity (OR=3.1; 95% CI 1.1, 9.3), treatment from a traditional healer (OR=2.3; 95% CI 1.5, 3.7), history of transfusion (OR=2.4; 95% CI 1.5, 3.9), and family history of cancer (OR=1.9; 95% CI 1.1, 3.1).

Conclusion—KSHV seroprevalence of 80% indicates a high prevalence in the general population in Cameroon. Among HIV-positive individuals, the strong association of KS with non-use of mosquito nets and treatment from traditional healers are compelling findings, consistent with recently reported data from East Africa.

Keywords

Kaposi's sarcoma (KS); Kaposi's sarcoma herpesvirus (KSHV); Human herpesvirus 8 (HHV-8); Human Immunodeficiency Virus (HIV); risk factors; Cameroon

Introduction

Kaposi's sarcoma (KS) is the most prevalent HIV and AIDS associated cancer worldwide [1–3]. Until the advent of the AIDS epidemic, KS was found in specific populations, notably individuals from equatorial Africa (endemic KS), older men from Eastern Europe and the Mediterranean (classic KS), and individuals who received an organ transplant or were immune-compromised (iatrogenic KS) [2].

Epidemic KS is considered the most common AIDS-associated malignancy [1,4], with an increased risk among HIV-positive individuals with lowered immune status [5,6]. Since the advent of combined anti-retroviral therapy (cART), the prevalence of epidemic KS has dramatically decreased in high income countries [5,7]. In Africa, however, KS continues to be one of the leading AIDS-defining illnesses, as well as one of the most prevalent cancers overall [3].

The etiologic agent that causes KS, human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma herpesvirus (KSHV), was discovered in 1994 [8]. The presence of KSHV alone, however, is not sufficient for the development of KS disease: a large proportion of individuals with KSHV never develop KS [6,9,10]. KSHV is transmitted chiefly via saliva [11–14], but the modes of transmission are likely different in different populations. In low KSHV prevalence areas, such as the US, KSHV mainly infects men who have sex with men (MSM), implicating risk factors related to sexual behavior [15]. In some regions of Africa, KSHV is very prevalent in the general population and increases with age beginning in childhood [16], suggesting that transmission is via non-sexual horizontal routes [14].

Cameroon is located within the "KS belt", the region along the equator in Africa that has the highest incidence of KS worldwide [17]. Endemic KS has been localized in areas of high

altitude, cooler temperatures, and moderate rainfall [18], conditions found in the Northwest and Southwest regions of Cameroon. Countries in the KS belt generally have higher KSHV prevalence compared to elsewhere in Africa [17,19]. In areas outside of the KS belt, geographic pockets of high KSHV prevalence do not seem to systematically present with high KS rates [19].

Cameroon has been reported to have one of the highest prevalence of KSHV in the world (62%) [20], as well as the highest prevalence of HIV in Western and Central Africa (5.3%) [21]. While prevalence estimates of epidemic KS in Cameroon vary [20,22] KS is one of the most commonly diagnosed cancers among men and women and is estimated to comprise 15–20% of all adult cancers [18]. The combination of the overall high prevalence of KSHV, geographic and environmental risk factors found in endemic KS regions, and the HIV epidemic in Cameroon, likely contribute to the high rates of KS [20,23,24].

To date, most prospective research on risk factors on AIDS-related KS has been conducted in East or Southern Africa. Little research of AIDS-related KS has been conducted in Central or West Africa, despite the intersection of known environmental and etiologic risk factors in this region. We report here results of a case-control study, including determination of KSHV seroprevalence and examination of risk factors for KS among HIV-positive individuals in Cameroon.

Materials & Methods

In 2005, the National Institute of Allergy and Infectious Diseases (NIAID) funded the International Epidemiologic Databases to Evaluate AIDS (IeDEA) to identify epidemiological trends and answer evolving research questions associated with HIV using large cohort studies [25]. In 2006, the National Cancer Institute (NCI) provided additional funding to study HIV-associated cancers. Yaoundé, Cameroon served as the sentinel site for cancer research in IeDEA-Central Africa, through its collaboration with the Oncology Department of the General Hospital of Yaoundé and with Solidarité Chimiothérapie (SOCHIMIO), the largest non-governmental organization providing support to cancer patients in Cameroon.

Study Design

This prospective, matched case-control study nested within IeDEA-Central Africa, was conducted from 2009–2011, with the primary aim to identify risk factors for the development of KS among HIV-positive and HIV-negative individuals. Cases were identified amongst patients in the IeDEA cohort who presented with signs and symptoms of KS, through the SOCHIMIO cancer registry, and amongst referrals to the Oncology Department of the General Hospital of Yaoundé. Trained cancer specialists confirmed KS diagnosis through clinical examination, and, if necessary, a skin biopsy. HIV-positive and HIV-negative controls were identified by referring physicians through the HIV Care and Treatment Centers and Voluntary Testing and Counseling Centers at the General Hospital and the Military Hospital, both IeDEA sites in Yaoundé. To be eligible, all participants were required to be 21 years of age or older, to have resided in Cameroon for at least 6 months prior to enrollment, and to provide written informed consent. The study was designed so that

four HIV-positive controls and two HIV-negative controls were matched to each KS case based on sex and 5-year age brackets. The protocol was reviewed and approved by the Cameroon National Ethics Committee and the Institutional Review Board (IRB) at RTI International.

Data collection

Physicians conducted a clinical examination and interview with each participant. A standardized questionnaire (see supplementary table 1) collected detailed information on potential risk factors for KS, including demographics, socio-economic status, environmental exposure, health-risk behaviors, reproductive health history, concurrent immunosuppressive conditions, and medical history. For HIV-positive cases and controls, information was also collected on suspected mode of HIV transmission and time since confirmed HIV infection. Additional clinical data on antiretroviral therapy (ART) was derived from a transfer form completed by the referring physician.

Clinical specimens and KSHV diagnosis

Whole blood, serum and saliva samples were collected from all participants at enrollment into the study. All specimen samples were shipped to the Viral Oncology Section at the Frederick National Laboratory for Cancer Research in Frederick, Maryland. Serum samples were tested for antibodies against two recombinant KSHV antigens, K8.1 and ORF73 using previously described ELISAs. ORF73 encodes LANA, which is expressed during latency and K8.1 encodes a glycoprotein that is expressed during lytic infection. ELISA methods, and relative interpretations, are described in [26].

Statistical analysis

Descriptive frequencies were obtained for key characteristics among cases and controls stratified by HIV status. Results of assays for K8.1 and ORF73 were analyzed separately and then combined: a subject was defined as seropositive for KSHV if they tested positive for K8.1 or ORF73.

Conditional logistic regression was used to obtain odds ratios (OR) and 95% confidence intervals (CI) for selected risk factors associated with KS status. Univariate analysis was conducted on KSHV serostatus and 22 questionnaire covariates. The initial multivariate model included variables with a significant unadjusted OR at $\alpha<.05$ and variables found to be associated with KS in the literature. HIV-related variables were excluded from the final model due to the limited data available. The final multivariate model was selected using a backwards stepwise algorithm. Data were analyzed using SAS v 9.2.

Results

Description of the Study Population

By the end of the enrollment period, we had accrued 175 cases, of which 161 (92%) were HIV-positive (epidemic KS) and 14 (8%) were HIV-negative (endemic KS), and 1002 controls, 680 (68%) HIV-positive and 322 (32%) HIV-negative (Table 1). As expected, HIV infection was strongly associated with KS risk (OR=5.45; 95% CI: 3.10, 9.56; p<.0001).

The prevalence of KSHV was 98% (158/161) in HIV-positive cases, 100% (14/14) in HIV-negative cases, 81% (550/680) in HIV-positive controls, and 80% (257/322) in HIV-negative controls. Characteristics of all study participants are presented in detail in Table 1.

Risk Factors for KS among HIV-positive Individuals

Risk factors for KS were investigated in HIV-subjects. In the univariate analysis (Table 2), KS was associated with a positive test to any or either KSHV antigen, presence of electricity in the home, not sleeping under a mosquito net, and history of tobacco use (p<.05). KS was also associated with having four or more lifetime sexual partners, inconsistent condom use, history of a sexually transmitted infection (STI), treatment by a traditional healer, history of a transfusion, family history of cancer, WHO HIV clinical stage of III or IV at the start of antiretroviral therapy (ART), and duration of ART of less than 18 months (p<.05). We analyzed variables found to be significant risk factors in other studies of KS, including the color of the soil where the participant spent time as a child, going barefoot as a child, and source of bathing water. However, none of these variables were shown to be significantly associated with KS in this analysis.

In the multivariate analysis (Table 3), KSHV seropositivity remained highly associated with KS disease (OR=9.6; 95% CI 2.9, 31.5; p=.0002). Not sleeping under a mosquito net (OR=1.9; 95% CI 1.2, 2.9; p=.006), receiving treatment from a traditional healer (OR=2.3; 95% CI 1.5, 3.7; p=.0002), having a history of transfusion (OR=2.4; 95% CI 1.5, 3.9; p=.0005), and a family history of cancer (OR=1.9; 95% CI 1.1, 3.1; p=.018) were positively associated with KS.

Discussion

Cameroon is a highly informative country in which to study the co-infection of HIV and KS because of the presence of environmental risk factors found in endemic KS areas and high rates of both KSHV and HIV. No study of KS of this magnitude has ever been performed in Cameroon or Central Africa, making this study the first of its kind. Our analysis revealed several important risk factors for KS among HIV-positive individuals, alongside KSHV seropositivity. In particular, use of a mosquito net and treatment from a traditional healer were of greatest interest due to possible relationships with risk factors previously described in the literature [27,28].

The majority of study participants, HIV-positive and HIV-negative, were KSHV seropositive. The extremely high proportion of KSHV seropositivity in HIV-positive (81%), and HIV-negative controls (80%), indicate that KSHV infection is likely much more prevalent in the general population of Cameroon than previously understood.

A high proportion of participants from all groups (33%-50%) classified their work as professional, indicating a higher socio-economic status. Higher SES have been associated with both endemic, [29] and epidemic KS [30]. However, neither occupation nor education was associated with KS among HIV-positive individuals in our study. In contrast, participants without electricity in the home were moderately more likely to have KS (OR=1.9; 95% CI 0.9, 4.5; p=.1028) as did participants who did not sleep under a mosquito

net (OR=1.9; 95% CI 1.2, 2.9; p=.006). Although electricity in the home and use of a mosquito net can indicate higher income and education [31,32] higher SES was not associated with KS risk in our study, so use of a mosquito bed net represents some other protective effect. Plasmodium parasitemia has previously been shown to be a risk factor for KSHV infection [28], and a possible association between malaria and development of KS merits further investigation.

We found that participants whose ethnic group was not classified as Bantu or Semi-bantu were slightly more likely to have KS as compared to Semi-bantu (OR=3.1; 95% CI 1.1, 9.3; p=.0702). Region of origin was highly correlated with ethnic group (Figure 1), and therefore ethnicity may be a proxy for environmental exposure related to endemic KS risk. Environmental cofactors reported in the literature include exposure to volcanic soils [18,33], going barefoot [29] and exposure to surface water [30]. The Semi-bantu typically originate from the cooler and drier western highlands (West and Northwest) and the Bantu from parts of the coastal South and Southwest regions characterized by long rainy seasons. Other ethnic groups typically live in the Northern regions, characterized by dry savanna (Extreme North) or volcanic mountains and plateaus (Adamawa and North).

Individuals located in areas of high rainfall may be more susceptible to KS due to greater exposure to surface water [34] or, potentially parasitic infections [28]. Although malaria is endemic throughout Cameroon, the coastal South and Southwest regions have the highest prevalence of malaria in the country [31,35]. Conversely, individuals in higher altitude regions in the North may be more susceptible to KS due to increased exposure to volcanic and iron-rich soils [18,36]. Although previous literature has shown an association between KS and playing outside barefoot as children, we only found a marginal association in our analysis (OR=2.8; 95% CI 0.8, 10.4). This association may be related to exposure to soil-transmitted helminthes, e.g. hookworm, a common outcome of walking barefoot, which has been shown to be associated with an increased prevalence of KSHV [28]. Malaria and hookworm cause anemia, and thus tissue hypoxia, which is a known activator of KSHV replication, which could promote KS [37]. Moreover, systemic parasitic infections can cause profound immunological abnormalities that may alter cellular immune responses to KSHV, thus promoting KS [38,39].

On the other hand, the effect of ethnicity on the risk of KS development could be also due to genetic factors. We do observe an association between KS and self-reported family history of cancer (OR=1.8, 95% CI, 1.2, 2.7; p=.0178). The role of host genetic factors in the risk of KS should be explored further.

We also found a significant association between KS and history of transfusion (OR=1.9, 95% CI 1.3, 3.8; p=.0005), and ever receiving treatment from a traditional healer (OR=2.4, 95% CI, 1.7, 2.4; p=.0002). Transfusion often occurs during hospitalization, which could have resulted from advanced HIV or undiagnosed KS. While the risk of KS among those who had transfusions should be explored further, the potential for unobserved confounding must be kept into account. The association of KS and traditional medicine could be related to the use of herbal products that when chewed or rubbed into the skin and mucosae may contribute to the transmission of KSHV through saliva and/or promote the development of

KS through abrasive micro-trauma to the skin [40]. A recent study on natural products that promote KSHV reactivation found that 9 of the 28 most active plant extracts were from West Africa and 3 of those were specifically from Cameroon [27]. Additional investigation on traditional treatments may be warranted.

Heterosexual HIV exposure was moderately significantly associated with KS status (OR 1.9, 95% CI, 1.3, 2.7; p=.0571) as compared to other or unknown origin of exposure. Heterosexual exposure is the most common modality of HIV transmission in Sub-Saharan Africa [41]. However, the absence of associations between KS and number of lifetime sexual partners or history of STIs reiterates the lack of evidence for sexual activity as a major route of KSHV transmission [42].

Finally, although the number of HIV-negative cases in this study (14) was not enough to provide statistically significant comparisons with the HIV-negative controls, they give us an interesting look into the potential differences between endemic and epidemic KS in Cameroon. Unlike the HIV-positive cases, the HIV-negative cases in our study were all male, of older ages, and mostly farmers. All of the HIV-negative cases tested positive to both KSHV antigens. This may be explained by an increase in the prevalence of seropositivity to KSHV antigens in older age, or could reflect an AIDS related deterioration of humoral immune responses in the HIV-positive cases.

Conclusion

This matched case-control study of KS among HIV-negative and HIV-positive participants in Cameroon is the first of its kind. The high prevalence of KSHV in both HIV-positive and HIV-negative participants indicates a notably higher prevalence of KSHV in the general population of Cameroon than previously understood. Multivariate risk factors for KS among HIV-positive participants included KSHV infection and cofactors, such as lack of mosquito bed net use, minority ethnicity, treatment by a traditional healer, history of transfusion, family history of cancer, and heterosexual origin of HIV infection. More research is needed to understand how the interactions of these risk factors with KSHV and HIV infection increase the risk of KS disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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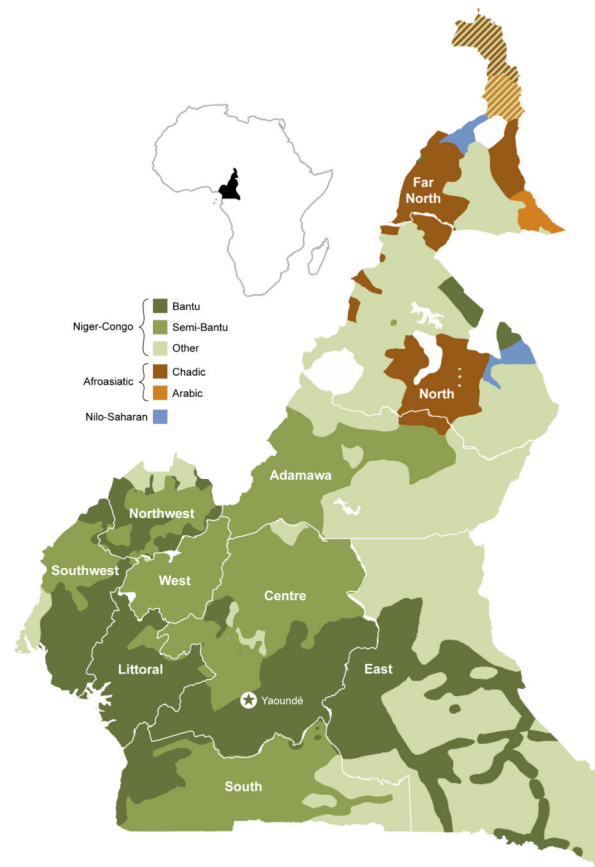
Figure 1.
Map of Cameroon showing the country's administrative subdivisions (regions) and a broad
ethnic classification of its population, according to ISO 639-3 standard designations.
(www.ethnologue.com)

Table 1

Descriptive characteristics of HIV-positive and HIV-negative KS cases and controls

	KS Cases		KS Controls	
	HIV-positive N (%)	**HIV-negative N (%)**	**HIV-positive N (%)**	**HIV-negative N (%)**
Total N	161	14	680	322
KSHV seropositivity				
K8.1 positive	154 (95.7)	14 (100.0)	527 (77.5)	241 (74.8)
Orf 73 positive	145 (90.1)	14 (100.0)	486 (71.5)	214 (66.5)
Overall positive	158 (98.1)	14 (100.0)	550 (80.9)	257 (79.8)
Proportion Male	91 (56.5)	14 (100.0)	407 (59.9)	188 (58.4)
Age range in years				
19–29	21 (13.0)	2 (14.3)	83 (12.2)	43 (13.4)
30–39	67 (41.6)	1 (7.1)	276 (40.6)	139 (43.2)
40–49	45 (28.0)	3 (21.4)	190 (27.9)	82 (25.5)
50	28 (17.4)	8 (57.1)	131 (19.3)	58 (18.0)
Occupation				
Professional	52 (32.5)	6 (42.9)	232 (34.2)	158 (49.1)
Semi-skilled	21 (13.1)	0 (0.0)	101 (14.9)	33 (10.2)
Trader/sales	29 (18.1)	1 (7.1)	172 (25.4)	48 (14.9)
Farmer	13 (8.1)	4 (28.6)	34 (5.0)	10 (3.1)
Unemployed	45 (28.1)	3 (21.4)	139 (20.5)	73 (22.7)
Marital status				
Single/Divorced/Widowed	77 (47.8)	4 (28.6)	272 (40.0)	115 (35.7)
Married	70 (43.5)	9 (64.3)	319 (46.9)	170 (52.8)
Open relationship	14 (8.7)	1 (7.1)	89 (13.1)	37 (11.5)
Educational Attainment				
None/primary	34 (21.1)	4 (28.6)	155 (22.8)	54 (16.8)
Secondary	96 (59.6)	6 (42.9)	363 (53.5)	192 (59.6)
Higher	31 (19.3)	4 (28.6)	161 (23.7)	76 (23.6)
Region of origin				
Littoral	9 (5.7)	1 (7.1)	32 (4.8)	30 (9.4)
South (South, Center, East)	98 (62.4)	8 (57.1)	358 (53.5)	126 (39.4)
West (West, NW, SW)	45 (28.7)	5 (35.7)	253 (37.8)	141 (44.1)
North (North, Adamawa, Extreme North)	5 (3.2)	0 (0.0)	26 (3.9)	23 (7.2)
Ethnic group				
Bantu	108 (67.1)	9 (64.3)	395 (58.1)	161 (50.0)
Semi-bantu	45 (28.0)	5 (35.7)	255 (37.5)	139 (43.2)
Other	8 (5.0)	0 (0.0)	30 (4.4)	22 (6.8)

KS = Kaposi's Sarcoma

HIV = Human Immunodeficiency Virus

N = Number

KSHV = Kaposi's Sarcoma Herpesvirus

Overall positive = Defined as having a positive test to either or both K8.1 and Orf73 ELISA tests.

Table 2

Unadjusted odds ratios (OR) and 95% confidence intervals (CI) of KS risk factors among HIV-positive cases and HIV-positive controls, stratified by selected demographic, socioeconomic and environmental factors.

	Cases HIV-positive N (%)	Controls HIV-positive N (%)	Univariate OR (95% CI)
Total N	**161**	**680**	
KSHV serostatus[a]			
K8.1 positive	154 (95.7)	527 (77.5)	6.3 (2.9,13.7)[*]
Orf 73 positive	145 (90.1)	486 (71.5)	3.6 (2.1,6.2)[*]
Overall positive	158 (98.1)	550 (80.9)	12.3 (3.9,39.0)[*]
Occupation			
Professional	52 (32.5%)	232 (34.2%)	0.7 (0.4,1.2)
Semi-skilled	21 (13.1%)	101 (14.9%)	0.7 (0.4,1.3)
Trader/sales	29 (18.1%)	172 (25.4%)	0.5 (0.3,0.9)[*]
Farmer	13 (8.1%)	34 (5%)	1.2 (0.6,2.6)
Unemployed	45 (28.1%)	139 (20.5%)	1.0
Marital status			
Single/Divorced/Widowed	77 (47.8%)	272 (40%)	1.3 (0.8,1.9)
Married	70 (43.5%)	319 (46.9%)	1.0
Open relationship	14 (8.7%)	89 (13.1%)	0.7 (0.4,1.3)
Education attainment			
None/primary	34 (21.1%)	155 (22.8%)	1.1 (0.64,1.93)
Secondary	96 (59.6%)	363 (53.5%)	1.4 (0.86,2.12)
Higher	31 (19.3%)	161 (23.7%)	1.0
House has electricity			
Yes	146 (90.7)	646 (95.0)	1.0
No	15 (9.3)	34 (5.0)	1.9 (1.01,3.6)[*]
Participant sleeps under a mosquito net			
Yes	64 (40.0)	344 (50.6)	1.0
No	96 (60.0)	336 (49.4)	1.5 (1.1,2.2)[*]
Region of origin			
Littoral	9 (5.7)	32 (4.8)	1.6 (0.7,3.5)
South (South, Center, East)	98 (62.4)	359 (53.5)	1.5 (1.0,2.3)[*]
West (West, NW, SW)	45 (28.7)	253 (37.8)	1.0
North (North, Adamawa, Extreme North)	5 (3.2)	26 (3.9)	1.1 (0.4,3.1)
Ethnic group			
Bantu	108 (67.1)	395 (58.1)	1.5 (1.1,2.3)[*]
Semi-bantu	45 (28.0)	255 (37.5)	1.0
Other	8 (5.0)	30 (4.4)	1.6 (0.7,3.6)

	Cases HIV-positive N (%)	Controls HIV-positive N (%)	Univariate OR (95% CI)
History of tobacco use			
Yes	50(31.1)	167 (24.6)	1.6 (1.1,2.5)[*]
No	111 (68.9)	512 (75.4)	1.0
History of alcohol use	161	680	
Yes	128 (79.5)	479 (70.4)	1.8 (1.2,2.8)[*]
No	33 (20.5)	201 (29.6)	1.0
Color of soil where spent time as a child			
Black	30 (18.9)	106 (15.8)	1.2 (0.8,1.9)
Brown	17 (10.7)	94 (14.0)	0.8 (0.4,1.4)
Red	103 (64.8)	437 (64.9)	1.0
White	9 (5.7)	36 (5.3)	1.1 (0.5,2.3)
As a child, how often did you play outside barefoot			
Ever (Always/Most of the time/Often/Rarely)	153 (96.8)	637 (95.1)	1.6 (0.6,4.2)
Never	5 (3.2)	33 (4.9)	1.0
Source of water - bathing			
Private source	58 (36.0)	219 (32.2)	1.0
Communal source	86 (53.4)	386 (56.8)	0.8 (0.6,1.2)
Surface water source	17 (10.6)	75 (11.0)	0.8 (0.4,1.4)
No. of regular sexual partners (lifetime)			
0–1	49 (32.0)	201 (31.4)	1.0
2–3	36 (23.5)	214 (33.4)	0.7 (0.4,1.1)
4+	68 (44.4)	226 (35.3)	1.3 (0.8,1.9)
History of condom use			
Never	18 (15.0)	61 (11.4)	2.0 (1.0,4.0)[*]
Sometimes	53 (44.2)	191 (35.8)	2.0 (1.2,3.4)[*]
Most of the time	22 (18.3)	80 (15.0)	2.0 (1.1,3.8)[*]
Always	27 (22.5)	201 (37.7)	1.0
History of an STI			
Yes	108 (68.4)	288 (57.8)	1.7 (1.1,2.4)[*]
No	50 (31.6)	283 (42.2)	1.0
Received treatment from a traditional healer			
Yes	106 (65.8)	304 (44.7)	2.4 (1.7,3.5)[*]
No	55 (34.2)	376 (55.3)	1.0
History of transfusion			
Yes	46 (28.9)	120 (17.8)	1.9 (1.3,2.8)[*]
No	113 (71.1)	556 (82.2)	1.0
Family history of cancer			

	Cases HIV-positive N (%)	Controls HIV-positive N (%)	Univariate OR (95% CI)
Yes	37 (24.8)	101 (15.3)	1.8 (1.2,2.7)[*]
No	112 (75.2)	560 (84.7)	1.0
Origin of HIV exposure			
Heterosexual sex	87 (54.0)	266 (39.3)	1.9 (1.3,2.7)[*]
Other/Unknown	74 (46.0)	410 (60.7)	1.0
History of ART			
Yes	88 (84.6)	457 (84.5)	0.9 (0.5,1.7)
No	16 (15.4)	84 (15.5)	1.0
HIV Clinical Stage at the start of ART			
I–II	10 (28.6)	96 (61.5)	1.0
III–IV	25 (71.4)	60 (38.5)	3.8 (1.7,8.6)[*]
Duration of ART			
<6.5 months	39 (44.3)	69 (15.3)	5 (2.9,8.6)[*]
6.5–18 months	16 (18.2)	80 (17.8)	2.0 (1.0,3.9)[*]
18 months	33 (37.5)	301 (66.9)	1.0

[*] $p<0.05$

[a] Referent group for KSHV serostatus is KSHV seronegative.

KS = Kaposi's Sarcoma

N = number

KSHV = Kaposi's Sarcoma Herpesvirus

Overall positive = Defined as having a positive test to either or both K8.1 and Orf73 ELISA tests.

STI = Sexually Transmitted Infection

HIV = Human Immunodeficiency Virus

ART = Anti-retroviral Therapy

Table 3

Multivariate odds ratios (OR) and 95% confidence intervals (CI) of KS risk factors among HIV-seropositive cases and HIV-seropostive controls, stratified by selected demographic, socioeconomic and environmental factors.

	Cases HIV-positive N (%)	Controls HIV-positive N (%)	Multivariate OR (95% CI)
Total N	**161**	**680**	
KSHV serostatus[a]			
K8.1 positive	154 (95.7)	527 (77.5)	---[1]
Orf 73 positive	145 (90.1)	486 (71.5)	---
Overall positive[b]	158 (98.1)	550 (80.9)	9.6 (2.9, 31.5)*
House has electricity			
Yes	146 (90.7)	646 (95.0)	1.0
No	15 (9.3)	34 (5.0)	1.9 (0.9, 4.5)
Participant sleeps under a mosquito net			
Yes	64 (40.0)	344 (50.6)	1.0
No	96 (60.0)	336 (49.4)	1.9 (1.2,2.9)*
Region of origin[c]			---
Ethnic group			
Bantu	108 (67.1)	395 (58.1)	1.5 (0.9,2.4)
Semi-bantu	45 (28.0)	255 (37.5)	1.0
Other	8 (5.0)	30 (4.4)	3.1 (1.1,9.3)*
History of tobacco use			
Yes	50(31.1)	167 (24.6)	1.1 (0.7,1.9)
No	111 (68.9)	512 (75.4)	1.0
History of alcohol use	161	680	
Yes	128 (79.5)	479 (70.4)	1.4 (0.8,2.5)
No	33 (20.5)	201 (29.6)	1.0
Color of soil where spent time as a child			
Black	30 (18.9)	106 (15.8)	1.5 (0.8,2.7)
Brown	17 (10.7)	94 (14.0)	0.8 (0.4,1.6)
Red	103 (64.8)	437 (64.9)	1.0
White	9 (5.7)	36 (5.3)	1.1 (.5,2.5)
As a child, how often did you play outside barefoot			
Ever (Always/Most of the time/Often/Rarely)	153 (96.8)	637 (95.1)	2.8 (0.8,10.4)
Never	5 (3.2)	33 (4.9)	1.0
Source of water - bathing			
Private source	58 (36.0)	219 (32.2)	1.0
Communal source	86 (53.4)	386 (56.8)	0.9 (0.6,1.5)

	Cases HIV-positive N (%)	Controls HIV-positive N (%)	Multivariate OR (95% CI)
Surface water source	17 (10.6)	75 (11.0)	0.7 (0.3,1.4)
No. of regular sexual partners (lifetime)			
0–1	49 (32.0)	201 (31.4)	1.0
2–3	36 (23.5)	214 (33.4)	0.8 (0.4,1.4)
4+	68 (44.4)	226 (35.3)	1.1 (0.7,1.9)
History of condom use[d]			---
History of an STI			
Yes	108 (68.4)	288 (57.8)	1.2 (.8,1.9)
No	50 (31.6)	283 (42.2)	1.0
Received treatment from a traditional healer			
Yes	106 (65.8)	304 (44.7)	2.3 (1.5,3.7)[*]
No	55 (34.2)	376 (55.3)	1.0
History of transfusion			
Yes	46 (28.9)	120 (17.8)	2.4 (1.5,3.9)[*]
No	113 (71.1)	556 (82.2)	1.0
Family history of cancer			
Yes	37 (24.8)	101 (15.3)	1.9 (1.1,3.1)[*]
No	112 (75.2)	560 (84.7)	1.0
Origin of HIV exposure			
Heterosexual sex	87 (54.0)	266 (39.3)	1.5 (1.0,2.4)[*]
Other/Unknown	74 (46.0)	410 (60.7)	1.0
History of ART[e]			---
HIV Clinical Stage at the start of ART[e]			---
Duration of ART[e]			---

[*] p<.05

[a] Referent group for KSHV serostatus is KSHV seronegative.

[b] The multivariate model included only the variable for "overall" KSHV serostatus, for individuals who were positive for either K8.1 or Orf73 antigens.

[c] Region of origin was not included in multivariate model because highly correlated with ethnic group.

[d] History of condom use was not included in the multivariate model because only those who responded "yes" to any sexual activity in the last 12 months answered the question about frequency of condom use.

[e] History of ART, HIV Clinical Stage at the start of ART, and duration of ART, were not included in the multivariate model due to unavailability of ART information for many participants.

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N = number

KSHV = Kaposi's Sarcoma Herpesvirus

Overall positive = Defined as having a positive test to either or both K8.1 and Orf73 ELISA tests.

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