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MAJOR ARTICLE

High Seroprevalence of Kaposi Sarcoma–Associated Herpesvirus in Men Who Have Sex With Men With HIV in the Southern United States

Sheena M. Knights,[1,2] Maverick Salyards,[1] Noelle Kendall,[1,3] Susana M. Lazarte,[1,2] Radhika Kainthla,[2,4] Wendell Miley,[5] Vickie Marshall,[5] Nazzarena Labo,[5] Denise Whitby,[5] Elizabeth Y. Chiao,[6] and Ank E. Nijhawan[1,2]

[1]Division of Infectious Diseases and Geographic Medicine, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [2]Department of Internal Medicine, Parkland Health, Dallas, Texas, USA, [3]Department of Physician Assistant Studies, Chapman University, Orange, California, USA, [4]Department of Internal Medicine, Division of Hematology and Oncology, University of Texas Southwestern Medical Center, Dallas, Texas, USA, [5]Viral Oncology Section, AIDS and Cancer Virus Program, Leidos Biomedical Inc, Frederick National Laboratory for Cancer Research, Frederick, Maryland, USA, and [6]Department of General Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Background. Disparities in mortality in human immunodeficiency virus (HIV)–associated Kaposi sarcoma have been described, particularly in Black men in the southern United States. It is unclear if there are racial/ethnic differences in the seroprevalence of Kaposi sarcoma–associated herpesvirus (KSHV) that may be contributing.

Methods. This is a cross-sectional study of men who have sex with men (MSM) and transgender women with HIV. Participants were recruited from an outpatient HIV clinic in Dallas, Texas, for a 1-time study visit and were excluded from analysis if they had any history of KSHV disease. Plasma was tested for antibodies to KSHV K8.1 or ORF73 antigens, and KSHV DNA was measured in oral fluids and blood by polymerase chain reaction. KSHV seroprevalence and viral shedding in blood and oral fluids were calculated. Additionally, independent risk factors for KSHV seropositivity were assessed by multivariable logistic regression analysis.

Results. Two hundred five participants were included in our analysis. Overall, KSHV seroprevalence was high (68%) with no significant difference between racial/ethnic groups. Among seropositive participants, KSHV DNA was detected in 28.6% of oral fluids and 10.9% of peripheral blood specimens, respectively. The factors most strongly associated with KSHV seropositivity were oral–anal sex (odds ratio [OR], 3.02), oral–penile sex (OR, 4.63), and methamphetamine use (OR, 4.67).

Conclusions. High local seroprevalence of KSHV is likely a key driver of the high burden of KSHV-associated diseases regionally, though it does not explain the observed disparities in KSHV-associated disease prevalence among racial/ethnic groups. Our findings support that KSHV is primarily transmitted via exchange of oral fluids.

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Correspondence: Sheena M. Knights, MD, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9113 (Sheena.Knights@UTSouthwestern.edu); Ank Nijhawan, MD, MPH, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9113 (Ank.Nijhawan@UTSouthwestern.edu).

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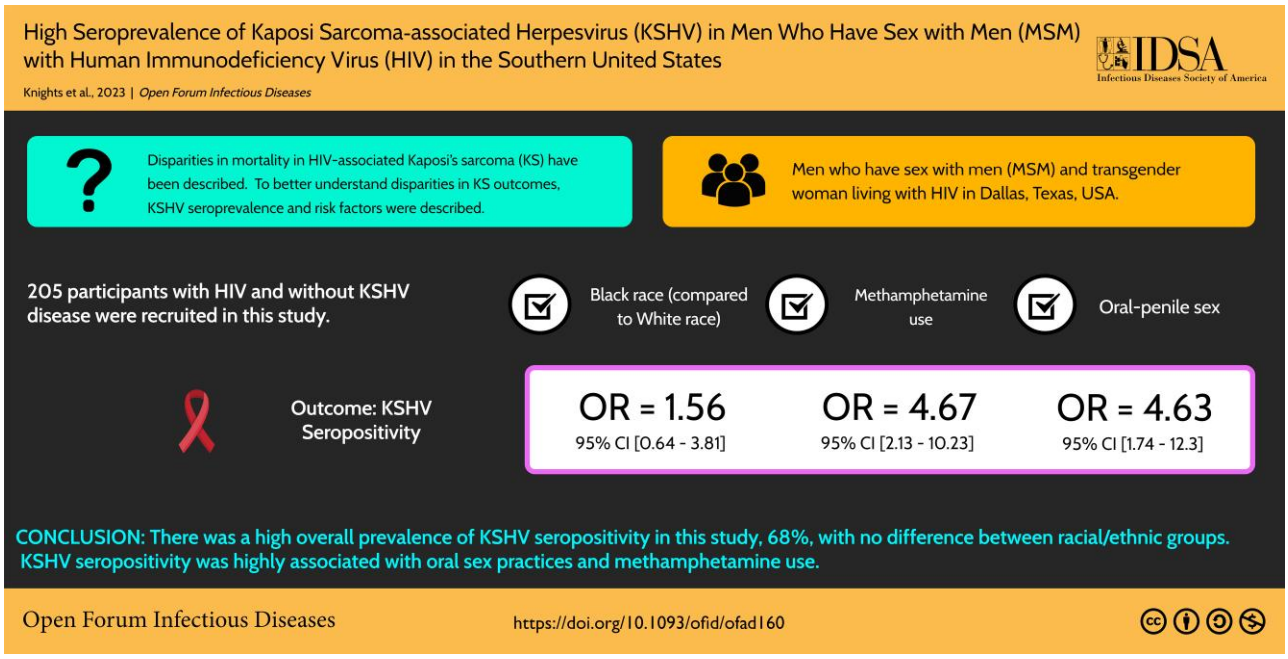
Graphical Abstract



This graphical abstract is also available at Tidbit: https://tidbitapp.io/tidbits/high-seroprevalence-of-kaposi-sarcoma-associated-herpesvirus-kshv-in-men-who-have-sex-with-men-msm-with-human-immunodeficiency-virus-hiv-in-the-southern-united-states

Keywords. epidemiology; HIV; human herpesvirus 8; Kaposi sarcoma; sexual and gender minorities.

Kaposi sarcoma (KS) remains one of the most common malignancies in people with human immunodeficiency virus (HIV) in the United States (US) [1]. Despite an overall decrease in KS incidence and mortality in the combination antiretroviral therapy (ART) era [2], certain subpopulations, particularly young Black men in the southern US, have not experienced the same decline in disease and in fact in some regions have faced an increase in KS diagnoses during this time period [3–7]. This disparity also extends to disease outcomes, as seen among people with HIV with KS in Dallas between 2009 and 2018, where mortality among Black patients was twice as high as non-Hispanic White and Hispanic patients within the same hospital system [8].

Kaposi sarcoma–associated herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the causative virus of KS [9]. Incidence of KS mirrors the prevalence of KSHV infection, which varies significantly by patient population and geographic region [10, 11]. KSHV seroprevalence has been reported at 3%–7% in the general population of the US [12–14], with much higher seroprevalence among MSM, particularly those with HIV, ranging from 38% to 70% [11, 15]. Differences in KSHV seroprevalence by geography and race in people with HIV in the US has also been described [11]. What remains unclear is whether racial/ethnic differences in KSHV seroprevalence continue to exist and if so, whether they drive the recently described disparities in KS incidence and mortality in highly impacted regions of the US.

To address this question and to further understand the disparities in regional KS outcomes, we sought to measure KSHV seroprevalence and describe risk factors associated with seroprevalent KSHV among men who have sex with men (MSM) and transgender women (TGW) with HIV in Dallas, Texas.

MATERIALS AND METHODS

Study Design

This is a cross-sectional study of KSHV seroprevalence among MSM and TGW with HIV in Dallas, Texas. Participants were recruited from an HIV clinic at Parkland Health, a large safety-net hospital system in Dallas, through referrals from medical providers, by word of mouth, and through self-referral by recruitment flyers. This study was approved by the University of Texas Southwestern Institutional Review Board (STU 2019-1204).

Potential participants were considered eligible to enroll if they were (1) aged ≥18 years; (2) a cisgender man or transgender woman; (3) HIV positive, as confirmed by either a combination of a positive third- or fourth-generation HIV Ag/Ab test with positive Geenius HIV 1/2 supplemental assay (Bio-Rad Laboratories) or enzyme-linked immunosorbent assay (ELISA)/Western blot, and/or detectable serum HIV RNA

nucleic acid amplification test; (4) reported sex with men (current or prior); and (5) spoke Spanish or English. Exclusion criteria included (1) known KSHV disease or (2) cognitive impairment interfering with ability to consent. Participants who received medical care outside of the Parkland system for their HIV were asked to complete a release of information request so their medical records could be obtained.

Study Procedures

All participants provided written informed consent prior to proceeding with study enrollment. Participants then completed an electronic survey utilizing REDCap, a secure, Health Insurance Portability and Accountability Act–compliant, web-based database to complete questions regarding substance use, sexual history, sexual practices, and date of HIV diagnosis. After completing the questionnaire, all participants had whole blood and serum collected using a PAXgene DNA tube [16] and a tiger-top tube, respectively. All participants also had oral fluids collected using an alcohol mouthwash protocol, into polypropylene tubes (Nalgene). All study procedures were completed at the same study visit and patients were compensated for their participation.

Patients self-reported their age, race/ethnicity, gender, country of birth, dates of HIV diagnosis and ART initiation, tobacco use, alcohol use, history of ever using recreational substances, history of sexually transmitted infections (STIs), number of sexual partners, age of sexual debut, and types of sexual practices. Electronic medical records were reviewed in order to abstract participants' most recent CD4 cell count, HIV viral load, insurance status, ART regimen, and any prior diagnosis of KSHV-associated disease. Additionally, history of alcohol use was assessed by the administration of a Substance Abuse and Mental Illness Symptoms Screener (SAMISS), and patients were considered to meet the criteria of alcohol use disorder if they obtained a SAMISS score of ≥5 [17].

Laboratory Procedures

Anti-KSHV immunoglobulin G (IgG) in plasma was measured as previously described using ELISA assays employing recombinant K8.1 and ORF 73 antigens [18] and a bead-based multiplex antibody assay that includes multiple KSHV-encoded antigens in a single assay in a flexible format [19]. These assays focused on 35 KSHV antigens to which antibodies have been shown in prior studies to be either prevalent in a variety of populations and/or elevated in association with disease risk, plus 4 key Epstein-Barr virus antigens as positive and negative controls. KSHV seropositivity was defined as ELISA or multiplex assay result above a prespecified cutoff value for either the K8.1 or ORF73. KSHV DNA load was measured on oral fluids and whole blood using CLIA-certified real-time quantitative polymerase chain reaction (PCR) assays targeting the KSHV K6 gene and ERV-3 housekeeping gene as previously described [20, 21]. In brief, DNA was extracted from pelleted oral cells collected via alcohol mouthwash rinse using the Qiagen blood mini kit, while the Qiagen PAXgene system was utilized to collect whole blood samples and extract KSHV DNA. All DNA was extracted using the manufacturer's instructions (Qiagen, Hilden, Germany). DNA samples were tested in triplicate reactions on the Applied Biosystems platform. The average was used to calculate viral load (VL) in oral fluids and whole blood, calculated as KSHV copies/mL and million cell equivalents, respectively, as previously described [22].

Statistical Methods

Based on a sample size calculation using seroprevalence of 30%, 10% precision estimate, and 95% confidence interval (CI), we targeted a sample size of 81 patients within each race/ethnicity (non-Hispanic White, non-Hispanic Black, and Hispanic), totaling approximately 243 participants for target enrollment. KSHV seroprevalence (defined as a proportion: number testing positive divided by total number tested in that population) was calculated for each racial/ethnic group and comparisons between groups were made using χ^2 test, *t* test, or Fisher exact test as appropriate. Additionally, univariate and multivariate logistic regression modeling were conducted to determine which characteristics were associated with positive KSHV serology and KSHV detection in oral fluids and blood. The variable race/ethnicity was included into the multivariate analysis a priori; other variables were included using a stepwise selection model, with a *P* value to enter the model of .05 and to remain in the model of .05. All statistical analyses were conducted using SAS statistical software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

All participants were recruited between January 2020 and July 2021. Overall, 220 participants were enrolled in the study. Fourteen participants were excluded due to history of Kaposi sarcoma and 1 participant was excluded due to unavailable KSHV serostatus (phlebotomy could not be performed), resulting in a total of 205 participants included in statistical analyses. There were 195 cisgender men, 7 TGW, and 3 gender-fluid/gender-nonconforming individuals who were assigned male sex at birth. Forty-nine participants (23.9%) identified as non-Hispanic White (hereafter referred to as White), 98 participants (47.8%) identified as non-Hispanic Black (hereafter referred to as Black), 54 participants (26.3%) identified as Hispanic of any race, and 4 participants identified as other race/ethnicity (2 Native American, 1 Asian, 1 other [not specified]). Overall median age was 46 years (interquartile range [IQR], 34–55 years), median CD4 count was 547 cells/μL (IQR, 325–784 cells/μL), and median HIV VL was 19 copies/mL (IQR, 0–66 copies/mL)/1.28 $\log_{10}$ copies/mL (IQR,

0–1.82 $\log_{10}$ copies/mL). One hundred forty participants (68.3%) were found to be KSHV seropositive and 65 participants (31.7%) were KSHV seronegative.

Patient characteristics by KSHV serology status are presented in Table 1. There were no differences in KSHV seropositivity by race/ethnicity, age, CD4 cell count, HIV VL, insurance status, current ART regimen, number of lifetime sexual partners, tobacco use history, history of alcohol abuse, or history of injection drug use (IDU). Figure 1 demonstrates KSHV seropositivity by race/ethnicity.

The results of univariate and multivariate analyses for predictors of KSHV seropositivity are shown in Table 2. Variables associated with KSHV seropositivity in univariate analyses include history of oral–penile sex (odds ratio [OR], 4.37 [95% CI, 1.80–10.62]), oral–anal sex (OR, 3.56 [95% CI, 1.91–6.64]), insertive ("top") anal sex (OR, 3.45 [95% CI, 1.59–7.48]), history of syphilis infection (OR, 2.11 [95% CI, 1.16–3.84]), methamphetamine use (OR, 4.45 [95% CI, 2.26–8.78]), and marijuana use (OR, 2.24 [95% CI, 1.17–4.29]). Notably, history of penetrative vaginal sex (OR, 1.13 [95% CI, .62–2.01]), and history of oral–vaginal sex (OR, 0.78 [95% CI, .42–1.45]) were not associated with KSHV seropositivity. History of receptive anal ("bottom") sex (OR, 1.99 [95% CI, .91–4.33]) trended toward an association with KSHV seropositivity but did not meet criteria for statistical significance. There was no association with KSHV seropositivity and age (median, 49 years [IQR, 38–57 years] in seronegative and 44 years [IQR, 33–54 years] in seropositive participants), race/ethnicity (OR, 0.75 [95% CI, .36–1.59] for Black compared to White participants; OR, 1.04 [95% CI, .44–2.46] for Hispanic compared to White participants), insurance status (OR, 1.36 [95% CI, .74–2.52] for Ryan White–funded participants compared to non–Ryan White–funded participants), CD4 count (OR, 2.36 [95% CI, .85–6.52] for those with CD4 ≤200 cells/μL compared to those with CD4 >200 cells/μL), HIV VL (OR, 0.99 [95% CI, .51–1.92] for VL ≤50 copies/mL compared to VL >50 copies/mL), ART regimen (OR, 0.91 [95% CI, .39–2.12] for integrase strand transfer inhibitor [INSTI]–based regimens compared to non-INSTI-based regimens), history of alcohol abuse by SAMISS score (OR, 0.84 [95% CI, .46–1.55]), history of tobacco use (OR, 0.99 [95% CI, .53–1.85]), IDU (OR, 1.31 [95% CI, .62–2.76]), or history of STIs (OR, 1.54 [95% CI, .77–3.10]). In multivariate analyses, race/ethnicity was not independently associated with KSHV seropositivity (OR, 1.56 [95% CI, .64–3.81] for Black participants compared to White participants; OR, 2.14 [95% CI, .75–6.16] for Hispanic participants compared to White participants). The variables most strongly independently associated with KSHV seropositivity were methamphetamine use (OR, 4.67 [95% CI, 2.13–10.23]), oral–penile sex (OR, 4.63 [95% CI, 1.74–12.34]), and oral–anal sex (OR, 3.02 [95% CI, 1.52–5.98]).

Oral fluid was analyzed for the presence of KSHV DNA in all participants. Of the 140 KSHV-seropositive individuals, 40 (28.6%) had detectable KSHV; among those who had quantifiable KSHV VL in oral fluids, median KSHV VL was 28 686 copies/mL (IQR, 3730–248 118 copies/mL). In 1 seronegative participant, oral fluid KSHV PCR was qualitatively positive.

Table 1. Patient Characteristics by Kaposi Sarcoma–Associated Herpesvirus Serology Result

Characteristic	KSHV Seronegative (n = 65)	KSHV Seropositive (n = 140)	*P* Value
Age, y, median (IQR)	49 (38–57)	44 (33–54)	.18
CD4, cells/μL, median (IQR)	578 (382–800)	511 (299–766)	.54
CD4 count >200 cells/μL	60 (92.3)	117 (83.6)	.09
HIV VL <50 copies/mL	48 (73.9)	103 (73.6)	.97
Race/ethnicity			.63
White	14 (21.5)	35 (25.0)	
Black	34 (52.3)	64 (45.7)	
Hispanic	15 (23.1)	39 (27.9)	
Other	2 (3.1)	2 (1.4)	
Injection drug use	13 (20.0)	38 (27.1)	.27
Drug use			
Marijuana	41 (63.1)	111 (79.3)	**.01**
Methamphetamines	14 (21.5)	77 (55.0)	**<.01**
Cocaine	34 (52.3)	80 (57.1)	.52
Heroin	3 (4.6)	20 (14.3)	**.04**
Sex practices			
Oral–anal	31 (47.7)	107 (76.4)	**<.01**
Oral–penile	50 (76.9)	131 (93.6)	**<.01**
Anal, insertive	47 (72.3)	126 (90.0)	**<.01**
Anal, receptive	51 (78.5)	123 (87.9)	.08
Vaginal	28 (43.1)	64 (45.7)	.72

Data are presented as No. (%) unless otherwise indicated. Values in bold met criteria for statistical significance.

Abbreviations: HIV, human immunodeficiency virus; IQR, interquartile range; KSHV, Kaposi sarcoma–associated herpesvirus; VL, viral load.

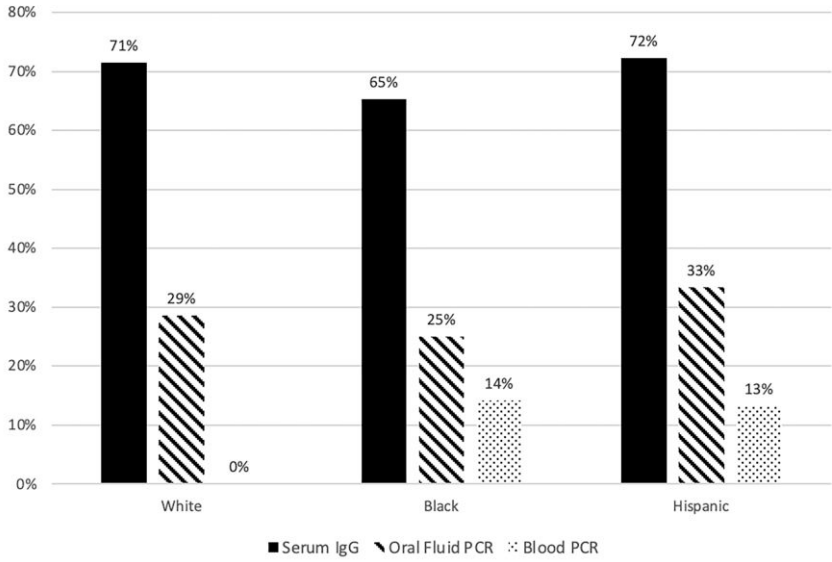


Figure 1. Kaposi sarcoma–associated herpesvirus (KSHV) seroprevalence and KSHV DNA detection by race/ethnicity (n = 205 for serum immunoglobulin G [IgG], n = 140 for oral fluid polymerase chain reaction [PCR], n = 138 for blood PCR).

Table 2. Multivariate Analysis of Risk Factors for Kaposi Sarcoma–Associated Herpesvirus Seropositivity

Risk Factor	Univariate		Multivariate	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Race/ethnicity				
White	Ref	…	Ref	…
Black	0.75 (.36–1.59)	.46	1.56 (.64–3.81)	.33
Hispanic	1.04 (.44–2.46)	.93	2.14 (.75–6.16)	.16
Oral–anal sex	3.56 (1.91–6.64)	<.01	3.02 (1.52–5.98)	<.01
Oral–penile sex	4.37 (1.80–10.62)	<.01	4.63 (1.74–12.34)	<.01
Methamphetamine use	4.45 (2.26–8.78)	< .01	4.67 (2.13–10.23)	<.01

Abbreviations: CI, confidence interval; OR, odds ratio.

Frequency of KSHV oral shedding in seropositive participants was compared by patient characteristics in Table 3. Recreational gamma hydroxybutyrate (GHB) use was positively associated with KSHV oral shedding (OR, 2.56 [95% CI, 1.14–5.76]). Methamphetamine use was not associated with increased rates of viral shedding (OR, 1.15 [95% CI, .55–2.42]), nor higher quantities of virus detected (median VL, 14 615 copies/mL [IQR, 2600–57 895 copies/mL] in those who never used methamphetamines vs 56 250 copies/mL [IQR, 6667–600 000 copies/mL] in those who have used methamphetamines; $P = .19$). There was no association between KSHV oral shedding and race/ethnicity (OR, 1.20 [95% CI, .48–3.03] for Black compared to White participants; OR, 0.80 [95% CI, .30–2.15] for Hispanic compared to White participants), age (median age, 45 years [IQR, 34–55 years] with negative oral fluid PCR, 43 years [IQR, 33–52 years] with positive oral fluid PCR), recent CD4 count (OR, 0.32 [95% CI, .09–1.16] for CD4 ≤200 cells/μL compared to CD4 >200 cells/μL), HIV VL (OR, 0.78 [95% CI, .34–1.75] for VL ≤50 copies/mL compared to VL >50 copies/mL), history of STIs (OR, 4.26 [95% CI, .94–19.3]), insertive anal sex (OR, 1.52 [95% CI, .40–5.78]), receptive anal sex (OR, 0.70 [95% CI, .24–2.04]), vaginal sex (OR, 0.83 [95% CI, .40–1.75]), number of lifetime sexual partners (OR, 1.30 [95% CI, .62–2.72] for >50 partners compared to ≤50 partners), current ART regimen (OR, 1.33 [95% CI, .45–3.92] for INSTI-based regimens compared to non-INSTI-based regimens), history of tobacco use (OR, 0.92 [95% CI, .42–2.00]), history of alcohol abuse (OR, 0.76 [95% CI, .35–1.68]), history of IDU (OR, 1.22 [95% CI, .54–2.74]), or history of marijuana use (OR, 0.92 [95% CI, .38–2.22]).

KSHV VL was measured in whole blood specimens of all but 3 participants; 2 of these 3 were KSHV seropositive. Twenty-five (12.4%) participants had KSHV detected in whole blood, 15 were KSHV seropositive, and 10 were KSHV seronegative. This

Table 3. Patient Characteristics by Oral Kaposi Sarcoma–Associated Herpesvirus Detection in Seropositive Participants

Characteristic	Oral Fluid PCR Negative (n = 100)	Oral Fluid PCR Positive (n = 40)	*P* Value
Age, y, median (IQR)	45 (34–55)	43 (33–52)	.40
CD4 ≤200 cells/μL	20 (20.0)	3 (7.5)	.08
HIV VL ≤50 copies/mL	75 (75.0)	28 (70.0)	.54
Race/ethnicity			.66
White	25 (25.0)	10 (25.0)	
Black	48 (48.0)	16 (40.0)	
Hispanic	26 (26.0)	13 (32.5)	
Other	1 (1.0)	1 (2.5)	
History of STI	78 (78.0)	35 (89.8)	.11
History of tobacco use	66 (66.0)	25 (64.1)	.83
Injection drug use	26 (26.0)	12 (30.0)	.63
Drug use			
Marijuana	79 (79.0)	31 (77.5)	.85
Methamphetamines	54 (54.0)	23 (57.5)	.71
Cocaine	54 (54.0)	26 (65.0)	.23
Heroin	14 (14.0)	6 (15.0)	.88
PCP	12 (12.0)	1 (2.5)	.08
GHB	19 (19.0)	15 (37.5)	**.02**

Data are presented as No. (%) unless otherwise indicated. Values in bold met criteria for statistical significance.

Abbreviations: GHB, gamma hydroxybutyrate; HIV, human immunodeficiency virus; IQR, interquartile range; PCP, phencyclidine; PCR, polymerase chain reaction; STI, sexually transmitted infection; VL, viral load.

resulted in 10.9% of seropositive participants and 15.4% of seronegative participants having detectable KSHV DNA in their blood. Four of 15 seropositive participants had a quantifiable VL of >3 copies/million cell equivalents, and 2 of the 10 seronegative participants had quantifiable virus (417 and 680 copies/million cell equivalents). The rest had qualitatively positive KSHV by PCR, but numbers were too low to quantify. None of these 10 seronegative participants had detectable KSHV in their saliva, and 7 of these 10 participants were aged >45 years. White participants were less likely to have detectable KSHV viremia than Black or Hispanic participants, and this difference was noted in the full sampled population ($P = .01$) as well as in the KSHV-seropositive population ($P = .04$). Among all sampled participants, 1 White participant (2.1%), 12 Black participants (12.4%), and 11 Hispanic participants (20.8%) were noted to have KSHV viremia. There was 1 additional participant whose race/ethnicity did not fit the above 3 categories. Within the seropositive participants, none of the White participants (0%), 9 Black participants (14.1%), or 5 Hispanic participants (13.2%) had KSHV viremia.

DISCUSSION

We found a high overall prevalence of KSHV seropositivity in this study, 68%, with no difference between racial/ethnic groups. This is in comparison to historical data which suggest a range of seroprevalence from 29% in MSM with HIV participating in the AIDS Cancer Cohort Study from October 1997 to January 2000 [23], to up to 70% in patients with HIV from certain regions participating in the AIDS Clinical Trials Group Longitudinal Linked Randomized Trials (ALLRT) study, from 1997 to 2009 [11]. The seroprevalence found in this population in our study is comparable to areas of higher KSHV endemicity in sub-Saharan Africa [24], while the prevalence in the general population in the US is estimated at 7% [12–14]. However, seroprevalence in healthy blood donors in Texas was estimated at 15% in 2001 [25], so geographic differences within the US are likely contributing to the high KSHV seroprevalence observed in our study.

We did not find a difference in KSHV seroprevalence between race/ethnicities to explain the disparities in clinical Kaposi sarcoma previously described [8]. Previous data have been mixed regarding the relationship between KSHV seroprevalence and race/ethnicity. The ALLRT study reported higher prevalence of KSHV seropositivity in White men compared to other race/ethnicities among people with HIV [11]. Another study that evaluated the general US population through the National Health and Nutrition Examination Survey (NHANES) III found higher seroprevalence in those who were Hispanic and Black compared to those who were White [12]. From our sample of MSM with HIV located in a single US city, we did not identify a clear relationship between KSHV prevalence and races/ethnicities to explain the higher mortality in KS seen in Black patients. It is likely that there is a complex interplay of social determinants of health that contribute to this mortality disparity, particularly in the southern US.

KSHV seropositivity was independently associated with practicing oral–anal sex and oral–penile sex, but not with oral–vaginal sex. This is consistent with viral transmission of

KSHV primarily by exchange of oral fluids rather than through sexual intercourse, as KSHV is shed more frequently, and in higher concentrations, in oral fluids compared to anal and genital fluids of both men and women [26, 27]. Furthermore, it emphasizes that in this population comprised of men and TGW with HIV, exchange of oral fluids during sexual activity with men and/or TGW, but not with women, is associated with transmission risk. In this study, shedding was frequent and oral viral loads tended to be high, even in individuals with well-controlled HIV, indicating that the risk of transmitting KSHV by MSM with HIV can remain high despite successful ART.

It was also noted that a history of methamphetamine use was independently associated with KSHV seropositivity. To our knowledge, this relationship has not been described before. It has been suggested that there is a relationship between use of inhaled nitrites ("poppers") and oral shedding of KSHV [26, 28]. Similarly to "poppers," methamphetamines are often used in the context of chemsex, which is the consumption of drugs to facilitate or enhance sexual activity, particularly among MSM [29]. The practice of chemsex, regardless of the agent used, is associated with higher rates of condomless sexual activity and other risky sexual behaviors [29]. It is possible that engaging in chemsex itself, rather than the specific drug used, is a risk factor for KSHV acquisition. However, specific underlying mechanisms have been proposed for certain drugs. "Poppers" in particular have been hypothesized to either cause direct cytotoxicity or induce KSHV virion production, which then leads to cytolysis [28]. Given the recognized impact of methamphetamines and other drugs on oral hygiene [30], it is possible that methamphetamine use could increase transmission of KSHV either by increasing viral shedding in those already infected and/or increasing susceptibility to primary KSHV infection in those who are naive to KSHV infection. This potential relationship of methamphetamine use in KSHV transmission in MSM with HIV requires further study.

Although this study was not powered to detect differences in KSHV DNA detection in oral fluids and peripheral blood, some interesting findings emerged in this cohort. In seropositive individuals, oral shedding was more frequent than viral detection in blood (28.6% vs 10.9%, respectively), and KSHV VLs were much higher in oral fluids compared to blood, consistent with previous studies [26, 27]. Additionally, there was an association of higher rates of KSHV oral shedding in those with a history of GHB use, which is notable for 2 reasons: (1) GHB intoxication is associated with hypersalivation [31], and (2) a related agent, sodium butyrate, is known to activate lytic replication in KSHV [32]. This suggests that GHB, in addition to poppers and methamphetamines as previously discussed, may be another recreational drug implicated in KSHV transmission within this high-risk population. Although there were no differences in oral shedding between race/ethnicity, White participants had notably lower viral load in blood than Black or Hispanic participants. It is difficult to fully interpret this finding due to the overall low proportion of KSHV detection in blood (n = 15/140); however, it is possible that this may have implications for the seemingly increased risk of developing KSHV-associated disease observed in minorities in certain regions within the US, particularly in the southern US.

We also noted a subpopulation of participants who were seronegative for KSHV and negative for KSHV in oral fluids, but did have detectable KSHV virus in blood. Since most of these were older patients (7 of 10 were over the age of 45), it is possible that some people may have lost their IgG over time as described in prior studies [33, 34]. Additionally, there was 1 participant as young as 19 years in this category, who may have been caught in the early stages of KSHV infection. This suggests that our KSHV seroprevalence estimate is likely an underestimate of true KSHV exposure in this population.

One limitation of this study is that because patients were primarily recruited from the clinic setting, this estimated seroprevalence may not be reflective of the true community seroprevalence among MSM and TGW with HIV. The vast majority of patients in this study had well-controlled HIV and were virologically suppressed on ART, so these results may not be applicable to those with undiagnosed or poorly controlled HIV. Another limitation of this study is that it was not powered to detect differences in oral shedding or viral detection in blood, so our ability to detect risk factors for these outcomes is diminished. Additionally, since this study is cross-sectional, we were unable to determine when KSHV was acquired or proximate risk factors for acquisition. Larger-scale epidemiological studies, including longitudinal studies that evaluate concurrent substance use with sexual practices, are required to better understand which factors drive KSHV transmission between individuals.

More than two-thirds of MSM and TGW with HIV were found to be seropositive for KSHV in Dallas, Texas, an area with a disproportionate incidence of Kaposi sarcoma, especially among Black and Hispanic men. KSHV seropositivity was highly associated with oral sex practices and methamphetamine use but did not differ by race/ethnicity. Future prospective, longitudinal studies are needed to better estimate incident KSHV infections and identify key risk factors for KSHV acquisition to improve disease prevention and reduce health disparities in this population.

Notes

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