Kaposi Sarcoma and KSHV Transmission in MSM & Other High-Risk Groups

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- No COIs to report

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Outline

- History of Kaposi's sarcoma and KSHV/HHV-8
- KSHV epidemiology
- KSHV-related diseases
  - Kaposi's sarcoma (KS)
  - Multicentric Castleman's disease (MCD)
  - Primary Effusion Lymphoma (PEL)
- Outcomes in KS

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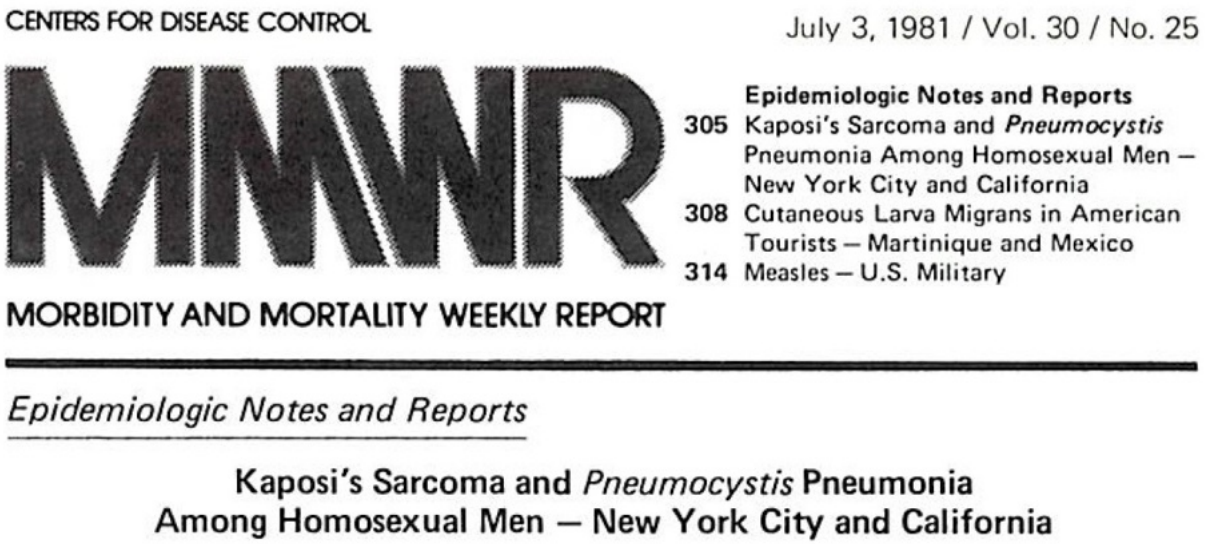
History

- Kaposi's sarcoma (KS) was first described in 1872 by Moritz Kaposi as "multiple idiopathic sarcoma of the skin"
  - 5 male patients with KS

- Kaposi was a dermatologist at the University of Vienna; also studied syphilis and lupus

HIV-Associated KS



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MORBIDITY AND MORTALITY WEEKLY REPORT

Epidemiologic Notes and Reports

Epidemiologic Notes and Reports

Kaposi's Sarcoma and *Pneumocystis* Pneumonia Among Homosexual Men — New York City and California

Identification of KSHV

- HHV-8, or KSHV, was first identified by a group at Columbia University in 1994

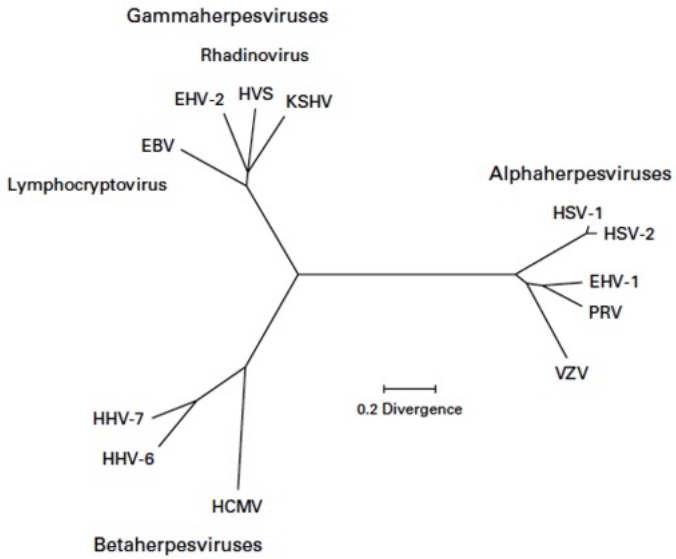
- Analyzed DNA sequences in KS tissue and non-diseased tissue from the same patient and essentially was able to identify this novel virus

Identification of Herpesvirus-Like DNA Sequences in AIDS-Associated Kaposi's Sarcoma

Yuan Chang,* Ethel Cesarman,† Melissa S. Pessin, Frank Lee, Janice Culpepper, Daniel M. Knowles,† Patrick S. Moore

KSHV

- Gamma herpesvirus, closely related to EBV
- Necessary but not sufficient to cause KS
- Can infect multiple types of cells: endothelial cells, B lymphocytes, monocytes and dendritic cells



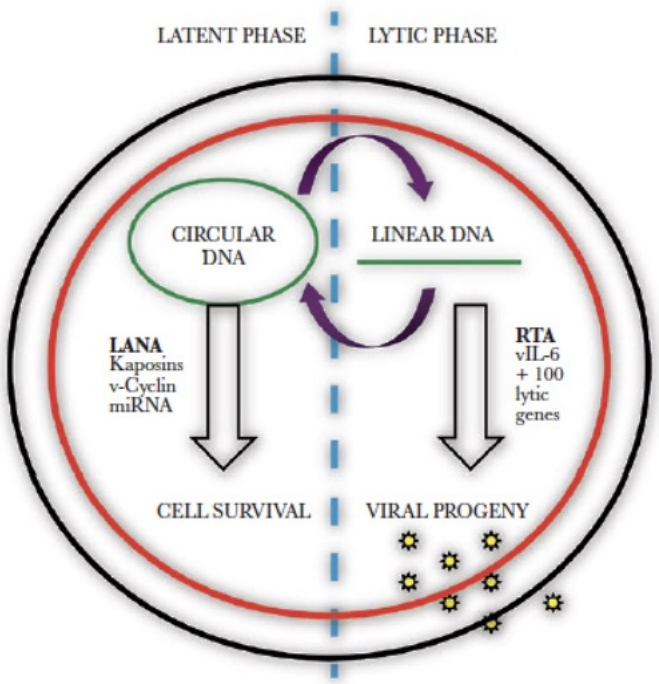
Antman & Chang, *NEJM,* 2000

KSHV Lifecycle/Pathogenesis

- 2 phases of infection
  - Latent phase
  - Lytic phase

- KSHV infection is predominantly latent

- Mechanisms behind conversion from latent to lytic infection are unclear



Cantos et al, *OFID* 2017

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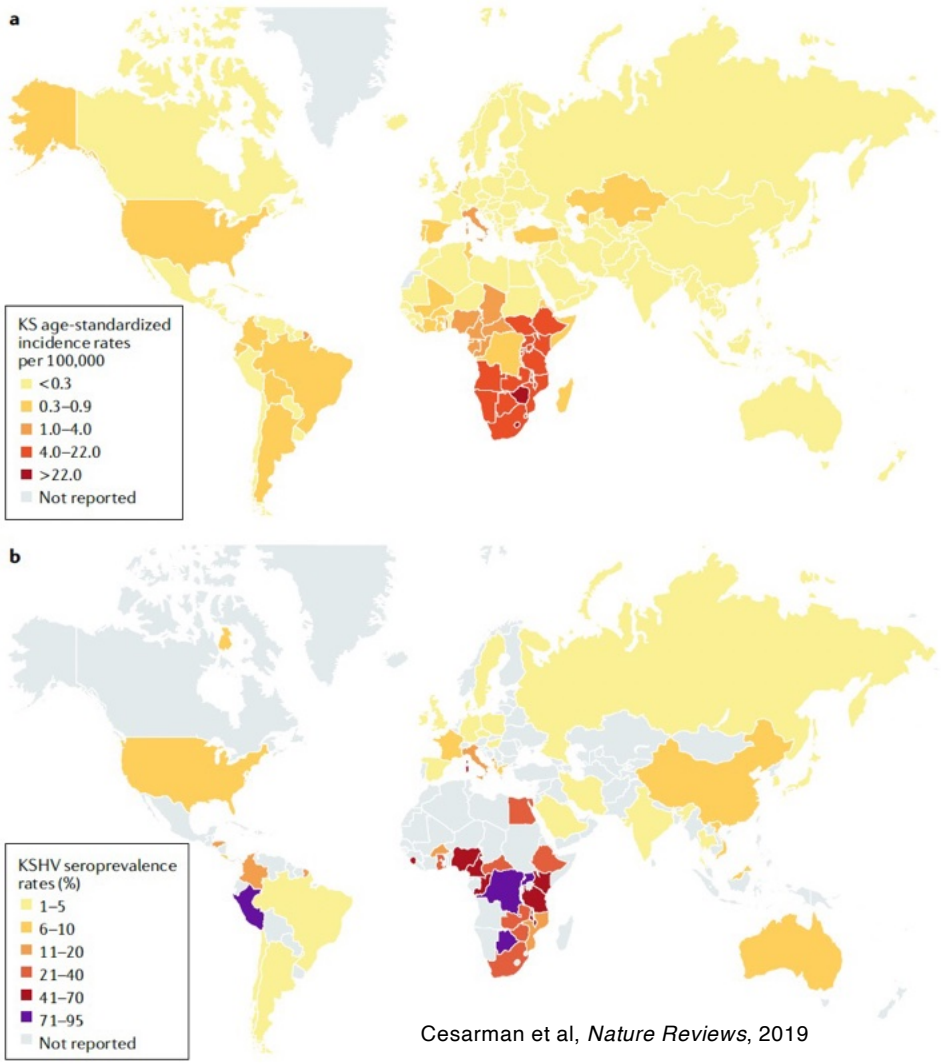
KSHV Epidemiology

- KSHV is unique among herpesviruses as it is not ubiquitous around the world
- Incidence of KS largely parallels local KSHV prevalence
- Highest seroprevalence is found in sub-Saharan African (50-90%)
- Next highest region seroprevalence is the Mediterranean region (14-26% of the general population)



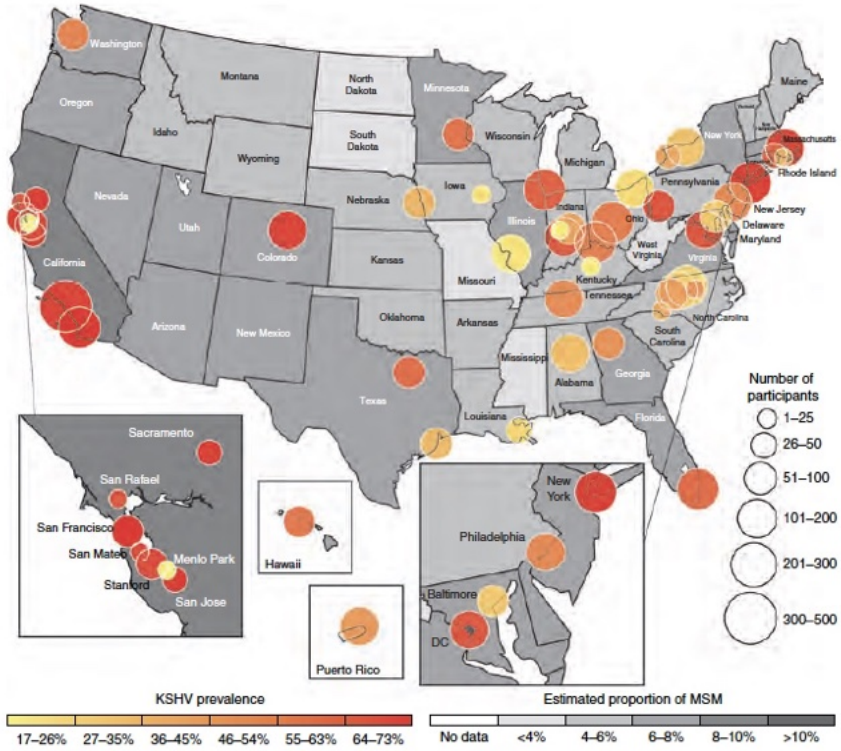
Cesarman et al, *Nature Reviews*, 2019

Parkland

UTSouthwestern Medical Center

KSHV Prevalence in the United States

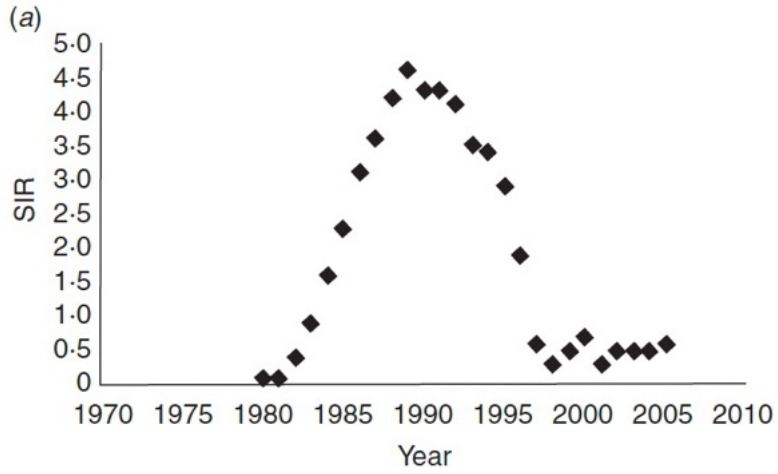
- Regional disparities within the US
  - Higher seroprevalence in urban areas
- General blood-donating population: 3-7%
- People living with HIV (both men and women): 38%
- MSM (with or without HIV): 30%



Labo et al, *AIDS,* 2015

Incidence of KS in the US

• KS incidence increased at the beginning of the HIV epidemic and has decreased in the post ART era



Armstrong et al. *Epidemiol. Infect.,* 2013

Incidence of KS Worldwide

Table 5. Clinic-based cohort studies estimating change in the incidence of Kaposi's sarcoma (KS) since availability of antiretroviral therapy (ART)

Authors	Year published	Cohort	Country	Incidence of KS per 100000 person-years		% Reduction in KS incidence[a]
				Pre-ART era	ART era	
Bedimo *et al.* [33]	2004	SHALOM	USA	2782	541	81%
Brodt *et al.* [34]	1997	Frankfurt AIDS	Germany	17500	4400	75%
Crum-Cianflone *et al.* [35▪]	2010	US Military Natural History	USA	650	180	72%
Gingues and Gill [36]	2006	Southern Alberta Clinic	Canada	3200	400	88%
Hessol *et al.* [37]	2004	WIHS	USA	160.5	36.9	77%
Int'l Collaboration[b] [38]	2000	Many[c]	Many[d]	1520	490	68%
Jones *et al.* [39]	2000	ASD	USA	4100	700	50%
Long *et al.* [40]	2008	John's Hopkins AIDS Clinic	USA	500	100	80%
Patel *et al.* [14]	2008	ASD and HOPS	USA	2500	250	90%
Portsmouth *et al.* [41]	2003	Chelsea and Westminster	UK	3000	3	66%
Seaberg *et al.* [42]	2010	MACS	USA	2515	327	87%

Semeere et al, *Curr Opin Oncol.,* 2012

How is KSHV Transmitted?

- Original reports hypothesize that KSHV is sexually transmitted
- More recent studies show that KSHV is most frequently shed in saliva
- HIV-positive persons shed KSHV more frequently than HIV-negative persons

TABLE 1. RATE OF DETECTION OF HUMAN HERPESVIRUS 8 (HHV-8) DNA BY A QUANTITATIVE PCR ASSAY AMONG 27 HHV-8–SEROPOSITIVE MEN WHO HAD SEX WITH MEN, ACCORDING TO THEIR HIV STATUS.*

TYPE OF SAMPLE	HIV-SERONEGATIVE MEN (N=16)		HIV-SEROPOSITIVE MEN (N=11)	
	STRONGLY POSITIVE	TRACE POSITIVE	STRONGLY POSITIVE	TRACE POSITIVE
	no. positive/total no. (%)			
Saliva	5/61 (8)	1/61 (2)	5/42 (12)	1/42 (2)
Pharyngeal swab	4/60 (7)	0/60	4/41 (10)	3/41 (7)
Nasal swab	0/62	1/62 (2)	0/41	1/41 (2)
Peripheral-blood mononuclear cell	2/58 (3)	1/58 (2)	3/40 (8)	4/40 (10)
Plasma	0/55	0/55	1/41 (2)	1/41 (2)
Semen	1/53 (2)	2/53 (4)	1/38 (3)	1/38 (3)
Prostatic secretions	0/58	2/58 (3)	0/33	1/33 (3)
Urethral swab	1/61 (2)	0/61	0/40	1/40 (2)
Anal swab	0/61	2/61 (3)	0/35	0/35

*Samples were collected during four consecutive weekly visits. Trace positive was defined as a finding of 1 to 10 copies of HHV-8 DNA per milliliter, and strongly positive as a finding of more than 10 copies per milliliter.

Pauk et al, *NEJM*, 2000

KSHV Shedding

- Not only is KSHV most frequently shed in oral samples, it is also found in highest concentrations there

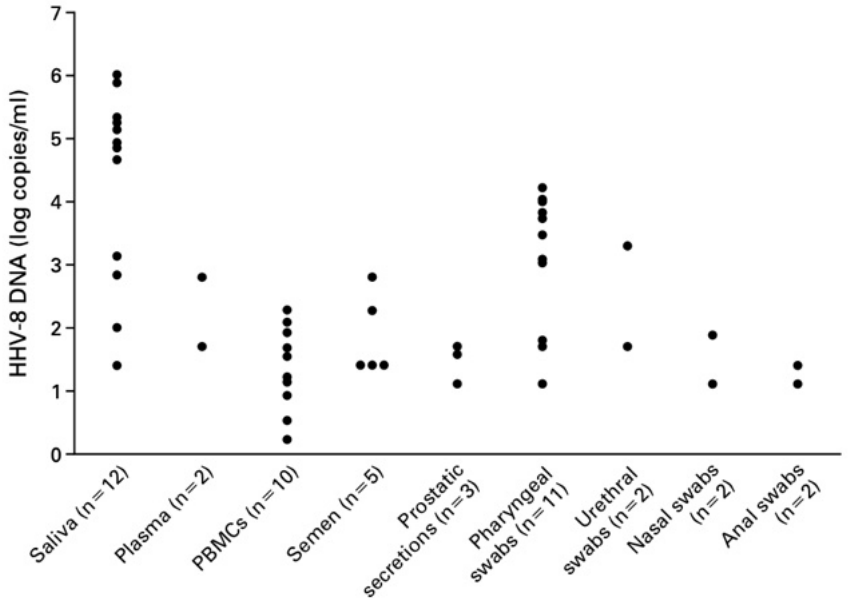


Figure 1. Quantity of Human Herpesvirus 8 (HHV-8) DNA in the Various Samples.
Values are expressed as the log number of copies of HHV-8 DNA per milliliter of sample or per milliliter of PCR digestion buffer into which each specimen swab was placed. PBMCs denotes peripheral-blood mononuclear cells. The numbers of positive samples are given in parentheses.

Pauk et al, *NEJM*, 2000

KSHV Shedding in Women

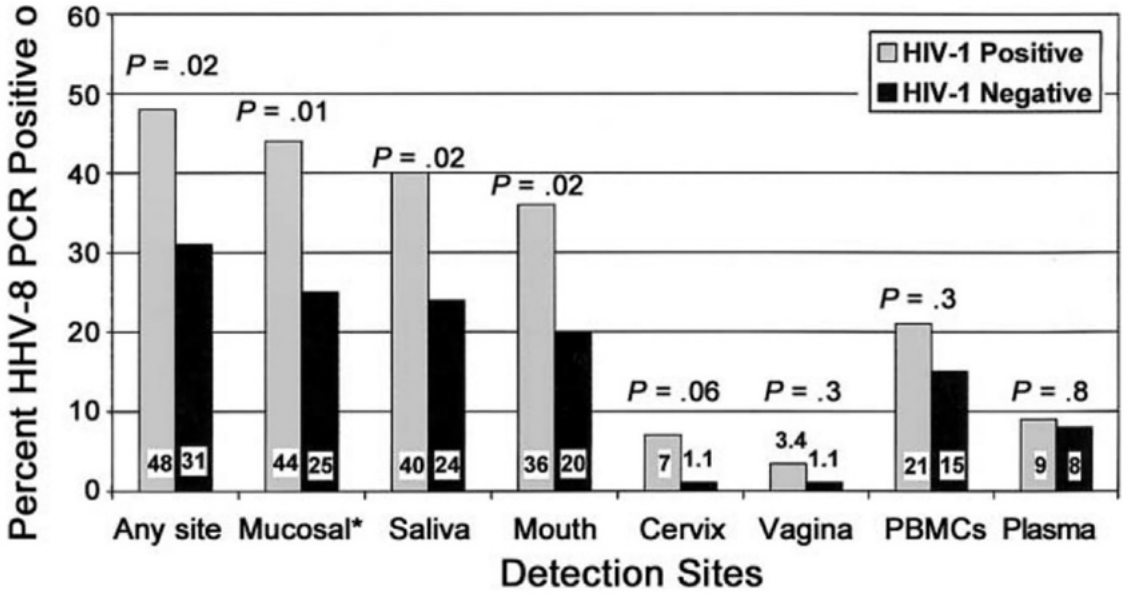


Figure 1.
Prevalence of detection of HHV-8, by HIV-1 serostatus. *, "Mucosal" includes oral (saliva and mouth) and genital (cervical and vaginal) sites.

Taylor et al, *J Infect Dis*, 2004

KSHV Epidemiology in Dallas, Texas

- Anecdotally, we saw a lot of bad outcomes in HIV-associated KS in our clinical practice

- We sought to describe the epidemiology of KSHV in our highest risk population in Dallas: HIV-positive MSM

- Collected demographics, HIV history through survey and chart review

- Each patient provided blood and saliva sample for analysis
  - All samples were processed by Denise Whitby's lab at the NCI

Open Forum Infectious Diseases
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]

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KSHV Epidemiology in Dallas, Texas (con't)

- We enrolled 205 patients without history of KSHV disease
- 140 of 205 patients (68.3%) were seropositive for KSHV
  - Compared to 3-7% in the general population in the US; 38% in the general HIV-positive population in the US
- 39 of 138 seropositive patients (28.3%) had positive KSHV PCR in saliva
  - Median viral load 23,636 copies per million cell equivalents
- 14 of 136 seropositive patients (10.3%) had positive KSHV PCR in blood

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.

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.

Knights et al., *OFID* 2023

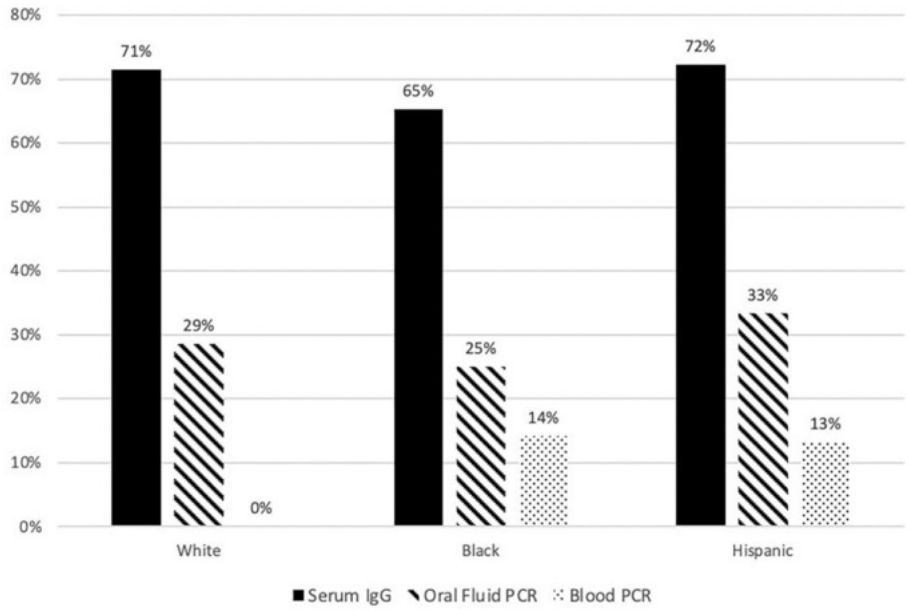

Figure 1. Kaposi sarcoma–associated herpesvirus (KSHV) seroprevalence and KSHV DNA detection by race/ethnicity (n = 205 for serum immunoglobulin G [IgG], n = 140 for oral fluid polymerase chain reaction [PCR], n = 138 for blood PCR).

Knights et al., *OFID* 2023

KSHV Subtypes

- KSHV can be subtyped by sequencing its K1 gene into six major subtypes (A through F) and several minor subtypes
- Subtypes are known to have a specific geographic distributions, with subtypes A and C being the most common subtypes seen in the United States
- As an exploratory aim, we sought to describe the K1 subtypes of KSHV virus seen in our cohort by whole genome sequencing (n = 40)

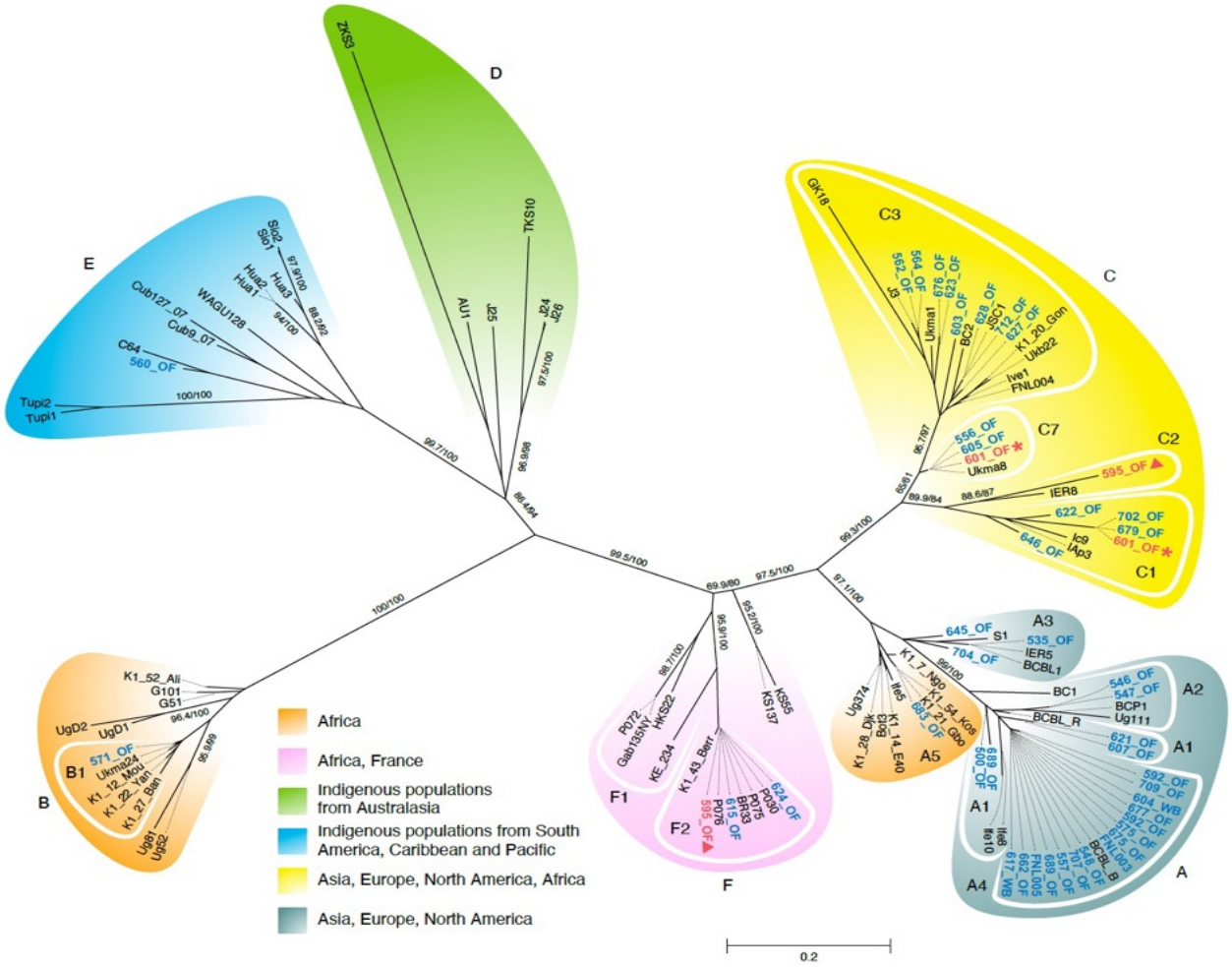

Figure created by
Vickie Marshall, MS

KSHV Epidemiology, Summary

- Saliva appears to be the primary mode of transmission for KSHV
- KSHV prevalence varies based on geographic region
  - Dallas, TX has locally high seroprevalence of KSHV which may explain the anecdotally high numbers of KS disease seen
- There was a larger than expected variety of KSHV K1 subtypes in our cohort
- It is likely that there are other areas of the US and the world with locally high KSHV prevalence which may contribute to locally high rates of KS disease

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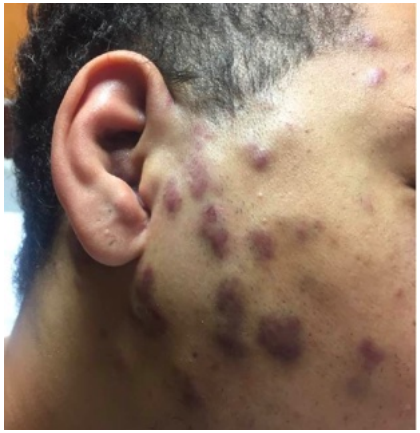
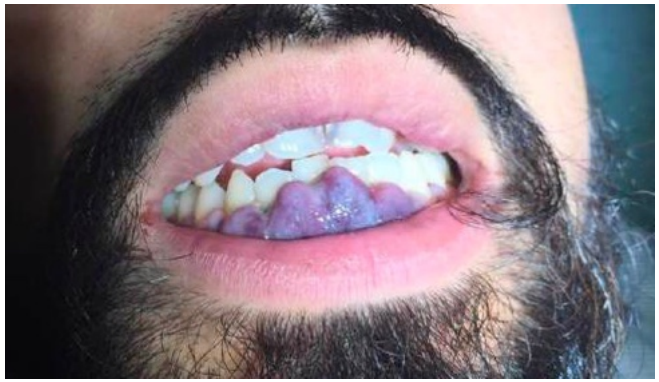
Kaposi's Sarcoma (KS)

- Neoplasm characterized by abnormal proliferation of endothelial cells and angiogenesis
  - Clinically appears as deep purple nodules at site of involvement

- 4 clinical subtypes
  - **Classic**: seen in those of Mediterranean/Ashkenazi Jewish origin, visceral involvement rare
  - **Endemic**: seen in those of sub-Saharan Africa origin
  - **Iatrogenic**: seen in iatrogenically immunosuppressed persons; clinical course variable
  - **Epidemic** or **HIV-associated**: most aggressive, associated with highest mortality (most common type in US)

- Historically, KS was the most common form of cancer seen in people living with HIV early in the HIV epidemic
  - Now 3rd most common after non-Hodgkin's lymphoma and lung cancer





	SIR (95% CI)		Adjusted SIR ratio (AIDS vs HIV only)*	
	HIV only	AIDS	Ratio (95% CI)	p value
All cancers	1·24 (1·20–1·28)	1·88 (1·85–1·91)	1·83 (1·77–1·89)	<0·0001
AIDS-defining cancers	6·99 (6·58–7·43)	17·34 (16·88–17·81)	3·15 (2·94–3·37)	<0·0001
Kaposi's sarcoma	276·91 (248·96–307·13)	585·77 (559·79–612·63)	3·21 (2·86–3·60)	<0·0001
AIDS-defining NHLs	5·90 (5·43–6·40)	14·01 (13·52–14·51)	3·12 (2·85–3·42)	<0·0001
DLBCL	5·05 (4·53–5·62)	12·64 (12·08–13·22)	3·32 (2·94–3·73)	<0·0001
Burkitt's lymphoma	17·49 (14·52–20·88)	21·51 (19·19–24·03)	1·63 (1·31–2·03)	<0·0001
Unspecified NHL	4·92 (4·09–5·87)	15·74 (14·72–16·81)	4·27 (3·52–5·17)	<0·0001
CNS NHL	30·44 (20·82–42·97)	206·50 (188·73–225·50)	10·09 (7·02–14·48)	<0·0001
Cervix	2·04 (1·66–2·48)	3·94 (3·53–4·39)	2·20 (1·74–2·76)	<0·0001
Non-AIDS-defining cancers	0·99 (0·96–1·02)	1·30 (1·27–1·32)	1·45 (1·39–1·51)	<0·0001
Virus-related non-AIDS-defining cancers	3·25 (3·02–3·50)	6·27 (6·06–6·49)	2·21 (2·03–2·40)	<0·0001
Human papillomavirus-related oral cavity or pharynx	1·15 (0·88–1·48)	1·84 (1·61–2·09)	1·76 (1·32–2·36)	0·0001
Anus	7·41 (6·39–8·56)	24·17 (22·92–25·48)	3·49 (2·98–4·08)	<0·0001
Liver	2·81 (2·48–3·17)	3·36 (3·14–3·59)	1·25 (1·08–1·44)	0·0029
Merkel cell carcinoma	1·84 (0·22–6·63)	2·87 (1·24–5·65)	1·56 (0·33–7·35)	0·5734†
Vagina	0·84 (0·10–3·02)	4·95 (3·14–7·43)	6·76 (1·58–28·91)	0·0100
Vulva	4·00 (2·54–6·00)	12·30 (10·26–14·62)	3·22 (2·04–5·08)	<0·0001
Penis	1·94 (0·97–3·48)	6·54 (5·34–7·93)	3·67 (1·94–6·92)	<0·0001
Hodgkin's lymphoma	4·64 (4·00–5·35)	9·42 (8·72–10·15)	2·12 (1·80–2·51)	<0·0001
Virus-unrelated non-AIDS-defining cancers	0·84 (0·81–0·87)	0·95 (0·93–0·97)	1·25 (1·20–1·31)	<0·0001
Lip	0·76 (0·09–2·75)	3·05 (1·81–4·83)	4·30 (0·96–19·27)	0·0568
Salivary gland	0·52 (0·19–1·14)	1·06 (0·70–1·55)	2·27 (0·92–5·58)	0·0745
Nasopharynx	1·29 (0·62–2·38)	1·17 (0·72–1·78)	0·90 (0·43–1·92)	0·7903†
Human papillomavirus-unrelated oral cavity or pharynx	1·35 (1·03–1·74)	2·54 (2·26–2·86)	2·20 (1·65–2·92)	<0·0001
Oesophagus	0·79 (0·55–1·10)	1·40 (1·19–1·64)	2·20 (1·51–3·21)	<0·0001
Stomach	0·69 (0·51–0·92)	0·76 (0·64–0·90)	1·18 (0·84–1·66)	0·3275
Small intestine	0·83 (0·50–1·30)	0·66 (0·46–0·92)	0·85 (0·48–1·53)	0·5931
Colon	0·68 (0·58–0·80)	0·58 (0·52–0·65)	0·95 (0·78–1·16)	0·5943
Rectum or rectosigmoid junction	0·60 (0·46–0·75)	0·72 (0·63–0·83)	1·40 (1·02–1·92)	0·0360‡
Intrahepatic bile duct	1·20 (0·44–2·61)	1·21 (0·68–2·00)	1·01 (0·39–2·61)	0·9800†
Gallbladder	1·03 (0·44–2·02)	1·47 (0·97–2·12)	1·39 (0·61–3·18)	0·4367
Extrahepatic bile duct	0·54 (0·11–1·59)	1·24 (0·72–1·99)	2·29 (0·67–7·80)	0·1865†
Pancreas	0·98 (0·77–1·22)	1·19 (1·04–1·36)	1·26 (0·96–1·65)	0·0953

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Kaposi's Sarcoma Staging

- HIV-associated KS is staged differently than most cancers
- Rather than the traditional TNM staging, ACTG suggests using TIS staging
  - Binary; based on good risk vs poor risk (e.g. T1I1S0)

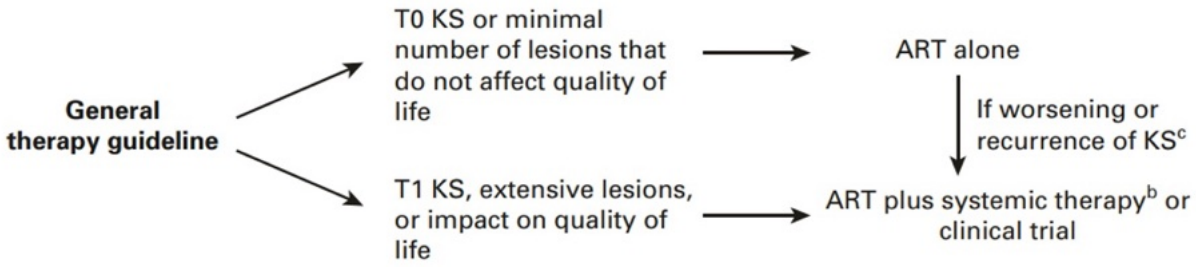
Table 2. Recommended Staging Classification

	Good Risk (0) (All of the Following)	Poor Risk (1) (Any of the Following)
Tumor (T)	Confined to skin and/or lymph nodes and/or minimal oral disease*	Tumor-associated edema or ulceration Extensive oral KS Gastrointestinal KS KS in other non-nodal viscera
Immune system (I)	CD4 cells ≥ 200/μL	CD4 cells < 200/μL
Systemic illness (S)	No history of OI or thrush No "B" symptoms† Performance status ≥ 70 (Karnofsky)	History of OI and/or thrush "B" symptoms present Performance status < 70 Other HIV-related illness (eg, neurological disease, lymphoma)

*Minimal oral disease is nonnodular KS confined to the palate.
†"B" symptoms are unexplained fever, night sweats, > 10% involuntary weight loss, or diarrhea persisting more than 2 weeks.

Diagnosis and Treatment of KS

- Biopsy of affected areas (e.g. skin, GI tract, lymph node, etc.)
- Those with limited disease (T0 stage) can be treated with ART alone
- If T1 disease is present, or lesions not regressing with ART, chemotherapy can be considered
  - Doxorubicin is 1st line
  - Paclitaxel also effective, but more side effects – 2nd line therapy



Ramaswani JCO 2022

Chemotherapy in KS

- The role of chemotherapy in KS treatment is somewhat controversial

- Chemotherapy has not been shown to improve survival in KS; thus the role of chemotherapy is often considered “palliative” rather than “curative”

- However, most studies that evaluated the mortality benefit of chemotherapy excluded patients with symptomatic visceral disease, or fungating lesions → the patients with the strongest indications for chemotherapy
  - Very small trials (< 100 pts), many single site phase II without comparator arm, variable ART requirements

- These studies have shown chemotherapy does not improve survival in less than advanced cases of KS. No data to show if there is a survival benefit in those with the most severe cases of KS

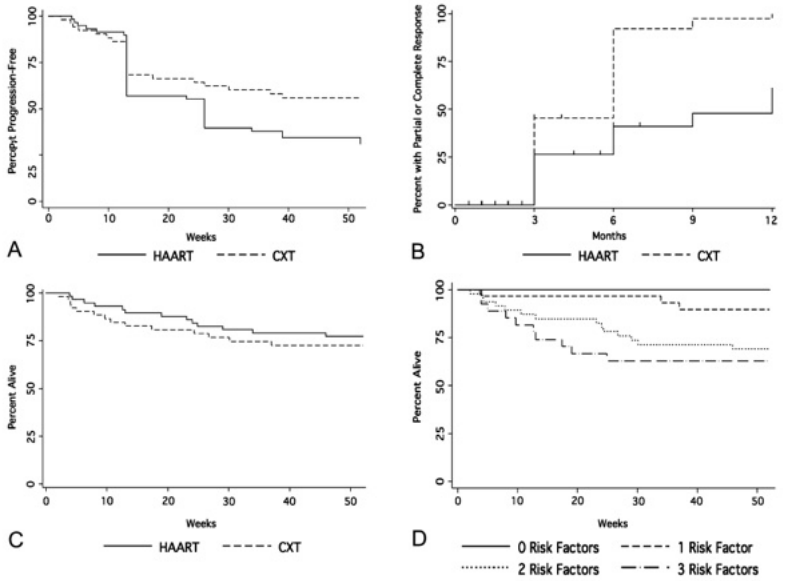
- More food for thought: chemotherapy agents are not widely available in many parts of Africa with the highest burden of KS

Chemotherapy in KS (con't)

- This is one of the few RCTs looking at chemotherapy efficacy + ART compared to ART alone in KS
  - Study conducted in South Africa

- Analysis included 59 participants in the ART arm, and 53 in the chemo + ART arm
  - Pts with symptomatic visceral disease and fungating lesions (i.e. urgent chemotherapy requirements) were excluded

- Results
  - No survival benefit to chemotherapy
  - Higher rates of tumor response with ART + chemo vs ART alone



Mosam et al., *J AIDS*, 2012

Special Considerations in HIV-associated KS

- KS-IRIS is common (6-34% of KS pts in Europe/US, up to 61% of KS pts in sub-Saharan Africa), and is associated with higher mortality than KS without IRIS
  - IRIS is more common when there is extensive disease (T1 stage), or when ART is given without chemotherapy
  - In those with advanced KS disease (T1 stage), exact timing of when to start ART in relation to chemotherapy to minimize IRIS risk has yet to be determined
    - Per DHHS guidelines: “Initiation of ART should not be delayed” in these situations

- Steroids are associated with exacerbation of KS; recommend avoiding unless necessary (Grade AIII recommendation)

Castleman's Disease

- Castleman's disease – lymphoproliferative disorder (not considered a neoplasm), characterized by follicular hyperplasia and hyaline vascular changes within the representative lymph node

- 3 main subtypes:
  - Unicentric Castleman's disease – involves a single lymph node
  - Idiopathic multicentric Castleman's disease – multiple lymph nodes involved, not associated with KSHV
  - **KSHV associated multicentric Castleman's disease – most common form seen in PWH**

Castleman's Disease

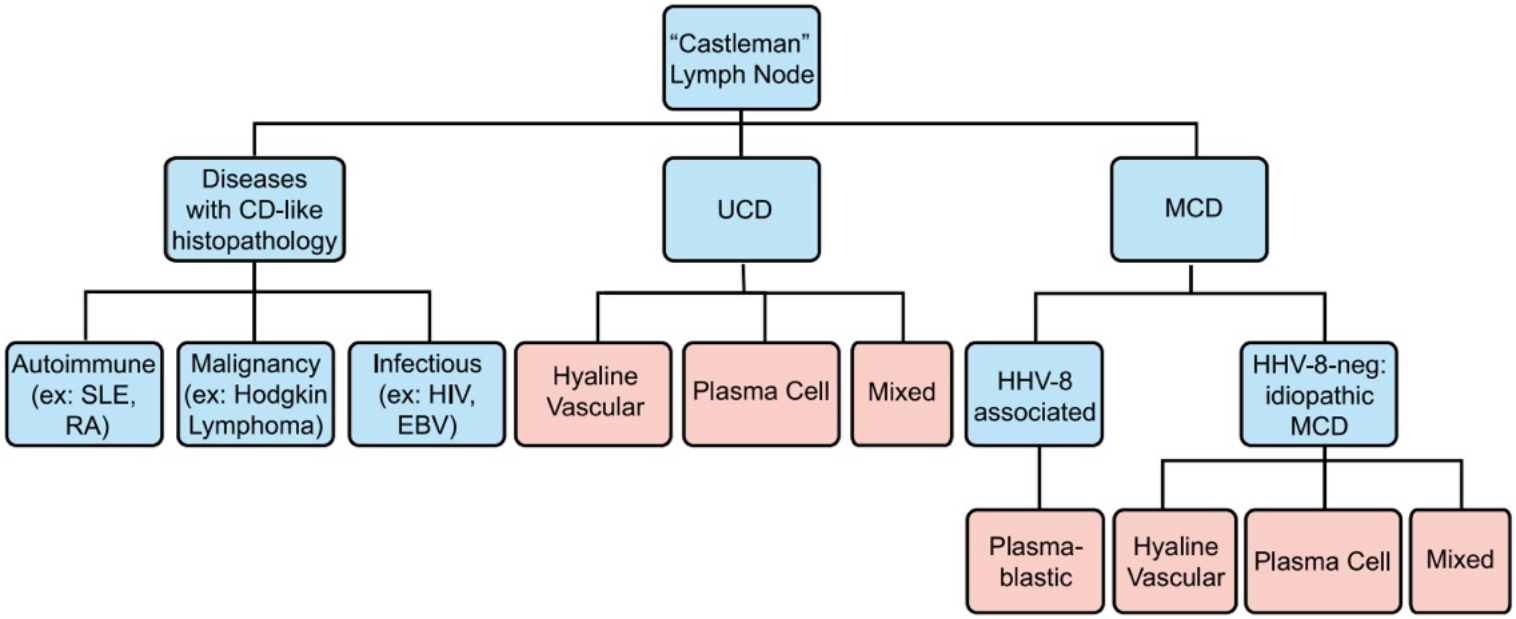


Figure 2. Diseases with Castleman-like lymph node histopathological features. Angiofollicular lymph node hyperplasia, or Castleman-like histopathological features are seen in unicentric and multicentric Castleman disease. These changes are nonspecific and can also be seen with other autoimmune diseases, malignancies, and infections. Disease states are listed in blue, and histopathological findings are listed in pink.

PMID: 24622327

Multicentric Castleman's Disease (MCD)

- Clinical Presentation
  - Fever (100%), lymphadenopathy (96%), hepatosplenomegaly (60-80%)
  - Concurrent Kaposi's sarcoma is common
    - 50% - 70% of patients with HHV-8 associated MCD have concurrent KS

- Diagnosis
  - Need lymph node biopsy and and consistent clinical presentation to make this diagnosis
    - Excisional lymph node biopsy preferable: need for analysis of LN architecture

  - Pathological findings:
    - Nodal expansions that leave the underlying LN architecture partially intact
    - Polyclonal proliferation of B cells and plasma cells
    - T cells show no evidence of aberrant immunophenotype

Multicentric Castleman's Disease (MCD)

- Treatment not standardized

- Rituximab – anti-CD20 monoclonal antibody
  - Can worsen KS if present. Important to assess for KS if MCD is diagnosed
  - Add doxorubicin to rituximab if KS is present
  - Add rituximab to chemotherapy regimen if concurrent PEL is present

- Antivirals (ganciclovir/valganciclovir, zidovudine) – in vitro data and case reports
  - Can be considered for adjunctive therapy

- Monoclonal antibodies to IL-6 (e.g. tocilizumab) – mostly case reports
  - Can be considered for adjunctive therapy

Multicentric Castleman's Disease (MCD)

- One study from Germany evaluated 52 patients with HIV-associated MCD
  - Marked difference in overall survival:
    - 5 year median survival in those who did not receive rituximab
    - Median survival not reached in those who did receive rituximab

- One study out of France evaluated 113 patients with HIV and KSHV-associated MCD
  - 2- and 5- year survival was 93% and 90% in patients who received rituximab
  - 2- and 5- year survival was 68% and 47% in patients who didn't receive rituximab
  - 9 out of 48 patients (19%) who received rituximab developed either reactivation or new diagnosis of Kaposi's sarcoma after rituximab initiation

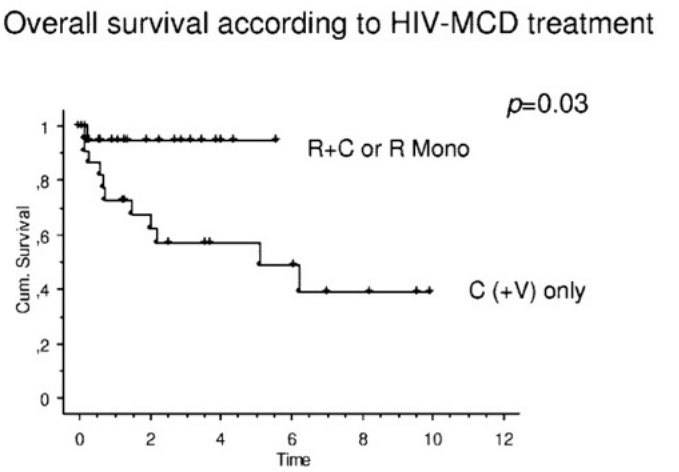


Figure 2. OS in patients with HIV-associated MCD stratified according to MCD treatment. When patients receiving rituximab only (R Mono) or receiving R + C were compared with patients receiving cytostatic therapy (with or without antiviral agents; C(+V) only), there was a significant effect on OS toward rituximab-based regimens. The mean estimated OS of patients with R or R + C was not reached, compared with 5.1 years ($P = .03$) in patients receiving C(+V).

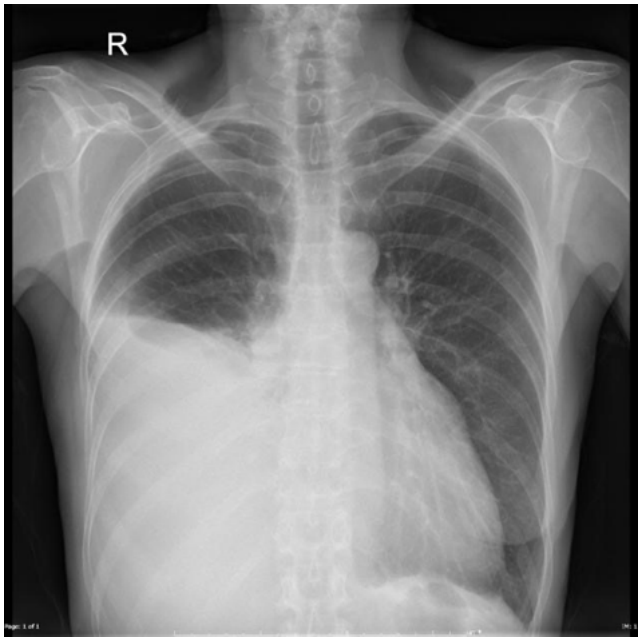
Hoffman et al., *Blood* 2011

Primary Effusion Lymphoma (PEL)

- B-cell non-Hodgkin's lymphoma that affects B-cells in serosal surfaces

- All cases involve KSHV, most (80%) are co-mediated by EBV

- Presentation:
  - Pleural, pericardial, peritoneal effusions – cytology from this fluid is diagnostic
  - Can also present as "extracavitary" disease – lymphadenopathy or mass lesions at any site similar to traditional lymphomas



PEL Diagnosis and Treatment

- Diagnosis: cytology of affected fluid and/or lymph node biopsy
- Treatment:
  - ART
  - Chemotherapy, exact regimen not standardized
    - Often CHOP or EPOCH-based chemotherapy regimens
    - Note: the “H” is hydroxydaunorubicin, often interchanged with doxorubicin → concurrent KS is often already treated in these chemotherapy regimens
- Prognosis is historically poor. Median survival 4 - 6 months

Outline

- History of Kaposi's sarcoma and KSHV/HHV-8
- KSHV epidemiology
- KSHV-related diseases
  - Kaposi's sarcoma (KS)
  - Multicentric Castleman's disease (MCD)
  - Primary Effusion Lymphoma (PEL)
- **Outcomes in KS**

KS Survival Disparities

Cancer Surveillance Research

Cancer Epidemiology, Biomarkers & Prevention

Trends in Kaposi's Sarcoma Survival Disparities in the United States: 1980 through 2004

Geetanjali D. Datta[1,2,3], Ichiro Kawachi[1], Cyrille Delpierre[2], Thierry Lang[2], and Pascale Grosclaude[2]

Reviewed cases of KS through the SEER database from 1980 - 2004

KS Survival Disparities (con't)

- White and Black patients had similar median survival time pre-ART
- Post-ART, disparities in median survival between Black and White patients grew
  - This disparity was seen regardless of T-stage of disease
- These disparities are likely under-appreciated, as median survival was not reached in many post-ART White patients at 143 months

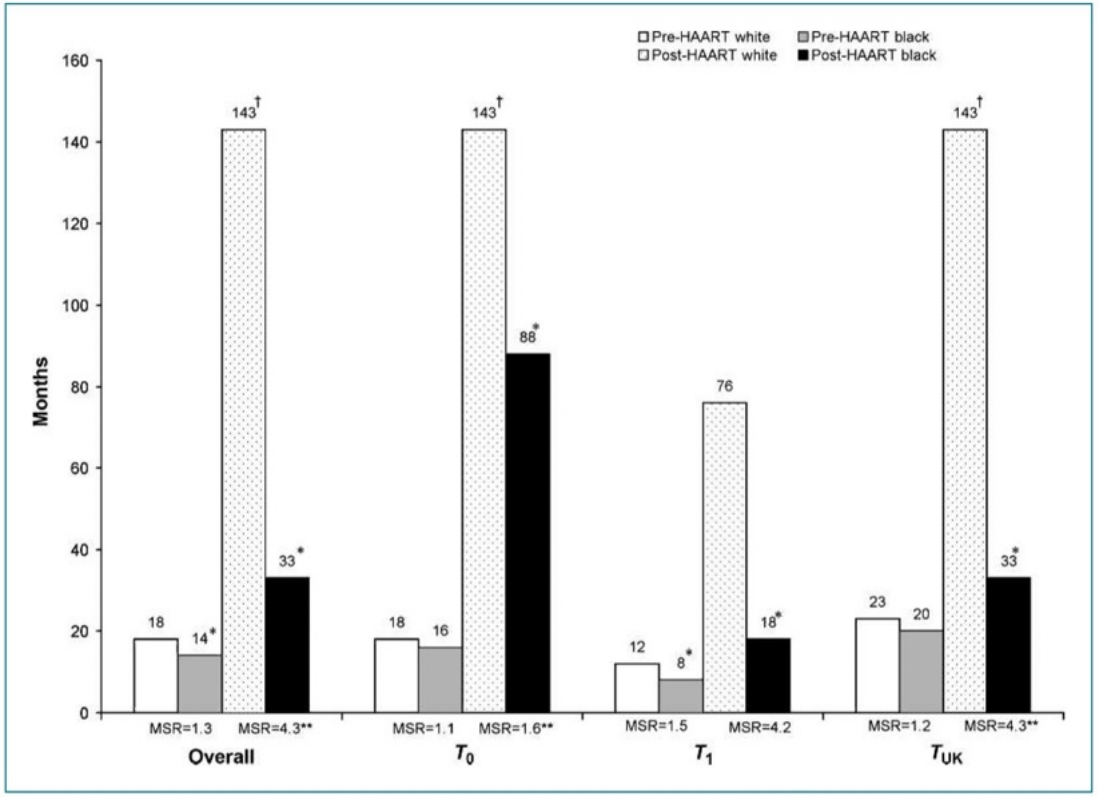


Figure 2. Median cause-specific survival time by race, tumor prognosis, and treatment era (SEER 1980-2004). †, median survival not reached at 143 mo. *, $P < 0.05$. **, underestimate, median survival not reached among white patients.

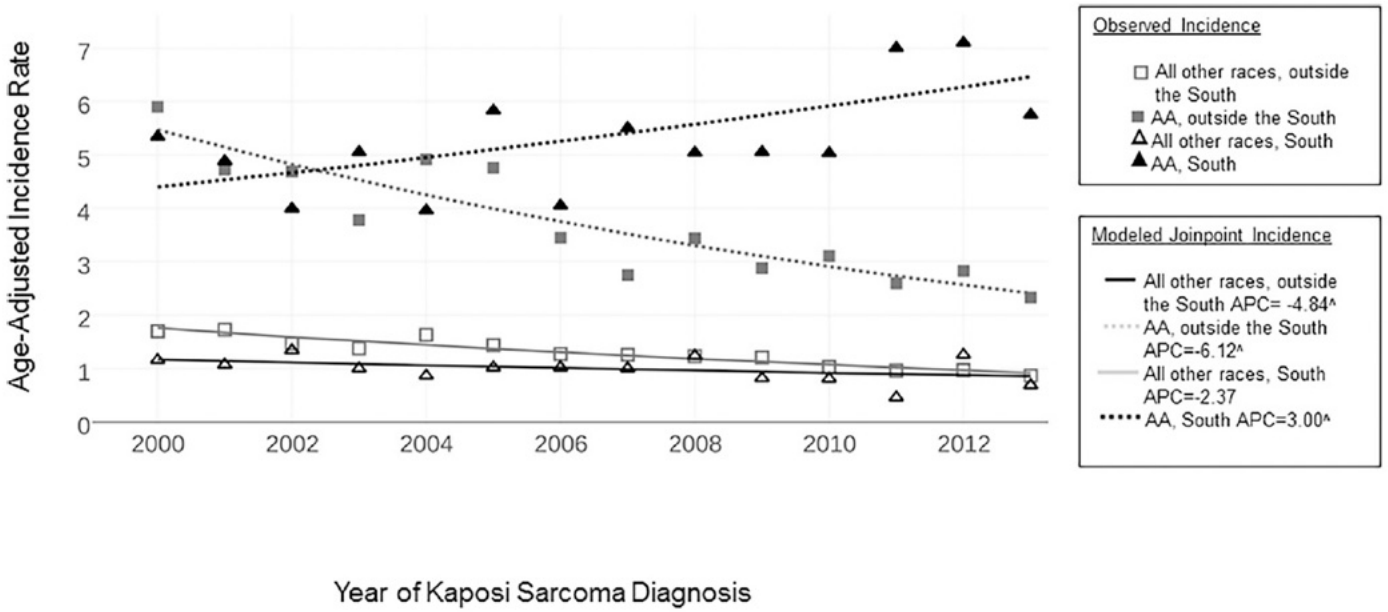
Disparities in KS Outcomes

Disparities in Kaposi sarcoma incidence and survival in the United States: 2000-2013

Kathryn E. Royse[1], Firas El Chaer[2,3], E. Susan Amirian[4,5], Christine Hartman[1], Susan E. Krown[6], Thomas S. Uldrick[7], Jeannette Y. Lee[8], Zachary Shepard[9], Elizabeth Y. Chiao[1,2]*

- Reviewed SEER cancer registry of KS patients between 2000-2013 (N=4455)

Disparities in KS Outcomes (con't)



^The Annual Percent Change (APC) is significantly different from zero at alpha=0.05

Fig 4. KS incidence in the U.S. by race and geographic, 2000–2013.

Disparities in KS Outcomes (con't)

- Incidence may be increasing in black men in the South

- Survival analysis also suggests that these patients have the lowest survival as well

- All-cause mortality and cancer-specific mortality were significantly higher in Black men than in White men (HR 1.5)

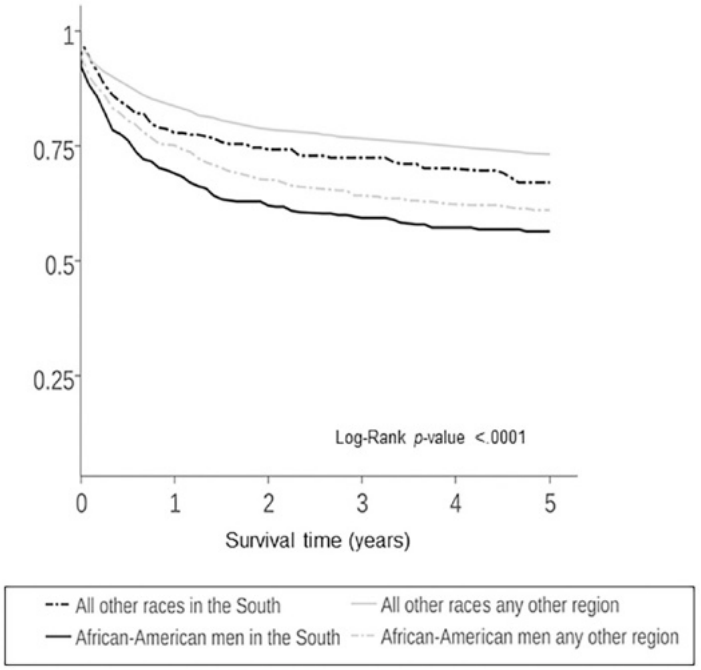


Fig 6. KS survival in the U.S. by Race and Geographic Region, 2000–2013, N = 3,793.

Kaposi's Sarcoma in Dallas, Texas

- Retrospective review of all patients with a diagnosis of both HIV and Kaposi's sarcoma between 2009 and 2018 at Parkland Health
  - Based on ICD-9 and -10 codes

- Parkland is a large safety-net hospital located near downtown Dallas

- 262 patients identified

- Mortality analysis performed

Kaposi's Sarcoma in Dallas, Texas (con't)

- Median follow up time: 43 months
- Median age at cancer dx: 38 years
  - Median CD4: 44 cells/μL
  - Median VL: 4.91 $\log_{10}$ copies/mL
- 30% were on ART at the time of KS diagnosis
- 4 concurrent MCD, 5 concurrent PEL
- 42% received chemotherapy
  - Majority (85%) received anthracycline-based therapy

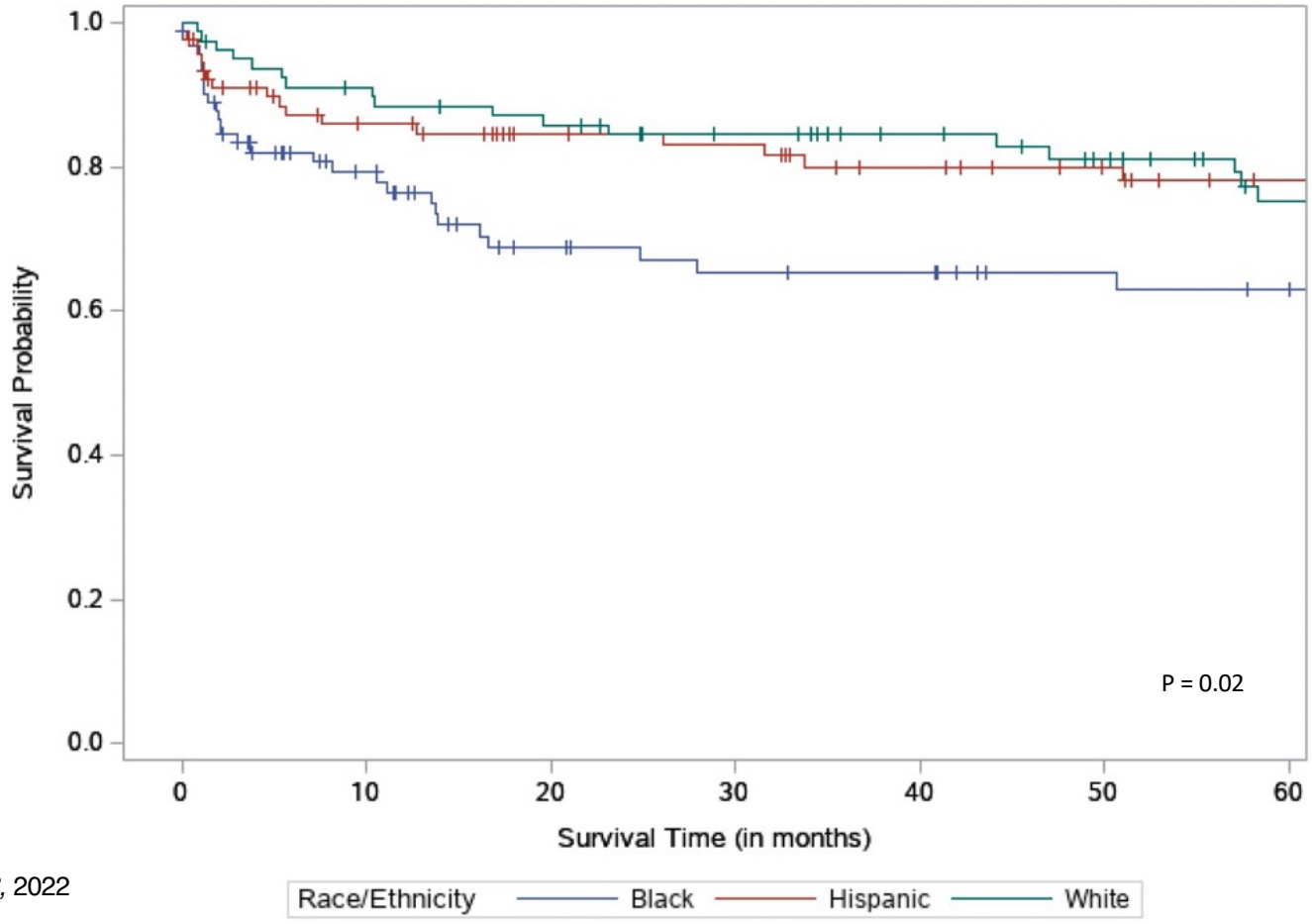
Knights et al, *AIDS*, 2022

Table 1. Patient characteristics.

Variables	$N = 262$
Gender	
Male	250 (95.4%)
Female	9 (3.4%)
Transgender female	3 (1.2%)
Ethnicity	
White	79 (30.3%)
Black	91 (34.9%)
Hispanic	91 (34.9%)
Asian	1 (0.4%)
Payor	
Ryan White/uninsured	147 (56.1%)
Medicare/Medicaid	58 (22.1%)
Private	16 (6.1%)
Jail	5 (1.9%)
HIV risk factor[a]	
MSM	203 (77.5%)
Heterosexual	71 (27.1%)
Injection drug use	17 (6.5%)
Sites of KS involvement	
Skin	230 (87.8%)
Naso/oropharynx	50 (19.1%)
Gastrointestinal	54 (20.6%)
Pulmonary/respiratory tract	65 (24.8%)
Lymph node	66 (25.2%)
Other[b]	26 (9.9%)
More than one sites	132 (50.4%)

KS, Kaposi's sarcoma.
[a]Some patients reported more than one risk factor for HIV.
[b]Other sites involved include: liver, spleen, pancreas, bone marrow, eye.

Parkland UTSouthwestern Medical Center



Knights et al, *AIDS,* 2022

Clinical Characteristics

Table 2. Clinical characteristics by race and ethnicity.

	White	Black	Hispanic	*P* value
$CD4^+$ median (cells/μl) (IQR)	49 (20–154)	39 (11–114)	56, (17–182)	0.17[a]
$CD4^+$ ≤50 cells/μl	49 (62%)	58 (63%)	49 (54%)	0.51
HIV VL median (log_{10} copies/ml) (IQR)	4.89 (2.79–5.34)	4.91 (3.89–5.59)	4.91 (2.92–5.42)	0.26[a]
VL >200 or 2.30 log_{10}	45 (57%)	62 (68%)	58 (64%)	0.32
Age in years at HIV diagnosis median (IQR)	33 (26–38)	**27 (22–31)**	32 (26–39)	**<0.01**[a]
Age in years at KS diagnosis median (IQR)	42 (37–47)	**34 (27–40)**	37 (31–43)	**<0.01**[b]
Payor (*N* = 225)				
Medicare/Medicaid	28%	24%	15%	0.08
RW/uninsured	47%	55%	65%	0.17
Private	3.8%	7.7%	6.6%	0.46
Jail	1.3%	2.2%	2.2%	0.49
IDU	16%	7%	4%	0.01
T1 stage (*N* = 253)	32%	**65%**	43%	**<0.01**
I1 stage (*N* = 236)	78%	91%	80%	0.06
S1 stage (*N* = 228)	50%	69%	64%	0.06
IRIS (*N* = 190)	1.2%	9.9%	2.2%	0.10
Two or more hospitalizations (*N* = 219)	19%	34%	29%	0.38
Presence of other AIDS-defining illnesses	54%	41%	57%	0.06
On ART (*N* = 211)	29%	32%	30%	0.82
Engaged in care (*N* = 161)	24%	30%	31%	0.47

N = 261 unless otherwise stated. ART, antiretroviral therapy; IDU, injection drug use; IRIS, immune reconstitution inflammatory syndrome; IQR, interquartile range; KS, Kaposi's sarcoma; OI, opportunistic infections; RW, Ryan White; SD, standard deviation; VL, viral load.
[a]*P* values reflect differences of log-transformed means of dependent variables using white as baseline.
[b]Raw data already normally distributed. *P* value reflects differences in means between ethnicities.

Knights et al, *AIDS*, 2022

Multivariate Analysis

Table 3. Multivariable survival analysis.

Risk factor	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Race and ethnicity				
Black[a]	2.21 (1.25–3.90)	0.01	2.07 (1.12–3.82)	0.02
Hispanic[a]	Ref	–	Ref	–
White	1.54 (0.86–2.76)	0.15	1.34 (0.68–2.63)	0.40
$CD4^+$ 50 or less[b]	2.30 (0.99–5.36)	0.054	–[c]	–[c]
T1 stage	2.14 (1.36–3.38)	<0.01	1.53 (0.88–2.66)	0.13
One hospitalization in first 6 months after KS diagnosis[d]	2.70 (1.33–5.50)	<0.01	2.44 (1.16–5.12)	0.02
At least two hospitalizations in first 6 months after KS diagnosis[d]	6.04 (3.01–12.09)	<0.01	5.27 (2.50–11.11)	<0.01
Injection drug use	1.83 (1.01–3.33)	0.048	2.41 (1.18–4.92)	0.02

CI, confidence interval; KS, Kaposi's sarcoma.
[a]Compared with patients of Hispanic ethnicity.
[b]Compared with patients with $CD4^+$ cell count greater than 200 cells/μl.
[c]Variable $CD4^+$ count did not meet significance criteria to enter the multivariate model.
[d]Compared with patients with zero hospitalizations.

Knights et al, *AIDS,* 2022

KS Outcomes - Conclusions

• Although incidence and mortality in KS have improved in the post-ART era, outcome disparities remain, particularly between White and Black patients

• Black patients with KS in our hospital were twice as likely to die as White and Hispanic patients with KS
  – Higher rates of T1 disease
  – Not explained by differences in CD4 count, VL, engagement to care or ART adherence

• There may be additional factors other than access to care contributing to this mortality difference between ethnicities that warrant further study

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