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Kaposi Sarcoma Incidence, Burden and Prevalence in United States People with HIV, 2000–2015

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Abstract

Background: The introduction of combination antiretroviral therapy (cART) has led to a significant reduction in Kaposi sarcoma (KS) incidence among people with HIV (PWH). However, it is unclear if incidence has declined similarly across key demographic and HIV transmission groups and the annual number of incident and prevalent KS cases remains unquantified.

Methods: Using population-based registry linkage data, we evaluated temporal trends in KS incidence using adjusted Poisson regression. Incidence and prevalence estimates were applied to CDC HIV surveillance data, to obtain the number of incident (2008–2015) and prevalent (2015) cases in the United States.

Results: Among PWH, KS rates were elevated 521-fold (95% confidence intervals [CI]: 498, 536) compared to the general population and declined from 109 per 100,000 person-years in 2000 to 47 per 100,000 person-years in 2015, at an annual percentage change of −6%. Rates declined substantially (p-trend<0·005) across all demographic and HIV transmission groups. Of the 5,306 new cases estimated between 2008 and 2015, 89% occurred among men who have sex with men. At the end of 2015, 1,904 PWH (0.20%) had been diagnosed with KS in the previous 5 years.

Conclusions: A consistent gradual decline in KS incidence has occurred among PWH in the United States during the current cART era. This decrease is uniform across key demographic and HIV transmission groups, though rates remain elevated relative to the general population.

Impact: Continued efforts to control HIV through early cART initiation and retention in care need to be maintained and possibly expanded to sustain declines.

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Keywords

HIV seropositivity; AIDS-related cancer; Kaposi sarcoma; cancer surveillance; men who have sex with men

Introduction

Kaposi sarcoma (KS) is a rare malignancy caused by Kaposi sarcoma-associated herpes virus (KSHV) (1) that occurs at highly elevated rates among persons with HIV (PWH) (2–4). KS is an AIDS-defining condition and is an indication of immune suppression (5). Though KS rates are elevated across subgroups of PWH, men who have sex with men (MSM) have the highest risk, (6–10) likely due to a higher prevalence of KSHV infection (11).

The use of combination antiretroviral therapy (cART) to treat HIV began in 1996 in the United States and has become increasingly widespread, leading to significant reductions in KS rates among PWH (12–14). Relative to the general population, KS rates in PWH were elevated 2,800-fold in the pre-cART era (1991–1995) (15) and 260-fold in 2009–12 (14). Despite this dramatic decrease in KS rates, it remains unclear if rates have declined similarly across demographic and HIV transmission groups in the United States, or if KS rates are actually increasing in some groups, as two recent studies have suggested (16,17). Identifying groups with increasing or even stable KS rates is critical, as KS may be an indicator of poor HIV control.

Recognizing these gaps in the epidemiology of KS, we utilized linked cancer and HIV registry data to identify a cohort of HIV-infected people to describe temporal trends in the incidence of KS over a recent 16-year period, both overall and within selected demographic and HIV transmission groups. In addition, we estimated the number of annual incident KS cases during 2008–2015 and the number of people diagnosed with KS in the last 5 years (5-year prevalence of KS) among PWH in the United States at the end of 2015.

Materials and Methods

Study Design and Study Population

Data were obtained from the HIV/AIDS Cancer Match (HACM) study, which is a population-based linkage study of 12 state and regional cancer and HIV registries across the United States (https://hivmatch.cancer.gov/). Specifically, data from Colorado (2000–2015), Connecticut (2005–2015), Georgia (2004–2012), Louisiana (2000–2015), Maryland (2008–2012), Michigan (2000–2015), North Carolina (2000–2014), New Jersey (2000–2012), New York (2001–2012), Puerto Rico (2003–2012), Texas (2000–2015) and Washington DC (2007–2015) were utilized. PWH were identified from the HIV registries, and follow-up for participants began at the latter of January 1 of the calendar year at the start of coverage for each registry, and the first of a person's HIV report date or AIDS diagnosis date. Participants 15 years or older were followed-up until death, the end of registry coverage or the end of our study period on December 31, 2015.

KS diagnosis, which was the outcome of interest, was identified in cancer registries using the ICD-O-3 histology code 9140 (18). Incident KS cases were defined as those with a KS diagnosis 4 or more months following HIV or AIDS diagnosis date. New KS cases recorded by the cancer registry 0 to 3 months after the earliest of HIV or AIDS diagnosis date were considered prevalent KS cases as the risk of KS is very high during this time period, likely due to concurrent diagnosis of HIV and cancer and cancer diagnosed during clinical work up related to new HIV diagnosis.

The state health departments of all states and Washington, DC, submit data on all HIV diagnoses to the Centers for Disease Control and Prevention's (CDC) National HIV Surveillance System. These national HIV surveillance data were adjusted for missing risk factor data (19) and were available for the full United States population during 2008–2015.

Statistical Analysis

Incident KS rates relative to the general population were estimated with standardized incidence ratios (SIRs) with data from the HACM Study. SIRs compared the observed incident KS cases among PWH to the expected number of cases based on general population rates, standardized by age, sex and race (non-Hispanic White, non-Hispanic Black). As HIV-associated KS cases strongly influence general population rates, incidence rates recorded for the general population prior to the start of the HIV epidemic (before 1980) from Surveillance, Epidemiology and End Results data were used to calculate the expected case counts (20,21). SIRs were calculated overall, and by age groups (<30, 30–39, 40–49, 50–59 and ≥60 years), sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, and Hispanic) and HIV transmission groups (MSM, male and female persons who inject drugs (PWID), male heterosexual/other, female heterosexual/other). The heterosexual/other category included those infected through mother to child transmission, receipt of clotting factor, transfusion/transplant or an undetermined transmission route.

Adjusted incidence rate ratios (aIRRs) were estimated for age groups, race/ethnicity, HIV transmission groups and time since HIV diagnosis (0·33–2, 2·01–5, 5·01–10, 10·01–15, 15·01–20, >20 years), and were also adjusted for registry and calendar year using Poisson regression models. Annual changes in rates were estimated using Poisson regression with single calendar years as a linear term, adjusting for 5-year age groups, race/ethnicity, HIV transmission groups, and registry. Adjusted annual incidence rates for each calendar year were obtained as marginal estimates from these models (22,23). Trends were assessed within strata defined by age groups (<30, 30–49, ≥50 years), race/ethnicity and HIV transmission groups. To examine if our observed trends were unduly influenced by the four HACM registries that had data beyond 2012, we compared the temporal trends in incidence for the period 2000–2012 to that of our entire 16-year period. As no difference was observed, trends were evaluated based on all available years. Joinpoint regression (24) was used to assess whether there were significant changes in the trajectory of incidence rates over time. In a sensitivity analysis, only those cases diagnosed 0 to 1 month after HIV report or AIDS diagnosis were excluded from incidence analysis.

To obtain annual estimates of the number of new KS cases (i.e. burden of incident KS cases) among persons with HIV during 2008–2015, incidence rates were estimated from

the Poisson models described above in strata defined by age group, race/ethnicity, HIV transmission group and calendar years. Rate estimates included both incident KS cases and new cases diagnosed 0–3 months after the start of follow-up, considered to be prevalent in our study, in order to fully capture the annual number of new KS cases in the United States. These predicted incidence rates using HACM data were then multiplied by CDC estimates of the number of PWH in the United States in the same strata.

The 5-year limited-duration prevalence of KS in the United States at the end of 2015 was estimated using data on both incident and prevalent (diagnosed 0–3 months after the start of follow-up) KS cases at the end of each calendar year (2010–2015) restricted to people 15 years or older. A generalized estimation equation (GEE) logistic regression model was used to account for repeated observations of participants in each calendar year with the predicted 5-year KS prevalence as the outcome. This model was adjusted for age group, race/ethnicity, HIV transmission group, registry and year. To quantify the number of PWH alive at the end of 2015 who had a KS diagnosis in the past 5 years, the 5-year limited duration KS prevalence was predicted based on HACM data from the GEE model in strata defined by age group, HIV transmission group and race/ethnicity and multiplied by the corresponding stratum specific total population of PWH in the United States in 2015, using CDC surveillance data. Except for the 5-year limited-duration prevalence where a parametric bootstrap was utilized, confidence intervals for incidence and burden estimates for the United States are based on non-parametric bootstrap resampling. All analyses were carried out in SAS (version 9·4).

Results

Characteristics of KS Rates among PWH

From 2000–2015, 2,837 incident KS cases occurred during 4,488,522 person-years of follow-up in the HACM Study (Table 1) and the overall crude incidence rate during this period was 63·2 per 100,000 person-years (81·2 in men and 15·8 in women). In addition, a total of 1,492 KS cases occurred during the first 3 months after HIV or AIDS diagnosis. By the demographic and HIV transmission groups examined, 70·7% of incident KS cases occurred among PWH aged 30–49 years, 93·1% occurred among men, 25·8% among non-Hispanic White PWH, 48·7% among non-Hispanic Black PWH, 24.3% among Hispanic PWH and 70·1% occurred among MSM. The overall SIR was 521 (95% confidence interval [CI]: 502, 540, Table 1) with the highest SIRs occurring among <30-year-olds (SIR: 358,000; 95% CI: 322,000, 397,000, Table 1), females (SIR: 680; 95% CI: 588, 783) and among MSM (SIR: 809; 95% CI: 774, 845).

The aIRRs presented in Table 1 show that compared to 15–29-year-olds, KS incidence rates were significantly higher among 30–39-year-olds (1·31; 95% CI: 1·16, 1·49, Table 1); however, in people 50 years or older rates were significantly lower (aIRR range: 0·47–0·66). Compared to non-Hispanic Whites, KS incidence was also significantly higher among non-Hispanic Blacks (1·50; 95% CI: 1·36, 1·65) and Hispanics (1·27; 95% CI: 1·14, 1·42). By HIV transmission group and time since HIV diagnosis, MSM and those with a recent HIV diagnosis, respectively had the highest KS incidence (Table 1). Results were similar

when incident cases were defined as those occurring more than one month after HIV report date or AIDS diagnosis date.

Trends in KS Incidence Rates, 2000–2015

During 2000–2015, KS rates declined an average annual percent change (AAPC) of 6·1% per year (95% CI: −7·0, −5·2% per year, Table 2) from an adjusted annual incidence rate of 108·9 per 100,000 person-years in 2000 to 46·6 per 100,000 person-years in 2015 (Figure 1), although beginning in 2012 we noted an apparent stabilization of KS rates (p=0·005). Substantial declines (p-trend<0·005) in KS rates were observed across age groups (AAPC range: −8·4·%, −3·5% per year, Table 2 and Supplementary Figure 1), race/ethnicity (AAPC range: −7·4%, −5·4% per year) and HIV transmission groups (AAPC range: −7·6%, −5·8% per year). KS rates also declined across all states included in our study (Supplementary Table 1).

Burden of New KS Cases Among PWH in the United States, 2008–2015

From 2008 to 2015, an estimated 5,306 (95% CI: 5,018, 5,616) incident KS cases occurred among PWH in the United States, declining from 719 incident KS cases in 2008 to 624 incident cases in 2015 (Figure 2). An estimated 23 KS cases occurred among 15–19-year-olds, 968 in 20–29-year-olds, 3,258 in 30–49-year-olds, 798 in 50–59-year-olds and 259 in ≥60-year-olds. Non-Hispanic Blacks (1,981; 37% of cases) and MSM (4,711; 89% of cases) respectively had the highest burden of incident KS cases (Figure 2).

Five-year prevalence of KS at the end of 2015

At the end of 2015, 0·20% (95% CI: 0·18%, 0·21%) of PWH in the United States had received a diagnosis of KS within the prior 5 years, corresponding to 1,904 prevalent cases (Table 3). By age group, the proportion of 5-year prevalent KS cases recorded in people <30 years was 0·21% (n=215 cases), 30–39 years 0·30% (n=486), 40–49 years 0·22% (n=539), 50–59 years 0·17% (n=497) and those 60 years or older had the lowest 5-year prevalence of 0·11% (n=166). By racial/ethnic group, non-Hispanic Whites and Hispanics had the highest KS prevalence of 0·24% (n=712) and 0·22% (n=458) respectively, and by HIV transmission group MSM had the highest prevalence [0·29% (n=1,686), Table 3].

Discussion

Our findings indicate that from 2000 to 2015 there was a >50% decrease in the incidence of KS among PWH in the United States and the slope of decline was similar across age, racial/ethnic and HIV transmission groups. In 2015, in the United States, among PWH an estimated 624 new cases of KS were diagnosed and the 5-year prevalence of KS was 1,904. The substantial decrease in KS incidence may be attributed to sustained efforts in recent years to diagnose HIV earlier and initiate cART shortly after diagnosis, maintain sustained suppression of HIV RNA, increased availability of cART, tolerability of newer cART regimens, increased adherence to simple formulations with once-daily dosing, and increased linkage of PWH to care and retention in care (25). Continued efforts to expand optimal cART treatment to those less likely to engage in care are needed to sustain or accelerate further declines in KS rates.

Recent reports have shown increasing KS rates among non-Hispanic Blacks, particularly in specific age groups in some southern states (16,17). Though we could not directly compare these published estimates to those in the current study due to differences in the states included in the analyses, we did not find evidence of increasing KS rates in any racial/ethnic group or state. Further, these prior studies utilized the general population as the denominator for rate estimation instead of the population of PWH, preventing the distinction between increasing KS occurrence among PWH and an increase in the at-risk population (i.e. increase in the number of PWH) over time. Subsequent analyses using cancer registry data and CDC HIV surveillance data have not shown increasing KS rates in these groups (26).

KS rates were highest among MSM compared to other HIV transmission groups, likely due to the elevated seroprevalence and the increased rate of sexual transmission of KSHV in MSM (11). This finding is also consistent with the 2-fold elevation in the seroprevalence of KSHV among PWID who are MSM compared to PWID who are male heterosexuals (27). KS incidence declined with increasing age. This is in contrast with the increased susceptibility to infections that occurs as people age and undergo immune senescence, and the increased risk of classic KS with age among immunocompetent individuals (28). Additionally, prior studies in the general population have shown an age-associated increase in the seroprevalence of KSHV among people 30 years or older (29). However, consistent with our findings, the risk of KS among older PWH has been reported to decrease with increasing time since HIV diagnosis (30,31) and is supported by the higher rate of cART adherence among older PWH (32,33).

Although the 5-year limited duration prevalence of KS among PWH is low the absolute number of prevalent cases in 2015, especially among MSM, is quite notable. The population of prevalent KS cases is likely to continue to grow further, as PWH continue to live longer after a KS diagnosis (34,35) when controlled on cART (34). Therefore; the unique needs of PWH who are KS survivors should be considered, such as their potential increased risk for second cancers (36–38).

A major strength of our study is the use of population-based data from 12 regions across the United States in addition to CDC HIV surveillance data for the whole United States to describe the epidemiologic trends for KS in the current cART era. Secondly, our examination of temporal trends across key demographic and HIV transmission strata has shown consistent declines in KS incidence across major demographic and HIV transmission groups. Additionally, our study includes all persons with diagnosed HIV in the United States and not just those continuously enrolled in care or adherent to cART. However, our findings are limited by the imperfect sensitivity of the HACM data match to identify HIV-infected cancer cases. As the sensitivity of the match has been reported to be 81%, it is likely that the burden of incident KS is underestimated (21). Another limitation of the study is the lack of information on cART and KSHV serostatus and incomplete information on CD4 cell counts and HIV RNA. Further, the 5-year limited duration prevalence at the end of 2015 is an underestimate of the true lifetime prevalence of KS among PWH in United States, as these 5-year limited duration prevalence estimates do not include KS diagnoses occurring prior to 2010.

In conclusion, this study provides a comprehensive description over a 16-year period of the current landscape of KS incidence, burden and prevalence across important population subgroups among PWH in the United States. Our findings indicate that though rates remain elevated relative to the general population there has been a consistent gradual decline in KS incidence among PWH in the United States during the current cART era, and this decrease is uniform across the demographic and HIV transmission groups examined. However, the number of PWH with a prior KS diagnosis at the end of 2015 is notable and the unique needs and risk profile of prevalent KS cases should be investigated further. As KS risk is strongly associated with immune suppression, increased HIV viral load and late initiation of cART, the continued strongly elevated risk of KS among PWH highlights the continued need for improvement in utilization of HIV diagnosis and treatment. Current efforts to control HIV in the United States through early initiation of cART, and linkage to and retention in care need to be expanded to sustain the recent declines in KS rates among PWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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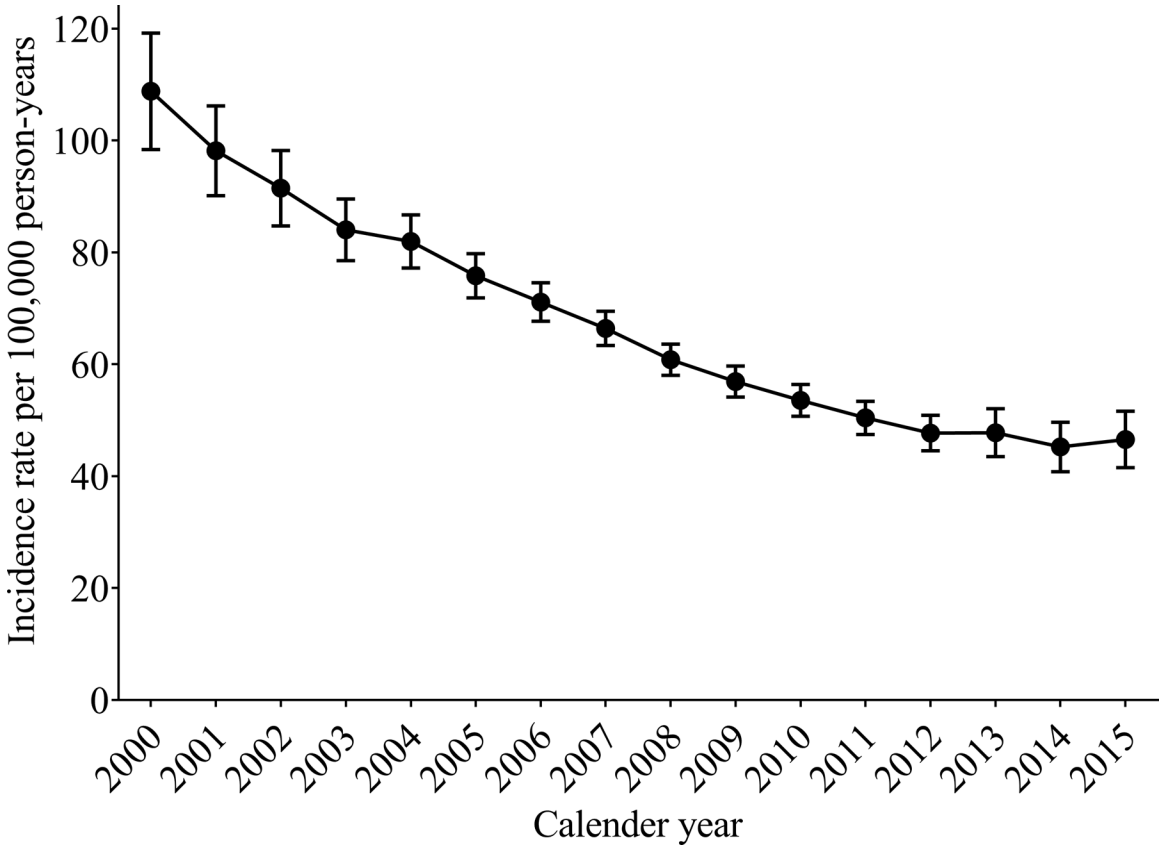

Figure 1:

Adjusted incidence rate* and 95% confidence intervals of Kaposi sarcoma by calendar year among people with HIV in the United States, 2000 to 2015.

* Adjusted for 5-year age groups, race/ethnicity, HIV transmission groups, and registry

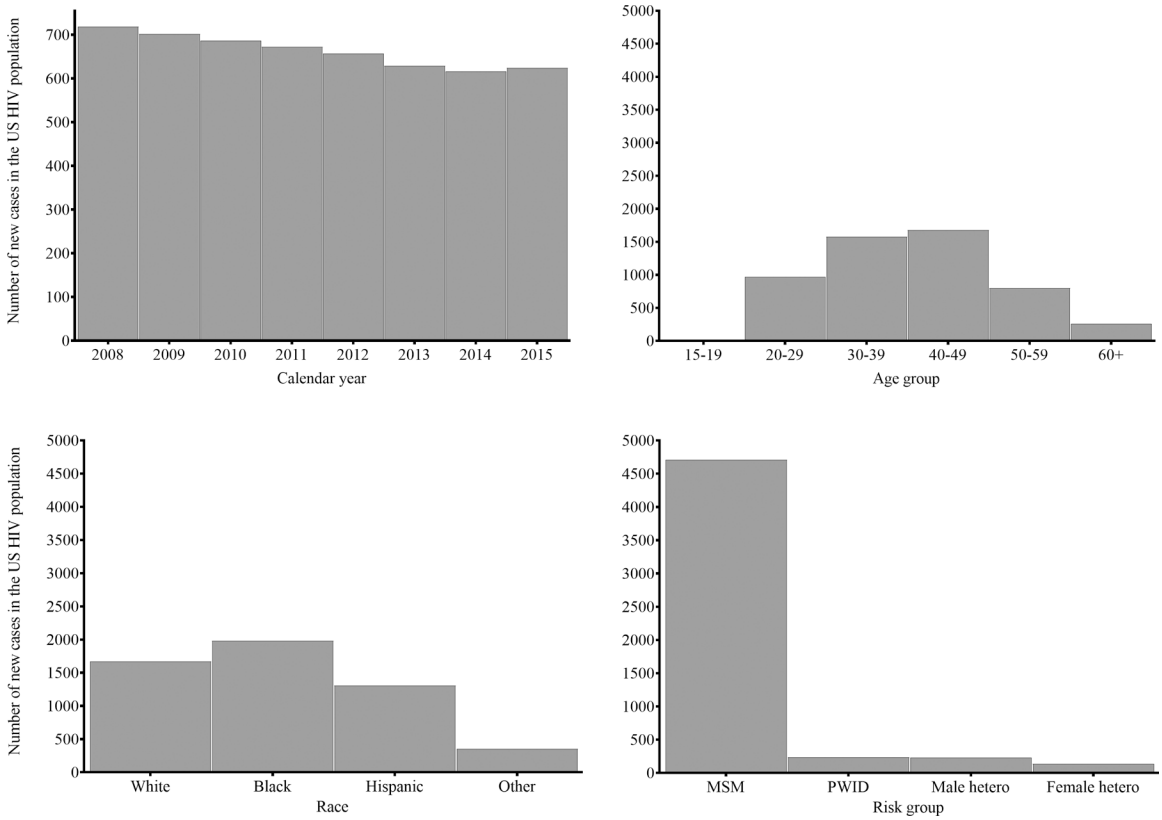

Figure 2:

Number of new Kaposi sarcoma cases among persons with HIV in the United States between 2008 and 2015 (N=5,306), by calendar year (A), age group (B), race/ethnicity (C) and HIV transmission group (D).

Table 1:

Characteristics of incident Kaposi sarcoma (KS) cases, person-years contributed and standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) among people with HIV in the HIV/AIDS Cancer Match Study, 2000 to 2015.

Characteristics	Incident cases	Person-years	SIR (95% CI)	Crude IR/100,000 person-years	IRR (95% CI)	aIRR[a] (95% CI)
Overall	2,837	4,488,522	521 (502, 540)	63.2	-	-
Attained age group, years						
15–29	363	444,533	358,000 (322,000, 397,000)	81·7	Ref	Ref
30–39	997	1,008,366	3,410 (3,210, 3,630)	98·9	1·21 (1·07, 1·37)	1·31 (1·16, 1·49)
40–49	1,010	1,644,373	873 (820, 929)	61·4	0·75 (0·67, 0·85)	0·94 (0·83, 1·07)
50–59	382	1,041,065	181 (164, 201)	36·7	0·45 (0·39, 0·52)	0·66 (0·57, 0·77)
≥ 60	85	350,184	45 (36, 56)	24·3	0·30 (0·23, 0·38)	0·47 (0·37, 0·60)
Race/Ethnicity						
Non-Hispanic White	733	1,168,603	458 (426, 493)	62·7	Ref	Ref
Non-Hispanic Black	1,381	2,189,236	513 (486, 541)	63·1	1·01 (0·92, 1·10)	1·50 (1·36, 1·65)
Hispanic	692	1,063,049	599 (555, 645)	65·1	1·04 (0·94, 1·15)	1·27 (1·14, 1·42)
Other/unknown[b]	31	67,634	-	45·8	0·73 (0·51, 1·05)	0·83 (0·58, 1·19)
HIV transmission group						
MSM	1,990	1,843,723	809 (774, 845)	107·9	Ref	Ref
Male and Female PWID	270	813,065	238 (210, 268)	33·2	0·31 (0·27, 0·35)	0·33 (0·29, 0·37)
Male heterosexual/other	451	873,030	279 (254, 306)	51·7	0·48 (0·43, 0·53)	0·46 (0·41, 0·51)
Female heterosexual/other	126	958,703	529 (441, 630)	13·1	0·12 (0·10, 0·15)	0·11 (0·09, 0·13)
Time since HIV diagnosis, years						
0·33–2	534	400,471	-	133·3	Ref	Ref
2·01–5	572	798,328	-	71·6	0·54 (0·48, 0·60)	0·56 (0·50, 0·64)
5·01–10	791	1,239,405	-	63·8	0·48 (0·43, 0·53)	0·55 (0·49, 0·62)
10·01–15	391	867,369	-	45·1	0·34 (0·30, 0·39)	0·44 (0·39, 0·51)
15·01–20	173	442,903	-	39·1	0·29 (0·25, 0·35)	0·44 (0·37, 0·53)
>20	48	165,100	-	29·1	0·22 (0·16, 0·29)	0·37 (0·27, 0·50)
Unknown	328	574,946	-	57·0	0·43 (0·37, 0·49)	0·50 (0·43, 0·57)

[a] In addition to calendar year and the 12 state and regional cancer and HIV registries, aIRR are mutually adjusted for other variables in the table.

[b]This category comprised Asian Americans, American Indians and those with an unknown racial/ethnicity classification.

Note: Data is shown only for persons with 4 or more months of follow-up in the study. An SIR was not calculated for the other/unknown category of race/ethnicity, because there is no expected case count for this category in the general population.

IR= incidence rate, aIRR= adjusted incidence rate ratios, MSM= men who have sex with men, PWID= people who inject drug

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Table 2:

Average annual percentage change (AAPC) in Kaposi sarcoma incidence rates and 95% confidence intervals (CIs) among people with HIV in the HIV/AIDS Cancer Match Study, 2000 to 2015.

	AAPC[a], %/year (95% CI)
Overall	−6·1 (−7·0, −5·2)
Attained age group, years	
15–29	−3·5 (−6·1, −0·9)
30–49	−5·5 (−6·5, −4·4)
≥50	−8·4 (−10·6, −6·1)
Race/Ethnicity	
Non-Hispanic White	−6·1 (−7·8, −4·4)
Non-Hispanic Black	−5·4 (−6·7, −4·0)
Hispanic	−7·4 (−9·2, −5·6)
Other/unknown[b]	−8·7 (−16·8, 0·2)
HIV transmission group	
MSM	−5·8 (−6·9, −4·8)
Male and Female PWID	−7·6 (−10·8, −4·2)
Male heterosexual/other	−7·4 (−9·7, −5·0)
Female heterosexual/other	−6·1 (−10·5, −1·4)

[a]Estimates are adjusted for attained age using 5-yr age groups, race/ethnicity, HIV transmission group, registry and calendar year.

[b]This category comprised Asian Americans, American Indians and those with an unknown racial/ethnicity classification.

Note: Data is shown only for persons with 4 or more months of follow-up.

MSM= men who have sex with men, PWID= people who inject drugs

Table 3:

Five-year prevalence of Kaposi sarcoma (KS) and 95% confidence intervals (CIs) among people with HIV in the United States at the end of 2015

	Number of prevalent KS cases	KS prevalence[a], % (95% CI)
Overall	1904	0·20 (0·18, 0·21)
Attained age group, years		
15–29	215	0·21 (0·16, 0·23)
30–39	486	0·30 (0·26, 0·32)
40–49	539	0·22 (0·19, 0·24)
50–59	497	0·17 (0·15, 0·18)
≥60	166	0·11 (0·09, 0·14)
Race/Ethnicity		
Non-Hispanic White	712	0·24 (0·21, 0·26)
Non-Hispanic Black	616	0·15 (0·13, 0·16)
Hispanic	458	0·22 (0·20, 0·25)
Other/unknown[b]	117	0·20 (0·16, 0·30)
HIV transmission group		
MSM	1686	0·29 (0·26, 0·31)
Male and Female PWID	59	0·05 (0·03, 0·06)
Male heterosexual/other	108	0·13 (0·11, 0·15)
Female heterosexual/other	51	0·03 (0·02, 0·03)

[a]Estimates are adjusted for age group, race/ethnicity, HIV transmission-group and the 12 state and regional cancer and HIV registries.

[b]This category comprised Asian Americans, American Indians and those with an unknown racial/ethnicity classification.

Note: Five-year prevalence was estimated using data on both incident (diagnosed 4 or more months after the start of follow-up) and prevalent (diagnosed 0–3 months after the start of follow-up) KS cases.

MSM= men who have sex with men, PWID= people who inject drugs