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Anal cancer incidence in men with HIV who have sex with men: are black men at higher risk?

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Conflicts of interest

There are no conflicts of interest.

Abstract

Objective: To assess differences in anal cancer incidence between racial/ethnic groups among a clinical cohort of men with HIV who have sex with men.

Design: Clinical cohort study

Methods: We studied men who have sex with men (MSM) in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) who initiated antiretroviral therapy (ART) under HIV care in CNICS. We compared anal cancer incidence between Black and non-Black men and calculated hazard ratios controlling for demographic characteristics (age, CNICS site, year of ART initiation), HIV disease indicators (nadir $CD4^+$, peak HIV RNA), and co-infection/behavioral factors including hepatitis B virus (HBV), hepatitis C virus (HCV), tobacco smoking and alcohol abuse.

Results: We studied 7473 MSM with HIV who contributed 41 810 person-years of follow-up after initiating ART between 1996 and 2014 in CNICS. Forty-one individuals had an incident diagnosis of anal cancer under observation. Crude rates of anal cancer were 204 versus 61 per 100 000 person-years among Black versus non-Black MSM. The weighted hazard ratio for anal cancer in Black MSM (adjusting for demographics, HIV disease factors, and co-infection/behavioral factors) was 2.37 (95% confidence interval: 1.17, 4.82) compared to non-Black MSM.

Conclusions: In this large multicenter cohort, Black MSM were at significantly increased risk for anal cancer compared to non-Black MSM. Further detailed studies evaluating factors impacting anal cancer incidence and outcomes in Black men with HIV are necessary. Inclusion of more diverse study cohorts may elucidate modifiable factors associated with increased anal cancer risk experienced by Black MSM.

Keywords

AIDS; anal cancer; HIV; men who have sex with men; racial disparities

Background

Rates of anal cancer in the United States have been on a steady rise for more than a decade, and racial/ethnic disparities in incidence and mortality in men have been documented [1]. Specifically, Black men are diagnosed with anal cancer at a younger age [2] and have higher incident anal cancer and anal cancer-associated mortality compared to other racial/ethnic groups [1]. Multiple studies have demonstrated that persons with human immunodeficiency virus (PWH) including women, men who have sex with women, and men who have sex with men (MSM) have higher incidence rates of anal cancer than persons without human immunodeficiency virus (HIV) [3–5]. Immune suppression secondary to HIV may play a key role in human papillomavirus (HPV) infection control [6,7]. Access to combination antiretroviral therapy (ART) has improved the longevity of PWH and reduced the risk of acquired immune deficiency syndrome (AIDS) in the United States. With this trend, there has also been a shift from AIDS-defining cancers to non-AIDS defining cancers, which overwhelmingly affect individuals aging with HIV [8–10].

Data on the trajectory of anal cancer incidence among PWH are inconsistent. Whereas some speak to an increasing anal cancer incidence, others report a plateauing or decreasing incidence in recent years [11–13]. The development of anal cancer in the setting of HIV is complex due to numerous biological and behavioral risks. These include poor HIV virologic control, diagnosis of AIDS, immunosuppression, high prevalence of smoking, multiple sexual partners, and the acquisition of and persistence of high-risk/oncologic HPV [5,14–18].

Data on factors contributing to anal cancer incidence, morbidity, and mortality in high-risk populations such as Black MSM and PWH are lacking [19]. Black MSM with HIV may represent the highest risk group for incident anal cancer, though few studies have evaluated incident anal cancer and associated risk factors in this population. Studies that have included Black MSM have demonstrated increased prevalence of high-risk HPV and anal dysplasia, a precursor to anal cancer, compared to White MSM [20]. Improved understanding of the factors associated with incident anal cancer in at-risk populations may assist the development of targeted interventions; however, Black MSM with HIV are underrepresented in many formative anal cancer research studies [20].

Using a well established multicenter U.S. cohort of PWH in HIV care, the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS), we evaluated racial disparities in incident anal cancer risk among the MSM population.

Methods

Design and study population

CNICS is a dynamic multicenter cohort of over 32 000 PWH in care at eight sites in the U.S. affiliated with CFARs (Case Western Reserve University, University of Alabama, University of North Carolina at Chapel Hill, Fenway Health, Johns Hopkins University, University of California San Francisco, University of California San Diego, and University of Washington (www.uab.edu/cnics/) [21]. CNICS collects and standardizes comprehensive clinical data from electronic medical records including demographic information, co-morbidities, behavioral exposures, medications, and laboratory assessments. Race/ethnicity were self-reported by patients at cohort entry. For this study, we included MSM with HIV who initiated ART under care in CNICS. A total of 14 317 adult MSM patients were enrolled in CNICS between 1 January 1996 and 30 September 2014. We excluded patients who initiated ART prior to enrolling in CNICS ($n = 5857$) to minimize lead-time bias. Additionally, we excluded those who initiated ART after 30 September 2014 ($n = 91$) or were enrolled in CNICS for less than 90 days ($n = 103$) to assure adequate follow-up time. Patients with no pre-ART nadir $CD4^+$ ($n = 74$), no pre-ART peak HIV RNA ($n = 141$), or pre-ART peak HIV RNA measurements that suggested unrecorded prior exposure to treatment (<1000 copies/mL) ($n = 578$) were also excluded.

Study site anal cancer screening characteristics

All eight CFAR sites were surveyed regarding anal cancer screening practices and access to high-resolution anoscopy (HRA). Providers at all CFAR sites started performing anal

cytology screening (anal Pap smear) at different time points during the study period with differing years of anal Pap initiation and populations targeted. Initiation year of targeted anal Pap screening and availability of HRA was known for seven of eight CFAR sites. The earliest year for anal Pap screening was 2000 (two sites) and the latest year was 2009 (two sites). All seven sites with known HRA information referred to specialists or performed onsite HRA. The earliest year for referred or onsite HRA was 2002 (two sites) and the latest year of HRA access was 2012 (two sites).

Anal cancer validation

Anal cancer cases diagnosed through December 2014 were verified through an established electronic data collection system previously described [10]. Data on TNM stage as per the American Joint Committee on Cancer Staging System [22] were collected at the time of anal cancer verification.

Statistical analysis

We followed patients from ART initiation to the earliest of the following: anal cancer diagnosis, death, or last clinical visit. Data were administratively censored on 31 December 2014, after which anal cancer diagnosis was no longer ascertained under this analysis. Crude incidence rates were calculated using Poisson models as the number of anal cancer diagnoses per 100 000 person-years of follow-up. We used a proportional sub-distribution hazards model [23] to compute hazard ratios and constructed cumulative incidence curves of anal cancer diagnosis in the presence of the competing risk of death. Robust standard errors were used for weighted hazard ratio estimates. The primary predictor was race (Black versus non-Black). We used stabilized inverse probability of exposure weights to control for factors predictive of anal cancer and exposures that may differ between race groups, and calculated cumulative incidence estimates standardized to the total study sample. Weighted models included age, pre-ART nadir $CD4^+$ cell count (lowest $CD4^+$ cell count), peak HIV RNA (highest HIV RNA), year of ART initiation, smoking status (defined as ever/never), alcohol abuse (yes/no per documented provider assessment), injection drug use as risk factor for HIV, HBV co-infection (determined by serologic testing), HCV co-infection (determined by serologic testing), and study site. Injection drug use was assessed at entry into the CNICS cohort; all other factors were assessed at ART initiation. Weighted analyses were performed utilizing two models controlling for: demographics (age, CNICS site, year of ART initiation) and HIV disease factors (nadir $CD4^+$, peak HIV RNA), and demographics, HIV disease factors, and co-infection/behavioral factors (HBV, HCV, smoking, alcohol abuse, and injection drug use) based on major categories of characteristics that influence acquisition of oncogenic HPV, anal cancer screening/monitoring practices, and progression of precancerous lesions to invasive anal cancer.

Restricted quadratic splines were used to model continuous variables (age, nadir $CD4^+$ cell count, peak HIV RNA, and year of ART initiation), with knots at the 5th, 35th, 65th, and 95th percentiles [24]. Stabilized inverse probability of censoring weights to account for potentially informative loss to follow-up. The product of the exposure and censoring weights had a mean of 1.0 (range: 0.2–10.4). Analyses were performed using SAS version 9.4 (SAS

Institute, Cary, North Carolina, USA) and figures were created using R version 3.4.1 (R Project, Vienna Austria).

Results

For our final analysis, we studied 7473 MSM with HIV who initiated ARTunder care in CNICS and contributed 41 810 person-years of follow-up time (Tables 1 and 2). In brief, 26% were Black and 74% were non-Black (62% White and 12% other race). The median age at study entry (ART initiation) was 36 years (interquartile range (IQR) 30–43). The median nadir $CD4^+$ cell count was 243 cells/μl (IQR 103–368) and peak HIV RNA 100 000 copies/ml (IQR 31 900–30 5611). A higher proportion of AIDS diagnosis was observed in Black versus non-Black MSM (Table 1). HBV, HCV, and sexually transmitted (chlamydia, gonorrhea, and syphilis) co-infection were identified in 6, 9, and 23% of MSM, respectively. Thirty percent reported history of smoking, 18% alcohol abuse, and 11% history of IDU (Table 1).

There were 41 cases of anal cancer identified in this cohort. Tumor histology was available on 39 cases and all were squamous cell carcinoma. Stage at diagnosis was unavailable in 25 (61.0%) and could not be determined in 2 (4.9%) of cases. For the 18 cases where stage at diagnosis was available, one (2.4%) had metastatic disease at anal cancer diagnosis.

The crude incidence rate of anal cancer in Black MSM was 204 per 100 000 person-years, versus 61 per 100 000 person-years in non-Black MSM (Table 2). The weighted hazard ratio for anal cancer in Black MSM (after adjusting for demographics, HIV disease factors, and co-infection/ behavioral factors was 2.37 (95% confidence interval: 1.17, 4.82) compared to non-Black MSM (Table 2). Starting approximately 5 years after ART initiation, there was separation in anal cancer risk among Black MSM compared to non-Black MSM (Fig. 1).

Discussion

Using data from a well established multicenter U.S. cohort of HIV infected patients in care at CFAR sites, we observed 4% 15-year weighted cumulative incidence of anal cancer in Black MSM with HIVand that Black men had 2.37 times the hazard of being diagnosed with anal cancer after starting ART as non-Black men, after adjusting for important factors. We also observed that the cumulative incidence of anal cancer clearly separated between Black and non-Black MSM after approximately five years on ART (Fig. 1). Thus, this study highlights potential racial differences related to anal cancer incidence among MSM with HIV on ART and raises awareness on the importance of providing equitable anal cancer prevention and screening practices relatively early in course of lifetime suppressive ART.

A recent large retrospective review of data from the National Inpatient Sample 2011 database described racial disparities related to anal cancer with Black men showing a statistically significant increase risk of anal cancer (relevant risk: 1.43, $P < 0.01$) compared to other race/ethnicities; however, there was a lack of key information such as risk behaviors and HIV status [25]. Similarly, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program indicate that Black men have higher anal cancer incidence rates (2.2 per 100 000) compared to all reported racial groups (1.6 per 100 000) [1] though

again risk behaviors and HIV status information were not available. Robbins *et al.*, using SEER and data from the HIV/AIDS Cancer Match (HACM) Study found an 83% excess of anal cancer cases in MSM ≥5 years removed from the onset of AIDS. The majority of excess anal cancer in this study was among White compared to Black men. Our findings are concerning as they suggest that Black MSM with HIV were more likely to develop anal cancer compared to non-Black MSM with HIV. It is well established that the PWH community is disproportionally burdened with anal cancer [8,26]. Considering that young Black MSM comprise the majority of incident HIV infection in the United States [27], and incident and prevalent high-risk HPV types have been demonstrated in cohorts of Black MSM with HIV, our results support the need to closely monitor Black MSM with HIV for incident anal cancer and encourage HPV vaccination.

In a recently published single institution retrospective cytology-based cohort, MSM had an increased rate of transition to high-grade squamous intraepithelial lesions (HSIL) (the precursor to cancer) compared to non MSM [28]. Interestingly, Black race was not associated with anal intraepithelial neoplasm (AIN) or disease progression; however, serial anal cytology examinations were lower in Black patients than other race/ethnicities, which may have biased the results [28]. Simard *et al.* [29] in a review of AIN cases using SEER data from San Francisco/Oakland Surveillance 2000–2009 found that the largest increase in incident AIN 3 over 10 years was among Black men; however, HIV status and risk behavior information were not available. The authors indicate that overall increases in AIN were in the context of a local screening program targeting PWH. A large study from the NA-ACCORD found higher rates of anal cancer in MSM with HIV compared to other men, women and persons using IDU with HIV. In this study, Black race was not significantly associated with elevated anal cancer risk but analyses were not limited to MSM. They acknowledged limitations including lack of data on sexual behavior, smoking status and anal cancer screening practices, factors that may influence HPV acquisition, progression to, and detection of anal cancer [4]. In our study, we were unable to assess the impact of anal cancer screening practices on observed racial differences in anal cancer incidence due to variable screening and access to HRA across study sites. This will be an important area of future investigations.

There is an association between the persistence of HPV-16 and HPV-18, oncogenic/high risk strains and the development of anal dysplasia in PWH [30]. HPV-16 is highly important in predicting HSIL [31] and anal cancer [32] in MSM with HIV. Strong determinants of anal HPV-16 infection in men include HIV infection and sexual preference [33]. IDU has previously been described to be independently associated with HPV-16 in MSM with HIV [34]. Causal relationships between behavior, HPV acquisition, and the development of anal dysplasia or anal cancer in Black MSM are not well established. However, a cross-sectional study determined that HIV infection was the only risk factor associated with oncogenic HPV infection in a cohort of predominantly Black MSM. This study also observed a high prevalence of oncogenic HPV strains including those other than HPV-16 and HPV-18 [35]. There is also the potential for propagation of oncogenic strains of HPV in sexual networks of Black MSM, which are often described as distinct from those of non-Black MSM with a higher tendency towards in race connectedness [20]. We did not have HPV specific testing and detailed sexual/behavioral data in our study population limiting our ability to search for

these associations. Smoking has previously been reported to be associated with abnormal anal cytology [36]. However, this relationship may be complex and associated with more focal findings [37]. In our cohort, given similar smoking prevalence between Black and non-Black MSM with HIV, correlations with dysplasia and anal cancer were not assessed. Again, after adjustment for several co-infection/behavioral factors linked to sexual activity and potential acquisition of HPV, we continued to observe independent higher risk for anal cancer among Black MSM.

After adjusting for demographics along with HIV disease factors such as nadir $CD4^+$ cell count and baseline HIV RNA, anal cancer risk remained higher for Black MSM than non-Black MSM. Other studies have found that better HIV control with ARTwas significantly associated with lower incidence of anal cancer [14]. We did not assess HIV suppression or immunologic recovery on ART.

Our study has limitations. First, this is a clinical cohort study and it is possible we may not have fully captured differences in anal cancer risk between the race groups, as detailed above. Second, though anal cancer cytology or HRA is not standard of care for PWH, some experts advocate for its use in MSM with HIV for the prevention of anal cancer [38,39]. We performed adjustments for CNICS site; however, site-specific anal screening practices and differences in access to cytology or HRA and treatment of precancerous anal lesions may have influenced anal cancer rates. Additionally, as our study spans the period before access to screening and HRA was available, we may not have captured all instances of cancer in our cohort. Third, due to the lack of comparable data in SEER and other national cohorts for anal cancer, HIV status, and risk behavior, we are unable to determine whether the increased risk of anal cancer noted in the Black MSM with HIV in CNICS reflects the same level of anal cancer risk nationally. Our multicenter cohort study addresses key gaps in formative anal cancer research on racial differences in incidence and risk factors among Black MSM with HIV [20]. We used a robust, geographically diverse and well characterized clinical cohort of PWH in long-term care on ART to observe significantly greater incidence of anal cancer among Black MSM after adjusting for many important demographic, HIV disease, and co-infection/behavioral factors. We believe these findings can influence HIV providers to apply equitable anal cancer prevention, screening, and management practices across all persons living long-term with HIV.

Additional large cohort studies are needed to understand whether our observed increased risk of anal cancer among Black MSM as it is possible that race is a surrogate for other social or behavioral factors associated with anal cancer risk. Future research needs to improve our understanding of anal cancer epidemiology, screening, and HPV type diversity in the context of optimal HIV management and immunosenescence in aging PWH. Multifaceted and equitable approaches to anal cancer prevention encouraging smoking cessation, age-appropriate HPV vaccination, reduced exposure and acquisition of HPV (i.e. partner reduction, correct and consistent use of condoms), improved linkage to HIV care, and promotion of anal cancer screening programs to reduce risk of anal cancer are needed among Black MSM with HIV.

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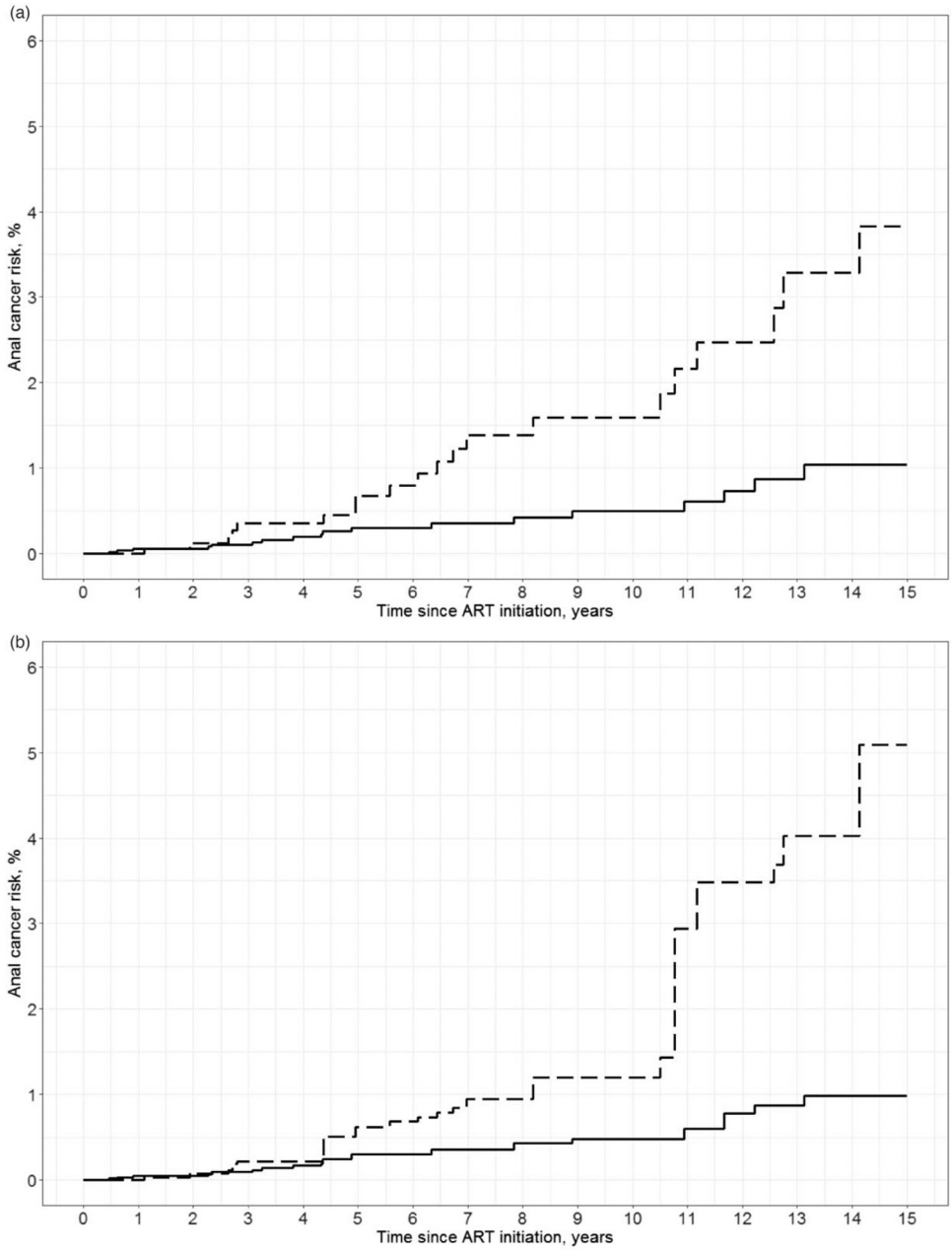

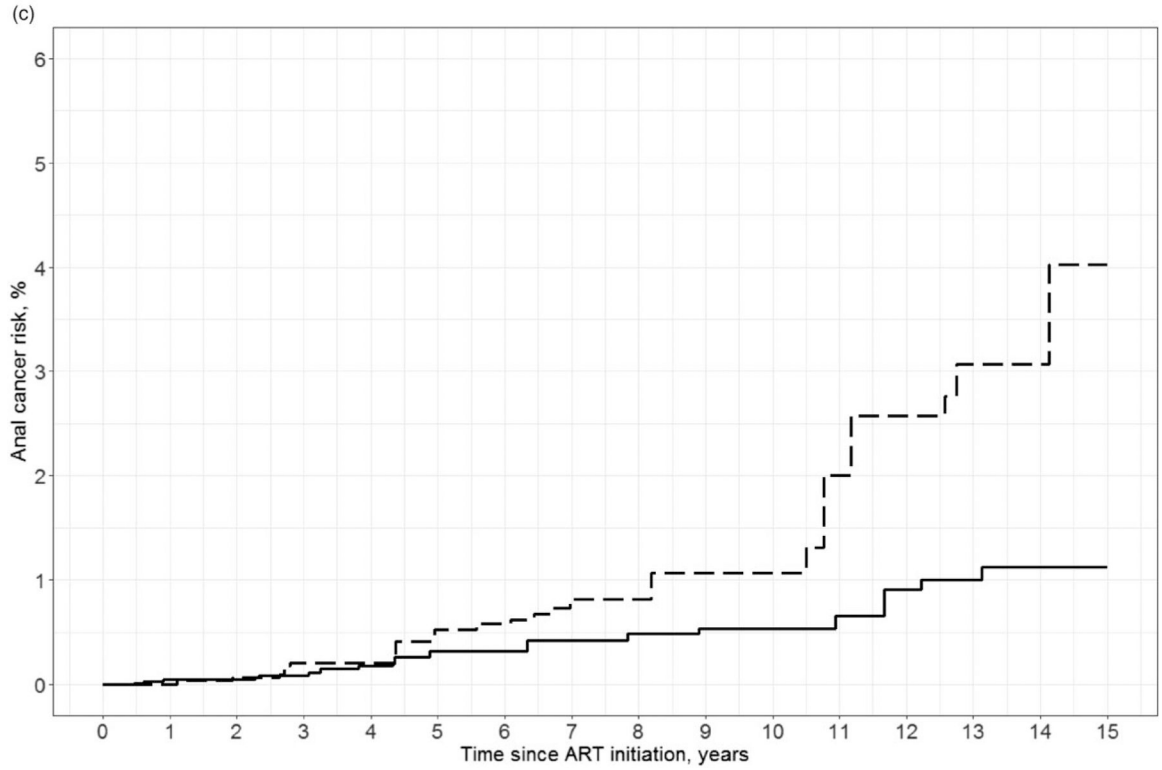

Fig. 1. Crude and weighted risk curves for anal cancer diagnosis, stratified by race.

Solid line, non-Black; dashed line, Black. (a) Crude; (b) weights included age, nadir $CD4^+$ cell count, peak HIV RNA, year of ART initiation, study site. (c) Weights included age, nadir $CD4^+$ cell count, peak HIV RNA, year of ART initiation, smoking, alcohol use, injection drug use, hepatitis B, hepatitis C, study site. ART, antiretroviral therapy.

Table 1.

Characteristics of 7473 men with HIV who have sex with men who initiated ART in the Center for AIDS Research Network of Integrated Clinical Systems Cohort between 1996 and 2014.

Characteristic	Overall (*n* = 7473) Median (IQR) or *N* (%)	Black race (*n* = 1977) Median (IQR) or *N* (%)	Non-Black race (*n* = 5496) Median (IQR) or *N* (%)
Age	36 (30, 43)	33 (26, 41)	37 (31, 44)
Nadir $CD4^+$ (cells/μl)	243 (103, 368)	220 (64, 350)	250 (118, 373)
Peak HIV RNA (copies/ml)	100 000 (31 900, 305 611)	83 200 (26 400, 267 715)	105 850 (34 207, 317 692)
Year of ART initiation	2008 (2003, 2011)	2009 (2003, 2012)	2008 (2003, 2011)
Smoking	2216 (29.7)	553 (28.0)	1663 (30.3)
Alcohol use	1358 (18.2)	329 (16.6)	1029 (18.7)
Injection drug use	820 (11.0)	121 (6.1)	699 (12.7)
AIDS	2117 (28.3)	637 (32.2)	1480 (26.9)
STI	1715 (22.9)	552 (27.9)	1163 (21.2)
HBV	439 (5.9)	142 (7.2)	297 (5.4)
HCV	663 (8.9)	183 (9.3)	480 (8.7)

AIDS, acquired immunodeficiency virus; ART, antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; STI, sexually transmitted infection; VL, viral load.

Table 2.

Anal cancer incidence rates and crude and weighted hazard ratios among men who have sex with men enrolled in the Center for AIDS Research Network of Integrated Clinical Systems cohort between 1996 and 2014, stratified by race.

	Anal cancer cases	*N*	Person-years	Incidence rate (95% CI) per 100 000 PY	Crude HR (95% CI)	Weighted[a] HR (95% CI)	Weighted[b] HR (95% CI)
Total	41	7473	41810	98.1 (72.2, 133.2)			
Black	22	1977	10 780	204.1 (134.4, 309.9)	3.17 (1.72, 5.84)	3.22 (1.51, 6.85)	2.37 (1.17, 4.82)
Non-Black	19	5496	31 030	61.2 (39.1, 96.0)	1	1	1

ART, antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio; PY, person-years.

[a]Adjusted for demographics (age, CNICS site, year of ART initiation) and HIV disease factors (nadir $CD4^+$ cell count and peak HIV RNA).

[b]Adjusted for demographics, HIV disease factors, and co-infection/behavioral factors (HBV, HCV, smoking, alcohol abuse, and injection drug use).