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Anal Cancers among HIV-Infected Persons: HAART Is Not Slowing Rising Incidence

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Abstract

Objective—To evaluate the incidence rates of anal cancer over the HIV epidemic and assess the impact of HAART use on anal cancer events.

Methods—We evaluated the incidence of and factors associated with anal cancer using longitudinal data from the prospective U.S. Natural History Study (1985-2008). Poisson regression and Cox proportional hazard models were utilized.

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Results—Among 4,506 HIV-infected males with 37,806 person-years (PY) of follow-up, anal cancer rates (per 100,000 PY) increased 5-fold, from 11 in the pre-HAART to 55 in the HAART era, $p=0.02$. Rates continued to increase, reaching 128 in 2006-2008. Persons with HIV infection for >15 years had a 12-fold higher rate than those with <5 years (348 vs. 28, $p<0.01$). At cancer diagnosis ($n=19$), median age was 42 years, median CD4 count was 432 cells/mm³, 74% had a CD4 nadir <200 cells/mm³, 42% had a prior AIDS event, and 74% had received HAART. From separate models, prior AIDS event (HR 3.88, $p=0.01$) and lower CD4 nadir (HR 0.85 per 50 cell, $p=0.03$) were associated with anal cancer, with a trend for a history of gonorrhea (HR 2.43, $p=0.07$). Duration of HAART use was not associated with a reduced risk of anal cancer (HR 0.94, $p=0.42$).

Conclusions—Incidence rates of anal cancer have progressively increased during the HIV epidemic. Persons with a longer duration of HIV infection have a substantially higher rate of anal cancer. Since HIV-infected persons are experiencing longer life expectancies and HAART does not appear protective of anal cancer, studies on preventive strategies are needed.

Keywords

HIV; anal cancer; incidence rates; antiretroviral therapy; HAART; epidemiology

Background

Cancers are an increasingly important cause of morbidity among HIV-infected persons. Recent data have shown that non-AIDS-defining cancers (NADCs) are now more common than the traditional AIDS-defining cancers (ADCs; Kaposi's sarcoma, non-Hodgkin's lymphoma, invasive cervical carcinoma) [1-3]. In the setting of reduced immune surveillance, viral co-infections may cause persistent infection and eventually carcinogenesis; several NADCs have been linked to viral co-infections. Human papillomavirus (HPV) can induce genetic changes important in the development of invasive cervical carcinoma; similar changes have been associated with anal intraepithelial neoplasia (AIN), and subsequently, anal squamous cell cancer [4-7].

Although anal cancer is uncommon in the general population [8], its incidence has been rising for the past several decades, possibly related to the rising number of immunosuppressed persons [9]. In the U.S., the rates of anal cancer among men who have sex with men (MSM) and immunosuppressed men now exceed the rates of cervical cancer among women [4]. As such, anal cancers have become an important cause of morbidity among HIV-infected persons [1,4].

Although some cohorts have described a rising rate of anal cancer among HIV-infected persons in the highly active antiretroviral therapy (HAART) era [10-13], this finding has not been universal [2,14], and the specific impact of antiretroviral therapy on anal cancer events remains unclear [4]. Therefore, we evaluated prospectively collected data from a large U.S. HIV Natural History Study (NHS) to evaluate incidence rates and factors associated with the development of anal cancer during the course of the HIV epidemic. Our study had the advantage of precisely examining HIV-related factors by utilizing individualized patient data including sequential time-updated CD4 counts, HIV RNA levels, and antiretroviral prescription dates.

Methods

We examined prospectively collected data as part of the U.S. Military NHS, a multicenter ongoing observational study, which enrolled 5,042 HIV-infected participants from 1985-2008 at seven geographic locations in the U.S. Participants were military beneficiaries

(active duty, retirees, and dependents) evaluated on a biannual basis with medical histories and blood collection for repository storage, as previously described [3]. Participants excluded from this analysis were those without a documented HIV-positive test date (n=126), HIV infection diagnosed prior to 1985 (n=10), age at HIV diagnosis of less than 18 years (n=5), persons with anal cancer prior to the estimated time of HIV seroconversion (n=0), and females (n=395) yielding 4,506 participants for our study. Females were excluded since they only accounted for 8% of our study population and only one anal cancer event occurred among women. Among those with a documented HIV negative date (61%), the median time from last HIV negative date to first HIV positive date was 16 months (IQR 10-25). The NHS study was approved by central and site Institutional Review Boards (IRB), and participants provided voluntary informed consent. This analysis was approved by the central IRB.

For calculating rates and for time-to-event methods, baseline was defined as the estimated time of HIV seroconversion, conservatively calculated as six months prior to the first documented HIV-positive test date [3]. The diagnosis of anal cancer was histopathologically confirmed; types of cancer located in the anal area that were not confirmed to be squamous cell (e.g., adenocarcinoma, carcinoid tumors, pre-invasive disease) were not included as anal cancer events in our analyses, but contributed to follow-up time in our models (n=4). Histopathologic specimens were not available for re-confirmation or HPV-testing for this study. For those with anal cancer, the event date was the date of cancer diagnosis. For those without cancer, the censoring date was the last study visit or date of death. Follow-up for this report ended August 1, 2008.

Data collected at HIV diagnosis included: demographics (age, gender, self-reported race/ethnicity), military duty status (active duty, retired, dependent), CD4 count (flow cytometry), HIV RNA levels, and medical conditions. Medical diagnoses collected included AIDS-defining conditions (CDC 1993 criteria, with the exception of an isolated CD4 count <200 cells/mm³) [15]; hepatitis B co-infection defined as at least two of three hepatitis B tests concurrently positive (core antibody, surface antigen and surface antibody); hepatitis C defined by a positive antibody test; sexually transmitted infections (STIs) to include gonorrhea, *Chlamydia trachomatis*, clinically diagnosed herpes simplex virus, and syphilis. Data on STIs were based on clinical and laboratory reports; no active surveillance was performed in our study cohort. Our database does not contain information on tobacco use. Data collected at each follow-up visit included: CD4 count, HIV viral load, updated medical history, and antiretroviral therapy dates. HAART was defined as two or more nucleoside reverse transcriptase inhibitors (NRTIs) in combination with at least one protease inhibitor or one nonnucleoside reverse transcriptase inhibitor (NNRTI), one NRTI in combination with at least one protease inhibitor and at least one NNRTI, or an abacavir- or tenofovir-containing regimen of three or more NRTIs. ART was defined as use of any antiretroviral therapy. Passive and active methods were used to collect information regarding deaths, including review of medical records, death certificates, and national death indices.

Statistical analyses included descriptive statistics to compare those with and without anal cancer. Medians are presented with interquartile ranges (IQRs). Kruskal–Wallis tests were used to compare medians; and chi-squared tests and Fisher's exact tests were used to compare proportions. Age-adjusted rates per 100,000 person-years (PY) were calculated for calendar periods and by duration of HIV infection, with each person contributing time to all intervals for which there was follow-up from baseline to the event or censoring time. Poisson regression models were used to calculate the age-adjusted rates and rate ratios. Rates for calendar periods were age-adjusted for age at entry into the interval; the rates by duration of HIV infection were adjusted to age at HIV diagnosis. Rate ratios were calculated

to test the hypothesis that rates remained constant over intervals of calendar time or duration of HIV infection.

In order to compare the risk of cancer in our HIV-positive cohort with the risk seen in the general population, standardized incidence rates (per 100,000 PY) of anal cancer were calculated for the pre-HAART era, the HAART era, and for the interval 2002-2006. Those standardized rates (overall and for specific age categories) were age-adjusted to the U.S. 2000 standard population for males, and compared to data provided in the National Cancer Institute Surveillance Epidemiology and End Results (SEER) Cancer Statistics Review for the period 2002-2006 [8] and age-specific published data [16].

Cox proportional hazard models were used to evaluate the association of specific factors with anal cancer. Variables that may change during follow-up (CD4 cell counts, HIV RNA levels, hepatitis B infection, STIs, AIDS events, and use of ART and HAART) were considered as time-updated covariates, using all available data between HIV diagnosis and the event or censoring time. All proportional hazards models were adjusted for year of HIV diagnosis and time-updated year of event. Multivariate models were also adjusted for age at HIV diagnosis.

Rates, rate ratios, and hazard ratios (HR) are given with 95% confidence intervals (CI). All p-values are two-sided. All analyses were conducted using SAS (version 9.2, SAS Institute, Cary, North Carolina, USA).

Results

Study Population at HIV Diagnosis

We studied 4,506 HIV-infected males with 37,806 PY of follow-up. At HIV diagnosis, the median age was 28 years (IQR 24-34) and ethnicity was African American (44%), Caucasian (44%), or other (12%). The median CD4 cell count was 508 (IQR 354-676) cells/mm³ and the median HIV RNA was 4.4 (IQR 3.8-4.9) log₁₀ copies/ml. At HIV diagnosis, 20% percent were co-infected with hepatitis B and 3% with hepatitis C. Characteristics at HIV diagnosis were not significantly different between those who did or did not subsequently develop anal cancer (data not shown).

Anal Cancer Cases

Nineteen patients developed squamous cell anal cancer during the study period. At anal cancer diagnosis (Table 1), the median age was 42 years (IQR 33-47; maximum age at time of cancer diagnosis was 60). The anal cancer event occurred at an age less than 44 years for 12 (63%). Ethnicity was reported as Caucasian for 53% of cases. Anal cancer developed a median of 12.8 years (IQR 4, 18) after HIV diagnosis. While the median CD4 count at time of anal cancer diagnosis was 432 (IQR 282-509) cells/mm³, 14 (74%) had a nadir CD4 cell count prior to diagnosis of <200 cells/mm³.

Regarding STIs prior to anal cancer diagnosis, 53% had evidence of prior hepatitis B infection, 32% had clinically diagnosed herpes simplex viral infection, 11% had syphilis, 42% had gonorrhea, and 16% had *Chlamydia trachomatis*. Overall, 13 (68%) of those with anal cancer had a history of a STI prior to cancer diagnosis. No patient with anal cancer had co-infection with hepatitis C.

Most anal cancer cases occurred during the HAART era: there were three cases during the pre-HAART period and 16 in the HAART era. For those with an anal cancer event during the HAART era, the median CD4 count at anal cancer diagnosis was 375 cells/mm³ (IQR 250-505), and 81% had a CD4 nadir of <200 cells/mm³. The median time from the nadir

CD4 count to anal cancer was 59 months (IQR 7-83). The median HIV RNA was 3.0 (IQR 1.4-4.4) $\log_{10}$ copies/ml, and 50% had a HIV RNA <1000 copies/ml. Prior to anal cancer diagnosis, seven (44%) patients had experienced a prior AIDS event, of which one was Kaposi's sarcoma. Any ART and HAART had been prescribed prior to diagnosis for 94% and 88%, respectively, and the median number of months on any ART and HAART was 123 (IQR 71-163) and 78 (IQR 61-115), respectively.

Incidence Rates and Trends of Anal Cancer

Anal cancer rates progressively increased over the epidemic. Per 100,000 PY, the age-adjusted rates (95% CI) in our study were 11 (2-60) in the pre-HAART era and 55 (9-339) in the HAART era (rate ratio 5.0, $p=0.02$) (Table 2a and Figure 1). The age-adjusted rates for intervals within the HAART era were 13 (1-125) in 1996-2000, 51 (6-423) in 2001-2005, and 128 (16-1042) in 2006-2008 (Table 2a). We also examined age-adjusted rates of anal cancer by duration of HIV infection (Table 2b). Persons with HIV infection for at least 15 years had a 12-fold higher rate of anal cancer compared to those infected for less than 5 years (348 vs. 28 per 100,000 PY, $p<0.001$) (Figure 1).

For males in the general population, the standardized rate of anal cancer among males for the interval 2002-2006 was 1.4 per 100,000 PY (age-adjusted to the U.S. 2000 Standard Population for males) [8]. The standardized rates for our study (age-adjusted to the same U.S. 2000 Standard Population for males) were 32 for the pre-HAART era, 56 for the HAART era, and 132 for the interval 2002-2006. Of note, 14 of 19 anal cancer cases in our study occurred during the era 2002-2006. For age specific categories in the general population for 1998-2003, the rates of squamous anal cancer were 0.47 and 2.77 per 100,000 PY for ages 18-49 and 50-64 years, respectively [16]. The standardized rates for these age categories at entry into the interval for our study during 2002-2006 were 94.7 and 24.3 per 100,000 PY, respectively.

Factors Associated with Anal Cancer

From separate Cox proportional hazards models (all adjusted for year of HIV diagnosis and time-updated calendar year of event; Table 3), the risk of anal cancer was higher for those with a prior AIDS event (HR=3.88; 95% CI 1.45-10.39; $p=0.01$) and lower nadir CD4 count (HR 0.85 per 50 cell; 95% CI 0.73-0.99; $p=0.03$). There was a trend towards an association with a history of gonorrhea (HR 2.43; 95% CI 0.93-6.36; $p=0.07$) with subsequent anal cancer. Time-updated CD4 count (HR=0.95 per 50 cell increase; 95% CI 0.87-1.04; $p=0.28$), time-updated HIV RNA level (HR=1.24 per 0.5 $\log_{10}$ increase, 95% CI 0.58-2.62; $p=0.58$), time-updated duration of HAART use (HR 0.94; 95% CI 0.82-1.08; $p=0.42$), and demographics were not associated with anal cancer. We also examined time-updated CD4 count and HIV RNA categories in separate models (Table 3) and in a combined model with both HIV RNA and CD4 cell count categories (data not shown) and found no significant associations with anal cancer.

Because nadir CD4 cell count and the occurrence of an AIDS event were strongly associated, the final multivariate models (Table 4) contain one of these explanatory variables but not both. In the first multivariate model, a prior AIDS event remained associated with anal cancer (HR 3.92; 95% CI 1.45-10.61; $p=0.01$), while gonorrhea had borderline significance (HR 2.44; 95% CI 0.93-6.43; $p=0.07$). When using time-updated CD4 nadir in the multivariate model, rather than an AIDS event, associations were similar (Table 4).

Discussion

Our study demonstrates that the incidence of anal cancer among HIV-infected persons is steadily rising despite the advances in antiretroviral therapy. The reasons for these trends are likely several-fold. With the advent of HAART and easier-to-tolerate HIV medications, there has been a steady reduction in competing causes of death and an increase in life expectancy [17]. As HIV-infected persons are living longer lives, there may be sufficient time for the accumulation of genetic mutations that are important for anal cancer development. Furthermore, prior studies have shown that HAART does not reduce HPV co-infections or rates of HPV-related dysplasia [18-20]. Together, these data suggest that the list of benefits from HAART may not include the prevention of anal cancer.

In our study, the incidence rate of anal cancer reached 128 per 100,000 PY during 2006-2008. This high incidence rate for anal cancer is similar to a recent study among HIV-infected MSM which showed a rate of 137 during the HAART era (1996-2006) [10]. These data suggest that anal cancer has become an increasingly important health issue among HIV-infected persons.

Our study was novel in that we also investigated the rate of anal cancer development by the duration of HIV infection. We found that persons infected with HIV for ≥ 15 years had a 12-fold higher rate of anal cancer compared to persons infected with HIV for < 5 years. Of note, these data were collected in a cohort that undergoes routine HIV testing with many participants having narrowly defined seroconversion dates. Although one other study suggested that length of human immunodeficiency virus disease was a risk factor for development of anal carcinoma, it was based on a study of only seven patients with anal cancer and seven with AIN [21]. Our data suggest that the rising rates of anal cancer in the HAART era may be explained, at least in part, by the longer life expectancies of HIV-infected persons.

Other factors associated with anal cancer in our study included a prior AIDS-defining event and low nadir CD4 counts. These factors may be markers for both prior immunosuppression and a longer duration of HIV infection. Similarly, immunosuppression is a known risk factor for anal cancer among organ transplant recipients [22]. Regarding the CD4 cell count, our cases had a relatively robust CD4 cell count at the time of cancer diagnosis (median, 432; IQR 282-509 cells/mm³). Although low CD4 counts were associated with abnormal anal cytology in other studies, no clear association has been noted with the development of anal cancer [21,23,24].

In our study, duration of HAART use was not significantly associated with a decreased risk of anal cancer. Other research concurs with this finding [10]; one study even demonstrated that HAART was associated with a higher risk of anal cancer [11], but it is unclear if this was a true effect of ART on cancer or attributable to population effects. The association of HAART use with decreased rates of opportunistic infections and other AIDS-defining conditions may allow for sufficient time for dysplasia to develop into anal cancer among HIV-infected persons. The lack of protection of HAART against anal cancers mirrors findings that antiretroviral therapy has no impact on the natural history of HPV in the anogenital tract or the likelihood of HPV co-infection [18-20]. These data suggest that regardless of HAART use, HIV-positive persons remain at risk for anal carcinoma.

Additional risk factors for anal cancer in other studies have included behavioral factors. Both AIN and anal cancer have been linked to a higher number of unprotected receptive anal sex partners [10,23], which is likely a surrogate for infection with multiple high-risk HPV strains. We examined the association of several types of prior STIs with the occurrence of anal cancer, and found a relationship between gonorrhea and anal cancer which had

borderline statistical significance. We did not find an association with any other STI or the number of STIs and anal cancer, but this may be due to the lack of data in our cohort on sexual preference or anal intercourse.

It is also important to note that anal cancer among HIV-infected persons is primarily a disease of younger men (median age of 42 years in our study). This mirrors other studies among HIV-positive persons with median ages of 43-49 years [10,11,25] and among transplant recipients [22]. These ages are significantly younger than the age of occurrence (generally, the sixth decade) among HIV-uninfected persons [8,25]. Among the general population, only 12% of anal cancers occur at an age of less than 44 years [8], however 63% of our cases occurred in this age category. Additionally, among persons 18-49 years of age, the standardized rate of anal cancer was 95 per 100,000 PY in our HIV cohort compared to 0.47 in the general population [16]. This suggests that HIV-infected persons may have a shorter time to the development of anal cancer than the general population; immunosuppression and persistent co-infection may accelerate the rate of progression from HPV to cancer. The estimated latency from time of HPV infection to cancer is 5-40 years in general population [12]. Although the time period among HIV-infected persons has not yet been defined, it may be significantly shorter.

The incidence rate of anal cancer in our study was significantly greater than seen in the general population. In the general U.S. population, the standardized age-adjusted incidence rate is 1.4 per 100,000 men per year during 2002-2006 compared to our standardized rate of 132 during the same time period [8]. Although most of our anal cancer events occurred during the interval 2002-2006, making a direct comparison less reliable, these data suggest that HIV is a risk factor for the development of anal cancer. This is supported by other studies demonstrating standardized incidence ratios (SIR) of 42.9 for anal cancer [1]. Since MSM have a higher rate of anal cancer than heterosexual men, part of the excessive rate may be due to the higher percentage of MSM within HIV-positive cohorts. However, HIV infection itself is also a risk factor, as shown by a recent study evaluating HIV-positive MSM compared to HIV-negative MSM who had rates of 69 vs. 14 per 100,000 PY, respectively [10].

Given the rising rates of anal cancer among HIV-infected persons, early diagnosis and treatment have been advocated as important strategies to reduce treatment-related morbidity as well as improve survival [26]. However, controversy remains in regards to routine screening for anal cancer, since the impact of screening on the morbidity or mortality of anal carcinomas is currently unknown [27]. Furthermore, the best approach to screening is also unclear. A recent study showed that despite negative cytology screenings from clinician-collected samples, a sizable number of HIV-infected persons still had abnormalities on anoscopy questioning whether a negative anal pap alone is adequate screening for high-risk populations [28]. Finally, the cost-effectiveness of screening for anal cancer or its precursors remains disputed [29,30]. While cervical cancer screening among women in the U.S. is widely accepted and has been successful, with the incidence rates now being similar for HIV-positive and HIV-negative women [31], whether anal cancer screening will also become standard practice is unknown. Further data on preventive strategies and the potential use of anal cancer screening practices are needed.

There are several limitations of our study, including the limited number of anal cancer events. Also, our dataset does not contain information on sexual orientation given the military policy of "don't ask, don't tell" (although prior data from our cohort suggest that approximately 60% of HIV-infected persons in our cohort are MSM [32]) and only limited information related to HPV infection. As with all analyses of observational data, other potential limitations include the possibility of unmeasurable confounders, and ascertainment

bias due to changing screening practices, although anal screening practices are not known to have changed in our cohort over time. Finally, our cohort does not collect information on staging and treatment information related to anal cancer.

The strengths of our study include the evaluation of 24 years of data spanning the HIV epidemic, including 13 years during the HAART era, to evaluate the effect of potent antiretroviral use on anal cancer. We also focused on squamous cell anal cancers, a unique feature compared to many other studies, in order to avoid confounding by examining heterogeneous cancers with varying pathogenic mechanisms. Finally, we examined prospectively captured data prior to the diagnosis of anal cancer among a geographically and racially diverse population of HIV-infected persons.

In summary, the incidence rates of anal cancer among HIV-infected men have dramatically increased during the HAART era and are occurring in relatively young men. Despite the beneficial effects of HAART use and high current CD4 counts on the prevention of several opportunistic infections and cancers, these factors may not significantly protect against the development of anal cancer. In fact, in our study, a longer duration of HIV was associated with higher rates of anal cancer. These data emphasize the urgent need for establishing screening and preventive strategies for anal cancers.

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Figure 1. Rate ratios of Calendar Period and Duration of HIV on the Development of Anal Cancer

Table 1
Characteristics¹ at Anal Cancer Diagnosis or at Censoring among HIV-Infected Males

Characteristic	Anal Cancer N=19	No Anal Cancer N= 4487
Demographics		
Age, years		
<20	0 (0%)	18 (0.4%)
20-29	3 (16%)	955 (21%)
30-39	5 (26%)	1806 (40%)
≥40	11 (58%)	1708 (38%)
Median (IQR)	42.2 (33.4-46.5)	37.2 (30.8-43.8)
Ethnicity		
Caucasian	11 (58%)	1981 (44%)
African American	8 (42%)	1991 (44%)
Other	0 (0%)	514 (12%)
Sexually Transmitted Infections		
Hepatitis B seropositive	10 (53%)	2081 (46%)
Hepatitis C seropositive	0 (0%)	312 (7%)
Herpes simplex virus (HSV)	6 (32%)	1254 (28%)
Syphilis	2 (11%)	835 (19%)
Gonorrhea	8 (42%)	1244 (28%)
Chlamydia	3 (16%)	593 (13%)
Any STI (HSV, syphilis, gonorrhea, chlamydia)	13 (68%)	2542 (57%)
Number of STIs		
None	6 (32%)	1950 (44%)
1	6 (32%)	1271 (28%)
2	3 (16%)	671 (15%)
3	2 (10%)	322 (7%)
≥4	2 (10%)	273 (6%)
HIV-Related Factors		
Duration of HIV infection, years, median (IQR)	12.8 (4.0-17.9)	7.3 (4.0-11.8)
AIDS-defining condition	8 (42%)	1275 (28%)
Nadir CD4 count, cells/mm ³		
<200	14 (74%)	1761 (40%)
200-500	3 (16%)	1982 (44%)
>500	2 (10%)	693 (15%)
Missing	0 (0%)	21 (0.5%)
Median (IQR)	134 (35-318)	257 (80-401)
Most recent CD4 count, cells/mm ³		
<200	2 (11%)	517 (11%)
200-500	10 (53%)	1157 (26%)
>500	5 (26%)	1514 (34%)

Characteristic	Anal Cancer N=19	No Anal Cancer N= 4487
Missing	2 (10%)	1299 (29%)
Median (IQR)	432 (282-509)	482 (302-680)
Most recent HIV RNA, log ₁₀ copies/ml		
<3	8 (42%)	1513 (34%)
3-5	7 (37%)	1018 (22%)
>5	1 (5%)	129 (3%)
Missing	3 (16%)	1827 (41%)
Median (IQR)	3.0 (1.4-4.4)	2.3 (1.4-4.1)
Antiretroviral Therapy		
ART ever prescribed	17 (90%)	3330 (74%)
Duration of ART use ² , years, median (IQR)	10.1 (5.4-12.4)	5.5 (2.7-9.8)
HAART ever prescribed	14 (74%)	2036 (45%)
Duration of HAART use ² , years, median (IQR)	6.5 (5.1-9.6)	5.5 (2.2-9.7)
Proportion of follow-up time on HAART ²	0.38 (0.24-0.46)	0.47 (0.25-0.67)

¹ Data are N (%) unless otherwise stated. For those with no anal cancer the characteristic is at time of last study visit or death.

² Among those who were ever prescribed antiretroviral therapy and HAART

Table 2
Table 2a. Age-Adjusted Incidence Rates¹ of Anal Cancer by Calendar Period among Males during the HIV Epidemic (1985-2008)

Interval	Number of People Followed	Years of Follow-up	Number of Events	Rate	95% CI	Rate Ratio	95% CI	P-value
Pre-HAART (1985-1995)	3252	18,905	3	11.0	2.0 - 60.2	Referent		
HAART (1996-2008)	3222	18,893	16	55.0	8.9 - 339.1	5.0	1.4-18.4	0.02
1985-1990	2391	7956	1	7.9	1.0 - 61.9			
1991-1995	3004	10944	2	11.0	1.2 - 99.3			
1996-2000	2547	8553	2	13.4	1.4 - 124.7			
2001-2005	2029	7483	7	51.1	6.2 - 442.9			
2006-2008	1546	2849	7	127.6	15.6 - 1042.2			
Overall	4506	37806	19	61.9	7.6 - 502.7			

Table 2b. Age-Adjusted Incidence Rates¹ of Anal Cancer by Duration of HIV Infection among Males during the HIV Epidemic (1985-2008)

HIV Duration ²	Number of People Followed	Years of Follow-up	Number of Events	Rate	95% CI	Rate Ratio	95% CI	P-value
0 to < 5 years	4506	19145	5	28.0	3.5-223.1	Referent		
5 to < 10 years	3108	11104	3	29.0	3.3-257.5	1.03	0.25-4.33	0.96
5 to < 10 years	3108	11104	3	29.0	3.3-257.5	1.03	0.25-4.33	0.96
10 to < 15 years	1468	5094	3	63.1	7.2-553.6	2.25	0.54-9.43	0.27
≥ 15 years	678	2463	8	347.6	49.0-2468.3	12.4	4.06-37.99	<0.001

¹ Rates are per 100,000 person-years of follow-up and are adjusted for age at entry into the interval

¹ Rates are per 100,000 person years of follow-up and are adjusted for age at HIV diagnosis

² Conditional on the participant having this duration of follow-up time

Table 3
Analyses for Time to an Anal Cancer Event¹

Factor(s)	Hazard Ratio	95% CI	P-value
Age at HIV diagnosis (per 10 years)	0.89	0.47 - 1.69	0.72
White ethnicity	1.85	0.74 - 4.60	0.19
Hepatitis B seropositive ²	0.76	0.29 - 1.99	0.57
Gonorrhea ²	2.43	0.93 - 6.36	0.07
Any STI ^{2,3}	1.41	0.51 - 3.91	0.51
Number of STIs ^{2,3}	1.08	0.87 - 1.33	0.49
AIDS-defining event ²	3.88	1.45 - 10.39	0.01
Nadir CD4 cell count ² (per 50 cells)	0.85	0.73 - 0.99	0.03
CD4 cell count ² (per 50 cells)	0.95	0.87 - 1.04	0.28
CD4 cell count strata ²			
<200 cells/mm ³	Referent		
200-500 cells/mm ³	0.99	0.27 - 3.69	0.99
>500 cells/mm ³	0.49	0.12 - 2.03	0.33
HIV RNA ² (per ½ log ₁₀)	1.24	0.58 - 2.62	0.58
HIV RNA ² >1000 copies/ml	1.56	0.58 - 4.17	0.38
Antiretroviral therapy use ²	2.10	0.55 - 8.03	0.28
Duration of HAART use ²	0.94	0.82-1.08	0.42

¹ Cox proportional hazards models adjusted for year of HIV diagnosis and time-updated calendar year of event. Each row represents a separate model.

² Time-updated covariate

³ The presence of herpes simplex virus, syphilis, gonorrhea, or Chlamydia

Table 4
Multivariate Analyses for Time to an Anal Cancer Event¹

Factor(s)	Hazard Ratio	95% CI	P-value
AIDS-defining event ²	3.92	1.45 – 10.61	0.01
Gonorrhea ²	2.44	0.93 - 6.43	0.07
Nadir CD4 cell count ² (per 50 cells)	0.85	0.73 – 0.99	0.03
Gonorrhea ²	2.47	0.93 – 6.52	0.07

¹ Cox proportional hazards models adjusted for age, year of HIV diagnosis, and time-updated calendar year of event

² Time-updated covariate