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The Impact of HIV Viral Control on the Incidence of HIV-Associated Anal Cancer

Elizabeth Y. Chiao, M.D., M.P.H.^{1,2}, Christine M. Hartman, Ph.D.^{1,2}, Hashem B. El-Serag, MD, MPH^{1,2}, and Thomas P. Giordano, M.D., M.P.H.^{1,2}

¹Department of Medicine, Baylor College of Medicine, Houston, TX, USA

²Houston Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX and Baylor College of Medicine, Department of Medicine, Houston, TX

Abstract

Background—Recent studies have shown that the incidence of squamous cell cancer of the anus (SCCA) has increased in the combined antiretroviral therapy (cART) era. The effect of undetectable HIV viral loads as a result of successful cART has not been evaluated.

Methods—We performed a retrospective cohort study among male U.S. Veterans diagnosed with HIV and followed between 1985–2009 using the Veterans Affairs Immunologic Case Registry (VA-ICR). We calculated age-adjusted incidence rates and rate ratios for SCCA. We conducted Cox proportional hazards ratios of SCCA in a multivariable model including time varying covariates of nadir CD4 count, and overall percentage of time with an undetectable HIV viral load.

Results—The age-adjusted SCCA incidence rate among the group who ever received cART was 146.8/100,000 person-years (CI 124.1, 172.6) and was not significantly higher than the SCCA rate of those who never received cART (134.3/100,000 person-years, CI 112.5, 159.0). In a multivariable model limited to veterans who had ever received cART (adjusted for demographic variables, nadir and most recent CD4 counts) individuals who had 61%–80% or 81%–100% of follow-up time with undetectable HIV viral loads had significantly decreased SCCA risk compared with those who had undetectable HIV viral loads <20% of the time (OR 0.56, $p=0.040$, and OR 0.55, $p=0.0004$, respectively).

Conclusion—HIV control as measured by the percent of time with undetectable HIV viral load appears to decrease the risk of SCCA. Optimizing cART adherence and HIV viral load control may decrease the risk of subsequent SCCA.

Background

Combination antiretroviral therapy (cART) has changed the epidemiology of HIV-related morbidity and mortality. While opportunistic infections and certain AIDS-defining malignancies have declined, several non-AIDS defining malignancies are increasing in the cART era, and account for an increasing proportion of deaths.¹ Although squamous cell

Corresponding Author and Request for Reprints: Elizabeth Y. Chiao, MD, MPH, Houston VA HSR&D, Michael E. DeBakey VA Medical Center (152), 2002 Holcombe Boulevard, Houston, Texas 77030, Phone: 713-794-8682, Fax: 713-748-7359, echiao@bcm.edu.

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cancer of the anus (SCCA) is a relatively rare cancer in the general population (estimated incidence of 1/100,000), individuals with HIV remain at a dramatically increased risk of SCCA in the cART era, estimated at 49–144/100,000 person-years.^{2–4} SCCA incidence has increased with the wide-spread availability of cART compared to the pre-cART era, but the specific effect of successful cART (as measured by undetectable HIV viral loads) has not been evaluated.^{2,3,5,6}

Like cervical cancer in women, SCCA is etiologically associated with high-risk human papillomavirus infection and progresses through phases of dysplasia to invasive cancer.⁷ Thus, it has been widely hypothesized that the increased SCCA incidence has occurred because of decreased HIV-associated mortality, allowing for the progression from high-risk HPV infection to anal dysplasia, and eventually to invasive SCCA.⁸ Cohort studies have demonstrated that SCCA incidence has increased in the cART era,^{2,3,5,6} and that HIV-related factors (such as low nadir CD4 count and duration of HIV infection) increase the risk for HIV-related anal cancer.^{9–11} However, these studies were not designed to measure the effect of successful cART on SCCA incidence because (1) none of these studies attenuated potential biases associated with differential survival among cART-treated and –untreated individuals and (2) none of these studies measured cART utilization over time. Careful analyses limited to homogeneous cohorts of only those individuals who received cART are needed.

The Veterans Administration (VA) has the largest integrated healthcare system in the United States, and is also the largest provider of HIV care in the United States.¹² The VA maintains system-wide clinical information (including laboratory, pharmacy, and clinical services use), and death data in a national registry of HIV-infected patients.¹² Utilizing these resources, we conducted a retrospective cohort study within the VA to elucidate the added impact of successful cART as measured by HIV viral load measurements to other known HIV-associated risk factors on the incidence of SCCA.

Methods

Data source

The VA HIV Clinical Case Registry (CCR) is a nationwide registry that contains health-related information on all known HIV-infected individuals utilizing VA services. It was established in 1992, and has been described in detail elsewhere.¹³ The CCR draws upon the electronic medical records of the over 60,000 HIV-infected patients cared for by the VA since the registry's inception, and includes all demographic, laboratory, pharmacy, outpatient clinic visit, and hospitalization data, as well as dates of death. For the present study, VA death data were supplemented with data from the Social Security and VA vital status files, and CCR race data were supplemented with data from the national inpatient patient treatment file (PTF) and outpatient clinics (OPC) files. The Institutional Review Board for Baylor College of Medicine and Affiliated Institutions, the Michael E. DeBakey VA Medical Center Research and Development Committee, and the VA CCR administration approved the study.

Subjects

The study population was comprised of HIV-infected male veterans entered into the registry between 1 January 1985 and January 1, 2009. Only patients who had well-documented vital statistics and HIV diagnosis dates were included (see Figure 1a). Patients who were over age 18, with at least one confirmed date for: (1) HIV test (HIV-1 Elisa, Western Blot, or HIV viral load), (2) ICD-9 for HIV (042 or V08), or at least one prescription for antiretroviral therapy were eligible for inclusion in the cohort. Female Veterans were excluded from the

overall cohort because they were a very small percentage of the population (<2%). Patients with an anal cancer diagnosis up to 90 days after their HIV diagnosis date were also excluded from the cohort. Finally, we excluded patients who did not have any CD4 cell count information during follow-up. When calculating incidence rates for Table 1, in order to ensure similar follow-up potential between the cART and the no cART cohorts, we included only those patients who had at least one HIV viral load.

cART only cohort

We further restricted the cohort for the univariate and multivariate Cox proportional hazard analyses to include only those individuals who ever received cART during their follow-up (See Figure 1b). CART was defined as filled VA pharmacy prescriptions for any combination of two nucleoside reverse transcriptase inhibitor (NRTI) drugs and one of the following: a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor (PI), or an integrase inhibitor drug. In addition, any combination of drugs from two of the following classes was considered cART: NNRTI, PI, integrase inhibitors, and entry inhibitors. Only FDA drugs approved prior to January 1, 2011 were included in the cART definition. In the analyses restricted to cART users, we excluded from the cohort those with less than 90 days of follow-up past their cART date. In addition to ensure no prevalent cases of SCCA were included in the cohort, we excluded persons who had SCCA diagnosed within 90 days of initiating cART. Finally, we excluded patients who did not have a CD4 cell count prior to or within 90 days of initiating cART, and those who did not have any HIV viral load results during follow-up.

Definition of variables

Invasive SCCA was defined as ICD-9 codes 154.2 and 154.3. We previously validated the anal cancer ICD-9 codes in the VA, and determined that these codes had a positive predictive value of 88%.¹⁴ We defined the variable “History of Drug Use” using ICD-9 codes for: opioid type dependence or abuse, cocaine dependence or abuse, amphetamine and other psychostimulant dependence or abuse, and combinations of opioid type drug dependence. To quantify non-HIV-related comorbidities, we applied Deyo’s modification of the Charlson score (excluding points for diagnosis of HIV infection from the score) to diagnoses recorded in the year before the index visit.^{15,16} Time to HIV diagnosis to cART initiation was calculated from the index date of HIV infection (date of either: first positive HIV Elisa, first ICD-9 code 042, V08, or first prescription for anti-retroviral therapy) to date of first filled cART prescription.

The most recent CD4 count and percent of time with an undetectable HIV viral load were time-updated variables. The most recent CD4 cell count was the most proximal CD4 cell count recorded prior to the event or censor date. A plasma HIV viral load <500 copies/mL was considered to be “undetectable” and was assigned a value of “200 copies/mL” for computational purposes due to changes in the lower limit of detection of the HIV viral load test during the study period. The nadir CD4 cell count was defined as the CD4 count at time of cART initiation. Percent of time with undetectable HIV viral load was calculated as the overall percent of time each individual had an undetectable HIV viral load during follow-up. Time updated variables were evaluated at an interval of every 7 days.

Outcomes

The main outcome was diagnosis of SCCA. Follow-up for the survival analyses ended at SCCA diagnosis, last encounter date recorded in the dataset before October 1, 2009, or death, whichever came first.

Statistical analysis for the entire cohort

In order to describe the demographic variables associated with SCCA risk, we calculated age-adjusted incidence rates of SCCA comparing individuals who ever received cART to individuals who never received cART and used a t-test for comparisons of means and a chi-square test for categorical variables.

Statistical analysis for the cART cohort

We conducted Cox time up-dated proportional hazard analyses using the cohort of only patients who were ever initiated on cART. Follow-up time was calculated from the date of the first confirmed HIV test for the cART sub-cohort. For the univariate analysis of the cART cohort, normally distributed continuous data were compared with analysis of variance and non-normally distributed data were compared with the Kruskal-Wallis test. Multivariate Cox proportional hazards modeling was performed to estimate the risk of SCCA, and mortality (data not shown) adjusted for nadir and current CD4 counts as well as percent of time with undetectable HIV viral load. We also adjusted the model for age, race, year of HIV diagnosis, and history of drug use. The proportional hazards assumption was tested and fulfilled for all models. Statistics were analyzed with SAS software (SAS Institute).

Results

SCCA Risk

Table 1 shows the age-adjusted incidence of SCCA among those individuals in the cohort with at least 1 HIV viral load measurement. The overall incidence of SCCA in this cohort was 134.4/100,000 (CI 112.7, 159.2). The age-adjusted incidence for the cohort who received cART was 146.8/100,000 (CI 124.1–172.6) compared to 134.3/100,000 (CI 61.3–96.9) who never received cART. In the cART cohort, the incidence of SCCA did not increase significantly by calendar year of SCCA diagnosis or last follow-up date.

Study Cohort

There were 45,231 male Veterans identified in the complete cohort, with a total of 307,495 person-years of follow-up, of these 377 veterans were diagnosed with SCCA. Among the 28,806 individuals (63% of the entire cohort) who received cART, there were a total of 166,632 person-years of follow-up and 302 veterans with SCCA. Table 2 describes the 2 cohorts and compares the characteristics of patients who received cART with those of persons who never received cART. Veterans who received cART were significantly different from those who did not receive cART in all measured categorical variables. Veterans who received cART were more likely to be older than 40 years of age (64% who received cART compared to 57% who never received cART), and to be African American (50% who received cART compared to 45% who never received cART). In addition, 68% of Veterans who ever received cART were diagnosed in the cART era (after 1996), compared to 26% of Veterans who never received cART. Veterans treated with cART were more likely to have more comorbid conditions. Patients ever treated with cART were more likely to have nadir CD4 count between 200–500. (Of note 64% of Veterans treated with cART had their nadir CD4 counts diagnosed at the time of cART initiation.)

Factors Associated with Increased Risk of SCCA among those who ever received cART

There were 302 Veterans who were diagnosed with SCCA among the 27,304 individuals who ever received cART. Table 3 presents the univariate analysis. Age was not associated with an increased risk of SCCA in this population. Compared to whites, blacks and Hispanics had a lower risk of SCCA (HR 0.44, $p < 0.0001$ and HR 0.41, $p = 0.0009$, respectively). Compared to those who received cART within 5 years of their HIV diagnosis,

those who received cART within 5–10 years of their HIV diagnosis had an increased risk of SCCA (HR 1.37, $p=0.045$). Those who received cART greater than 10 years after their HIV diagnosis had a non-significant increased risk of SCCA (HR 1.56, $p=0.192$). In addition, those individuals with a higher recent CD4 count (>500) had a decreased risk of SCCA (HR 0.38, $p<0.0001$), compared to those whose most recent CD4 count was <200 . Furthermore, those with a higher nadir CD4 count (>500) had a markedly decreased risk of SCCA (HR 0.08, $p=0.0005$) compared with those who had a nadir CD4 count <200 . Those who had an undetectable HIV viral load between 61 and 80% of the time, and those with undetectable HIV viral load 81–100% of the time were also less likely to develop SCCA (HR 0.52, $p=0.001$ and HR 0.50, $p<0.001$, respectively). Of note, the median number of HIV viral load tests and CD4 counts per patient in the cART cohort were 17 and 20, respectively.

Multivariable analysis of SCCA Risk among those who ever received cART

Table 4 shows the results of the multivariable Cox regression analysis of SCCA risk among the 27,304 men in the cohort who received cART. Both nadir CD4 cell count at cART initiation and percent of time with undetectable HIV viral load were independently associated with SCCA risk. Compared to those with nadir CD4 <200 , individuals with CD4 cell count 200–350 had a HR 0.42 ($p<0.0001$) for SCCA and those with CD4 >350 had an even lower risk of HR 0.34 ($p<0.0001$). In addition, compared to those who had undetectable HIV viral loads 20% of their follow-up time, those with undetectable HIV viral loads 61–80% of the time had an adjusted HR of 0.56 ($p=0.004$) and those with undetectable HIV viral loads 81–100% of the time had an adjusted HR of 0.55 ($p=0.0004$). Age at cART initiation, year of HIV diagnosis, and most recent CD4 cell count were not associated with SCCA risk. History of drug use was also associated with decreased risk of SCCA (HR 0.71, $p=0.017$). In addition, Black and Hispanic race/ethnicity were both associated with a decreased risk of SCCA (HR 0.43, $p<0.001$, and HR 0.40, $p=0.0006$, respectively) compared with whites.

Discussion

To our knowledge, this study is the first large cohort study to demonstrate that maintaining undetectable HIV viral loads independently decreases the incidence of SCCA above and beyond other known SCCA risk factors such as nadir CD4 count. We found that individuals with excellent viral HIV control (between 80–100%) of their follow-up time have an approximately half of the risk of SCCA after adjusting for the effect of CD4 count. Previous cohort studies have generally found that SCCA remained stable or increased in the cART era, without being able to elucidate the specific role of cART in modifying that risk. Our study demonstrates that viral suppression through effective cART utilization does decrease the risk of SCCA, and may be an important observation for SCCA prevention among HIV-infected individuals.

Although effective utilization of cART has been shown to decrease the incidence of anal intraepithelial neoplasia (AIN)¹⁷, it has been hypothesized that cART has little effect on the progression of AIN to cancer.⁸ We did find non-significant higher rates of SCCA in the cART era compared to the pre-cART era, which may suggest that the decrease for cART-associated SCCA risk may not be as immediate as for other virally mediated AIDS-defining malignancies, including KS and non-Hodgkin's lymphoma, (possibly as a result of a longer latency time associated with dysplastic changes from HPV infection). However, maximal cART-related HIV viral suppression may significantly decrease the risk for SCCA, possibly by decreasing AIN incidence if not decreasing the progression from AIN to cancer progression.

Our findings support the results of a recent study evaluating the effect of cART on cervical high-risk HPV infection and related squamous intraepithelial lesions (SILs) in women. Minkoff et al¹⁸ found that adherent and effective cART utilization decreases both prevalent and incident HPV infections and SILs. They hypothesize that previous studies may have yielded mixed results because among other reasons, adherence and effectiveness of cART had not been evaluated. Another study conducted by de Pokomandy et al¹⁹ also found that men treated with the same cART regimen for 4 years had a marginally decreased risk of high-grade anal intraepithelial neoplasia incidence compared to those who had been on the same cART regimen for < 4 years, after adjusting for nadir CD4 count and HPV types. Our results suggest that the effect of cART may be extended from pre-cancerous HPV-associated lesions to the incidence of invasive SCCA.

Although several cohort studies reported that nadir CD4 cell count is associated with anal cancer incidence,^{20–22} studies evaluating the effect of HIV viral load on SCCA incidence have been mixed. Silverberg et al²² found that most recent HIV viral load was not associated with SCCA risk, however, they did not evaluate any cumulative markers of HIV viral load control. Our results corroborate the findings of one previous study that evaluated the effect of HIV viral load on SCCA risk. Guiget et al²³ found that among 74 cases of SCCA, the cumulative time with HIV viral load > 100,000 c/ul was associated with a statistically increased risk of SCCA (HR=1.2, CI: 1.1–1.4). However, this cohort was not limited to only individuals treated with cART, thus, they were not able to quantify the role of effective cART, as measured by undetectable HIV viral loads on the risk of SCCA. By utilizing the variable “percent of time with undetectable HIV viral load”, our study is the first to measure the cumulative effect of HIV viral control as a result of cART use on SCCA risk. Thus, our study now provides evidence that suppressing HIV viral load through effective cART nearly halves the risk of SCCA compared to individuals with poor HIV viral load control. Ensuring undetectable HIV viral load control by ensuring effective cART utilization may be an important aspect of SCCA prevention among HIV-infected individuals.

The increase of SCCA incidence in the cART era has led to recommendations for SCCA screening using anal cytology and high-resolution anoscopy in the U.S.²⁴ However, clinical guidelines regarding the recommendation for SCCA screening remain vague. For example, New York State HIV treatment guidelines recommend yearly anal cytology for certain subgroups of HIV-infected individuals,²⁵ yet, national guidelines do not recommend anal cytology screening for SCCA.²⁶ In some regions, resources for anal cytology and the follow-up high-resolution anoscopy screening procedures remain limited. The data provided from this study highlight the effect of nadir CD4 cell count at cART initiation and viral suppression. Additional analyses are needed to confirm this hypothesis.

Our study has several limitations. First, it was a retrospective cohort study and thus may be subject to unmeasured confounders such as smoking. Of note, smoking has not been shown to be associated with changes in CD4 count or HIV viral load; therefore, smokers were likely distributed evenly in the nadir CD4 and percent undetectable HIV viral load categories.²⁷ Second, we do not have a direct measurement for categorizing men who have sex with men (MSM), who are more likely to have anal HPV infection and thus have higher risk of SCCA. Of note, we did find that individuals who are black/Hispanic and have a history of IVDU are at lower risk for SCCA, which may indicate that these variables may have somewhat adjusted for HIV-risk behavior. In addition, data suggest that MSMs have better adherence to HIV medication compared to intravenous drug users.²⁸ Thus, if MSMs have the highest risk of SCCA due to behavioral factors, but are also the most likely to have high nadir CD4 counts and high percentages of undetectable HIV viral loads, then the decreased SCCA incidence seen in our study associated with high nadir CD4 counts and undetectable HIV viral loads may actually underestimate the decrease in risk of SCCA.

attributable to nadir CD4 count and percent undetectable HIV viral load. We also utilized a relatively new measure of HIV viral load control, “percent of time with undetectable HIV viral loads,” which may not adequately describe the true time that individuals had an undetectable HIV viral load. However, we postulate that this variable is a better measure of overall HIV viral control compared to a single HIV viral load measurement. Finally, we conducted this study among male veterans. Thus the generalizability of these data remain somewhat limited.

In summary, our study demonstrates that maintaining control of HIV replication as a result of cART use is independently associated with a nearly halving the risk of SCCA. Further, individuals who start cART with a nadir CD4 cell count greater than 350 are at nearly two-thirds a lower risk of SCCA. These findings have several important implications. First, they provide further support for initiating cART at higher CD4 cell counts and maintaining suppressed HIV viral loads. In addition, the findings also suggest that further research evaluating a targeted approach for anal cytology and high-resolution anoscopy screening based on nadir CD4 cell count and HIV viral load suppression may be warranted. Further clinical studies evaluating the optimal approaches to the detection and prevention of SCCA, and other HPV-associated malignancies among HIV-infected individuals are necessary.

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a: **b:** **Figure 1.***a:* Patient Selection Criteria for inclusion in the "Full study Cohort"*b:* Patient selection criteria for inclusion in the "cART Cohort"

Table 1

Age-Adjusted Incidence of SCCA Among a Cohort of HIV-Infected U.S. Veterans

	Number of cancers	Person-years follow-up	Age- adjusted Incidence of Invasive SCCA per 100,000 person years, (Lower and Upper Confidence Intervals)
Complete Cohort *	345	211,043	134.4 (112.7, 159.2)
Overall cART Cohort *	302	166,362	146.8 (124.1, 172.6)
Never cART cohort *	27	16,680	134.3 (112.5, 159.0)
Calendar Year of SCCA diagnosis or last follow-up (cART cohort only)			
1996–2000	45	29,932	154.8 (131.4, 181.2)
2001–2005	124	69,581	137.2 (115.2, 162.2)
2006–2009	133	66,849	144.1 (121.5, 169.6)

* Includes only those individuals within the cohort who had at least one HIV viral load measured

Table 2

Characteristics of 45,231 individuals in total cohort and a comparison of the 28,806 individuals who received any CART with the ones who did not.

	Total cohort (%) N=45,231	Patients who received CART (%) N=28,806	Patients who never received CART (%) N=16,425	p-Value
Age at first HIV diagnosis date				<.0001
< 30	3710 (8)	2357 (8)	1353 (8)	
30–40	13827 (31)	8204 (28)	5623 (34)	
40–50	16781 (37)	10829 (38)	5952 (36)	
50–60	7700 (17)	5407 (19)	2293 (14)	
60	3213 (7)	2009 (7)	1204 (7)	
Race				<.0001
White	16857 (37)	10764 (37)	6093 (37)	
African American	21800 (48)	14481 (50)	7319 (45)	
Hispanic	3587 (8)	2210 (8)	1377 (8)	
Unknown/Other	2987 (7)	1351 (5)	1636 (10)	
First year of HIV diagnosis				<.0001
Pre-CART era 1985–1995	21255 (47)	9142 (32)	12113 (74)	
CART era 1996–2009	23976 (53)	19664 (68)	4312 (26)	
Time from HIV to first cART				
<5 years		22203 (81)		
5–10 years		4100 (15)		
>10 years		1001 (4)		
Use of illegal drugs				<.0001
No	30869 (68)	18670 (65)	12199 (74)	
Yes	14362 (32)	10136 (35)	4226 (26)	
Nadir CD4 count at event censor				<.0001
CD4 < 200	28977 (64)	17977 (62)	11000 (67)	
CD4 200–500	12956 (29)	9310 (32)	3646 (22)	
CD4 > 500	3298 (7)	1519 (5)	1779 (11)	
Deyo score without AIDS at event or censor				<.0001
0	28821 (64)	15641 (54)	13180 (80)	
1	10303 (23)	8296 (29)	2007 (12)	
2 and above	6107 (14)	4869 (17)	1238 (8)	
Time since first HIV diagnosis to event or censor				<.0001
< 90 days	1636 (4)	232 (1)	1404 (9)	
90–365 days	4004 (9)	1263 (4)	2741 (17)	
1 to 2 years	4799 (11)	1618 (6)	3181 (19)	
2 to 5 years	10610 (23)	5188 (18)	5422 (33)	
5 to 10 years	11522 (25)	9069 (31)	2453 (15)	
> 10 years	12660 (28)	11436 (40)	1224 (7)	
Invasive Anal Cancer				<.0001

	Total cohort (%) N=45,231	Patients who received CART (%) N=28,806	Patients who never received CART (%) N=16,425	p-Value
No	44854 (99)	28477 (99)	16377 (100)	<.0001
Yes	377 (1)	329 (1)	48 (0)	
Death (before event or at censor)				
No	25850 (57)	22117 (77)	3733 (23)	
Yes	19381 (43)	6689 (23)	12692 (77)	

Factors associated with Increased risk of Squamous Cell Cancer of the Anus Among 27,304 HIV-infected Veterans who Ever Received HAART

Table 3

	Frequency at event or censor		Survival analysis with time dependent variables	
	No Cancer N=27,002	Cancer N=302	Unadjusted HR & CI	p-Value
Age at HAART Initiation (continuous)	Mean & SD	Mean & SD		
Age	46.8, 9.8	45.1, 9.3	0.99 (0.98, 1.01)	0.78
Nadir CD4 Count at HAART initiation (continuous) CD4	250, 219	154, 148	0.99 (0.99, 1.00)	<.0001
Race	No. (%)	No. (%)		
White	10092 (37)	180 (60)	1	
Black	13605 (50)	98 (32)	0.44 (0.34, 0.56)	<.0001
Hispanic	2074 (8)	15 (5)	0.41 (0.24, 0.69)	0.0009
Unknown/ Other	1231 (5)	9 (3)	0.67 (0.34, 1.30)	0.234
Time From HIV Diagnosis to cART Initiation				
< 5 Years	21974 (81)	229 (76)	1	
5–10 Years	4036 (15)	64 (21)	1.37 (1.04, 1.80)	0.027
> 10 Years	992 (4)	9 (3)	1.56 (0.80, 3.05)	0.192
Most Recent CD4 Count at event or censor				
CD4 < 200	7234 (27)	100 (33)	1	
CD4 200 – 500	10574 (39)	138 (46)	0.67 (0.51, 0.86)	0.002
CD4 > 500	9194 (34)	64 (21)	0.38 (0.28, 0.53)	<.0001
Nadir CD4 Count prior to cART Initiation				
CD4 < 200	16776 (62)	245 (81)	1	
CD4 200 – 500	8831 (33)	55 (18)	0.36 (0.27, 0.49)	<.0001
CD4 > 500	1395 (5)	2 (1)	0.08 (0.02, 0.34)	0.0005
Illegal Drug Use at event or censor				
No	17416 (64)	232 (78)	1	
Yes	9586 (36)	70 (23)	0.61 (0.47, 0.80)	<.0001
Deyo Score without AIDS at event or censor				
0	14365 (53)	169 (56)	1	
1	7959 (29)	96 (32)	1.34 (1.04, 1.74)	0.024

	Frequency at event or censor		Survival analysis with time dependent variables	
	No Cancer N=27,002	Cancer N=302	Unadjusted HR & CI	p-Value
2 and above	4678 (17)	37 (12)	1.29 (0.90, 1.85)	0.171
Percent undetectable HIV Viral Load at event or censor				
20%	5982 (22)	113 (37)	1	
21% – 40%	2973 (11)	42 (14)	0.79 (0.55, 1.13)	0.196
41% – 60%	3326 (12)	43 (14)	0.80 (0.56, 1.14)	0.207
61% – 80%	4078 (15)	33 (11)	0.52 (0.36, 0.78)	0.001
81% – 100%	10643 (39)	71 (24)	0.50 (0.37, 0.68)	<.0001

Table 3

Multivariate analysis of Anal Cancer Risk among HIV-infected Veterans on HAART.

	Adjusted HR N=27,304 (302 cancers)	p-Value
Age at HAART Initiation (continuous)	1.00 (0.99, 1.02)	0.772
Race		
White	1	
Black	0.43 (0.33, 0.56)	<.0001
Hispanic	0.40 (0.23, 0.67)	0.0006
Unknown/ Other	0.75 (0.38, 1.47)	0.403
Time From HIV Diagnosis to HAART		
< 5 Years	1	
5–10 Years	1.33 (1.01, 1.77)	0.045
> 10 Years	1.78 (0.91, 3.48)	0.093
Illegal Drug Use		
No	1	
Yes	0.71 (0.53, 0.94)	0.017
Current CD4 count		
CD4 count < 200	1	
CD4 count 200 – 350	0.95 (0.70, 1.29)	0.734
CD4 count > 350	0.81 (0.59, 1.11)	0.188
Nadir CD4 count at HAART initiation		
CD4 count < 200	1	
CD4 count 200 – 350	0.42 (0.31, 1.58)	<.0001
CD4 count > 350	0.34 (0.23, .50)	<.0001
Percent Undetectable HIV Viral Load		
20%	1	
21% – 40%	0.85 (0.59, 1.22)	0.371
41% – 60%	0.86 (0.59, 1.23)	0.398
61% – 80%	0.56 (0.37, 0.83)	0.004
81% – 100%	0.55 (0.40, 0.77)	0.0004