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Cumulative HIV viremia and non-AIDS-defining malignancies among a sample of HIV-infected male veterans

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Abstract

Introduction—Research suggests cumulative measurement of HIV exposure is associated with mortality, AIDS, and AIDS-defining malignancies. However, the relationship between cumulative HIV and non-AIDS-defining malignancies (NADMs) remains unclear. The aim of this study was to evaluate the effect of different HIV measures on NADM hazard among HIV-infected male veterans.

Methods—We performed a retrospective cohort study utilizing Veterans Affairs HIV Clinical Case Registry data from 1985–2010. We analyzed the relationship between HIV exposure (recent HIV RNA, % undetectable HIV RNA, and HIV copy-years viremia) and NADM. To evaluate the effect of HIV, we calculated hazard ratios for three common virally-associated NADM (i.e., hepatocarcinoma (HCC), Hodgkin lymphoma (HL), squamous cell carcinoma of the anus (SCCA)) in multivariable Cox regression models.

Results—Among 31,576 HIV-infected male veterans, 383 HCC, 211 HL, and 373 SCCA cases were identified. In multivariable regression models, cross-sectional HIV measurement was not associated with NADM. However, compared to <20% undetectable HIV, individuals with 80% had decreased HL (aHR=0.62; 95%CI=0.37–1.02) and SCCA (aHR=0.64; 95%CI=0.44–0.93). Conversely, each log-10 increase in HIV copy-years was associated with elevated HL (aHR=1.22; 95%CI=1.06–1.40) and SCCA (aHR=1.36; 95%CI=1.21–1.52). Model fit was best with HIV copy-years. Cumulative HIV was not associated with HCC.

Conclusion—Cumulative HIV was associated with certain virally-associated NADM (i.e., HL, SCCA), independent of measured covariates. Findings underline the importance of early treatment

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initiation and durable medication adherence to reduce cumulative HIV burden. Future research should prioritize how to best apply cumulative HIV measures in screening for these cancers.

Keywords

HIV; viral load measurement; non-AIDS defining cancer; Hodgkin lymphoma; Squamous cell carcinoma of the anus

Introduction

Combination anti-retroviral therapy (cART) dynamically transformed the epidemiology of HIV in the United States. Since cART, the incidences of opportunistic infections and AIDS-defining malignancies (ADM) have declined.¹ However, over the same interval, non-AIDS-defining malignancies (NADM) have increased, and now NADM collectively represent over one-half of cancers diagnosed in HIV-infected individuals.²⁻⁵

Several NADM (e.g., hepatocellular carcinoma (HCC), Hodgkin lymphoma (HL), squamous cell carcinoma of the anus (SCCA)) are mediated by oncogenic viruses.⁶⁻⁸ In vitro data suggests HIV interacts with other oncogenic viruses and may facilitate viral activity and proliferation.^{9,10} Thus, in the current HIV era defined by increased life expectancy and longer duration of cancer susceptibility, cumulative HIV may be a valuable measure to classify future cancer risk.

While serial collection of HIV RNA is available, cross-sectional values have been more commonly utilized.¹¹ Recently, research has shown a stronger association between cumulative HIV and increased risk of AIDS and mortality, compared to cross-sectional HIV measurements.¹² Furthermore, Zoufaly et al.¹³ examined 6,022 HIV-infected patients receiving cART and observed an association between cumulative HIV and ADM (i.e., non-Hodgkin lymphoma). However, while HIV-infected individuals have been shown to have an excess of ADM and NADM, the effect of cumulative HIV on NADM risk has not been adequately evaluated.¹⁴ If associated with NADM risk, cumulative HIV may be a functional instrument to identify high-risk individuals for cancer screening. The aim of our study was to evaluate the association between three different cross-sectional and cumulative HIV measures and virally-associated NADM hazard (i.e., HCC, HL, SCCA; representing the three most prevalent virally-associated NADM¹⁵) among US male veterans diagnosed with HIV infection between 1985 and 2010.

Methods

This study was approved by the Institutional Review Board of Baylor College of Medicine (Houston, Texas).

Study Population

The Department of Veterans Affairs (VA) HIV Clinical Case Registry (CCR) is a nationwide registry containing health-related information on all known HIV-infected VA users^{16,17}. The registry draws upon the electronic medical records of over 65,000 HIV-infected patients cared for by the VA since the registry's inception. Following the

identification and registration of HIV-infected veterans, all past clinical data are electronically retrieved. The database is automatically updated electronically. On-site HIV coordinators provide maintenance and verification. The registry includes demographic, laboratory, pharmacy, outpatient and hospitalization data, and vital status.

66,991 HIV-infected adult veterans were enrolled in the VA HIV CCR between 1985 and 2010. Figure 1 describes criteria used to define the final sample. The study population was restricted to HIV-infected veterans over age 18 with documented CD4 and HIV measurement. Inclusion required a confirmed HIV diagnosis date, based on 1) the presence of multiple *International Classification of Diseases, Ninth Revision* (ICD-9) code for HIV (042 or V08), or 2) a combination of ICD-9 code for HIV, positive HIV-related test (e.g., ELISA, Western Blot, quantifiable HIV RNA measurement), or prescription delivery of cART. To avoid inclusion of individuals erroneously added to the registry, individuals without adequate HIV diagnostics (i.e., only a single ICD code for HIV and no lab or pharmacy records) or vital statistics were removed (n=6,769). HIV index date was defined as the earliest ICD-9 code, positive test, or prescription delivery. Due to limited number of females in the population (<2%), only male veterans were included in our analyses. Additionally, we removed individuals whose death or censor date was the same as their HIV index. To analyze the effect of cumulative HIV on individuals treated in the modern treatment era, we conducted our analyses using only individuals ever receiving cART, defined as any combination of 2 nucleoside reverse transcriptase inhibitors classes and 1 of either NNRTI or PI classes, integrase inhibitors, or CCR5 inhibitors and any combination of two classes. 31,576 HIV-infected veterans were included in the final sample.

Virally-associated NADM

The primary outcome was diagnosis of incident virally-associated NADM (i.e., HCC, HL, SCCA), identified from inpatient and outpatient ICD-9 codes (HCC=155.0, HL=201.4-9, SCCA=154.2-3). The follow-up interval for longitudinal analyses spanned from the index visit to NADM diagnosis, death or December 31, 2010 (the final date of the current CCR iteration), whichever occurred first. To minimize inclusion of patients with prevalent NADM, individuals diagnosed with NADM prior to or within 6 months after the initial HIV diagnosis date were excluded.

Data management and calculating HIV RNA load

To account for potential differences follow-up visit frequency, each individual's follow-up duration was divided into 7-day intervals. Each interval had a unique beginning and end date. Laboratory values were updated at the beginning of each interval, with the last observation carried forward when no new measurement was available.

HIV RNA load was modeled using three different strategies. Recent viral load was captured as a time-updated (7-day intervals), noncumulative HIV measurement. Recent viral load was modeled as the log copies/mL.

Two different cumulative HIV measurements were also generated. The first was a time-updated measurement of the cumulative percentage of follow-up HIV RNA was in the

undetectable range, as shown in the equation below (Eq. 1). For continuity across study years and standardization of operational procedures at different contributing VA facilities, the threshold for undetectable HIV RNA was established as <500 copies/mL.

$$\% \text{time undetectable HIV RNA} = \sum_{j=1}^{j_i} ([t_i(j) - t_i(j-1)] \times [U_j]) / t_i(j) \quad (\text{Eq. 1})$$

Where $t_i(j-1)$ and $t_i(j)$ represent the beginning and end date, respectively, of each follow-up interval and U_j represents whether or not HIV RNA was in the undetectable range over the referred interval.

Based upon evidence from research in cART medication adherence and the association between adherence and virologic failure, the % time undetectable HIV RNA was modeled as a categorical variable <20%, 20-39%, 40-59%, 60-79%, and 80%.^{18,19}

The final method of measurement, HIV copy-years viremia, has been previously developed and utilized to predict all-cause mortality among HIV-infected individuals.¹¹ The measurement represents an area-under-the-curve estimate, analogous to pack-years smoking. A complete description can be found elsewhere.¹²

Briefly, each HIV RNA measurement was attributed to its respective 7-day interval. Subsequently, using the equation (Eq. 2) shown below, we calculated cumulative HIV exposure, where $t_i(j-1)$ and $t_i(j)$ represent the beginning and end date, respectively, of each follow-up interval and VL_j represents the HIV RNA load over the referred interval. HIV copy-years is expressed in number of HIV copies multiplied by years (per mL of plasma). For example, 100,000 copy-years can represent having 10,000 HIV copies every day for 10 years or 100,000 HIV copies every day for 1 year.

$$\text{Copy - Years Viremia} = \sum_{j=1}^{j_i} \left(\frac{[t_i(j) - t_i(j-1)]}{365} \right) \times [VL_j] \quad (\text{Eq. 2})$$

Similar to previous studies, HIV copy-years was modeled as log copy-years/mL.^{11,12}

Statistical Analysis

Descriptive statistics were calculated to determine the distributions of sociodemographic and clinical variables in the study population. Characteristics were described in the overall cohort and separately in individuals diagnosed with HL, SCCA, and HCC. Spearman rank correlation coefficients were utilized to evaluate the correlation among the raw and transformed HIV measures. Additionally, we calculated incidence rates of HL, SCCA, and HCC.

Cox proportional hazards regression models were constructed to determine the individual effects of each of three different HIV measurements on the time to incident HL, SCCA, and HCC. Separate crude and multivariable regression models were fit for each different HIV measure and NADM, respectively. To adjust for potential confounding, covariates were

selected for multivariable regression models based on clinical relevance. These variables were age at HIV diagnosis, race/ethnicity, illicit drug use (defined by ICD-9 code), Deyo modification of the Charlson comorbidity index (excluding points allotted for HIV diagnosis), and the HIV diagnosis era (e.g., pre-cART 1985-1995, early-cART 1996-2001, late-cART 2002-2010). Initial immune function was estimated using nadir CD4 count before cART initiation. For individuals who received cART concurrent with the earliest HIV diagnosis, the first CD4 count was captured as the nadir. Time-updated CD4 has been shown to be associated with cancer risk and was included to describe fluctuating immune status throughout the follow-up period. Additional variables representing diagnoses of well-documented risk factors were included in models evaluating HCC (i.e., hepatitis C virus, cirrhosis) and SCCA (i.e., condyloma). Akaike information criterion assessed model fit.²⁰ Analyses were performed using SAS[®] version 9.1.

Results

Sample characteristics

Participant characteristics for 31,576 HIV-infected veterans who met inclusion criteria (Figure 1) and for strata defined by NADM diagnosis are provided in Table 1. Mean age at HIV diagnosis was 45 years (SD=10). Over one-half were racial/ethnic minorities. 35% had used illicit drugs. HIV diagnoses were captured from 1985-2010. Most HIV diagnoses occurred in the late cART era, but a greater proportion of individuals with NADM were diagnosed with HIV before 1996 (43-48%; $p<0.01$).

Overall, 45% of individuals, but 66% of SCCA cases ($p<0.01$), had a CD4 nadir before cART initiation <200 cells/ μ L. Over the study interval, mean recent CD4 was 427 cells/ μ L (SD=284). At the end of follow-up (e.g., censoring/death, NADM diagnosis), 55% of the cohort had CD4 >350 . The mean number of HIV measurements collected annually per individual was 3.2 (SD=3.1), and on average, each individual contributed 9 years (SD=5) of follow-up. At the time of NADM or censoring, the mean recent HIV RNA was 40,687 copies/mL (SD=185,182), highest among HL cases (mean=48,719; SD=123,896). At the final study observation, the mean % time undetectable HIV RNA was 49% (SD=34%). Overall, 27% had % time undetectable HIV $<20\%$, but 52% of HL cases and 43% of SCCA cases experienced this low level of viral load control ($p<0.01$). The mean HIV copy-years was 212,743 (SD=467,984), overall, and was highest among SCCA (mean=328,641; SD=654,596).

Table 2 describes rank correlations between the different HIV measurements utilized in the current analyses. All correlations were in the projected directions (e.g., recent HIV and HIV copy-years were directly correlated with one another and inversely correlated with % time undetectable HIV). While correlations between different measures varied in strength, all correlations were statistically significant ($p<0.01$).

Association between HIV RNA load measures and NADM incidence

During the study interval, 383 HCC (Incidence rate (IR) =133/100,000 person-years; 95% CI=124-142/100,000), 211 HL (IR=70/100,000 person-years; 95% CI=59-79/100,000),

and 373 SCCA (IR=129/100,000 person-years; 95% CI=119-138/100,000) were diagnosed. The unadjusted associations of the three HIV RNA measures with HCC, SCCA, and HL incidence are provided in Table 3. HIV copy-years was a significant predictor of NADM hazard. Per log-10 copy-years/mL increase in cumulative HIV, there was a significant increase in HL (HR=1.26; 95% CI=1.11-1.42), SCCA (HR=1.48; 95% CI=1.33-1.66), and HCC (HR=1.15; 95% CI=1.05-1.26).

The results from separate Cox regression models for each HIV RNA measure, adjusted for age, race/ethnicity, illicit drug use, era of HIV diagnosis, comorbidity, and pre-treatment nadir and recent CD4, are described in Table 4 (additional covariates included in SCCA (i.e., condyloma) and HCC (i.e., cirrhosis, hepatitis C) models). In the adjusted models, the relationship between NADM hazard and recent HIV RNA was not statistically significant. However, the association between the two cumulative HIV RNA measures and HL and SCCA hazard was robust to multivariate adjustment. Compared to individuals with <20% time undetectable HIV RNA, individuals with 80% time undetectable had a decreased hazard for HL (adjusted HR=0.62; 95% CI=0.37-1.02) and SCCA (aHR=0.64; 95% CI=0.44-0.93). The relationship between HIV copy-years and HL and SCCA was also significant. HL (aHR=1.22; 95% CI=1.06-1.40) and SCCA (aHR=1.36; 95% CI=1.21-1.52) hazard increased per log-10 increase in HIV copy-years. The results from analyses of HCC did not support a relationship between HIV RNA exposure and HCC risk. A comprehensive table of results from each of the adjusted models, complete with all covariates, has been provided as an online supplement (see Appendix 1).

Comparison of model fit between different HIV RNA metrics

Model fit was evaluated using Akaike information criterion. The difference between models incorporating each distinct HIV exposure variable was small. However, in each scenario, the HIV copy-years model was slightly superior, suggesting improved prognostic significance (data not shown).

Discussion

To our knowledge, the present study is the first to compare the relationship between cross-sectional and cumulative HIV metrics and the time to incidence of individual virally-associated NADM. Principally, results indicated elevated cumulative HIV exposure was associated with HL and SCCA incidence among our sample. The relationship with HCC was less stable. Additionally, compared to non-cumulative recent HIV RNA level, cumulative HIV copy-years provided better-fitting models to predict time to NADM incidence. Our findings suggest not all NADM are the same, but provide initial evidence to support a potential role for cumulative HIV in monitoring the development of certain virally-associated NADM.

Research has shown cumulative HIV measures are associated with mortality¹¹ and ADM diagnosis.^{13,21} Mugavero et al examined the association between cumulative HIV and all-cause mortality.¹¹ The authors reported higher cumulative HIV copy-years increased the risk of death. Additionally, another study evaluated the effect of cumulative HIV, as the duration in years of HIV exposure >500 copies/mL, on any ADM or NADM diagnosis,

respectively.²¹ The authors observed longer HIV exposure was associated with increased ADM incidence but not NADM. However, there were few NADM events and the study was not powered to investigate virally-associated or individual NADM diagnoses separately. In another recent study of cART and non-cART users, we observed higher % time undetectable HIV RNA was associated with decreased SCCA risk.²² However, this study did not assess different HIV measures or other NADM.

In the current study, HL and SCCA risk increased with higher cumulative HIV copy-years and decreased with better % time undetectable HIV. The underlying mechanisms explaining the association between HIV and NADM remain unclear. However, HIV may directly affect oncogenesis via tissue, cellular, or genetic mechanisms.²³⁻²⁵ Additionally, persistent replication, as noted by cumulative HIV, is associated with immunodeficiency and dampened clearance of latent viral coinfections (e.g., EBV, HPV, HHV8), potentially predisposing individuals to malignancies caused by other oncogenic viruses.²⁶

HIV-related HL is known to be associated with Epstein-Barr virus coinfection.²⁷ Previous research has suggested EBV levels may remain high under conditions of insufficient HIV control.²⁸ Therefore, cumulative HIV may indicate underlying EBV burden. Friis et al²⁹ suggested that even after cART initiation, it may take 1-2 years or longer to achieve effective EBV control. Additionally, HIV antigens are known to drive B-cell stimulation. In turn, chronic stimulation leads to uncontrolled B-cell division, possibly boosting the opportunity for malignant clone development and expansion.³⁰

HIV-related SCCA is also associated with persistent oncogenic viral infection, namely human papillomavirus (HPV).^{31,32} HIV-infected individuals are more likely than non-infected individuals to have anal HPV infection, including infection with multiple and high-risk oncogenic HPV genotypes, even in the absence of anal intercourse.³³⁻³⁵ HIV-infected individuals also experience longer durations of persistent HPV infection.³³ HPV proliferation involves a coordinated and complex interaction between HPV oncoproteins and Rb, p53 and other targets.³⁶ Similar to EBV, persistent HPV infection has been observed to be associated with HIV proliferation and cellular immune deficit.³⁷ Additional evidence suggests HIV and HPV genes reciprocally interact, either directly or via cytokine-mediated mechanisms, resulting in increasing amounts of HPV and enhancing the potential for malignant progression.¹⁰

HIV impacted HCC development differently than other virally-associated NADM studied. HIV has been shown to accelerate cirrhosis development.³⁸ However, in the current study, there was not a significant relationship between HIV and HCC, independent of cirrhosis. It is possible that the interface between HIV and HCV at the cellular level may be less direct than what occurs between HIV and EBV or HPV. Additionally, there may be effects of cART on HCV and HBV burden not captured here.

Our results highlight the effects of cumulative HIV on HL and SCCA incidence, independent of measured covariates, and support previous hypotheses that HL and SCCA may be different than other NADM.³⁹ Additionally, our results coincide with previous population-based findings^{12,40} and support previous molecular observations regarding the

relationships between HIV and the proliferation of other oncogenic viruses.^{10,28} The two cumulative measurements evaluated in the current study provide information about the overall impact of intermittently-controlled or continuous HIV replication using opposing methodologies. Specifically, one approach captures HIV directly while the other illustrates the absence of viremia. The relationships between each measure and cancer incidence were representative of this pattern. However, HIV copy-years provided improved model fit. One difference and potential advantage of HIV copy-years is the measure's ability to more exactly quantify the duration of exposure over time. For future studies, this level of precision may be the best measure of cumulative HIV to incorporate into risk stratification for ADM, HL and SCCA.

The findings from the current study should be viewed within the context of the study design. The retrospective cohort study design employed may be subject to unmeasured confounders (e.g., smoking). However, lifestyle factors such as smoking have not been shown to effect changes in HIV load.⁴¹ Additionally, all individuals included in the current sample had received cART, but the type and duration of treatment regimens received were not measured. Data for the present study was extracted from a national, system-wide VA registry of HIV-infected veterans. A principal strength was this resource provides one of the largest data repositories of HIV-infected individuals. However, certain limitations are inherent in such large registry databases. Most relevant to our analyses were potential variations in follow-up visit frequency. We attempted to reduce the potential for information bias by segmenting the follow-up period into one-week intervals, establishing equivalent visit frequencies per individual. However, some individuals may have experienced longer intervals without updated HIV measurements. In our data, the average number of HIV measurements collected annually was over 3 and was not different between NADM cases and non-cases. Finally, this study was conducted exclusively on male veterans, which may have implications on the generalizability of its findings.

In the current sample of HIV-infected male veterans, uncontrolled HIV replication, as indicated by cumulative HIV copy-years and % time undetectable HIV RNA, was associated with HL and SCCA development, independent of measured covariates. Cumulative HIV copy-years demonstrated the most robust association with the cancers studied and may provide the most sensitive metric to better describe the impact of HIV viremia and underlying viral coinfection. Thus, copy-years may be the most appropriate measure of HIV viral load control for future epidemiologic research assessing HIV-associated outcomes. Additional research is needed to define implementation strategies for cumulative HIV measurements as a screening tool for virally-associated cancers associated with chronic HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Flow chart of selection criteria generating final cohort of HIV-infected veterans

Table 1
Characteristics of HIV-infected male veterans who received any cART, stratified by NADM

	Overall N=31,576	HL n=211	SCCA n=373	HCC n=383
Age at HIV diagnosis [mean (SD)]	45 (10)	44(10)	42 (10)	47 (8)
HIV RNA Load [mean (SD)]	40687 (185182)	48719 (123786)	37426 (148064)	23386 (94935)
% undetectable HIV RNA [mean (SD)]	49 (34)	31 (32)	33 (31)	44 (31)
HIV copy-years viremia [mean (SD)]	212743 (467984)	145359 (297232)	328641 (654596)	145893 (336380)
	N (%)	n (%)	n (%)	n (%)
Race/ethnicity				
White, non-Hispanic	12043 (38)	83 (39)	225 (60)	131 (34)
African American, non-Hispanic	15610 (49)	103 (49)	124 (33)	193 (51)
Hispanic	2396 (8)	23 (11)	15 (4)	50 (13)
Other	1527 (5)	2 (1)	9 (3)	9 (2)
Year of first HIV diagnosis				
Pre-cART 1985-1995	9200 (29)	92 (44)	178 (48)	163 (43)
Early cART 1996-2001	9672 (31)	76 (36)	128 (34)	132 (34)
Late cART 2002-2010	12704 (40)	43 (20)	67 (18)	88 (23)
Use of illicit drugs				
No	20680 (65)	148 (70)	287 (77)	204 (53)
Yes	10896 (35)	63 (30)	86 (23)	179 (47)
DEYO without AIDS co-morbidity score				
0	16600 (53)	127 (66.9)	215 (58)	196 (51)
1	9222 (29)	43 (22.6)	113 (30)	122 (32)
2 and above	5754 (18)	20 (10.5)	45 (12)	65 (17)
Nadir CD4 count prior to cART				
CD4 < 200	14300 (45)	106 (50)	247 (66)	179 (47)
CD4 200-350	8701 (28)	56 (27)	77 (21)	116 (30)
CD4 > 350	8575 (27)	49 (23)	49 (13)	88 (23)
CD4 count at time of event/censor				

	Overall N=31,576	HL n=211	SCCA n=373	HCC n=383
CD4 < 200	8179 (26)	60 (30)	118 (32)	116 (30)
CD4 200-350	5895 (19)	62 (31)	101 (27)	100 (26)
CD4 > 350	17493 (55)	80 (39)	153 (41)	167 (44)

HL=Hodgkin lymphoma; SCCA=Squamous cell carcinoma of the anus; HCC=Hepatocellular carcinoma; cART=combination antiretroviral therapy

Table 2
Spearman rank correlations between measures of HIV viremia

	Recent HIV RNA Load	% undetectable HIV RNA	HIV copy-years viremia
1. Recent HIV RNA Load (Log ₁₀ copies/mL)	1.00		
2. % undetectable HIV RNA (<20, 20-39, 40-59, 60-79, 80%)	-0.51	1.00	
3. HIV copy-years viremia (Log ₁₀ copy-years/mL)	0.35	-0.53	1.00

Note: *p*-values for all correlations were statistically significant (*p*<0.01)

Table 3
Crude hazard ratio for non-AIDS-defining cancers by different HIV exposure metrics

	HL			SCCA			HCC		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Recent HIV RNA Load									
Log ₁₀ copies/mL	1.06	1.01-1.11	0.02	1.02	0.98-1.06	0.26	0.95	0.91-0.99	0.01
% undetectable HIV RNA									
<20%	1			1			1		
20-39%	0.95	0.60-1.51	0.83	1.08	0.82-1.43	0.58	1.39	1.02-1.89	0.04
40-59%	0.72	0.43-1.19	0.20	0.84	0.61-1.15	0.27	2.01	1.50-2.68	<0.01
60-79%	0.68	0.42-1.09	0.11	0.68	0.47-0.99	0.04	1.55	1.11-2.16	<0.01
80%	0.63	0.44-0.89	<0.01	0.74	0.53-1.02	0.07	1.56	1.14-2.12	<0.01
HIV copy-years viremia									
Log ₁₀ copies × years/mL	1.26	1.11-1.42	0.0003	1.48	1.33-1.66	<0.0001	1.15	1.05-1.26	0.01

HL=Hodgkin lymphoma; SCCA=Squamous cell carcinoma of the anus; HCC=Hepatocellular carcinoma.

Table 4
Adjusted hazard ratio for non-AIDS-defining cancers by different HIV exposure metrics

	HL			SCCA ^a			HCC ^b		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Recent HIV RNA Load									
Log ₁₀ copies/mL	1.00	0.94-1.05	0.88	1.01	0.97-1.05	0.60	0.96	0.92-1.00	0.06
% undetectable HIV RNA									
<20%	1			1			1		
20-39%	0.85	0.56-1.29	0.44	1.05	0.79-1.40	0.73	1.27	0.93-1.74	0.13
40-59%	0.67	0.41-1.10	0.11	0.81	0.58-1.13	0.21	1.81	1.94-2.44	<0.01
60-79%	0.84	0.51-1.37	0.48	0.63	0.42-0.93	0.02	1.28	0.90-1.82	0.18
80%	0.62	0.37-1.02	0.06	0.64	0.44-0.93	0.02	1.39	0.98-1.99	0.07
HIV copy-years viremia									
Log ₁₀ copies × years/mL	1.22	1.06-1.40	0.005	1.36	1.21-1.52	<0.0001	1.02	0.93-1.13	0.67

HL=Hodgkin lymphoma; SCCA=Squamous cell carcinoma of the anus; HCC=Hepatocellular carcinoma. All adjusted regression models included the following additional variables: age at HIV diagnosis, race/ethnicity, use of illicit drugs, era of HIV diagnosis (pre-cART, early cART, late cART), Deyo modification of the Charlson comorbidity index, nadir CD4 count (prior to cART initiation), and recent CD4 count.

^aRegression model for SCCA also included condyloma.

^bRegression model for HCC also included hepatitis C and cirrhosis.