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Association of Immunosuppression and Human Immunodeficiency Virus (HIV) Viremia With Anal Cancer Risk in Persons Living With HIV in the United States and Canada

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Background. People living with human immunodeficiency virus (HIV; PLWH) have a markedly elevated anal cancer risk, largely due to loss of immunoregulatory control of oncogenic human papillomavirus infection. To better understand anal cancer development and prevention, we determined whether recent, past, cumulative, or nadir/peak CD4+ T-cell count (CD4) and/or HIV-1 RNA level (HIV RNA) best predict anal cancer risk.

Methods. We studied 102 777 PLWH during 1996–2014 from 21 cohorts participating in the North American AIDS Cohort Collaboration on Research and Design. Using demographics-adjusted, cohort-stratified Cox models, we assessed associations between anal cancer risk and various time-updated CD4 and HIV RNA measures, including cumulative and nadir/peak measures during prespecified moving time windows. We compared models using the Akaike information criterion.

Results. Cumulative and nadir/peak CD4 or HIV RNA measures from approximately 8.5 to 4.5 years in the past were generally better predictors for anal cancer risk than their corresponding more recent measures. However, the best model included CD4 nadir (ie, the lowest CD4) from approximately 8.5 years to 6 months in the past (hazard ratio [HR] for <50 vs ≥500 cells/μL, 13.4; 95% confidence interval [CI], 3.5–51.0) and proportion of time CD4 <200 cells/μL from approximately 8.5 to 4.5 years in the past (a cumulative measure; HR for 100% vs 0%, 3.1; 95% CI, 1.5–6.6).

Conclusions. Our results are consistent with anal cancer promotion by severe, prolonged HIV-induced immunosuppression. Nadir and cumulative CD4 may represent useful markers for identifying PLWH at higher anal cancer risk.

Keywords. HIV infection; CD4+ T-cell count; HIV-1 RNA viral load; anal cancer; risk.

Anal cancer risk is markedly elevated among people living with human immunodeficiency virus (HIV; PLWH), especially those with AIDS and men who have sex with men (MSM) [1, 2]. Immunosuppression is associated with persistent oncogenic human papillomavirus (HPV) infection, which promotes development of anal high-grade squamous intraepithelial lesions/anal intraepithelial neoplasia 2-3 (HSIL/AIN2-3) but may play a lesser role in HSIL/AIN2-3 progression to anal cancer [3–6]. Despite improvements in immune function after the introduction of effective antiretroviral therapy (ART) in 1996, most studies of anal cancer incidence trends in PLWH have reported an increase or no change over time [7–15], with an apparent decline in recent years [1, 2]. Among non-AIDS–defining cancers, anal cancer exhibits the highest relative risk in PLWH compared with the general population [1].

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Immunosuppression and HIV viremia have been associated with anal cancer risk, but the time courses over which they exert their effects are unclear. Increased anal cancer risk has been associated with lower CD4+ T-cell count (CD4) [8–10, 16–26] and higher HIV-1 RNA level (HIV RNA) [18, 24, 26–28], even after mutual adjustment [18, 24, 26, 27]. It remains unknown whether risk is driven by recent, past, cumulative, or nadir/peak (ie, the lowest CD4 and the highest HIV RNA) CD4 and/or HIV RNA. Evidence suggests that past (ie, 6–7 years before diagnosis) [23], cumulative (ie, duration with CD4 <200 cells/μL) [18], and nadir (ie, the lowest CD4 ever or before ART initiation) [8, 23, 24, 26] CD4 are better risk predictors than recent CD4 and that cumulative HIV RNA (eg, duration with HIV RNA >100 000 copies/mL) is a better predictor than recent HIV RNA [18, 27].

To contribute to our understanding of anal carcinogenesis and help tailor approaches to prevention, we aimed to determine whether recent, past, cumulative, or nadir/peak CD4 and HIV RNA measures best predict anal cancer risk among PLWH in the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [29].

METHODS

Study Sample

Our study population included PLWH (aged ≥18 years) from 21 cohorts in the United States and Canada that contributed data, including cancer diagnoses, to the NA-ACCORD (1996–2014) [15, 29]. Cohorts submitted demographic and clinical data using standardized collection methods. Incident invasive anal cancers were validated using a standardized process of either cancer registry linkage or manual review of medical records and pathology reports [15]. Institutional review board approval was obtained for each cohort.

Follow-up started at the latest of the following dates: 1 January 1996, NA-ACCORD entry (first of 2 HIV primary care visits ≤1 year apart), cohort-specific start for cancer reporting, 18th birthday, or 360 days before the later of the first CD4 or HIV RNA measurement. Follow-up ended at the earliest of anal cancer diagnosis, cohort-specific end for cancer reporting, death, or 540 days after the earlier of the last CD4 or HIV RNA measurement. We excluded persons with <2 CD4 or <2 HIV RNA measurements or with follow-up ≤180 days.

Time-updated CD4 and HIV RNA Measures

We estimated CD4 and HIV RNA values at 30-day intervals using observed laboratory measurements, as previously described (Supplementary Methods) [30]. Based on these estimated values, we constructed time-updated CD4 and HIV RNA measures that were all lagged by at least 180 days to reduce the possibility of reverse causality. Thus, we examined CD4 and HIV RNA lagged by 180 days (approximately 6 months; defined as "recent") and then by longer lag (lagged by 360 day [approximately 1 year] increments from 540 to 1620 days, and by 720 day [approximately 2 years] increments from 1620 to 3060 days).

We also constructed lagged cumulative and nadir/peak measures during prespecified moving time windows. Cumulative measures were CD4 or HIV RNA average (ie, normalized by time) and proportion of time CD4 <200 cells/μL or HIV RNA >500 copies/mL. Nadir/peak measures were lowest CD4 and highest HIV RNA. The duration of the "early" (more distant past) and "late" (more recent past) windows was 1440 days (approximately 4 years). The early window was lagged by 1620 days (ie, covered approximately 8.5 to approximately 4.5 years in the past), and the late window was lagged by 180 days (ie, covered approximately 4.5 years to approximately 6 months in the past). The "overall" (early and late combined) window (2880 days duration; approximately 8 years) covered 3060 to 180 days (approximately 8.5 years to approximately 6 months) in the past.

Analyses of these various measures were restricted to persons with follow-up duration greater than the examined lag or window start (eg, the late window [starting at 1620 days in the past] can only be assessed among persons with follow-up >1620 days). Thus, the analyzed sample size decreased with increasing lag or amount of time in the past of the window start.

Statistical Analyses

We assessed associations between CD4 and HIV RNA measures and anal cancer risk using cohort-stratified Cox regression models with follow-up time as the time scale using counting process syntax [31] to account for time-varying covariates updated at 30-day intervals. We modeled these measures as categorical variables (calculating likelihood ratio global P values) and as continuous variables to test for trends (P_{trend}).

To identify a final model with the most robust independent CD4 and/or HIV RNA predictors, we compared models using the Akaike information criterion (AIC), which accounts for both model fit and parsimony. A smaller AIC indicates a better model; a difference in AIC that is >10 between models is considered meaningful [32]. Models being compared must use the same participant set. To make valid comparisons across all models, we examined AICs among persons with follow-up >3060 days (N = 34 625; anal cancer cases = 170). To choose CD4 measures for further testing, we compared separate models including each CD4 measure individually. Then, to select the best CD4 measure(s), we compared models that included the measures chosen for further testing, 2 at a time in the same model. We did the same for HIV RNA measures. To develop our final model, we compared models including combinations of the best CD4 and/or HIV RNA measures in the same model.

All models were adjusted for sex, race/ethnicity, and baseline age and calendar period. We did not adjust for history of AIDS due to its expected high collinearity with CD4 nadir and other CD4 or HIV RNA measures. In the primary analysis, we did

not adjust for HIV risk group or smoking due to a large number of unknowns, and we did not adjust for ART use because ART initiation during the study period was affected by prior CD4 [33]. In separate sensitivity analyses, we adjusted for HIV risk group, smoking, and cumulative ART use in our final model and assessed whether HIV risk group modified the association between the predictors and anal cancer risk in our final model (Supplementary Methods).

We used SAS version 9.4 (SAS Institute Inc., Cary, NC) to perform analyses, and a 2-sided *P* value of .05 to determine statistical significance.

RESULTS

Among 122 840 PLWH included in the 21 NA-ACCORD cohorts, 102 777 persons were eligible for this study (Table 1). Excluded persons had <2 CD4 or <2 HIV RNA measurements (n = 13 701) or no follow-up time (n = 6362). Most eligible persons were male (85%), of white (44%) or black race/ethnicity (40%), and started follow-up during the period 1996–2003 (57%). At baseline, most were aged ≥40 years (57%) and ART naive (67%), with CD4 ≥200 cells/μL (69%) and HIV RNA >500 copies/mL (70%). Persons diagnosed with anal cancer (n = 492) included a larger proportion of males (96%), persons of white race/ethnicity (61%), and persons who started follow-up during the period 1996–1999 (55% vs 32%). At baseline, they were more likely to be aged ≥40 years (64%) but less likely to be ART naive (57%) or to have a CD4 ≥200 cells/μL (49%).

Selection of Individual CD4 or HIV RNA Measures for Further Testing

In separate models, anal cancer risk was significantly associated with each CD4 and HIV RNA measure, except HIV RNA lagged by 180 and 540 days (Tables 2–4). Models with stronger associations (ie, higher hazard ratios [HRs]) and lower AICs were largely concentrated in single measures lagged by ≥1260 days (ie, occurring approximately 8.5 to approximately 3.5 years in the past) and in early cumulative and nadir/peak measures (ie, from 3060 to 1620 days [approximately 8.5 to approximately 4.5 years] in the past). Based on the results from separate models and models that included 2 cumulative or nadir/peak measures of the same type for CD4 (eg, early and late CD4 average in the same model) and HIV RNA, respectively (Supplementary Results; Supplementary Tables 1 and 2), we chose several CD4 measures (1620 day lag, early and overall average, early and overall proportion of time CD4 <200 cells/ μL, and early and overall nadir) and HIV RNA measures (3060 day lag, early average, and early peak) for further consideration.

Selection of Best CD4 Predictor(s)

We fit models including the CD4 measures chosen for further consideration above, 2 at a time. The model with both overall

Table 1. Baseline Characteristics of Study Sample, North American AIDS Cohort Collaboration on Research and Design, 1996–2014

	All (N = 102 777)	Anal Cancer Cases (n = 492)
Characteristic	n (%)	n (%)
Sex		
Male	87 059 (84.7)	470 (95.5)
Female	15 718 (15.3)	22 (4.5)
Race/ethnicity		
Black	41 331 (40.2)	156 (31.7)
White	44 741 (43.5)	302 (61.4)
Hispanic	6934 (6.8)	13 (2.6)
Other	4100 (4.0)	9 (1.8)
Unknown, imputed	5671 (5.5)	12 (2.4)
Age, y		
18–29	13 107 (12.8)	18 (3.7)
30–39	30 890 (30.1)	160 (32.5)
40–49	35 930 (35.0)	188 (38.2)
≥50	22 850 (22.2)	126 (25.6)
Calendar period		
1996–1999	32 426 (31.6)	272 (55.3)
2000–2003	25 949 (25.2)	133 (27.0)
2004–2007	19 870 (19.3)	55 (11.2)
2008–2011	18 287 (17.8)	28 (5.7)
2012–2014	6245 (6.1)	4 (0.8)
Combination antiretroviral therapy naive		
No	34 022 (33.1)	210 (42.7)
Yes	68 755 (66.9)	282 (57.3)
CD4 count, cells/μL		
<50	11 259 (11.0)	87 (17.7)
50 to <100	6856 (6.7)	62 (12.6)
100 to <200	13 596 (13.2)	104 (21.1)
200 to <350	22 252 (21.7)	120 (24.4)
350 to <500	20 058 (19.5)	59 (12.0)
≥500	28 756 (28.0)	60 (12.2)
HIV RNA level, copies/mL		
≤500	30 987 (30.1)	133 (27.0)
>500 to <10 000	20 738 (20.2)	113 (23.0)
10 000 to <100 000	30 394 (29.6)	138 (28.0)
≥100 000	20 658 (20.1)	108 (22.0)
HIV risk group		
Injection drug use	12 695 (12.4)	33 (6.7)
Men who have sex with men	32 669 (31.8)	222 (45.1)
Heterosexual	16 134 (15.7)	29 (5.9)
Other	2089 (2.0)	4 (0.8)
Unknown, imputed[a]	5636 (5.5)	14 (2.9)
Unknown, not imputed[a]	33 554 (32.6)	190 (38.6)
Smoking status		
Ever	54 994 (53.5)	350 (71.1)
Never	19 491 (19.0)	102 (20.7)
Unknown, imputed[a]	15 711 (15.3)	19 (3.9)
Unknown, not imputed[a]	12 581 (12.2)	21 (4.3)

Abbreviation: HIV, human immunodeficiency virus.

[a]We imputed HIV risk group and smoking status for persons with unknown values, except for cohorts with a high proportion of unknowns, or, for smoking, with all the knowns being smokers.

CD4 nadir and early proportion of time CD4 <200 cells/μL showed an AIC that was meaningfully lower than any other model containing 1 or 2 CD4 measures (data not shown). These 2 measures were highly correlated (Supplementary Table 3; Spearman correlation coefficient, –0.77; $P < .0001$), as were most cumulative and nadir CD4 measures.

Selection of the Best HIV RNA Predictor(s)

We fit models including the HIV RNA measures chosen for further consideration above, 2 at a time. None of these models showed an AIC that was meaningfully lower than that for early HIV RNA average alone, the single HIV RNA measure with the lowest AIC (data not shown). Although the AIC difference between separate models for early HIV RNA average and early HIV RNA peak was not meaningful (Table 4), when they were included in the same model, only early HIV RNA average remained significant (global $P = .0061$).

Final Model

We compared models with combinations of the best CD4 predictors (overall nadir and early proportion of time CD4 <200 cells/μL) and HIV RNA predictors (early average; Table 5). The model with the 2 CD4 measures prevailed as the model with the lowest AIC. Furthermore, early HIV RNA average lost its significance when added to this model. Thus, our final model included overall CD4 nadir (HR for <50 vs ≥500 cells/μL, 13.4; 95% confidence interval [CI], 3.5–51.0; $P_{trend} < .0001$) and early proportion of time CD4 <200 cells/μL (HR for entire vs no time, 3.1; 95% CI, 1.5–6.6; $P_{trend} = .0030$). In sensitivity analyses (data not shown), the HRs for these 2 measures did not meaningfully change after our final model was adjusted for HIV risk group, smoking, or cumulative ART use and were not significantly different between MSM and other/unknown HIV risk groups ($P = .69$ for overall CD4 nadir and $P = .065$ for early proportion of time CD4 <200 cells/μL).

The median overall CD4 nadir at the end of follow-up was 137 cells/μL (interquartile range [IQR], 38–256) among anal cancer cases compared with 259 cells/μL (IQR, 134–401) among noncases. The median time from CD4 nadir to anal cancer diagnosis was 4.9 years (IQR, 3.0–7.4).

DISCUSSION

Among PLWH in the United States and Canada, the most robust independent predictors for anal cancer risk were overall CD4 nadir (ie, lowest CD4 from approximately 8.5 years to approximately 6 months in the past) and early cumulative CD4 (ie, proportion of time CD4 <200 cells/μL from approximately 8.5 to approximately 4.5 years in the past). HIV RNA measures did not further improve anal cancer risk prediction. Our results confirmed the association between HIV-related immunosuppression and anal cancer risk [8–10, 16–26]; suggested a key role for severe, prolonged immunosuppression in anal carcinogenesis; and favored a greater role of immunosuppression at earlier compared with late phases of anal carcinogenesis.

Similar to our study, a previous study found nadir and cumulative CD4 to be independent predictors of anal cancer risk [25]. Other studies have found nadir [8, 9, 16, 19, 23, 24, 26] or cumulative CD4 [18, 21] to be associated with anal cancer risk and found nadir [8, 23, 24, 26], cumulative [18], and past [23] CD4 to be better predictors than recent CD4. Furthermore, PLWH with a prior AIDS diagnosis, which captures a history of severe immunosuppression (ie, a low CD4 nadir), have an elevated anal cancer risk compared to PLWH without AIDS [1].

In our study, based on AICs and strengths of association, single past CD4 measures (ie, lagged by approximately 3.5 to approximately 8.5 years) and early cumulative and nadir CD4 measures (from approximately 8.5 to approximately 4.5 years in the past) were generally better predictors of anal cancer risk than more recent CD4 measures, with early proportion of time CD4 <200 cells/μL included in our final model. Furthermore, only early measures remained significant when both early and late CD4 measures of the same type were modeled together (Supplementary Table 1). Nevertheless, as overall CD4 nadir was highly correlated with both early and late CD4 nadir, it was difficult to definitively tease apart these 3 constructs. Moreover, besides capturing severity of immunosuppression, overall CD4 nadir likely captured cumulative immunosuppression, as it was highly correlated with cumulative CD4 measures.

We and others have found cumulative HIV RNA measures to be significantly associated with anal cancer risk [18, 24, 26, 27] and to be better predictors than recent HIV RNA [18, 27]. However, when we added early HIV RNA average to a model with our 2 key CD4 predictors, it lost statistical significance and the model fit did not improve. These results suggest that the HIV RNA effect was entirely mediated by its effect of lowering CD4 [34], with no independent HIV RNA effect. In contrast, the only other study to comprehensively evaluate different CD4 and HIV RNA measures determined both cumulative CD4 and cumulative HIV RNA to be independent key predictors [18].

Prolonged immunosuppression-driven loss of control of oncogenic HPV infection is considered the primary mechanism that drives anal carcinogenesis in PLWH [3–5]. Lower CD4 is associated with increased anal HPV infection prevalence and persistence, greater amounts of HPV DNA, more HPV types in anal specimens, higher incidence and prevalence of anal intraepithelial neoplasia, and faster progression to HSIL/AIN2-3 [3, 4]. However, HIV-induced immunosuppression may not be critical for HSIL/AIN2-3 progression to anal cancer [3–6], and HPV-associated genetic instability and other factors (eg, smoking) that lead to genetic changes in HSIL/AIN2-3 may have a greater influence on progression [3, 4]. Our results generally supported this model, with early CD4 measures being better predictors for anal cancer risk than late CD4 measures. Nevertheless, our identification of overall CD4 nadir (ie, from

Table 2. Recent and Past CD4 Count Measures and Anal Cancer Risk, North American AIDS Cohort Collaboration on Research and Design, 1996–2014

CD4 Count Measure (cells/μL)	Anal Cancer Cases	Hazard Ratio (95% Confidence Interval)[a]	Global *P* Value (Akaike Information Criterion)[b]
180 d (approximately 6 mo) lag (ie, "recent")			
<50	27	4.1 (2.7, 6.3)	<.0001 (2603)
50 to <100	34	4.6 (3.1, 6.7)	…
100 to <200	73	3.1 (2.3, 4.2)	…
200 to <350	135	2.6 (2.0, 3.3)	…
350 to <500	106	1.8 (1.4, 2.3)	…
≥500	117	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.91 (0.89, 0.93)	…
540 d (approximately 1.5 y) lag			
<50	34	5.8 (3.9, 8.7)	<.0001 (2591)
50 to <100	27	3.7 (2.4, 5.7)	…
100 to <200	88	3.8 (2.9, 5.1)	…
200 to <350	113	2.2 (1.7, 2.9)	…
350 to <500	92	1.6 (1.2, 2.1)	…
≥500	106	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.90 (0.88, 0.92)	…
900 d (approximately 2.5 y) lag			
<50	25	4.6 (2.9, 7.2)	<.0001 (2596)
50 to <100	32	4.6 (3.1, 6.9)	…
100 to <200	79	3.6 (2.6, 4.8)	…
200 to <350	98	2.0 (1.5, 2.7)	…
350 to <500	74	1.4 (1.0, 1.8)	…
≥500	98	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.90 (0.88, 0.92)	…
1260 d (approximately 3.5 y) lag			
<50	36	8.0 (5.4, 12.0)	<.0001 (2584)
50 to <100	25	4.2 (2.7, 6.6)	…
100 to <200	66	3.4 (2.4, 4.7)	…
200 to <350	80	1.9 (1.4, 2.5)	…
350 to <500	69	1.5 (1.1, 2.0)	…
≥500	83	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.89 (0.86, 0.91)	…
1620 d (approximately 4.5 y) lag			
<50	33	9.5 (6.2, 14.7)	<.0001 (2575)
50 to <100	28	6.0 (3.8, 9.5)	…
100 to <200	58	3.8 (2.6, 5.4)	…
200 to <350	65	1.9 (1.4, 2.8)	…
350 to <500	74	2.1 (1.5, 2.9)	…
≥500	62	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.88 (0.86, 0.91)	…
2340 d (approximately 6.5 y) lag			
<50	27	9.0 (5.6, 14.6)	<.0001 (2581)
50 to <100	14	3.6 (2.0, 6.6)	…
100 to <200	47	3.6 (2.4, 5.5)	…
200 to <350	53	1.9 (1.3, 2.8)	…
350 to <500	48	1.6 (1.1, 2.4)	…
≥500	50	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.88 (0.86, 0.91)	…
3060 d (approximately 8.5 y) lag			
<50	13	6.3 (3.3, 12.2)	<.0001 (2580)
50 to <100	18	6.6 (3.7, 11.9)	…
100 to <200	37	4.2 (2.6, 6.8)	…
200 to <350	47	2.5 (1.6, 3.9)	…
350 to <500	23	1.2 (0.7, 2.0)	…
≥500	32	1.0 (ref)	…
Per 50 cells/μL[c]	…	0.87 (0.84, 0.90)	…

[a]Each measure was individually included in a cohort-stratified Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period. The N and number of anal cancer cases used for the model of each measure was: 180 d lag (N = 102 777; number of anal cancer cases = 492), 540 d lag (94 458; 460), 900 d lag (79 882; 406), 1260 d lag (68 953; 359), 1620 d lag (60 006; 320), 2340 d lag (45 343; 239), and 3060 d lag (34 625; 170).

[b]Global *P* value and Akaike information criterion from models among persons with follow-up >3060 days (N = 34 625; number of anal cancer cases = 170).

[c]$P_{trend} < .0001$.

Table 3. Recent and Past Human Immunodeficiency Virus RNA Level Measures and Anal Cancer Risk, North American AIDS Cohort Collaboration on Research and Design, 1996–2014

Human Immunodeficiency Virus RNA Level Measure (copies/mL)	Anal Cancer Cases	Hazard Ratio (95% Confidence Interval)[a]	Global *P* Value (Akaike Information Criterion)[b]
180 d (approximately 6 mo) lag (ie, "recent")			
≤500	341	1.0 (ref)	.14 (2643)
>500 to <10 000	66	0.9 (0.7, 1.2)	…
10 000 to <100 000	59	1.0 (0.8, 1.3)	…
≥100 000	26	1.3 (0.9, 1.9)	…
Per log10 copies/mL[c]	…	1.01 (0.93, 1.11)	…
540 d (approximately 1.5 y) lag			
≤500	288	1.0 (ref)	.086 (2642)
>500 to <10 000	77	1.1 (0.8, 1.4)	…
10 000 to <100 000	63	1.2 (0.9, 1.5)	…
≥100 000	32	1.8 (1.2, 2.7)	…
Per log10 copies/mL[c]	…	1.13 (1.03, 1.23)	…
900 d (approximately 2.5 y) lag			
≤500	233	1.0 (ref)	.013 (2638)
>500 to <10 000	74	1.2 (0.9, 1.6)	…
10 000 to <100 000	70	1.5 (1.1, 1.9)	…
≥100 000	29	2.0 (1.3, 2.9)	…
Per log10 copies/mL[c]	…	1.22 (1.11, 1.33)	…
1260 d (approximately 3.5 y) lag			
≤500	189	1.0 (ref)	<.0001 (2624)
>500 to <10 000	70	1.3 (1.0, 1.7)	…
10 000 to <100 000	70	1.7 (1.3, 2.3)	…
≥100 000	30	2.5 (1.7, 3.7)	…
Per log10 copies/mL[c]	…	1.27 (1.16, 1.39)	…
1620 d (approximately 4.5 y) lag			
≤500	165	1.0 (ref)	<.0001 (2627)
>500 to <10 000	61	1.1 (0.8, 1.5)	…
10 000 to <100 000	62	1.6 (1.2, 2.1)	…
≥100 000	32	2.8 (1.9, 4.2)	…
Per log10 copies/mL[c]	…	1.31 (1.19, 1.45)	…
2340 d (approximately 6.5 y) lag			
≤500	105	1.0 (ref)	.0002 (2629)
>500 to <10 000	59	1.5 (1.1, 2.0)	…
10 000 to <100 000	53	1.8 (1.3, 2.6)	…
≥100 000	22	2.7 (1.7, 4.3)	…
Per log10 copies/mL[c]	…	1.32 (1.18, 1.48)	…
3060 d (approximately 8.5 y) lag			
≤500	66	1.0 (ref)	<.0001 (2619)
>500 to <10 000	37	1.3 (0.9, 1.9)	…
10 000 to <100 000	50	2.5 (1.7, 3.7)	…
≥100 000	17	3.1 (1.8, 5.3)	…
Per log10 copies/mL[c]	…	1.49 (1.30, 1.70)	…

[a]Each measure was individually included in a cohort-stratified Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period. The N and number of anal cancer cases used for the model of each measure was: 180 d lag (N = 102 777; number of anal cancer cases = 492), 540 d lag (94 458; 460), 900 d lag (79 882; 406), 1260 d lag (68 953; 359), 1620 d lag (60 006; 320), 2340 d lag (45 343; 239), and 3060 d lag (34 625; 170).

[b]Global *P* value and Akaike information criterion from models among persons with follow-up >3060 days (N = 34 625; number of anal cancer cases = 170).

[c]P_{trend} < .0001, except for 180 d lag (P_{trend} = .75) and 540 d lag (P_{trend} = .0086).

approximately 8.5 years to approximately 6 months in the past) as a key predictor suggests a role for severe, prolonged immunosuppression in both HSIL/AIN2-3 development and progression.

HIV-encoded proteins may also contribute to HSIL/AIN2-3 development by facilitating initial HPV infection [35] or by upregulating HPV oncogenes [5, 36]. Although our finding of no independent HIV RNA effect contradicts this hypothesis, HIV RNA may be an imperfect marker for viral protein effects.

ART's role in preventing anal carcinogenesis is unclear [3–5]. If severe, prolonged immunosuppression in the presence of infection with oncogenic HPV types is a key risk factor in anal carcinogenesis,

Table 4. Cumulative and Nadir/Peak CD4 Count and Human Immunodeficiency Virus RNA Level Measures During Moving Time Windows and Anal Cancer Risk, North American AIDS Cohort Collaboration on Research and Design, 1996–2014

	Moving Time Window					
	Early (3060 to 1620 d in the Past)		Late (1620 to 180 d in the Past)		Overall (3060 to 180 d in the Past)	
Measure[a]	Anal Cancer Cases	HR (95% CI)	Anal Cancer Cases	HR (95% CI)	Anal Cancer Cases	HR (95% CI)
CD4 count average, cells/μL						
<50	10	12.2 (6.0, 24.8)	15	7.6 (4.3, 13.3)	8	20.7 (9.5, 45.0)
50 to <100	18	9.1 (5.1, 16.2)	24	5.4 (3.4, 8.6)	14	9.3 (5.0, 17.3)
100 to <200	28	3.7 (2.2, 6.1)	60	3.8 (2.7, 5.3)	30	4.4 (2.7, 7.2)
200 to <350	43	2.4 (1.5, 3.7)	74	2.0 (1.5, 2.8)	45	2.7 (1.7, 4.1)
350 to <500	36	1.7 (1.1, 2.7)	66	1.5 (1.1, 2.0)	35	1.6 (1.0, 2.6)
≥500	35	1.0 (ref)	81	1.0 (ref)	38	1.0 (ref)
Per 50 cells/μL[b]	…	0.86 (0.83, 0.90)	…	0.88 (0.86, 0.91)	…	0.86 (0.83, 0.89)
Global *P* value (AIC)[c]	…	<.0001 (2577)	…	<.0001 (2594)	…	<.0001 (2569)
Proportion of time CD4 count <200 cells/μL						
0.00	73	1.0 (ref)	148	1.0 (ref)	61	1.0 (ref)
>0.00 to 0.25	29	2.1 (1.4, 3.3)	44	1.7 (1.2, 2.5)	36	1.8 (1.2, 2.7)
>0.25 to 0.50	12	2.1 (1.1, 3.8)	24	2.3 (1.5, 3.5)	19	2.7 (1.6, 4.6)
>0.50 to 0.75	10	2.2 (1.2, 4.3)	26	3.2 (2.1, 4.8)	18	3.6 (2.1, 6.2)
>0.75 to <1.00	9	2.1 (1.1, 4.3)	32	4.1 (2.8, 6.0)	16	4.0 (2.3, 7.1)
1.00	37	7.9 (5.3, 11.9)	46	4.7 (3.4, 6.6)	20	10.3 (6.1, 17.1)
Per 20% of time CD4 <200 cells/μL[b]	…	1.39 (1.29, 1.49)	…	1.36 (1.28, 1.43)	…	1.46 (1.35, 1.58)
Global *P* value (AIC)[c]	…	<.0001 (2572)	…	<.0001 (2591)	…	<.0001 (2575)
CD4 count nadir, cells/μL						
<50	45	12.6 (6.1, 26.0)	61	7.0 (4.4, 11.2)	54	22.9 (7.1, 73.9)
50 to <100	17	5.5 (2.4, 12.5)	34	4.5 (2.7, 7.6)	20	11.2 (3.3, 37.7)
100 to <200	35	4.1 (1.9, 8.5)	77	3.8 (2.4, 6.0)	35	7.6 (2.3, 24.8)
200 to <350	49	3.2 (1.6, 6.6)	80	2.2 (1.4, 3.5)	47	6.5 (2.0, 20.9)
350 to <500	15	1.5 (0.6, 3.4)	42	1.6 (1.0, 2.6)	11	2.6 (0.7, 9.4)
≥500	9	1.0 (ref)	26	1.0 (ref)	3	1.0 (ref)
Per 50 cells/μL[b]	…	0.82 (0.78, 0.86)	…	0.85 (0.82, 0.88)	…	0.79 (0.75, 0.84)
Global *P* value (AIC)[c]	…	<.0001 (2564)	…	<.0001 (2583)	…	<.0001 (2562)
HIV RNA level average, copies/mL						
≤500	47	1.0 (ref)	122	1.0 (ref)	44	1.0 (ref)
>500 to <10 000	41	1.2 (0.8, 1.9)	81	1.3 (1.0, 1.8)	51	1.4 (0.9, 2.1)
10 000 to <100 000	61	2.4 (1.6, 3.5)	88	1.9 (1.4, 2.5)	59	2.2 (1.5, 3.3)
≥100 000	21	5.3 (3.1, 8.9)	29	3.6 (2.4, 5.5)	16	5.4 (3.0, 9.8)
Per log10 copies/mL[b]	…	1.58 (1.36, 1.84)	…	1.36 (1.23, 1.52)	…	1.56 (1.33, 1.83)
Global *P* value (AIC)[c]	…	<.0001 (2607)	…	.0001 (2628)	…	<.0001 (2617)
Proportion of time HIV RNA level >500 copies/mL						
0.00	31	1.0 (ref)	95	1.0 (ref)	25	1.0 (ref)
>0.00 to 0.25	29	1.6 (0.9, 2.6)	51	1.2 (0.8, 1.7)	42	1.6 (1.0, 2.7)
>0.25 to 0.50	19	1.6 (0.9, 2.8)	49	1.8 (1.3, 2.6)	24	1.5 (0.9, 2.7)
>0.50 to 0.75	21	1.8 (1.0, 3.2)	47	1.9 (1.3, 2.8)	32	2.4 (1.4, 4.1)
>0.75 to <1.00	40	3.1 (1.9, 5.1)	57	2.2 (1.6, 3.2)	41	3.7 (2.2, 6.4)
1.00	30	2.5 (1.5, 4.3)	21	0.9 (0.6, 1.5)	6	1.8 (0.7, 4.5)
Per 20% of time HIV RNA >500 copies/mL[b]	…	1.21 (1.11, 1.31)	…	1.11 (1.04, 1.18)	…	1.25 (1.14, 1.37)
Global *P* value (AIC)[c]	…	.0002 (2629)	…	.0001 (2627)	…	<.0001 (2625)
HIV RNA level peak, copies/mL						
≤500	31	1.0 (ref)	95	1.0 (ref)	25	1.0 (ref)
>500 to <10 000	24	1.2 (0.7, 2.0)	44	1.0 (0.7, 1.4)	23	1.3 (0.7, 2.2)
10 000 to <100 000	54	1.9 (1.2, 3.0)	92	1.6 (1.2, 2.1)	54	1.9 (1.1, 3.0)
≥100 000	61	3.2 (2.1, 5.1)	89	2.3 (1.7, 3.1)	68	2.8 (1.7, 4.5)
Per log10 copies/mL[b]	…	1.49 (1.30, 1.70)	…	1.30 (1.19, 1.43)	…	1.43 (1.25, 1.64)
Global *P* value (AIC)[c]	…	<.0001 (2615)	…	.0001 (2628)	…	<.0001 (2626)

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio.

[a]Each measure was individually included in a cohort-stratified Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period. The N and number of anal cancer cases for each moving window was: early (N = 34 625; number of anal cancer cases = 170), late (60 006; 320), and overall (34 625; 170).

[b]P_{trend} < .0001, except for early proportion of time HIV RNA level >500 copies/mL (P_{trend} = .0010).

[c]Global *P* value and AIC from models among persons with follow-up >3060 days (N = 34 625; number of anal cancer cases = 170).

Table 5. Best CD4 Count and Human Immunodeficiency Virus RNA Level Predictors and Final Model for Anal Cancer Risk, North American AIDS Cohort Collaboration on Research and Design, 1996–2014

Best Predictor	Anal Cancer Cases	Separate Models[a]	Combined Models[b]			
			Model 1 (Final Model)	Model 2	Model 3	Model 4
		HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Overall CD4 count nadir, cells/μL[c]						
<50	54	22.9 (7.1, 73.9)	13.4 (3.5, 51.0)	18.4 (5.5, 61.7)	…	11.7 (3.0, 46.1)
50 to <100	20	11.2 (3.3, 37.7)	8.1 (2.1, 31.2)	10.1 (2.9, 35.0)	…	7.9 (2.0, 31.0)
100 to <200	35	7.6 (2.3, 24.8)	6.2 (1.7, 22.2)	7.3 (2.2, 24.0)	…	6.1 (1.7, 22.2)
200 to <350	47	6.5 (2.0, 20.9)	6.5 (2.0, 20.9)	6.4 (2.0, 20.8)	…	6.4 (2.0, 20.9)
350 to <500	11	2.6 (0.7, 9.4)	2.6 (0.7, 9.4)	2.6 (0.7, 9.4)	…	2.6 (0.7, 9.4)
≥500	3	1.0 (ref)	1.0 (ref)	1.0 (ref)	…	1.0 (ref)
Global *P* value	…	<.0001	<.0001	<.0001	…	<.0001
Per 50 cells/μL	…	0.79 (0.75, 0.84)	0.85 (0.79, 0.92)	0.82 (0.77, 0.87)	…	0.87 (0.80, 0.93)
P_{trend}	…	<.0001	<.0001	<.0001	…	.0002
AIC	…	2562	…	…	…	…
Early proportion of time CD4 count <200 cells/μL[d]						
0.00	73	1.0 (ref)	1.0 (ref)	…	1.0 (ref)	1.0 (ref)
>0.00 to 0.25	29	2.1 (1.4, 3.3)	1.4 (0.7, 2.7)	…	1.9 (1.2, 2.9)	1.3 (0.7, 2.6)
>0.25 to 0.50	12	2.1 (1.1, 3.8)	1.1 (0.5, 2.5)	…	1.7 (0.9, 3.2)	1.1 (0.5, 2.4)
>0.50 to 0.75	10	2.2 (1.2, 4.3)	1.1 (0.4, 2.6)	…	1.8 (0.9, 3.5)	1.0 (0.4, 2.4)
>0.75 to <1.00	9	2.1 (1.1, 4.3)	0.9 (0.4, 2.3)	…	1.6 (0.8, 3.3)	0.9 (0.3, 2.2)
1.00	37	7.9 (5.3, 11.9)	3.1 (1.5, 6.6)	…	5.8 (3.7, 9.1)	2.9 (1.4, 6.1)
Global *P* value	…	<.0001	.0009	…	<.0001	.0015
Per 20% of time CD4 <200 cells/μL	…	1.39 (1.29, 1.49)	1.17 (1.05, 1.29)	…	1.31 (1.20, 1.42)	1.15 (1.04, 1.28)
P_{trend}	…	<.0001	.0030	…	<.0001	.0065
AIC	…	2572	…	…	…	…
Early HIV RNA level average, copies/mL[d]						
≤500	47	1.0 (ref)	…	1.0 (ref)	1.0 (ref)	1.0 (ref)
>500 to <10 000	41	1.2 (0.8, 1.9)	…	0.9 (0.6, 1.3)	1.1 (0.7, 1.6)	0.9 (0.6, 1.3)
10 000 to <100 000	61	2.4 (1.6, 3.5)	…	1.2 (0.8, 1.8)	1.6 (1.0, 2.4)	1.2 (0.7, 1.8)
≥100 000	21	5.3 (3.1, 8.9)	…	1.9 (1.0, 3.4)	2.5 (1.4, 4.5)	1.7 (0.9, 3.2)
Global *P* value	…	<.0001	…	.089	.014	.15
Per log10 copies/mL	…	1.58 (1.36, 1.84)	…	1.17 (0.99, 1.39)	1.28 (1.09, 1.51)	1.14 (0.96, 1.35)
P_{trend}	…	<.0001	…	.064	.0030	.15
AIC	…	2607	…	…	…	…
Combined models' AIC	…		2551	2561	2567	2551

Abbreviations: AIC, Akaike information criterion; CI, confidence interval; HR, hazard ratio; HIV, human immunodeficiency virus.

[a]Each measure was individually included in a cohort-stratified Cox model adjusted for sex, race/ethnicity, and baseline age and calendar period among persons with follow-up >3060 days (N = 34 625; number of anal cancer cases = 170).

[b]From cohort-stratified Cox model with combinations of key predictors as covariates and adjusted for sex, race/ethnicity, and baseline age and calendar period among persons with follow-up >3060 days.

[c]CD4 count nadir from 3060 to 180 days (approximately 8.5 years to approximately 6 months) in the past.

[d]Proportion of time CD4 count <200 cells/μL and HIV RNA level average from 3060 to 1620 days (approximately 8.5 to approximately 4.5 years) in the past.

then ART would have little preventive effect if initiated late, once immunosuppression has already played its main role of promoting HSIL/AIN2-3 [4]. Presumably a high proportion of persons who initiated ART at the start of the ART era already had experienced severe, prolonged immunosuppression, likely explaining the lack of decline in anal cancer incidence at that time [2, 7–15]. The trend toward earlier ART initiation since then [37] might explain the apparent decreasing incidence since 2008 [1, 2].

Nevertheless, anal cancer risk remains markedly elevated in PLWH [1], so optimization of prevention and screening efforts are needed. Early HIV diagnosis and prompt ART initiation [38, 39] could prevent the severe, prolonged immunosuppression associated with increased anal cancer risk. Vaccination against oncogenic HPV infection, especially among young MSM, and smoking cessation could also reduce risk and merit incorporation into primary HIV care

[39]. Furthermore, a firm evidence base needs to be developed for HSIL/AIN2-3 screening and management in PLWH [39, 40]. Anal cancer screening may be more effective if targeted to high-risk subgroups such as MSM, especially young MSM with AIDS [2]. Nadir and cumulative CD4, along with having a prior AIDS diagnosis (a proxy for low CD4 nadir), may represent useful markers for identifying patients at higher risk for anal cancer to target for screening and other prevention efforts.

Our study's limitations included a lack of information on anal HPV infection (including HPV genotype), anal intercourse frequency (a risk factor for HPV infection), presence of anal warts (an indicator of HPV infection), and anal cancer screening. HIV risk group and smoking data were incomplete; nevertheless, adjusting for these variables in sensitivity analyses revealed that our final model was highly robust. Furthermore, our study included a low percentage of females and Hispanics and only US and Canadian populations, limiting generalizability. Finally, none of the examined CD4 or HIV RNA measures fully characterize HIV-associated immune dysfunction (before or after ART).

Our study's strengths included large sample size and number of events, coverage across 19 years during the ART era among people with varied characteristics and from diverse North American locations, validated anal cancer diagnoses, and comprehensive evaluation of various CD4 and HIV RNA measures, capturing exposures that occurred as far back as approximately 8.5 years. Our approach of examining cumulative and nadir/peak measures during moving windows of fixed duration may be superior to examining these measures during total follow-up time, which varies by person.

In summary, we found CD4 nadir from approximately 8.5 years to approximately 6 months in the past and cumulative CD4 (ie, proportion of time CD4 <200 cells/μL) from approximately 8.5 to approximately 4.5 years in the past, in combination, to be the most robust independent predictors of anal cancer risk. Besides capturing severity of immunosuppression during the approximately 8-year window, CD4 nadir likely also captured cumulative immunosuppression. As evidence suggested that CD4 in the early part of the window had the greatest influence on risk, our results were consistent with severe, prolonged immunosuppression affecting the earlier stages in anal carcinogenesis. Initiating ART promptly upon HIV diagnosis, as currently recommended [38], and monitoring nadir and cumulative CD4 to help target prevention efforts may be important for anal cancer prevention in PLWH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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