Short Communication: HIV RNA Levels Predict AIDS-Defining and Non-AIDS-Defining Cancers After Antiretroviral Therapy Initiation Among HIV-Infected Adults

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Abstract

Whether poor virologic control is associated with incident cancers after initiation of combination antiretroviral therapy (ART) remains unclear. In a large cohort, time-updated HIV RNA levels $\geq 1,000$ copies/ml predicted AIDS-defining cancers (ADCs), non-AIDS-defining cancers (NADCs), and skin cancers. Virologic control may be an important strategy in reducing cancer events among HIV-infected persons.

AN INCREASING NUMBER OF HIV-infected adults worldwide are receiving antiretroviral therapy. As a result, there has been a dramatic decrease in the rate of AIDS-defining conditions and improvement in life expectancy.¹ Similarly, the incidence rates of cancers, specifically AIDS-defining cancers (ADCs), have diminished.² Despite these advances, cancers remain an important cause of morbidity and mortality among HIV-infected persons. Currently most cancers among HIV patients in the developed world occur after the initiation of combination antiretroviral therapy (ART) and are classified as non-AIDS-defining cancers (NADCs).^{3,4} However, there are few data on the effect of ongoing immunocompetence and HIV viremia on incident cancers after ART initiation.⁵ We prospectively studied a large cohort of HIV-infected persons to determine the effect of HIV control to help inform preventive strategies for cancers in an era of expansive ART use.

We conducted a substudy within the U.S. Military HIV Natural History Study (NHS), a large prospective study conducted at five geographically diverse sites across the United States. The NHS includes biannual study visits consisting of clinical interviews, physical examinations, and the collection of medical record data including antiretroviral use, CD4 counts, and HIV RNA levels.⁶ Participants in the study are adult military beneficiaries, the majority of whom have narrowly defined seroconversion windows. HIV-infected adults who initiated ART (defined as ≥ 3 full-dose antiretroviral medications) during the period of 1/1/1996 to 12/31/2012 were identified ($n=2,981$). We included those who had at least two study visits after ART initiation (exclude

$n=392$) and who had laboratory data at the time of ART initiation (exclude $n=351$), for a final population of $n=2,238$. We did not exclude patients who had cancer prior to ART initiation, but these specific cancers or their recurrences were not included as cases in the current analyses.

The outcome of interest was incident cancer after ART initiation obtained from a detailed medical record review in which the diagnosis of cancer was based on physician diagnosis supported by laboratory, radiologic, and/or histopathologic results.⁷ Cancers were categorized as ADCs (Kaposi's sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer) and NADCs (all other cancers, except squamous and basal cell skin cancers mirroring prior studies). Since our cohort also collected data on nonmelanoma (i.e., squamous and basal cell) skin cancers, we evaluated these cancers using separate analyses. To ensure that ART was not initiated as a result of the diagnosis of a cancer, we included only cancers that developed > 30 days after ART initiation.

Exposures of interest included the HIV RNA level (Roche Molecular Systems Amplicor) at the time of ART initiation as well as time-updated measures collected every 6 months thereafter. During follow-up, a total of 27,908 HIV RNA measures every 6 months were available with 5,790 values missing; for these, we utilized a carried-forward approach. HIV viremia was examined as a continuous variable and then using categories. The secondary exposure of interest was time-updated CD4 counts. A 6-month lag time was utilized for HIV RNA levels and CD4 counts to ensure that the observed value was measured prior to cancer diagnosis and treatment.

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Covariates in the statistical models included demographics, year of HIV diagnosis, year of ART initiation, time from HIV diagnosis (first HIV positive test) to ART initiation, chronic hepatitis B virus (HBV; defined as a positive surface antigen on ≥ 2 occasions separated by ≥ 6 months), and chronic hepatitis C virus (HCV; defined as a positive antibody or HCV RNA test).

Incidence rates were calculated as the number of cancer diagnoses by person-years (PY) of follow-up. Univariate and multivariate Cox proportional hazard models evaluated the association of time-updated HIV RNA levels and CD4 counts with incident cancers. Participants were followed from the date of ART initiation to the first occurrence of cancer diagnosis, death, lost to follow-up, or end of study period (December 31, 2012). Variables that may change during follow-up (CD4 counts, HIV RNA levels, and chronic HBV or HCV) were utilized as time-updated covariates, using all available data between HIV diagnosis time and the censoring event. All univariate factors were included in the multivariate models and removed in a stepwise fashion based on an alpha of 0.05. All final models were a priori adjusted for age, year of ART initiation, and time from HIV diagnosis to ART initiation. Hazard ratios (HR) are reported with 95% confidence intervals (CI). All tests were two-sided, and a p -value less than 0.05 was considered statistically significant. Models were separately fitted for ADCs and NADCs. In addition, a separate model was performed specifically examining non-melanoma skin cancers. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

Participant characteristics are shown in Table 1. Seventy-eight percent were documented seroconverters with a median seroconversion window of 1.3 (IQR 0.8, 2.2) years. Overall, a total of 164 (7%) HIV-infected persons developed incident cancer during 16,849 PY of follow-up [incidence rate of 973 cases (95% CI 830, 1134) per 100,000 PY]. Most cancers were NADCs [$n=75$; rate 445 cases (95% CI 350, 558) per 100,000 PY] compared with ADCs [$n=37$; rate 220 (95% CI 154, 303) cases per 100,000 PY]. ADCs were most commonly Kaposi's sarcoma (KS) ($n=20$; 119 cases/100,000 PY) followed by non-Hodgkin's lymphoma (NHL) ($n=17$; 101 cases/100,000 PY). NADCs included anal cancer ($n=22$; 131 cases/100,000 PY), prostate cancer ($n=17$; 101 cases/100,000 PY), Hodgkin's lymphoma ($n=8$; 48 cases/100,000 PY), melanoma ($n=6$; 36 cases/100,000 PY), renal cell carcinoma ($n=5$; 30 cases/100,000 PY), lung cancer ($n=4$; 24 cases/100,000 PY), and other ($n=13$). Finally, the non-melanoma skin cancers included basal cell ($n=39$; 231 cases/100,000 PY) and squamous cell ($n=13$; 77 cases/100,000 PY) cancers.

Characteristics at ART initiation in the unadjusted analyses that predicted ADCs included higher time-updated HIV RNA levels, lower time-updated CD4 counts, chronic HBV infection, and longer time from HIV diagnosis to ART initiation (Table 1). Predictors in the final multivariate model included higher time-updated HIV RNA levels (HR 1.79 per $\log_{10}$ copies/ml, 95% CI 1.36, 2.36), lower time-updated CD4 counts (HR 0.67 per 100 cells/mm³, 95% CI 0.55, 0.81), and chronic HBV (HR 2.27, 95% CI 1.08, 4.79) (Table 2). In a separate model using categorized measures and adjusted for the same factors shown in Table 2, HIV RNA levels $\geq 1,000$ copies/ml were associated with ADCs. Likewise, a time-updated CD4 category ≥ 200 cells/mm³ was associated with

a reduced risk of ADCs compared with a CD4 < 200 (data not shown). Finally, various lag times between HIV RNA measurements and ADC risk were examined, and it was found that higher HIV RNA levels at each time point (using 6-month intervals) between ART initiation and cancer diagnosis (a median of 5 years apart) were predictive at all of the time points and had similar magnitudes of associations.

For NADCs, characteristics in the unadjusted analyses that predicted cancer included higher time-updated HIV RNA levels and older age (Table 1). Predictors of NADCs in the final multivariate model included HIV RNA levels (HR 1.74 per $\log_{10}$ copies/ml, 95% CI 1.46–2.08), age (HR 1.06, 95% CI 1.03, 1.08), and time from HIV diagnosis to ART start (HR 1.06 per year, 95% CI 1.01, 1.12) (Table 2). Models using categorized time-updated values showed that HIV viremia ≥ 400 copies/ml was significantly associated with NADCs, but found no associations with any CD4 category (data not shown). When examining various lag times over the median 7-year period between ART initiation and NADC diagnosis, HIV RNA levels were most predictive closest to the time of cancer diagnosis (HR 1.91, 95% CI 1.63, 2.24), with slightly lower magnitudes of associations at times earlier from cancer diagnosis (e.g., 2 years prior to cancer: HR 1.47, 95% CI 1.20, 1.80). No significant associations were found for HIV RNA levels ≥ 3 years before the cancer diagnosis.

Predictors in the final multivariate model for basal and squamous skin cancers found HIV RNA levels (HR 1.75 per $\log_{10}$ copies/ml, 95% CI 1.42–2.14) and age (HR 1.05, 95% CI 1.01–1.09) were significant, while African American race was protective (HR 0.08, 95% CI 0.03–0.27) (Table 2).

In addition, we analyzed time-updated HIV RNA levels and CD4 counts as predictors for the most common individual ADCs and NADCs using separate models. In the final multivariate model, KS was predicted by time-updated HIV RNA levels (HR 1.83, 95% CI 1.30, 2.59) and time-updated CD4 counts (HR 0.68, 95% CI 0.53, 0.87). NHL was also predicted by time-updated HIV RNA levels, but with a smaller magnitude of association (HR 1.09, 95% CI 1.03, 1.16), and time-updated CD4 counts (0.64, 95% CI 0.47, 0.88). Finally, anal cancer was predicted by the time-updated HIV RNA levels (HR 1.91, 95% CI 1.42, 2.57), but not by the time-updated CD4 counts.

In summary, this study evaluated the relationship between time-updated continuous HIV RNA levels and CD4 counts on incident cancers after ART initiation. While prior studies have examined single values at ART initiation or at cancer diagnosis,^{5,8} studies examining the effect of ongoing HIV control over time and its potential effect on cancers after ART initiation are needed. Since an increasing number of patients are receiving ART worldwide and cancers remain a leading cause of morbidity among the aging HIV population, identifying predictors of cancer in this setting is critically important.

Our study found that after ART initiation, time-updated HIV RNA levels $\geq 1,000$ copies/ml were a risk factor for both ADCs and NADCs with similar associations and effect sizes. Furthermore, for the development of NADCs, there did not appear to be a “safe” detectable level as values ≥ 400 copies/ml were significantly associated with incident cancer. Prior studies have shown a strong relationship between HIV viremia and ADCs; however, the relationship with NADCs has been mixed, likely a result of varying study methodologies.^{4,5,9–14}

TABLE 1. DESCRIPTIVE CHARACTERISTICS AT ANTIRETROVIRAL THERAPY INITIATION AND UNADJUSTED HAZARD RATIOS FOR PREDICTORS OF CANCER

Characteristic	Cancer N = 164											
	No cancer N = 2,074			ADCs N = 37			NADCs N = 75			Nonmelanoma skin cancers N = 52		
	N (%)	N (%)	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value	N (%)	HR (95% CI)	p-value	
Age, median (IQR) years	34.1 (22.2)	33.8 (11.0)	34.9 (8.1)	1.01 (0.97, 1.05)	0.54	38.6 (14.0)	1.05 (1.02, 1.08)	<0.0001	39.8 (10.5)	1.07 (1.04, 1.10)	<0.001	
Race												
White	953 (42.6)	851 (41.0)	16 (43.2)	Ref		37 (49.3)	Ref		49 (94.2)	Ref		
African American	963 (43.0)	908 (43.8)	17 (45.9)	1.14 (0.57, 2.25)	0.72	35 (46.7)	1.02 (0.64, 1.62)	0.94	3 (5.8)	0.07 (0.02, 0.23)	<0.001	
Other	322 (14.4)	315 (15.2)	4 (10.8)	0.87 (0.29, 2.60)	0.80	3 (4.0)	0.31 (0.09, 0.99)	0.048	0 (0.0)	—	—	
Sex												
Male	2063 (92.2)	1910 (92.1)	37 (100)	Ref		67 (89.3)	Ref		49 (94.2)	Ref		
Female	176 (7.8)	164 (7.9)	0 (0)	—	—	8 (10.7)	1.43 (0.69, 3.00)	0.34	3 (5.8)	0.85 (0.26, 2.73)	0.78	
Chronic hepatitis B ^{a,b}	210 (9.4)	174 (8.4)	15 (40.5)	3.66 (1.79,7.47)	0.0004	13 (17.3)	1.34 (0.73, 2.44)	0.34	8 (15.4)	1.12 (0.53, 2.39)	0.77	
Hepatitis C ^{a,b}	188 (8.4)	168 (8.1)	7 (18.9)	2.06 (0.90, 4.75)	0.0881	9 (12.0)	1.05 (0.52, 2.10)	0.90	4 (7.7)	0.63 (0.23, 1.75)	0.37	
CD4 count ^b , median (IQR) per 100 cells/mm ³	330 (480)	340 (230)	210 (320)	0.56 (0.47, 0.68)	<0.001	320 (290)	0.95 (0.88, 1.03)	0.1788	300 (250)	0.97 (0.89, 1.06)	0.53	
<200	485 (21.7)	431 (20.8)	18 (48.6)	Ref		24 (32.0)	Ref		12 (23.1)	Ref		
200–349	708 (31.6)	664 (32.0)	8 (21.6)	0.13 (0.05, 0.39)	0.0003	17 (22.7)	0.51 (0.20, 1.33)	0.17	19 (36.5)	1.73 (0.35, 8.62)	0.50	
350–499	621 (27.7)	584 (28.2)	5 (13.5)	0.19 (0.08, 0.45)	0.0001	18 (24.0)	1.13 (0.52, 2.42)	0.76	14 (26.9)	3.86 (0.89, 16.77)	0.07	
≥ 500	424 (18.9)	395 (19.0)	6 (16.2)	0.03 (0.01, 0.10)	<0.001	16 (21.3)	0.54 (0.26, 1.14)	0.11	7 (13.5)	2.14 (0.51, 9.03)	0.30	
HIV RNA level ^b , median (IQR) log ₁₀ copies/ml	4.5 (2.4)	4.5 (1.2)	4.9 (1.1)	2.34 (1.81, 3.03)	<0.001	4.3 (1.3)	1.48 (1.24, 1.76)	<0.0001	4.4 (1.3)	1.53 (1.24, 1.88)	<0.001	
<400	144 (6.4)	132 (6.4)	2 (5.4)	Ref		8 (10.7)	Ref		2 (3.8)	Ref		
400–999	87 (3.9)	79 (3.8)	1 (2.7)	4.68 (1.20, 18.3)	0.0265	4 (5.3)	3.58 (1.80, 7.08)	<0.001	3 (5.8)	4.73 (2.10, 10.63)	<0.001	
1,000–9,999	437 (19.5)	402 (19.4)	6 (16.2)	8.90 (3.31, 23.98)	<0.001	16 (21.3)	2.59 (1.37, 4.92)	0.003	13 (25.0)	4.84 (2.34, 10.03)	<0.001	
≥ 10,000	1,570 (70.2)	1,461 (70.4)	28 (75.7)	10.63 (4.31, 26.21)	<0.001	47 (62.7)	2.31 (1.27, 4.19)	0.006	34 (65.4)	3.18 (1.53, 6.60)	0.002	
Time from HIV diagnosis to ART initiation, median (IQR) years	2.3 (6.3)	2.3 (6.3)	7.6 (6.9)	1.11 (1.03, 1.21)	0.007	5.4 (9.0)	1.02 (0.96, 1.09)	0.44	5.1 (8.5)	0.96 (0.89, 1.04)	0.28	

^aThere were 8 missing values for hepatitis B virus status and 20 for hepatitis C virus status.

^bVariables were time updated in the unadjusted Cox proportional hazard models.
ADC, AIDS-defining cancers; NADCs, non-AIDS-defining cancers; ART, antiretroviral therapy.

TABLE 2. MULTIVARIATE MODELS OF PREDICTORS OF CANCERS AMONG HIV-INFECTED PERSONS AFTER ANTIRETROVIRAL THERAPY INITIATION, 1996–2012

Characteristic	Hazard ratio (95% CI)	p-value
ADCs model		
Time-updated HIV RNA, per log ₁₀ copies/ml	1.79 (1.36, 2.36)	<0.0001
Time-updated CD4 cell count, per 100 cells/mm ³	0.67 (0.55, 0.81)	<0.0001
Chronic hepatitis B virus (HBV)	2.27 (1.08, 4.79)	0.03
NADCs model		
Time-updated HIV RNA, per log ₁₀ copies/ml	1.74 (1.46, 2.08)	<0.0001
Age, per 1 year	1.06 (1.03, 1.08)	<0.0001
Time from HIV diagnosis to ART Initiation, per 1 year	1.06 (1.01, 1.12)	0.0487
Nonmelanoma skin cancer model		
Time-updated HIV RNA, per log ₁₀ copies/ml	1.75 (1.42, 2.14)	<0.0001
Age, per 1 year	1.05 (1.01, 1.09)	0.0059
Race		
White	Ref	
African American	0.08 (0.03, 0.27)	<0.0001

Models utilized stepwise regression techniques to determine the final adjusted model. All models were adjusted for age at the time of ART initiation, year of ART initiation (before or after 2000), time-updated CD4 count, time-updated HIV RNA level, and time (years) from HIV diagnosis to ART initiation. Only significant factors in the final model are shown.

We also described the time periods of viremia that were most associated with subsequent diagnosis of ADCs and NADCs, and found that viremia was associated with nonmelanoma skin cancers among HIV-infected persons, novel findings of the current study.

The pathogenesis of these associations may be related to chronic immune activation and inflammation.^{9,15} Direct oncogenic effects of the HIV may occur including activating protooncogenes, inhibiting tumor suppressor genes, causing genetic alterations, and/or sensitizing tissues to carcinogens.^{10,16–18} This study provides epidemiologic support of the link between the HIV viremia and cancers, and highlights the potential importance of virologic control in limiting the risk of cancer among HIV patients after ART initiation. While studies have debated whether antiretrovirals are related to cancer,¹⁹ recent studies have found no relationship³ or a protective effect,⁴ hence the benefits of therapy in controlling HIV are likely more important than any potential medication-related adverse effects.

Other factors associated with the development of NADCs in our study cohort included older age and longer time from HIV diagnosis to ART initiation. These data support considerations for enhancing cancer screening among the aging HIV-infected population and for the early initiation of ART. In addition to HIV RNA levels and CD4 counts, ADCs were predicted by chronic HBV infection; this relationship may be related to the shared routes of transmission (high-risk sexual behaviors) of HBV and HHV-8 (the etiologic agent of KS). Finally, skin cancers were predicted by increasing HIV RNA

levels and age, with the additional finding of white race consistent with the published literature.

Despite studying a large HIV cohort during the ART era (1996–2012), limitations of the current study include a relatively small number of cancers post-ART initiation; thus, some individual cancer types could not be studied separately, but we did perform models for the most common cancer types. Data on tobacco and alcohol use were not available for the entire study period, and we did not examine illicit substance use, although rates are low in the military setting. Detectable HIV viral loads may have occurred due to non-adherence, virologic failure, or intermittent release from viral reservoirs. We utilized a cut-point of ≥ 400 copies/ml since this defined a detectable RNA level during most of the study period; hence, we did not study effects of lower levels of viremia.

Our study had several strengths including being multisite with detailed and prospectively collected data including every 6-month time-varying CD4 count and RNA measures. We evaluated a group of early diagnosed HIV patients with data on the timing of HIV infection and time to ART initiation. Finally, the median follow-up time was nearly a decade, allowing for the evaluation of cancers that may accumulate over time with aging.

In summary, HIV-infected persons remain at high risk for cancers despite ART initiation, and prevention should be a key goal. Nonsuppressed HIV RNA levels ($\geq 1,000$ copies/ml) are risk factors for ADCs, NADCs, and skin cancers, highlighting the critical importance of prompt and continual virologic control after ART initiation. This study provides additional support regarding the benefits of ongoing control of HIV replication among HIV-infected persons.

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Author Disclosure Statement

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