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Relationship of immunologic response to antiretroviral therapy with non-AIDS-defining cancer incidence

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Abstract

Objective—To estimate the association between immunologic response to antiretroviral therapy (ART) and non-AIDS-defining cancer (NADC) incidence in HIV-infected patients.

Design—Prospective cohort including patients with ≥1 CD4 count and HIV-1 RNA measure after ART initiation between 1996 and 2011 in the Centers for AIDS Research Network of Integrated Clinical Systems, a collaboration of 8 HIV clinics at major academic medical centers in the United States.

Methods—Measures of immunologic response were six-month CD4 post-ART, latest CD4, and CD4 count-years, a cumulative measure of CD4 lymphopenia. Cox regression with inverse probability-of-exposure weights was used to calculate adjusted hazard ratios (HR) of virus-related and virus-unrelated NADC incidence.

Results—Among 9389 patients at ART initiation, median CD4 count was 200 cells/mm^3 (IQR=60–332), and median HIV-1 RNA was 4.8 $\log_{10}$copies/ml (IQR=4.3–5.4). Median follow-up was 3.3 years (IQR=1.5–6.5). After six months of ART, median CD4 count was 304 cells/mm^3 (IQR=163–469). 164 NADCs were diagnosed during study follow-up; 65 (40%) considered virus-related. Virus-related NADCs were inversely associated with six-month CD4 (HR per 100

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cells/mm^3 increase=0.71), latest CD4 (HR per 100 cells/mm^3 increase=0.70), and CD4 count-years (HR per 200 cell-years/mm^3 increase=0.91) independent of CD4 at ART initiation, age, and HIV-1 RNA response. No associations were found with virus-unrelated NADCs.

Conclusions—Poor CD4 response was strongly associated with virus-related NADC incidence, suggesting an important role for T-cell-mediated immunity in pathogenesis. Lower CD4 proximal to cancer diagnosis may be a result of subclinical cancer. Intensified cancer screening should be considered for patients on ART with low CD4 counts.

Keywords

Antiretroviral therapy; Cancers; HIV infections; Immune reconstitution; CD4; Tumor virus infections

Introduction

Among HIV-infected individuals the burden of non-AIDS-defining cancers (NADCs) is increasing[1], with malignancies such as lung cancer, anal cancer, and Hodgkin lymphoma contributing to substantial morbidity and mortality[1–3]. This is largely due to aging of the HIV population[4, 5] and a high prevalence of risk behaviors such as tobacco use, alcohol use, and sexual behaviors[6]. However, HIV infection and the resultant immune suppression may also increase cancer risk[7, 8]. More severe immunosuppression, as quantified through nadir CD4 and current CD4, is associated with greater incidence of several NADCs[7, 9–11]. Effective antiretroviral therapy (ART) would be expected to reduce NADC risk, but prior studies have not found consistent associations between ART use and lower NADC incidence[4, 12–14]. These inconsistencies may partly be due to differences in the effectiveness of ART between patients. Immunologic response to ART, as measured by CD4 counts, is likely a major mediator of ART effects on NADC incidence.

While patterns of cancer incidence differ over time after ART initiation[15, 16], the reasons for these patterns are not well understood, including the impact of immunologic ART response. We evaluated the relationship between immunologic ART response and NADC incidence among HIV-infected patients initiating a first ART regimen in the Center for AIDS Research Network of Integrated Clinical Systems (CNICS) between 1996 and 2011.

Methods

Study Population

CNICS is a network of eight U.S. HIV clinical cohorts that collects data from HIV-infected patients 18 years of age or older through electronic medical records[17]. CNICS includes detailed information on antiretroviral treatment, laboratory measures, demographics, and diagnoses, including cancer diagnoses, which have been ascertained and verified through a standardized data collection process[18]. Each CNICS site obtained local institutional review board approval.

We included patients who initiated a first ART regimen, defined as ≥3 different antiretrovirals, at one of the CNICS sites between Jan. 1, 1996 and Aug. 30, 2011. Among

these patients, we included those who: 1) had a CD4 count and HIV-1 RNA measure within 12 months prior to ART initiation; 2) were alive for more than six months post-ART initiation; and 3) had ≥1 CD4 count and HIV-1 RNA measure within the first six months post-ART initiation.

Measures of Immunologic ART Response

Several measures were used to characterize immunologic ART response based on CD4 cell counts obtained as a part of routine clinical care. Six-month CD4 count, a measure of early immunologic response, was defined as the latest CD4 measurement taken within the first six months after ART initiation. Latest CD4 count, a time-varying measure of immunologic response, was updated whenever a patient had a new CD4 count result. Finally, CD4 count-years, a time-varying measure of cumulative immunologic response, takes into account both the magnitude and duration of immunologic response using the trapezoidal rule to estimate the area under the curve across multiple CD4 count measurements. Specifically, the accumulation of CD4 count-years is calculated by multiplying the average of two consecutive CD4 counts by the time interval between the two counts and then summing the values across all intervals between counts. Similar methods have been used to calculate cumulative HIV viremia[19, 20]. As an example, a patient with a CD4 count of 300 for the first year after ART initiation, and a patient with a CD4 count of 200 for the first six months and a CD4 count of 400 for the second six months, would both have accumulated 300 CD4 count-years one year after ART initiation.

All immunologic measures were considered continuously and categorically to identify the most accurate parameterization with relation to NADC incidence. Because immunologic measures proximal to cancer diagnoses may be more likely to be affected by subclinical cancer, analyses were done with 6-month (and 12-month) exposure lags in which immunologic measures were used to predict NADC diagnoses that occurred more than 6 (and 12) months after the immunologic ART response measurement.

Statistical Analysis

At-risk time for NADC incidence started after the first six months of ART to avoid the inclusion of cancers that developed before ART initiation and to allow time for at least one CD4 count to be obtained after ART initiation. For analyses with 6-month and 12-month exposure lags, at-risk time started at 12 and 18 months, respectively, to allow a minimum of six months to assess immunologic measures. Patients remained in follow-up irrespective of ART changes or interruptions until the first of: NADC diagnosis, death, loss-to-follow-up (>12 months without a clinic visit), last date of cancer ascertainment for each CNICS site (range: May 31, 2010-Aug. 31, 2011), and administrative censoring 10 years after ART initiation.

Cox proportional hazards regression was used to estimate hazard ratios (HR) and 95% confidence intervals (95%CI) as measures of association and precision, respectively. Immunologic response associations were considered with incidence of all NADCs[21], NADCs known to be related to viral co-infections (HPV: anal, squamous cell oral cavity/pharynx, penis, vagina/vulva; EBV: Hodgkin lymphoma; HBV and HCV: liver cancer)[18,

22], and virus-unrelated NADCs. Multivariable Cox regression was used to adjust for time-fixed confounders measured at ART initiation, including CD4 count, age, prior antiretroviral use, calendar year, race, sex, transmission risk, and CNICS site, with inverse-probability weights used to further adjust for time-varying plasma HIV-1 RNA level.

Inverse-probability weights were applied to account for time-varying confounding introduced by the virologic response occurring before the immunologic response[23–25]. These weights were calculated using linear regression models to estimate the probability density of the observed CD4 counts for each patient with covariates for the HIV-1 RNA measurements from the prior two clinical visits. Application of these weights in the multivariable Cox regression models allows estimation of effects of immunologic response independent of the prior virologic response. In addition, inverse-probability-of-censoring weights were applied to account for differential censoring by prior HIV-1 RNA measurements, and inverse-frequency weights were applied to account for differences in the frequency of obtaining CD4 count tests[24–26]. For each observation, all calculated weights were multiplied together to create a single weight that was used in the regression models (mean total weight=1.02, SD=0.79). As six-month CD4 count was a time-fixed measure not subject to time-varying confounding, total weights for this measure did not incorporate inverse-probability weights to account for time-varying virologic response (mean=1.00, SD=0.17), but models were adjusted for the HIV RNA measure prior to the six-month CD4 count.

All immunologic measures were assessed separately as predictors in bivariable and weighted, multivariable regression models. Associations were also estimated among patients with a CD4 count at ART initiation <200 cells/mm^3 and ≥200 cells/mm^3 to assess effect measure modification. To determine which immunologic measure was the strongest independent predictor, Akaike's information criterions (AICs) were calculated for each multivariable regression model and compared to assess the relative model fit. The lowest AIC represents the model with the best fit to the data indicating the most predictive CD4 response measure.

Sensitivity analyses were conducted among patients without NADC diagnoses prior to six months of ART and among patients with no prior exposure to single or dual antiretroviral therapy. All statistical analyses were conducted using SAS version 9.2.

Results

Patient Characteristics

Of the 25,337 patients enrolled in CNICS at the time of this study, 11,485 initiated a first ART regimen at a CNICS site between 1996 and 2011 and had CD4 count and HIV RNA measures within 12 months prior to ART initiation. Among these patients, 9,389 were alive and had obtained ≥1 HIV RNA level and CD4 count at six months after ART initiation.

The 9,389 patients included were representative of the entire CNICS population: 20% were female, 43% white, and 41% black (Table 1). The median age at ART initiation was 38 years (IQR=32–45), and the median calendar year of ART initiation was 2004 (IQR=2000–

2007). Most patients initiated a PI-based (47%) or NNRTI-based (43%) ART regimen, while a minority initiated a regimen with both a PI and a NNRTI (4%), a triple-NRTI regimen (5%), or a regimen including an entry or integrase inhibitor (2%). At first combination ART initiation, 27% of patients had evidence of prior antiretroviral exposure, including single or dual antiretroviral therapy use. The median HIV-1 RNA level at ART initiation was 4.8 $\log_{10}$ copies/ml. Within six months of ART initiation 64% of patients were virologically suppressed (<400 copies/ml).

After six months of ART, patients were followed for a median of 3.3 years (IQR=1.5–6.5) with a total of 41,538 person-years of follow-up. Over the course of follow-up 692 deaths occurred and 3,156 patients were lost-to-follow-up. Follow-up was censored for 46% of patients at the last date of cancer ascertainment, and 1,104 patients were censored at 10 years post-ART initiation.

Immunologic response

The median CD4 count at ART initiation was 200 cells/mm^3 (IQR=60–332). After ART initiation, patients contributed a median of 9 CD4 measurements (IQR=4–17). The median CD4 count was 260 cells/mm^3 (IQR: 121–419) during the first six months of ART, 324 cells/mm^3 (IQR=182–504) in the second six months and 358 cells/mm^3 (IQR=213–539) in months 12–18 of ART. More than two years after ART initiation, median CD4 count values only increased slightly (Figure 1). Patients accumulated a median of 1925 cells*years/mm^3 (IQR=1239–2686) by the 54–60 month time interval after ART initiation equivalent to having an average CD4 count of 385 cells/mm^3 over five years (Figure 1). By ten years after ART initiation, the median CD4 count-years accumulated was 4572 cells*years/mm^3 (IQR=3144–6152) equivalent to having an average CD4 count of 457 cells/mm^3 over ten years.

Immunologic response and NADC incidence

In total, 164 NADCs were diagnosed at a median of 3.8 years after ART initiation (IQR=2.0–6.8) for a total incidence rate of 395 per 100,000 person-years. Sixty-five NADCs were categorized as virus-related with the most frequent being anal cancer (N=26). Ninety-nine NADCs were virus-unrelated with the most frequent being lung cancer (N=22) (Table 2).

Higher values for six-month CD4 count, latest CD4 count, and CD4 count-years were all associated with lower NADC incidence (Table 3). When examined by type of NADC, all immunologic measures were strongly, and inversely associated with virus-related NADCs, even after adjustment for CD4 count at ART initiation, prior HIV-1 RNA measures, age, and other demographic and clinical variables. In weighted multivariable regression a 100 cell/mm^3 increase in a patient's six-month CD4 count was associated with a 29% lower hazard of virus-related NADC incidence (95%CI=5%–47%) (Table 3). Similarly, a 100 cell/mm^3 increase in the latest CD4 count was associated with a 30% lower hazard of virus-related NADC incidence (95%CI=7%–48%). Finally, a 200 cells*years/mm^3 increase in CD4 count-years was associated with a 9% lower hazard of virus-related NADC incidence (95%CI=3%–16%). The CD4 count-years association with virus-related NADC incidence

appeared stronger among patients with a CD4 count at ART initiation <200 cells/mm^3 (Adjusted HR=0.89, 95%CI=0.82–0.98) compared to patients with a CD4 count ≥200 cells/mm^3 (Adjusted HR=0.94, 95%CI=0.81–1.08). When included in these models, CD4 count at ART initiation was inversely, but weakly associated with virus-related NADC incidence (adjusted HR in model with latest CD4=0.90, 95%CI=0.75–1.08).

All measures were assessed with 6-month and 12-month exposure lags. Latest CD4 count was less strongly associated with virus-related NADCs that occurred more than six months after the CD4 measurement (adjusted HR with 6-month exposure lag=0.85, 95%CI=0.75–0.95; Table 3) while other CD4 response measure associations did not change appreciably.

When AICs from separate models for each of the three immunologic response measures were compared, the AIC was lowest for the latest CD4 count model both in bivariable and multivariable analyses (AICs: latest CD4=1070.6, six-month CD4=1075.0, CD4 count-years=1076.8), indicating that this was the strongest predictor of virus-related NADC incidence. However, after 6-month and 12-month exposure lags were implemented AICs were lowest for the model using the six-month post-ART CD4 count (6-month lag AICs: latest CD4=975.8, six-month CD4=972.6, CD4 count-years=974.0), indicating that this measure was the strongest predictor of virus-related NADCs occurring at least six months after measurement.

When immunologic measures were categorized, associations indicated that virus-related NADC incidence decreased further with each increasing category of improved immunologic response. For example, when compared to the reference category of CD4 count-years <600 cells*years/mm^3, CD4 count-years between 600–1600 cells*years/mm^3 had a HR of 0.83 (95%CI=0.41, 1.65) and CD4 count-years >1600 cells*years/mm^3 had a HR of 0.30 (95%CI=0.10, 0.85) for virus-related NADCs (Figure 2). Similar findings were observed for latest CD4 count and six-month CD4 count categories.

No immunologic measures were associated with virus-unrelated cancer incidence in any analyses despite improved precision due to a larger number of cancer events (Table 3).

Similar associations were observed in sensitivity analyses in which only the 6876 antiretroviral naïve patients were included. For instance, among this subgroup a 100 cell/mm^3 increase in a patient's six-month CD4 count was associated with a 27% lower hazard of virus-related NADC incidence (95%CI: 11%–41%) in weighted, multivariable analyses. Results were also similar in analyses in which 382 patients were excluded with NADC diagnoses prior to six month post-ART initiation. Of these 382 patients excluded due to prior NADC diagnoses, 10 had another cancer diagnosis after six months of ART.

Discussion

In this study, a greater CD4 ART response was associated with lower NADC incidence, specifically for NADCs related to viral co-infections (HPV, EBV, HBV or HCV). This association was independent of CD4 count at ART initiation, HIV-1 RNA response, age, and other patient factors, and was consistently observed for measures of early, time-varying, and cumulative time-varying immunologic ART response. Inverse associations were

specific to virus-related NADCs. No associations were observed for virus-unrelated NADCs. As we did not censor patients with ART interruptions or switches, our measures of immunologic response are influenced by the clinical realities of ART failure or toxicity, consistency of ART drug supply, and patient adherence.

CD4 count-years were used as a novel measure to capture the degree and duration of immune response. This may be particularly relevant to virus-related NADCs as longer periods of immunosuppression may provide greater susceptibility to acquisition, reactivation, or persistence of oncogenic viruses[27–33]. Cumulative immunologic ART response was most protective among patients with a CD4 count <200 cells/mm^3 at ART initiation highlighting the importance of prompt initiation of effective ART as a cancer prevention strategy for severely immunosuppressed patients. However, in our analysis, CD4 count-years was not a stronger predictor of NADC incidence than latest CD4 count or six month CD4 count, indicating that this more complex measure may not be of clinical importance for NADCs.

Latest CD4 count was the strongest predictor of virus-related NADC incidence. This may reflect immunosuppression and greater oncogenic potential of viral co-infections facilitating the transition to cancer. Conversely, greater CD4 declines proximal to cancer diagnosis may be a marker of immune dysregulation caused by sub-clinical cancer. In particular, Hodgkin lymphoma is known to decrease T-cell populations in HIV-infected and HIV-uninfected populations[32, 34–36]. Regardless, declines in a patient's most recent CD4 count could be an important indicator to identify HIV-infected individuals for intensified cancer screening strategies.

While subclinical cancer may alter the latest CD4 count before diagnosis, it is less likely that subclinical cancer is present for CD4 measurements taken well before cancer diagnosis. When cancer diagnoses were excluded that occurred less than 6 and 12 months after CD4 count measurement, all immunologic measures remained associated, but six-month post-ART CD4 count became the strongest predictor of virus-related NADC incidence. The strong association of early immunologic response as captured by the six-month post-ART CD4 count may indicate that the initial early recovery from severe immunosuppression is the most important component of the immunologic ART response for reducing virus-related NADC risk. Potent initial ART regimens and early interventions to maximize ART adherence may be important methods of cancer prevention in the HIV population.

Several prior studies have found similar associations with cancer incidence. Our results parallel those previously found in the ATHENA cohort, in which cumulative exposure to CD4 counts <200 cells/mm^3 and latest CD4 count were both associated with infection-related NADC risk[37]. Latest CD4 count has been shown to be associated with virus-related NADC incidence in a number of studies including both ART-treated and ART-naïve populations, and these associations have been attributed to the increased risk of oncogenic infection[7, 10, 37]. However, as mentioned previously, separating immunologic effects of subclinical malignancy from effects of CD4 lymphopenia resulting from HIV may be difficult.

The interaction between inadequate immune recovery and HPV-associated dysplasia and malignancy may be of particular interest. Low CD4 counts increase the risk of developing cervical cytologic abnormalities[30, 31]. However, effective ART has not been convincingly associated with decreased risk of cervical[38] or anal dysplasia[39]. Multiple factors including competing risks (i.e. prolonged survival on ART allowing greater opportunities for development of dysplasia and cancer) and immunologic experience before and after ART initiation may need to be accounted for when examining this question. Further work should be conducted examining the relationships between immunologic measures, specific oncogenic viruses, and precancerous abnormalities.

Our findings are generalizable to other HIV-infected populations in the U.S. given that CNICS is a large multi-site clinical cohort from diverse geographic areas. Another strength was our use of comprehensive clinical data on CD4 count and HIV-1 RNA measurements with recently verified cancer diagnoses[18, 40]. The use of advanced analytic methods allowed us to accurately estimate cumulative and time-updated immunologic measures and adequately account for confounding due to the close correlation with virologic measures. This study is the first to our knowledge to estimate associations of cumulative immunologic response with NADC incidence and compare them to other immunologic measures in a U.S. HIV-infected population.

A number of limitations should be considered. With the exception of hepatitis B and C, we could not confirm the presence of oncogenic viral infection at the time of virus-related NADC diagnosis, and for certain cancers in this category, tumors may not have had oncogenic viruses present in tissue (e.g. oral pharyngeal squamous cell carcinoma associations with HPV[41]). If a poorer immunologic response increases the risk of viral oncogenesis, then associations would likely be stronger for confirmed virus-associated cancers. Second, we also had limited information on behavioral cancer risk factors, such as tobacco and alcohol use. However, in a previous CNICS sub-study tobacco and alcohol use were not significantly associated with ART adherence, and thus may be unlikely to greatly confound immunologic response associations with NADC incidence[42]. Finally, information was only available while patients attended a CNICS site. We could not fully capture a patient's immunologic experience prior to ART, though we adjusted for CD4 count at ART initiation. Additionally, one-third of patients were lost-to-follow-up and may have experienced different cancer incidence or immune recovery patterns than those observed.

In summary, our findings demonstrate that CD4 count response after ART initiation influences risk for virus-related NADCs. Associations persisted after adjusting for CD4 at ART initiation, indicating that, beyond the effects of immune status at ART initiation, changes in immune status after ART initiation impact virus-related NADC risk with the influence of early CD4 response being most notable. This highlights the importance of adherence to effective, durable ART to reduce risk of virus-associated cancers in a population at increased risk for repeated episodes of infection with oncogenic viruses. Following ART initiation, if a patient's latest CD4 count is low this may be an indication to initiate more frequent screening for virus-related NADCs, such as the anal Pap smear for

detection of anal dysplasia. This population may also benefit from new screening modalities not currently used in the general U.S. population.

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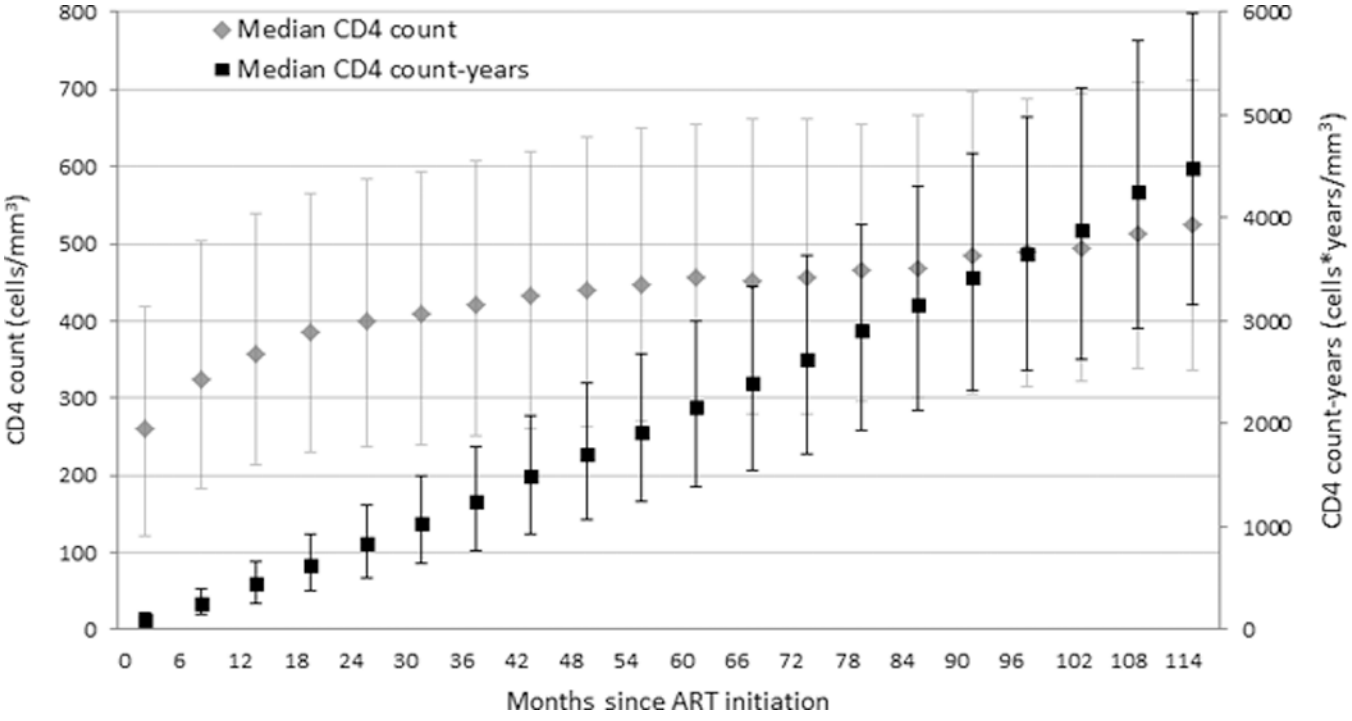

Figure 1.

Distribution of latest CD4 counts and CD4 count-years by six month time intervals over the first ten years after combination antiretroviral therapy (ART) initiation. Symbol=median value, Lines=interquartile range.

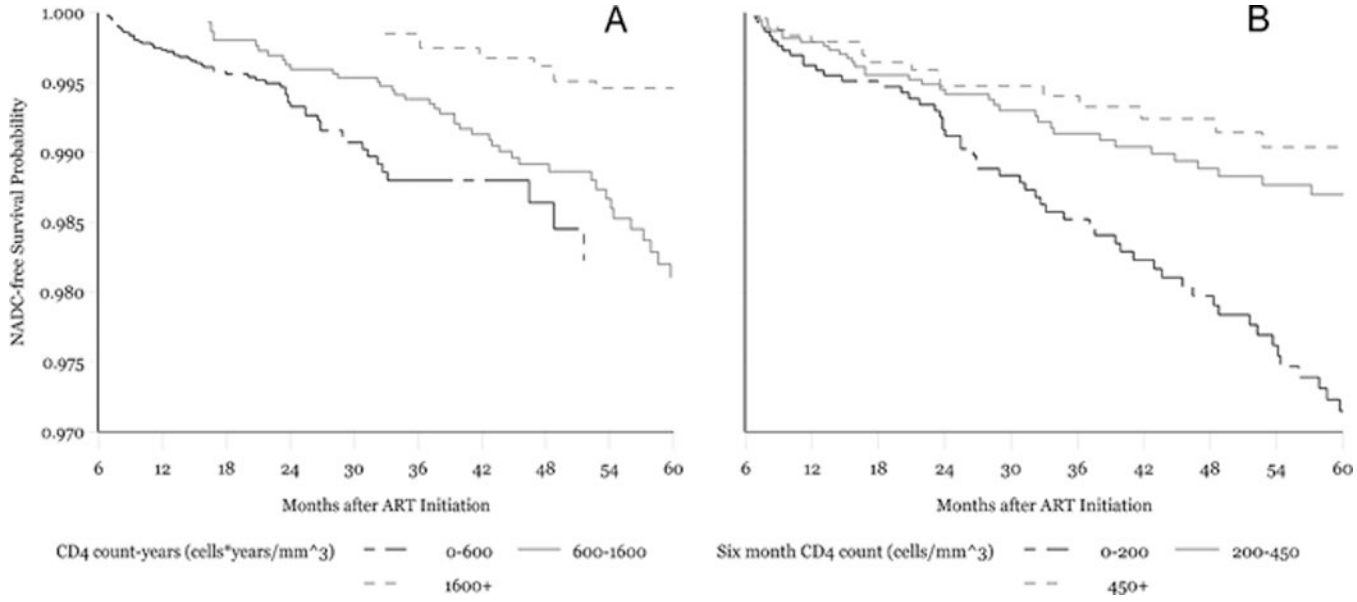

Figure 2.

Time to first virus-related NADC diagnosis from six months to five years after antiretroviral therapy (ART) initiation by CD4 count-years category (A) and six-month CD4 count category (B).

Survival probabilities were calculated using the Kaplan-Meier method, with death, loss-to-follow-up, and end of cancer ascertainment as censoring events. For CD4 count-years, no patients had accumulated more than 600 CD4 count-years by six months post-ART. At the time at which patients accumulated enough CD4 count-years to qualify for a higher CD4 count-years category they were censored from the lower category and included in the higher CD4 count-year category risk set as late entries. The first patients accumulated more than 600 CD4 count-years at 16 months post-ART (start of solid gray line), and the first patients accumulated more than 1000 CD4 count-years at 33 months (start of dotted gray line).

Table 1

Demographic and clinical characteristics of 9389 patients at combination antiretroviral therapy (ART) initiation in the CFAR Network of Integrated Clinical Systems, 1996–2011

Characteristic	N (%)
Total	9389
Female Sex	1900 (20.2)
Age (years)[a]	38 (32–45)
Race	
White	4032 (43.2)
Black	3814 (40.9)
Hispanic	1065 (11.4)
Other/Unknown	478 (5.1)
Injection drug user	1688 (18.0)
Men who have sex with men	5192 (55.3)
Antiretroviral exposure prior to first ART	2513 (26.8)
ART initiation year[a]	2004 (2000–2007)
ART regimen type	
PI	4415 (47.0)
NNRTI	4025 (42.9)
3+ NRTI	458 (4.9)
NNRTI+PI	351 (3.7)
Other[b]	140 (1.5)
HBV infection prior to ART initiation	**1894 (20.1)**
HCV infection prior to ART initiation	**1562 (16.5)**
HIV RNA at ART initiation (log_{10}copies/mL)[a]	4.8 (4.3–5.4)
HIV RNA suppression within 6 months of ART initiation[c]	**6009 (64.0)**
CD4 count at ART initiation (cells/mm^3)[a]	200 (60–332)

[a] Median (IQR) given instead of N (%)

[b] includes regimens with an integrase inhibitor, fusion inhibitor, or entry inhibitor

[c] HIV RNA suppression defined as achieving <400 copies/mL

ART=combination antiretroviral therapy, PI=protease inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor, NRTI=nucleoside reverse transcriptase inhibitor, HBV=hepatitis B virus, HCV=hepatitis C virus

Table 2

Non-AIDS-defining cancer diagnoses occurring more than six months after combination antiretroviral therapy (ART) initiation in the Center for AIDS Research Network of Integrated Clinical Systems, 1996–2011

Type of NADC	Number of diagnoses	Median time from ART initiation to cancer diagnosis in years (interquartile range)
Total	164	3.8 (2.0–6.8)
Virus-related	65	3.2 (1.9–5.8)
Squamous cell anal	25	3.8 (2.2–6.3)
Hodgkin lymphoma	16	2.6 (1.9–3.9)
Liver	13	3.7 (1.6–7.2)
Squamous cell oral cavity/pharynx	8	3.3 (1.3–6.3)
Other[a]	3	4.0 (2.5–7.7)
Virus-unrelated	99	3.6 (1.4–6.7)
Lung	21	3.6 (1.0–7.0)
Prostate	17	4.3 (0.8–6.0)
Breast	10	5.2 (3.5–6.5)
Melanoma	9	1.9 (1.4–4.0)
Colorectal	7	2.7 (2.1–6.3)
Other[b]	35	3.0 (1.7–6.7)

[a] Other virus-related cancers include penis, vaginal, and vulva.

[b] Other virus-unrelated cancers include bladder, esophagus, kidney, larynx, leukemia, multiple myeloma, ovary, pancreas, peritoneum, small intestine, soft tissue, testicular, thyroid uterus, or non-squamous cell oral cavity/pharynx

As follow-up started at 6 months after ART initiation, all included cancer diagnoses occurred at least 0.5 years after ART initiation.

ART=combination antiretroviral therapy, NADC=non-AIDS-defining cancer

Table 3

Associations of measures of immunologic response to combination antiretroviral therapy (ART) with non-AIDS-defining cancer incidence

Measures of immunologic ART response	Bivariable[a]	Weighted, Multivariable[b]		
	No lag	No lag	6-month lag	12-month lag
	Hazard Ratio (95% CI)			
All NADCs		**(N=164)**	**(N=140)**	**(N=125)**
Six month CD4 (per 100 cells/mm^3)	0.90 (0.83, 0.97)	0.83 (0.72, 0.96)	0.85 (0.73, 0.98)	0.82 (0.70, 0.97)
Latest CD4 (per 100 cells/mm^3)	0.87 (0.81, 0.93)	0.90 (0.76, 1.07)	0.90 (0.83, 0.97)	0.92 (0.84, 1.02)
CD4 count-years (per 200 cells*years/mm^3)	0.97 (0.94, 1.00)	0.99 (0.95, 1.04)	0.97 (0.92, 1.01)	0.97 (0.92, 1.02)
Virus-related NADCs[c]		**(N=65)**	**(N=59)**	**(N=52)**
Six month CD4 (per 100 cells/mm^3)	0.75 (0.65, 0.87)	0.71 (0.53, 0.95)	0.69 (0.51, 0.93)	0.69 (0.50, 0.96)
Latest CD4 (per 100 cells/mm^3)	0.78 (0.70, 0.87)	0.70 (0.55, 0.89)	0.85 (0.75, 0.95)	0.85 (0.74, 0.96)
CD4 count-years (per 200 cells*years/mm^3)	0.89 (0.84, 0.95)	0.92 (0.85, 0.99)	0.87 (0.79, 0.96)	0.89 (0.80, 0.98)
Virus-unrelated NADCs[d]		**(N=99)**	**(N=81)**	**(N=73)**
Six month CD4 (per 100 cells/mm^3)	0.98 (0.89, 1.07)	0.90 (0.77, 1.04)	0.94 (0.81, 1.09)	0.91 (0.77, 1.06)
Latest CD4 (per 100 cells/mm^3)	0.93 (0.85, 1.00)	1.00 (0.86, 1.16)	0.93 (0.83, 1.03)	0.98 (0.85, 1.12)
CD4 count-years (per 200 cells*years/mm^3)	1.01 (0.97, 1.04)	1.02 (0.98, 1.06)	1.00 (0.96, 1.05)	1.00 (0.95, 1.06)

Each association with an immunologic ART response measure was estimated using a separate regression model.

[a] Bivariable regression models only included the immunologic ART response measure, without weighting or adjustment for other covariates.

[b] For latest CD4 count and CD4 count-years, weights were applied to account for confounding from HIV RNA measurements from the prior two visits, differential censoring by prior HIV RNA measurements, and differential frequency of CD4 count measurements. The mean total weight was 1.02 (SD=0.79). For six-month CD4 count weights were applied to account for differential censoring and differential frequency of CD4 count measurements (mean=1.00, SD=0.17). Multivariable analyses additionally adjusted for CD4 at ART initiation, HIV RNA at ART initiation, prior antiretroviral use, age at ART initiation, year of ART initiation, sex/MSM, IDU, race, CNICS study site.

[c] Virus-related NADCs included squamous cell anal, Hodgkin lymphoma, liver, squamous cell oral cavity/pharynx, penis, vagina, and vulva cancer.

[d] Virus-unrelated NADCs included lung, prostate, breast, colorectal, melanoma, kidney, bladder, esophagus, kidney, larynx, leukemia, multiple myeloma, ovary, pancreas, peritoneum, small intestine, soft tissue, testicular, thyroid uterus, or non-squamous cell oral cavity/pharynx

ART=combination antiretroviral therapy, NADC=non-AIDS-defining cancer, CI=confidence interval