Incidence of Non-AIDS-Defining Cancer in Antiretroviral Treatment-Naïve Subjects after Antiretroviral Treatment Initiation: An ACTG Longitudinal Linked Randomized Trials Analysis

Supriya Krishnan^a Jeffrey T. Schouten^b Denise L. Jacobson^a
Constance A. Benson^c Ann C. Collier^d Susan L. Koletar^e Jorge Santana^f
Fred R. Sattler^g Ronald Mitsuyasu^h for the ACTG-ALLRT Protocol Team

^aCenter for Biostatistics in AIDS Research, Harvard School of Public Health, Boston, Mass., ^bDepartment of Surgery, University of Washington School of Medicine, Seattle, Wash., ^cDivision of Infectious Diseases, University of California, San Diego, Calif., ^dUniversity of Washington School of Medicine and Harborview Medical Center, Seattle, Wash., ^eDivision of Infectious Diseases, Ohio State University, Columbus, Ohio, ^fUniversity of Puerto Rico, School of Medicine, Puerto Rico, P.R., ^gUniversity of Southern California, and ^hCenter for Clinical AIDS Research and Education, University of California, Los Angeles, Calif., USA

Key Words

HIV • Cancer, non-AIDS-defining • Antiretroviral treatment • CD4 T cell counts

Abstract

Background: Prospective data on factors associated with the non-AIDS-defining cancer (NADC) incidence in HIV-infected individuals are limited. **Methods:** We examined the NADC incidence in 3,158 antiretroviral treatment (ART)-naïve subjects after ART initiation in AIDS Clinical Trials Group trials; extended follow-up was available for 2,122 subjects. Poisson regression was used to examine the associations between covariates and incident NADC. **Results:** At ART initiation, subjects (median age 37 years) were 40% non-Hispanic whites, and 82% were male; 23% had CD4+ T cell count ≤ 50 cells/mm³ and 25% had CD4 >350 cells/mm³. Median follow-up was 3.8 years. Among 64 incident NADCs, the most common were 8 anal cancers, 8 basal cell carcinomas, 8 Hodgkin's disease, and 6 lung cancers. In univariate models, age, smoking and recent (time-updated) CD4 were associated with incident NADC. There was no association between ini-

tial ART drug class (protease inhibitor, nucleoside reverse transcriptase inhibitor and nonnucleoside reverse transcriptase inhibitor) and NADC. After adjusting for age, race and sex: smoking [relative risk = 2.12 (95% CI = 1.1–4.08)] and recent CD4 (≤ 50 cells/mm³: 3.58, 1.22–10.45; 51–200 cells/mm³: 2.54, 1.30–5.0; 201–350 cells/mm³: 2.37, 1.32–4.26 vs. >350 cells/mm³) were associated with NADC. **Conclusion:** Smoking and lower recent CD4 levels, but not initial ART drug class, were associated with NADC. Strategies for maintaining higher CD4 cell counts and successful smoking cessation may reduce the NADC incidence in the HIV-infected population.

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Introduction

Historically, AIDS-defining cancers (especially Kaposi's sarcoma and non-Hodgkin's lymphoma) accounted for a substantial proportion of the morbidity and mortality in HIV-infected subjects [1]. Since the introduction of potent antiretroviral therapy (ART) in 1996,

the rates of these malignancies have decreased. However, there has been an increase in the incidence of non-AIDS-defining cancers (NADCs) in the HIV-infected population and NADCs now account for the majority of cancers seen in persons living with HIV [2–5] and an increasing proportion of deaths in HIV-infected persons [6]. A recent meta-analysis showed that HIV-infected persons have twice the risk for NADCs than the general population [7].

It is important to characterize the factors that are associated with NADC. Knowledge of these factors will aid in designing strategies for cancer screening, prevention and treatment in HIV-infected patients. A recent study suggested that use of potent ART, specifically nonnucleoside reverse transcriptase inhibitors (NNRTIs), may be associated with increased cancer risk [8]. Nadir and/or recent CD4+ T cell levels have been associated with the risk of NADC, although results have been varied [9–11]. A high prevalence of smoking and other lifestyle factors in the HIV-infected population have also been implicated [1]; however, there is a limited body of evidence to support these observations.

Our objective was to examine the incidence of NADC and factors associated with NADC in HIV-infected, ART-naïve subjects who initiated ART regimens in AIDS Clinical Trials Group (ACTG) randomized trials, many of whom were followed prospectively in the ACTG Longitudinal Linked Randomized Trials (ALLRT) Protocol (A5001).

Methods

ALLRT is a prospective cohort of HIV-infected subjects (age ≥ 13) who participated in ACTG ‘parent’ clinical trials with randomized ART or treatment regimens [12]. The ALLRT cohort includes subjects who were ART-naïve or ART-experienced at the time of entry into their parent trial. All ALLRT subjects provide written informed consent, and ACTG sites that enroll patients to ALLRT are approved by their designated institutional review board. Enrollment in ALLRT began in 2000 and follow-up is ongoing.

The present analysis focused on the ALLRT parent trials that enrolled ART-naïve subjects from 1998 to 2004 [13–20]; all regimens in these studies were multidrug regimens that included an NNRTI and/or a protease inhibitor (PI). A total of 3,208 treatment-naïve subjects were enrolled in these parent trials. After excluding 16 subjects with a diagnosis of an AIDS-defining malignancy (10 Kaposi sarcomas, 3 lymphomas and 3 cervical cancers; median age of subjects = 40 years) before study entry, 3,192 subjects were included in the analysis cohort. Of these 3,192, 2,148 (67%) were enrolled in ALLRT, and continued to be followed after completion of the parent trial.

The ‘baseline’ visit for all subjects was the parent trial entry visit (prior to start of study ART). When subjects were enrolled in the parent trial, visits were scheduled according to the parent trial protocol. When the parent study ended, data collection continued every 16 weeks according to the ALLRT protocol. Data were recorded by the study site staff using standard ACTG forms.

Outcome Measurement

For this analysis, the outcome was the diagnosis of a non-AIDS-defining malignancy (this category includes all cancers except Kaposi’s sarcoma, B cell non-Hodgkin’s lymphoma, primary central nervous system lymphoma and cervical cancer) [21]. The cancer diagnoses were collected as part of the parent study and the ALLRT protocols using ACTG diagnosis appendices. At each clinic visit, site personnel recorded all newly diagnosed malignancies (except squamous cell carcinoma of the skin) on standard ACTG case report forms. All NADCs were reviewed by two of the study investigators (J.S. and R.M.). The review process included all supporting data from the case report forms for each malignancy. Additional documentation was requested from the study sites, if required to confirm each diagnosis. Seven malignancies could not be confirmed by the review [either in situ malignancy ($n = 3$) or insufficient information to confirm the cancer diagnosis ($n = 4$); the follow-up time for these subjects was censored at the reported date of diagnosis. Finally, the malignancies were classified as prevalent (preentry) and incident (postentry) based on the date of diagnosis. For this analysis, we excluded subjects with prevalent malignancies at baseline ($n = 34$). The final dataset included 64 subjects with incident NADC among 3,158 subjects.

Analysis

Person-years at risk were calculated from the parent study entry until first cancer diagnosis, death, end of follow-up or June 2008 (whichever came first). There were 12 subjects who developed AIDS-defining cancer after parent study entry; the follow-up for these subjects was censored at the date of AIDS-defining cancer diagnosis. AIDS-defining cancers and other AIDS-defining events in the ALLRT protocol are described in the paper by Smurzynski et al. [22]. The incidence rate of NADC was calculated as the number of incident cases divided by the total person-years at risk. Baseline covariates examined included age, race, sex, nadir (pretreatment) CD4+ T cell count, HIV-1 RNA level, ART regimen at randomization and cigarette smoking status. Smoking status was not collected in the parent trials, and was available only for the subjects enrolled in ALLRT. Subjects were classified as ‘ever-smokers’ or ‘never-smokers’ based on the first evaluation of smoking status in ALLRT; smoking status was classified as missing for those who did not enroll in ALLRT. ART regimen at randomization was classified by the major class of antiretroviral drugs: (1) PI-containing regimen versus regimen without PI, (2) nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen versus regimen without NRTI, and (3) NNRTI-containing regimen versus regimen without NNRTI.

Each subject’s follow-up time from baseline was divided into 16-week intervals. For each interval, the CD4+ T cell count from the previous 16-week interval was used to evaluate the association between ‘recent CD4+ T cell count’ and NADC (for example, for follow-up from week 192 to 208, CD4+ T cell levels for week 192 were used). The ‘last value carried forward’ method was used for

Table 1. Subject characteristics

Characteristic		Total	Incident NADC	
			no	yes
Total, n		3,158	3,094	64
Age at entry, years	Mean (SD)	38 (9)	37 (9)	45 (11)
	Median (Q1–Q3)	37 (31–43)	37 (31–43)	43 (38–53)
Race	White non-Hispanic	1,262 (40)	1,227 (40)	35 (55)
	Black non-Hispanic	1,176 (37)	1,156 (37)	20 (31)
	Hispanic	641 (20)	632 (20)	9 (14)
	Asian/Pacific Islander	55 (2)	55 (2)	0
	Native American/Alaskan	16 (1)	16 (1)	0
	Unknown	8 (0)	8 (0)	0
Sex	Male	2,575 (82)	2,521 (81)	54 (84)
	Female	583 (18)	573 (19)	10 (16)
Body mass index at entry	<25	1,706 (54)	1,665 (54)	41 (64)
	25–29	930 (29)	917 (30)	13 (20)
	≥30	434 (14)	427 (14)	7 (11)
	Missing	88 (3)	85 (3)	3 (5)
Smoking status at entry ¹	Ever-smoker	1,303 (41)	1,260 (41)	41 (64)
	Missing smoking status	1,038 (33)	1,027 (33)	11 (17)
	Never-smoker	817 (26)	807 (26)	12 (19)
Hepatitis C status at entry ¹	Ever positive	217 (7)	208 (7)	9 (14)
	Never positive	1,742 (55)	1,700 (55)	42 (66)
	Missing	1,197 (38)	1,184 (38)	13 (20)
Hepatitis B status at entry ¹	Ever positive	787 (25)	770 (25)	17 (26)
	Never positive	1,175 (37)	1,142 (37)	33 (52)
	Missing	1,196 (38)	1,182 (38)	14 (22)
CD4 level at entry	Mean (SD)	236 (197)	236 (198)	220 (179)
	Median (Q1–Q3)	207 (62–352)	207 (62–353)	219 (48–324)
	≤50 cells/mm ³	717 (23)	701 (23)	16 (25)
	51–200 cells/mm ³	825 (26)	810 (26)	15 (23)
	201–350 cells/mm ³	812 (26)	790 (26)	22 (34)
	>350 cells/mm ³	795 (25)	789 (25)	11 (17)
	Missing	9 (0)	9 (0)	0
HIV RNA at entry	>100,000 copies/ml	1,478 (47)	1,441 (47)	37 (58)
	10,000–100,000 copies/ml	1,362 (43)	1,339 (43)	23 (36)
	≤10,000 copies/ml	312 (10)	308 (10)	4 (6)
	Missing	6 (0)	6 (0)	0
Initial ART regimen	NRTI only	370 (12)	360 (12)	10 (16)
	PI + NRTI	784 (25)	766 (25)	18 (28)
	PI + NNRTI	261 (8)	257 (8)	4 (6)
	NRTI + NNRTI	1,285 (41)	1,263 (41)	22 (34)
	PI + NRTI + NNRTI	458 (14)	448 (14)	10 (16)

Values are number (%) unless otherwise specified.

¹ Smoking status and hepatitis B and C status only available for those enrolled in ALLRT.

Table 2. Types of incident NADCs (n = 64)

Type of cancer	Frequency
Anal cancer	8
Basal cell carcinoma	8
Hodgkin's disease	8
Lung cancer	6
Carcinoma of unknown primary site	6
Breast cancer	4
Prostate cancer	3
Bowen's disease	2
Gastric cancer	2
Hepatocellular carcinoma	2
Testicular cancer	2
Tonsillar cancer	2
Other cancers ¹	11

¹ Other cancers: bladder cancer (n = 1), bone cancer (n = 1), leukemia (n = 1), laryngeal cancer (n = 1), liver cancer (n = 1), lip/oral cancer (n = 1), melanoma (n = 1), rectal cancer (n = 1), thyroid cancer (n = 1), oropharynx carcinoma (n = 1), and T cell lymphoma (n = 1).

missing CD4+ T cell values. Similarly, the association between 'recent' HIV-1 RNA and NADC was also examined. Poisson regression (using generalized estimating equations with robust standard errors) was used to examine the univariate and multivariate associations between covariates and incident NADC. Age, race and sex were included in the multivariate model, regardless of statistical significance. For all other variables, only those with a p value <0.05 were included in the multivariate model. All analyses were conducted using SAS (version 9).

Results

A total of 3,158 HIV-infected subjects who were ART-naïve at parent trial entry were included in this analysis. The overall median follow-up time was 3.8 years; 2,122 subjects were enrolled in the ALLRT protocol and were followed after the parent trial ended. The median follow-up was 2.3 years for those who did not enroll in ALLRT, and 5.2 years for those who enrolled in ALLRT. The median age at baseline for the entire cohort was 37 years (table 1), and 82% were male. Overall, 40% were white, non-Hispanic, 37% were black, non-Hispanic and 20% were Hispanic. At baseline, the median nadir CD4+ T cell count was 207 cells/mm³.

After baseline (parent trial entry), there were 64 subjects with incident NADC. The median follow-up was 2.1 years for the cases and 3.8 years for the noncases. The median age was 43 years for the cases and 37 years for the

noncases (table 1). At baseline, 67% of the cases and 41% of the noncases reported cigarette smoking. The median nadir CD4+ T cell count at entry was 219 and 207 cells/mm³ for the cases and noncases, respectively.

The unadjusted incidence rate for NADC in this cohort was 4.05 cases/1,000 person-years (64 cases and 14,797 person-years). Among the incident cancers, the most common types were 8 anal cancers, 8 basal cell carcinomas, 8 Hodgkin's lymphomas, and 6 lung cancers (table 2). All 8 basal cell carcinomas were among whites. Seven of the 8 Hodgkin's lymphomas were in males and all 4 breast cancers were in females.

In univariate analyses (table 3), increasing age was associated with a higher risk of NADC. Compared to other races, the white race had a higher relative risk (RR = 1.65, 95% CI = 1.01–2.70). All basal cell carcinomas occurred among whites; when we excluded the basal cell carcinomas from the analysis, race was moderately associated with NADC, but the association was no longer statistically significant (p = 0.3, results not shown).

Compared to nonsmokers, smokers had a higher RR (RR = 2.56, 95% CI = 1.34–4.86, p = 0.004). Relative to a nadir CD4+ T cell count >350 cells/mm³, the RR for nadir CD4+ T cell count of 201–350 cells/mm³ was 2.11 (95% CI = 1.02–4.34); the associations for other CD4+ T cell levels were not significant.

Compared to baseline HIV-1 RNA viral load <10,000 copies/ml, those with a viral load >100,000 copies/ml had an RR of 1.93 (0.69, 5.44), but the association was not statistically significant. There was no association between randomized initial ART regimen and NADC using the following comparisons: (1) PI-containing regimen versus regimen without PI; (2) NRTI-containing regimen versus regimen without NRTI, and (3) NNRTI-containing regimen versus regimen without NNRTI (table 3).

We also examined the association between recent (time-updated every 16 weeks) CD4+ T cell counts and NADC. Recent CD4 levels were associated with NADC; relative to recent CD4 levels >350 cells/mm³, the RR for CD4 levels ≤50 cells/mm³ was 3.34 (1.18–9.53).

Age, sex, race, smoking status and recent CD4+ T cell levels were included in the final multivariable model (table 4). Recent CD4 levels were associated with NADC after adjustment for other covariates. Smokers also had a higher RR for development of NADC compared to never-smokers (p = 0.02) in the multivariable model. The higher risk for smokers was present even after excluding the lung cancer cases from the analysis (RR = 1.89, 0.97–3.66, p = 0.06).

Table 3. Univariable associations for NADCs

		Number of cases	Person-years	RR (95% CI)	p value
Age at entry per 10-year increase		–	–	1.92 (1.55, 2.39)	<0.0001
Race ¹	White	35	6,269	1.65 (1.01, 2.70)	0.04
	Nonwhite	29	8,528	1.0	
Sex	Male	54	11,991	1.26 (0.64, 2.47)	0.5
	Female	10	2,806	1.0	
Body mass index at entry	<25	41	8,010	1.44 (0.65, 3.21)	0.4
	25–29	13	4,624	0.79 (0.32, 1.99)	0.6
	≥30	10	2,163	1.0	
Smoking status at entry ²	Ever-smoker	41	7,123	2.56 (1.34, 4.86)	0.004
	Missing smoking status	11	2,320	1.94 (0.86, 4.40)	0.1
	Never-smoker	12	5,354	1.0	
Hepatitis C status at entry ²	Ever positive	9	1,224	1.89 (0.92, 3.87)	0.08
	Missing status	13	2,747	1.22 (0.65, 2.27)	0.5
	Never positive	42	10,826	1.0	
CD4 at entry	≤50 cells/mm ³	16	3,443	1.64 (0.77, 3.52)	0.2
	51–200 cells/mm ³	15	3,818	1.38 (0.63, 3.00)	0.4
	201–350 cells/mm ³	22	3,662	2.11 (1.02, 4.34)	0.04
	>350	11	3,874	1.0	
HIV RNA at entry	>100,000 copies/ml	37	7,169	1.93 (0.69, 5.44)	0.2
	10–100,000 copies/ml	23	6,132	1.39 (0.48, 4.05)	0.5
	<10,000 copies/ml	4	1,495	1.0	
PI-containing regimen at parent entry	Yes	32	7,193	1.06 (0.65, 1.73)	0.8
	No	32	7,604	1.0	
NRTI-containing regimen at parent entry	Yes	60	13,791	1.11 (0.40, 3.07)	0.8
	No	4	1,006	1.0	
NNRTI-containing regimen at parent entry	Yes	36	9,358	0.75 (0.45, 1.22)	0.25
	No	28	5,439	1.0	
Recent (time-updated) CD4	≤50 cells/mm ³	4	445	3.34 (1.18, 9.53)	0.02
	51–200 cells/mm ³	13	1,738	2.76 (1.42, 5.35)	0.003
	201–350 cells/mm ³	21	3,005	2.58 (1.45, 4.60)	0.001
	>350 cells/mm ³	26	9,609	1.0	

¹ Due to small numbers of cases, race was classified as white and nonwhite (black non-Hispanic, Hispanic, Asian/Pacific Islander, Native American/Alaskan and other).

² Smoking and hepatitis C status available only for ALLRT; for those with missing status, an indicator variable was included in the model.

Discussion

In this large prospective cohort of HIV-infected subjects (median follow-up = 3.8 years), the unadjusted incidence rate for NADCs was 4.05 cases/1,000 person-years. The most common malignancies were anal cancer, basal cell carcinoma, Hodgkin's lymphoma, and lung cancer. Although other HIV-infected cohort studies have reported similar observations [4, 8, 23] and suggest that the incidence of NADC is on the rise in the potent ART era [4, 8], the longitudinal and robust nature of the ACTG data-

base provided a unique opportunity to examine predisposing factors for cancer. Indeed inclusion of ART-naïve patients starting ART provided important information on factors associated with an increased risk of NADCs among HIV-infected patients. Our results indicated that older age, white race, low recent CD4+ T cell count, and a history of cigarette smoking were associated with an increased risk of NADC.

Due to the availability of potent ART therapy, HIV-infected patients are now living longer and are experiencing several non-AIDS-related conditions that are associ-

Table 4. Multivariate analysis for RR and 95% CI for NADC

	RR (95% CI)	p value
Age (10-year increase)	1.84 (1.45, 2.34)	<0.0001
Sex		
Male	1.08 (0.55, 2.12)	0.8
Female	1.0	
Race ¹		
White	1.58 (0.94, 2.66)	0.08
Nonwhite	1.0	
Recent (time-updated) CD4 levels ²		
≤50 cells/mm ³	3.58 (1.22, 10.45)	0.02
51–200 cells/mm ³	2.54 (1.30, 5.00)	0.01
201–350 cells/mm ³	2.37 (1.32, 4.26)	0.004
>350 cells/mm ³	1.0	
Smoking status		
Ever-smoker	2.12 (1.10, 4.08)	0.02
Missing smoking status ³	1.76 (0.76, 4.09)	0.2
Never-smoker	1.0	

¹ Due to small numbers of cases, race was classified as white and nonwhite (black non-Hispanic, Hispanic, Asian/Pacific Islander, Native American/Alaskan and other).

² p value for trend = 0.0004.

³ Smoking available only for those who enrolled in ALLRT; for those with missing smoking status, an indicator variable was included in the model.

ated with aging. Older age was associated with an increased risk of NADC in our cohort. Our finding that the RR for the white race was higher than for other races is consistent with previous reports [4, 24], but could be related to the high number of basal cell carcinomas in whites (since the association was no longer significant when basal cell carcinomas were excluded from the analysis).

Our results indicated that a low recent CD4+ T cell count is associated with an increased risk of NADC. Other studies have also noted that the risk of NADCs may be related to CD4 counts [8, 11, 25–27]. In the FIRST study, recent CD4 counts were associated with the risk of non-AIDS diseases, but sample size limited the estimation of the risk for individual types of non-AIDS diseases [25]. A recent report from the Veterans Aging Cohort Study found that median CD4 counts at the first study visit were lower for HIV-infected patients with cancer than those without cancer [26]; our study had the advantage of being able to examine the association between time-updated CD4 levels and NADC in a younger population that was antiretroviral drug-naïve at study entry. Our results indicate that relative to a CD4 >350 cells/mm³, the risk for

NADC is higher even for a CD4+ cell count of 201–350 cells/mm³; this risk continues to rise for lower levels of CD4, and the risk for a CD4 count of ≤50 cells/mm³ is 3.58 (1.22, 10.45) relative to CD4 of >350 cells/mm³ (p value for trend = 0.0004). An apparent and plausible explanation for the association between lower CD4 levels and NADC is that cancer immune surveillance may be impaired in people with lower CD4 cells [28].

HIV-infected patients have a high prevalence of lifestyle behaviors such as smoking and exposure to other oncogenic viruses such as human papilloma virus and hepatitis viruses (HBV and HCV) that are known risk factors for cancer [29]. Our results show an association between cigarette smoking and increased risk of cancer in HIV-infected patients, a factor not evaluated in other recent studies [8, 11, 27]. The association was independent of age, race, sex and CD4 levels, and was present even after the lung cancers were excluded from the analysis. Smoking has previously been reported as a risk factor for several nonlung cancers, for example anal cancer both in HIV-infected [30] and general populations [31, 32] and Hodgkin's lymphoma [33]. Although we were not able to assess smoking for each of the nonlung cancers, we did find an elevated risk when evaluating all nonlung cancers together. This suggests that behavioral factors such as smoking may be an important target for cancer prevention in HIV-infected subjects.

A recent study suggested that the NNRTI drug class use may be associated with an increased risk of NADC [8] and PIs are actively being evaluated as cancer therapeutics [34]. Others have speculated that nucleoside analogues may pose a slight oncogenic risk [35]. We did not find an association between initial ART regimen and NADC in our cohort. Unlike the study of Powles et al. [8], all of our study subjects were treated with multidrug regimens, many of which are still in current use. Also, the subjects in our cohort were randomized to their initial ART regimens, eliminating bias in the choice of their ART.

Our study has some limitations. The subjects included in this analysis are research study participants who chose to enroll in an ACTG clinical trial of ART in naïve (previously untreated) HIV-infected individuals and who were then enrolled in a long-term follow-up. While this limits the generalizability of our findings to the entire HIV-infected population seen at ACTG sites, the advantage of this approach is that it is prospective and allows us to calculate the cancer incidence and to pinpoint the time of tumor development with regard to ART initiation. Due to the small numbers of cancers, we were not

able to examine risk factors for specific types of cancers. Our results are therefore limited to NADCs in general, and are not specific for a particular type of cancer. Also, 84% of the cohort was male, and we were not able to examine NADCs in men and women separately. Smoking status was available only for those subjects who were enrolled in ALLRT. In the regression models, those with missing smoking status were classified into a separate category. Finally, we did not have information on coinfections with human papilloma virus, sexually transmitted diseases, family history of cancer or other lifestyle factors such as prolonged sun exposure, sexual behavior, alcohol use or other toxin exposure.

A primary strength of our study is the unique cohort of HIV-infected subjects who were treatment-naïve at entry, randomized to treatment regimens in clinical trials, and rigorously monitored and followed long-term after completion of the original clinical trial. This prospectively followed cohort of subjects had regularly scheduled visits during their parent trial and during follow-up in ALLRT, which ensured that all diagnoses were captured using standardized methods. Our study had the advantage of being able to examine time-updated CD4 levels for all subjects. Because our cohort was ART-naïve at parent study entry and patients were randomized to initial ART regimens, we were able to examine if the initial ART regimen was associated with cancer risk without the bias that can occur when ART is selected rather than randomly assigned. We also had data on cigarette smoking for the majority of the cohort, and could analyze the influence of this important behavioral factor on the risk of NADC.

While it is not possible to identify specific mechanisms for individual NADC development in the setting of HIV/AIDS, we can speculate on several possibilities. Of greatest impact is the association of immune deficiency with tumor development, as shown in a meta-analysis of immunosuppressed organ transplant recipients and HIV patients [36]. Other possible mechanisms are: im-

mune activation and activation of protooncogenes or inhibition of tumor suppressor genes by HIV, endothelial abnormalities and increased susceptibility to environmental carcinogens, and possibly HIV-induced genetic instability and/or epigenetic changes which may predispose to cancer development (for example, increased microsatellite abnormalities in HIV lung cancer patients) [1].

This study of NADC in HIV-infected subjects has important implications for HIV clinicians and researchers. Patients with HIV are living longer and cancer rates in this population are rising. Cancer screening should be emphasized for HIV patients, and clinicians should maintain a high degree of suspicion and alertness to signs of possible malignancies. Our study results suggest that smoking cessation in the HIV-infected population is an important priority. Programs that alert HIV-infected persons to the increased risk of smoking for the development of multiple types of cancer and effectively assist HIV-infected persons to quit smoking are needed. Specific classes of ART therapy do not appear to increase the risk of NADC. However, lower CD4 levels are associated with a higher cancer risk, evidenced by the association with recent CD4 level and NADC. Consideration of initiating ART at higher CD4 counts, consistent with new guidelines [37], may be appropriate especially in persons with an additional risk for NADC.

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