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Exposure to Antiretroviral Therapy and Risk of Cancer in HIV-infected Persons

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Abstract

Objective—The incidence of certain non-AIDS-defining cancers (NADC) in HIV patients has been reported to have increased in the combination antiretroviral therapy (ART) era. Studies are needed to directly evaluate the effect of ART use on cancer risk.

Design—We followed 12,872 HIV+ Kaiser Permanente members whose complete ART history was known for incident cancers between 1996-2008.

Methods—Cancers, identified from SEER-based cancer registries, were grouped as AIDS-defining cancers (ADC), infection-related NADC or infection-unrelated NADC. We also evaluated the most common individual cancer types. Rate ratios (RR) for ART use (yes/no) and cumulative duration of any ART, PI and NNRTI therapy were obtained from Poisson models adjusting for demographics, pre-treatment or recent CD4 count and HIV RNA levels, years known HIV-infected, prior antiretroviral use, HIV risk, smoking, alcohol/drug abuse, overweight/obesity, and calendar year.

Results—The cohort experienced 32,368 person-yrs (py) of ART, 21,249 py of PI therapy, and 15,643 py of NNRTI therapy. The mean follow-up duration was 4.5 years. ADC rates decrease with increased duration of ART use [$RR_{/year}$=0.61, 95% CI (0.56-0.66)]; the effect was similar by therapy class. ART, PI or NNRTI therapy duration was not associated with infection-related or

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infection-unrelated NADC [$RR_{/year\ ART}$=1.00 (0.91-1.11) and 0.96 (0.90-1.01), respectively], except a higher anal cancer risk with longer PI therapy [$RR_{/year}$=1.16 (1.02-1.31)].

Conclusions—No therapy class-specific effect was found for ADC. ART exposure was generally not associated with NADC risk, except for long term use of PI, which might be associated with increased anal cancer risk.

Keywords

Combination antiretroviral therapy; HIV infection; protease inhibitor; non-nucleotide reverse transcriptase inhibitor; cancer; cohort study

Introduction

Despite the overall success of combination antiretroviral therapy (ART) in treating HIV disease, HIV-infected persons continue to be at higher risk for developing AIDS-defining cancers (ADC) and several types of non-AIDS defining cancers (NADC) when compared with the general population[1-4], even after adjusting for traditional cancer risk factors[5]. People with HIV are characterized by immunosuppression, chronic immune activation, and long-term exposure to antiretroviral agents. These factors have been speculated to mediate the increased cancer risk among HIV-infected persons [6].

The most compelling evidence exists for an effect of immunodeficiency and cancer risk. A seminal meta-analysis by Grulich et al [7] compared cancer risk in HIV/AIDS patients and organ transplant recipients, two populations that share few risk factors except for immunodeficiency. Cancers elevated in both populations included all those with a known or suspected viral etiology, as well as lung, stomach, kidney, melanoma, multiple myeloma and leukemia. A strong, direct relationship between lower CD4 count and increased risk for Kaposi Sarcoma and non-Hodgkin lymphoma among HIV-infected persons is well-established[8-10]. With regards to NADC, recent studies (including our own[5]) have noted associations between low CD4 count and increased incidence of Hodgkin lymphoma[5, 11-15], anal[5, 13, 14, 16, 17], lung,[5, 12-14] and liver cancers [5, 13, 18]. In contrast, higher HIV RNA levels has been linked to higher risk for ADCs, but not NADCs[13, 19-21].

The effect of ART use on cancer risk has also been studied, although most of these studies classified ART use as ever/never[22, 23]. Few studies have looked at individual non-AIDS-defining cancers and have adjusted for traditional cancer risk factors. Furthermore, while ART use overall has been associated with reduced risk of Kaposi sarcoma and non-Hodgkin lymphoma [4, 15, 24-26], it is not known if part of the decreased incidence observed for AIDS-defining and some non-AIDS-defining cancers in the ART era are mediated by a direct effect of ART, in addition to a broader indirect effect through better immune surveillance for malignancy. It has been suggested by experimental data that certain antiretroviral agents, such as protease inhibitors (PI), may have anti-carcinogenic properties including cell cycle arrest and cell death induction[27, 28]. These anti-cancer properties of antiretrovirals may therefore exert a direct protective effect on cancer development.

Additional research on the effects of ART on cancer risk is needed to inform the development of clinical management and cancer screening guideline for people living with HIV infection. To address the gaps in the literature, we conducted a cohort study of 12,872 HIV-infected persons in Kaiser Permanente Northern and Southern California to examine the effects of ART therapy duration on risk of individual cancer types adjusting for traditional risk factors, and to explore whether there is any potential direct protective effect of antiretrovirals on carcinogenesis.

Methods

Study Design, Settings and Participants

We conducted a cohort study from 1996 to 2008 of adult HIV-infected individuals within Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC), both of which are large integrated healthcare delivery systems providing comprehensive medical care to more than 6.6 million members who are demographically representative of insured Californians[29]. HIV-infected individuals were identified from KP-maintained HIV registries, which included all known cases of HIV infection dating back to the early 1980's for KPNC and to 2000 for KPSC. HIV-infected individuals were initially identified for inclusion in the registries by a positive HIV antibody test, quantifiable HIV RNA measurements, prescription of an HIV antiretroviral, HIV/AIDS-related diagnosis, or other evidence of HIV infection from electronic sources. Confirmation of cases was done by medical chart review and comparisons of case lists with KP HIV clinics.

Eligible subjects for this study consisted of all adult (≥18 years of age) HIV-infected individuals who were KP health plan members during the ART era. In addition, since our objective was to examine the effect of cumulative ART duration on the risk of cancer, we only included individuals for whom ART duration was known. Duration of ART could be established for all patients in KPNC, since the chart review completed at registry inclusion collected the date of first ART use, even if ART was initiated prior to KP membership. In KPSC, since chart reviews did not capture the first ART date, we only included patients with at least 6 months prior KP membership history with no ART.

The baseline date for analysis was assigned as the earliest date after 1996 (2000 for KPSC) when a member met all of the following criteria: 18 years of age, known to be HIV infected, and in HIV care, defined as the first recorded CD4 cell count measurement in the health system. Study subjects were followed from baseline until the earliest of death, cancer diagnosis, health plan disenrollment, or December 31, 2008. The institutional review boards at KPNC and KPSC approved this study and provided waivers of informed consent.

Data Sources

The primary data sources for this study were KP's electronic medical records including HIV and cancer registries, pharmacy utilization, inpatient and outpatient diagnosis, laboratory records, administrative files, and mortality databases.

Outcome ascertainment

We identified incident cancers among our study cohort by record linkage with the KPNC and KPSC cancer registries, which are contributing sites to the Surveillance, Epidemiology, and End Results (SEER) Program. Cancer case ascertainment is considered highly valid since reporting of cancers to the California Cancer Registry and the National Cancer Institute SEER program is mandated under state law. The primary endpoints examined were incident ADC, infection-related NADC, and infection-unrelated NADC. ADC included Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer. For Kaposi sarcoma, outpatient diagnosis based on International Classification of Disease (ICD)-9th edition code 176.xx was also used to supplement data obtained from cancer registries for case identification. NADC included all cancers that are not ADC. A subset of NADC with known infectious cause were categorized as infection-related NADC[7, 30, 31]: these were vagina, vulva, penis, anal squamous cell, and certain oral cavity/pharynx squamous cell cancers defined by Chaturvedi et al[31] which are HPV-related; liver cancer which is hepatitis B and C-related; stomach cancer which is Helicobacter pylori-related; and Hodgkin lymphoma which is Epstein-Barr Virus-related. All other NADC were considered infection-unrelated. In addition, we also considered the following individual cancer types that were among the most common cancers in HIV-infected persons, with at least 20 cases among ART users in our study population: Kaposi sarcoma, non-Hodgkin lymphoma, anal cancer (both squamous cell carcinoma and non-squamous cell carcinoma), Hodgkin lymphoma, prostate, and lung cancer.

Assessment of ART exposure

Use of antiretrovirals was ascertained using KP's electronic pharmacy system, which included prescriptions dispensed at all KP medical offices. Use of ART among HIV-infected individuals was defined as use of three or more antiretrovirals. ART use was examined as: (1) no ART use vs. any ART use; and (2) cumulative duration of any ART, PI and NNRTIs. Cumulative therapy duration was calculated as the actual length of time covered by dispensed prescriptions, which inherently accounted for periods of non-adherence. Specifically, if a particular ART was discontinued, or there was a period of non-adherence, the duration variable was not updated until that therapy was started again.

Other covariates

Other factors considered as potential confounders included demographics (age, sex, race/ethnicity), HIV disease factors (pre-treatment CD4 cell count and HIV RNA level, duration of known HIV infection, HIV transmission risk group and prior exposure to single or dual antiretrovirals), and traditional cancer risk factors (alcohol/drug abuse, overweight/obesity and tobacco use). Data on demographics and HIV disease factors were collected from HIV registries. Measurements of CD4 cell counts and HIV RNA levels were obtained from the KP laboratory databases. CD4 cell count was modeled as a continuous variable. HIV RNA level was also modeled as a continuous variable and was log transformed. Traditional cancer risk factors were assessed using KP's inpatient and outpatient diagnosis and utilization files. Alcohol/drug abuse diagnoses were captured by ICD-9 codes 291, 292, 303-305.0, 305.2-305.5, overweight or obesity diagnoses were captured by ICD-9 codes 278, 259.9,

V85 as well as KP internal weight/height files, and tobacco use was captured by ICD-9 codes 305.1, V15, V65, 649, as well as KP internal social history files.

Statistical analysis

The distribution of demographics and other potential confounders among the study cohort was calculated. Crude incidence as rate per 100,000 person-years was then computed for each cancer outcome of interest among person-time of no ART use and any ART use. Crude rate ratios for ART use status (no use vs. any use) were calculated using bivariate Poisson models. Adjusted rate ratios for any ART use in reference to no use as well as by duration of use were estimated by multivariable Poisson models adjusting for potential confounders. When the duration of PI and NNRTI use were examined, PI and NNRTI use were mutually adjusted in the model. P-value for test of linear trend was calculated.

To examine the overall effect of ART on cancer risk, we adjusted for pre-treatment CD4 cell count and HIV RNA level. For person-time after ART initiation, the value of CD4 cell count and HIV RNA level was kept at the pre-treatment value closest to treatment initiation. To examine the direct effect of ART on cancer development independent of ART's effect on CD4 cell count and HIV RNA level, CD4 cell count and HIV RNA level were adjusted as time-updated variables, i.e. as recent CD4 cell count and HIV RNA level measured in the prior 6-month period in an alternative model.

We also performed several sensitivity analyses. First, cancer cases diagnosed within 6 months of study baseline were excluded to avoid the inclusion of potential prevalent cancer cases that should not be attributed to current ART use duration. A second sensitivity analysis replaced pre-treatment CD4 with nadir CD4 (i.e., lowest recorded in KP) to further clarify observed associations of cancer risk with ART use. Finally, for anal cancer, given the potential for strong confounding by sexual orientation, we also conducted stratified analysis for MSM and other males. There were no female anal cancer cases identified, precluding a stratified analysis in this group. All analyses were performed with SAS (Version 9.1; Cary, North Carolina, USA), using proc GENMOD for Poisson regression.

Results

A total of 12,872 HIV-infected individuals with complete data on antiretroviral use were included in the study. The mean age of the study population was 40 years (Table 1). Ninety percent of the study subjects were male, and approximately half (44%) were racial/ethnic minorities. The majority of the subjects were men who have sex with men (62%). Of all subjects, 21% were exposed to single and/or dual antiretrovirals prior to study baseline. Mean CD4 cell count at study baseline was 364/uL.

Table 2 shows the crude incidence rates of the cancers of interest by ART use status. Kaposi sarcoma and non-Hodgkin lymphoma were the most commonly diagnosed cancers, regardless of ART use status. For NADC, anal cancer was the most commonly diagnosed NADC among person-time exposed to ART. On the other hand, lung cancer was the most commonly diagnosed cancer among person-time not exposed to ART, followed by prostate cancer (Table 2). In the unadjusted analyses, ART use was significantly associated with a

lower rate of ADC, yet, a higher rate of infection-related NADCs, largely driven by anal cancer (Table 2).

AIDS defining cancer (ADC)

In the multivariable analyses examining any ART use vs. no use, overall ART use remained strongly associated with lower incidence of ADC. This association was diminished when recent CD4 cell count and HIV RNA level were included in the model (Table 3).

In the multivariable analyses examining duration of overall ART, PI and NNRTI use, the longer the duration of overall ART/PI/NNRTI use, the lower the incidence of Kaposi sarcoma and non-Hodgkin lymphoma. These inverse associations with Kaposi sarcoma were observed both with adjustment of pre-treatment CD4 cell count and HIV RNA level [Rate Ratio (RR)$_{\text{/year increase ART}}$=0.54, 95% confidence interval (0.47-0.61), p-value for trend <0.01] (Table 4) and with adjustment of time-updated, recent CD4 cell count and HIV RNA level [RR$_{\text{/year increase ART}}$=0.80 (0.72-0.90), p-value for trend <0.01] (Table 5). However, for non-Hodgkin lymphoma, both durations of PI and NNRTI use were no longer significantly associated with reduced risk when adjusting for recent CD4 cell count and HIV RNA level [RR$_{\text{/year increase}}$=0.91 (0.82-1.00), p=0.06 for PI and 0.91 (0.77-1.06), p=0.23 for NNRTI] (Table 5).

Non-AIDS defining cancer (NADC)

In the multivariable analyses examining any ART use vs. no use, overall ART use was associated with lower risk of non-infection related NADC (Table 3). In the model adjusting for recent CD4 cell count and HIV RNA, overall ART use was associated with a lower incidence of prostate cancer [RR=0.34 (0.15-0.78), Table 3].

In the multivariable analyses examining duration of overall ART, PI and NNRTI use, no clear dose-response relationship with overall ART, PI or NNRTI use duration was seen for NADC, infection-related or infection-unrelated, anal cancer, lung cancer, prostate cancer or Hodgkin lymphoma, when pre-treatment CD4 cell count and HIV RNA level were adjusted for in the model (Table 4). Similar results were observed in sensitivity analyses which adjusted for nadir CD4 cell count, which is not surprising given pre-treatment CD4 likely corresponds closely with the lowest CD4 measurement for an individual (data not shown).

When recent CD4 cell count and HIV RNA were included in the model, an association was observed between anal cancer and duration of PI therapy [RR$_{\text{/year increase}}$ 1.16 (1.02-1.31)] (Table 5). Similar results were found when we stratified the analysis by MSM (number of anal cancer cases=41) and other males (number of anal cancer cases=11). The rate ratio estimates and 95% confidence intervals were 1.17 (1.01-1.36) and 1.15 (0.91-1.45) per year increase for PI therapy, respectively. No association was observed between duration of NNRTI use and anal cancer risk. On the other hand, an inverse association was seen between prostate cancer and duration of overall ART use [p-value for trend <0.01] and PI therapy [p-value for trend =0.02] (Table 5). No clear association was found between any ART use and risk of lung cancer and Hodgkin lymphoma in analyses adjusting for recent CD4 cell count and HIV RNA level.

Finally, sensitivity analyses that excluded the first 6 months of follow up for all subjects resulted in similar results suggesting the inclusion of potentially prevalent cancers was not a significant issue.

Discussion

We found that the association between ART use and reduced risk ADC appeared to be mediated in part by ART's effect on CD4 cell count and HIV RNA level, but not completely. Our results suggest that ART might have a direct protective effect on ADC, independent of ART's effect in increasing CD4 cell count. We found similar effects of PI and NNRTI on Kaposi sarcoma and non-Hodgkin lymphoma, suggesting lack of a therapy class effect on risk of ADC. In addition, we also observed an increased risk of anal cancer with increased duration of overall ART or PI use. On the other hand, an inverse association was found for duration of overall ART or PI use and risk of prostate cancer.

The finding that overall ART use was associated with reduced risk of Kaposi sarcoma and non-Hodgkin lymphoma upon adjusting for recent CD4 cell count and HIV RNA level suggests that antiretrovirals may confer additional anti-cancer benefits other than maintaining immune function. PI agents have been shown to confer a broad-spectrum of anti-cancer properties. In experimental studies, the observed anti-cancer mechanisms included inhibition of phosphoinositide 3-kinase (PI3K)/Akt pathway, induction of caspase-dependent apoptosis and caspase-independent cell death through induction of endoplasmic reticulum stress and autophagy[32, 33]. In addition to direct cytotoxicity, some PI drugs also demonstrate the ability to induce cell cycle arrest[34]. The anti-proliferation and cell death induction effects of PI agents have been shown in a large number of cell lines of several types of cancer, both *in vitro* and *in vivo*[33]. NNRTI agents also demonstrate anti-cancer effects in experimental models. NNRTI inhibits endogenous reverse transcriptase encoded by long interspersed nuclear element-1 (LINE-1) and human endogenous retroviruses (HERVs) by binding to the reserve transcriptase protein and inducing a conformational change resulting in reduced enzyme activity. The downstream effects are reduced cell growth and induced differentiation, as shown in cancer cell line and murine cancer models[28, 35, 36]. Additional epidemiologic and laboratory data will be needed before a causal, direct effect of ART, independent of CD4 cell count and HIV viral replication can be confirmed.

The effect of ART use on the risk of NADC has been controversial in the literature. While some studies reported a protective effect of ART use on risk of NADC [13, 19, 37], others reported an adverse association (mainly between NNRTI users and risk of Hodgkin lymphoma)[17], or no association [15, 38]. The conflicting results may be due to limitations in study methods that masked the variation in study population in terms of ART use history, baseline risk of cancer, etc. For example, most of these studies defined ART use as a binary variable for use vs. no use, and did not examine any dose-response relationship with duration of use, or agent-specific effects. Furthermore, the number of overall NADC was too low to conduct cancer type-specific analysis. Guiguet and colleagues have examined ART duration (≤ or > 6 months) and risk of individual cancer types identified by ICD-9 codes using the French Hospital Database. They did not find ART use to be a predictor of risk for

several NADC, including anal, lung, liver cancer, and Hodgkin lymphoma[13]. On the other hand, ADC, NADC grouped by infection-related vs. not, or prostate cancer were not examined in this study. In the present study, with a relatively large number of ADC and NADC cases, we further examined the effects of duration of use, ART therapy class, and by individual cancer type. We did not find clear association between ART use and risk of NADC, infection-related or infection-unrelated, lung cancer or Hodgkin lymphoma.

An increased anal cancer risk was observed for long term use of ART, particularly PI therapy. This finding is somewhat consistent with calendar trends of anal cancer incidence reported by others [16, 39, 40] . Among those who examined risk factors for anal cancer among HIV-infected persons, Piketty et al also reported an increased anal cancer risk in ART users[16]. Powles et al, on the other hand, reported lack of association between ART use and risk of anal cancer[17]. It is unclear what the potential underlying biological mechanism is for the observed association of anal cancer and PI therapy. In fact there are some alternative explanations. For instance, the higher cancer risk with longer duration ART use may be explained by prolonged exposure to human papillomavirus (HPV), the causative agent of anal cancer; however our analyses did adjust for known years HIV-infected. Alternatively more vigilant screening for anal cancer among those on ART might explain the higher risk among ART users. However, the ART class effect observed here argues against both explanations. Another possibility is residual confounding by sexual orientation since MSM have a known increased risk of anal cancer, and MSM may also contribute the longest duration of PIs. However, multivariable models did adjust for HIV risk, and sensitivity analyses indicated similar results by ART class for MSM and other men. Despite these assurances, confounding cannot be ruled out since we did not have information on sexual practices, such as having unprotected anal sex.

The other cancer identified to be associated with ART was prostate cancer, with decreased rates with long-term ART use, specifically PI use. This inverse association was only observed in models that adjusted for recent CD4 cell count and HIV RNA levels. Thus, if the association is causal, this suggests that PIs protect against prostate cancer through a mechanism not mediated by CD4 and/or HIV RNA. This is notable given the observed decreased risk of prostate cancer among HIV patients we and others have reported previously. Although the reason for the decreased risk is unknown, some have suggested it is due to reduced prostate-specific antigen screening[41]. Preliminary data from our group, however, suggests HIV patients are more vigilantly screened for prostate cancer [42]. Our results suggest a direct protective effect of PIs, consistent with in vivo and in vitro studies demonstrating antitumor effects for PIs on prostate cancer cells [43, 44].

Some potential limitations in our study should be considered when interpreting the results. First, our measurement for certain cancer risk factors, such as tobacco use, alcohol/drug abuse, and overweight/obesity were based on documentation in the electronic medical records rather than direct patient survey. For cancers where routine screening procedures exist, such as prostate cancer and colorectal cancer, we did not take into account the screening behavior that may vary between ART use subgroups. However, there is little reason to suspect differential cancer screening behaviors between ART use subgroups (e.g., PI or NNRTI). On the other hand, it is possible that ART users may be more attentive to

cancer screening than non-ART users. This, however, would not explain the reduced prostate cancer risk observed with ART use. An additional limitation was the focus on overall ART and ART class effects. Follow-up studies focusing on individual ART medications, or first-line versus second-line ART may be further informative. In addition, it should be noted that our results have limited generalizability to women, as women made up only 10% of the cohort. Lastly, adjusting for recent CD4 and HIV RNA in the multivariable model using standard approaches may bias the results, if there is a unadjusted factor that is both causally related to CD4/HIV RNA, and itself modifies cancer risk[45]. However, we are not aware of any other such factors that are not included in our model to cause significant bias through this manner.

Despite these limitations, our study has several important strengths. As described earlier, our study addresses several major gaps in the literature on this topic by examining class-specific effect, dose-response relationship by duration of use and cancer-type specific analysis. In addition, this study was based on a well-defined, large population-based cohort of HIV-infected individuals with complete information on antiretroviral use history. The ascertainment of HIV status, cancer diagnosis, and ART use was highly valid with the collection of data from disease registries and pharmacy databases. We found that the protective effect of ART on ADC does not vary by therapy class. Thus, we did not find evidence in support of ART regimen choices, such as PI-based ART, to reduce the burden of ADC. Our findings also suggested a potentially adverse effect of long term use of PIs on anal cancer, and a protective effect for prostate cancer. Given the lack of known biological plausibility, these findings require further confirmation by other studies. Nevertheless, given the lifelong commitment to ART and the long cancer induction period, continued evaluation of cancer risk in this population is needed.

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Chao C supervised data collection at Kaiser Permanente Southern California, assisted with the study design, co-led the data analysis and led the manuscript writing. Leyden WA and Xu L performed data collection and the statistical analysis. Horberg M, Abrams D, Klein D and Towner W provided clinical inputs regarding HIV treatment and oncology and provided critical revision of the manuscript. Quesenberry CP provided senior statistical consultation to the study design and analysis. Silverberg MJ conceptualized the study, obtained study funding, and led the data analysis. All authors contributed to the writing of the manuscript.

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Table 1

Cohort baseline characteristics

	HIV-infected individuals N=12,872
Age, mean (sd)	40.1 (9.8)
Male, %	90.0
Race/ethnicity (among known), %	
White	54.2
Black/African-American	20.0
Hispanic/Latino	20.5
Asian/Pacific Islander	4.5
Other	0.8
% unknown of total	5.1
HIV exposure risk, %	
Men who have sex with men	61.6
Injection drug use	6.2
Heterosexual	14.9
Other	1.7
Unknown	15.6
Years of known HIV infection, mean (sd)	2.8 (4.1)
CD4 cell count, mean (SD)	364.4 (278.9)
HIV RNA, mean (SD)	50,926.8 (103,655.9)
Prior AIDS diagnosis (CDC AIDS)	23.02
Prior AIDS diagnosis (Clinical AIDS)	10.5
Prior use of antiretrovirals (single and/or dual)	21.1
Person-years of antiretroviral use	
Any ART use (mean/person)	32,368 (3.8)
PI (mean/person)	21,249 (3.6)
NNRTI (mean/person)	15,643 (2.8)
No antiretroviral use	19,479
Ever tobacco use, %	43.78
Ever alcohol abuse, %	12.40
Ever drug abuse, %	17.08
Ever overweight/obese diagnosis, %	38.50

Table 2

Crude rates and Crude rate ratios of cancer by ART use status

	No ART use		ART use		ART vs. no ART use	
	n/p-yr	rate[1]	n/p-yr	rate[1]	Crude rate ratio[2] (95% CI)	p-value
ADC	240/18062	1329	215/36810	584	0.44 (0.37-0.53)	<0.01
NADC: Infection-related[3]	19/18417	103	78/39000	200	1.94 (1.17-3.20)	0.01
NADC: Infection-unrelated	64/18336	349	160/38738	413	1.18 (0.89-1.58)	0.26
Kaposi sarcoma	182/18155	1002	131/37266	352	0.35 (0.28-0.44)	<0.01
Non-Hodgkin lymphoma	64/18366	348	95/38879	244	0.70 (0.51-0.96)	0.03
Prostate	11/16490	67	31/35290	88	1.32 (0.66-2.62)	0.43
Anal	8/18433	43	44/39157	112	2.59 (1.22-5.50)	0.01
Lung	16/18452	87	24/39335	61	0.70 (0.37-1.32)	0.28
Hodgkin lymphoma	5/18450	27	24/39231	61	2.26 (0.86-5.92)	0.10

[1] Crude rate per 100,000 person-years

[2] RR comparing cancer rate by ART use status (no ART use as the reference group) from Poisson regression models.

[3] Hodgkin lymphoma, liver, anal squamous cell carcinoma, vulvar, vaginal, penile, and HPV-related oral/pharynx cancers.

Table 3

Antiretroviral use, recent CD4, HIV RNA and risk of cancer in HIV+ subjects

	Adjusting for pre-treatment CD4 cell count and HIV RNA level[1]		Adjusting for time-updated CD4 cell count and HIV RNA level[2]	
	Adjusted RR for ART use (95% confidence interval) and p-value			
ADC	0.22 (0.18-0.28)	<0.01	0.62 (0.50-0.77)	<0.01
Kaposi sarcoma	0.18 (0.14-0.24)	<0.01	0.53 (0.41-0.68)	<0.01
Non-Hodgkin lymphoma	0.36 (0.24-0.52)	<0.01	0.89 (0.62-1.29)	0.54
NADC: infection related[3]	1.30 (0.73-2.31)	0.38	1.13 (0.63- 2.01)	0.68
NADC: infection unrelated	0.68 (0.48-0.96)	0.03	0.74 (0.52-1.05)	0.09
Anal	1.13 (0.48-2.65)	0.78	1.57 (0.68-3.63)	0.29
Prostate	0.71 (0.31-1.60)	0.41	0.34 (0.15-0.78)	0.01
Lung	0.57 (0.26-1.27)	0.17	0.60 (0.27-1.34)	0.21
Hodgkin lymphoma	2.70 (0.91-8.03)	0.07	1.54 (0.51-4.66)	0.44

[1] Poisson model with time-updated use of ART, pre-treatment CD4 (continuous) and HIV RNA (continuous, log transformed), age, sex, race, year, smoking, overweight, alcohol/drug abuse, HIV transmission risk group, known years of HIV infection and prior exposure to single and/or dual antiretrovirals.

[2] Same model but replacing pre-treatment CD4 and HIV RNA with recent CD4 and HIV RNA.

[3] Hodgkin lymphoma, liver, anal squamous cell carcinoma, vulvar, vaginal, penile, and HPV-related oral/pharynx cancers.

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Table 4

Adjusted rate ratio for cancer by duration of overall ART, PI and NNRTI use: adjusting for pre-treatment CD4 cell count and HIV RNA level.

	ADC	Infection-related NADC	Infection-unrelated NADC	Kaposi sarcoma	Non-Hodgkin lymphoma	Anal	Prostate	Lung	Hodgkin's lymphoma
	Rate ratio (95% confidence interval)								
Any ART use[1]									
Duration of use[2]	0.61 (0.56-0.66)	1.00 (0.91-1.11)	0.96 (0.90-1.01)	0.54 (0.47-0.61)	0.69 (0.62-0.76)	1.04 (0.91-1.20)	0.89 (0.79-1.01)	1.05 (0.91-1.22)	0.94 (0.76-1.16)
p for trend[2]	<0.01	0.96	0.14	<0.01	<0.01	0.55	0.07	0.49	0.54
PI use[3]									
Duration of use[2]	0.69 (0.64-0.75)	1.07 (0.97-1.17)	0.97 (0.92-1.03)	0.62 (0.55-0.71)	0.77 (0.70-0.86)	1.08 (0.96-1.23)	0.91 (0.80-1.02)	0.97 (0.85-1.12)	1.02 (0.84-1.24)
p for trend[2]	<0.01	0.17	0.34	<0.01	<0.01	0.20	0.11	0.71	0.84
NNRTI use[3]									
Duration of use[2]	0.65 (0.58-0.74)	1.03 (0.91-1.17)	0.98 (0.92-1.06)	0.55 (0.45-0.67)	0.74 (0.63-0.87)	1.02 (0.87-1.20)	1.01 (0.88-1.17)	1.05 (0.89-1.25)	1.12 (0.89-1.41)
p for trend[2]	<0.01	0.61	0.66	<0.01	<0.01	0.79	0.86	0.56	0.34

[1] This model does not include terms for PI and NNRTI use duration.

[2] Rate ratio for per year increase in duration of use. P-value for linear trend is based on the continuous variable for therapy duration.

[3] PI and NNRTI estimates were derived from the same Poisson model with terms for duration of PI and NNRTI use, pre-treatment CD4 cell count (continuous) and HIV RNA level (continuous, log transformed), age, sex, race, year, smoking, overweight, alcohol/drug abuse, HIV transmission risk group, known years of HIV infection and prior exposure to single and/or dual antiretrovirals. This model does not include overall ART use duration.

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Table 5

Adjusted rate ratio for cancer by duration of overall ART, PI and NNRTI use: adjusting for recent CD4 cell count and HIV RNA level.

	ADC	Infection-related NADC	Infection-unrelated NADC	Kaposi sarcoma	Non-Hodgkin lymphoma	Anal	Prostate	Lung	Hodgkin's Lymphoma
	Rate Ratio (95% confidence interval)								
Any ART use[1]									
Duration of use[2]	0.84 (0.78-0.90)	1.02 (0.92-1.13)	0.98 (0.92-1.03)	0.80 (0.72-0.90)	0.87 (0.78-0.96)	1.13 (0.99-1.30)	0.83 (0.74-0.94)	1.07 (0.93-1.24)	0.91 (0.73-1.14)
p for trend[2]	<0.01	0.67	0.41	<0.01	0.01	0.07	<0.01	0.33	0.41
PI use[3]									
Duration of use[2]	0.86 (0.80-0.94)	1.08 (0.98-1.18)	0.99 (0.94-1.04)	0.84 (0.75-0.94)	0.91 (0.82-1.00)	1.16 (1.02-1.31)	0.87 (0.77-0.98)	0.99 (0.86-1.13)	1.00 (0.81-1.22)
p for trend[2]	<0.01	0.11	0.66	<0.01	0.06	0.02	0.02	0.84	0.97
NNRTI use[3]									
Duration of use[2]	0.88 (0.78-1.00)	1.04 (0.92-1.18)	1.00 (0.93-1.07)	0.81 (0.67-0.99)	0.91 (0.77-1.06)	1.05 (0.89-1.23)	0.96 (0.83-1.11)	1.07 (0.90-1.27)	1.12 (0.87-1.43)
p for trend[2]	0.05	0.55	0.90	0.04	0.23	0.60	0.59	0.46	0.37

[1] This model does not include terms for PI and NNRTI use duration.

[2] Rate ratio for per year increase in duration of use. P-value for linear trend is based on the continuous variable for therapy duration.

[3] PI and NNRTI estimates were derived from the same Poisson model with terms for duration of PI and NNRTI use, time-updated recent CD4 cell count (continuous) and HIV RNA level (continuous, log transformed), age, sex, race, year, smoking, overweight, alcohol/drug abuse, HIV transmission risk group, known years of HIV infection and prior exposure to single and/or dual antiretrovirals. This model does not include overall ART use duration.