Incidence of Non-AIDS-Defining Malignancies in HIV-Infected Vs. Non-Infected Patients in the HAART Era: Impact of Immunosuppression

Roger J. Bedimo, MD, MS [Assistant Professor of Medicine],
VA North Texas Health Care System and University of Texas Southwestern Medical Center Dallas, TX

Kathleen A. McGinnis, MS,
VA Pittsburgh Healthcare System, Pittsburgh, PA

Melinda Dunlap, MD [Assistant Professor of Medicine],
UT Southwestern Medical Center, Dallas, TX

Maria C. Rodriguez-Barradas, MD, and
Michael E. DeBakey VA Medical Center, and Baylor College of Medicine, Houston, TX

Amy C. Justice, MD, PhD [Professor of Medicine]
Yale University School of Medicine, West Haven, CT.

Abstract

Background—The incidence of non-AIDS-defining malignancies (non-ADM) is reported as unchanged or increasing in the HAART era. Whether incidence of non-ADM is significantly higher in HIV-infected than in HIV-uninfected patients remains unclear.

Methods—Incidence rates of malignancies were calculated in a cohort of veterans in care for HIV-infected and age, race, and gender-matched uninfected patients from 1997 to 2004. For HIV-infected patients CD4 counts closest to first observation date were compared between those with and without cancer.

Results—33,420 HIV-infected and 66,840 HIV-uninfected patients were followed for a median of 5.1 and 6.4 years. The Incidence rate ratio [IRR] of HIV-infected to HIV-uninfected was 1.6 (1260 vs. 841/100,000 person-years; 95% CI: 1.5–1.7). IRR for individual cancers was highest for anal cancer (14.9; CI: 10.1–22.1). Among HIV-infected patients, median CD4 counts were lower for those

Corresponding Author: Roger J. Bedimo, MD, MS, FACP, Assistant Professor of Medicine, UT Southwestern Medical Center, Chief, Infectious Disease Section, VA North Texas Health Care System, Director, ID Fellowship Training Program, UT Southwestern Medical Center., 4500 South Lancaster Road, Dallas, TX 75216, Office: 214-857-0397 (VAMC); 214-648-9914 (UTSW); Fax: 214-302-1433. **Corresponding Author's Institution**: VA North Texas Health Care System

with non-ADM (249 vs. 270, p=0.02), anal cancer (154 vs. 270; p<0.001), and Hodgkin's (217 vs. 270; p=0.03). Prostate cancer was associated with a higher CD4 count (310 vs. 270; p<0.001).

Conclusions—In the HAART era, the incidence of non-ADMs is higher among HIV-infected than HIV-uninfected patients, adjusting for age, race, and gender. Some non-ADMs do not appear to be associated with significantly lower CD4 counts.

Keywords

AIDS-defining malignancies; Non-AIDS-defining malignancies; Incidence; HAART

Introduction

Prior to HAART, certain AIDS-defining malignancies (ADMs: non-Hodgkins lymphoma, Kaposi's sarcoma and invasive cervical carcinoma) were found to be highly correlated with the degree of immunosuppression. With use of HAART and the resulting improved survival[1, 2], the incidence of ADMs has declined[3, 4]. Yet, the incidence of malignancies not known to be associated with immunosuppression (non-AIDS-defining malignancies or non-ADMs [5]) have been found to be significantly more common than in the general population [3, 5−7]. Recent studies suggest that the incidence of selected non-ADMs has increased in the HAART era [6, 8−12], but these studies have not included matched cohorts of HIV-positive and HIV-negative patients.

We used data from the United States Veterans Affairs Healthcare System to compare rates of non-ADMs between HIV-infected and matched HIV-uninfected patients receiving care during the period of 1997 through 2004 (HAART era), and determine the association of non-ADM incidence with the degree of immunosuppression at baseline among HIV-infected patients. The purpose of this study is to determine whether HIV infection is associated with an increase in the risk of non-ADMs, and to determine whether this risk is associated with the patients' level of immunosuppression. A better characterization of the incidence of non-ADMs, and their risk factors will likely allow for identification and implementation of screening and preventive measures specific to this population, as well as improvement of the outcomes of patients with HIV and cancer.

Methods

Use of VA national administrative data was approved by the VA Pittsburgh Healthcare System and University of Pittsburgh institutional review boards (Pittsburgh, PA). VA electronic medical record data from patient treatment files and outpatient clinic files were used. [13] We adapted an algorithm developed by Fasciano et al [13] using *International Classification of Diseases, ninth revision* (ICD-9-CM) diagnostic codes to identify patients with a first HIV or AIDS diagnosis from October 1997 to September 2004. Our modifications required patients to have one or more inpatient or two or more outpatient HIV-related codes rather than a single inpatient or outpatient HIV-related codes. Our program searched for the following ICD-9-CM codes: AIDS (042), asymptomatic HIV (V08), and related Diagnostic Related Group codes (488–490). We have previously demonstrated that requiring at least two outpatient codes or one inpatient code results in substantial improvement in positive predictive value (88% vs. 69%) without a substantial decrement in sensitivity, specificity, or negative predictive value[14]. For each HIV-positive veteran identified, we identified two HIV-negative patients matched on age, sex, race, geographic location, and in care in the same year. This methodology is described in full elsewhere [15]. Subjects were followed from the date of their first HIV-related diagnostic code, or their matching date. Subjects were censored at their date of death, or last encounter within the VA before September 2004.

We searched for diagnostic codes for cancers in inpatient files from October 1990 and in outpatient files from October 1996 through September 2004. We using ICD-9-CM site-specific cancer codes as identified by Surveillance Epidemiology and End Results (SEER)[16]. Cancers were included if the veteran had one or more inpatient or two or more outpatient cancer diagnoses of the same type. Patients with cancer diagnosis prior to their HIV diagnosis or match date were excluded from analyses for that particular cancer. For the overall category of non-ADM we included all cancers except lymphoma, Kaposi's sarcoma, cervical carcinoma, skin, and ill-defined cancers. We excluded skin and ill-defined cancers because of concern of overlap with other cancer categories.. The non-ADMs we examined individually are: anal, lung, melanoma, prostate, Hodgkins, and liver. For comparison purposes, we also incude the ADM: Kaposi's Sarcoma, Non-Hodgkin's lymphoma (NHL), and cervical carcinoma.

CD4 data were available for HIV-infected veterans who were also enrolled in the Immunology Case Registry (ICR). The ICR is a VA registry designed to collect data on all HIV-infected veterans in care[15] . Of the VACS Virtual Cohort HIV-infected veterans, 86% were also enrolled in the ICR. Additionally, the CD4 dataset ends at February 2003, but our identification date goes until September 2004. Of HIV-infected veterans in the ICR and with a first observation date prior to February 2004, 86% (22,725) have a baseline CD4 value. We created a variable for number of clinic visits during the first year of observation. Primary care visits and infectious disease subspecialty visits were included in this category. We include infectious disease visits because that is where HIV-infected patients receive much of their "general" care. Multiple clinic visits on the same day were counted as only one visit.

Because hepatitis C virus and alchol use are known cancer risk factors [17], we describe the prevalence for HIV-infected and uninfected veterans in the VACS Virtual Cohort. We considered alcohol abuse or dependence present if there were one or more inpateint or two or more outpateint ICD-9 diagnosis codes. Hepatits C virus was considered present if there were one or more inpatient or two or more outpatient ICD-9 diagnosis codes or a positive laboratory value for hepatitis C virus.

Analyses

Demographic characteristics, observation time, fiscal year identified in cohort, number of clinic visits, hepatitis C infection, and alcohol abuse and dependence were described for the HIV-infected and uninfected veterans. Incidence rates (IRs) per 100,000 person years of specific non-ADMs, ADMs, and total non-ADMs were calculated and compared between HIV-infected and uninfected patients. Time at risk (person-years) was calculated from date of enrollment into the cohort to date of cancer diagnosis or last documented clinic visit or date of death. HIV-infected compared with HIV-uninfected age-, race-, and gender-adjusted incidence rate ratios (IRRs) and 95% confidence intervals (CI) were calculated using Poisson regression analysis. As a sub-analysis, IRs and IRRs by year of entering the cohort (two year groupings) were also calculated for total non-ADMs. We also ran the poisson models limiting follow-up time to a maximum of two years.

Median CD4 cell counts closest to first observation date were compared between those with and without cancer, using Wilcoxon rank-sum tests, to determine the association of immunosuppression with rates of malignancies in HIV-infected patients. CD4 count at first observation was used to allow an analysis of immunodeficiency as a risk factor for cancer. If counts at cancer diagnosis were used, there would be no means of comparing counts between those with and without cancer. Comparing counts at diagnosis among those with cancer and counts at baseline for those who did not develop cancer would be inherently biased because, all else equal, CD4 counts decrease with time. Further, the cancer itself may affect the CD4 cell count, making the value obtained at or immediately after a cancer diagnosis difficult to interpret.

Results

A total of 33,420 HIV-infected and 66,840 age-, gender-, race/ethnicity- and location- matched HIV-uninfected patients were identified in the VACS Virtual Cohort. Of those, 32,942 (98.6%) of HIV-infected and 64,966 (97.2%) of HIV-uninfected had greater than zero days of observation time. Almost half of the HIV-infected and uninfected subjects (46.4% and 46.5%) were identified in fiscal year 1997, the majority representing patients already in care, with slightly decreasing numbers of subjects identified for most of the subsequent years. Years subsequent to 1997 represent patients new to HIV care in the VA system, not necessarily newly infected. The mean age of the patients were 45.8 (SD: 10.0) in the HIV-infected group and 46.1 (SD: 10.1) in the HIV-uninfected group. The proportion of males in each group was 97.8. Race/ethnicity was similar between groups. Overall, 32% were White, 43% African-American, 8% Hispanic, and 17%, other/unkown. The median follow-up time was 5.1 years for the HIV-infected patients and 6.4 years for the HIV-uninfected patients. HIV-infected patients had a median of 5 visits (Interquartile Range(IQR): 3–8) in the year following identification in cohort compared to a median of 2 visits (IQR: 1–3) for HIV-uninfected patients. Alcohol abuse or dependence was similar between groups (21% for HIV-infected vs. 20% for HIV-uninfected). However, Hepatits C infection was more common among HIV-infected veterans (36% vs. 12%; Table 1).

In Poisson models adjusted for gender, race/ethnicity, and age, IRRs indicate that HIV-infected veterans were more likely to have anal, lung, melanoma, Hodgkins, and liver cancer than HIV-uninfected veterans. Likelihood of prostate cancer was similar between HIV-infected and HIV-uninfected patients (IRR: 1.0; CI: 0.9–1.1).

A total of 2128 and 3142 non-ADMs were diagnosed among the HIV-infected and unifected groups, respectively. IRs (per 100,000 person-years) were 1260.5 among HIV-infected and 841.8 among HIV-uninfected. The non-ADMs HIV-infected to uninfected IRR was 1.6 (95% CI: 1.5–1.7) (Table 2). IRs of non-ADMs were also compared for consecutive two-year periods. There was statistically significant decline in the rate of non-ADMs among the HIV-uninfected patients from 1998–99 to 2000–01 (p=.003). Conversely, rates on non-ADMs remained stable over time among the HIV-infected group (Figure 1). HIV-infected to uninfected IRRs for each two-year period (from 1996–1997 to 2002–2003) were statistically significant, and increased from 1998–1999 and onward: 1996–1997 IRR: 1.6; 95% CI 1.5–1.7; 1998–1999 IRR: 1.5; 95% CI: 1.3 – 1.7; and 2002–2003 IRR: 2.0; 95% CI: 1.6 – 2.6. Patterns were similar for IRRs using a maximum of two years of follow-up time (data not shown).

Compared to HIV-infected patients without cancer the median CD4 counts were lower for patients with non-ADM (249 vs. 270, p=0.02), anal cancer (156 vs. 270; p<0.001), and Hodgkin's (217 vs. 269; p=0.03). For all other non-ADM, there was no statistically significant difference between the median CD4 counts of cancer patients and non-cancer patients, with the notable exception of prostate cancer which was associated with a higher CD4 count (311 vs. 266; p<0.001).

We also report the IRs, IRRs, and CD4 counts for the ADM. ADM have higher IRs as expected. Among HIV-infected pateints, CD4 counts are statistically significantly lower for patients with each ADM than for those without (Table 2).

Discussion

In the HAART era, the incidence of non-ADMs is significantly higher among HIV-infected than age-, race-, and gender-matched HIV-uninfected patients. After a median follow-up time of over 5 years, the IRR of all non-ADM among HIV-infected patients was 1.6 (95% CI: 1.5–1.7). This 60% higher rate of non-ADM among HIV-infected patients was consistent for two

time-periods representing early and more recent HAART eras (1996–1997 to 2002–2003, respectively). Further, cancers other than those strongly asssociated with HCV infection (hepatoma) or men who have sex with men (anal cancer) demonstrated significantly increased IRR when HIV infected patients were compared with demographically similar uninfected patients.

Patients with non-ADMs tend to have somewhat lower CD4 counts than non-cancer patients. This effect appears to be largely driven by anal cancers which not only have a significantly higher IRR (in HIV-infected vs. HIV-uninfected patients), but appear to be significantly associated with immunosuppression in our cohort, whith the median CD4 count of anal cancer patients being only 58% of that of non-cancer patients. Both the very high IRR and the association of immunosuppression make the epidemiology of this malignancy more similar to that of ADM than non-ADM . Indeed, the biology of anal cancer – with its strong association with Human Papilloma Virus (HPV) infection – is very similar to that of cervical cancer, which is included among ADMs. Prostate cancer patients had higher median CD4 count than non-cancer patients with HIV infection. This result, consistent with previous observations of a high mean CD4 count in HIV patients with prostate cancer,[18] is intriguing, but it should also be noted that prostate cancer was equally common among HIV infected and uninfected subjects.

Congruent to our findings, a previously published analysis of linked population-based AIDS and cancer registry data from 11 geographically diverse areas in the United States [7] concluded that selected non-ADM, including Hodgkin's disease, lung cancer, soft tissue malignancies, lip and testicular cancer were potentially associated with immunosuppression. Consistent with this observation, an interesting study has recently been published comparing cancer incidence in population-based cohort studies of people with HIV/AIDS and solid organ transplantation (another immunosuppressed population in which epidemiologic studies have also found a wide range of cancers) 19. The authors interpreted their finding of similar spectra and a similar pattern of increased risk of cancer in the two populations as strongly suggesting that immune deficiency is the likely underlying cause.

However, with the exception of anal cancer and Hodgkin's disease, an association has not been consistently found between advancing immunosuppression and the development of non-ADM (Table 2) among HIV infected patients[4, 5, 7, 20]. Indeed, even if patients with non-ADMs tend to have slightly lower CD4 counts than non-cancer patients in some cohorts, these malignancies do not appear to share the same association with degree of immunosuppression as the AIDS-defining malignancies [4, 7]. One possible explanation of the increased risk is that, despite improved immune function on HAART, cancer immune surveillance is still inadequate in patients with HIV.

It is possible that despite the matching, the current findings reflect an overrepresentation of traditional cancer risk factors among the HIV-infected patients, especially viral co-infections (HCV and HPV) and smoking status. Several studies have described an increased prevalence and recurrence of both cervical HPV infection and invasive cervical cancer among HIV-1 positive women compared to HIV-1 negative patients, especially among those with low CD4 cell counts[21, 22]. The prevalence of oral, anal, and cervical HPV infection in HIV-positive individuals compared with HIV-negative individuals increases with progressively lower CD4 + levels, as does incident high-grade intraepithelial neoplasia (CIN) [22⁻25]. While we do not have the rates of HPV infection among HIV-infected and uninfected patients in the VACS Virtual Cohort, it could be inferred by the proportion of men who have sex with men in both groups in the VACS Ongoing Study Cohort, (47.5% and 6.4% respectively) that the HPV infection rates would be higher in HIV-infected patients.

An excess risk of traditionally smoking-related cancers is seen in HIV-infected patients [3, 4, 6, 7]. Importantly, Crothers et al., [26] found (through a self-administered questionnaire) nearly equivalent rates of current or past smoking history in 1,014 HIV-infected and 713 HIV-uninfected veterans enrolled in the Veterans Aging Cohort 5 Site Study in 2001 and 2002 (75% vs. 76%). Regardless, after controlling for smoking, rates of lung cancer are higher in HIV-infected than uninfected patients [27]. Consistent with a prior analysis of by McGinnis et al. [17], we find that rates of alcohol abuse and dependence are similar in among HIV-infected and uninfected patients in the VACS Virtual Cohort (21% and 20% respectively), but HCV co-infection is more common among HIV-infected than uninfected patients (36% vs. 12%).

A possible limitation to our study is that our findings may be explained by ascertainment bias. Specifically, the HIV-infected patients were seen more often than uninfected patients and therefore may have had more opportunity to be have a diagnosis of cancer made and recorded resulting in the HIV infected patients appearing to have higher rates of cancer when the rates were not truly different. We think this is unlikely. First, if ascertainment bias explained our results, we would have expected a more uniform effect across cancers. Instead only a handful of cancers were more common and, among HIV infected individuals, these cancers were more common among more immunosuppressed individuals. Second, cancer rates among the uninfected comparators in our cohort are higher than those reported by SEER for the general population [16, 17]. This suggests that, if anything, our estimate of rates among the controls may be upwardly biased. Specifically, controls had to have a reason to seek medical care—one of which might be symptoms of cancer. Thus, our estimate of relative rates comparing HIV infected individuals to HIV uninfected demographic controls receiving care in the VA may instead be a conservative estimate of the true difference in rates. Finally, others have also found increased rates of specific non-ADMs among those with HIV infection [4, 6, 12]. There remains the strong possibility that HIV itself and/or HAART use have an oncogenic potential, which would be likely to be more evident as survival of HIV patients lengthens, and treatment duration is prolonged [28, 29].

There was an increase in IRR of non-ADM over time in our cohort, with the highest rates being recorded in the later years of the follow-up period. All patients were observed exclusively in the HAART era (1997 through 2004), and HAART use among participants of the VACS is estimated at 80% [26, 30]. Data on use of HAART by individual patients in the cohort is not included in this analysis, and the potential impact of HAART on the incidence of malignancies was not evaluated. However, other studies have shown significantly higher incidence of non-ADMs in the HAART era, compared to the pre-HAART era [4, 8, 11, 27, 31]. We have shown that all studies that failed to show an increase in non-ADM rates in the HAART era had an average follow-up time of less than 1 year per patient in the HAART era. When follow-up time in the HAART era was greater than 1 year per patient, an increase in rates was oberved (author reply to Dal Maso et al [32]).

The strengths of our study include a thorough description of the VACS cohort, including ascertainment of the rates of several cancer risk factors, including smoking, substance abuse and HCV co-infection, which cannot be ascertained in population-based comparison groups [3, 7, 12][3, 4, 6]; matching, and a long median follow-up time, compared to some previous studies which allows more lag time for detection of cancer incidences [3, 6, 32]. In addition, for ascertainment of patient diagnoses (HIV and malignancy diagnoses) we used a validated method requiring at least 2 outpatient and one inpatient diagnostic codes, which maximizes the positive predictive value of the identification algorithm [15]. Our major limitations include the uneven distribution of some cancer risk factors (such as HCV infection) within the two groups and the overrepresentation of males making it difficult to adequately evaluate rates of female-specific cancers.

In conclusion, after adjusting for age, race and gender, the incidence of non-ADMs is significantly higher among HIV-infected than HIV-uninfected patients in the HAART era. This pattern is consistent throughout the observation period and is not only true of cancers associated with HCV infection or homosexual orientation. These trends warrant a high index of suspicion for malignancies among HIV providers, and a renewed focus on understanding the mechanisms underlying the increased rates.

Acknowledgments

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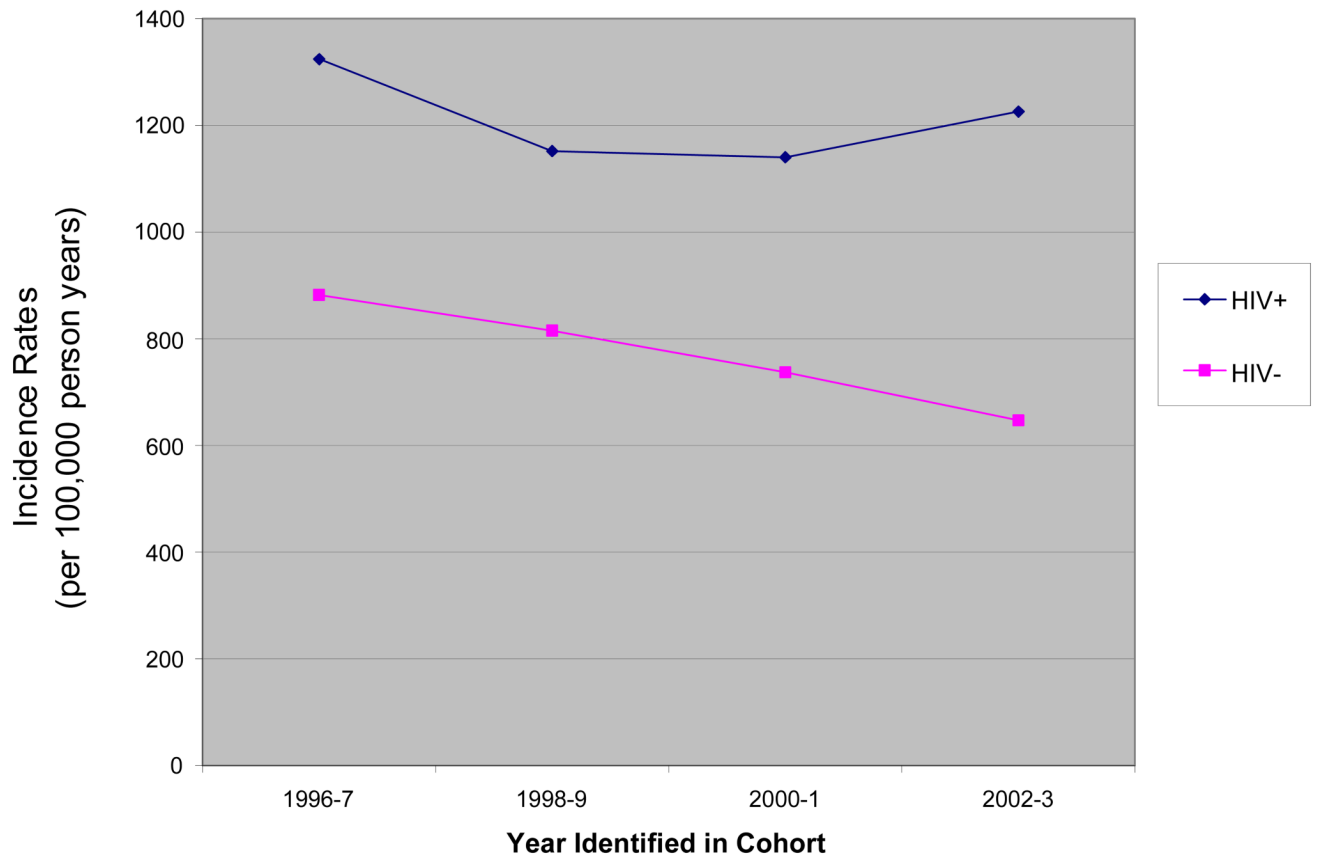
Figure 1.
Incidence Rates of Non-ADM, by Year Identified in Cohort

Table 1

Characteristics of VACS Virtual Cohort

	HIV-infected (n=32,942)	HIV-uninfected (n=64,966)
Age, mean in years (SD)	45.8 (10.0)	46.1 (10.1)
Female, No. (%)	724 (2.2)	1,430 (2.2)
Race/Ethnicity, No (%)		
White	10,665 (32.4)	21,141 (32.5)
Black	14,163 (43.0)	28,260 (43.5)
Hispanic	2,472 (7.5)	4,961 (7.6)
Other/Unknown	5,642 (17.1)	10,604 (16.3)
Year Identified (%)		
1997	15,298 (46.4)	30,235 (46.5)
1998	3,605 (10.9)	7,115 (11.0)
1999	2,850 (8.7)	5,649 (8.7)
2000	2,393 (7.3)	4,786 (7.4)
2001	2,361 (7.2)	4,661 (7.2)
2002	2,239 (6.8)	4,380 (6.7)
2003	2,307 (7.0)	4,473 (6.9)
2004	1,889 (5.7)	3,667 (5.6)
Median observation time in years	5.1	6.4
Median number of visits during year after first observation date (Interquartile Range)	5 (3–8)	2 (1–3)
Hepatitis C positive (%)	35.8	11.6
Alcohol abuse or dependence (%)	21.1	19.6

Table 2

IRs and IRRs of Cancers and CD4 Counts for HIV+ Patients

| Cancer | Frequency | | Incidence Rate[1] | | HIV+ to HIV− | | Median CD4 in HIV+ | | |
| | | | | | IRR[3] | | Cancer | | |
Type	HIV+	HIV−	HIV+	HIV−	IRR[3]	(95% CI)	Yes	No	P-value
Anal	195	29	111.2	7.4		14.9 (10.1–22.1)	156	270	<0.001
Lung	504	604	287.9	155.5		2.0 (1.8–2.2)	246	269	0.2
Melanoma	96	124	54.6	31.9		1.7 (1.3–2.3)	267	268	0.3
Prostate	441	1041	259.8	277.9		1.0 (0.9–1.1)	311	266	<.001
Hodgkin's	135	62	76.9	15.9		4.9 (3.6–6.6)	217	269	0.03
Liver	172	144	97.8	36.9		2.8 (2.2–3.5)	271	268	0.3
All non-ADM[2]	2128	3142	1260.5	841.8		1.6 (1.5–1.7)	249	270	.02
Kaposi's Sarcoma	661	7	382.3	1.80		209.8 (99.6–441.8)	160	272	<.001
NHL	691	196	398.1	50.4		8.02 (6.84–9.40)	171	272	<.001
Cervical	12	2	292.5	22.8		12.8 (2.9–57.3)	154	340	.03

[1] per 100,000 person-years

[2] includes all cancers except KS, lymphoma, cervical, skin, and ill-defined

[3] Incidence Rate Ratios (IRR) and 95% Confidence Intervals (CI) adjusted for age, race, and gender using Poisson models