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Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997–2012

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Abstract

Objective—Utilizing the Veterans Aging Cohort Study, the largest HIV cohort in North America, we conducted one of the few comprehensive comparisons of cancer incidence time

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trends in HIV-infected (HIV+) versus uninfected persons during the antiretroviral therapy (ART) era.

Design—Prospective cohort study.

Methods—We followed 44,787 HIV+ and 96,852 demographically-matched uninfected persons during 1997–2012. We calculated age-, sex-, and race/ethnicity-standardized incidence rates (IR) and incidence rate ratios (IRR, HIV+ versus uninfected) over four calendar periods with IR and IRR period trend p-values for cancer groupings and specific cancer types.

Results—We observed 3,714 incident cancer diagnoses in HIV+ and 5,760 in uninfected persons. The HIV+ all cancer crude IR increased between 1997–2000 and 2009–2012 (p-trend=0.0019). However, after standardization, we observed highly significant HIV+ IR declines for all cancer (25% decline; p-trend<0.0001), AIDS-defining cancers (ADC; 55% decline; p-trend<0.0001), non-AIDS-defining cancers (NADC; 15% decline; p-trend=0.0003), and non-virus-related NADC (20% decline; p-trend<0.0001); significant IRR declines for all cancer (from 2.0 to 1.6; p-trend<0.0001), ADC (from 19 to 5.5; p-trend<0.0001), and non-virus-related NADC (from 1.4 to 1.2; p-trend=0.049); and borderline significant IRR declines for NADC (from 1.6 to 1.4; p-trend=0.078) and virus-related NADC (from 4.9 to 3.5; p-trend=0.071).

Conclusion—Improved HIV care resulting in improved immune function most likely contributed to the HIV+ IR and the IRR declines. Further promotion of early and sustained ART, improved ART regimens, reduction of traditional cancer risk factor (e.g., smoking) prevalence, and evidence-based screening could contribute to future cancer incidence declines among HIV+ persons.

Keywords

acquired immunodeficiency syndrome; HIV infections; neoplasms; cancer; Veterans

INTRODUCTION

Cancer is a leading cause of death among persons living with HIV/AIDS [1–4]. Before the advent of combination antiretroviral therapy (ART) in 1996, AIDS-defining cancers (ADC; Kaposi sarcoma [KS], non-Hodgkin lymphoma [NHL], and invasive cervical cancer) represented most cancer cases among HIV-infected (HIV+) persons [5]. The introduction of ART was followed by a substantial ADC incidence rate (IR) decline [5–13]. Simultaneously, the increasing lifespan and consequent aging of the HIV+ population [14] resulted in an increased crude non-AIDS-defining cancer (NADC) IR [5, 6, 8, 12, 15] and a shift in cancer burden from ADC to NADC [5]. Although the crude NADC IR increased between the pre-ART and ART eras, once age and other demographic factors were taken into account, the NADC IR declined [5], remained steady [11], or increased [12, 13].

Cancer time trend studies restricted to the ART era have for the most part focused on a limited number of cancer types and have varied in range and recency of calendar years studied [11, 16–26]. Studies of adjusted IR time trends that classified NADC into broad groupings have produced inconsistent results [20, 23–25]. Evidence supports decreasing trends for lung cancer and Hodgkin lymphoma and an increasing trend for liver cancer, but

results for anal cancer have been inconsistent; many nonsignificant trends for specific NADC have been observed, perhaps due to insufficient statistical power [11, 16–19, 21–23, 26]. The ADC adjusted IR has continued to decline during the ART era [9, 11, 17, 18, 20, 23, 24].

Despite the continued decline of the ADC IR, the relative risk (HIV+ versus uninfected) remains elevated, even in the more recent ART era [9, 11, 23]. The relative risk for NADC (grouped) [11, 12, 20, 23] and for specific NADC, including oral cavity and pharynx, anal, lung, and liver cancers and Hodgkin lymphoma, is elevated as well [27–29]. However, few studies have examined time trends in cancer relative risk during the ART era [9, 16, 18, 19, 23]. Several of these studies compared HIV+ persons with the general population using standardized incidence ratios [18, 19], but we are aware of only one study (from Kaiser Permanente in California during 1996–2007) that examined cancer incidence rate ratio (IRR) time trends in HIV+ versus demographically-similar uninfected persons across a range of cancer groupings and specific types [23].

Our objective was to conduct a comprehensive assessment of cancer incidence time trends during the ART era (1997–2012) in the Veterans Aging Cohort Study (VACS), a large, national HIV cohort that includes a demographically-similar uninfected comparison group.

METHODS

The VACS is an open cohort assembled from national Veterans Health Administration (VA) databases (e.g., demographic, vital status, inpatient and outpatient encounters, laboratory results) with no direct researcher-patient contact [30]. VACS enrolls HIV+ Veterans when they begin HIV care in the VA and matches two uninfected Veterans by age, sex, race/ethnicity, and clinical site. VA Connecticut Healthcare System and Yale University Institutional Review Boards have approved this study.

We linked VACS to the Veterans Affairs Central Cancer Registry (VACCR), a national registry of cancer cases diagnosed or treated at the VA [31] and mapped International Classification of Diseases for Oncology, Third Edition (ICD-O-3) [32] topography and morphology codes from VACCR records to specific cancer types, consistent with Surveillance, Epidemiology, and End Results (SEER) recoding algorithms [33]. We then further classified select NADC anatomic sites (oral cavity and pharynx, anal, liver, vagina, vulva, penis) into virus-related NADC (virus-NADC; Appendix Table 1) and non-virus-related NADC (non-virus-NADC). We used the following cancer group classification: all cancer; ADC; all NADC; virus-NADC; non-virus-NADC; non-lung, non-virus-NADC; and poorly specified cancers (Appendix Table 1). For cancer group IR analyses, the endpoint for a given subject was the first diagnosis of a cancer type classified in the group. To calculate the proportion of cancer cases by cancer type or group, we included all incident cancer cases, not just the first diagnosis per subject. For example, a subject diagnosed with both prostate and colorectal cancer contributed two non-virus-NADC cases.

For each cancer group or type and calendar period (1997–2000, 2001–2004, 2005–2008, or 2009–2012), we used the direct method to calculate age-, sex-, and race/ethnicity-

standardized IRs [34] stratified by HIV status; a standardized IRR (HIV+ versus uninfected); and 95% confidence intervals (95% CI). Henceforth, “IR” and “IRR” signify standardized calculations, whereas “crude IR” signifies a non-standardized crude incidence rate. IRs provide information about HIV-status-specific absolute risk (after controlling for demographic factors) whereas IRRs provide information about risk in HIV+ relative to uninfected.

For direct standardization, we used the age (5-year groups), sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other/unknown) person-year distribution of the entire VACS as the standard weights, with age and calendar period classified at each day of observation [35]. We calculated observation time for each subject from 180 days after VACS entry date to the earliest of: diagnosis date for the specific cancer group or type being analyzed, death date, loss to follow-up date (last VA visit plus 180 days), or September 30, 2012. We excluded the first 180 days of observation time to remove prevalent cancer cases.

To calculate the IR p-trend across calendar periods, we used the Cochran-Armitage test of trend in counts to calculate the one degree-of freedom total chi-square statistic and p-value [36], taking the standardization into account. For the IRR p-trend across calendar periods, we calculated the one degree-of freedom Mantel-Haenszel chi-square statistic and p-value [37, 38].

We performed statistical analyses using SAS version 9.4 [39]. We defined statistical significance as $p<0.05$ (two-sided).

RESULTS

Between 1997 and 2012, among the 44,787 HIV+ persons who contributed 329,084 person-years of observation time to this analysis, 3,519 persons developed 3,714 incident primary cancers. Among 96,852 uninfected persons who contributed 820,676 person-years, 5,434 persons developed 5,760 incident primary cancers. HIV+ and uninfected persons had similar distributions of age, sex, race/ethnicity, alcohol abuse/dependence, and smoking status (Table 1). The mean age at cohort entry was 48 years. Both groups were mostly male and approximately half non-Hispanic black. Hepatitis C virus (HCV) and hepatitis B virus (HBV) infections were more prevalent among HIV+ persons (21% HCV chronic, 3% HBV +) than uninfected persons (10% HCV chronic, 0.3% HBV+). Of total observation time, 16% was in 1997–2000, 25% in 2001–2004, and 30% each in 2005–2008 and 2009–2012.

All cancer

Although the all cancer crude IR increased over the four periods in the HIV+ (p-trend=0.0019, Figure 1), once age-, sex-, and race/ethnicity-standardized, the IR declined significantly (p-trend<0.0001). In the uninfected, the increase in the crude all cancer IR (p-trend<0.0001) was more pronounced than in HIV+, but there was no significant trend in the standardized IR (p-trend=0.074). With decreasing HIV+ IRs and stable uninfected IRs, the IRR declined (p-trend<0.0001, Figure 2), but remained elevated during the most recent calendar period (IRR=1.6; 95% CI: 1.5–1.7; Table 2).

AIDS-defining cancers

Among HIV+, the proportion of cancer cases that were ADC decreased from 31% in 1997–2000 to 11% in 2009–2012 (Figure 3). The ADC IR decreased in the HIV+ across the four periods (p-trend<0.0001; Table 2). In the uninfected, the IR increased modestly (p-trend=0.014), driven by the increase in the NHL IR (Table 2). Resultant IRRs decreased significantly across periods (p-trend<0.0001; Figure 2), but remained elevated in the most recent period (IRR=5.5; 95% CI: 3.7–8.4). In the HIV+, both the NHL and KS IR declined by more than one-half between 1997–2000 and 2009–2012 (both p-trends<0.0001). In the uninfected, the NHL IR increased across periods (p-trend=0.021), and there were no KS cases. The NHL IRR dropped from 12 (95% CI: 5.8–24) in 1997–2000 to 3.6 (95% CI: 2.3–5.5) in 2009–2012 (p-trend<0.0001). Due to the small proportion of females (3%), invasive cervical cancer did not meaningfully contribute to the ADC time trends.

Virus-related non-AIDS-defining cancers

Among HIV+, the proportion of cancer cases that were virus-NADC increased from 16% in 1997–2000 to 21% in 2009–2012 (Figure 3). In the latter period, 44% of virus-NADC were hepatocellular carcinoma (HCC) and 33% were anal squamous cell carcinoma (SCC). The virus-NADC IR was stable for HIV+ (p-trend=0.43, Table 2) but increased significantly for uninfected (p-trend=0.0082), driven by an increasing HCC IR trend. Consequently, the virus-NADC IRR decreased across the four periods with a borderline significant trend (p-trend=0.071; Figure 2), but remained elevated during the most recent period (IRR=3.5; 95% CI: 2.7–4.5; Table 2). The HCC IR increased in HIV+ (p-trend=0.043), but moreso in uninfected (p-trend<0.0001), resulting in an IRR decrease from 9.8 (95% CI: 2.9–33) in 1997–2000 to 2.1 (95% CI: 1.5–2.8) in 2009–2012 (p-trend=0.0002). The human papillomavirus (HPV)-related oral cavity and pharynx SCC IR did not change significantly for HIV+ (p-trend=0.43), but decreased in the uninfected (p-trend=0.023), resulting in an increasing IRR trend (p-trend=0.048). We observed no trend in the anal SCC IR or IRR. In HIV+ between 1997–2000 and 2001–2004, the Hodgkin lymphoma IR fell from 55 to 28 cases per 100,000 person-years and then stabilized (p-trend=0.047), with no IRR trend (p-trend=0.79). For each mentioned virus-NADC, we found a significantly elevated IRR in the most recent calendar period.

Non-virus-related non-AIDS-defining cancers

Among HIV+, the proportion of cancer cases that were non-virus-NADC increased from 51% in 1997–2000 to 68% in 2009–2012 (Figure 3). Thus, the majority of incident cancer cases were non-virus-NADC, which includes common cancer types such as colorectal, lung, and prostate. During 2009–2012, 27% of non-virus-NADC were lung cancers and 35% were prostate cancers. We observed a decreasing trend for the HIV+ IR (p-trend<0.0001; Table 2), uninfected IR (p-trend=0.0011), and IRR (p=0.049; Figure 2), but the IRR remained slightly elevated during the most recent period (IRR=1.2; 95% CI: 1.1–1.3). The lung cancer IR decreased significantly in both HIV+ (p-trend=0.0008) and uninfected (p-trend=0.0017), with the IRR significantly elevated between 1.7 and 2.0 over the four periods (p-trend=0.52). Lung cancer was the only non-virus-NADC type with consistently elevated IRRs across periods. After removing lung cancer from the non-virus-NADC group, the IRR trend was no

longer significant (p-trend=0.12) and the IRR moved toward the null and was only marginally or borderline significant in each calendar period.

DISCUSSION

We utilized the largest HIV cohort in North America to conduct one of the few comprehensive assessments of cancer incidence time trends among HIV+ versus uninfected patients during the ART era. We observed a growing cancer burden among HIV+, evidenced by an increasing crude IR trend. However, after taking age, sex, and race/ethnicity into account, we observed highly significant HIV+ IR declines for all cancer (25% decline between 1997–2000 and 2009–2012), ADC (55% decline), NADC (15% decline), and non-virus-NADC (20% decline); highly significant IRR declines for all cancer (from 2.0 to 1.6) and ADC (from 19 to 5.5); and marginally or borderline significant IRR declines for NADC (from 1.6 to 1.4), virus-NADC (from 4.9 to 3.5), and non-virus-NADC (from 1.4 to 1.2). While these declines were encouraging, it is important to note that the all cancer IR was still 60% higher in HIV+ compared with uninfected in 2009–2012, driven mainly by ADC, virus-NADC, and within the non-virus-NADC group, lung cancer (IRR=1.8).

We found that the continuing decline in the HIV+ ADC IR and the ADC IRR during the ART era that also has been observed by others [9, 11, 17, 18, 20, 23, 24] has extended through 2012 both for ADC overall and for KS and NHL, the main ADC components in our predominantly male cohort. The significant HIV+ NADC IR decline that we observed during the ART era was not observed by others [11, 22], perhaps due to shorter calendar times of observation or fewer cancer diagnoses resulting in less statistical power. However, the NADC IRR decline that we observed, which took into account the decline in the uninfected NADC IR that also occurred during the observation period, was only borderline significant, similar to the Kaiser Permanente California result [23].

We found no evidence for a trend in the HIV+ virus-NADC IR, consistent with findings from the HIV Outpatient Study [24], but inconsistent with a study from northern Italy, which observed an increasing trend (but with no reported p-trend) [20] and with the Kaiser study, which observed a significant decreasing trend [23]. However, the borderline significant decreasing trend that we observed in the virus-NADC IRR, which took into account the increasing uninfected virus-NADC IR trend (driven by the increasing HCC IR trend), was consistent with the significant decreasing IRR trend observed in the Kaiser study [23]. In the VACS cohort, HCC accounted for almost 40% of virus-NADC among HIV+ and almost 60% of virus-NADC among uninfected persons. HCC may be less common in other populations, accounting for differences in virus-NADC trends.

The significant decreasing trend we observed in the HIV+ non-virus-NADC IR was consistent with findings from the HIV Outpatient Study [24], but inconsistent with results from northern Italy, where a borderline significant increasing trend was observed [25] and from Kaiser, where no trend was observed, either in the HIV+ IR or in the IRR [23]. The decreasing non-virus-NADC IRR trend that we observed, which took the decreasing uninfected non-virus-NADC IR trend into account, was only marginally significant. Furthermore, removal of lung cancer, the only non-virus-NADC with an elevated IRR in

each of the four periods, resulted in a nonsignificant IRR trend with marginally or borderline significant period-specific IRRs of only 1.1 to 1.2. This reflected the fact that most of the common epithelial cancer types, including colorectal and prostate, did not exhibit elevated incidence in HIV+ patients, consistent with the literature [27, 28]. We observed no trend in the prostate cancer IR in either HIV+ or uninfected persons, with the IRR consistently null across the four periods. These results suggested stable prostate specific antigen screening rates during 1996–2012, with similar screening rates in HIV+ and uninfected persons.

With respect to specific NADC types, the decreasing HIV+ IR trends for lung cancer and Hodgkin lymphoma and the increasing trend for HCC were consistent with previous reports [17–19]. However, we observed no trend in the lung cancer IRR, which took into account the decreasing uninfected lung cancer IR trend. This result was inconsistent with studies that observed a decreasing lung cancer IRR (or SIR) trend [18, 19, 23]. Furthermore, we observed a decreasing HCC IRR trend, which was driven by the steeply increasing uninfected HCC IR trend. Other studies have observed no HCC IRR (or SIR) trend [18, 19, 23]. We observed no trend in the HIV+ anal cancer IR or in the IRR; trends observed in other studies have been inconsistent [16–19, 22, 23, 26].

In general, time trends in cancer incidence are determined by secular trends in the prevalence of cancer risk factors. The decreasing lung cancer and increasing HCC IR trends in both HIV+ and uninfected were consistent with secular trends in the United States general population [40], driven by decreasing smoking prevalence [41] and increasing duration of chronic HCV infection [42], respectively.

Among HIV+ persons, the prevalence of traditional cancer risk factors, particularly smoking and oncogenic virus infections, is elevated [43], although prevalence time trends have not been well-characterized. Furthermore, impaired immune function and inflammation resulting from HIV infection itself are associated with appreciable cancer risk [27, 44]. The strong inverse association between CD4 count and ADC risk is well-established, and evidence has accumulated in favor of a weaker, more subtle inverse association between CD4 count and risk for virus-NADC and possibly some non-virus-NADC [27, 44]. Thus, the decreasing ADC trends were probably driven by improvements in HIV care since the introduction of ART, including higher CD4 count at diagnosis [45], earlier post-diagnosis initiation of ART [46], improved ART regimens [47, 48], increased ART adherence [49], and increased virological suppression [49, 50]. These HIV care trends likely contributed to the decreasing NADC trends as well.

We found that among HIV+ persons the shift in cancer burden from ADC to NADC (especially non-virus-NADC) has continued (Figure 3). By 2009–2012, only 11% of HIV+ cancer cases were ADC, and four of the five most commonly diagnosed cancer types (prostate, lung, HCC, NHL, and anal SCC) were NADC, although prostate cancer did not exhibit elevated incidence among HIV+ persons.

Our results have implications for cancer prevention among HIV+ persons. First, given the continued elevated ADC and NADC IRRs and the association between impaired immune function and increased ADC and, to a lesser extent, NADC risk, it is likely that even further

improvements in HIV care would result in further declines in cancer incidence, especially for NHL, now the most common ADC.

Second, lung, liver, anal, and prostate cancers represent targets for prevention due to their high incidence. Prevention research efforts in the setting of HIV infection should include smoking cessation [51, 52]; validation and optimization of computed tomography screening for lung cancer [53, 54], ultrasonography screening for HCC [55], and anal dysplasia screening for anal cancer [56]; optimization of HBV vaccination for HCC [57, 58] and HPV vaccination for HPV-related cancers [59–63]; and optimization of HCV [64, 65], HBV [57, 66], and alcohol abuse/dependence treatment [67, 68] for HCC. Prostate specific antigen screening for prostate cancer is controversial [69].

Our study had limitations. First, due to the paucity of females in VACS, we were unable to assess female cancer type time trends or to generalize our results to females. Second, VACCR does not capture 10–20% of cancer cases, in part due to utilization of healthcare outside the VA system [29, 31], resulting in underestimation of IRs. However, in a validation study we determined that IRRs are either unbiased or possibly biased downward [29], meaning that the “true” IRRs would be at least as high as the IRRs we observed. The elevated IRRs we observed were generally consistent with the literature [27, 28].

Our study also had strengths. First, VACS is the largest HIV cohort in North America and one of the few to include a demographically-similar uninfected comparison group, which is superior to a general population comparison group for identifying HIV-specific effects. Second, although cancer case ascertainment was incomplete, the positive predictive value of VACCR diagnoses is high [29]. Finally, our study extended from the start of the ART era through 2012, the most extensive cancer time trends study performed to date.

In summary, after adjusting for demographic factors, we observed a generalized decline in both absolute and relative cancer incidence among HIV+ persons during the ART era. HIV+ IRs declined for all cancer groups except virus-NADC, and IRRs declined for all cancer groups, although IRR trends for NADC, virus-NADC and non-virus-NADC were only marginally or borderline significant. In spite of these declines, the all cancer IR remained 60% higher in HIV+ compared with uninfected in 2009–2012, driven mainly by elevated IRRs for ADC, virus-NADC, and lung cancer. Improved HIV care most likely contributed to the declines, and we could anticipate that further adoption of early and sustained ART combined with ongoing ART regimen enhancements will produce additional declines in cancer incidence. Research and clinical practice efforts to reduce cancer risk factor prevalence and to promote evidence-based screening could also contribute to future cancer incidence declines among HIV+ persons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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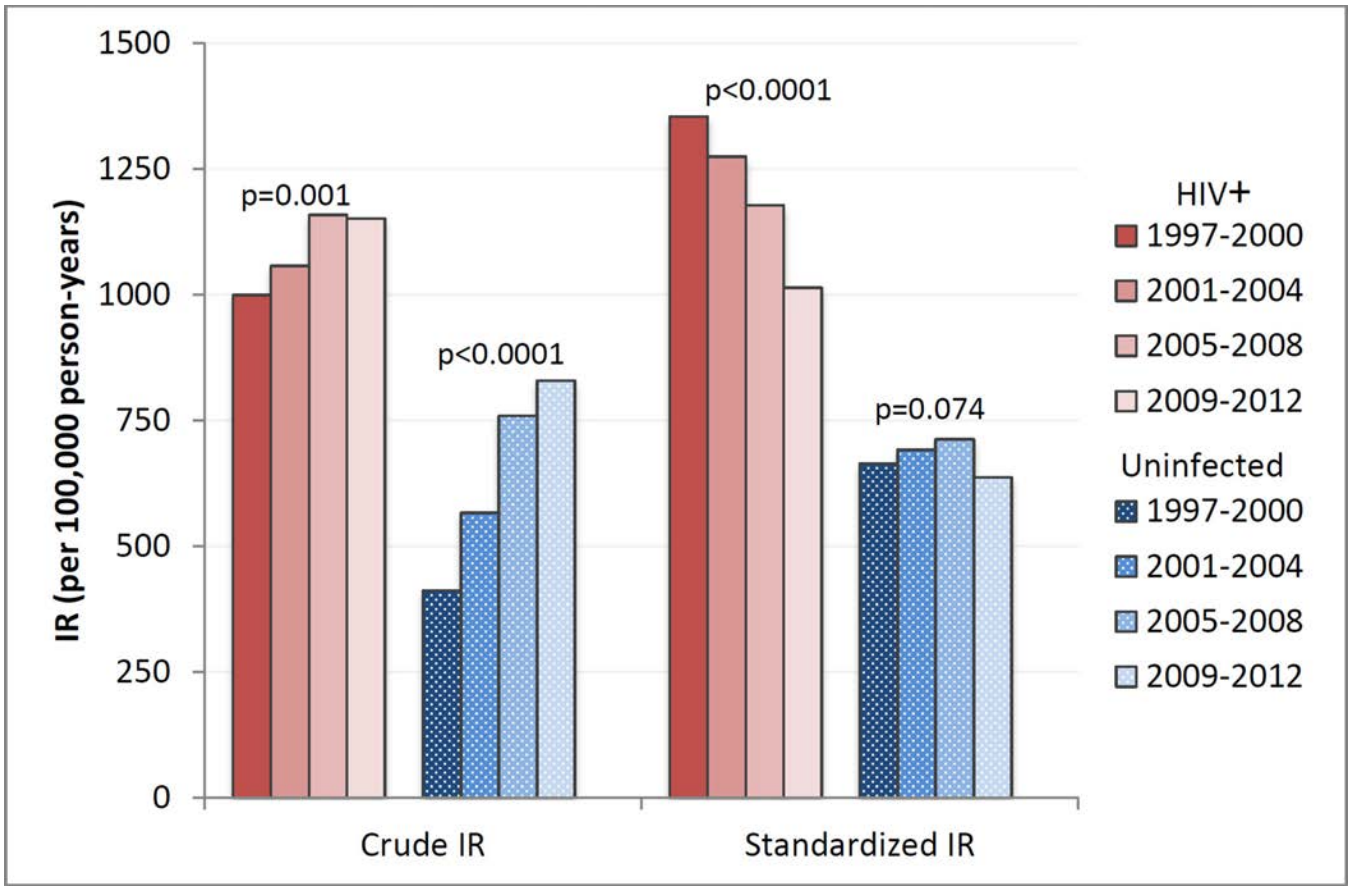

Figure 1. All cancer crude and standardized IRs by HIV status and calendar period and p-values for IR period trend

HIV+, HIV-infected; IR, incidence rate.

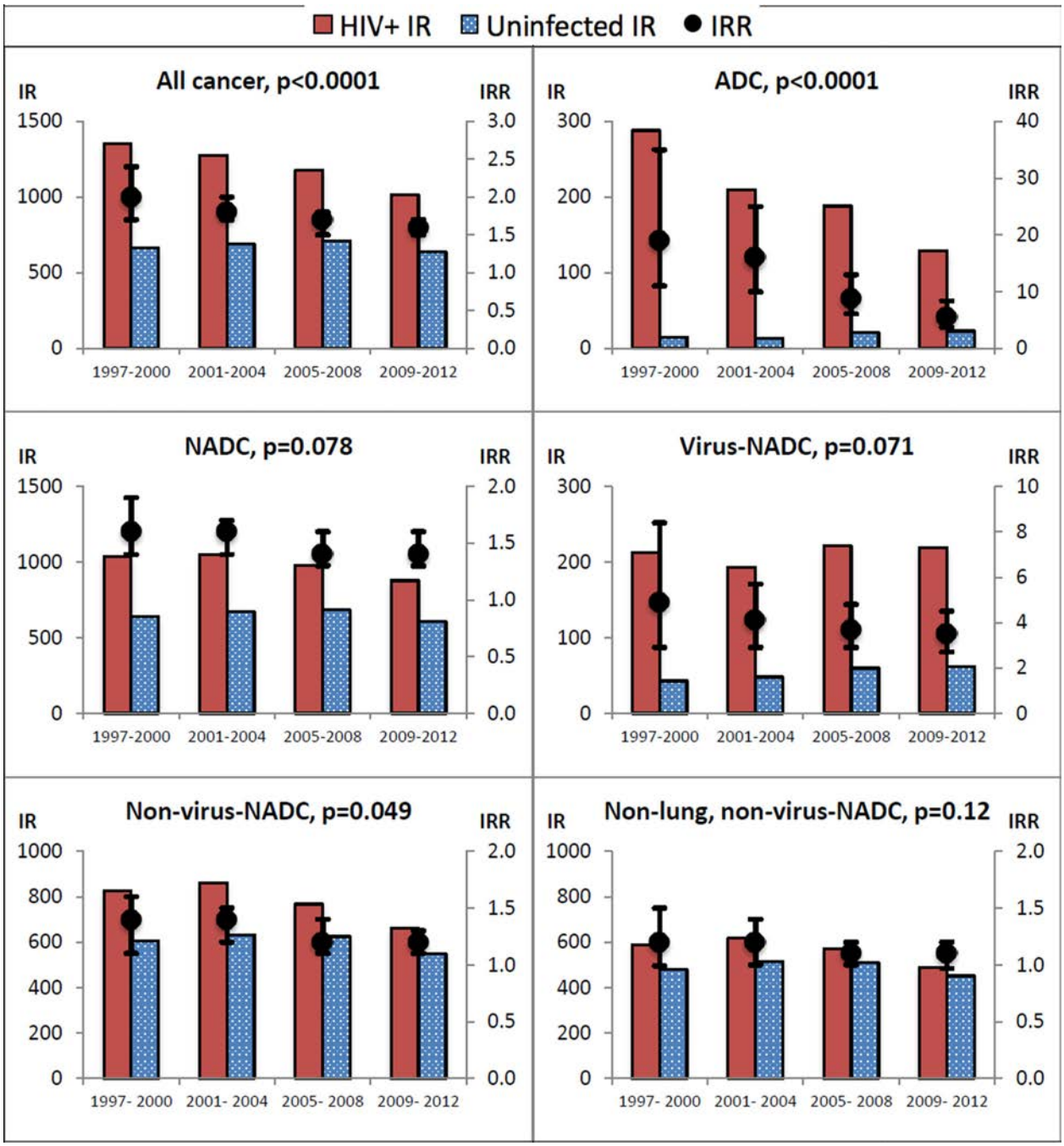

Figure 2. Cancer group IRs (per 100,000 person-years) by HIV status and calendar period, IRRs with 95% confidence intervals by period, and p-values for IRR period trend

ADC, AIDS-defining cancer; HIV+, HIV-infected; IR, standardized incidence rate; IRR, standardized incidence rate ratio; NADC, non-AIDS-defining cancer; Non-virus-NADC, non-virus-related non-AIDS-defining cancer; Virus-NADC, virus-related non-AIDS-defining cancer. Note that Y-axis scale varies by cancer group.

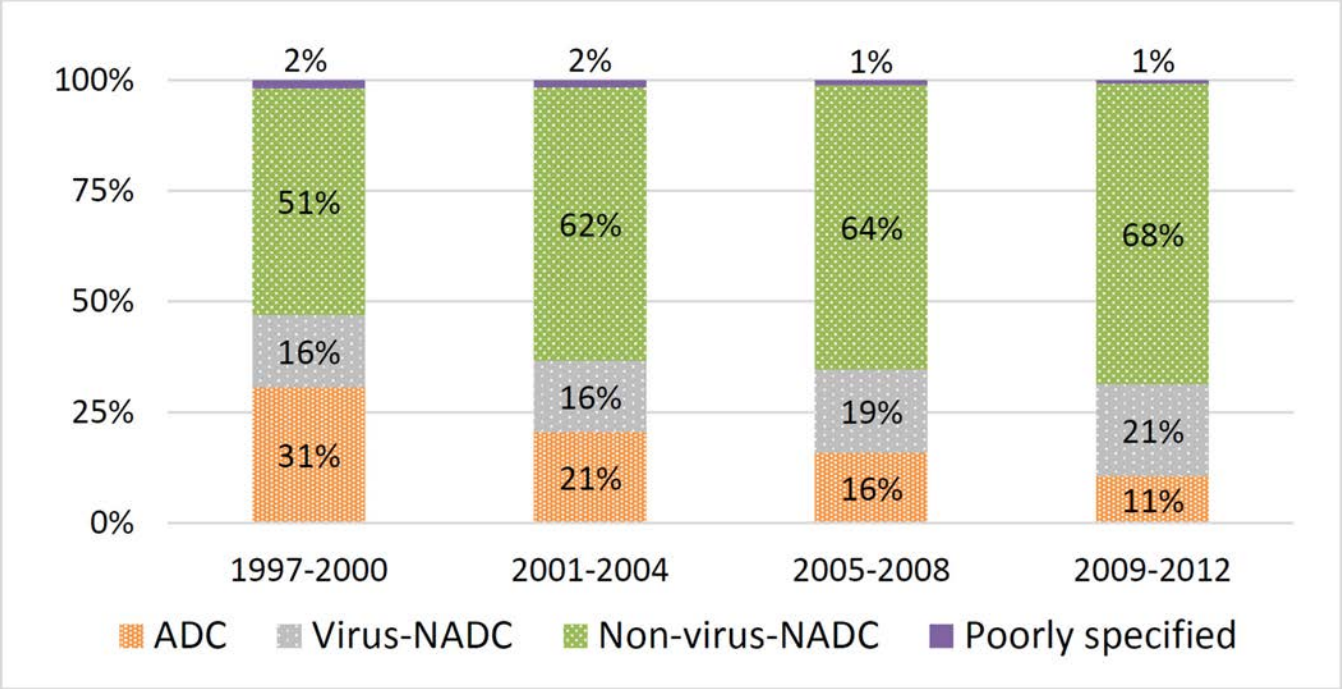

Figure 3. Proportion of cancer cases among HIV+ patients by cancer group in each calendar period

ADC, AIDS-defining cancer; HIV+, HIV-infected; Non-virus-NADC, non-virus-related non-AIDS-defining cancer; Virus-NADC, virus-related non-AIDS-defining cancer. To calculate cancer group proportions, we included all incident cancer cases, not just the first diagnosis for each subject. For example, a subject diagnosed with both Kaposi sarcoma and colorectal cancer during the observation period contributed one ADC case and one non-virus-NADC case, and a subject diagnosed with both hepatocellular carcinoma and Hodgkin lymphoma contributed two virus-NADC cases.

Table 1

Baseline characteristics of subjects who contributed observation time.

	HIV+ (N=44,787)		Uninfected (N=96,852)	
	N	%	N	%
Age at enrollment years				
20–29	1,973	4	4,077	4
30–39	8,210	18	17,138	18
40–49	17,574	39	37,157	38
50–59	11,632	26	25,929	27
60–69	4,174	9	9,580	10
≥70	1,224	3	2,971	3
Sex				
Female	1,119	2	2,583	3
Male	43,668	98	94,269	97
Race/ethnicity				
Non-Hispanic white	17,311	39	38,138	39
Non-Hispanic black	21,888	49	45,676	47
Hispanic	3,191	7	7,418	8
Other/unknown	2,397	5	5,620	6
Alcohol abuse/dependence				
No	29,487	66	65,117	67
Yes	15,300	34	31,735	33
Smoking status				
Never	9,856	22	24,919	26
Ever	27,395	61	59,647	62
Unknown	7,536	17	12,286	13
Hepatitis C virus status[a]				
HCV negative	24,166	54	51,628	53
Chronic HCV	9,423	21	9,694	10
HCV exposure	3,453	8	3,967	4
Never tested/unknown	7,745	17	31,563	33
Hepatitis B virus status[b]				
HBV negative	31,317	70	41,279	43
HBV positive	1,181	3	282	0.3
HBV acute resolved	428	1	153	0.2
Unconfirmed HBV	570	1	177	0.2
Never tested/unknown	11,291	25	54,961	57

[a]Definitions: HCV negative, negative HCV antibody test result(s) only; Chronic HCV, positive HCV RNA test; HCV exposure, positive HCV antibody test, but negative or unknown HCV RNA test; Never tested/unknown, no HCV laboratory test results available.

[b]Definitions: HBV negative, negative HBV surface antigen test result(s) only; HBV positive, at least two positive HBV surface antigen tests over 6 months apart; HBV acute resolved, positive HBV surface antigen test followed by only negative test results; Unconfirmed HBV, one positive HBV surface antigen test not confirmed with additional testing; Never tested/unknown, no HBV laboratory test results available.

Table 2

Numbers of cancer cases, IRs (per 100,000 person-years) and IRRs with 95% CI by calendar period, and p-values for period trend, for cancer groups and specific cancer types

Cancer group/ type	HIV	1997–2000				2001–2004				2005–2008				2009–2012				IR p-trend	IRR p-trend
		# ca	IR	IRR	95% CI	# ca	IR	IRR	95% CI	# ca	IR	IRR	95% CI	# ca	IR	IRR	95% CI		
All cancer																			
Grouped[a]	+	561	1,354	2.0	1.7–2.4	855	1,274	1.8	1.7–2.0	1,061	1,177	1.7	1.5–1.8	1,042	1,013	1.6	1.5–1.7	<0.0001	<0.0001
	−	516	664			1,137	692			1,827	712			1,954	636			0.074	
ADC																			
Grouped[a]	+	174	288	19	11–35	183	210	16	10–25	177	188	8.8	6.1–13	117	129	5.5	3.7–8.4	<0.0001	<0.0001
	−	14	15			24	13			56	21			71	23			0.014	
Non-Hodgkin lymphoma	+	94	173	12	5.8–24	113	134	10	6.1–17	105	110	5.1	3.4–7.7	77	82	3.6	2.3–5.5	<0.0001	<0.0001
	−	14	15			24	13			56	21			70	23			0.021	
Kaposi sarcoma	+	82	117	-		72	78	-		74	79	-		40	47	-		<0.0001	≠[c]
	−	0	0			0	0			0	0			0	0			≠	
NADC																			
Grouped[a]	+	380	1,039	1.6	1.4–1.9	671	1,050	1.6	1.4–1.7	885	979	1.4	1.3–1.6	929	878	1.4	1.3–1.6	0.0003	0.078
	−	494	639			1,107	675			1,755	684			1,867	607			0.028	
Virus-NADC																			
Grouped[a]	+	92	212	4.9	2.9–8.4	142	193	4.1	2.9–5.7	211	222	3.7	2.9–4.8	227	219	3.5	2.7–4.5	0.43	0.071
	−	36	43			89	48			162	60			202	62			0.0082	
HPV-related oral cavity and pharynx SCC	+	7	18	0.61	0.24–1.5	17	26	1.3	0.67–2.4	21	21	1.2	0.69–2.0	29	27	1.7	1.0–2.9	0.43	0.048
	−	22	29			37	20			49	18			49	16			0.023	
Anal SCC	+	29	67	94	12–717	60	73	26	10–66	69	72	33	14–77	76	76	77	28–218	0.61	0.16

Cancer group/ type	HIV	1997–2000 # ca	IR	IRR	95% CI	2001–2004 # ca	IR	IRR	95% CI	2005–2008 # ca	IR	IRR	95% CI	2009–2012 # ca	IR	IRR	95% CI	IR p-trend	IRR p-trend
	−	1	1			5	3			6	2			4	1			0.61	
Liver HCC	+	26	63	9.8	2.9–33	43	64	3.3	1.8–5.9	91	95	2.7	1.9–3.9	101	87	2.1	1.5–2.8	0.043	0.0002
	−	8	6			36	19			96	35			142	42			<0.0001	
Penis SCC[b]	+	3	7	3.3	0.20–54	3	5	4.9	0.42–57	5	5	4.1	0.73–23	3	3	5.8	0.46–73	0.22	≠
	−	1	2			2	1			3	1			1	0			≠	
Hodgkin lymphoma	+	27	55	12	2.9–51	22	28	6.5	2.4–18	27	29	8.7	3.4–23	23	29	9.3	3.1–28	0.047	0.79
	−	4	5			9	4			8	3			6	3			0.46	
Non-virus-NADC Grouped[a]	+	290	825	1.4	1.1–1.6	538	862	1.4	1.2–1.5	692	767	1.2	1.1–1.4	721	661	1.2	1.1–1.3	<0.0001	0.049
	−	465	605			1,031	633			1,603	625			1,688	548			0.0011	
Non-lung, non-virus NADC, grouped[a]	+	199	586	1.2	0.99–1.5	387	617	1.2	1.0–1.4	515	570	1.1	1.0–1.2	535	488	1.1	0.97–1.2	0.0011	0.12
	−	368	479			843	515			1,315	511			1,384	452			0.022	
Non-HPV-related oral cavity and pharynx SCC	+	15	40	1.4	0.65–3.2	27	34	1.3	0.75–2.1	32	33	1.8	1.1–2.9	26	24	1.4	0.80–2.3	0.10	0.86
	−	26	28			49	27			50	19			53	18			0.013	
Oral cavity and pharynx non-SCC	+	1	1	0.58	.069–4.9	1	1	0.18	.035–0.97	3	3	0.90	0.25–3.2	2	2	0.74	0.17–3.2	≠	≠
	−	3	2			8	5			9	3			8	3			0.67	
Esophagus	+	3	13	0.75	0.20–2.7	10	14	0.86	0.40–1.8	14	15	0.92	0.51–1.7	15	12	0.81	0.46–1.4	0.71	1.00
	−	11	17			29	17			46	17			47	15			0.52	
Stomach	+	4	17	3.0	0.36–24	7	10	0.96	0.38–2.4	9	10	0.79	0.39–1.6	14	11	1.1	0.58–2.3	0.73	0.51
	−	7	6			18	11			33	13			30	10			0.36	

Cancer group/ type	HIV	1997–2000 # ca	IR	IRR	95% CI	2001–2004 # ca	IR	IRR	95% CI	2005–2008 # ca	IR	IRR	95% CI	2009–2012 # ca	IR	IRR	95% CI	IR p-trend	IRR p-trend
Small Intestine	+	1	8	4.8	.095–239	0	0	0	–	0	0	0	–	4	4	2.3	0.42–13	≠	≠
	−	2	2			7	4			8	3			6	2			0.58	
Colorectal	+	17	44	0.95	0.47–1.9	41	63	1.2	0.81–1.8	57	62	1.1	0.79–1.5	39	36	0.94	0.65–1.4	0.15	0.63
	−	36	46			91	52			154	57			122	38			0.079	
Liver non-HCC	+	4	12	4.0	0.48–34	1	2	0.67	.098–4.6	5	6	3.9	0.73–21	4	4	3.4	0.56–21	0.24	0.81
	−	2	3			5	3			4	1			3	1			0.14	
Biliary tract	+	0	0	0	–	2	2	1.5	0.22–11	5	5	3.5	0.69–18	4	4	0.93	0.31–2.8	≠	≠
	−	1	1			3	1			4	2			14	4			0.0068	
Pancreas	+	4	10	1.5	0.32–7.3	6	8	0.77	0.31–1.9	18	19	1.3	0.70–2.3	24	21	1.3	0.75–2.2	0.031	0.71
	-	8	7			19	11			42	15			54	16			0.0069	
Nasal cavity, middle ear, and sinus	+	5	7	-	–	1	1	0.56	.080–4.0	2	2	2.0	0.25–16	4	3	9.8	0.76–127	0.29	≠
	−	0	0			4	2			3	1			1	0			≠	
Larynx	+	15	35	1.4	0.61–3.0	24	39	1.7	0.95–3.2	23	25	1.3	0.74–2.1	18	14	1.3	0.71–2.5	0.0013	0.68
	−	20	26			43	22			53	20			37	11			0.0002	
Lung and bronchus	+	92	240	1.9	1.3–2.7	155	246	2.0	1.5–2.5	190	202	1.7	1.4–2.0	200	175	1.8	1.5–2.2	0.0008	0.52
	−	100	129			205	125			324	122			333	98			0.0017	
Soft tissue	+	2	7	2.6	0.21–31	6	7	7.9	1.1–55	5	5	2.2	0.57–8.8	5	5	1.3	0.38–4.3	0.66	0.15
	−	4	3			2	1			7	2			11	4			0.12	
Melanoma skin	+	9	15	1.3	0.43–3.7	16	20	2.9	1.2–7.0	22	23	2.1	1.1–3.9	12	11	0.97	0.49–1.9	0.41	0.28
	−	10	12			13	7			30	11			35	11			0.54	
Male breast[b]	+	2	9	3.5	0.23–54	1	1	0.50	.071–3.5	0	0	0	–	1	1	0.45	.072–2.8	≠	≠
	−	1	2			4	2			3	1			5	1			0.42	

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Cancer group/ type	HIV	1997–2000 # ca	IR	IRR	95% CI	2001–2004 # ca	IR	IRR	95% CI	2005–2008 # ca	IR	IRR	95% CI	2009–2012 # ca	IR	IRR	95% CI	IR p-trend	IRR p-trend
Female breast[b]	+	0	0	0	–	3	326	2.6	0.30–23	3	105	0.86	0.24–3.2	2	78	0.86	0.19–3.8	≠	≠
	−	2	264			4	125			8	121			8	91			0.24	
Prostate[b]	+	55	206	0.91	0.65–1.3	142	265	1.1	0.87–1.3	204	233	0.93	0.80–1.1	263	232	1.0	0.89–1.2	0.89	0.77
	−	146	227			374	247			635	250			715	226			0.37	
Testis[b]	+	0	0	0	–	3	3	1.3	0.29–5.9	3	4	1.2	0.28–5.0	2	2	1.8	0.21–16	≠	≠
	−	3	1			5	2			6	3			2	1			0.71	
Bladder	+	7	17	0.49	0.21–1.1	17	27	1.4	0.70–2.6	13	13	1.0	0.53–1.9	25	22	1.6	0.90–2.8	0.92	0.040
	−	28	34			30	20			36	13			49	14			0.0003	
Kidney	+	12	32	2.3	0.79–6.5	22	31	1.2	0.67–2.0	31	31	0.89	0.60–1.3	31	30	0.94	0.62–1.4	0.84	0.075
	−	18	14			48	27			94	35			92	32			0.0028	
Brain and nervous system	+	4	6	2.0	0.38–11	0	0	0	–	4	4	1.0	0.31–3.2	1	1	0.39	.077–2.0	≠	≠
	−	3	3			8	5			10	4			8	2			0.36	
Thyroid	+	1	1	0.31	.029–3.4	3	4	0.68	0.20–2.3	5	5	0.56	0.24–1.3	7	8	0.71	0.32–1.6	0.013	0.65
	−	3	3			12	6			22	9			27	12			0.0032	
Other lymphatic and hematopoietic tissue	+	4	8	2.2	0.28–17	9	15	2.3	0.73–7.3	14	15	1.9	0.87–4.3	7	8	1.2	0.47–3.1	0.73	0.28
	−	4	4			11	6			18	8			23	7			0.46	
Myeloma	+	8	20	2.5	0.67–9.6	5	8	0.71	0.26–1.9	11	12	1.0	0.52–2.1	8	7	0.73	0.34–1.6	0.074	0.12
	−	8	8			18	12			30	11			27	10			0.96	
Leukemia	+	9	28	2.1	0.65–6.9	10	16	1.0	0.48–2.3	17	18	1.5	0.79–2.9	14	14	1.8	0.80–4.0	0.18	0.85
	−	11	13			25	15			31	12			21	8			0.037	
Other	+	15	39	1.7	0.76–4.0	24	32	2.4	1.2–4.7	26	27	2.6	1.4–4.9	15	13	1.2	0.59–2.3	0.0010	0.40

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Cancer group/ type	HIV	1997–2000 # ca	IR	IRR	95% CI	2001–2004 # ca	IR	IRR	95% CI	2005–2008 # ca	IR	IRR	95% CI	2009–2012 # ca	IR	IRR	95% CI	IR p-trend	IRR p-trend
	−	17	23			27	13			29	11			32	11			0.032	
Poorly specified																			
Grouped[a]	+	11	31	3.0	0.83–11	15	20	3.2	1.3–8.4	13	14	1.7	0.78–3.6	9	8	1.0	0.48–2.3	0.0009	0.020
	−	8	10			11	6			22	8			28	8			0.82	

ADC, AIDS-defining cancer; ca, cancer; HCC, hepatocellular carcinoma; IR, standardized incidence rate; IRR, standardized incidence rate ratio; KS, Kaposi sarcoma; NADC, non-AIDS-defining cancer; NHL, non-Hodgkin lymphoma; Non-virus-NADC, non-virus-related non-AIDS defining cancer; SCC, squamous cell carcinoma; Virus-NADC, virus-related non-AIDS defining cancer; 95% CI, 95% confidence interval.

[a]For cancer group analyses, the endpoint for a given subject was the first diagnosis of a cancer type classified in the group.

[b]We used sex-specific weights to calculate penis SCC and male breast, female breast, prostate, and testicular cancer IRs.

[c]≠denotes cancer types with less than 12 cases in HIV+ or uninfected over the entire study period (p-trend not calculated).The following cancer types had less than 12 HIV+ cases and less than 12 uninfected cases over the entire study period and were not included in the table: invasive cervical (1 HIV+, 1 uninfected); vulva SCC (1 HIV+); anal non-SCC (4 HIV+, 3 uninfected); retroperitoneum and peritoneum, non-mesothelioma (1 HIV+, 3 uninfected); other digestive organ (3 HIV+, 1 uninfected); pleura, non-mesothelioma (1 HIV+, 0 uninfected); trachea, mediastinum, and other respiratory organ (0 HIV+, 1 uninfected); bone and joint (1 HIV+, 1 uninfected); non-epithelial skin (11 HIV+, 7 uninfected); uterus or corpus (0 HIV+, 3 uninfected); ovary (0 HIV+, 2 uninfected); other male genital organ (3 HIV+, 1 uninfected); other urinary organ (5 HIV+, 9 uninfected); eye and orbit (3 HIV+, 4 uninfected); other endocrine organ including thymus (1 HIV+, 7 uninfected); and mesothelioma (4 HIV+, 7 uninfected). The following cancer types had no HIV+ cases and no uninfected cases: vagina SCC; vagina non-SCC; vulva non-SCC; other female genital organ; and penis non-SCC.