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Cancer incidence in the Multicenter AIDS Cohort Study before and during the HAART era: 1984–2007

Eric C. Seaberg, PhD[1], **Dorothy Wiley, PhD**[2], **Otoniel Martínez-Maza, PhD**[3], **Joan S. Chmiel, PhD**[4], **Lawrence Kingsley, PhD**[5], **Yiwei Tang, MS**[1], **Joseph B. Margolick, MD PhD**[6], and **Lisa P. Jacobson, ScD**[1] **for the Multicenter AIDS Cohort Study (MACS)**

[1]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland. [2]Department of Epidemiology, UCLA School of Public Health, Los Angeles, California. [3]Departments of Obstetrics & Gynecology and Microbiology, Immunology & Molecular Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA. [4]Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL. [5]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania. [6]Department of Molecular Microbiology and Immunology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

Abstract

Background—The incidence of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) among human immunodeficiency virus (HIV)-infected individuals declined following the introduction of highly active antiretroviral therapy (HAART) in the mid 1990s, but the cancer risk associated with HIV infection during the HAART era remains to be clarified.

Methods—We compared cancer incidence among HIV-infected and -uninfected participants in the Multicenter AIDS Cohort Study (MACS) between 1984 and 2007 to the expected incidence using US population-based data from the Surveillance, Epidemiology, and End Results (SEER) Program, and we compared age and race adjusted cancer incidence rates by HIV status and over time within the MACS. Exact statistical methods were used for all analyses.

Results—933 incident cancers were observed during 77,320 person-years of follow-up. Compared to SEER, MACS HIV-infected men had significantly ($p<0.05$) elevated rates of KS (standardized incidence ratio (SIR)=139.10), NHL (SIR=36.80), Hodgkin's lymphoma (HL) (SIR=7.30), and anal cancer (SIR=25.71). Within MACS, HIV infection was independently associated with each of these cancers across the entire follow-up period, and KS (incidence rate ratio (IRR)=54.93), NHL (IRR=11.18), and anal cancer (IRR=18.50) were each significantly elevated among HIV-infected men during the HAART era. Among these men, the incidence of KS and NHL declined (IRR=0.13 and 0.23, respectively), anal cancer incidence increased (IRR=5.84), and HL incidence remained statistically unchanged (IRR=0.75) from the pre-HAART to the HAART era.

Conclusion—Cancer risk remains elevated among HIV-infected men who have sex with men, highlighting the continuing need for appropriate cancer screening in this population.

Corresponding author: Eric C. Seaberg, PhD, MPH, Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, Room E-7634, Baltimore, MD 21205, USA, Telephone: 410-955-4320, Fax: 410-955-7587, eseaberg@jhsph.edu.

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Keywords

HIV infection; cancer incidence; malignancy; AIDS-defining malignancy; HAART

INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) in the mid 1990s led to a substantial decline in the incidence of the acquired immunodeficiency syndrome (AIDS)-defining-malignancies (ADMs) Kaposi's sarcoma (KS) and, to a lesser degree, non-Hodgkin's lymphoma (NHL) among individuals infected with human immunodeficiency virus (HIV) (1–5), but the incidence of these ADMs remains elevated (3;5). During the HAART era, increased morbidity and mortality from several non-ADMs have also been reported in this population (6–8). With HIV-infected individuals living longer in the HAART era (1;9) and because the risk of most human malignancies increases with age (10), it is important to determine whether HIV infection is associated with long-term cancer risk independent of aging (11;12).

Many recent studies linking HIV infection with cancer risk have only examined HIV-infected populations (3;4;8;13;14). More robust information about the association between HIV infection and cancer can be obtained from studies that include an internal comparison group comprised of HIV-uninfected individuals of similar demographics and lifestyle behaviors. To that end, we investigated the association between HIV infection and cancer using data from the Multicenter AIDS Cohort Study (MACS).

MATERIALS and METHODS

Study Cohort

The MACS is an ongoing observational study of 6972 men who reported having had sex with men (MSM) in four metropolitan areas of the United States (Baltimore MD, Chicago IL, Pittsburgh PA, and Los Angeles CA) that began enrollment in 1984. Recruitment and follow-up procedures were described previously (15;16). During semi-annual study visits, interviewer-administered questionnaires were completed, physical examinations were performed, and biological specimens were obtained for laboratory determinations of HIV/AIDS disease biomarkers and for repository storage. HIV seropositivity was determined using enzyme-linked immunosorbent assays and confirmed with Western blot assays (15). All data obtained before March, 2008, were included in this analysis. To allow for lag in reporting of incident cancers, we censored follow-up time at March 31, 2007, which provided up to 23 years of accrued follow-up time. Eighteen participants with no follow-up data were excluded from this analysis as were five participants who lacked information about race. None of these 23 excluded participants were diagnosed with cancer. The MACS protocol and forms (available at http://statepi.jhsph.edu/macs/macs.html) were approved by the institutional review board at each site. All study participants provided written informed consent.

Study outcomes – cancer classification

Cancers were ascertained continuously during follow-up using a variety of methods including study interviews, medical record abstraction and review, report by self or next of kin, and review of vital status records including data from the National Death Index. Through November, 2005, the MACS documented the site and histology of all cancers using the International Classification of Diseases for Oncology, 1st edition, (ICD-O-1) codes. Since December, 2005, all cancers have been documented using the 3rd edition (ICD-O-3)

codes. During 2006, all ICD-O-1 site and histology codes were converted to the corresponding ICD-O-3 codes using a standardized algorithm (IARCcrgTools Version 2.03) available from the International Agency for Cancer Registries (17) and then reviewed by study personnel.

A total of 1027 cancers were documented in the MACS through March 2007. For this analysis, we excluded 94 cancers (all 66 squamous or basal cell skin cancers since these were not documented by SEER, 21 cancers with an unknown source of documentation, and seven cancers diagnosed before the date of enrollment) leaving 933 incident cancers. We combined related cancers into a common category when the number of observed cancers was small. For example, the following eight cancers were classified as oral cavity/pharyngeal cancers: tongue (n=2), floor of mouth (n=1), gum (n=1), nasopharynx (n=1), tonsil (n=2), and hypopharynx (n=1). This classification yielded 26 separate cancer categories that were based on SEER cancer site recodes for ICD-O-3(18).

Primary Exposures – Risk factors

The primary exposures of interest were HIV infection and HAART. HIV status was coded using a time-varying covariate where seroconverters were classified as HIV-negative prior to seroconversion and HIV-positive thereafter. To investigate the association of HAART with cancer incidence, we implemented an instrumental variable approach that has been used previously in analyses of the effectiveness of HAART on AIDS and death to account for confounding by indication (19). Specifically, we stratified follow-up time into two periods, the pre-HAART era (1984–1995) and the HAART era (1996–2007), to evaluate the association between HIV infection and cancer incidence during calendar periods without and with effective HIV therapies. For cancers with sufficient numbers in the HAART era, we also examined cancer incidence in the early HAART (1996–2000) and current HAART (2001–2007) eras.

Because lung cancer occurred only among MACS participants with a history of smoking, we restricted the lung cancer analyses to the men who reported having ever smoked cigarettes. We also adjusted for smoking in the lung cancer models using time-varying indicator variables to represent a cumulative smoking history of less than 10 pack-years, 10 to 20 pack-years, 20 to 30 pack-years, and more than 30 pack-years. We did not incorporate any other cancer-specific risk factors into these analyses.

External comparison population

We compared cancer incidence in the MACS to that in the US population-based Surveillance, Epidemiology, and End Results (SEER) Program (20). Corresponding to the MACS enrollment beginning in 1984, we restricted the SEER data to the nine registries involved in the SEER project at that time and used all the cancer incidence data from these nine registries between 1984 and 2007.

Statistical Analysis

Incidence rates (IR) were computed as the number of incident cancers observed divided by the number of person-years (PY) of follow-up obtained among those at-risk for the given cancer, where the follow-up time available for each person was the number of years from the baseline visit until the earliest of the cancer diagnosis date, death, loss to follow-up, or March 31, 2007. Because each cancer was analyzed individually, men who developed more than one cancer (e.g., KS and lung cancer) were classified as having incident cancer in both analyses.

For external comparisons between MACS and SEER, we calculated the standardized incidence ratio (SIR), the ratio of the observed to expected number of incident cancers in the MACS, adjusted for age (5-year categories), sex (males only), race (Caucasian, African-American, Other), and calendar year. We estimated SIRs using methods for indirect standardization (21) and generated exact 95% confidence intervals and p-values (22) separately for HIV-infected and -uninfected men. Because a large proportion of KS in the general population occurs among HIV-infected individuals, the SIR for KS in an HIV-infected population tends to be underestimated when it is based on concurrent SEER data. To account for this bias, we also calculated the SIRs for KS using the SEER data from 1973–1979(23).

Direct comparisons of the cancer incidence rates by HIV status and calendar period were performed using Poisson regression where the covariate effects were summarized using the incidence rate ratio (IRR). All models were adjusted for age and race, and the lung cancer models were also adjusted for pack-years using time-dependent covariates. Exact 95% confidence intervals and two-sided p-values were obtained using StatXact (Release 8.0, Cytel Software Corporation, Cambridge, MA) and LogXact (Release 8.0, Cytel Software Corporation). Statistical significance was inferred for two-sided p-values less than 0.05.

RESULTS

The median age of the 6949 MACS participants at enrollment was 32.6 years; 73% of the men were Caucasian, and 42% were HIV positive. During follow-up, 586 (15%) of the 4009 men who were HIV negative at enrollment became infected with HIV. Overall, the median follow-up time was 9.7 years, and 42% of the 77,320 person-years of accumulated follow-up time were accrued by HIV-infected men. Cigarette smoking was common among both HIV-infected (45% active and 19% former smokers) and uninfected men (40% active and 20% former smokers). Among men who had ever smoked, the cumulative exposure was slightly higher for HIV-uninfected men both at enrollment (median pack-years: 14.6 for HIV-infected and 15.6 for HIV-uninfected) and at the end of follow-up (18.2 and 19.1 pack-years, respectively).

The 933 incident cancers were diagnosed in 868 participants; 63 men were diagnosed with two cancers and 1 with three cancers. The overall cancer IR was 1206.7 per 100,000 PYs, which differed significantly by HIV status, age, race, and calendar time (Table 1). Cancer incidence was highest among HIV-infected men, Caucasians and other non-African Americans, and prior to 1996. Regarding age, incidence was highest among men 30 to 39 years old which was due to the incidence of ADMs among HIV-infected men during the pre-HAART era (data not shown). Among HIV-infected men, the overall cancer IRs in the pre-HAART and HAART eras were, respectively, 3601.5 (95% CI 3343.8 to 3871.3) and 965.9 (95% CI 798.8 to 1157.6) per 100,000 PYs. The corresponding IRs among HIV-uninfected men were 137.3 (95% CI 98.1 to 186.9) and 291.2 (95% CI 213.2 to 388.4) per 100,000 PYs.

Comparisons of cancer-specific incidence in the MACS to that from the SEER program are shown in Table 2. The most frequent cancer among HIV-infected MACS participants was KS (n=552) followed by NHL (n=194). Of the non-ADMs, the most common cancers were anal cancer (n=15), prostate cancer (n=12), and Hodgkin's lymphoma (HL) (n=9) among HIV-infected men, and prostate cancer (n=25) and melanoma (n=7) among men without HIV. Overall, we observed 86 incident cancers among the HIV-uninfected MACS participants, and this number was significantly lower than the 160.0 cancers that were expected (SIR=0.53, 95% CI: 0.43 to 0.66). No specific cancer occurred significantly more often than expected among these men, but colon, lung, and renal cancers occurred

significantly less often than expected. In contrast, overall cancer incidence was significantly higher than expected (SIR=10.79, 95% CI: 10.07 to 11.53) among HIV-infected men, and this was driven largely by KS and NHL which comprised 88% of all cancers in this subgroup. HIV-infected men also had significantly elevated SIRs for all non-ADMs (SIR=1.46, 95% CI: 1.19 to 1.78), and individually for anal cancer, testicular cancer, HL, and poorly defined cancers.

Direct comparisons of cancer incidence rates among HIV-infected and uninfected MACS participants are shown in Table 3. Adjusted for age and race (and for smoking in the lung cancer analysis), HIV infection was significantly associated with higher rates of anal cancer (IRR=13.57), HL (IRR=13.29), poorly defined cancers (IRR=9.53), and, as expected, with both KS (IRR=374.73) and NHL (IRR=48.71). HIV-infected men also had elevated rates of liver (IRR=5.69), testicular (IRR=3.97), melanoma (IRR=2.68), oral cavity/pharyngeal (IRR=2.64), and lung (IRR=2.59) cancers, but these differences were not significant at the 0.05 level.

We restricted the comparisons of cancer incidence in the pre-HAART versus HAART eras to the seven cancers that occurred in at least 10 MACS participants (KS, NHL, anal cancer, HL, lung cancer, melanoma, and prostate cancer). The results, stratified by HIV status, are shown in Table 4. Among HIV-infected men, the age- and race-adjusted incidence of KS and NHL declined by 87% and 77%, respectively, from the pre-HAART era to the HAART era. In contrast, anal cancer incidence increased significantly (IRR=5.84) in this group following the introduction of HAART, while the IRs for the other non-ADMs remained statistically unchanged. None of the age- and race- (and smoking-) adjusted cancer IRs changed significantly over time among HIV-uninfected men.

While the adjusted incidence of KS and NHL declined dramatically following the introduction of HAART, the incidence of both cancers (IRR = 54.93 and 11.18, respectively) remained significantly elevated among HIV-infected versus –uninfected men during the HAART era (Table 5). Among men with HIV, the incidence of both KS and NHL continued to decline significantly from the early HAART era (1996–2000) to the current HAART era (2001–2007) with the adjusted IRRs comparing the late to early HAART eras being 0.44 (95% CI 0.20, 0.92) for KS and 0.23 (95% CI 0.10, 0.52) for NHL. Nevertheless, the incidence of both ADMs remained significantly higher among HIV-infected versus -uninfected men during the current HAART era: IRR=17.76 (95% CI 2.59, 771.24) for KS and IRR=6.44 (95% CI 1.61, 37.37) for NHL.

Among the non-ADMs evaluated during the HAART era (Table 5), the incidence of anal cancer was significantly higher among HIV-infected versus –uninfected men (IRR=18.50). In contrast to the temporal findings for KS and NHL, anal cancer incidence increased from the early HAART era to the current HAART era among HIV-infected men (IRR=3.11; 95% CI 0.60, 31.44), but this increase was not statistically significant. The age-, race-, and pack-years-adjusted incidence of lung cancer was also elevated among HIV-infected men during the HAART era (IRR=5.98), but this difference was not statistically significant either. Similarly, HIV was not associated with the incidence of HL, melanoma, or prostate cancer during the HAART era.

DISCUSSION

This dramatic decline of the incidence of KS and NHL in the MACS since HAART was introduced in the mid 1990s is consistent with reports that HAART has greatly reduced the likelihood of HIV-related outcomes including cancer (2;3) and mortality (24). In contrast to other reports (4), however, we found that the incidence of these ADMs continued to decline

during the HAART era among HIV-infected men which offers hope that the excess risk of KS and NHL due to HIV may one day be eliminated. Increased HAART use or the development of more effective HAART regimens over time might explain the continued decline in the incidence of these ADMs during the HAART era. It is also possible that cancer incidence during the early HAART era was elevated due to the lag between the beginning of the wide-spread availability of HAART in 1996 and the time when HAART could begin to impact cancer incidence since a portion of the cancers detected during the early HAART era were likely to have existed, yet were early stage and remained undetected, during the pre-HAART era. Other possible explanations include a cancer reporting lag in the MACS, even though our study design accounted for this lag, and a survival bias where persons at highest risk for developing these cancers were removed from the cohort over time. Nevertheless, like others (4), we found that HIV infection remained significantly associated with an increased risk of these ADMs after 2000. Further analyses of the etiologic mechanisms underlying the development of these cancers are required to determine whether the excess risk of ADMs due to HIV can be entirely eliminated by HAART.

The incidence of anal cancer among HIV-infected MACS participants was significantly elevated when compared both to the external SEER population and to the HIV-uninfected MACS participants. Adjusted for age and race, anal cancer incidence increased significantly from the pre-HAART era to the HAART era, and it did not decrease during the HAART era. In a prior MACS analysis, anal cancer risk during the HAART era was found to be elevated among those with more exposure to unprotected receptive anal intercourse, and concurrent HAART use did not decrease this risk (25). Thus, MACS data are consistent with the finding that HAART may not be associated with the regression or clearance of anal intraepithelial neoplasias or their causally-associated *Human papillomavirus* infections during the HAART era (26;27). Whether more effective HAART regimens or earlier HAART initiation might affect the development of anal cancer remains unknown.

The potential link between HIV infection and lung cancer has received much attention recently. In contrast to other studies (28;29), we did not observe a statistically significant association between HIV infection and lung cancer among MACS participants with a history of smoking cigarettes after controlling for age, race, and pack-years. Although the adjusted lung cancer incidence rate among MACS smokers during the HAART era was nearly 6 times greater for HIV-infected versus uninfected men, this result must be interpreted with great caution given the small number of lung cancers observed since 1996 in the MACS and the extremely wide confidence interval for this estimate.

HL was strongly and significantly associated with HIV infection in the MACS, and the incidence of HL was similar in the pre-HAART and HAART eras. This finding is consistent with another report that HL incidence did not differ significantly by calendar period or by the use of combination ARV therapy (30). Among persons diagnosed with AIDS, one study group noted that the unadjusted incidence of HL increased by more than 50% after HAART became widely available, a result that they attributed to “HAART-related improvements in CD4 counts” and interpreted as suggesting that the characteristic Reed-Sternberg cells may require the presence of CD4 T-cells for HL to develop (31). Because the incidence of HL in the MACS did not increase in the HAART era, further analyses that incorporate CD4 data are required to determine whether our data are consistent with this hypothesis.

We also observed a significant excess of poorly defined cancers among the HIV-infected MACS participants. Interestingly, nine of these 10 cancers did not have a documented cancer site suggesting that they may have been diagnosed very late in the disease course, after widespread metastasis. Thus, it is plausible that HIV infection had an impact on the

progression and late diagnosis of these cancers, but it is unknown whether or not HIV was etiologically related to their onset.

The most commonly observed non-ADM in our study was prostate cancer which, adjusted for age and race, occurred at similar rates among HIV-infected and -uninfected MACS participants. This finding is not inconsistent with the conflicting reports from other studies that found HIV/AIDS to be associated with an increased (14;32) or decreased (4;33) risk of prostate cancer. While these studies either focused on men with a prior AIDS diagnosis or were based primarily on a comparison with external population-based data, our internal comparison of HIV-infected and –uninfected men provides a direct evaluation of the association between HIV infection and prostate cancer.

Other non-ADMs that have been reported to be increased among HIV-infected men include melanoma(32), liver cancer(34), oral cancer(13), stomach cancer(35), and testicular seminoma (36). None of these were significantly associated with HIV infection in our study. Several explanations may account for these results. Because these cancers were rarely observed in the MACS, we had little statistical power to detect a significant association. For example, we found that HIV infection had an adjusted IRR of 5.69 for liver cancer, but with only five liver cancers the corresponding 95% CI was very wide. Additionally, any study, including ours, may be subject to confounding. Indeed, the present study considered only age, race, and calendar time (and smoking for lung cancer) as potential confounders. Accrual of additional follow-up and further detailed cancer-specific analyses that incorporate important cancer-specific risk factors are needed to determine whether or not HIV infection is etiologically important in the development of these cancers.

This study has important strengths and limitations. A particular strength was the inclusion of an internal HIV-uninfected comparison group. Studies that restrict the comparison of cancer incidence among HIV-infected individuals to an external population are particularly subject to inherent differences between the study population and the external comparison group. While those designs are important and useful given the relative infrequency of many cancers among HIV-infected individuals, more accurate risk estimates can be obtained from studies with an internal comparison group and individual-level risk factor data, such as those from an earlier MACS analysis of anal cancer (25).

An additional strength of our study, a long follow-up period with more than 10 years during both the pre-HAART and HAART eras, allowed us to assess cancer incidence trends before and after the introduction of HAART. Consequently, we had sufficient data to determine that while the incidence rates of both KS and NHL declined significantly following the introduction of HAART, a significant excess burden of both ADMs remains among HIV-infected men in the current HAART era.

One limitation of our study is that we observed only a small number of many cancers and, thus, had limited statistical power to detect an association between those cancers and HIV infection. This limitation might be related to the finding of significantly fewer cancers overall among HIV-uninfected men than were expected according to the SEER data. Possible explanations for this observation include cancer underascertainment, or that MACS participants had generally low risk for most cancers. Indeed, MACS participants, particularly those enrolled prior to 2001, are highly educated and affluent, and these two characteristics have been linked to a lower cancer risk(37). In addition, MACS participants willingly enrolled into this study in which they were repeatedly asked about their health and lifestyles; this selection process may have resulted in a cohort of men at lower risk for cancer than the general population. A second limitation is that the MACS cohort was limited to mostly Caucasian MSM. While we cannot generalize our results to women or to other

racial and HIV risk groups, our findings regarding ADMs before versus during the HAART era are consistent with those from another study performed in a largely minority cohort of women in the United States.(38) Finally, with the exception of smoking, we did not account for other etiologically important cancer-specific risk factors including coinfection with oncogenic viruses (e.g., HPV, HCV, KSHV) which will be considered in future analyses.

Given the continued excess cancer risk among individuals infected with HIV in the HAART era, appropriate screening programs need to be considered for HIV-infected MSM. Specifically, screening for anal squamous intraepithelial lesions among MSM has been shown to be cost effective (39) and should be offered to this population. We also observed a non-significantly elevated incidence of liver cancer among HIV-infected men suggesting that vaccination should be offered to those at risk for becoming infected with the hepatitis B virus (HBV), and that HBV-active HAART regimens should be considered for HIV/HBV co-infected individuals. Based on our data showing that HIV-infection was not associated with the incidence of other cancers for which screening programs exist, the current American Cancer Society screening guidelines for other cancers should be applied to all MSM regardless of HIV status.

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Table 1

Overall and stratified cancer incidence rates in the MACS.

	Number of incident cancers	PYs	IR per 100,000 PYs	Exact 95% CI	Exact p-value
All	933	77320	1206.7	(1130.2, 1286.3)	
Age (years)					
<30	58	7911	733.2	(556.7, 947.8)	<0.0001
30–39	400	27778	1440.0	(1301.5, 1587.4)	
40–49	313	26681	1173.1	(1045.9, 1309.6)	
50+	162	14949	1083.7	(923.2, 1264.0)	
Race					
Caucasian	793	63797	1243.0	(1157.6, 1332.2)	0.009
African-American	68	7999	850.1	(660.1, 1077.7)	
All others	72	5523	1303.6	(1020.0, 1641.7)	
HIV Status					
Negative	86	44937	191.4	(153.1, 236.4)	<0.0001
Positive	847	32383	2615.6	(2441.6, 2797.1)	
Calendar Period					
1984–1995	770	49410	1558.4	(1449.8, 1672.0)	<0.0001
1996–2007	163	27910	584.0	(497.8, 680.9)	

Abbreviations:
PY: Person-years
IR: Incidence rate
CI: Confidence interval

Table 2

Comparison of the observed cancer incidence in the MACS to the expected cancer incidence based on data from the SEER Program by HIV status (1984–2007).

		HIV Negative					HIV Positive			
Cancer	**SEER Cancer Site Recodes for ICD-O-3**	**Obs**	**Exp**	**SIR**	**Exact 95% CI**		**Obs**	**Exp**	**SIR**	**Exact 95% CI**
Oral cavity/pharynx	20010–20100	3	6.8	0.44	(0.09, 1.29)		5	3.6	1.38	(0.45, 3.23)
Colon	21041–21049	3	10.0	**0.30**	**(0.06, 0.87)**		1	4.6	0.22	(0.006, 1.22)
Rectum	21051, 21052	4	5.5	0.72	(0.20, 1.85)		3	2.6	1.13	(0.23, 3.31)
Anus	21060	2	0.8	2.50	(0.30, 9.03)		15	0.6	**25.71**	**(14.39, 42.40)**
Liver	21071	2	2.2	0.91	(0.11, 3.28)		3	1.4	2.17	(0.45, 6.34)
Pancreas	21100	2	3.2	0.63	(0.08, 2.29)		2	1.5	1.37	(0.17, 4.95)
Other digestive systems	21010–21130 (*except* 21041–21071, 21100)	3	6.7	0.45	(0.09, 1.31)		2	3.3	0.61	(0.07, 2.20)
Lung	22030	6	19.7	**0.30**	**(0.11, 0.66)**		9	8.3	1.09	(0.50, 2.07)
Other respiratory	22010, 22020, 22050, 22060	3	3.1	0.98	(0.20, 2.87)		2	1.5	1.35	(0.16, 4.89)
Bones and joints	23000	0	0.4	0	(0, 9.87)		1	0.2	4.09	(0.10, 22.80)
Soft tissues	24000	2	1.2	1.63	(0.20, 5.90)		0	0.8	0	(0, 4.78)
Melanoma	25010	7	14.1	0.50	(0.20, 1.03)		9	7.3	1.23	(0.56, 2.34)
Other skin	25020	1	0.6	1.55	(0.04, 8.63)		0	0.4	0	(0, 9.59)
Prostate	28010	25	34.5	0.72	(0.47, 1.07)		12	13.3	0.90	(0.47, 1.57)
Testis	28020	2	3.8	0.52	(0.06, 1.89)		7	2.8	2.48	(0.997, 5.11)
Bladder	29010	3	8.0	0.37	(0.08, 1.09)		1	3.3	0.31	(0.008, 1.71)
Kidney and renal pelvis	29020	1	5.6	**0.18**	**(0.004, 0.99)**		2	2.9	0.69	(0.08, 2.47)
Brain	31010, 31040	0	3.3	0	(0, 1.11)		1	1.9	0.52	(0.01, 2.89)
Thyroid	32010	2	2.2	0.92	(0.11, 3.33)		1	1.4	0.73	(0.02, 4.06)
Other endocrine	32020	0	0.3	0	(0, 13.78)		1	0.2	5.80	(0.15, 32.30)
Hodgkin’s lymphoma	33011, 33012	1	1.7	0.57	(0.01, 3.19)		9	1.2	**7.30**	**(3.34, 13.85)**
Non-Hodgkin’s lymphoma	33041, 33042	6	9.0	0.66	(0.24, 1.44)		194	5.3	**36.80**	**(31.80, 42.36)**
Myeloma	34000	2	1.7	1.16	(0.14, 4.21)		3	0.8	3.56	(0.73, 10.40)
Leukemia	35011–35043	2	2.0	1.02	(0.12, 3.68)		2	1.1	1.80	(0.22, 6.52)

		HIV Negative					HIV Positive			
Cancer	**SEER Cancer Site Recodes for ICD-O-3**	**Obs**	**Exp**	**SIR**	**Exact 95% CI**		**Obs**	**Exp**	**SIR**	**Exact 95% CI**
Kaposi's sarcoma [1]	36020	2	5.5	0.36	(0.04, 1.31)		552	4.0	**139.10**	**(127.67, 151.14)**
Poorly defined cancers	37000	2	3.4	0.59	(0.07, 2.13)		10	1.7	**6.04**	**(2.90, 11.11)**

Abbreviations: Obs: Observed; Exp: Expected; SIR: Standardized incidence ratio; CI: Confidence Interval; ICD-O-3: International classification of diseases for oncology, third edition.

SIRs significantly different from 1 are shown in **BOLD**.

[1] Using the methods of Chaturvedi et al (23), the Kaposi's sarcoma SIRs (exact 95% CI) were **29.13 (3.53, 105.24)** for HIV negative men and **17381.45 (15954.16, 18886.28)** for HIV positive men.

Table 3

Adjusted cancer incidence in the MACS by HIV status.

	Cancer incidence by HIV status adjusted for age and race [1]	
Cancer	**Adjusted IRR**	**Exact 95% CI**
Oral cavity/pharynx	2.64	(0.50, 17.30)
Colon	0.77	(0.01, 10.45)
Rectum	1.25	(0.17, 7.86)
Anus	**13.57**	**(3.01, 126.49)**
Liver	5.69	(0.45, 300.36)
Pancreas	2.27	(0.16, 32.88)
Other digestive systems	1.48	(0.12, 13.71)
Lung [1]	2.59	(0.80, 9.02)
Other respiratory	1.18	(0.10, 10.51)
Bones and joints [2]	INF	(0.02, INF)
Soft tissues [3]	0	(0, 9.74)
Melanoma	2.68	(0.85, 8.91)
Other skin [3]	0	(0, 588.74)
Prostate	1.22	(0.54, 2.60)
Testis	3.97	(0.74, 39.55)
Bladder	0.61	(0.01, 7.91)
Kidney and renal pelvis	2.45	(0.12, 152.88)
Brain [2]	INF	(0.03, INF)
Thyroid	0.65	(0.01, 12.55)
Other endocrine [2]	INF	(0.10, INF)
Hodgkin’s lymphoma	**13.29**	**(1.81, 588.91)**
Non-Hodgkin’s lymphoma	**48.71**	**(21.91, 134.64)**
Myeloma	2.11	(0.22, 27.64)
Leukemia	1.08	(0.08, 15.32)
Kaposi’s sarcoma	**374.73**	**(106.67, 3800.54)**
Poorly defined cancers	**9.53**	**(1.97, 91.25)**

Abbreviations:
IRR: Incidence rate ratio
CI: Confidence interval
INF: Infinity

Adjusted IRRs significantly different from 1 are shown in **BOLD**.

[1]The Poisson regression model for lung cancer was restricted to 4300 men who reported having ever smoked cigarettes, and was adjusted for age, race, and pack-years.

[2]When no incident cancers were observed among the HIV-uninfected group, the IRR calculation involves division by zero and results in an undefined parameter estimate which is represented in this table by INF (*infinity*). In these cases the upper bound of the exact 95% CI is unbounded.

[3] When no incident cancers were observed among the HIV-infected group, both the IRR and the lower bound of the exact 95% CI are reported as zero.

Table 4

Incidence of the seven most frequently observed cancers in the MACS during the HAART era vs. pre-HAART era, stratified by HIV status.

	Number of incident cancers		Cancer incidence in the HAART era vs. the pre-HAART era	
	Pre-HAART era (1984–1995)	**HAART era (1996–2007)**	**Adjusted IRR**	**Exact 95% CI**
AIDS-defining malignancies				
Kaposi's Sarcoma				
HIV positive	514	38	**0.13**	**(0.09, 0.18)**
HIV negative	1	1	0.95	(0.01, 106.91)
Non-Hodgkin's lymphoma				
HIV positive	161	33	**0.23**	**(0.15, 0.35)**
HIV negative	1	5	3.39	(0.33, 182.18)
Non AIDS-defining malignancies				
Anus				
HIV positive	3	12	**5.84**	**(1.24, 38.90)**
HIV negative	1	1	0.42	(0.01, 32.82)
Hodgkin's lymphoma				
HIV positive	6	3	0.75	(0.09, 4.89)
HIV negative [1]	1	0	0	(0, 642.91)
Lung [2]				
HIV positive	6	3	0.42	(0.06, 2.29)
HIV negative	5	1	0.19	(0.004, 2.01)
Melanoma				
HIV positive	6	3	0.40	(0.05, 2.41)
HIV negative	3	4	1.18	(0.16, 9.37)

	Number of incident cancers		Cancer incidence in the HAART era vs. the pre-HAART era	
	Pre-HAART era (1984–1995)	HAART era (1996–2007)	Adjusted IRR	Exact 95% CI
Prostate				
HIV positive	2	10	1.72	(0.33, 17.44)
HIV negative	5	20	2.10	(0.74,7.40)

Abbreviations:
IRR: Incidence rate ratio
CI: Confidence interval

Adjusted IRRs significantly different from 1 are shown in **BOLD**.

[1]When no incident cancers were observed during the HAART era, both the IRR and the lower bound of the exact 95% CI are reported as zero.

[2]The Poisson regression models for lung cancer were restricted to the 2261 HIV-infected and 2039 HIV-uninfected men who reported having ever smoked cigarettes and were adjusted for age, race, and pack-years.

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Table 5

Incidence of the seven most frequently observed cancers in the MACS during the HAART era by HIV status

	Cancer incidence among HIV infected vs. uninfected MACS participants					
	HIV-infected		HIV-uninfected		HIV-infected vs. HIV-uninfected	
	N	IR	N	IR	Adjusted IRR	Exact 95% CI
AIDS-defining malignancies						
Kaposi's sarcoma	38	327.1	1	6.3	**54.93**	**(9.11, 2243.97)**
Non-Hodgkin's lymphoma	33	274.9	5	31.7	**11.18**	**(4.24, 37.30)**
Non AIDS-defining malignancies						
Anus	12	99.3	1	6.3	**18.50**	**(2.57, 823.04)**
Hodgkin's lymphoma [1]	3	24.8	0	0	INF	(0.57, INF)
Lung [2]	3	24.8	1	6.3	5.98	(0.47, 320.86)
Melanoma	3	24.8	4	25.4	1.85	(0.25, 12.24)
Prostate	10	82.9	20	127.5	1.09	(0.44, 2.53)

Abbreviations:
HIV: Human immunodeficiency virus
N: Number of incident cancers
IR: Incidence rate per 100,000 person-years
IRR: Incidence rate ratio
CI: Confidence interval

Adjusted IRRs significantly different from 1 are shown in **BOLD**.

[1] When no incident cancers were observed among the HIV-uninfected group, the IRR involves division by zero and results in an undefined parameter estimate which we represent with INF (*infinity*). In these cases the upper bound of the exact 95% CI is unbounded.

[2] The Poisson regression model for lung cancer was restricted to the 2522 men with follow-up during the HAART era who reported having ever smoked cigarettes and was adjusted for age, race, and pack-years.