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HIV INFECTION AND THE RISK OF CANCERS WITH AND WITHOUT A KNOWN INFECTIOUS CAUSE

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Abstract

Objective—To evaluate the risk of cancers with and without a known infectious cause in HIV-infected persons.

Design—Retrospective cohort study.

Methods—Adult HIV-infected and matched HIV-uninfected members of Kaiser Permanente followed between 1996 and 2007 for incident AIDS-defining cancers (ADC), infection-related non-AIDS-defining cancers (NADC) (anal squamous cell, vagina/vulva, Hodgkin's lymphoma, penis, liver, HPV-related oral cavity/pharynx, stomach) and infection-unrelated NADC (all other NADC).

Results—We identified 20,277 HIV-infected and 202,313 HIV-uninfected persons. HIV-infected persons experienced 552 ADC, 221 infection-related NADC, and 388 infection-unrelated NADC. HIV-uninfected persons experienced 179 ADC, 284 infection-related NADC, and 3,418 infection-unrelated NADC. The rate ratio (RR) comparing HIV-infected and HIV-uninfected persons for ADC was 37.7 (95% CI: 31.7–44.8), with decreases in the RR over time ($p < 0.001$). The RR for infection-related NADC was 9.2 (95% CI: 7.7–11.1), also with decreases in the RR over time ($p < 0.001$). These results were largely influenced by anal squamous cell cancer and Hodgkin's lymphoma. The RR for infection-unrelated NADC was 1.3 (95% CI: 1.2–1.4), with no change in the RR over time ($p = 0.44$). Among infection-unrelated NADC, other anal, skin, other head and neck, and lung cancer rates were higher and prostate cancer rates lower in HIV-infected persons. Among all infection-unrelated NADC, the RR decreased over time only for lung cancer ($p = 0.007$).

Conclusions—HIV-infected persons are at particular risk for cancers with a known infectious cause, although the higher risk has decreased in the antiretroviral therapy era. Cancers without a known infectious cause are modestly increased in HIV-infected persons.

Keywords

HIV; cancer; incidence; coinfection; cohort

INTRODUCTION

With effective combination antiretroviral therapy (ART) use, HIV-infected persons in developed countries have experienced a precipitous decline in AIDS-defining cancers (ADC) and opportunistic infections, but a rise in other chronic conditions associated with aging. In the ART era, non-AIDS-defining cancers (NADC) are now more common than AIDS-defining cancers [1–3]. Despite this change in the distribution of cancers, ADC and many NADC continue to pose a higher risk for HIV-infected persons than for the general population [2,4]. NADC that are consistently found more commonly among HIV-infected persons include Hodgkin's lymphoma, skin, lung, anal squamous cell, and oral cavity/pharynx cancers, while others including prostate and breast cancer appear to occur less frequently [5].

One reason for the continued higher risk of certain cancers among HIV-infected persons is the higher prevalence of traditional cancer risk factors such as smoking [6–8], alcohol use [7,9], and oncogenic virus coinfection, including human papillomavirus (HPV) or hepatitis B and C [10–13]. At the same time, HIV infection and associated immunodeficiency may also contribute to the higher risk. It is possible, for example, that the impaired immune system may result in the general reduced immune surveillance for malignant cells [14]. Alternatively, an impaired ability of the immune system to suppress oncogenic viruses may also result in a higher risk of these cancers [12,15].

However, prior studies have been limited by small sample sizes, inclusion of AIDS cases only, and a lack of HIV-uninfected controls. Here, we compared the incidence of cancers between a large cohort of HIV-infected and matched HIV-uninfected persons from the same integrated health care system, Kaiser Permanente (KP). This setting provides a unique perspective on this topic since all subjects have comprehensive medical insurance coverage, and thus outcome differences attributable to variations in access to care and preventive services are reduced. In addition, the comprehensive HIV and cancer disease registries maintained at KP allow for high quality outcome ascertainment.

An additional unique feature of this study is the exploration of the epidemiology of cancers with and without a known infectious cause (referred to throughout as infection-related and infection-unrelated NADC). Specifically, we hypothesized that infection-related NADC would pose the highest risk for HIV-infected compared to HIV-uninfected persons. We further postulated that the higher risk for infection-related NADC for HIV-infected persons may decrease during the ART era with improving immune function in HIV-infected persons.

METHODS

Study design, setting and participants

We conducted a retrospective cohort study from 1996 to 2007 of adult HIV-infected and HIV-uninfected persons within Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC), large integrated health care delivery systems providing comprehensive medical services to more than six million health plan members, representing roughly 30% of insured Californians [16].

The HIV-infected study population here consisted of persons ≥ 18 years of age with KP membership after 1996 in KPNC and after 2000 in KPSC, corresponding to the earliest year in the ART era with comprehensive coverage for the respective HIV registries. The start of follow-up (i.e., index date) for HIV-infected patients was assigned as the earliest date after 1/1/96 (1/1/00 for KPSC) when a member was both ≥ 18 years of age and known to be HIV-infected. Next, HIV-uninfected persons were selected from the pool of active health plan members ≥ 18 years of age during index years observed for HIV-infected persons. HIV-

uninfected persons were eligible for selection during all years when they were members, but once selected as a control, were excluded from other index year selection pools. HIV-uninfected persons were also excluded if they were ever included in the HIV registries through 2007. HIV-uninfected persons were then frequency-matched 10:1 by index year, age on December 31 of the index year (5-year age groups), sex, and medical center. The start of follow-up for HIV-uninfected patients was assigned as the earliest date after January 1 of the index year they were selected when they were ≥ 18 years of age.

Data Sources

The KPNC HIV Registry includes all known cases of HIV infection since the early 1980's and the KPSC HIV registry includes cases identified since 2000. Confirmation of cases is done by medical chart review and comparisons of case lists with HIV clinics. Data elements maintained in the HIV registries include sex, race/ethnicity, HIV exposure risk (e.g., men who have sex with men, injection drug use), dates of known HIV and AIDS diagnoses and dates of death. We identified all incident cancers by linkage with the KPNC and KPSC cancer registries. The KP cancer registries are contributing sites to the Surveillance, Epidemiology, and End Results (SEER) program registry and KP registry's data are of comparable accuracy and completeness to that of SEER. All medical facilities in California are required by law to report all newly diagnosed cases of cancer to the California Cancer Registry (CCR), through a network of 10 regional registries that together capture the cancer incidence experience of the entire state. All registries follow SEER practices in verifying and coding incident cancers. SEER requirements include categorization of histopathology, invasiveness, tumor size, extension, and lymph node involvement.

Cancer endpoints

The primary endpoints examined were incident ADC and NADC. A subset of NADC with a known infectious cause were further categorized as infection-related NADC [17–19]: these were vagina, vulva, penis, squamous cell anal, and certain squamous cell oral cavity/pharynx cancers defined by Chaturvedi et al. [19] which are all HPV-related; liver cancer which is hepatitis B and C-related; stomach cancer which is *Helicobacter pylori*-related; and Hodgkin's lymphoma which is Epstein-Barr Virus-related. All other cancers were considered infection-unrelated NADC. Individual infection-unrelated NADC analyzed separately included those with four or more cases among HIV-infected persons. Persons with multiple cancers contributed events to each applicable category.

Statistical methods

Subjects were followed from first enrollment after 1/1/96 until the earliest of a cancer diagnosis, health plan disenrollment, death or 12/31/07. We first computed cancer incidence rates per 100,000 person-years. Next, rate ratios (RR) for the incidence of cancer in HIV-infected compared with HIV-uninfected persons were obtained from Poisson regression models adjusted for attained age, sex, race/ethnicity, and calendar year. Race/ethnicity for those with missing information was imputed based on subjects age at index and census block group characteristics including: median household income, % less than high school diploma, % White, % Black, % Hispanic, and % Asian. Next, standard multiple imputation methods [20] were used to obtain adjusted RRs. However, inferences were unchanged for all cancers compared to models that did not include race/ethnicity (data not shown); thus, subsequent analyses did not consider this factor.

Next, we examined linear changes over time in the incidence of cancers in both HIV-infected and HIV-uninfected persons. These models included age, sex, a linear term for calendar period (1996–99, 2000–03, 2004–07) and an HIV/calendar period interaction term. Finally, we evaluated whether the RR for HIV infection status changed over time during 1996–99, 2000–

03 and 2004–07. These models included age, sex, categorical variables for each calendar period, and corresponding HIV/calendar period interaction terms. Changes of the RR for HIV infection status over time was assessed by the likelihood ratio test.

Analyses were performed with SAS (Version 9.1, Cary, North Carolina, USA), using proc GENMOD for Poisson regression, and proc MI and MIANALYZE for multiple imputation. The institutional review boards at KP approved this study and provided waivers of informed consent.

RESULTS

We identified 20,277 HIV-infected persons contributing 85,309 person-years (mean 4.2 years per person) and 202,313 HIV-uninfected persons contributing 1,013,645 person-years (mean 5.0 years per person) (Table 1). The HIV-infected group was predominantly male (90%), White (56%), and consisted mostly of men who have sex with men (74%), with a mean age at start of follow-up of 41 years. HIV-uninfected persons in this study were identical to HIV-infected persons for matching factors of age, sex and index year. The HIV-uninfected cohort had fewer Blacks and Whites, but more Asians and Hispanics compared to the HIV-infected cohort among those with known race/ethnicity. Figure 1 displays the similarly increasing mean age of HIV-infected and HIV-uninfected persons during study follow-up. CD4+ T-cell counts also increased over time for HIV-infected persons with a mean of 311 in 1996 and 529 in 2007.

Among HIV-infected persons, 552 had an ADC, 221 had an infection-related NADC, and 388 had an infection-unrelated NADC (Table 2). Thus, counting all ADC, which have viral etiologies [17,18], and infection-related NADC, 67% of cancers in HIV-infected persons had a known infectious cause. In contrast, among HIV-uninfected persons, 179 had an ADC, 284 had an infection-related NADC, and 3,418 had an infection-unrelated NADC, corresponding to only 12% of cancers with a known infectious cause.

Crude rates for all cancers but breast and prostate cancer were higher among HIV-infected persons compared with rates among HIV-uninfected persons (Table 2). Adjusted RRs comparing HIV-infected with HIV-uninfected persons (reference) were 37.7 ($p<0.001$) for ADC, 9.2 ($p<0.001$) for infection-related NADC, and 1.3 ($p<0.001$) for infection-unrelated NADC (Table 2). Most individual infection-related NADC were significantly elevated in HIV-infected persons, including anal squamous cell (RR=101.6, $p<0.001$), vagina/vulva (RR=19.5, $p<0.001$), Hodgkin's lymphoma (RR=19.4, $p<0.001$), penis (RR=5.8, $p=0.006$), liver (RR=2.7, $p<0.001$), and HPV-related oral squamous cell cancers (RR=2.0, $p=0.034$). Stomach cancer was the only individual infection-related NADC not associated with HIV infection. Infection-unrelated NADC that were increased in HIV-infected persons were other anal (RR=35.3, $p<0.001$), non-melanoma skin (RR=10.6, $p<0.001$), other head and neck (RR=2.7, $p<0.001$), lung (RR=1.9, $p<0.001$), and melanoma (RR=1.5, $p=0.006$); HIV-infected persons also had a lower rate of prostate cancer with an RR of 0.7 ($p=0.002$). Other infection-unrelated NADC were not associated with HIV infection.

As shown in Figure 2, there was an 8% annual decline ($p<0.001$) in infection-related NADC for HIV-infected persons compared to a 6% annual increase ($p=0.007$) for HIV-uninfected persons ($p<0.001$ for difference by HIV status). These trends were similar to trends for ADC rates, which declined 12% annually ($p<0.001$) for HIV-infected persons, and increased 5% annually ($p=0.091$) for HIV-uninfected persons ($p<0.001$ for difference by HIV status) (data not shown). Results for two individual infection-related NADC, anal squamous cell cancer and Hodgkin's lymphoma, are also shown in Figure 2. For anal squamous cell cancer, there was a 9% annual decline ($p=0.002$) for HIV-infected persons, and a 4% annual decline ($p=0.68$) for HIV-uninfected persons ($p=0.57$ for difference by HIV status). The risk for Hodgkin's

lymphoma did not change over time for HIV-infected persons (3% annual decline; $p=0.50$), but increased by 17% ($p=0.035$) among HIV-uninfected persons ($p=0.032$ for difference by HIV status). Other infection-related NADC did not change significantly over time for HIV-infected persons, and demonstrated similar trends to HIV-uninfected persons (data not shown). Of note, there were borderline differences comparing annual changes in HIV-infected and HIV-uninfected vagina/vulva cancer rates (-6% vs. 17% ; $p=0.087$).

The crude rates for infection-unrelated NADC steeply increased over time for HIV-infected and HIV-uninfected persons (Figure 2), which was explained by the advancing age of the cohort (Figure 1). In adjusted models, infection-unrelated NADC rates did not change substantially over time with a 3% annual increase ($p=0.15$) for HIV-infected persons and a 1% annual increase ($p=0.066$) for HIV-uninfected persons ($p=0.44$ for difference by HIV status) (Figure 2). Trends in rates for all individual infection-unrelated NADC were similar by HIV infection status, and none showed significant changes among HIV-infected persons (data not shown). Of note were borderline differences comparing annual changes in HIV-infected and HIV-uninfected colorectal cancer rates (9% vs. -1% ; $p=0.12$) (data not shown).

We also evaluated whether the association of HIV infection status and cancer risk changed over time (Table 3). The RR (i.e., HIV-infected vs. HIV-uninfected cancer rate) decreased for ADC from 89.9 in 1996–99 to 22.5 in 2004–07 ($p<0.001$). The RR also decreased for infection-related NADC from 16.9 in 1996–99 to 6.2 in 2004–07 ($p<0.001$). However the RR did not change over time for infection-unrelated NADC ($p=0.44$). Among individual infection-related NADC, the RR for anal squamous cell cancer decreased from 159.9 in 1996–99 to 94.0 in 2004–07, but differences over time were not statistically significant ($p=0.83$). Similarly, the RR for Hodgkin's lymphoma decreased from 43.3 in 1996–99 to 12.0 in 2004–07 ($p=0.10$). Among infection-unrelated cancers, only lung cancer demonstrated statistically significant differences over time with an RR of 3.9 in 1996–99 and 2.1 in 2004–07 ($p=0.010$).

DISCUSSION

We determined that infection-related cancers (ADC and infection-related NADC combined) comprised almost 70% of all cancers in HIV-infected persons enrolled in an integrated healthcare system in California compared to only 12% in HIV-uninfected persons of similar age and sex. HIV-infected persons had a more than nine-fold increased risk of infection-related NADC compared to HIV-uninfected persons, which was largely influenced by differences in risk for anal squamous cell cancer and Hodgkin's lymphoma. HIV-infected persons also had a 30% increased risk of infection-unrelated NADC compared to HIV-uninfected persons, including a higher risk of other anal, skin, other head and neck, and lung cancers, but lower risk of prostate cancer. Infection-related NADC risk declined over time for HIV-infected persons and increased for HIV-uninfected persons. In contrast, the overall infection-unrelated NADC risk did not change over time for HIV-infected or HIV-uninfected persons.

The substantially greater risk for cancers with a known infectious cause in HIV-infected persons compared with HIV-uninfected persons may be explained by higher virus co-infection rates, as demonstrated by others for human herpesvirus-8, HPV and hepatitis B and C [10–13]. However, general population prevalence for certain viruses, such as Epstein-Barr Virus [21], are very high and cannot account entirely for the large difference observed here for Hodgkin's lymphoma. Alternatively, the greater risk for infection-related cancers observed in HIV-infected persons, could be further explained by the fact that the suppressed immune system in HIV-infected persons may reduce the ability to control infections and therefore suppress the oncogenic viral process. This mechanism is supported by a large meta-analysis by Grulich et al. [17] who compared cancers elevated in persons with HIV infection and organ transplant recipients. These two very different populations have few shared risk factors for

cancer except both populations have suppressed immune systems [17,22]. Most of the cancers seen with higher frequency in both populations compared to general population rates had a known infectious cause including ADC, as well as the same infection-related NADC we report here. Others have demonstrated a higher risk of Hodgkin's lymphoma [2,6,23–26], oral cavity/pharynx [2,23], anal [26,27], liver [22] and penis [23] cancers with advanced immunosuppression measured mainly by closer proximity to an AIDS diagnosis [2,23–25] or low CD4+ T-cell counts [4,6,26,27]. One study, however, indicated a non-linear association of Hodgkin's lymphoma risk and CD4+ T-cell counts [28].

Further evidence of a strong link between immune function and infection-related cancer risk is provided by our observation that the increased risk of both ADC and infection-related NADC in HIV-infected persons compared to HIV-uninfected persons has narrowed in recent years. This observation is consistent with improvements during the ART era in immune function possibly leading to better control of co-infections [12,15]. In fact, a recent study demonstrated that prolonged ART use predicts Hepatitis B virus clearance [29], although studies of the effect of ART on other viruses were inconclusive, including Hepatitis C [30], anal HPV [31], cervical HPV [32] and Epstein-Barr Virus [33]. Others have actually demonstrated increases in the incidence of Hodgkin's lymphoma [2,4], anal cancer [4,27,34], and liver [2] cancer during the ART era, suggesting that these cancers may not be strongly associated with immune reconstitution resulting from ART use. It is not clear why trends are somewhat different in our study, since we observed no changes over time in HIV-infected persons for any cancer in adjusted models, with the exception of declines in anal squamous cell cancer. One possible explanation is that many prior studies compared rates between the pre-ART and ART eras, while ours focused *only* in the ART era. Piketty et al. [27], for example, in the largest study focusing on anal cancer, found an increasing trend for years 1992–2004, but no change for years 1999–2004. It is also possible that trends may be different for certain subgroups. Our cohort of predominantly HIV-infected White MSM, had very high anal squamous cell cancer rates early in the ART era. Therefore, it is possible that improvements in immune function may have a bigger impact in our population. Nevertheless, our findings need replication in other settings.

We also report here our finding that the risk of infection-unrelated cancers is only marginally increased in HIV-infected persons compared with HIV-uninfected persons. The meta-analysis by Grulich et al. [17] demonstrated that other cancers not known to be associated with an infection were also elevated in both immunosuppressed populations, that is HIV-infected persons and transplant recipients, including lung and kidney cancers, multiple myeloma, and leukemia. Others have linked infection-unrelated cancers and immunosuppression [2,23,24, 35,36], most commonly for lung cancer [2,23,35]. However, because the reported increased risk for infection-unrelated cancers is not large, results are more likely to be attributed to unmeasured confounding. Unfortunately, few cohorts have the necessary data for complete adjusted analyses. A recent study of skin cancer suggested that the higher risk of melanoma for HIV-infected persons was more likely due to confounding by sun exposure or perhaps increased medical surveillance than due to immunosuppression [37]. However, there is some indication that the excess risk of lung cancer in HIV-infected persons remains even after accounting for cigarette use [35,38,39]. Thus, a general effect of immune function on some infection-unrelated cancers is possible, but further research is warranted.

This study had certain limitations. First, we did not account for cancer risk factors such as smoking or alcohol use. However, it is not likely that confounding by these and other factors entirely explained the observed results for cancers with a known infectious cause, given the large effect sizes. Infection-unrelated NADC, on the other hand, had much smaller effect sizes and may in fact be explained by confounding factors. A related limitation was the ecologic evaluation of changes in cancer risk over time. Although we did adjust for differences in age

and sex over time, it is possible that changes in cancer risk factors confounded our results. However, if this were the case, one would expect broader changes in cancer risk, rather than declines only among infection-related cancers. Furthermore, there is no data to suggest that HIV-infected persons have shown dramatic improvements in the prevalence of risk factors, such as smoking, alcohol use or viral coinfection. Therefore, we believe results are more likely attributable to improvements over time in immune function. Nevertheless, studies incorporating individual-level data are needed to address these questions. Finally, we had limited generalizability to women, the uninsured, and certain racial/ethnic minorities.

The major strength of our study is the selection and follow-up of large, well-characterized populations of HIV-infected persons and matched HIV-uninfected persons from the same health care system. Study results are likely to be highly generalizable to those with access to healthcare since KP provides care to approximately 30% of all insured Californians in its most populated areas, and data indicate members are very similar to the local surrounding and statewide population with respect to age, sex and race/ethnicity, with only slight underrepresentation of those in lower and higher income and education categories [16]. Furthermore, demographics of HIV-infected KP members are very similar to reported AIDS cases in California [40]. Another strength is the high quality case ascertainment of HIV infection status and cancer diagnoses. Finally, this analysis is unique in that we evaluated differences in the epidemiology of cancers with and without a currently known infectious cause.

In summary, we found that almost 70% of cancers in HIV-infected persons have a currently known infectious cause compared to only 12% in HIV-uninfected persons. These results have implications for prevention of cancers in HIV-infected persons. First, we found little evidence for the need for a different screening approach compared to general guidelines for breast, prostate or colorectal cancer among HIV-infected persons. However, the higher risk of lung cancer should be evaluated further including the possible association of this cancer with immune function, and the need for greater smoking risk reduction. Prevention efforts in HIV-infected persons, however, should continue to focus on infection-related cancers, including the evaluation of more routine vaccinations for infections such as hepatitis B, and possibly the extension of the recently approved HPV vaccine to adolescent boys. However, the HPV vaccine has not been evaluated in HIV-infected persons, nor has it been evaluated for the prevention of HPV-associated cancers other than cervical cancer. For anal squamous cell cancer, universal screening guidelines for the detection of early lesions may also greatly benefit this population. Finally, our study supports the concept of earlier initiation of ART [41,42], since the burden of infection-related cancers may be reduced further with improved immune function.

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REFERENCES

1. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, et al. Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study. *Aids* 2009;23:41–50. [PubMed: 19050385]

2. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, et al. Cancer risk in people infected with human immunodeficiency virus in the United States. *Int J Cancer* 2008;123:187–194. [PubMed: 18435450]
3. Silverberg MJ, Neuhaus J, Bower M, Gey D, Hatzakis A, Henry K, et al. Risk of cancers during interrupted antiretroviral therapy in the SMART study. *Aids* 2007;21:1957–1963. [PubMed: 17721103]
4. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, et al. Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992–2003. *Ann Intern Med* 2008;148:728–736. [PubMed: 18490686]
5. Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. *Curr Opin Oncol* 2007;19:446–451. [PubMed: 17762569]
6. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, Kofler A, et al. Cancer risk in the Swiss HIV Cohort Study: associations with immunodeficiency, smoking, and highly active antiretroviral therapy. *J Natl Cancer Inst* 2005;97:425–432. [PubMed: 15770006]
7. Hessel NA, Seaberg EC, Preston-Martin S, Massad LS, Sacks HS, Silver S, et al. Cancer risk among participants in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 2004;36:978–985. [PubMed: 15220706]
8. Phelps RM, Smith DK, Heilig CM, Gardner LI, Carpenter CC, Klein RS, et al. Cancer incidence in women with or at risk for HIV. *Int J Cancer* 2001;94:753–757. [PubMed: 11745473]
9. Murillas J, Del Rio M, Riera M, Vaquer P, Salas A, Leyes M, et al. Increased incidence of hepatocellular carcinoma (HCC) in HIV-1 infected patients. *Eur J Intern Med* 2005;16:113–115. [PubMed: 15833677]
10. Evans, AS.; Kaslow, RA. *Viral Infections of Humans: Epidemiology and Control*. 4th edition. New York and London: Plenum Medical Book Company; 2006.
11. Martin JN, Ganem DE, Osmond DH, Page-Shafer KA, Macrae D, Kedes DH. Sexual transmission and the natural history of human herpesvirus 8 infection. *N Engl J Med* 1998;338:948–954. [PubMed: 9521982]
12. Palefsky JM, Minkoff H, Kalish LA, Levine A, Sacks HS, Garcia P, et al. Cervicovaginal human papillomavirus infection in human immunodeficiency virus-1 (HIV)-positive and high-risk HIV-negative women. *J Natl Cancer Inst* 1999;91:226–236. [PubMed: 10037100]
13. Vallet-Pichard A, Pol S. Hepatitis viruses and human immunodeficiency virus co-infection: pathogenesis and treatment. *J Hepatol* 2004;41:156–166. [PubMed: 15246224]
14. Burnet FM. The concept of immunological surveillance. *Prog Exp Tumor Res* 1970;13:1–27. [PubMed: 4921480]
15. Rauch A, Gaudieri S, Evison J, Nolan D, Cavassini M, Weber R, et al. Low current and nadir CD4+ T-cell counts are associated with higher hepatitis C virus RNA levels in the Swiss HIV cohort study. *Antivir Ther* 2008;13:455–460. [PubMed: 18572759]
16. Gordon NP. How Does the Adult Kaiser Permanente Membership in Northern California Compare with the Larger Community? In.
17. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007;370:59–67. [PubMed: 17617273]
18. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer* 2006;118:3030–3044. [PubMed: 16404738]
19. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26:612–619. [PubMed: 18235120]
20. Little, RJ.; Rubin, DB. *Statistical Analysis with Missing Data*. 1st edition. New York, NY: John Wiley and Sons, Inc.; 1987.
21. Mueller, NE.; Birmann, B.; Parsonnet, J.; Schiffman, M.; Stuver, S. Infectious Agents. In: Schottenfeld, D.; Fraumeni, JF., Jr, editors. *Cancer Epidemiology and Prevention*. 3rd edition. Oxford University Press; 2006.

22. Serraino D, Piselli P, Busnach G, Burra P, Citterio F, Arbustini E, et al. Risk of cancer following immunosuppression in organ transplant recipients and in HIV-positive individuals in southern Europe. *Eur J Cancer* 2007;43:2117–2123. [PubMed: 17764927]
23. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *Jama* 2001;285:1736–1745. [PubMed: 11277828]
24. Goedert JJ, Cote TR, Virgo P, Scoppa SM, Kingma DW, Gail MH, et al. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998;351:1833–1839. [PubMed: 9652666]
25. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. *Aids* 1999;13:839–843. [PubMed: 10357384]
26. Bedimo R. Non-AIDS-defining malignancies among HIV-infected patients in the highly active antiretroviral therapy era. *Curr HIV/AIDS Rep* 2008;5:140–149. [PubMed: 18627663]
27. Piketty C, Selinger-Leneman H, Grabar S, Duvivier C, Bonmarchand M, Abramowitz L, et al. Marked increase in the incidence of invasive anal cancer among HIV-infected patients despite treatment with combination antiretroviral therapy. *Aids* 2008;22:1203–1211. [PubMed: 18525266]
28. Biggar RJ, Jaffe ES, Goedert JJ, Chaturvedi A, Pfeiffer R, Engels EA. Hodgkin lymphoma and immunodeficiency in persons with HIV/AIDS. *Blood* 2006;108:3786–3791. [PubMed: 16917006]
29. Lee T, Nuñez M. Longer duration of HBV-active antiretroviral therapy is linked to favorable virological outcome in HIV-HBV co-infected patients. *HIV Clin Trials* 2009;10 epub ahead of print.
30. Cooper CL, Cameron DW. Review of the effect of highly active antiretroviral therapy on hepatitis C virus (HCV) RNA levels in human immunodeficiency virus and HCV coinfection. *Clin Infect Dis* 2002;35:873–879. [PubMed: 12228825]
31. Palefsky JM, Holly EA, Ralston ML, Da Costa M, Bonner H, Jay N, et al. Effect of highly active antiretroviral therapy on the natural history of anal squamous intraepithelial lesions and anal human papillomavirus infection. *J Acquir Immune Defic Syndr* 2001;28:422–428. [PubMed: 11744829]
32. Heard I, Schmitz V, Costagliola D, Orth G, Kazatchkine MD. Early regression of cervical lesions in HIV-seropositive women receiving highly active antiretroviral therapy. *Aids* 1998;12:1459–1464. [PubMed: 9727566]
33. Stevens SJ, Blank BS, Smits PH, Meenhorst PL, Middeldorp JM. High Epstein-Barr virus (EBV) DNA loads in HIV-infected patients: correlation with antiretroviral therapy and quantitative EBV serology. *Aids* 2002;16:993–1001. [PubMed: 11953465]
34. Hessol NA, Pipkin S, Schwarcz S, Cress RD, Bacchetti P, Scheer S. The Impact of Highly Active Antiretroviral Therapy on Non-AIDS-Defining Cancers among Adults with AIDS. *Am J Epidemiol* 2007;165:1143–1153. [PubMed: 17344204]
35. Chaturvedi AK, Pfeiffer RM, Chang L, Goedert JJ, Biggar RJ, Engels EA. Elevated risk of lung cancer among people with AIDS. *Aids* 2007;21:207–213. [PubMed: 17197812]
36. Grulich AE, Li Y, McDonald A, Correll PK, Law MG, Kaldor JM. Rates of non-AIDS-defining cancers in people with HIV infection before and after AIDS diagnosis. *Aids* 2002;16:1155–1161. [PubMed: 12004274]
37. Lanoy E, Dore GM, Madeleine MM, Toro JR, Fraumeni JF Jr, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. *Aids* 2009;23:385–393. [PubMed: 19114864]
38. Engels EA, Brock MV, Chen J, Hooker CM, Gillison M, Moore RD. Elevated incidence of lung cancer among HIV-infected individuals. *J Clin Oncol* 2006;24:1383–1388. [PubMed: 16549832]
39. Kirk GD, Merlo C, P OD, Mehta SH, Galai N, Vlahov D, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis* 2007;45:103–110. [PubMed: 17554710]
40. California Department of Health Services, Office of AIDS. California AIDS Surveillance Report, Cumulative Cases as of December 31. 2005.
41. Kitahata, M.; Gange, S.; Moore, R. Initiating rather than Deferring HAART at a CD4+ Count >500 Cells/mm3 Is Associated with Improved Survival, Paper #71. 16th Conference on Retroviruses and Opportunistic Infections; Feb 8–11; Montreal, Canada. 2009.
42. Sterne, J. When Should HIV-1-infected Persons Initiate ART? Collaborative Analysis of HIV Cohort Studies, Paper #72LB. 16th Conference on Retroviruses and Opportunistic Infections; Feb 8–11; Montreal, Canada. 2009.

Figure 1. Changes in age and CD4+ T-cell counts over time for study participants

Mean age of HIV-infected and HIV-uninfected persons for years 1996 to 2007. Mean CD4+ T-cell counts over time also presented for HIV-infected persons. Numbers of HIV-infected and HIV-uninfected persons each year are also presented.

Age- and sex-adjusted annual % change in cancer rate

	Cancer	HIV+		HIV-		P (HIV+ vs. HIV-)
		%	P	%	P	
—	Infection-related	-8	<0.001	6	0.007	<0.001
— a	Anal squamous cell	-9	0.002	-4	0.68	0.57
— h	Hodgkin's	-3	0.50	17	0.035	0.032
- - -	Infection-unrelated	3	0.15	1	0.066	0.44

Figure 2. Calendar trends for cancers in HIV-infected and HIV-uninfected persons

Crude incidence rates for any infection-related NADC and any infection-unrelated NADC presented for years 1996–99, 2000–03, and 2004–07. Also presented are individual cancers that either showed statistically significant trends among HIV-infected persons, or differences in trends comparing HIV-infected and HIV-uninfected persons. Annual % change in cancer rates obtained from Poisson regression models adjusting for HIV status, age, sex, calendar period (continuous) and HIV status/calendar period interaction. P-values are presented for annual % change within groups, and for the comparison of HIV+ vs. HIV– annual % change.

Table 1**Study population**

	HIV+	HIV–
N	20,277	202,313
Person-years	85,309	1,013,645
Mean years follow-up (sd)	4.2 (3.6)	5.0 (3.6)
Index year, n (%)		
1996–99	6,459 (31.9)	64,639 (32.0)
2000–03	8,747 (43.1)	86,937 (43.0)
2004–07	5,071 (25.0)	50,737 (25.1)
Mean age (sd) at index	40.9 (9.7)	40.6 (9.9)
Male, n (%)	18,342 (90.5)	182,991 (90.5)
Race/ethnicity, n (% among known)		
Asian/Pacific Islander	726 (3.9)	15,292 (13.4)
Black/African-American	3,483 (18.9)	13,316 (11.7)
Hispanic/Latino	3,837 (20.8)	29,935 (26.3)
Other	140 (0.8)	1,497 (1.3)
White	10,254 (55.6)	53,842 (47.3)
n unknown (% of total)	1,837 (9.1)	88,431 (43.7)
HIV exposure risk, n (%)		
Men who have sex with men	11,222 (73.7)	--
Injection drug use ^I	1,179 (7.7)	--
Heterosexual	2,501 (16.4)	--
Other	330 (2.2)	--
n unknown (% of total)	5,045 (24.9)	--
Any ART use prior to index, n (%)	5,534 (27.3)	--
CDC AIDS prior to index, n (%)	5,573 (27.5)	--
Mean CD4 (sd) at index	388.9 (286.8)	--
Mean HIV log RNA at index	4.8 (5.1)	--

SD, standard deviation

^I With or without also reporting men who have sex with men

Table 2

Infection-related and -unrelated cancer rates by HIV infection status

	HIV-infected		HIV-uninfected		RR (95% CI) ²	P
	Cases	Rate/ ¹	Cases	Rate/ ¹		
Any ADC	552	668.7	179	17.7	37.7 (31.7–44.8)	<0.001
KS	314	377.3	6	0.6	633.6 (280.3–1432.2)	<0.001
NHL	255	302.6	167	16.5	18.1 (14.8–22.1)	<0.001
Invasive Cervix	2	23.9	6	6.1	2.9 (0.5–16.2)	0.220
Any NADC	600	723.9	3678	369.5	1.9 (1.7–2.0)	<0.001
Infection-related NADC	221	262.6	284	28.1	9.2 (7.7–11.1)	<0.001
Anal squamous cell	110	130.2	11	1.1	101.6 (54.3–189.9)	<0.001
Vagina/vulva	22	264.9	12	12.1	19.5 (9.2–41.1)	<0.001
Hodgkin's lymphoma	47	55.4	29	2.9	18.7 (11.6–30.1)	<0.001
Penis	4	5.2	8	0.9	5.8 (1.7–19.8)	0.006
Liver	22	25.9	94	9.3	3.3 (2.1–5.4)	<0.001
HPV-related oral squamous cell ³	11	13.0	56	5.5	2.0 (1.1–3.9)	0.034
Stomach	5	5.9	74	7.3	0.8 (0.3–2.0)	0.654
Infection-unrelated NADC	388	463.5	3418	343.1	1.3 (1.2–1.4)	<0.001
Other anal	32	37.7	10	1.0	35.3 (17.1–73.0)	<0.001
Non-melanoma skin	11	12.9	12	1.2	10.6 (4.6–24.4)	<0.001
Other head and neck	31	36.5	140	13.9	2.7 (1.8–4.1)	<0.001
Sarcoma	8	9.4	45	4.5	2.1 (1.0–4.4)	0.064
Lung	54	63.6	342	33.9	1.9 (1.4–2.5)	<0.001
Melanoma	52	61.4	359	35.6	1.5 (1.1–2.0)	0.006
Testes	9	11.8	62	6.8	1.7 (0.8–3.4)	0.162
Kidney	16	18.8	126	12.5	1.5 (0.9–2.5)	0.152
Hematologic ⁴	17	20.0	141	14.0	1.4 (0.8–2.3)	0.192
Colorectal	41	48.3	410	40.7	1.2 (0.9–1.6)	0.290
Breast	15	17.7	201	19.9	0.9 (0.5–1.6)	0.734
Brain/CNS	4	4.7	53	5.2	0.9 (0.3–2.4)	0.797
Prostate	74	97.0	1195	131.9	0.7 (0.5–0.9)	0.002

CI, confidence interval; NADC, non-AIDS-defining cancer; RR, rate ratio

¹ crude rate per 100,000 person-years

² Rate ratios from Poisson regression models included terms for HIV status, age, sex, calendar period, and race/ethnicity. Standard multiple imputation methods were used with imputation for missing race/ethnicity.

³ Using definition described by Chaturvedi et al. [19]

⁴ Multiple myeloma and leukemia

Table 3Adjusted rate ratios¹ for HIV-infected versus HIV-infected cancer rate by calendar period

	Rate ratio (95% confidence interval) for HIV+ vs. HIV-			p ²
	1996–99	2000–03	2004–07	
Any ADC	89.9 (59.2–136.5)	39.5 (29.8–52.3)	22.5 (17.4–29.1)	<0.001
NHL	34.4 (21.6–54.7)	22.6 (16.3–31.2)	11.3 (8.3–15.3)	<0.001
Any NADC	2.6 (2.1–3.2)	2.0 (1.7–2.3)	1.9 (1.7–2.1)	0.042
Infection-related NADC³	16.9 (11.0–25.9)	12.2 (9.1–16.4)	6.2 (4.8–8.1)	<0.001
Anal squamous cell	159.9 (38.0–672.5)	122.9 (49.1–307.8)	94.0 (33.2–266.3)	0.83
Hodgkin's lymphoma	43.3 (12.1–155.4)	28.6 (11.8–68.9)	12.0 (6.4–22.8)	0.097
Liver	3.3 (0.9–11.7)	4.5 (1.7–11.4)	2.4 (1.3–4.3)	0.54
HPV-related oral squamous cell ⁴	4.0 (0.8–19.8)	3.0 (1.2–7.2)	1.4 (0.4–4.7)	0.49
Infection-unrelated NADC³	1.4 (1.0–1.9)	1.3 (1.0–1.5)	1.5 (1.3–1.7)	0.44
Other head and neck	2.3 (0.9–6.0)	1.6 (0.7–3.5)	3.8 (2.2–6.3)	0.169
Lung	3.9 (2.1–7.1)	1.1 (0.6–1.9)	2.1 (1.4–3.2)	0.010
Melanoma	2.3 (1.2–4.5)	1.8 (1.1–2.9)	1.5 (1.0–2.4)	0.57
Kidney	0.7 (0.1–5.3)	1.7 (0.6–4.2)	1.7 (0.9–3.3)	0.66
Hematologic ⁵	0.8 (0.1–6.0)	1.8 (0.8–4.0)	1.4 (0.7–2.8)	0.70
Colorectal	0.6 (0.2–1.8)	1.2 (0.7–2.0)	1.5 (1.0–2.2)	0.26
Breast	1.5 (0.4–4.9)	1.0 (0.4–2.4)	0.7 (0.3–1.6)	0.61
Prostate	0.3 (0.1–1.1)	0.8 (0.6–1.2)	0.8 (0.6–1.1)	0.26

NADC, non-AIDS-defining cancer

¹ Rate ratios from Poisson regression models included terms for HIV status, age, sex, calendar period and HIV status/calendar period interaction² P-value tests overall difference in rate ratio over the three calendar periods.³ Few events for certain cancers among either HIV+ or HIV- persons precluded the evaluation of calendar-era specific RRs including penis, vagina/vulva, and stomach cancers among infection-related cancers and other anal, non-melanoma skin, sarcomas, and testes cancers among infection-unrelated cancers⁴ Using definition described by Chaturvedi et al. [19]⁵ Multiple myeloma and leukemia