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Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals

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Abstract

Objective—To investigate trends, patient characteristics, and survival associated with AIDS-defining cancer (ADC) and non-AIDS defining cancer (NADC) in the HAART era.

Design—Retrospective analysis of all incident malignancies occurring in 1996–2005 among 2566 patients in an urban HIV clinic.

Methods—Clinical profiles of NADC were compared with ADC and the general cohort. Incidence was examined by Poisson analysis. Standardized incidence ratios (SIR) compared cancer risk with that in the general population. Survival was analyzed by Kaplan–Meier and Cox proportional hazards models.

Results—Between 1996 and 2005, 138 ADC and 115 NADC were diagnosed. ADC rates decreased from 12.5 to 3.5 cases/1000 person-years ($P < 0.001$ for trend) while NADC rates increased from 3.9 to 7.1 cases/1000 person-years ($P = 0.13$ for trend). Incidence of the most common NADC was higher than expected, including cancers of the lung [$n = 29$; SIR, 5.5; 95% confidence interval (CI), 3.7–8.0], liver ($n = 13$, SIR, 16.5; 95% CI, 8.8–28.2), anus ($n = 10$; SIR, 39.0; 95% CI, 18.7–71.7), head and neck ($n = 14$; SIR, 5.1; 95% CI, 2.8–8.6), and Hodgkin's lymphoma ($n = 8$; SIR, 9.8; 95% CI, 4.2–19.2). Survival after cancer diagnosis did not differ between ADC and NADC. Advanced age was associated with NADC ($P < 0.01$ for trend) and increased mortality in ADC (age ≥ 50 years adjusted hazard ratio, 2.21; 95% CI, 1.00–4.89).

Conclusions—Rates of ADC decreased while NADC increased within this cohort. Several NADC occurred at rates significantly higher than expected. Screening and suspicion for NADC should increase in care for HIV-infected patients.

Keywords

HIV; malignancy; cancer; HAART; lung cancer

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Introduction

Since 1996, use of HAART has decreased morbidity and mortality associated with HIV infection and AIDS [1]. In the current HAART era, AIDS-associated causes of morbidity and mortality have decreased, and noninfectious processes, including cardiovascular disease, non-AIDS malignancies, and pulmonary disease, represent an increasing proportion of total burden of disease [1–7]. With improved survival, the HIV-infected population is also aging, and the number of individuals diagnosed with AIDS over the age of 50 years has more than quintupled since 1996 [8].

Similar to other opportunistic illnesses, the AIDS-defining cancers (ADC) Kaposi sarcoma and non-Hodgkin's lymphoma (NHL) have decreased in incidence since 1996 [9]. The rates of cervical cancer, however, have not changed [9–13]. While Kaposi sarcoma and NHL continue to constitute the majority of malignancies observed in persons with AIDS, non-AIDS-defining cancers (NADC) represent an increasing proportion of the cancers observed, and, compared with the general population, HIV-infected populations experience elevated risk of a number of NADC, including anal cancer, lung cancer, liver cancer, and cancers of the head and neck [9,14,15]. For the HIV clinician, these changing patterns have important implications regarding cancer screening, diagnosis, and treatment. This study of a large, urban cohort of HIV-infected patients examines the incidence rates, patient characteristics, and survival outcomes associated with malignancy between 1996 and 2005.

Methods

The Johns Hopkins University AIDS Service provides comprehensive primary and subspecialty medical care and social services. All patients who enroll in continuity care are offered the opportunity to join the prospective, observational study of the clinical cohort. At baseline, an exhaustive evaluation of medical and social histories, physical examination, and laboratory studies are recorded and these data are prospectively updated from the clinic-based medical record by trained data monitors every 6 months, with new medical diagnoses, hospitalizations and procedures, pharmaceutical prescriptions and filling, and laboratory and radiographic results. A separate death database of cohort participants is maintained and updated, using the Maryland Bureau of Vital Statistics and the National Death Index for participants who are lost to follow-up for more than 1 year. Maintenance of the database and use of its contents for analysis of patient outcomes are approved by the Institutional Review Board of the Johns Hopkins University School of Medicine.

For this analysis, a retrospective analysis was performed of the 2566 HIV-infected patients enrolled in the clinical cohort who contributed any person-time from January 1, 1996 through December 31, 2005 and all cases of pathologically confirmed, incident malignancies diagnosed were identified. To confirm identified cases and screen for missed cases, identifying information of patients in the cohort were matched with the Tumor Registry of the Johns Hopkins Hospital Kimmel Cancer Center, which records all cases of malignancy diagnosed or treated at the Johns Hopkins Hospital since 1995. Nonmelanoma skin cancer was excluded from the analyses as this is not systematically ascertained and not thought to cause significant morbidity or mortality. As only a small number of each cancer type occurred, cases were grouped into ADC and NADC for most analyses examining trends in incidence and survival.

Demographic and clinical variables at baseline and at the time of cancer diagnosis were evaluated to analyse the characteristics of the cancer patients and the general cohort. Demographic variables included age, race (White, Black, or Other), and sex. HIV transmission risk factors included injection drug use, men who had sex with men, and heterosexual transmission, defined as heterosexual activity with a partner infected with HIV or at high risk

for HIV. Risk factor assignment was not mutually exclusive. Clinical variables included CD4 cell counts (cells/ μ l) and plasma HIV-1 RNA (copies/ml) at baseline and the time of cancer diagnosis. HAART was defined as concomitant use of three antiretroviral drugs, either from two classes (nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, or a fusion inhibitor) or three nucleoside reverse transcriptase inhibitors. Patients were considered to be taking HAART if they were receiving any of these combinations for more than 30 days. Chronic hepatitis B virus (HBV) infection was defined by repeated detection of plasma HBV surface antigen. Chronic hepatitis C virus (HCV) infection was defined by detection of plasma anti-HCV antibody. Opportunistic infections were defined by the *1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults* by the Centers for Disease Control and Prevention [16]. Univariate analyses compared sociodemographic and clinical characteristics of those with NADC, ADC, and the general cohort. Continuous data were categorized and categorical data were compared using χ^2 tests.

Poisson regression was used to compare ADC and NADC incidence rates over time. To compare rates of specific cancers with rates in the general population, the standardized incidence ratios (SIR) were calculated, defined as the ratio of the observed number of cancer cases to the expected number of cases. Expected cases were estimated using age-, race-, sex-, and calendar year of diagnosis-specific rates occurring in Detroit, Michigan, USA, as recorded in the Surveillance Epidemiology and End Results database [17]. Data from Detroit were used as it is similar in size and socioeconomic distribution to Baltimore [18]. Averaged national rates for Kaposi sarcoma from 1973 to 1979 were used to estimate expected cases because contemporaneous general population rates for Kaposi sarcoma are distorted by the large number of cases in HIV-infected persons [9]. Head and neck cancers included all cancers of the mouth, oropharynx, nasal passage, sinuses, and larynx. Squamous cell carcinoma of the rectum was included with anal cancers. Exact 95% confidence intervals (CI) were calculated for each SIR [19].

Survival analysis included Kaplan–Meier estimates and Cox proportional hazards models using all-cause mortality as the outcome of interest. For NADC and ADC, estimated survival was calculated as time from cancer diagnosis to death. Survival curves were statistically compared using log-rank tests. Mortality associated with demographic and clinical variables for NADC and ADC was analyzed in univariate and multivariate Cox proportional hazards models with preselected clinical and demographic variables believed to be associated with increased mortality among HIV-infected persons and, therefore, potential confounders. All reported *P* values are two sided and all statistical analyses were carried out using Stata 9.0 (Stata Corporation, College Station, Texas, USA).

Results

The Johns Hopkins AIDS clinic cohort followed a total of 2566 individuals, contributing a total of 19 491 person-years of follow-up between January 1, 1996 and December 31, 2005. At clinic enrollment, patients diagnosed with an NADC were older than patients in the general cohort and those diagnosed with an ADC (median ages 45, 38, and 35 years, respectively; *P* <0.001; Table 1). Compared with patients with ADC, patients with NADC were also more likely to be injection drug users (26% and 49%, respectively; *P* = 0.001) and to have chronic HCV infection (30% and 50%, respectively; *P* = 0.003). Patients with ADC were more likely to be immunosuppressed than those with NADC and the general cohort at clinic enrollment (*P* <0.001). Baseline HIV viral load tended to be greater in persons diagnosed with an ADC than those diagnosed with an NADC or the general cohort (HIV-1 RNA ≥ 5.0 log₁₀ copies/ml in 47%, 24%, and 28%, respectively; *P* = 0.003).

Patients diagnosed with an NADC also tended to have longer durations of clinic follow-up compared with those diagnosed with an ADC and the general cohort (median follow-up times 5.2, 3.5, and 4.5 years, respectively; $P = 0.029$). At the time of cancer diagnosis, those with NADC were more likely to be older than those with ADC ($P < 0.001$) (Table 2). They also had higher CD4 cell counts ($P < 0.001$), were less likely to have a history of opportunistic infections (57% and 70%, respectively; $P = 0.033$), and, of those taking HAART at cancer diagnosis, were more likely to be virologically suppressed (59% and 57%, respectively; $P = 0.007$). However, those with NADC or ADC did not significantly differ by history of HAART exposure preceding or at the time of cancer diagnosis.

Importantly, patient profiles also varied within subtypes of NADC and ADC. For example, 26 of the 29 cases of lung cancer and 10 of the 13 cases of liver cancer occurred in Black patients; 7 of the 10 cases of anal cancer occurred in White patients, and the 14 cases of head and neck cancer were nearly evenly divided between races. Among ADC, Kaposi sarcoma and NHL occurred predominantly in males (91% and 78%, respectively) and approximately two-thirds of both groups had CD4 cell counts < 200 cells/ μ l at the time of cancer diagnosis; however, of the 15 cases of cervical cancer, only five women had CD4 cell counts < 200 cells/ μ l at the time of cancer diagnosis. Most Kaposi sarcoma and anal cancer occurred in men who have sex with men (74 and 90%, respectively).

Since 1996, 115 cases of NADC were diagnosed for an overall incidence rate of 5.9/1000 person-years, including 29 cases of lung cancer, 14 cases of head and neck cancers, 13 cases of liver cancer, and 10 cases of anal cancer. There were 138 cases of ADC for an overall incidence rate of 7.1/1000 person-years, which included 68 cases of Kaposi sarcoma, 55 cases of NHL, and 15 cases of cervical cancer. The 55 NHL included 26 cases of diffuse large B cell lymphoma, 21 cases of primary CNS lymphoma, 2 cases of Burkitt lymphoma, and 6 cases of other or unknown lymphomas.

The incidence of ADCs decreased from over 12/1000 person-years in 1996 to < 4 /1000 person-years in 2005 ($P < 0.001$ for trend). In contrast, NADC incidence tended to increase between 1996 and 2005 from 3.9 to 7.1/1000 person-years ($P = 0.13$ for trend) (Fig. 1). Poisson analysis of trends of specific cancers was only statistically significant for Kaposi sarcoma and NHL. Kaposi sarcoma incidence steadily fell from 5/1000 person-years in 1996 to 1/1000 person-years in 2005 ($P = 0.023$ for trend), and NHL incidence also decreased from > 5 /1000 person-years in 1996 to 1/1000 person-years in 2005 ($P = 0.012$ for trend). Cervical cancer incidence remained statistically unchanged at 1–2/1000 person-years. Rates of lung, liver, and head and neck cancers all tended to increase from 1996 to 2005; however, none of these trends were statistically significant owing to small sample size (data not shown).

Risk of a number of cancer types was elevated among the HIV-infected cohort compared with the general population (Table 3). Risks of the three ADC were between 16- and 5000-fold that of the general population. Similarly, risk of the four NHL types were between 4- and 2100-fold that the general population. Of the most common NADC observed in our cohort, the risks were between 5- and 39-fold that of the general population, in particular for cancer of the lung (SIR, 5.5; 95% CI, 3.7–8.0), head and neck (SIR, 5.1; 95% CI, 2.8–8.6), liver (SIR, 16.5; 95% CI, 8.8–28.2), and anus (SIR, 39.0; 95% CI, 18.7–71.7). Compared with the general population, this HIV-infected population also demonstrated statistically significantly increased rates of esophageal cancer, bladder cancer, Hodgkin's lymphoma, and melanoma; however, there was no difference in the risk of breast, prostate, or colorectal cancers.

Overall there was no statistical difference in mortality from time of cancer diagnosis between those diagnosed with an ADC and those diagnosed with an NADC (Fig. 2); however, during the first 2 years following cancer diagnosis, persons with an ADC experienced increased

mortality compared with those diagnosed with an NADC ($P = 0.06$). Overall, the median survival time from diagnosis of all ADC was 315 days (95% CI, 220–623); more specifically, the median survival time of NHL was 119 days, Kaposi sarcoma 422 days, and cervical cancer 1199 days. The overall median survival time of NADC was 654 days (95% CI, 295–845); more specifically, the median survival time of liver cancer was 91 days, lung cancer 175 days, head and neck cancer 730 days, and anal cancer 970 days.

Demographic and clinical characteristics associated with increased mortality among those with ADC and NADC are shown in Table 4. Among those with ADC, age >50 years at the time of cancer diagnosis was significantly associated with an approximate doubling of the risk of death compared with age <40 years, after adjusting for race, gender, and CD4 cell count at time of cancer diagnosis (adjusted hazard ratio, 2.21; 95% CI, 1.00–4.89). Women diagnosed with an ADC experienced nearly twice the risk of death compared with men in the multivariate model (adjusted hazard ratio, 1.96; 95% CI, 1.12–3.48). CD4 cell count at the time of cancer diagnosis was highly associated with mortality risk among those diagnosed with an ADC in both the univariate and multivariate analyses; however, virological suppression at cancer diagnosis was not associated with mortality risk. When the multivariate models were stratified by virological suppression, the trend of increased mortality risk with increased immunosuppression remained; however, the trend was statistically significant only among patients who were not suppressed. Additionally, analysis of patients with very high plasma viral load ($\geq 5.0 \log_{10}$ copies/ml) at the time of diagnosis of ADC found viral load not to be significantly associated with mortality risk in univariate analysis. However, when stratified by HIV-1 RNA, <5.0 or >5.0 $\log_{10}$ copies/ml, the trend of increased mortality risk with increased immunosuppression was statistically significant only for patients with HIV-1 RNA <5.0 $\log_{10}$ copies/ml (data not shown). Finally, age, gender, race, and CD4 cell count at the time of cancer diagnosis were not significantly associated with increased mortality among those diagnosed with a NADC.

Discussion

This paper has several important findings. First, since 1996, rates of ADC have markedly decreased while NADC rates have tended to increase and have become more frequent than ADC within this cohort. Currently, several NADC, particularly lung, liver, anal, and head and neck cancers, occur at rates significantly higher than those expected in the general population. While individuals diagnosed with NADC are healthier in regards to their HIV disease at the time of cancer diagnosis, their survival is as poor as those diagnosed with ADCs.

Cancer rates in this urban cohort mirrored trends seen nationally [9]. The sharp decline in ADC has resulted from a decreasing incidence of Kaposi sarcoma and NHL, which are strongly associated with immunosuppression [20]. While decreasing rates of Kaposi sarcoma were observed prior to 1996, the precipitous decline of Kaposi sarcoma and NHL since 1996 has been caused by use of HAART [9–13,21]. The trends in incidence of cervical cancer and NADC have been less consistent in the HAART era, probably because they are less associated with degree of immunosuppression than Kaposi sarcoma and NHL [10,12,14,20]. In this study, greater immunosuppression was observed at both clinic enrollment and cancer diagnosis among those with ADC. The two cancer groups did not differ by history of HAART exposure at the time of cancer diagnosis; however, of those patients taking HAART at the time of cancer diagnosis, patients diagnosed with an NADC were more likely to be virologically suppressed than patients diagnosed with an ADC. This may suggest that, while HAART protects against ADC, patients receiving virological benefit from HAART are still at risk of developing NADC. Additionally, the unreliable prognostic value of CD4 cell count at the time of ADC diagnosis for patients with either suppressed or very high viral loads in this study adds to recent investigations of the role of viral load in risk of opportunistic clinical outcomes [22]. Finally,

this study reveals that NADC now forms the majority of cancer cases observed in this urban clinical cohort, which is consistent with the trend of several recent studies [9,12,15].

Consistent with other studies, incidence of Kaposi sarcoma, NHL, and cervical cancer was greater among this urban HIV-infected cohort than in the general population [9,12,15,23]. The incidence of cervical cancer has not changed since 1996, and one study demonstrated no elevated risk of cervical cancer among HIV-infected women compared with uninfected women in the setting of rigorous gynecological screening [24]. While the Johns Hopkins AIDS Service provides comprehensive gynecological services and has demonstrated high screening rates, these results suggest further efforts to increase screening and follow-up are needed to improve clinical care [25].

The increased incidence of specific NADC in HIV-infected populations has been attributed to the high rates of smoking, alcohol use, and chronic infection by oncogenic viruses such as the hepatitis viruses and human papilloma virus [12,18,26]. Following national trends, the most common NADC in this cohort was lung cancer, observed at rates exceeding expected incidence. The increased risk of lung cancer in HIV-positive patients is at least partly independent of smoking history [18,27]. Additionally, liver cancer, head and neck cancers, anal cancer, bladder cancer, esophageal cancer, Hodgkin's lymphoma, and melanoma were observed at rates greater than would be expected in the general population [9,12,14,15,21,28]. The elevated risk of liver cancer is likely partly a result of the high rates of HCV and HBV infection in this cohort. Of the 13 identified with liver cancer, nine individuals were chronically infected with HCV (69%), six were chronically infected with HBV (46%), and three were infected with both HCV and HBV (23%).

Consistent with the literature, rates of prostate cancer, breast cancer, and colorectal cancer were comparable to the general population [9,14,24]. These findings argue against increased screening as a possible explanation for why HIV-infected populations have higher rates of malignancy. Indeed, it is possible that lower rates of these common cancers indicate insufficient routine cancer screening of HIV-infected individuals [26,29].

Our study revealed an association of older age at clinic enrollment and diagnosis of NADC, and there was an increased risk of mortality associated with older age at cancer diagnosis among those with ADC. The role of age in malignancy risk in HIV-infected populations is unclear. A study of people with AIDS over the age of 60 years in the pre-HAART era found that the NADC seen were similar to those seen in younger persons with AIDS [23]. Given the aging of the HIV-infected population in the United States and the known increase in cancer with advancing age, further studies are necessary to understand the role of age in cancer epidemiology in this population.

NADC has increasingly contributed to overall mortality among HIV-infected populations in industrialized countries [5–7]. In a recent retrospective study in France, malignancies were the second most common cause of death after AIDS, to which ADC and NADC contributed nearly equally (15% and 13% of all deaths, respectively) [30]. Our study revealed equivalent survival following diagnosis of an ADC or NADC. Among deaths from an ADC, female sex, CD4 cell count, and age at the time of cancer diagnosis were associated with increased risk of mortality. Interestingly, among NADC deaths, neither age nor CD4 cell count was associated with increased mortality risk. There was a trend for increased mortality in Black patients; however, in our cohort, both lung and liver cancer were common NADC, had higher mortality rates than other NADC, and were disproportionately diagnosed among Blacks. Previous work has not demonstrated increased mortality in HIV-infected patients with lung cancer compared with seronegative patients [31]. Future cohort studies will need to evaluate the relationship between race and mortality from NADC.

There are several limitations to our study. First, the number of cases of specific cancer types was too small to analyze for specific factors associated with incidence and survival; therefore, we were limited to making general observations regarding ADC and NADC. Additionally, though the population is representative of HIV in urban settings, these results are based upon patients from a single institution with a high proportion of injection drug users and indigent patients. Also, malignancy diagnosed for a patient at another hospital may have been missed by this analysis; however, our hospital serves as the primary care center for these patients, and a recent analysis demonstrated that 96% of all admissions occurred at our hospital (unpublished data). Given that care for patients with cancer is longitudinal, we believe that we captured almost all the cases. We also did not have data on cigarette or alcohol use for all individuals in the cohort; therefore, we could not analyze the roles of these important risk factors for cancer. Finally, our survival analysis used death from all causes and did not differentiate deaths caused by AIDS or by cancer.

This study of cancer epidemiology in an urban cohort of HIV-infected patient has important implications for HIV clinicians and researchers. From a clinical perspective, it demonstrates an increasing incidence of NADC, and it underscores the importance of prevention and early clinical evaluation of patients possibly symptomatic for one of the common NADC, particularly lung cancer, head and neck cancers, liver cancer, and anal cancer. While patients diagnosed with NADC typically do not present with advanced HIV disease, their mortality is comparable to those with ADC. This study corroborates a number of other studies of cancer trends, risks, and mortality in the HAART era, including elevated rates of several NADC compared with the general population. Given the general observations noted in our study, combined cohort studies of risk of specific NADC and associated mortality risks may help to evaluate many of these pressing questions.

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References

1. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998;338:853–860. [PubMed: 9516219]
2. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS* 1999;13:1933–1942. [PubMed: 10513653]
3. Vittinghoff E, Scheer S, O'Malley P, Colfax G, Holmberg SD, Buchbinder SP. Combination antiretroviral therapy and recent declines in AIDS incidence and mortality. *J Infect Dis* 1999;179:717–720. [PubMed: 9952385]
4. Lewden C, Salmon D, Morlat P, Bevilacqua S, Jougla E, Bonnet F, et al. Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS. *Int J Epidemiol* 2005;34:121–130. [PubMed: 15561752]
5. Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. *J Infect Dis* 2002;186:1023–1027. [PubMed: 12232845]
6. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006;43:27–34. [PubMed: 16878047]

7. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145:397–406. [PubMed: 16983127]
8. Mack KA, Ory MG. AIDS and older Americans at the end of the twentieth century. *J Acquir Immune Defic Syndr* 2003;33(Suppl 2):S68–S75. [PubMed: 12853855]
9. Engels EA, Pfeiffer RM, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, et al. Trends in cancer risk among people with AIDS in the United States 1980–2002. *AIDS* 2006;20:1645–1654. [PubMed: 16868446]
10. Bower M, Palmieri C, Dhillon T. AIDS-related malignancies: changing epidemiology and the impact of highly active anti-retroviral therapy. *Curr Opin Infect Dis* 2006;19:14–19. [PubMed: 16374212]
11. Cheung MC, Pantanowitz L, Dezube BJ. AIDS-related malignancies: emerging challenges in the era of highly active anti-retroviral therapy. *Oncologist* 2005;10:412–426. [PubMed: 15967835]
12. Clifford GM, Polesel J, Rickenbach M, Dal Maso L, Keiser O, 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]
13. Gates AE, Kaplan LD. AIDS malignancies in the era of highly active antiretroviral therapy. *Oncology (Williston Park)* 2002;16:441–451. 456, 459. [PubMed: 12017534]
14. Herida M, Mary-Krause M, Kaphan R, Cadranet J, Poizot-Martin I, Rabaud C, et al. Incidence of non-AIDS-defining cancers before and during the highly active antiretroviral therapy era in a cohort of human immunodeficiency virus-infected patients. *J Clin Oncol* 2003;21:3447–3453. [PubMed: 12972519]
15. Gallagher B, Wang Z, Schymura MJ, Kahn A, Fordyce EJ. Cancer incidence in New York state AIDS patients. *Am J Epidemiol* 2001;154:544–556. [PubMed: 11549560]
16. Centers for Disease Control and Prevention. 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS among Adolescents and Adults. *MMWR Recomm Rep* 1992;41:1–19.
17. National Cancer Institute. SEER Cancer Statistics Review, 1975–2002. Bethesda, MD: National Cancer Institute; 2005. <http://seer.cancer.gov>
18. 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]
19. Breslow, NE.; Day, NE. The Design and Analysis of Cohort Studies. II. International Agency for Research on Cancer Scientific Publications No. 82; Lyon: 1987. Statistical Methods in Cancer Research.
20. Mbulaitye SM, Biggar RJ, Goedert JJ, Engels EA. Immune deficiency and risk for malignancy among persons with AIDS. *J Acquir Immune Defic Syndr* 2003;32:527–533. [PubMed: 12679705]
21. International Collaboration on HIV, Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000;92:1823–1830. [PubMed: 11078759]
22. D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA, Angel JB. *Pneumocystis jirovecii* pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/μl when viral replication is suppressed. *AIDS* 2007;21:1711–1715. [PubMed: 17690568]
23. Biggar RJ, Kirby KA, Atkinson J, McNeel TS, Engels E. Cancer risk in elderly persons with HIV/AIDS. *J Acquir Immune Defic Syndr* 2004;36:861–868. [PubMed: 15213571]
24. Hessol 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]
25. Sheth AN, Moore RD, Gebo KA. Provision of general and HIV-specific health maintenance in middle aged and older patients in an urban HIV clinic. *AIDS Patient Care STDS* 2006;20:318–325. [PubMed: 16706706]
26. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000;92:1500–1510. [PubMed: 10995805]

27. Kirk GD, Merlo C, O' Driscoll P, 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]
28. Frisch M, Biggar RJ, Engels EA, Goedert JJ. Association of cancer with AIDS-related immunosuppression in adults. *JAMA* 2001;285:1736–1745. [PubMed: 11277828]
29. Bini EJ, Park J, Francois F. Use of flexible sigmoidoscopy to screen for colorectal cancer in HIV-infected patients 50 years of age and older. *Arch Intern Med* 2006;166:1626–1631. [PubMed: 16908796]
30. Bonnet F, Lewden C, May T, Heripret L, Jouglu E, Bevilacqua S, et al. Malignancy-related causes of death in human immunodeficiency virus-infected patients in the era of highly active antiretroviral therapy. *Cancer* 2004;101:317–324. [PubMed: 15241829]
31. Brock MV, Hooker CM, Engels EA, Moore RD, Gillison ML, Alberg AJ, et al. Delayed diagnosis and elevated mortality in an urban population with HIV and lung cancer: implications for patient care. *J Acquir Immune Defic Syndr* 2006;43:47–55. [PubMed: 16936558]

Fig. 1. Poisson analysis of incidence rates of non-AIDS-defining cancer (NADC) and AIDS-defining cancer (ADC) 1996–2000.

Fig. 2. Survival following cancer diagnosis for non-AIDS-defining cancer (NADC) versus AIDS-defining cancer (ADC)
Log-rank test of survival equality, 0.74.

Table 1

Baseline demographic and clinical characteristics of subjects with non-AIDS-defining cancer, AIDS-defining cancer, and the general cohort at enrollment.

	NADC	ADC	Cohort	<i>P</i> values ^a
No. (%)	115 (45.5)	138 (54.5)	2566	
Median age (years)	45	35	38	
Age groups (years) [No. (%)]				
<30	6 (5.2)	22 (15.9)	392 (15.3)	<0.001
30–39	20 (17.4)	75 (54.4)	1116 (43.5)	
40–49	62 (53.9)	32 (23.2)	785 (30.6)	
≥50	27 (23.5)	9 (6.5)	273 (10.6)	
Gender [No. (%)]				
Male	91 (79.1)	105 (76.1)	1734 (67.6)	0.005
Female	24 (20.9)	33 (23.9)	832 (32.4)	
Race [No. (%)]				
White	29 (25.2)	41 (29.7)	583 (22.7)	0.323
Black	85 (73.9)	94 (68.1)	1935 (75.4)	
Other	1 (0.9)	3 (2.2)	48 (1.9)	
HIV transmission risk factors [No. (%)] ^b				
Men who had sex with men	40 (36.7)	73 (55.3)	731 (29.4)	<0.001
Injection drug use	53 (48.7)	34 (25.8)	1035 (41.6)	
Heterosexual ^c	45 (48.0)	38 (28.8)	1192 (47.9)	<0.001
Median CD4 cell count (cells/μl)	319	157	281	
CD4 cell count (cells/μl) groups [No. (%)]				
>350	50 (43.5)	39 (28.3)	1042 (40.7)	<0.001
201–350	31 (27.0)	19 (13.8)	539 (21.0)	
51–200	21 (18.3)	33 (23.9)	529 (20.7)	
≤50	13 (11.3)	47 (34.1)	451 (17.6)	
Median HIV-1 RNA (log ₁₀ copies/ml)	3.92	4.34	4.42	
HIV-1 RNA (log ₁₀ copies/ml) groups [No. (%)]				
<2.60	16 (14.3)	19 (14.4)	330 (14.2)	0.003
2.60–3.99	30 (26.8)	14 (10.6)	520 (22.3)	
4.0–4.99	39 (34.8)	37 (28.0)	834 (35.8)	
≥5.0	27 (24.1)	62 (47.0)	648 (27.8)	
History of HAART prior to enrolment [No. (%)] ^d				
Chronic HBV infection	31 (27.0)	36 (26.1)	630 (24.6)	0.775
Chronic HCV infection	15 (13.0)	15 (10.9)	227 (8.9)	0.230
	57 (49.6)	41 (29.7)	1060 (41.3)	0.004

NADC, non-AIDS-defining cancer; ADC, AIDS-defining cancer; HBV, hepatitis B; HCV, hepatitis C.

^a χ^2 tests comparing NADC, ADC, and general cohort.

^b Risk factor assignment is not mutually exclusive.

^c History of heterosexual activity with a partner with known HIV infection or with a partner at high risk for HIV infection.

^d Defined in the Methods.

Table 2

Demographic and clinical characteristics of non-AIDS-defining cancer cases and AIDS-defining cancer cases at cancer diagnosis.

	NADC	ADC	<i>P</i> values ^a
No. (%)	115 (45.5)	138 (54.5)	
Median age (years)	48	38	
Age (years) group [No. (%)]			
<30	1 (0.9)	9 (6.5)	<0.001
30–39	14 (12.2)	72 (52.2)	
40–49	53 (46.1)	45 (32.6)	
≥50	47 (40.9)	12 (8.7)	
Median CD4 cell count (cells/μl)	270	60	
CD4 cell count (cells/μl) group [No. (%)]			
>350	43 (37.4)	20 (15.0)	<0.001
201–350	34 (39.6)	14 (10.5)	
51–200	27 (23.5)	37 (27.8)	
≤50	11 (9.6)	62 (46.6)	
History of opportunistic infection [No. (%)] ^b	65 (57.4)	97 (70.3)	0.033
History of HAART [No. (%)]	83 (72.2)	93 (67.4)	0.410
Taking HAART at cancer diagnosis [No. (%)]	68 (59.1)	70 (50.7)	0.181
Taking HAART and HIV-1 RNA <400 copies/ml [No. (%)]	39 (59.1)	23 (35.4)	0.007

NADC, non-AIDS-defining cancer; ADC, AIDS-defining cancer.

^a χ^2 tests comparing NADC, ADC, and general cohort.

^b Defined in the Methods.

Table 3
Standardized incidence ratios for AIDS-defining and non-AIDS-defining cancers.

Cancer type	Observed	SIR (95% CI)
AIDS-defining cancer		
Kapos sarcoma	68	5600 (4400–7200)
Non-Hodgkin's lymphoma	55	23.1 (17.8–30.0)
Diffuse large B cell	26	30.8 (20.1–45.3)
Primary CNS	21	2100 (1300–3200)
Burkitt	2	26.3 (3.2–94.8)
Other/unknown	6	4.8 (1.7–10.4)
Cervical	15	16.6 (9.3–27.4)
Non-AIDS-defining cancer		
Head and neck	14	5.1 (2.8–8.6)
Esophagus	3	5.2 (1.1–15.1)
Stomach	2	2.4 (0.3–8.8)
Small intestine	0	0 (0–11.1)
Colon and rectum	2	0.5 (0.1–1.9)
Anal	10	39.0 (18.7–71.7)
Liver	13	16.5 (8.8–28.2)
Pancreas	1	1.0 (0.03–5.7)
Lung	29	5.5 (3.7–8.0)
Bones and joints	0	0 (0–29.3)
Soft tissue	0	0 (0–7.8)
Melanoma	4	4.0 (1.1–10.1)
Breast	3	0.6 (0.1–1.8)
Uterus	0	0 (0–6.6)
Ovary	0	0 (0–10.3)
Vagina and vulva	0	0 (0–30.3)
Prostate	5	0.6 (0.2–1.5)
Testis	0	0 (0–5.5)
Penis	1	24.2 (0.6–134.7)
Bladder	4	4.1 (1.1–10.5)
Kidney	5	2.9 (1.0–6.8)
Brain	0	0 (0–5.2)
Thyroid	0	0 (0–3.7)
Hodgkin's lymphoma	8	9.8 (4.2–19.2)
Multiple myeloma	2	3.0 (0.4–10.7)
Leukemia	0	0 (0–3.6)
Mesothelioma	0	0 (0–0.1)
Miscellaneous/other	3	4.0 (0.8–8.3)

SIR, standardized incidence ratio; CI, confidence interval.

Table 4

Univariate and multivariate Cox proportional hazards models of mortality among AIDS-defining and non-AIDS defining cancer at cancer diagnosis.

	No. of deaths	HR (95% CI)	P value	Adjusted HR (95% CI) ^a	P value
AIDS-defining cancer					
Age group (years)					
<40	53	1.0 (ref)	—	1.0 (ref)	—
40–49	24	0.94 (0.58–1.52)	0.79	1.05 (0.63–1.76)	0.84
≥50	9	1.39 (0.66–2.95)	0.38	2.21 (1.00–4.89)	0.05
Gender					
Male	64	1.0 (ref)	—	1.0 (ref)	—
Female	22	1.30 (0.79–2.14)	0.30	1.96 (1.12–3.48)	0.02
Race					
White	24	1.0 (ref)	—	1.0 (ref)	—
Black	62	1.35 (0.83–2.19)	0.22	1.15 (0.68–1.93)	0.60
Injection drug use	23	1.00 (0.61–1.63)	1.00		
HIV-1 RNA <400 copies/ml ^b	17	0.48 (0.22–1.02)	0.06		
CD4 cell count group(cells/μl)					
>350	8	1.0 (ref)	—	1.0 (ref)	—
201–350	4	0.72 (0.22–2.40)	0.60	0.83 (0.25–2.79)	0.76
51–200	24	1.84 (0.82–4.10)	0.14	2.26 (0.98–5.23)	0.06
≤50	47	2.71 (1.27–5.75)	0.01	4.02 (1.75–9.26)	0.001
Non-AIDS-defining cancer					
Age group (years)					
<40	9	1.0 (ref)	—	1.0 (ref)	—
40–49	33	1.70 (0.78–3.72)	0.18	1.75 (0.77–3.99)	0.18
≥50	30	1.41 (0.64–3.10)	0.39	1.67 (0.71–3.90)	0.24
Gender					
Male	54	1.0 (ref)	—	1.0 (ref)	—
Female	18	1.68 (0.96–2.95)	0.07	1.48 (0.81–2.73)	0.21
Race					
White	13	1.0 (ref)	—	1.0 (ref)	—
Black	59	1.96 (1.07–3.60)	0.03	1.76 (0.95–3.29)	0.07
History of injection drug use	39	1.30 (0.81–2.09)	0.28		
HIV-1 RNA <400 copies/ml ^b	23	0.57 (0.34–0.95)	0.03		
CD4 cell count group (cells/μl)					
>350	28	1.0 (ref)	—	1.0 (ref)	—
201–350	17	0.75 (0.41–1.38)	0.36	0.76 (0.41–1.39)	0.37
51–200	19	1.17 (0.64–2.14)	0.62	1.33 (0.70–2.52)	0.38
≤50	8	1.11 (0.48–2.58)	0.80	1.21 (0.50–2.90)	0.67

HR, hazards ratio; CI, confidence interval.

^a Adjusted HR from multivariate model that included age, gender, race, and CD4 cell count at the time of cancer diagnosis. Multivariate models did not include mean values of variables.

^b Reference group are those with HIV-1 RNA ≥400 copies/ml at the time of cancer diagnosis.