

# Factors Associated With Cancer Incidence and With All-Cause Mortality After Cancer Diagnosis Among Human Immunodeficiency Virus-Infected Persons During the Combination Antiretroviral Therapy Era

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**Background.** Little is known about survival and factors associated with mortality after cancer diagnosis among persons infected with human immunodeficiency virus (HIV).

**Methods.** Using Poisson regression, we analyzed incidence rates of acquired immune deficiency syndrome (AIDS)-defining cancers (ADC), non-AIDS-defining infection-related cancers (NADCI), and non-AIDS-defining noninfection-related cancers (NADCNI) among HIV Outpatient Study participants seen at least twice from 1996–2010. All-cause mortality within each cancer category and by calendar period (1996–2000, 2001–2005, 2006–2010) were examined using Kaplan-Meier survival methods and log-rank tests. We identified risk factors for all-cause mortality using multivariable Cox proportional hazard models.

**Results.** Among 8350 patients, 627 were diagnosed with 664 cancers. Over the 3 time periods, the age- and sex-adjusted incidence rates for ADC and NADCNI declined (both  $P < .001$ ) and for NADCI did not change ( $P = .13$ ). Five-year survival differed by cancer category (ADC, 54.5%; NADCI, 65.8%; NADCNI, 65.9%;  $P = .018$ ), as did median CD4 cell count (107, 241, and 420 cells/mm<sup>3</sup>;  $P < .001$ ) and median log<sub>10</sub> viral load (4.1, 2.3, and 2.0 copies/mL;  $P < .001$ ) at cancer diagnosis, respectively. Factors independently associated with increased mortality for ADC were lower nadir CD4 cell count (hazard ratio [HR] = 3.02; 95% confidence interval [CI], 1.39–6.59) and detectable viral load ( $\geq 400$  copies/mL; HR = 1.72 [95% CI, 1.01–2.94]) and for NADCNI, age (HR = 1.50 [95% CI, 1.16–1.94]), non-Hispanic black race (HR = 1.92 [95% CI, 1.15–3.24]), lower nadir CD4 cell count (HR = 1.77 [95% CI, 1.07–2.94]), detectable viral load (HR = 1.96 [95% CI, 1.18–3.24]), and current or prior tobacco use (HR = 3.18 [95% CI, 1.77–5.74]).

**Conclusions.** Since 1996, ADC and NADCNI incidence rates have declined. Survival after cancer diagnosis has increased with concomitant increases in CD4 cell count in recent years. Advances in HIV therapy, including early initiation of combination antiretroviral therapy, may help reduce mortality risk among HIV-infected persons with cancer.

**Keywords.** all-cause mortality; cancer; HIV; risk factors; survival.

In the era of combination antiretroviral therapy (cART), life expectancy of human immunodeficiency virus (HIV)-infected persons living in industrialized nations has improved substantially [1–8] but remains

decreased compared with uninfected counterparts, [9,10] due in part to an excess of comorbidities not traditionally associated with HIV infection, including certain cancers. [11–14]

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The results of several studies have shown that persons infected with HIV have an elevated cancer risk compared with the general population, [15–18] which may be attributable in part to the higher prevalence of traditional cancer risk factors in the HIV-infected population, including smoking, [19–21] alcohol use, [21,22] and coinfection with oncogenic viruses. [23–26] However, persistent chronic inflammation and HIV-related immunodeficiency may also affect cancer incidence as well as survival after cancer diagnosis. [27–29] In the cART era, cancer is a major cause of death among persons infected with HIV, [11,30] and the epidemiology of cancer among persons infected with HIV is changing. [31] However, little is known about survival among persons infected with HIV with newly diagnosed cancer in the United States. Most published studies are either from cohorts in other (non-US) countries or evaluate survival among persons infected with HIV with a single cancer type in small cohorts. [32–39]

We examined cancer incidence and all-cause mortality after cancer diagnosis among HIV-infected persons enrolled in the HIV Outpatient Study (HOPS). In addition, we examined factors associated with cancer incidence and those associated with mortality after cancer diagnosis. Furthermore, we evaluated survival after cancer diagnosis stratified by cancer type (acquired immune deficiency syndrome [AIDS]-defining, non-AIDS-defining infection-related cancers [NADCI], and non-AIDS-defining noninfection-related cancers [NADCNI]) and included a variable for HOPS calendar period of cancer diagnosis, stratified into 3 time periods (1996–2000, 2001–2005, 2006–2010), to account for improvements in patient management and HIV treatments during the cART era.

## METHODS

### Study Population: The HIV Outpatient Study

The HOPS is an ongoing, prospective, observational cohort study of HIV-infected patients receiving care since 1993. For the present analyses, we analyzed data from 15 HIV clinics (university-based, public, and private) in 10 US cities (Atlanta, GA; Chicago, IL; Denver, CO; Stonybrook, NY; Oakland/San Leandro, CA; Walnut Creek, CA; Philadelphia, PA; Tampa, FL; Portland, OR; and Washington DC) participating in the HOPS on and after January 1, 1996. Patient data, including sociodemographic characteristics, symptoms and signs, diagnoses, treatments, and laboratory values, were abstracted from medical charts and entered into an electronic database by trained staff. These data were reviewed for quality and analyzed centrally. Since its inception, the HOPS protocol has been reviewed and approved annually by the institutional review boards of the Centers for Disease Control and Prevention and each local site. Written informed consent was obtained from all participants.

### Patient Selection and Definitions

We included patients active in the HOPS on or after January 1, 1996 with at least 2 HOPS visits. Start of observation (baseline date) was defined as January 1, 1996, or date of the first HOPS visit thereafter, with first HOPS visit being no later than December 31, 2010. We analyzed data on incident cancer cases diagnosed from 1996 through 2010, focusing on first cancer diagnosis events and ignoring subsequent diagnoses of the same cancer in the same patient. Persons with a prevalent cancer of a given type, ie, cancer diagnosis prior to start of observation (baseline date), were excluded from the analysis for that particular cancer type. Ascertainment of prevalent cancers for our study was based on both self-reported history and standardized medical record review of all cancer data in the HOPS database.

Deaths were ascertained through periodic matches with the Social Security Death Index (last done in September 2011). We analyzed the HOPS dataset updated through March 31, 2013 to allow for mortality reporting lag; however, for analysis, records were censored at December 31, 2010. For cancer incidence, patients were followed from baseline date to the earlier of first incident cancer diagnosis, last HOPS contact plus 183 days, December 31, 2010, or death if it occurred within 183 days of last HOPS contact. For mortality analyses, patients were followed from the date of first incident cancer diagnosis to the earlier of last HOPS contact plus 183 days, December 31, 2010, or death if it occurred within 183 days of last HOPS contact. Recorded deaths that occurred later than last HOPS contact plus 183 days were censored.

Our cancer case classification was decided by 1 investigator and reviewed and adjudicated by another for concurrence. Because cART use and cancer prevention strategies and treatment have changed over time, we created a categorical variable for calendar period (1996–2000, 2001–2005, 2006–2010) to include in our analyses. For cancer incidence analyses, patients can be represented in more than 1 calendar period and in more than 1 cancer category (as defined below).

Acquired immune deficiency syndrome-defining cancers (ADC) included Kaposi's sarcoma, non-Hodgkin lymphoma including central nervous system lymphoma, and invasive cervical cancer. Because it is biologically plausible that infection-related cancers, which are mediated by oncogenic viruses, may be more common among persons infected with HIV, we decided to further classify non-ADC into infection-related or noninfection related. [17] Non-AIDS-defining infection-related cancers included Hodgkin's lymphoma, Merkel cell carcinoma, Castleman's disease, leiomyosarcoma, squamous cell carcinoma (all anatomic locations), and cancers of the anus, stomach, liver, vagina, vulva, penis, and oropharynx. Non-AIDS-defining noninfection-related cancers included basal cell carcinoma of the skin, melanoma, hidradenoma, myeloma, leukemia, neuroma, adenocarcinoma, sarcoma, and cancers of the lung, bone,

brain, breast, ovaries, bladder, ureter, prostate, testicle, colon, thyroid, esophagus, kidney, pancreas, gallbladder, uterus, skin, pituitary, and others not considered NADCI [17] (Appendix Table).

Acquired immune deficiency syndrome-defining conditions included candidiasis, coccidioidomycosis, cryptococcal meningitis, systemic cryptococcosis, cytomegalovirus (CMV) colitis, CMV retinitis, CMV esophagitis, CMV pneumonitis, herpes encephalitis, herpes bronchitis or pneumonitis, histoplasmosis, HIV encephalopathy, invasive cervical cancer, Kaposi's sarcoma, disseminated infection with *Mycobacterium avium* complex, non-Hodgkin lymphoma, progressive multifocal leukoencephalopathy, *Pneumocystis* pneumonia, toxoplasmosis, *Mycobacterium tuberculosis* of any site, disseminated tuberculosis or extrapulmonary tuberculosis, and wasting syndrome.

Hepatitis B infection was defined as having any of the following diagnosis codes: acute hepatitis B, chronic hepatitis B, hepatitis B with delta virus; or having a positive laboratory result for any of the following: hepatitis B surface antigen, hepatitis B E antigen, hepatitis B viral load, hepatitis B core antigen, or hepatitis B core antibody. Hepatitis C infection was defined as having a diagnosis or a positive hepatitis C viral load.

### Statistical Analysis

To calculate cancer incidence, we included cases of cancer during follow-up that were a different type (ADC, NADCI, or NADCNI) from any prevalent cancer for each patient. An incident cancer was a cancer first diagnosed after baseline, and of a type not also diagnosed in the patient at or before baseline. A person with multiple cancer types during the study period could be included in more than 1 of the cancer categories (ADC, NADCI, or NADCNI). Therefore, a patient could be included in more than 1 of the incidence analyses, but for the mortality analysis, the patient's first incident cancer type determined cancer category inclusion. We calculated baseline age (<40, 40 to 50, and >50 years) and sex-adjusted incidence rates per 100 000 person-years of observation time for ADC, NADCI, and NADCNI for 3 consecutive 5-year time periods: 1996–2000, 2001–2005, and 2006–2010, because estimated annual incidence rates were low and imprecise, and cART uptake increased steadily across these time periods. Age of patients followed in each time period was calculated at the beginning of each respective time period. We compared age- and sex-adjusted cancer incidence rates by calendar period of cancer diagnosis, cancer category, and for selected cancer types within each category. Likewise, we compared age- and sex-adjusted mortality rates after cancer diagnosis by calendar period of diagnosis and cancer category, with age calculated at date of cancer diagnosis. Confidence intervals for the rates were calculated assuming a Poisson distribution for the rates. Trends in incidence rates across the 3 time periods were evaluated using linear regression. Differences in patients' median age, median CD4

cell count, and median viral load by calendar period or cancer category were assessed using a Kruskal-Wallis test. Mortality risks were compared statistically using hazard rate models as described below.

To evaluate factors associated with incidence of specific cancer categories, we used multivariable Poisson regression models, with a log-transformed offset variable for years of follow-up, that considered the following categorical variables: calendar period of observation to which follow-up time could be contributed by each patient (1996–2000, 2001–2005, 2006–2010), age at baseline (<40, 40 to 50, and >50 years), sex, race (non-Hispanic white race vs other race/ethnicity), HIV risk group (men who have sex with men [MSM] vs other risk), history of AIDS-defining conditions (yes vs no), nadir CD4 cell count at baseline (<200 cells/mm<sup>3</sup> vs higher), undetectable viral load at baseline (HIV RNA <400 copies/mL vs higher), hepatitis B infection (current/prior vs none), history of tobacco use (current/prior vs never), and antiretroviral exposure (cART use vs no cART use). Variables retained for the final models were identified by a backward stepwise selection process, excluding variables one at a time in the order of highest *P* value >.05, and included some factors that were clinically important (decided upon before analysis) but not necessarily statistically significant (cART use, nadir CD4 cell count, HIV RNA <400 cells/mL, and hepatitis B infection). In some analyses, due to small cell sizes, categories for variables such as nadir CD4 count were collapsed or grouped in the modeling process (see Table 1 for full variable definitions).

To evaluate factors associated with mortality after incident cancer diagnosis, we used Kaplan-Meier survival methods and log-rank statistical tests for univariate comparisons. We then used multivariable Cox proportional hazards regression models that considered the following variables determined at cancer diagnosis: calendar period of cancer diagnosis, age (in units of 10 years as a continuous variable), race (non-Hispanic white race vs other race/ethnicity), nadir CD4 cell count (<200 cells/mm<sup>3</sup> vs higher), undetectable viral load (<400 copies/mL vs higher), tobacco use (current/prior vs never use), and antiretroviral exposure (cART use vs no cART use). Similar to the Poisson analysis, we retained for the final models variables identified by a backward stepwise selection process, excluding variables one at a time in the order of highest *P* value >.05; we kept selected variables in the final models that were not significant. If a variable was significant in the analysis of 1 cancer outcome, it was forced into the other 2 analyses. The earliest incident cancer diagnosis date defined the start of follow-up for each person when determining survival time; persons contributing more than 1 incident cancer were included only once in the survival analyses and assigned to the category corresponding to the person's first incident cancer type. Observation continued until death (if documented within 183 days [ie, ~6 months] of last patient contact), or was censored at last patient contact plus

**Table 1. Baseline Characteristics of HIV Outpatient Study Participants, 1996–2010**

| Characteristic*  | All Patients  | Patients Without Incident Cancer | Patients With Incident Cancer | P Value | Incident AIDS-Defining Cancer | Incident non-AIDS-Defining Infection-Related Cancer | Incident non-AIDS-defining non-infection-related cancer |
|--|---------------|----------------------------------|-------------------------------|---------|-------------------------------|---|---|
| No. of patients  | 8350          | 7723                             | 627                           |         | 249                           | 178   | 237   |
| Total years of observation <sup>a</sup>                  | 45 080        | 40 326                           | 4754                          |         | 1549                          | 1486  | 2088  |
| Years of observation, median (IQR) <sup>a</sup>          | 3.9 (1.6–8.4) | 3.7 (1.6–8.1)                    | 7.2 (3.2–11.9)                | <.001   | 4.9 (2.0–10.0)                | 8.3 (4.6–12.4)                                      | 8.6 (4.9–13.5)  |
| Median age (IQR), years                                  | 38 (32–44)    | 38 (32–44)                       | 41 (35–48)                    | <.001   | 38 (33–44)                    | 41 (35–47)  | 45 (38–52)  |
| Age, years, no. (%)                                      |               |                                  |                               | <.001   |                               |   |   |
| <40  | 4641 (55.6%)  | 4389 (56.8%)                     | 252 (40.2%)                   |         | 130 (52.2%)                   | 73 (41.0%)  | 67 (28.3%)  |
| 40–50  | 2809 (33.6%)  | 2558 (33.1%)                     | 251 (40.0%)                   |         | 103 (41.4%)                   | 75 (21.1%)  | 85 (35.9%)  |
| >50  | 900 (10.8%)   | 776 (10.1%)                      | 124 (19.8%)                   |         | 16 (6.4%)                     | 30 (16.9%)  | 85 (35.9%)  |
| Male, no. (%)  | 6621 (79.3%)  | 6077 (78.7%)                     | 544 (86.8%)                   | <.001   | 219 (88.0%)                   | 160 (89.9%)   | 196 (82.7%)   |
| Race, no. (%)  |               |                                  |                               | <.001   |                               |   |   |
| Non-Hispanic white                                       | 4387 (52.5%)  | 3975 (51.5%)                     | 412 (65.7%)                   |         | 157 (63.1%)                   | 117 (65.7%)   | 170 (71.7%)   |
| Non-Hispanic black                                       | 2728 (32.7%)  | 2587 (33.5%)                     | 141 (22.5%)                   |         | 54 (21.7%)                    | 40 (22.5%)  | 50 (21.1%)  |
| Hispanic   | 915 (11.0%)   | 859 (11.1%)                      | 56 (8.9%)                     |         | 30 (12.1%)                    | 15 (8.4%)   | 12 (5.1%)   |
| Other race/ethnicity                                     | 320 (3.8%)    | 302 (3.9%)                       | 18 (2.9%)                     |         | 8 (3.2%)                      | 6 (3.4%)  | 5 (2.1%)  |
| HIV transmission risk, no. (%)                           |               |                                  |                               | <.001   |                               |   |   |
| Men who have sex with men                                | 4728 (56.6%)  | 4328 (56.0%)                     | 400 (63.8%)                   |         | 173 (69.5%)                   | 114 (64.0%)   | 134 (56.5%)   |
| High risk heterosexual contact                           | 2081 (24.9%)  | 1975 (25.6%)                     | 106 (16.9%)                   |         | 30 (12.1%)                    | 26 (14.6%)  | 60 (25.3%)  |
| Intravenous drug use                                     | 1028 (12.3%)  | 951 (12.3%)                      | 77 (12.3%)                    |         | 33 (13.3%)                    | 25 (14.0%)  | 23 (9.7%)   |
| Other/unknown  | 513 (6.1%)    | 469 (6.1%)                       | 44 (7.0%)                     |         | 13 (5.2%)                     | 13 (7.3%)   | 20 (8.4%)   |
| Insurance/payer, no. (%)                                 |               |                                  |                               | .06     |                               |   |   |
| Private  | 4020 (48.1%)  | 3691 (47.8%)                     | 329 (52.5%)                   |         | 125 (50.2%)                   | 93 (52.3%)  | 129 (54.4%)   |
| Public   | 3136 (37.6%)  | 2925 (37.9%)                     | 211 (33.7%)                   |         | 86 (34.5%)                    | 64 (36.0%)  | 73 (30.8%)  |
| Other/missing/none                                       | 1194 (14.3%)  | 1107 (14.3%)                     | 87 (13.9%)                    |         | 38 (15.3%)                    | 21 (11.8%)  | 35 (14.8%)  |
| History of AIDS-defining conditions at baseline, no. (%) | 1952 (23.4%)  | 1733 (22.4%)                     | 219 (34.9%)                   | <.001   | 125 (50.2%)                   | 52 (29.2%)  | 57 (24.1%)  |
| Nadir CD4 cell count                                     |               |                                  |                               |         |                               |   |   |
| n  | 8216          | 7613                             | 603                           |         | 233                           | 173   | 232   |
| Median cells/mm <sup>3</sup> (IQR)                       | 199 (58–352)  | 206 (63–357)                     | 115 (28–260)                  | <0.001  | 50 (14–143)                   | 125 (37–278)  | 193 (60–333)  |
| Log <sub>10</sub> HIV RNA                                |               |                                  |                               |         |                               |   |   |
| n  | 7723          | 7119                             | 604                           |         | 232                           | 176   | 233   |
| Median copies/mL (IQR)                                   | 3.7 (2.3–4.8) | 3.7 (2.3–4.8)                    | 3.8 (2.3–4.9)                 | 0.051   | 4.5 (2.8–5.1)                 | 3.7 (2.3–4.7)                                       | 3.6 (2.3–4.6)   |
| HIV RNA <400 copies/mL at baseline                       |               |                                  |                               |         |                               |   |   |
| n  | 7723          | 7119                             | 604                           |         | 232                           | 176   | 233   |
| <400 copies/mL   | 2423 (31.4%)  | 2254 (31.7%)                     | 169 (28.0%)                   | 0.07    | 51 (22.0%)                    | 55 (31.3%)  | 68 (29.2%)  |
| HBV infection, no. (%)                                   | 184 (2.2%)    | 165 (2.1%)                       | 19 (3.0%)                     | 0.19    | 6 (2.4%)                      | 11 (6.2%)   | 2 (0.8%)  |
| HCV infection, no. (%)                                   | 808 (9.7%)    | 755 (9.8%)                       | 53 (8.5%)                     | 0.31    | 18 (7.2%)                     | 18 (10.1%)  | 19 (8.0%)   |
| Current/history of tobacco use, no. (%)                  | 4660 (55.8%)  | 4289 (55.5%)                     | 371 (59.2%)                   | 0.09    | 132 (53.0%)                   | 122 (68.5%)   | 139 (58.7%)   |
| ARV exposure at baseline, no. (%)                        |               |                                  |                               | 0.006   |                               |   |   |
| ARV-naive  | 2607 (31.2%)  | 2437 (31.6%)                     | 170 (27.1%)                   |         | 74 (29.7%)                    | 41 (23.0%)  | 66 (27.9%)  |
| cART-only  | 790 (9.5%)    | 734 (9.5%)                       | 56 (8.9%)                     |         | 15 (6.0%)                     | 21 (11.8%)  | 23 (9.7%)   |
| Any non-cART   | 1890 (22.6%)  | 1714 (22.2%)                     | 176 (28.1%)                   |         | 69 (27.7%)                    | 45 (25.3%)  | 74 (31.2%)  |
| Unknown/incomplete ARV history                           | 3063 (36.7%)  | 2838 (36.8%)                     | 225 (35.9%)                   |         | 91 (36.6%)                    | 71 (39.9%)  | 74 (31.2%)  |

Abbreviations: AIDS, acquired immune deficiency syndrome; ARV, antiretroviral; cART, combination antiretroviral therapy; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOPS, HIV Outpatient Study; IQR, interquartile range; py, person-years.

\* All variables measured at baseline unless otherwise noted.

<sup>a</sup> Through last HOPS contact + 183 days or death.

183 days (when patients not known to be deceased were assumed to be alive), whichever occurred first. We examined all-cause mortality; we did not analyze mortality due to cancer because this outcome could not be reliably ascertained in the database. Due to small sample sizes, some factors were included as continuous variables while others were collapsed into categories for the modeling process.

Summaries of descriptive data, univariate analyses, Cox proportional hazards regression, Poisson modeling, and the survival analyses that generated Kaplan-Meier curves were performed using SAS version 9.3 (SAS Institute, Cary, NC). Statistical comparisons with two-sided *P* values <.05 were considered significant.

## RESULTS

### Study Participant Characteristics

Among 8350 HOPS participants included in this analysis, the median age at baseline was 38 years (interquartile range [IQR], 32–44), 79.3% were male, 52.5% were non-Hispanic white, and 56.6% were MSM. At baseline initiation of observation, the median nadir CD4 cell count was 199 cells/mm<sup>3</sup> (IQR, 58–352), 31.4% had an undetectable viral load (HIV RNA <400 copies/mL), and 55.8% reported current or past tobacco use (Table 1). Of the 8350 participants, 627 (7.5%) were diagnosed with a total of 664 cancers. Participants with incident cancer were significantly more likely than persons without cancer to be older, male, non-Hispanic white, MSM, have a history of AIDS-defining conditions, have a lower median nadir CD4 cell count, and exposure to antiretrovirals at baseline (all *P* < .001; Table 1). Characteristics of participants by cancer category are also shown in Table 1. Over the calendar periods examined, the median age of patients followed during each time period increased significantly from 36 years (IQR, 31–42; period 1996–2000) to 43 years (IQR, 36–49; period 2006–2010) (*P* < .001), the median nadir CD4 cell count of patients followed in each time period increased significantly from 222 (IQR, 71–390) to 283 (IQR, 122–450) cells/mm<sup>3</sup> (*P* < .001), and the median cohort baseline log<sub>10</sub> viral load decreased significantly from 3.8 (IQR, 2.4–4.8) to 3.6 (IQR, 2.0–4.7) copies/mL (*P* < .001).

### Cancer Incidence and Associated Factors

Over the 3 time periods, the age- and sex-adjusted incidence rates per 10<sup>5</sup> person-years for ADC decreased (*P* < .001), NADCI showed no significant trend (*P* = .13), and NADCNI decreased (*P* < .001) (Figure 1a).

In multivariable analyses (Table 2), factors associated with increased rates of incident ADC included early calendar period (1996–2000 vs 2006–2010), age 40–50 years at baseline, being a man who had sex with other men, having a history of an AIDS-defining condition at baseline, and having a nadir CD4 cell count <200 cells/mm<sup>3</sup>. Factors associated with incident NADCI

included early calendar period (1996–2000 vs 2006–2010), age ≥40 years at baseline, non-Hispanic white race, having a nadir CD4 cell count <200 cells/mm<sup>3</sup>, baseline history of hepatitis B infection, prior or current tobacco use at baseline, and cART use at baseline. Factors associated with incident NADCNI included early calendar period (1996–2000 vs 2006–2010), age ≥40 years at baseline, non-Hispanic white race, not being a man who had sex with other men, and having a detectable viral load.

### Factors Associated With All-Cause Mortality After Cancer Diagnosis

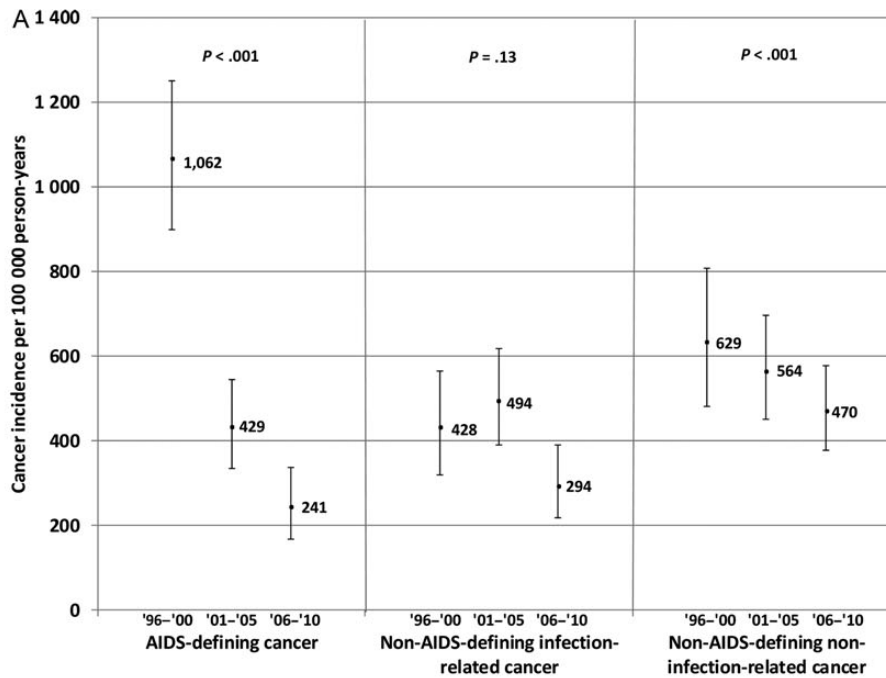
Over the 3 time periods, the age- and sex-adjusted mortality rates per 10<sup>5</sup> person-years after cancer diagnosis decreased for ADC (*n* = 249 patients, 104 deaths; *P* < .001) and for NADCNI (*n* = 237 patients, 75 deaths; *P* < .001), whereas for NADCI there was no significant change (*n* = 178 patients, 56 deaths; *P* = .53) (Figure 1b).

Factors associated with all-cause mortality among persons with ADC were nadir CD4 cell count <200 cells/mm<sup>3</sup> and HIV RNA ≥400 copies/mL. Among persons with NADCI, no associated factors were identified. Among persons with NADCNI, associated risk factors were older age at cancer diagnosis, non-white race, nadir CD4 cell count <200 cells/mm<sup>3</sup>, viral load ≥400 copies/mL, and prior or current history of tobacco use (Table 3).

Overall, 5-year survival differed significantly by cancer category (54.5% for ADC vs 65.8% for NADCI and 65.9% for NADCNI; *P* = .018), as did median CD4 cell count at diagnosis (107, 241, and 420 cells/mm<sup>3</sup>, respectively; *P* < .001) and median log<sub>10</sub> viral load at diagnosis (4.1, 2.3, and 2.0 copies/mL, respectively; *P* < .001) (Figure 2a). In addition, 5-year survival after any cancer diagnosis during 1996–2000, 2001–2005, and 2006–2010 improved in each consecutive period (51.7%, 68.2%, and 67.2%, respectively; *P* < .001), as did median CD4 cell counts at diagnosis (149, 329, and 374 cells/mm<sup>3</sup>, respectively, *P* < .001) and median log<sub>10</sub> viral load at diagnosis (3.5, 2.7, and 1.7 copies/mL, respectively; *P* < .001) (Figure 2b).

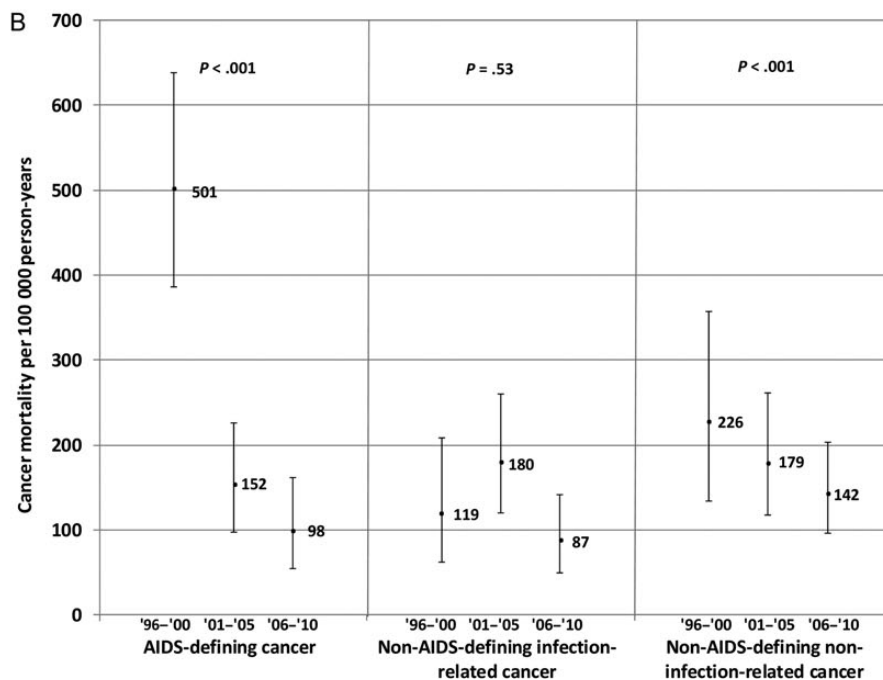
## DISCUSSION

Our data suggest that the incidence rates for ADC and NADCNI have decreased over time while incidence of NADCI has not changed significantly in age- and sex-adjusted analyses. The concomitant increase in median CD4 cell count and decrease in median log<sub>10</sub> viral load at cancer diagnosis among HOPS participants over the same time periods suggest that the reduced incidences of cancers related to advanced HIV disease and noninfection-related cancers are likely related to improved immunity, possibly mediated through improved tumor surveillance. In our Poisson analysis, incidence rates of all types of cancers decreased over time, with statistically significant



Age- and sex-adjusted incidence (95% Poisson confidence intervals) for select cancers by time period and cancer category

|       | AIDS-Defining   |                 |                 | Non-AIDS-Defining Infection-Related |                 |                  | Non-AIDS-Defining Noninfection-Related |          |                 |                  |                  |
|-------|-----------------|-----------------|-----------------|-------------------------------------|-----------------|------------------|--|----------|-----------------|------------------|------------------|
|       | 1996–2000       | 2001–2005       | 2006–2010       | HL                                  | 1996–2000       | 2001–2005        | 2006–2010                              | BCC      | 2001–2005       | 2006–2010        |                  |
| ICC   | 135 (36.8–346)  | 285 (157–561)   | 106 (21.8–309)  | HL                                  | 61.2 (26.4–121) | 69.5 (39.2–133)  | 19.4 (4.0–56.7)                        | BCC      | 229 (154–351)   | 142 (88.7–214)   | 133 (85.3–198)   |
| KS    | 654 (530–799)   | 183 (122–263)   | 133 (78.8–210)  | Anal/rectal                         | 124 (82.9–221)  | 171 (112–248)    | 121 (73.1–190)                         | Lung     | 134 (71.2–229)  | 90.0 (49.2–151)  | 53.2 (29.2–105)  |
| NHL   | 317 (232–445)   | 172 (119–258)   | 73.0 (37.7–128) | SCC                                 | 213 (136–317)   | 146 (103–235)    | 104 (70.4–178)                         | Prostate | 128 (55.1–251)  | 109 (70.1–206)   | 84.5 (46.2–142)  |
| CNS-L | 59.2 (45.9–155) | 12.8 (1.5–46.2) | 13.4 (1.6–48.4) | Liver                               | 31.3 (11.4–107) | 38.1 (14.0–82.9) | 26.3 (11.6–68.7)                       | Melanoma | 57.4 (21.0–125) | 44.7 (18.0–92.0) | 33.5 (12.3–72.8) |



**Figure 1.** (A) Age- and sex-adjusted cancer incidence stratified by time period and cancer category with 95% Poisson confidence intervals, HIV Outpatient Study, 1996–2010. (B) Age- and sex-adjusted mortality after cancer diagnosis and by period and cancer category with 95% Poisson confidence intervals, HIV Outpatient Study, 1996–2010. Abbreviations: BCC, basal cell carcinoma of the skin; CNS-L, central nervous system lymphoma; ICC, invasive cervical cancer; KS, Kaposi’s sarcoma; NHL, non-Hodgkin lymphoma; HL, Hodgkin’s lymphoma; SCC, squamous cell carcinoma of the skin. Note: *P* values in figure were obtained from linear modeling of the incidence over the 3 time periods within each cancer category.

**Table 2. Multivariable Poisson Regression of Factors Associated With Cancer Incidence by Cancer Category, HIV Outpatient Study, 1996–2010 (n = 8350 Persons; With 664 Cancers)**

| Characteristic                                       | Incident AIDS-Defining Cancer Rate Ratio (95% CI) | P Value | Incident Non-AIDS-Defining Infection-Related Cancer Rate Ratio (95% CI) | P Value | Incident non-AIDS-defining noninfection-related cancer Rate Ratio (95% CI) | P Value |
|--|---|---------|---|---------|--|---------|
| <b>Calendar Period of Observation</b>                |   |         |   |         |  |         |
| 1996–2000  | referent  |         | referent  |         | referent   |         |
| 2001–2005  | 0.46 (0.37–0.57)                                  | <.001   | 1.11 (0.82–1.49)  | .52     | 1.05 (0.82–1.35)   | .70     |
| 2006–2010  | 0.29 (0.24–0.36)                                  | <.001   | 0.49 (0.39–0.62)  | <.001   | 0.70 (0.57–0.86)   | <.001   |
| <b>Age at baseline, years</b>                        |   |         |   |         |  |         |
| <40  | referent  |         | referent  |         | referent   |         |
| 40–50  | 1.40 (1.14–1.72)                                  | .001    | 1.62 (1.28–2.06)  | <.001   | 2.13 (1.69–2.68)   | <.001   |
| >50  | 0.70 (0.46–1.05)                                  | .08     | 2.16 (1.57–2.97)  | <.001   | 7.32 (5.80–9.24)   | <.001   |
| Non-Hispanic white race (vs all others) <sup>a</sup> | 1.18 (0.95–1.47)                                  | .14     | 1.42 (1.11–1.83)  | .006    | 2.49 (1.99–3.13)   | <.001   |
| <b>HIV Transmission Risk<sup>a</sup></b>             |   |         |   |         |  |         |
| Men who have sex with men                            | 1.52 (1.21–1.91)                                  | <.001   | 1.26 (0.98–1.61)  | .07     | 0.71 (0.58–0.87)   | <.001   |
| Heterosexual/IDU/other/unknown                       | referent  |         | referent  |         | referent   |         |
| AIDS-defining condition at baseline                  | 2.24 (1.81–2.78)                                  | <.001   | 1.17 (0.91–1.50)  | .24     | 1.01 (0.80–1.27)   | .92     |
| Nadir CD4 cell count <200 cells/mm <sup>3</sup>      | 2.36 (1.86–2.98)                                  | <.001   | 1.78 (1.40–2.25)  | <.001   | 1.09 (0.89–1.32)   | .41     |
| HIV RNA <400 copies/mL at baseline                   | 0.81 (0.63–1.04)                                  | .10     | 0.95 (0.74–1.22)  | .68     | 0.74 (0.60–0.91)   | .005    |
| HBV infection at baseline                            | 0.76 (0.38–1.49)                                  | .42     | 2.44 (1.55–3.83)  | <.001   | 0.43 (0.16–1.16)   | .09     |
| Current/history of tobacco use at baseline           | 0.92 (0.75–1.12)                                  | .40     | 1.76 (1.39–2.23)  | <.001   | 1.10 (0.91–1.33)   | .30     |
| cART use at baseline                                 | 0.96 (0.64–1.44)                                  | .83     | 1.51 (1.07–2.14)  | .020    | 1.18 (0.86–1.62)   | .30     |

Note: Not all patients included in all analyses due to missing nadir CD4 cell count or viral load.

Abbreviations: AIDS, acquired immune deficiency syndrome; cART, combination antiretroviral therapy; CI, confidence interval; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IDU, injecting drug use.

<sup>a</sup> Race/ethnicity and HIV exposure risk were collapsed due to small numbers for some groups and/or similar rate ratios.

decreases between the first and last observation period (1996–2000 vs 2006–2010). Low nadir CD4 cell count (<200 cells/mm<sup>3</sup>) was associated with incidence of both ADC and NADCI. Our findings are similar to other published studies, which demonstrated that lower CD4 cell count was an independent predictor of cancer incidence. [40,41] Incidences of all 3 cancer categories were lower in later time periods, consistent with the hypothesis that improved HIV therapy in recent years may have had a protective effect. Furthermore, detectable viral load was associated with increased incidence of NADCI. This finding suggests that achieving and maintaining viral suppression may reduce cancer risk, which is especially relevant because persons with HIV infection live longer.

The overall 5-year survival rates after diagnosis of ADC, NADCI, and NADCI were significantly different. As expected, patients with ADC had significantly lower median CD4 cell

counts and higher median log<sub>10</sub> viral loads at diagnosis and lower survival rates than patients with non-AIDS-defining cancers (Figure 2a). In addition, 5-year survival after any cancer diagnosis improved over time in the cART era, as did the median CD4 cell count at cancer diagnosis. These findings suggest that improved immunity may favorably influence mortality among HIV-infected persons with cancer, an observation consistent with results from other studies that have shown that the severity of immunosuppression is predictive of mortality from cancer. [35,38,42] In addition, because 5-year survival improved over time, we observed a concomitant improvement in median log<sub>10</sub> viral load at cancer diagnosis, suggesting that virologic suppression may help improve survival of HIV-infected persons with cancer.

Mortality after cancer diagnosis was significantly associated with low nadir CD4 cell count (<200 cells/mm<sup>3</sup>) and detectable viral load (≥400 copies/mL) at cancer diagnosis for persons

**Table 3. Multivariable Cox Proportional Hazards Analysis of Factors Associated With All-Cause Mortality After Incident Cancer Diagnosis by Cancer Category, HIV Outpatient Study, 1996–2010**

| Characteristic                                       | Incident AIDS-Defining Cancer HR (95% CI) (n = 249, Deaths = 94) | P Value | Incident Non-AIDS-Defining Infection-Related Cancer HR (95% CI) (n = 178, Deaths = 53) | P Value | Incident Non-AIDS-Defining Noninfection-Related Cancer HR (95% CI) (n = 237, Deaths = 72) | P Value |
|--|--|---------|--|---------|---|---------|
| <b>Calendar Period of Cancer Diagnosis</b>           |  |         |  |         |   |         |
| 1996–2000  | referent   |         | referent   |         | referent  |         |
| 2001–2005  | 0.68 (0.35–1.33)   | .26     | 0.68 (0.28–1.64)   | .39     | 0.59 (0.28–1.23)  | .16     |
| 2006–2010  | 0.42 (0.06–3.08)   | .40     | 0.00 <sup>b</sup>  | .99     | 0.55 (0.13–2.29)  | .41     |
| Age at cancer diagnosis, years/10                    | 1.02 (0.77–1.35)   | .90     | 1.23 (0.90–1.69)   | .19     | 1.50 (1.16–1.94)  | .002    |
| Non-Hispanic white race (vs all others) <sup>a</sup> | 1.14 (0.74–1.76)   | .56     | 0.71 (0.40–1.27)   | .25     | 0.52 (0.31–0.87)  | .013    |
| Nadir CD4 cell count <200 cells/mm <sup>3</sup>      | 3.02 (1.39–6.59)   | .005    | 1.43 (0.77–2.68)   | .26     | 1.77 (1.07–2.94)  | .027    |
| HIV RNA <400 copies/mL                               | 0.58 (0.34–0.99)   | .046    | 0.66 (0.37–1.17)   | .15     | 0.51 (0.31–0.85)  | .010    |
| Current/history of tobacco use                       | 0.94 (0.63–1.43)   | .78     | 1.69 (0.87–3.26)   | .12     | 3.18 (1.77–5.74)  | <.001   |
| cART use   | 1.26 (0.61–2.59)   | .54     | 0.77 (0.30–1.99)   | .59     | 0.84 (0.41–1.68)  | .61     |

Note: not all patients included in all analyses due to missing nadir CD4 cell count or viral load.

Abbreviations: CI, confidence interval; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HR, hazard ratio.

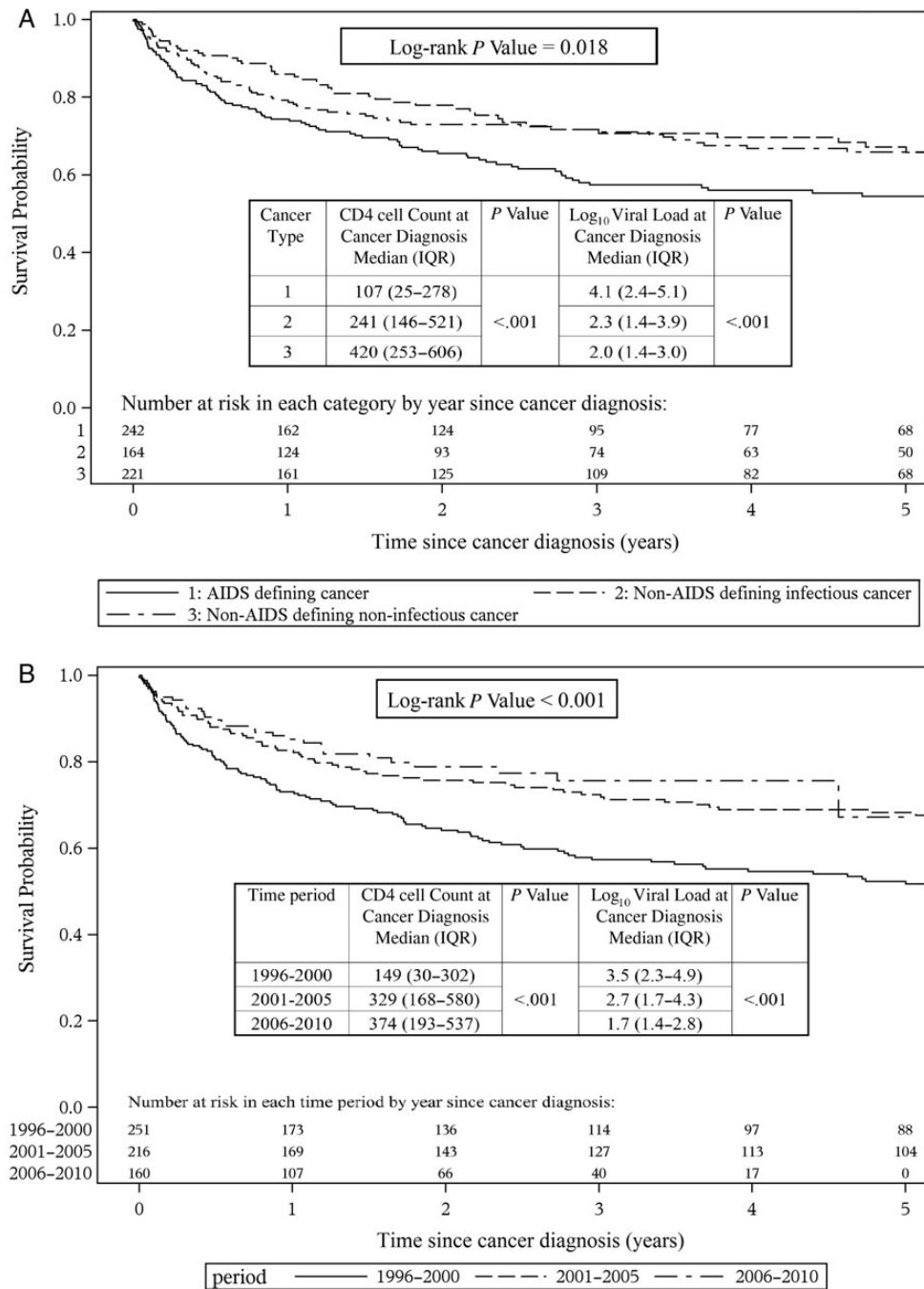
<sup>a</sup> Race/ethnicity variables collapsed due to small numbers for some groups and/or similar hazard ratios.

<sup>b</sup> A CI could not be calculated because there were no deaths in this time period.

with ADC and for persons with NADCNI in our multivariable analysis. This finding suggests that early initiation of cART and maintenance of virologic suppression may improve survival among HIV-infected persons with these cancers. It is also likely that improvement in modalities of cancer therapies may also have contributed to improved survival. For persons with NADCNI, mortality was also significantly associated with age at cancer diagnosis, non-Hispanic black race, low nadir CD4 cell count, detectable viral load, and tobacco use. These data suggest that although mortality was associated with traditional risk factors such as age and tobacco use, persons of black race were at increased risk of death after their cancer diagnosis. We noted that persons of race or ethnicity other than non-white Hispanic were significantly more likely to have public health insurance (data not shown). Together, these data suggest that although mortality from NADCNI was associated with traditional risk factors such as tobacco use, social inequalities and health disparities may contribute to mortality risk. In addition, the association of low nadir CD4 count with mortality among persons with non-AIDS noninfection-related cancers suggests that profound immunosuppression contributes to the risk of death, further underscoring the importance of diagnosing and treating persons infected with HIV early.

Our study had several limitations. Our data are collected from HIV-infected persons receiving care in HIV specialty clinics in select cities across the United States, and non-Hispanic blacks and Hispanics are somewhat underrepresented in this cohort, thus our findings may not be generalizable to the entire HIV-infected population. Cancer case ascertainment in the HOPS is currently underway for a subset of sites as part of a cancer validation for the North American AIDS Cohort Collaboration on Research and Design to which the HOPS contributes data; however, a low case ascertainment rate would bias towards underestimating cancer incidence. We may also have misclassified cases in terms of cancer type, but we believe any misclassification has been minimized and probably would result in a minimal or insignificant error. We do not have consistent individual data on stage and grade of cancer, coinfection with all oncogenic viruses, especially human papillomavirus, and thus could not examine their independent effects on cancer incidence and mortality among persons with cancer. Furthermore, we were unable to examine mortality stratified by specific cancer type because of the small sample sizes in each cancer category and also because of difficulty in accurately documenting cancer-specific mortality; instead, we present all-cause mortality among persons with cancer. Lastly, we were unable to compare rates in our HIV-infected population with those in the general population.





**Figure 2.** A, Survival after cancer diagnosis by cancer type (Kaplan-Meier curves), the HIV Outpatient Study, 1996–2010. B, Survival after cancer diagnosis by time period (Kaplan-Meier curves), the HIV Outpatient Study, 1996–2010.

Collectively, our findings suggest that virologic suppression has a beneficial role in terms of reducing risk for cancer among persons infected with HIV, especially for ADC and NADCI. Other studies have shown that cART may be protective against developing malignant disease, [29,43] and our study is consistent with those findings given the reduced incidence and mortality in recent years. Furthermore, our findings support the early

initiation of cART to suppress HIV viral replication and maintain higher CD4 cell counts to prevent immune system damage, because viral suppression and improved immunity may help delay or reduce mortality and increase survival times among HIV-infected persons with cancer. [29,34,35,39,44]

Clinicians should be aware of the elevated cancer risks among their HIV-infected patients. [15] Among patients with

concerning signs and symptoms as well as relevant coinfections (eg, viral hepatitis) and behavioral risk factors (eg, tobacco use), clinicians should have a low threshold to aggressively pursue a potential diagnosis of cancer. Cancer prevention and early cancer detection and treatment should be considered priorities in the long-term management of HIV-infected persons. In particular, primary prevention strategies such as tobacco cessation and vaccination against oncogenic viruses such as hepatitis B and human papillomavirus should be optimized. Potential benefits of early cART initiation, both for reducing the incidence of non-AIDS-defining cancers and for improving survival of patients already diagnosed with various cancer types, warrant further study.

## ETHICAL CONSIDERATIONS

The investigation followed the guidelines of the U.S. Department of Health and Human Services regarding protection of human subjects. The study protocol was approved and renewed annually by each participating institution's ethical review board. All study participants provided written, informed consent.

## Notes

**Author contributions.** The HIV Outpatient Study (HOPS) Investigators include the following persons and sites: John T. Brooks, Kate Buchacz, and Marcus D. Durham (Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention [CDC], Atlanta, GA); Kathleen C. Wood, Darlene Hankerson, Rachel Debes, Thila Subramanian, Cheryl Akridge, Harlan Hayes, Carl Armon, Bonnie Dean, Jeff Binkley, and Sam Bozzette (Cerner Corporation, Vienna, VA); Frank J. Palella, Joan S. Chmiel, Carolyn Studney, Saira Jahangir, (Feinberg School of Medicine, Northwestern University, Chicago, IL); Kenneth A. Lichtenstein and Cheryl Stewart (National Jewish Medical and Research Center Denver, CO); John Hammer, Kenneth S. Greenberg, Barbara Widick, and Rosa Franklin (Rose Medical Center, Denver, CO); Bivenenido G. Yangco and Kalliopie Chagaris (Infectious Disease Research Institute, Tampa, FL); Doug Ward, Troy Thomas, and Fletcher Neale (Dupont Circle Physicians Group, Washington, DC); Jack Fuhrer, Linda Ording-Bauer, Rita Kelly, and Jane Esteves (State University of New York [SUNY], Stony Brook, NY); Ellen M. Tedaldi, Ramona A. Christian, Faye Ruley, Dania Beadle, and Princess Graham (Temple University School of Medicine, Philadelphia, PA); Richard M. Novak, Andrea Wendrow, and Renata Smith, (University of Illinois at Chicago, Chicago, IL); Benjamin Young, Barbara Widick, and Mia Scott (APEX Family Medicine, Denver, CO).

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## APPENDIX

**Appendix Table A1. Cancer Definition as Determined by Diagnosis in Source Data and Number of Incident Cancers by Cancer Type (664 Cancers Among 627 Patients)**

| Source Data                                  |                            |                                     |
|--|----------------------------|-------------------------------------|
| Diagnosis Code and Anatomic Site             | Number of Incident Cancers | Cancer Categories Used for Analysis |
| AIDS-Defining Cancers                        |                            |                                     |
| Kaposi's sarcoma (all sites)                 | 143                        | Kaposi's sarcoma                    |
| Non-Hodgkin's lymphoma*                      | 77                         | Non-Hodgkin's lymphoma              |
| Cervix uteri                                 | 17                         | Cervical (invasive)                 |
| Central nervous system lymphoma              | 12                         | Central nervous system lymphoma     |
| Non-AIDS-Defining Cancers                    |                            |                                     |
| Infection-Related                            |                            |                                     |
| Anus, anal canal, anorectum                  | 62                         | Anal                                |
| Vagina, vulva (females)                      | 3                          | Vaginal                             |
| Hodgkin's lymphoma                           | 22                         | Hodgkin's Lymphoma                  |
| Liver  | 14                         | Liver                               |
| Penis  | 1                          | Penile                              |
| Stomach                                      | 1                          | Stomach                             |
| Oral cavity, pharynx, larynx                 | 8                          | Oropharyngeal                       |
| Castleman's disease                          | 1                          | Castleman's                         |
| Merkel cell carcinoma                        | 0                          | Merkel                              |
| Leiomyosarcoma                               | 1                          | Leiomyosarcoma                      |
| Squamous cell carcinoma (all sites)          | 65                         | Squamous                            |
| Noninfection-Related                         |                            |                                     |
| Adenocarcinoma (all sites)                   | 5                          | Adenocarcinoma                      |
| Basal cell carcinoma (skin)                  | 70                         | Basal cell carcinoma                |
| Lung, bronchus                               | 37                         | Lung                                |
| Melanoma of skin                             | 19                         | Melanoma                            |
| Leukemia (all sites)                         | 2                          | Leukemia                            |
| Colon, rectum, rectosigmoid junction         | 6                          | Colorectal                          |
| Esophagus                                    | 4                          | Esophageal                          |
| Kidney, renal pelvis, ureter, urinary organs | 5                          | Renal                               |
| Testicles                                    | 5                          | Testicular                          |
| Multiple myeloma                             | 1                          | Multiple myeloma                    |
| Bone   | 3                          | Bone                                |
| Brain  | 3                          | Brain                               |
| Breast                                       | 8                          | Breast                              |
| Pancreas                                     | 10                         | Pancreatic                          |
| Pituitary                                    | 1                          | Pituitary                           |
| Prostate                                     | 35                         | Prostate                            |
| Thyroid                                      | 2                          | Thyroid                             |
| Neuroma                                      | 1                          | Neuroma                             |
| Hidradenoma                                  | 1                          | Hidradenoma                         |
| Nonmelanomatous skin                         | 11                         | Other skin                          |
| Bladder, urachus, ureteric orifice           | 3                          | Bladder                             |
| Uterus                                       | 1                          | Uterine                             |
| Ovary, fallopian tube, uterine adenexa       | 0                          | Ovarian                             |
| Gallbladder                                  | 0                          | Gallbladder                         |
| Intrahepatic and extrahepatic bile ducts     | 0                          | Biliary                             |
| Other non-AIDS, noninfectious cancers        | 4                          | Other cancer                        |

Abbreviation: AIDS, acquired immune deficiency syndrome.

\* Includes central nervous system lymphoma.