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Authors

Engels, Eric A
Yanik, Elizabeth L
Wheeler, Willian
et al.

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Cancer-Attributable Mortality Among People With Treated Human Immunodeficiency Virus Infection in North America

Eric A. Engels,[1] Elizabeth L. Yanik,[1] Willian Wheeler,[2] M. John Gill,[3] Meredith S. Shiels,[1] Robert Dubrow,[4] Keri N. Althoff,[5] Michael J. Silverberg,[6] John T. Brooks,[7] Mari M. Kitahata,[8] James J. Goedert,[1] Surbhi Grover,[9] Angel M. Mayor,[10] Richard D. Moore,[11] Lesley S. Park,[12] Anita Rachlis,[13] Keith Sigel,[14] Timothy R. Sterling,[15] Jennifer E. Thorne,[11] and Ruth M. Pfeiffer[1]; for the North American AIDS Cohort Collaboration on Research and Design of the International Epidemiologic Databases to Evaluate AIDS

[1]National Cancer Institute, Bethesda and [2]Information Management Services, Inc., Rockville, Maryland; [3]University of Calgary, Alberta, Canada; [4]Yale School of Public Health, New Haven, Connecticut; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; [6]Kaiser Permanente Northern California, Oakland; [7]Centers for Disease Control and Prevention, Atlanta, Georgia; [8]University of Washington, Seattle; [9]University of Pennsylvania, Philadelphia; [10]Unversidad Central del Caribe, Bayamon, Puerto Rico; [11]Johns Hopkins School of Medicine, Baltimore, Maryland; [12]Stanford School of Medicine, California; [13]Sunnybrook Health Sciences Centre, University of Toronto, Ontario, Canada; [14]Icahn School of Medicine at Mount Sinai, New York; and [15]Vanderbilt School of Medicine, Nashville, Tennessee

Background. Cancer remains an important cause of morbidity and mortality in people with human immunodeficiency virus (PWHIV) on effective antiretroviral therapy (ART). Estimates of cancer-attributable mortality can inform public health efforts.

Methods. We evaluated 46 956 PWHIV receiving ART in North American HIV cohorts (1995–2009). Using information on incident cancers and deaths, we calculated population-attributable fractions (PAFs), estimating the proportion of deaths due to cancer. Calculations were based on proportional hazards models adjusted for age, sex, race, HIV risk group, calendar year, cohort, CD4 count, and viral load.

Results. There were 1997 incident cancers and 8956 deaths during 267 145 person-years of follow-up, and 11.9% of decedents had a prior cancer. An estimated 9.8% of deaths were attributable to cancer (cancer-attributable mortality rate 327 per 100 000 person-years). PAFs were 2.6% for AIDS-defining cancers (ADCs, including non-Hodgkin lymphoma, 2.0% of deaths) and 7.1% for non-AIDS–defining cancers (NADCs: lung cancer, 2.3%; liver cancer, 0.9%). PAFs for NADCs were higher in males and increased strongly with age, reaching 12.5% in PWHIV aged 55+ years. Mortality rates attributable to ADCs and NADCs were highest for PWHIV with CD4 counts <100 cells/mm^3. PAFs for NADCs increased during 1995–2009, reaching 10.1% in 2006–2009.

Conclusions. Approximately 10% of deaths in PWHIV prescribed ART during 1995–2009 were attributable to cancer, but this fraction increased over time. A large proportion of cancer-attributable deaths were associated with non-Hodgkin lymphoma, lung cancer, and liver cancer. Deaths due to NADCs will likely grow in importance as AIDS mortality declines and PWHIV age.

Keywords. HIV; AIDS; cancer; mortality; aging.

Since the advent of effective antiretroviral therapy (ART) in 1996, mortality of individuals with human immunodeficiency virus (HIV) infection has declined substantially [1–3]. However, immune reconstitution may be incomplete with ART, and people with HIV (PWHIV) experience effects of chronic inflammation and immune activation [4–6]. Moreover, PWHIV continue to have elevated risk for some cancers [7, 8] due to immune abnormalities, coinfection with oncogenic viruses (eg, human papillomavirus, hepatitis B and C viruses [HBV, HCV]), and tobacco use [9, 10]. Cancers in PWHIV are typically divided into AIDS-defining cancers (ADCs: Kaposi sarcoma [KS], non-Hodgkin lymphoma [NHL], and cervical cancer), which can mark the onset of advanced immunosuppression, and non-AIDS–defining cancers (NADCs: all other cancers).

The decrease in overall mortality among PWHIV is largely explained by declining mortality from AIDS, although AIDS (including ADCs) still accounts for a sizeable proportion of deaths [2, 11–13]. As PWHIV live longer and age, the incidence of some NADCs has risen, and the overall burden of cancer has increased [7, 14]. Furthermore, HIV-infected cancer patients have worse survival from their cancer than HIV-uninfected cancer patients [15–17]. Recent studies of PWHIV in Europe, North America, and Australia, which have classified deaths based on clinical information or death certificate diagnoses, have assigned 7%–15% of deaths as due to ADCs and 12%–27% to NADCs [2, 11–13, 18, 19]. One challenge in interpreting these results is that it is difficult to assign a single underlying cause of death [20, 21], especially in people with multiple comorbidities. Furthermore, PWHIV may die outside hospitals, and low

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Correspondence: E. A. Engels, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Dr, Room 6E226, Bethesda, MD 20892 (engelse@exchange.nih.gov; ee36h@nih.gov)

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autopsy rates limit the information available to assign cause of death [12, 19].

Difficulties in determining cause of death for cancer patients have led to an emphasis on relative mortality methods to measure cancer-related mortality in other contexts [21]. These methods assess whether excess mortality is present in cancer patients compared with the general population and attribute any excess deaths to the cancer. Similarly, one can estimate the proportion of deaths in a population due to cancer premised on a statistical calculation of cancer-attributable mortality, that is, a population-attributable fraction (PAF) [22, 23]. This approach uses only information on the incidence of cancer and overall mortality in people with and without cancer, and it does not require clinical determination of causes of death.

Assessment of cancer mortality can help in the evaluation of the overall impact of cancer in PWHIV and target research, prevention, and treatment for maximum public health benefit. In the present study, we analyzed data from a large North American consortium of HIV cohorts to estimate the cancer-attributable mortality among PWHIV treated with ART during 1995–2009.

METHODS

North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a consortium of more than 20 cohort studies of PWHIV linked into clinical care or followed in a classic cohort study in the United States or Canada [24]. Cohorts follow PWHIV at defined intervals or abstract information from electronic medical records and administrative databases. For the present study, 13 cohorts provided data on demographic and clinical characteristics, incident cancers, and mortality (see the Acknowledgments). The study was approved by human subjects committees at participating sites and, for the NA-ACCORD collaboration, at Johns Hopkins School of Medicine.

Cancers were ascertained during routine cohort follow-up and validated through review of medical records and pathology reports or by linkage with a cancer registry [25]. We considered only first cancers in the analyses. CD4 count and HIV RNA (viral load) measurements were captured at baseline and updated during follow-up. Smoking status (ever vs never) was available for 72% of patients and imputed for another 15% based on demographic information, ART use, initial CD4 count and viral load, and vital status; data were insufficient for imputation for 13% of patients. HBV and HCV coinfections were identified based on documented serological and molecular test results [26].

PWHIV were followed from 1 January 1995, entry into the participating cohort, the cohort's first date of validated cancer ascertainment, or 6 months after ART initiation and availability of a CD4 count measurement, whichever came last. Follow-up ended at death, end of cohort ascertainment of cancer diagnoses and deaths, or 31 December 2009, whichever came first. For the main analysis, we excluded 1438 people (3.0% of otherwise eligible individuals) who had a prevalent cancer diagnosed prior to follow-up, because some people may start ART in response to a cancer diagnosis, which might affect the PAF. Our main results therefore address a question that can be framed as "What is the subsequent mortality due to cancer in a population of PWHIV receiving ART who have no prior cancer when initially assessed?"

We used Cox proportional hazards models to estimate hazard ratios (HRs) for the associations between cancer diagnosis (considered as a time-updated risk factor) and overall mortality. These models evaluated associations with cancer overall, ADCs and NADCs overall, and the most common individual cancers (KS; NHL; lung, anal, and liver cancers; and other remaining cancers together). Age was used as the time scale, which adjusted the HRs for age. We evaluated unadjusted models as well as models additionally adjusted for demographic factors (sex, race, HIV risk group, attained calendar year, cohort) and time-updated HIV disease markers (CD4 count, viral load; see Table 2 footnote).

We calculated the PAF for cancer-attributable mortality using the formula $PAF = P_d \times (HR - 1)/HR$, where P_d is the proportion of people who died with a cancer diagnosed previously during follow-up and HR is from the unadjusted or adjusted Cox models described above [22]. We expressed the PAF as a percentage of deaths and also calculated a cancer-attributable mortality rate, defined as PAF × (number of deaths)/(person-time of follow-up), where deaths and person-time were assessed for the entire population or population subgroup. The variance of the PAF was calculated using an influence function-based approach (see Supplementary Material for details). We present results for the overall cohort, as well as for subgroups stratified by sex, attained age, most recent CD4 count, and attained calendar period.

In sensitivity analyses, we recalculated the PAF for lung cancer after further adjustment for smoking and for liver cancer adjusting for HBV and HCV status. In another sensitivity analysis, we added back the individuals excluded because of a prevalent cancer diagnosed before follow-up.

RESULTS

The study included 46 956 PWHIV receiving ART in 13 North American cohorts (Table 1). The majority were male (83.3%), and the most common specified transmission risk group was men who have sex with men (31.0%), although a large proportion were in other/unknown HIV risk groups. At study entry, the median age was 42.5 years, 30.3% of PWHIV had CD4 counts <200 cells/mm^3, and 40.8% had viral loads <500 copies/mL. Among individuals with known or imputed smoking status, 75.5% were ever smokers. HBV and HCV prevalence was 7.0% and 23.7%, respectively.

Table 1. Characteristics of Cohort of 46 956 Human Immunodeficiency Virus–Infected Individuals in North America at the Start of Follow-up

Characteristic	Number	Percentage
All	46 956	100
Sex and risk group		
Male	39 108	83.3
MSM (+/- IDU)	14 537	31.0
Male IDU (no MSM)	2003	4.3
Male other/unknown	22 568	48.1
Female	7848	16.7
Female IDU	1199	2.6
Female other/unknown	6649	14.2
Age at entry, y		
18–34.9	9643	20.5
35–41.9	12 706	27.1
42–48.9	12 358	26.3
49+	12 249	26.1
Race		
White, non-Hispanic	21 435	45.6
Black, non-Hispanic	19 103	40.7
Other/unknown	6418	13.7
Calendar year of entry		
1995–1998	11 399	24.3
1999–2001	13 555	28.9
2002–2005	13 503	28.8
2006–2009	8499	18.1
Initial CD4 count, cells/mm^3		
0–49	3526	7.5
50–99	3138	6.7
100–199	7562	16.1
200–499	21 057	44.8
500+	11 673	24.9
Initial HIV viral load, copies/mL		
<500	19 178	40.8
500–1999	4764	10.1
2000–19 999	4358	9.3
20 000–199 999	4687	10.0
200 000+	1579	3.4
Unknown	12 390	26.4
Smoking status		
Ever (known or imputed)	30 936	65.9
Never (known or imputed)	10 026	21.4
Unknown and not imputed	5994	12.8
Hepatitis B virus infection		
Yes	3294	7.0
No	43 662	93.0
Hepatitis C virus infection		
Yes	11 107	23.7
No	35 849	76.3

Abbreviations: HIV, Human Immunodeficiency Virus; IDU, injection drug user; MSM, men who have sex with men.

Participants were followed for 267 145 person-years (mean 5.7 years). During this time, 8956 PWHIV died (overall mortality 3352 per 100 000 person-years). The proportion of follow-up time spent with a CD4 count 500+ cells/mm^3 increased over time, from 26% before 1 January 2001 to 39% after 31 December 2005. A total of 1997 people were diagnosed with a first cancer during follow-up (Table 2). Overall, 1069 PWHIV (53.5%) with cancer died, and deaths in individuals with cancer comprised 11.9% of all deaths (ie, $P_d = 11.9\%$).

PAFs were similar based on unadjusted or adjusted HRs (Table 2), so we focused on adjusted results. Based on an adjusted HR of 5.54 for death following cancer, the adjusted PAF for overall cancer-attributable mortality was $P_d \times (HR - 1)/HR = (0.119)(4.54)/(5.54) = 9.8\%$ (95% confidence interval, 9.1%–10.5%). This PAF translates into a cancer-attributable mortality rate of 327 per 100 000 person-years.

As shown in Table 2, 2.6% of deaths were attributable to ADCs and 7.1% to NADCs, yielding cancer-attributable mortality rates of 86 and 239 per 100 000 person-years, respectively. Among individual cancers, the largest contributions to mortality were from lung cancer (PAF 2.3%), NHL (2.0%), liver cancer (0.9%), KS (0.5%), and anal cancer (0.4%). Since only 1 death was preceded by a diagnosis of cervical cancer, the PAF for cervical cancer was essentially 0%. Other individual NADCs (including breast, colorectal, oral cavity/pharynx, and prostate cancers and Hodgkin lymphoma) were too infrequent among decedents to analyze separately (data not shown).

Table 3 and Figure 1 show estimates for population subgroups. Cancer-attributable mortality was higher in males than females (PAF 10.2% vs 7.2%), largely due to higher mortality attributable to NADCs (7.5% vs 4.9%). Cancer-attributable mortality increased with age, reaching 13.9% in PWHIV aged ≥55 years. Because overall mortality also increased with age, there was a correspondingly large increase in the overall cancer-attributable mortality rate with age, from 144 to 751 per 100 000 person-years in people aged <40 years vs ≥55 years, respectively. Moreover, as shown in Figure 1, this increase was due to an increase in mortality attributable to NADCs (from 2.1% to 12.5% of deaths, or from 43 to 679 per 100 000 person-years), as PAFs and cancer-attributable mortality rates for ADCs decreased across age categories.

PAFs for overall cancer were somewhat similar in PWHIV with the lowest and highest recent CD4 counts (<100 cells/mm^3: 7.6% vs 500+ cells/mm^3: 8.8%; Table 3). This pattern reflects different contributions from ADCs and NADCs; the PAF for ADCs was highest among individuals with CD4 <100 cells/mm^3, while the PAF for NADCs was lowest in this group. Nonetheless, overall mortality rates were highest in PWHIV with CD4 counts <100 cells/mm^3, so cancer-attributable mortality rates were highest in this group as well and declined sharply with increasing CD4 counts (Table 3, Figure 1).

Across calendar periods, PAFs for cancer overall increased from 7.7% to 12.1% (Table 3). This pattern reflects a strong decline over time in overall mortality, while the cancer-attributable mortality rate remained constant (Figure 1). For ADCs, PAFs and cancer-attributable mortality rates both declined substantially. For NADCs, in contrast, the PAF increased to 10.1%

Table 2. Cancer-Attributable Mortality Among Human Immunodeficiency Virus–Infected Individuals in North America

Cancer	Total Cancer Cases, N	Deaths With Prior Cancer, N	Pd, %[a]	Unadjusted Analysis			Adjusted Analysis[b]		
				HR	PAF, %	(95% CI)	HR	PAF, %	(95% CI)
Total	1997	1069	11.9	6.27	10.0	(9.3–10.7)	5.54	9.8	(9.1–10.5)
AIDS-defining cancers	570	303	3.4	6.22	2.8	(2.5–3.2)	4.11	2.6	(2.2–2.9)
Kaposi sarcoma	252	95	1.1	3.45	0.8	(0.5–1.0)	2.06	0.5	(0.3–0.8)
Non-Hodgkin lymphoma	312	207	2.3	9.70	2.1	(1.8–2.4)	7.23	2.0	(1.7–2.3)
Cervix	6	1	0.0	—	0.0	—	—	0.0	—
Non-AIDS–defining cancers	1427	766	8.6	5.89	7.1	(6.5–7.7)	5.91	7.1	(6.5–7.7)
Lung	265	222	2.5	20.33	2.4	(2.0–2.7)	14.71	2.3	(2.0–2.6)
Anus	154	62	0.7	3.13	0.5	(0.3–0.6)	2.73	0.4	(0.3–0.6)
Liver	103	80	0.9	23.95	0.9	(0.7–1.1)	31.26	0.9	(0.7–1.1)
Other	905	402	4.5	3.81	3.3	(2.9–3.7)	4.04	3.4	(2.9–3.8)

Abbreviations: CI, confidence interval; HR, hazard ratio; PAF, population-attributable fraction; Pd, proportion of deaths with a prior cancer.

[a]P_d expresses the number of deaths preceded by cancer as a proportion of all deaths in the cohort (N = 8956).

[b]Hazard ratios are computed using age as the time scale and are adjusted for sex, race (non-Hispanic white, non-Hispanic black, other), human immunodeficiency virus (HIV) risk group (men who have sex with men, injection drug users, other/unknown), attained calendar year (before 1/1/2001, 1/1/2001–6/30/2003, 7/1/2003–12/31/2005, after 12/31/2005), cohort, most recent CD4 count (0–49, 50–99, 100–199, 200–499, 500+ cells/mm^3), and most recent HIV viral load (unknown, <500, 500–1999, 2000–19999, 20000–199999, 200000+ copies/mL).

after 31 December 2005, reflecting a rise in cancer-attributable mortality along with the decline in overall mortality.

Sensitivity Analyses

PAF estimates were unchanged when regression models were further adjusted for smoking (for lung cancer) or HBV and HCV (for liver cancer) (not shown). In another sensitivity analysis, we included 1438 PWHIV with a prevalent cancer. Of these individuals, 455 died during follow-up, which increased the overall proportion of deceased PWHIV with a prior cancer (P_d) to 0.162. In this larger cohort, the adjusted HR associating cancer and death was 4.67, yielding a PAF of 12.7%.

DISCUSSION

Among PWHIV in North America treated with ART during 1995–2009, we estimate that 9.8% of all deaths were attributable to cancer. A larger proportion of deaths was attributable to NADCs (7.1%) than ADCs (2.6%). More than half of cancer-attributable deaths were attributable to NHL, lung cancer, and liver cancer; KS and anal cancer also contributed measurably.

The PAFs for these cancers are a manifestation of both the elevated incidence of new cases in PWHIV and the high subsequent mortality associated with a cancer diagnosis (manifested in the strong HRs). With widespread ART use, KS and NHL incidence have declined over time [7]. However, NHL remains one of the most common cancers in PWHIV in the United States, along with lung and anal cancers [27]. In our PWHIV population, liver cancer was less common than anal cancer but it was more common among decedents, and the HR associated with mortality was much larger for liver cancer (Table 2). As a result, the PAF was more than twice as high for liver cancer (0.9%) than for anal cancer (0.4%). Mortality following cancer diagnosis is affected by the inherent aggressiveness of tumors and whether patients receive effective treatment. Although we lacked data to assess cancer treatment in this study, PWHIV often have complex social and medical problems that prevent access to appropriate care [28].

Cancer-attributable mortality differed noticeably across population subgroups (Table 3), which to some extent reflects variation in cancer incidence and trends in overall mortality. Mortality attributable to NADCs was much higher in males than females and increased strongly with age. Mortality rates attributable to ADCs and NADCs were highest at low CD4 counts, although the corresponding PAF for NADCs was not especially high, because of high overall mortality in severely immunosuppressed individuals. Likewise, a growing proportion of all deaths during 1995–2009 period were attributed to NADCs, reaching 10.1% of all deaths after 31 December 2005. This pattern largely reflects the strong decline in overall mortality among PWHIV along with increasing mortality attributable to NADCs.

The PAF calculations assume that the association between cancer and mortality reflects a causal relationship, so that the corresponding deaths would be prevented if cancer could be eliminated or its treatment improved. A key assumption is thus that there is no unmeasured confounding of the association between cancer and mortality. We adjusted the Cox models for various demographic and clinical characteristics, and while the HRs changed noticeably in some instances, the unadjusted and adjusted PAFs were very similar. This similarity arises because the factor (HR − 1)/HR used in the PAF calculation is close to 1.00 whenever the HR is large, so that PAF≈P_d. However, if there were substantial residual confounding, our PAF estimates would not accurately capture the mortality caused by cancer.

Our overall PAF estimates are noticeably lower than those for cancer-related mortality presented in studies based on ascertained causes of death, that is, 7%–15% deaths reported

Table 3. Cancer-Attributable Mortality, Stratified Analyses

Subgroup	Total Deaths	Deaths With Prior Cancer			Population-Attributable Fraction, % (95% Confidence Interval)[a]			Overall Mortality Rate, per 100 000 Person-Years	Cancer-Attributable Mortality Rate, per 100 000 Person-Years[a]		
		All	ADC	NADC	All	ADC	NADC		All	ADC	NADC
Sex											
Male	7744	968	270	698	10.2 (9.4–11.0)	2.6 (2.2–3.0)	7.5 (6.8–8.1)	3495	356	91	261
Female	1212	101	33	68	7.2 (5.6–8.8)	2.2 (1.3–3.2)	4.9 (3.6–6.2)	2658	192	59	131
Age, y											
<40	1476	125	89	36	6.9 (5.5–8.4)	4.8 (3.6–6.1)	2.1 (1.3–2.9)	2071	144	100	43
40–44	1409	130	55	75	7.6 (6.1–9.2)	3.0 (1.9–4.0)	4.5 (3.4–5.7)	2567	195	76	117
45–54	3540	372	110	262	8.7 (7.7–9.8)	2.4 (1.8–3.0)	6.2 (5.4–7.1)	3755	329	91	234
55+	2531	442	49	393	13.9 (12.3–15.4)	1.2 (0.6–1.7)	12.5 (11.1–14.0)	5417	751	63	679
Most recent CD4 count, cells/mm^3											
<100	3983	398	195	203	7.6 (6.7–8.6)	3.7 (3.0–4.4)	3.9 (3.2–4.5)	13 988	1068	514	539
100–199	1471	206	47	159	11.4 (9.6–13.3)	2.4 (1.5–3.3)	8.9 (7.2–10.5)	4674	535	114	414
200–499	2483	361	54	307	12.6 (11.2–14.0)	1.8 (1.2–2.4)	10.7 (9.4–12.1)	2143	270	38	230
500+	1019	104	7	97	8.8 (6.7–10.5)	0.4 (-0.1 to 0.9)	8.2 (6.4–10.1)	1116	96	4	92
Calendar period											
Before 1/1/2001	1992	178	82	96	7.7 (6.4–9.0)	3.4 (2.6–4.3)	4.2 (3.2–5.1)	4788	368	165	201
1/1/2001–6/30/2003	2140	210	67	143	8.1 (6.8–9.3)	2.4 (1.7–3.2)	5.6 (4.5–6.6)	3782	305	91	211
7/1/2003–12/31/2005	2318	301	82	219	10.5 (9.1–12.0)	2.6 (1.9–3.4)	7.8 (6.6–9.0)	3154	333	83	245
After 12/31/2005	2506	380	72	308	12.1 (10.7–13.6)	1.9 (1.2–2.6)	10.1 (8.7–11.4)	2625	318	50	264

Abbreviations: ADC, AIDS-defining cancer; NADC, non-AIDS–defining cancer.

[a]Population-attributable fraction and cancer-attributable mortality rates are based on hazard ratios adjusted for or stratified on sex, risk group, race, attained calendar year, most recent CD4 count, most HIV viral load, and cohort; the Cox models use age as the timescale.

from ADCs and 12%–27% from NADCs [2, 11–13, 18, 19]. Nonetheless, there are several reasons why we do not believe the PAF calculations substantially underestimated mortality due to cancer in our population. Notably, the PAF must always be less than P_d, because there cannot be more deaths attributable to cancer than there are deaths preceded by cancer. Thus, the maximum possible cancer-attributable mortality for our HIV population would be P_d = 11.9%, which is not far from our PAF estimate of 9.8%. It is unlikely that cancers were greatly underascertained in NA-ACCORD, because participating cohorts made substantial efforts to identify cancer cases, and standardized incidence ratios (comparing cancer risk in NA-ACCORD to the general population) are similar to those from other published estimates [8, 29–31]. Future analyses of NA-ACCORD data on reported causes of death, which are currently being compiled, will complement our results and provide information on deaths related to other important conditions.

Our main analysis assessed PWHIV receiving ART who, at the start of follow-up, had no prior history of cancer. Because it takes time for such a cohort to accumulate incident cancers and subsequent deaths, this restriction may have led us to underestimate PAFs, especially for earlier calendar intervals. In a sensitivity analysis, we therefore also included people with preexisting cancer, which increased the proportion of PWHIV in the cohort who died with a prior cancer, but the overall PAF increased only to 12.7%. Thus, our exclusion of PWHIV with prevalent cancer probably cannot entirely explain the above-mentioned differences with other studies. Our results could differ from those from prior studies if some deaths were misclassified in those studies, due to lack of detailed clinical information or the presence of multiple illnesses. Alternatively, our generally lower estimates could reflect differences in the HIV populations in terms of demographics, comorbid medical conditions, receipt of ART, or access to cancer care.

Important strengths of our study include the availability of a large representative population of PWHIV and validated data on cancers and deaths. We briefly note that Simard et al. previously estimated cancer-attributable mortality among people with AIDS in the United States during 1996–2006 [23] using a different PAF formula that required assigning cancer status at the start of discrete 6-month intervals. Because cancers may have occurred within the intervals, the Simard et al approach likely missed some cancer-associated deaths. In contrast, the current PAF method evaluated the association between cancer and death over a continuous timescale, so that deaths that occurred shortly after cancer diagnosis were appropriately assessed.

A limitation of our study is that we did not have validated data on incident cancers after 2009, so we could not estimate cancer-attributable mortality in more recent years. Two additional points should be discussed. First, our results resemble an "intent-to-treat" analysis of cancer-attributed mortality among PWHIV prescribed ART, that is, individuals were considered to be receiving ART continuously after initiation. This approach

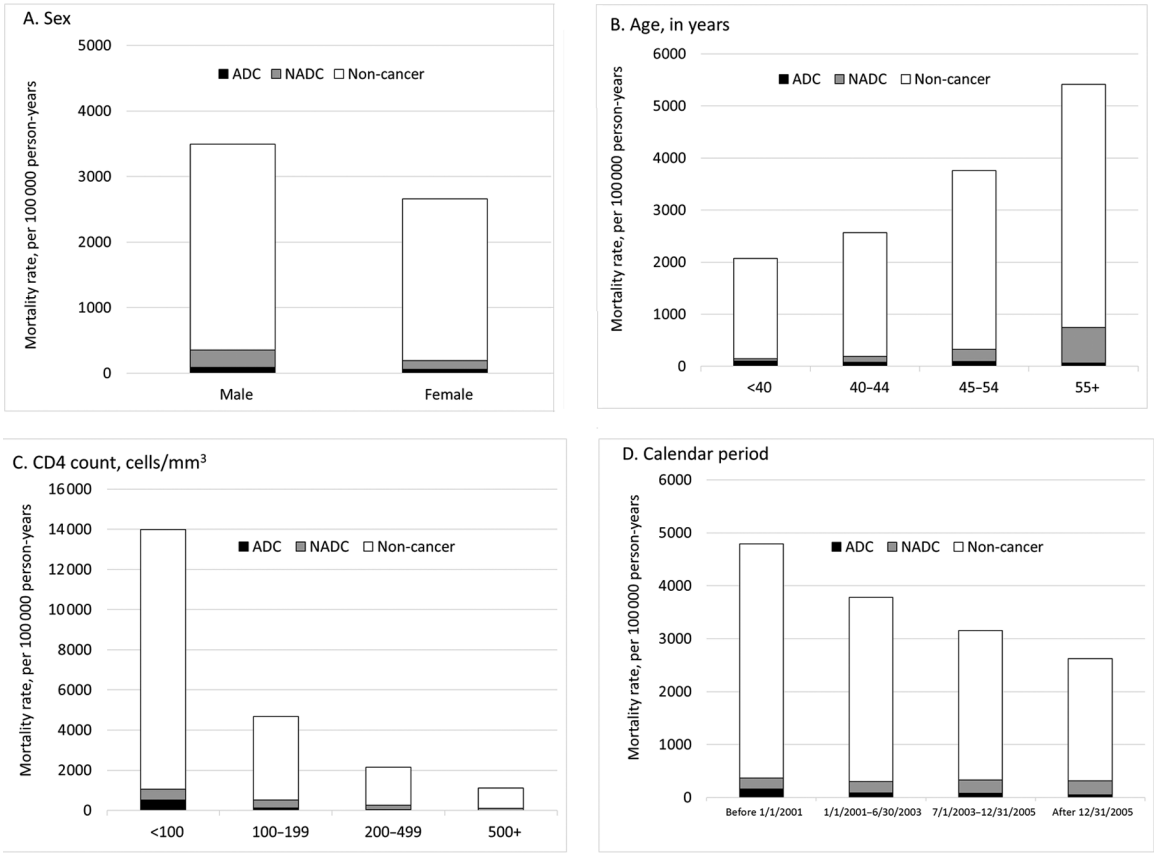

Figure 1. Cancer-attributable and noncancer mortality rates. The panels display estimates of mortality attributable to AIDS-defining cancer, non-AIDS–defining cancer, and the remaining noncancer mortality among human immunodeficiency virus–infected people in North America. The 3 rates are stacked to total the overall mortality rate. Results are shown stratified according to sex (panel A), age (panel B), most recent CD4 count (panel C), and calendar period (panel D). The vertical scale varies across the panels. Abbreviations: ADC, AIDS-defining cancer; NADC, non-AIDS–defining cancer.

was used because patients are supposed to continue ART after initiation, and complete and accurate adherence information is difficult to obtain. However, we expect that not all patients were fully adherent, and some patients had documented periods of nonuse. Second, we examined only first cancers, so deaths were attributed to these rather than any subsequent malignancies. Subsequent cancers were somewhat uncommon (only 96 of 1997 PWHIV [4.8%] with a first cancer were later diagnosed with another). Also, to the extent that the subsequent cancers were caused by treatment of the first cancer (e.g., effects of radiation or chemotherapy-induced immunosuppression), it would be appropriate to attribute any deaths to the first cancer.

Cancer mortality among PWHIV estimated in our study (327 per 100 000 person-years) was much higher than in the US general population during 2014 (186 per 100 000 person-years; National Center for Health Statistics, http://www.cdc.gov/nchs/fastats/deaths.htm). Our results highlight important opportunities to reduce cancer mortality for PWHIV receiving ART. First, clinical and public health efforts should focus on reducing cancer incidence, by facilitating adherence to ART, enabling smoking cessation, and treating HBV and HCV infections [32] (see also https://aidsinfo.nih.gov). Second, screening for lung, liver, and anal cancers in appropriate high-risk groups may identify cancers when they are more amenable to treatment [33, 34]. Third, HIV-infected cancer patients must be provided access to timely and effective cancer treatment that is coordinated by experienced HIV and cancer specialists [28].

In conclusion, we found that approximately 10% of deaths in PWHIV prescribed ART during 1995–2009 were attributable to cancer, but this fraction increased over time. A large proportion of these deaths were attributable to NHL, lung cancer, and liver cancer. Deaths due to NADCs will likely grow in importance as AIDS mortality declines further and PWHIV age.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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NA-ACCORD Collaborating Cohorts and Representatives (cohorts that contributed data to this study are indicated by an asterisk): AIDS Clinical Trials Group Longitudinal Linked Randomized Trials: Constance A. Benson and Ronald J. Bosch. AIDS Link to the IntraVenous Experience: Gregory D. Kirk. Fenway Health HIV Cohort: Stephen Boswell, Kenneth H. Mayer, and Chris Grasso. HAART Observational Medical Evaluation and Research: Robert S. Hogg, P. Richard Harrigan, Julio S.G. Montaner, Benita Yip, Julia Zhu, Kate Salters, and Karyn Gabler. HIV Outpatient Study*: Kate Buchacz and John T. Brooks. HIV Research Network*: Kelly A. Gebo and Richard D. Moore. Johns Hopkins HIV Clinical Cohort*: Richard D. Moore. John T. Carey Special Immunology Unit Patient Care and Research Database, Case Western Reserve University: Benigno Rodriguez. Kaiser Permanente Mid-Atlantic States: Michael A. Horberg. Kaiser Permanente Northern California*: Michael J. Silverberg. Longitudinal Study of Ocular Complications of AIDS: Jennifer E. Thorne. Multicenter Hemophilia Cohort Study–II*: Charles Rabkin. Multicenter AIDS Cohort Study: Lisa P. Jacobson and Gypsyamber D'Souza. Montreal Chest Institute Immunodeficiency Service Cohort: Marina B. Klein. Ontario HIV Treatment Network Cohort Study: Sean B. Rourke, Anita R. Rachlis, Jason Globerman, and Madison Kopansky-Giles. Retrovirus Research Center, Bayamon Puerto Rico: Robert F. Hunter-Mellado and Angel M. Mayor. Southern Alberta Clinic Cohort*: M. John Gill. Study of the Consequences of the Protease Inhibitor Era*: Steven G. Deeks and Jeffrey N. Martin. Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy: Pragna Patel and John T. Brooks. University of Alabama at Birmingham 1917 Clinic Cohort*: Michael S. Saag, Michael J. Mugavero, and James Willig. University of North Carolina at Chapel Hill HIV Clinic Cohort*: Joseph J. Eron and Sonia Napravnik. University of Washington HIV Cohort*: Mari M. Kitahata, Heidi M. Crane, and Daniel R. Drozd. Vanderbilt Comprehensive Care Clinic HIV Cohort*: Timothy R. Sterling, David Haas, Peter Rebeiro, Megan Turner, Sally Bebawy, and Ben Rogers. Veterans Aging Cohort Study*: Amy C. Justice, Robert Dubrow, and David Fiellin. Women's Interagency HIV Study*: Stephen J. Gange and Kathryn Anastos. NA-ACCORD Study Administration: Executive Committee: Richard D. Moore, Michael S. Saag, Stephen J. Gange, Mari M. Kitahata, Keri N. Althoff, Rosemary G. McKaig, and Aimee M. Freeman. Administrative Core: Richard D. Moore, Aimee M. Freeman, and Carol Lent. Data Management Core: Mari M. Kitahata, Stephen E. Van Rompaey, Heidi M. Crane, Daniel R. Drozd, Liz Morton, Justin McReynolds, and William B. Lober. Epidemiology and Biostatistics Core: Stephen J. Gange, Keri N. Althoff, Alison G. Abraham, Bryan Lau, Jinbing Zhang, Jerry Jing, Sharada Modur, Cherise Wong, Brenna Hogan, Fidel Desir, Bin Liu, and Bin You.