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HIV Infection Is Associated with an Increased Risk for Lung Cancer, Independent of Smoking

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Abstract

Background—Human immunodeficiency virus (HIV)–infected persons have an elevated risk for lung cancer, but whether the increase reflects solely their heavy tobacco use remains an open question.

Methods—The Acquired Immunodeficiency Syndrome (AIDS) Link to the Intravenous Experience Study has prospectively observed a cohort of injection drug users in Baltimore, Maryland, since 1988, using biannual collection of clinical, laboratory, and behavioral data. Lung cancer deaths were identified through linkage with the National Death Index. Cox proportional hazards regression was used to examine the effect of HIV infection on lung cancer risk, controlling for smoking status, drug use, and clinical variables.

Results—Among 2086 AIDS Link to the Intravenous Experience Study participants observed for 19,835 person-years, 27 lung cancer deaths were identified; 14 of the deaths were among HIV-infected persons. All but 1 (96%) of the patients with lung cancer were smokers, smoking a mean of 1.2 packs per day. Lung cancer mortality increased during the highly active antiretroviral therapy era, compared with the pre–highly active antiretroviral therapy period (mortality rate ratio, 4.7; 95% confidence interval, 1.7–16). After adjusting for age, sex, smoking status, and calendar period, HIV infection was associated with increased lung cancer risk (hazard ratio, 3.6; 95% confidence interval, 1.6–7.9). Preexisting lung disease, particularly noninfectious diseases and asthma, displayed trends for increased lung cancer risk. Illicit drug use was not associated with increased lung cancer risk. Among HIV-infected persons, smoking remained the major risk factor; CD4 cell count and HIV load were not strongly associated with increased lung cancer risk, and trends for increased risk with use of highly active antiretroviral therapy were not significant.

Conclusions—HIV infection is associated with significantly increased risk for developing lung cancer, independent of smoking status.

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Lung cancer is the third most common malignancy among HIV-infected persons, following only the AIDS-defining cancers, Kaposi sarcoma and non-Hodgkin lymphoma, in incidence [1, 2]. Epidemiological studies have shown an increased risk for lung cancer among HIV-infected persons [3–14]. With prolonged survival because of the availability of HAART, morbidity and mortality attributable to lung cancer may increase in the next decades among those infected with HIV.

Notably, questions remain as to whether the observed association between HIV infection and lung cancer simply reflects a high prevalence of smoking among HIV-infected persons or is an independent effect of HIV infection [15]. Prior studies of lung cancer in HIV-infected persons have had several limitations, including the lack of appropriate HIV-uninfected control groups, reliance on lung cancer rates among the general population for comparison with those among HIV-infected populations, limited follow-up experience during the HAART era, and the small number of lung cancer cases [3–14]. Perhaps most importantly, prior findings may be affected by uncontrolled confounding by smoking, which is the dominant risk factor for lung cancer. Because HIV-infected persons typically use tobacco more heavily than the general population, inadequate control for this powerful risk factor could lead to an apparent association of HIV infection with lung cancer [15].

We evaluated lung cancer mortality among participants in the AIDS Link to the Intravenous Experience (ALIVE) Study, a large, long-standing cohort of injection drug users [16]. Using a longitudinal assessment of smoking among both HIV-infected and uninfected participants during an extended follow-up period, we were able to examine the association between HIV infection and lung cancer, while directly accounting for smoking exposure.

METHODS

Study population

The ALIVE Study prospectively collects demographic, behavioral, and clinical information on HIV-infected and uninfected injection drug users in Baltimore, Maryland [16]. At its inception in 1988, ALIVE recruited 2946 injection drug users; 735 additional participants were enrolled through recruitment during 1994–1995, 1998, and 2000. All participants were >17 years of age and did not have AIDS at entry into the study. The ALIVE Study was continually approved by the Johns Hopkins Committee on Human Research.

Data collection

ALIVE Study participants underwent biannual visits that included structured interviews, a computer-based risk questionnaire, clinical examination, and collection of blood specimens. Detailed information was elicited regarding lifestyle factors, including smoking status and illicit drug use. Because of the standardized 6-month visit structure, questionnaire items focused on behavior during this time period. Self-reported antiretroviral use was updated at each visit. HAART was defined as use of at least 3 antiretroviral drugs, 1 of which was a protease inhibitor, a nonnucleoside reverse-transcriptase inhibitor, or abacavir. The HAART era was defined as beginning on 1 July 1996. Hospital admissions for lung disease were identified, and diagnoses were confirmed through standardized medical record review. HIV

antibody testing of uninfected subjects was performed using commercial tests interpreted with standard criteria. T cell subsets were determined by flow cytometry. Plasma HIV RNA load was determined by RT-PCR (Amplicor HIV-1 Monitor test, version 1.5; Roche).

Lung cancer mortality ascertainment

Deaths among ALIVE Study participants were ascertained from family members or partners through regular study follow-up procedures [17] and also through linkage with the National Death Index (updated through 2003). Subsequently, death certificates were obtained from state archives and reviewed to confirm lung cancer as the cause of death.

Statistical analyses

The effect of HIV status on lung cancer death rates in both the pre-HAART and HAART eras was evaluated using Poisson regression techniques. Cox proportional hazards regression models were used to examine the association of HIV infection with lung cancer death, controlling for other covariates. Because age is strongly associated with lung cancer risk and time from study entry was not of biological importance, age was selected as the time scale for the Cox models. Therefore, with the effect of age incorporated into the baseline hazard, risk estimates were automatically adjusted for age. A priori, we focused on the effects of HIV infection after adjustment for age, sex, smoking status, and calendar periods corresponding to the availability of HAART. In further analysis, we sequentially evaluated the effect of HIV infection on lung cancer mortality, adjusting for drug use and preexisting lung disease. In this predominantly African American population, racial differences were not discernable, and therefore, the presented analyses were not adjusted for race.

Because preexisting lung disease could represent clinical symptoms of undiagnosed lung cancer, we excluded all medical conditions diagnosed within 3 years of lung cancer death. Similarly, for other behavioral or clinical covariates to have biologically influenced lung cancer development, exposures would have been required to occur before disease onset. Therefore, the 3-year latency exclusion period was applied to all time-dependent covariates, including smoking, drug use, prior lung disease, HIV status, and HIV disease markers (i.e., CD4 cell count and HIV RNA load). We lagged these exposure variables by 3 years in the Cox models, such that the hazard at time *(t)* was modeled as a function of the exposure (i.e., smoking, drug use, or pneumonia) at time $t - 3$.

Tobacco smoking was evaluated as a time-dependent covariate, updated after each visit to represent the cumulative mean number of packs of cigarettes smoked per day during the entire follow-up period; visits missing data on cigarette smoking (327 of 38,169 visits; 0.86%) were included by imputing zero packs smoked during the preceding period. When smoking exposure was analyzed using baseline smoking status or the cumulative pack-years reported during follow-up visits, similar results were obtained. This was likely because of the consistency of smoking reported over time; smoking was reported at 91% of follow-up visits of those who reported ever having smoked.

Injection drug use was evaluated as a time-dependent variable based on the average intensity of use (categorized into less than daily or daily or more) during the 6 months prior to the

visit. Inhalation of illicit drugs (including heroin, crack, and marijuana) was reported less frequently than injection drug use, and was therefore analyzed as a time-dependent indicator variable (never vs. ever) that was updated after each visit. Similarly, clinical diagnoses of lung disease (further separated into noninfectious and infectious causes) were evaluated as time-dependent variables (representing 0, 1, or, in some analyses, >1 cumulative diagnoses).

RESULTS

Characteristics of the ALIVE cohort

At cohort inception, the median age of ALIVE Study participants was 35 years, 75% were male, 92% were African American, and 24% were infected with HIV. An additional 334 participants were identified as undergoing HIV seroconversion during follow-up. At entry, 84% of participants reported smoking, and of these persons, 45% smoked at least 1 pack per day and 10% smoked at least 2 packs per day. Sixty-seven percent of participants reported smoking at every follow-up visit, and only 7% never reported smoking cigarettes. Neither the prevalence of ever smoking (92% for HIV-infected patients vs. 94% for HIV-uninfected persons; *P* p .17), nor the mean amount of cigarettes smoked (0.9 packs per day for both), differed by HIV status. All subjects had a baseline history of injection drug use; during follow-up, these subjects reported recently using injection drugs at 59% of the visits. Smoking illicit drugs was reported at some point during follow-up by 76% of participants.

Lung cancer deaths among ALIVE Study participants

For 27 participants, the underlying cause of death was lung cancer (table 1); 14 of these patients were infected with HIV (4 patients experienced seroconversion during follow-up). All documented HIV seroconversions occurred at least 4 years prior to lung cancer–associated death. At death, HIV-infected persons with lung cancer were younger than HIV-uninfected persons (median age, 51 years vs. 55 years; *P* p .06). Similar sex, race, smoking status, and drug-use patterns and preexisting lung disease diagnoses were observed by HIV status among persons with lung cancer (*P* 1 .20, for all comparisons). All but 1 person with lung cancer reported smoking cigarettes. Both HIV-infected and HIV-uninfected persons reported smoking a mean of 1.2 packs of cigarettes per day.

Most lung cancer deaths (22 [81%] of 27 deaths) occurred during follow-up in the HAART era. Among all study participants, irrespective of HIV status, the lung cancer mortality rate was 4.7-fold (95% CI, 1.7–16-fold) higher in the HAART era, compared with the pre-HAART era (table 2). In both periods, the lung cancer mortality rate was higher among those with HIV infection (table 2), although this difference was not statistically significant. Overall, in an analysis unadjusted for age, HIV infection was associated with a 50% increased incidence of lung cancer death (mortality rate ratio, 1.5; 95% CI, 0.66– 3.5).

Predictors of lung cancer mortality

In both univariate and multivariate analyses, smoking was strongly associated with lung cancer mortality (table 3). An increase in the amount of cigarettes smoked of 1 pack per day conferred a 1.8-fold increased risk for lung cancer. No significant effect of sex or HAART era on lung cancer risk was observed. After adjusting for age, sex, smoking status, and

HAART era (table 3), lung cancer mortality was higher among HIV-infected patients than among HIV-uninfected participants (hazard ratio [HR], 3.6; 95% CI, 1.6–7.9). Because HIV-infected patients with lung cancer were younger than HIV-uninfected patients with lung cancer, adjustment for age was the primary factor responsible for the increase in the HR for HIV infection in the model in table 3, compared with the mortality rate ratio in table 2. When alternative methods for characterizing smoking exposure were used (i.e., baseline smoking status and cumulative pack-years), the adjusted HR estimates for lung cancer death among HIV-infected patients remained stable (HR, 4.2 [95% CI, 1.9–9.3] and 3.3 [95% CI, 1.5–7.1], respectively).

In further univariate and multivariate analyses adjusting for sex, smoking status, and HIV status, we examined the effects of drug-use behavior and clinical diagnoses of preexisting lung disease (table 4). Illicit drug use, either through the injection or inhaled route, was not significantly associated with lung cancer mortality; the independent association of HIV infection with lung cancer mortality was changed little after adjustment for drug use. Previous episodes of lung disease appeared to increase lung cancer risk (table 4), with similar risk estimates for both noninfectious lung disease and for any pulmonary infection. However, a significant association was observed only in further analysis including patients experiencing ≥2 episodes of noninfectious lung disease (adjusted HR, 24; 95% CI, 2.8–200), compared with those without any diagnosis of noninfectious lung disease. The independent association of HIV infection with lung cancer persisted and was of similar magnitude in each of these analyses (table 4).

HIV disease markers, HAART, and lung cancer mortality

Among the 14 HIV-infected patients with lung cancer, the median CD4 cell count nadir was 260 cells/μL (interquartile range [IQR], 88–408 cells/μL), and the median peak HIV RNA load was 52,537 copies/mL (IQR, 10,829–338,063 copies/mL). Only 5 (36%) of 14 HIV-infected patients with lung cancer had received a diagnosis of AIDS prior to death. Four of 10 HIV-infected patients who died of lung cancer after 1 July 1996 reported receiving HAART at some time during the follow-up period. In an analysis restricted to the 1192 HIV-infected participants (table 5), smoking remained the primary predictor of lung cancer mortality. Prior hospitalization for asthma was the only other risk factor associated with lung cancer in univariate analysis; in multivariate analysis the effect was of only borderline significance (table 5). In univariate analysis, lung cancer mortality was not related to a lower CD4 cell count or higher HIV RNA load (table 5); similar results were observed after multivariate adjustment (data not shown). Durable HIV suppression was associated with a reduction in lung cancer risk, and indicators of an increased frequency of HAART use were associated with increased risk. However, these associations were not statistically significant, and interpretation is limited by the small number of patients and the inability to fully account for nonadherent or inconsistent HAART use. No effects of illicit drug use by injected or inhaled routes on lung cancer mortality were observed among HIV-infected participants.

DISCUSSION

As persons with HIV infection survive into older ages, lung cancer may increase as a cause of morbidity and mortality [18, 19]. Epidemiological studies suggest that there is an elevated risk for lung cancer among HIV-infected individuals [3, 4, 6–10, 12, 13]. Tobacco smoking clearly explains part of this increased lung cancer risk, because HIV-infected persons tend to smoke heavily, compared with HIV-uninfected individuals [20–22]. Because smoking is the major etiologic agent of lung cancer, heavier smoking among HIV-infected persons would result in higher rates of lung cancer. Importantly, we present strong evidence that HIV infection contributes to lung cancer, independent of smoking status. ALIVE Study participants reported heavy tobacco use, and smoking status was similar among HIV-infected and HIV-uninfected participants. After adjusting for individual smoking exposure, we identified a statistically significant ~3.5-fold elevated risk for lung cancer associated with HIV infection.

Previous investigations of HIV infection and lung cancer have been based on linkages of AIDS and cancer registries [3, 7–9, 12] or on comparison of lung cancer rates from observational HIV cohorts with rates from cancer registry data [4, 6, 10, 11, 13, 14], but limited or no data were available on smoking status. Although these studies have demonstrated elevated lung cancer risk among HIV-infected individuals (relative risks, 2–11, compared with the general population) [3, 4, 6–14], it has not been clear whether the elevated risk was solely because of heavy smoking among the HIV-infected population. In contrast to these studies, the ALIVE Study has collected smoking information systematically for both HIV-infected and HIV-uninfected participants in the same cohort using identical follow-up procedures. To our knowledge, only 1 previously published study has reported a direct comparison of lung cancer outcomes between HIV-infected and HIV-uninfected participants in the same cohort [23]. That study, which involved HIV-infected and HIV-uninfected women, included 5 cases of lung cancer, considered smoking history only at baseline, and found a 3.3-fold nonsignificant increased risk of lung cancer associated with HIV infection. The ALIVE Study includes a larger number of cases and incorporates longitudinal smoking data obtained during a long follow-up period.

If the increased risk of lung cancer among HIV-infected persons is not fully explained by smoking, further mechanisms can be postulated, including (1) an oncogenic role of HIV infection itself; (2) a direct consequence of HIV-related immunosuppression and decreased immune surveillance, similar to other AIDS-defining malignancies; (3) lung damage from recurrent infections, which are more common in HIV-infected persons; or (4) an HIV-mediated increase in susceptibility to tobacco carcinogens, such as through increases in genomic instability [24].

Evidence to evaluate these potential mechanisms is scarce. Although limited experimental data suggest that HIV *tat* gene product may modulate expression of growth-related genes, amplification of HIV sequences in lung carcinoma tissue has not been demonstrated [24, 25]. Consistent with prior findings [6, 18], we did not demonstrate strong associations of HIV load or CD4 cell count with lung cancer risk, arguing against a major effect of either the virus itself or of immunosuppression. Other studies suggest that lung cancer risk has

changed during the HAART era [4, 10, 26]. Although we observed increased lung cancer mortality in the HAART era (table 2), there was no significant effect of either the HAART era or of individual HAART use on lung cancer risk after controlling for age and smoking (tables 3 and 5).

Most prior studies among HIV-uninfected populations [27–33], although not all studies [34, 35], have reported that preexisting lung disease increases risk for subsequent lung cancer.

In several studies, the highest lung cancer risk was associated with asthma [27, 30, 32, 34, 36]. Among HIV-infected populations, associations of lung cancer with preexisting lung disease have not been fully investigated. A prior registry linkage study reported nonsignificant increased risk for lung cancer associated with cytomegalovirus pneumonia and pulmonary tuberculosis but not with *Pneumocystis jirovecii* pneumonia [12]. To avoid reverse causality—that is, to avoid including any clinical diagnoses occurring as a result of preclinical lung cancer—we performed a conservative analysis with a 3-year latency exclusion period [31]. In addition, we used this lag for other exposure variables, as well, to exclude exposure assessment during biologically irrelevant periods after occult lung cancer is likely to already exist. We found trends of increased lung cancer risk with all categories of preexisting lung disease, particularly non-infectious diseases, such as asthma. However, these risk estimates generally overlapped unity and were based on small numbers of subjects.

In several prior studies of HIV-infected individuals, lung cancer risk was higher among injection drug users than among other HIV risk groups [6, 8, 10, 13]; perhaps this finding was related to differences in smoking habits [37]. Also, inhaling illicit drugs may promote the direct delivery of potential toxins or contaminants into the lungs, providing a biologically plausible mechanism for inducing local changes that could lead to lung cancer [38]. Because our study population was restricted to injection drug users, differences in smoking prevalence or intensity, as well as unrecognized potential confounders, have largely been adjusted for in the analyses. However, we found little evidence for a role of illicit drugs in the etiology of HIV-associated lung cancer.

Our study had several limitations. First, we relied on ascertainment of lung cancer deaths, rather than incident cases. However, because of the poor survival of lung cancer patients, mortality can serve as an excellent surrogate for incidence [39]; this is particularly true for an unscreened study population that presents at advanced stages of disease [14]. In addition, our methods of ascertainment of lung cancer mortality were identical for HIV-infected and HIV-uninfected participants.Second, the number of lung cancer deaths was small, limiting some analyses. Third, we did not have information on the histologic subtypes of lung cancer, which could have provided some indirect assessment of the impact of smoking [18]. Finally, our study population is predominantly African American and male, most were heavy smokers, and all had a history of injection drug use. Therefore, generalization of our findings to HIV-infected persons of other races or risk groups or with less-intensive smoking behaviors should be considered cautiously.

In conclusion, our data support the hypothesis that HIV infection increases lung cancer risk and provide evidence that this effect is independent of smoking status. Additional research should attempt to understand the biological mechanisms of how HIV infection may accelerate the process of lung carcinogenesis. Because of the large number of HIV-infected persons with histories of heavy smoking who are surviving longer because of HAART, lung cancer is likely to become an increasing problem for this population. Improved understanding of the risk for lung cancer associated with smoking among HIV-infected persons will aid counseling for smoking cessation and development of interventions to reduce the impact of tobacco use. Close monitoring of lung cancer trends among HIV-infected persons and pooling of HIV cohort data to further examine the risk for lung cancer associated with HIV disease markers and with prolonged HAART use is warranted.

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Table 1

Demographic, behavioral, and clinical characteristics of 27 patients with lung cancer in the AIDS Link to the Intravenous Experience Study cohort.

Variable	Patients (*n* = 27)
Age at time of death, median years (range)	53 (40–68)
Male sex	19 (70)
Race	
Black	25 (93)
Other	2 (7)
HIV infected	14 (52)
Ever smoked cigarettes	26 (96)
Mean no. of packs of cigarettes per day (range)	1.2 (0.0–2.0)
Daily injection of drugs	7 (26)
Ever inhaled illicit drugs	18 (67)
Preexisting lung disease	
1 Hospital admission	4 (15)
≥2 Hospital admissions	2 (7)
Prior noninfectious lung disease	
1 Hospital admission	0 (0)
≥2 Hospital admissions	1 (4)
Hospitalized for asthma	1 (4)
Pulmonary infection	
1 Prior pulmonary infection	4 (15)
Recurrent pulmonary infection	2 (7)
Pneumonia	
1 Prior pneumonia diagnosis	4 (15)
Recurrent pneumonia diagnosis	2 (7)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Exposure variables (except for age, sex, and race) were determined at the follow-up visit closest to 3 years prior to death or at the last visit.

Table 2

Lung cancer mortality among AIDS Link to Intravenous Experience Study participants in the pre-HAART and HAART eras.

Time period, HIV status	No. of persons who died of lung cancer	Follow-up, person-years	Mortality rate per 10^5 person-years	Mortality rate ratio (95% CI)
Pre-HAART era				
HIV uninfected	1	5344	18.7	1.0
HIV infected	4	4858	82.3	4.4 (0.44–220)
All	5	10,202	49.0	
HAART era				
HIV uninfected	12	6250	192	1.0
HIV infected	10	3383	296	1.5 (0.60–3.9)
All	22	9633	228	
Both eras combined				
HIV uninfected	13	11,594	112	1.0
HIV infected	14	8241	170	1.5 (0.66–3.5)

NOTE. HAART era is defined as beginning on 1 July 1996.

Table 3

Predictors of lung cancer mortality in the AIDS Link to Intravenous Experience Study cohort.

	Univariate model	Multivariate model[a]
Variable	**Hazard ratio (95% CI)**	**Hazard ratio (95% CI)**
Sex		
Male	1.0	1.0
Female	2.0 (0.88–4.7)	1.9 (0.82–4.4)
Mean no. of packs of cigarettes smoked		
Per 1 pack/day increase	1.8 (1.3–2.6)	1.8 (1.3–2.5)
HIV status		
Uninfected	1.0	1.0
Infected	3.4 (1.6–7.4)	3.6 (1.6–7.9)
Time period		
Pre-HAART era	1.0	1.0
HAART era	1.9 (0.69–5.1)	1.7 (0.62–4.6)

[a] Multivariate model includes adjustment for all other variables in the table. All models include adjustment for age (see Methods).

Table 4

Association of selected behavioral and clinical factors with lung cancer mortality and the effect on the HIV risk estimate.

	Univariate model[a]	Multivariate model[b]	HIV risk estimate[c]
Variable	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Daily injection of drugs			3.6 (1.6–8.0)
No	1.0	1.0	
Yes	0.61 (0.26–1.5)	0.55 (0.23–1.3)	
Inhaled illicit drugs			3.5 (1.6–7.7)
Never	1.0	1.0	
Ever	1.0 (0.44–2.3)	0.97 (0.42–2.3)	
Any lung disease[d]			3.5 (1.5–7.9)
None	1.0	1.0	
≥1 episode	2.1 (0.83–5.1)	1.2 (0.45–3.1)	
Noninfectious lung disease[d]			3.6 (1.6–7.9)
None	1.0	1.0	
≥1 episode	2.1 (0.28–16)	1.7 (0.22–13)	
Asthma			3.6 (1.6–7.9)
None	1.0	1.0	
≥1 episode	4.8 (0.64–36)	4.8 (0.63–36)	
Any pulmonary infection[d]			3.4 (1.5–7.7)
None	1.0	1.0	
≥1 episode	2.3 (0.91–5.6)	1.3 (0.49–3.4)	
Bacterial pneumonia			3.5 (1.5–8.1)
None	1.0	1.0	
1 episode	1.4 (0.32–5.8)	0.94 (0.21–4.1)	
≥2 episodes	3.1 (0.70–13)	1.3 (0.26–6.1)	

NOTE. HR, hazard ratio.

[a] Exposure variables determined at the follow-up visit closest to 3 years prior to death or at the last visit.

[b] Multivariate model includes adjustment for sex, mean no. of packs of cigarettes smoked per day, and HIV status. All models include adjustment for age (see Methods).

[c] The adjusted HR estimated for HIV infection, controlling for sex, smoking status, and the variable specified.

[d] Lung disease includes hospital admissions with diagnoses of both noninfectious lung disease (including chronic bronchitis, emphysema, and asthma) and pulmonary infections (including pneumonia of any etiology and pulmonary tuberculosis).

Table 5

Predictors of lung cancer mortality among HIV-infected participants.

	Univariate model[a]	Multivariate model[b]
Variable	**HR (95% CI)**	**HR (95% CI)**
Sex		
Male	1.0	1.0
Female	2.2 (0.72–6.6)	1.9 (0.61–6.0)
Mean no. of packs of cigarettes smoked		
Per 1 pack/day increase	1.6 (1.1–2.4)	1.7 (1.1–2.5)
Daily injection of drugs		
No	1.0	
Yes	0.79 (0.26–2.5)	
Inhaled illicit drugs		
Never	1.0	
Ever	1.4 (0.37–5.0)	
Any lung disease[c]		
None	1.0	
≥1 episode	1.7 (0.54–5.0)	
Noninfectious lung disease[c]		
None	1.0	
≥1 episode	2.2 (0.28–17)	
Hospitalized for asthma		
Never	1.0	
≥1 episode	11 (1.4–90)	7.9 (0.93–68)
Pulmonary infection[c]		
None	1.0	
≥1 episode	1.9 (0.62–5.7)	
Bacterial pneumonia		
None	1.0	
Any	1.2 (0.32–4.3)	
Nadir CD4 cell count, cells/μL		
<200	0.76 (0.09–6.6)	
200–500	1.1 (0.14–9.1)	
>500	1.0	
At least 75% of CD4 cell counts >200 cells/μL		
No	1.0	
Yes	0.78 (0.22–2.8)	
Peak HIV RNA load		
Per 1 log increase	1.1 (0.51–2.6)	
At least 25% of HIV RNA loads <10^4 copies/mL		
No	1.0	

	Univariate model[a]	Multivariate model[b]
Variable	**HR (95% CI)**	**HR (95% CI)**
Yes	0.58 (0.13–2.6)	
Any HAART use		
No	1.0	
Yes	2.2 (0.38–12)	
HAART use reported at ≥25% of visits		
No	1.0	
Yes	2.7 (0.48–15)	
Time period[d]		
Pre-HAART era	1.0	
HAART era	1.3 (0.40–4.3)	

NOTE. HR, hazard ratio.

[a] Exposure variables (except for sex) were determined at the follow-up visit closest to 3 years prior to death or at the last visit.

[b] Multivariate model includes adjustment for all other variables listed in this column. All models include adjustment for age (see Methods).

[c] Lung disease includes hospital admissions with diagnoses of both noninfectious lung disease (including chronic bronchitis, emphysema, and asthma) and pulmonary infections (including pneumonia of any etiology and pulmonary tuberculosis).

[d] HAART era is defined as beginning on 1 July 1996.