

# HIV as an independent risk factor for incident lung cancer

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**Background:** It is unclear whether the elevated rate of lung cancer among HIV-infected persons is due to biological effects of HIV, surveillance bias, or excess smoking. We compared the incidence of lung cancer between HIV-infected and demographically similar HIV-uninfected patients, accounting for smoking and stage of lung cancer at diagnosis.

**Design:** Data from the Veterans Aging Cohort Study Virtual Cohort were linked to data from the Veterans Affairs Central Cancer Registry, resulting in an analytic cohort of 37 294 HIV-infected patients and 75 750 uninfected patients.

**Methods:** We calculated incidence rates of pathologically confirmed lung cancer by dividing numbers of cases by numbers of person-years at risk. We used Poisson regression to determine incidence rate ratios (IRRs), adjusting for age, sex, race/ethnicity, smoking prevalence, previous bacterial pneumonia, and chronic obstructive pulmonary disease.

**Results:** The incidence rate of lung cancer in HIV-infected patients was 204 cases per 100 000 person-years [95% confidence interval (CI) 167–249] and among uninfected patients was 119 cases per 100 000 person-years (95% CI 110–129). The IRR of lung cancer associated with HIV infection remained significant after multivariable adjustment (IRR 1.7; 95% CI 1.5–1.9). Lung cancer stage at presentation did not differ between HIV-infected and uninfected patients.

**Conclusion:** In our cohort of demographically similar HIV-infected and uninfected patients, HIV infection was an independent risk factor for lung cancer after controlling for potential confounders including smoking. The similar stage distribution between the two groups indicated that surveillance bias was an unlikely explanation for this finding.

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## Introduction

Lung cancer is the most common non-AIDS-defining cancer (NADC) and leading source of NADC mortality among HIV-infected individuals [1,2]. Increased rates of lung cancer in HIV-infected patients, compared with uninfected patients, have been demonstrated in multiple prior studies [3–10]. This increased incidence has not been clearly explained and could potentially be attributed to higher smoking rates or increased healthcare surveillance in the HIV-infected population compared with uninfected populations.

The relative contribution of smoking to the increased risk of lung cancer associated with HIV infection remains a major question. A number of studies have shown a higher prevalence of smoking in HIV-infected patients compared with most of the general US population [9,11], although some cohorts have demonstrated similar smoking prevalence in HIV-infected and uninfected participants [12,13]. Several cohort studies reporting lung cancer incidence rates adjusted for smoking prevalence were variously affected by important limitations including lack of complete smoking data or use of estimated smoking rates only; small numbers of lung cancer cases; lack of an uninfected comparison group; or reporting from early in the combination antiretroviral therapy (cART) era when mortality due to AIDS events still dominated clinical outcomes [4,6,14,15].

Surveillance bias could also result in a higher rate of lung cancer detected in HIV-infected individuals, who generally tend to have more contact with the healthcare system than uninfected individuals [16]. Despite this, some studies have suggested that HIV-infected patients with lung cancer are more likely to present with advanced stage disease, suggesting cancer diagnosis may be delayed in this group [4,17]. Because no previous study has had sufficient lung cancer cases or an appropriate uninfected comparison group to adequately characterize the pattern of lung cancer stage at presentation in HIV-infected patients, the role of surveillance bias in assessing lung cancer incidence in these patients is unclear.

To overcome some of the limitations of previous studies, we used data from a large, national, cART era cohort to compare the incidence of lung cancer between HIV-infected patients and a demographically similar uninfected comparison group, adjusting for smoking and other lung cancer risk factors.

## Methods and materials

### Cohort

We used data from the Veterans Aging Cohort Study Virtual Cohort (VACS-VC), a large cohort assembled

from national Veterans Affairs Health Information System databases. The cohort included HIV-infected veterans enrolled in the Veterans Affairs Health System from fiscal year 1997–2008, identified utilizing data from several Veterans Affairs databases with a validated algorithm previously described in detail [18]. Cohort index dates for HIV-infected patients were assigned using the date associated with the earliest inpatient or outpatient HIV-related International Classification of Diseases (ICD-9) diagnostic code during this period. To assemble an uninfected comparison group, for each HIV-infected individual, we chose two race/ethnicity-matched, age-matched, sex-matched, and Veterans Affairs healthcare site-matched uninfected patients with an inpatient or outpatient encounter in the index year of the HIV-infected case.

To minimize the possibility of surveillance bias associated with entry into care, we began observation time 6 months after each individual's index date and excluded lung cancer cases that occurred in the 6 months after the index date. Each individual was then followed prospectively until the date of last Veterans Affairs follow-up, death, or cancer diagnosis. The analytic cohort included 37 294 HIV-infected patients and 75 750 uninfected patients who contributed observation time. The Institutional Review Boards of the Veterans Affairs Connecticut Healthcare System and Yale University School of Medicine approved this cohort study.

### Lung cancer identification

We identified lung cancer cases that occurred among cohort members by linking the VACS-VC with the Veterans Affairs Central Cancer Registry (VACCR). The VACCR is a national cancer registry aggregating data provided by local cancer registries at Veterans Affairs medical centers nationwide. The database utilizes International Classification of Diseases for Oncology codes for categorizing cases based on cancer topography and morphology [19]. We defined lung cancer as topography code C34 (bronchus and lung) in combination with behavior code three (malignant) and morphology codes 8002, 8010, 8012–3, 8020, 8022, 8032–3, 8041, 8042, 8044, 8045, 8046, 8070–3, 8076, 8082, 8140, 8240, 8246, 8249–50, 8253, 8255, 8260, 8310, 8480–1, 8490, 8550, 8560, and 8572, indicating carcinoma. We identified a total of 1359 lung cancer cases that occurred among members of VACS-VC. We excluded 243 of these cases, considered to be prevalent cases, because they occurred prior to or up to 6 months after the index date. Of the remaining cases, we excluded 45 (4%) that were not pathologically confirmed, leaving a total of 1071 incident lung cancer cases for analysis.

### Additional variables

From the Veterans Affairs administrative databases, we obtained data on age, sex, race, and ethnicity [18]. Baseline characteristics were identified during the period

from 12 months prior to the index date to 6 months after the index date. Chronic obstructive pulmonary disease (COPD), alcohol abuse, drug abuse, bacterial pneumonia, tuberculosis, and *Pneumocystis jirovecii* pneumonia (PCP) as well as other AIDS-defining diagnoses were established using relevant ICD-9 codes during the baseline period. Baseline diagnosis of hepatitis C virus (HCV) infection utilized both ICD-9 codes and HCV-related laboratory tests. Laboratory values and use of cART medications were obtained from Veterans Affairs laboratory results and pharmacy databases. Receipt of cART was defined as the presence of a multidrug antiretroviral regimen filled by the pharmacy for at least 2 months during the baseline window. Nadir CD4 cell count was determined using the lowest CD4 cell count after reviewing all available values for each HIV-infected patient during the observation period, excluding values identified in the 6-month period prior to cancer diagnosis.

We derived smoking prevalence from Veterans Affairs Health Factors database, a computerized clinical provider reminder and reporting system that periodically reminds clinicians to perform assessments of tobacco use and records the results of structured interviews. These assessments are performed at multiple patient encounters and, therefore, an aggregate variable was derived, based on the most frequently reported smoking behavior, as we have found that this methodology has better agreement with self-reported smoking status derived from patient-completed surveys than does the single *Health Factors* smoking prevalence reported closest to the index date. Using these data, patients were defined as current, former, or never smokers; these categories have been validated against self-report from two other Veterans Affairs datasets and found to have substantial agreement (weighted  $\kappa$ -statistics 0.68, 0.74) [20]. Smoking data from the *Health Factors* dataset were available for 80% of the HIV-infected cohort members and for 85% of those without HIV infection.

### Statistical analysis

All analyses were performed using SAS 9.2 (SAS Institute Inc., Cary, North Carolina, USA). We compared baseline characteristics in HIV-infected and uninfected members of the cohort using the Wilcoxon rank-sum test for continuous nonnormally distributed variables such as viral load and CD4 cell count, the *t*-test for normally distributed variables such as age, and the  $\chi^2$ -test for categorical variables such as tumor type and stage at diagnosis. We calculated incidence rates of lung cancer among HIV-infected and uninfected patients by dividing numbers of cases by person-years at risk. We calculated the incidence rate ratio (IRR) and 95% confidence interval (CI) for lung cancer comparing HIV-infected to uninfected patients using Poisson regression. We then determined the adjusted IRR using age, sex, race/ethnicity, smoking prevalence, and baseline diagnoses of bacterial pneumonia and COPD as covariates. The latter

two variables were included because they have been associated with lung cancer in prior studies [21–23]. Although alcohol and drug abuse were associated with HIV status, they did not contribute to the model and were removed from the final regression. To avoid bias from missing smoking data, missing values of the three-level smoking variable were imputed via multiple imputation [24]. An identical adjusted model was also run on the dataset excluding all individuals with missing smoking values (“complete case”) and provided a similar result to the imputed model; therefore, we only present the multiple imputation results.

Because residual confounding by smoking of the association between HIV infection and lung cancer risk has been a major concern in epidemiologic studies, we performed two analyses to assess whether our primary association of interest, HIV and lung cancer incidence, remained robust after accounting for smoking in different ways. First, we calculated smoking prevalence stratum-specific IRRs, adjusted for the other covariates (age, sex, race/ethnicity, and baseline diagnoses of pneumonia and COPD). We also performed a sensitivity analysis in which we substantially overestimated smoking prevalence in HIV-infected individuals in our adjusted complete-case regression model by recoding all HIV-infected former and never smokers as current smokers.

Finally, to determine whether smoking, our main covariate of interest, modified the relationship between HIV infection and lung cancer, we included interaction terms between HIV infection and smoking status in the adjusted model. In a similar manner, we tested for effect modification by COPD and age.

## Results

### Baseline characteristics

Our cohort included 37 294 HIV-infected and 75 750 uninfected Veterans who were followed for a median of 5.8 [interquartile range (IQR): 2.7–9.6] and 7.3 (IQR: 3.5–10.5) years, respectively ( $P < 0.001$ ). The cohort was primarily composed of male Veterans with a median age of 46 years (Table 1). The cohort was almost half non-Hispanic black and almost 40% non-Hispanic white. HIV-infected patients were more likely to be current smokers and less likely to be never smokers than uninfected patients ( $P < 0.001$ ). Baseline COPD prevalence did not differ by HIV status ( $P = 0.15$ ). Baseline drug abuse, alcohol abuse, HCV infection, and bacterial pneumonia were more prevalent in HIV-infected patients than in uninfected patients ( $P$ -values for all characteristics  $< 0.001$ ).

### Unadjusted incidence of lung cancer

Our analysis identified 457 cases of incident lung cancer among HIV-infected patients and 614 cases among

**Table 1. Baseline characteristics of cohort.**

Characteristic	HIV-infected (n = 37 294)		Uninfected (n = 75 750)		P-value
	N	%	N	%	
Age, years, median (range)	46 (20–92)		46 (20–103)		<0.001
Sex					
Female	879	2	1771	2	1.00
Male	36 415	98	73 979	98	
Race/ethnicity					
Non-Hispanic white	14 153	39	29 843	38	<0.001
Non-Hispanic black	18 037	48	35 616	48	
Hispanic	2778	7	5840	8	
Other	2326	6	4451	6	
Smoking status					
Current smoker	17 961	48	34 527	46	<0.001
Former smoker	4177	11	11 212	15	
Never smoked	7529	20	18 344	24	
Unknown	7627	20	11 667	15	
Drug abuse	7053	19	9531	13	<0.001
Alcohol abuse	6010	16	11 068	15	<0.001
Hepatitis C virus infection	12 887	35	11 040	15	<0.001
Chronic obstructive pulmonary disease	1523	4	2959	4	0.15
Bacterial pneumonia	2004	5	624	1	<0.001
Died during follow-up	10 880	29	9465	13	<0.001

uninfected patients during the observation period with incidence rates of 204 cases per 100 000 person-years among HIV-infected patients (95% CI: 167–249) and 119 cases per 100 000 person-years (95% CI: 110–129) in uninfected patients. This yielded an unadjusted IRR of 1.7 (95% CI: 1.5–2.0) for the association of HIV infection with incident lung cancer. Median age at lung cancer diagnosis was 57 years in HIV-infected patients compared with 59 years in HIV-uninfected patients ( $P < 0.001$ , data not otherwise shown).

### Risk factors for lung cancer in HIV-infected patients

Next, we compared the characteristics of HIV-infected patients who developed lung cancer with HIV-infected patients who did not develop lung cancer during the follow-up period (Table 2). HIV-infected patients who were diagnosed with lung cancer were older and were more likely to be current smokers and less likely to be never smokers than HIV-infected patients who did not develop lung cancer. HIV-infected lung cancer cases and noncases differed by race ( $P < 0.001$ ), with cases more likely to be white. Baseline CD4 cell count and median nadir CD4 cell count did not differ between HIV-infected patients with and without lung cancer, nor did use of cART. However, baseline median HIV RNA was lower in those diagnosed with lung cancer than in those without lung cancer ( $P = 0.01$ ). Baseline diagnoses of tuberculosis and PCP were not different between HIV-infected patients with and without lung cancer; however, HIV-infected patients who developed incident lung cancer were more likely to have had a baseline diagnosis of bacterial pneumonia ( $P = 0.01$ ) or COPD ( $P < 0.001$ ) than those who did not develop lung cancer.

### Adjusted incidence rate ratio for lung cancer

The adjusted IRR for lung cancer among all study individuals (HIV-infected compared with HIV uninfected), calculated by Poisson regression, demonstrated an independent association with HIV infection (IRR 1.7; 95% CI: 1.5–1.9; Table 3) after adjusting for age, sex, race/ethnicity, smoking, and baseline COPD and bacterial pneumonia. Increasing age was significantly associated with lung cancer incidence. Individuals of Hispanic ethnicity had a decreased risk of lung cancer compared with non-Hispanic whites (IRR 0.6; 95% CI: 0.4–0.8.) Current smokers and former smokers had a substantially greater risk of lung cancer compared with never smokers (current smokers IRR 6.3, 95% CI: 4.7–8.4; former smokers IRR 3.0, 95% CI: 2.2–4.1.) A COPD diagnosis was associated with increased lung cancer risk (IRR 1.9; 95% CI: 1.5–2.3) as was a diagnosis of bacterial pneumonia (IRR 1.5; 95% CI: 1.1–2.0.)

### Stratified analysis, sensitivity analysis, and interactions

To further confirm the independence of the association between HIV infection and lung cancer incidence, we calculated smoking prevalence stratum-specific IRRs, adjusted for the other covariates, and found similar IRRs for the association between HIV and lung cancer incidence in all smoking strata (Table 4). The IRR in each stratum was highly significant, except for the never smoker stratum, which was borderline significant. We also ran a sensitivity analysis with a model that significantly overestimated smoking prevalence in the HIV-infected patients by recoding all HIV-infected former and never smokers as current smokers; despite this overestimation, HIV infection maintained a

**Table 2. Baseline characteristics of HIV-infected patients by lung cancer diagnosis.**

Characteristic	HIV-infected		HIV-infected		P-value
	Lung cancer cases (n = 457)		No lung cancer (n = 36837)		
	N	%	N	%	
Age, years, median (range)	51 (34–83)		45 (20–92)		<0.001
Sex					
Male	448	98	35 967	98	0.6
Female	9	2	870	2	
Race					
Non-Hispanic white	216	47	13 937	38	<0.001
Non-Hispanic black	212	46	17 825	48	
Hispanic	24	5	2754	7	
Other	5	1	2321	6	
Smoking status					
Current smoker	262	57	17 699	48	<0.001
Former smoker	55	12	4122	11	
Never smoked	19	4	7510	20	
Unknown	121	26	7506	20	
Drug abuse	76	17	6977	19	0.2
Alcohol abuse	73	16	5937	16	0.9
Median baseline CD4 cell count (IQR)	286 (139–448)		282 (119–473)		0.6
Median nadir CD4 cell count (IQR)	222 (88–386)		229 (110–380)		0.5
Median baseline HIV RNA (IQR)	5124 (409–42 320)		10 078 (500–75 000)		0.01
Combination antiretroviral therapy	94	16	6576	16	0.08
Hepatitis C virus infection	170	37	12 717	33	0.9
Chronic obstructive pulmonary disease	51	11	1472	4	<0.001
Pulmonary infections					
PCP	15	3	1215	3	0.9
Tuberculosis	9	2	544	1	0.4
Bacterial pneumonia	38	8	1966	5	0.01
Other AIDS-defining illnesses					
Kaposi's sarcoma	3	0.7	298	0.8	0.9
Cytomegaloviral disease	2	0.4	285	0.8	0.6
HIV wasting	5	1	253	0.7	0.3
HIV dementia	5	1	253	0.7	0.2
Oral candidiasis	5	1	212	0.6	0.2
Cryptococcosis	4	0.9	267	0.7	0.6
Histoplasmosis	0	0	107	0.3	0.9
Herpes zoster	9	2	727	2	0.9
Toxoplasmosis	0	0	28	0.1	0.9
Died during follow-up	320	70	10 560	30	<0.001

IQR, interquartile range; PCP, *Pneumocystis jirovecii* pneumonia.

statistically significant independent association with lung cancer incidence (IRR 1.2; 95% CI:1.1–1.4.)

Finally, we found no significant interactions between HIV infection and current smoking ( $P=0.5$ ), former smoking ( $P=0.9$ ), COPD ( $P=0.3$ ), or age ( $P=0.6$ ).

### Tumor morphology and stage at diagnosis

Adenocarcinoma was the most common tumor morphology in both HIV-infected and uninfected lung cancer cases (Table 5). The distribution of tumor morphology did not differ in HIV-infected and uninfected patients. The majority of cancers were diagnosed at late stage in both HIV-infected and uninfected patients, with approximately 70% of cancers being either stage 3 or 4. The distribution of stage at diagnosis also did not differ in patients with and without HIV infection.

### Discussion

In our cART era cohort of more than 110 000 Veterans, we found that HIV-infected Veterans had a significantly higher incidence of lung cancer than uninfected Veterans, and that HIV infection was an independent risk factor for lung cancer after controlling for potential confounders including smoking. This is the largest cohort study with both HIV-infected and uninfected individuals and individual-level smoking data to evaluate lung cancer incidence. Our analysis includes 457 cases of incident lung cancer among HIV-infected patients, more than eight times that of any previous analysis with individual-level smoking data.

Risk of lung cancer among HIV-infected individuals has been more pronounced in most previous studies, with IRRs ranging from 2.2 to 4.7 when comparing

**Table 3. Adjusted incidence rate ratios for lung cancer in the full study cohort of HIV-infected and uninfected patients.**

Characteristic	IRR	P-value	95% CI
HIV infection	1.7	<0.001	1.5–1.9
Age <sup>a</sup>	2.3	<0.001	2.2–2.5
Female sex	0.8	0.5	0.5–1.5
Race/ethnicity			
Non-Hispanic white	–	–	–
Non-Hispanic black	1.0	0.4	0.8–1.1
Hispanic	0.6	<0.001	0.4–0.8
Other race	0.2	<0.001	0.1–0.4
Smoking exposure			
Never smoker	–	–	–
Former smoker	3.0	<0.001	2.2–4.1
Current smoker	6.3	<0.001	4.7–8.4
Chronic obstructive pulmonary disease	1.9	<0.001	1.5–2.3
Previous bacterial pneumonia	1.5	0.007	1.1–2.0

CI, confidence interval; IRR, incidence rate ratio.

<sup>a</sup>10-year increments.

HIV-infected with uninfected persons [4,6,9,10,25]. However, a recent study that compared HIV-infected and uninfected individuals enrolled in Kaiser Permanente observed a demographically-adjusted IRR of 1.8 and an IRR of 1.2 in an adjusted analysis including smoking [26]. Our findings are similar to those from the AIDS Linked to the Intravenous Experience (ALIVE) cohort, a single-site cohort of IDUs with HIV-infected and uninfected individuals. The most recent analysis from this cohort found a hazard ratio of 2.3 for the incidence of lung cancer in HIV-infected compared with uninfected individuals after adjustment for smoking [10]. This study was limited by the characteristics of the underlying cohort; the patients in the analysis were from both the pre-cART era and the current era, were almost exclusively African-Americans from a single site, and reported a very high baseline prevalence of smoking (94%). Our findings confirm the independent association between HIV infection and lung cancer incidence found in the ALIVE study and, similarly, we find that smoking conveys a much greater magnitude of risk for lung cancer than HIV infection.

We adjusted for confounding by smoking using a categorical assessment of smoking prevalence, but did not have data to adjust for smoking intensity and duration. However, we note that in a smaller cohort of HIV-

infected and uninfected Veterans in which we collected self-reported smoking histories, uninfected current and former smokers had significantly greater pack-year exposure than HIV-infected current and former smokers [13]. Also, the ALIVE cohort reported no difference in smoking intensity between their HIV-infected and uninfected participants [9]. In our stratified analysis, we noted a consistent magnitude of association of HIV infection with lung cancer risk across smoking strata, supporting an independent association. Additionally, in a sensitivity analysis where we assumed all HIV-infected former and never smokers were current smokers, HIV infection persisted as a significant risk factor for lung cancer. Nevertheless, we cannot completely rule out the presence of residual confounding by smoking.

Although certain previous studies have suggested that HIV-infected patients with lung cancer are more likely to present with advanced stage disease [4,17], the largest cART era series with morphology and stage data found similar distributions of morphologic type and stage at presentation in 75 HIV-infected lung cancer patients compared with historical controls [27]. Our study confirmed similar morphologic type and stage distributions between HIV-infected and uninfected patients, with the added strength of an internal comparison group. The stage distribution observed in our cohort was similar to that reported from population-based Surveillance Epidemiology and End Results data [28], with most cancers presenting at late stage. Thus, despite a greater frequency of healthcare encounters in the HIV-infected patients compared with the HIV-uninfected patients in our cohort [16], the increased incidence of lung cancer among the HIV-infected patients does not appear to be explained by more vigilant surveillance.

Other factors included in our adjusted analysis demonstrated an independent association with lung cancer risk, including age, COPD, and bacterial pneumonia. The association of age and lung cancer risk is well recognized; age did not modify the relationship between HIV infection and lung cancer risk, indicating that the association between HIV infection and lung cancer risk did not vary by age. COPD has been linked previously to an increased risk of lung cancer, independent of smoking [21]. Although baseline COPD was a risk factor for lung cancer in our analysis, we found no evidence that the

**Table 4. Adjusted lung cancer incidence rate ratios associated with HIV stratified by smoking exposure.**

Smoking strata	HIV-infected lung cancer cases	Uninfected lung cancer cases	IRR <sup>a</sup>	P-value	95% CI
Never smoker	19	30	1.6	0.08	0.9–3.0
Former smoker	55	91	1.7	<0.001	1.2–2.4
Current smoker	262	370	1.5	<0.001	1.3–1.7
Missing smoking data	121	114	2.1	<0.001	1.6–2.7

CI, confidence interval; IRR, incidence rate ratio.

<sup>a</sup>Adjusted for age, sex, race/ethnicity, chronic obstructive pulmonary disease, and previous pneumonia.

**Table 5. Lung cancer morphology and stage at diagnosis by HIV status.**

Characteristic	HIV-infected		Uninfected		P-value
	Lung cancer cases (n = 457)		Lung cancer cases (n = 614)		
	No.	%	No.	%	
<b>Morphology</b>					
Adenocarcinoma	164	36	218	36	0.22
Squamous cell carcinoma	136	30	168	28	
Non-small cell carcinoma, unspecified	71	16	95	16	
Small cell carcinoma	37	8	71	11	
Carcinoma, unspecified	27	5	30	4	
Large cell carcinoma	15	4	19	3	
Neuroendocrine carcinoma	4	1	11	2	
Sarcomatous carcinoma	3	1	2	0.3	
<b>Stage at diagnosis</b>					
Stage 1	85	19	109	18	0.7
Stage 2	28	6	40	7	
Stage 3	129	28	175	29	
Stage 4	183	40	265	42	
Unknown or unstageable	32	7	25	4	

association between HIV infection and lung cancer risk differed according to baseline COPD status. A recently published study from the AIDS-Cancer Match, a registry linkage study, demonstrated an increased risk of lung cancer in AIDS patients with prior recurrent episodes of bacterial pneumonia [23]. We found that HIV-infected patients who developed lung cancer were more likely to have a baseline bacterial pneumonia diagnosis, but that this relationship did not explain the excess risk of lung cancer noted in HIV-infected patients in our adjusted model.

Although our primary study goal was to compare lung cancer incidence in HIV-infected and uninfected patients, in univariate analyses we also compared HIV-infected patients who developed incident lung cancer with HIV-infected patients who did not develop lung cancer with respect to baseline CD4 cell count, nadir CD4 cell count, and baseline cART exposure, noting no differences. This was consistent with other cohort studies in HIV-infected patients [5,9,29]. However, a meta-analysis comparing cancer incidence in studies of HIV/AIDS patients and organ transplant recipients found similar risk increases for lung cancer in both groups, suggesting a causal role for immunosuppression [30]. Furthermore, in other cohorts, recent (as opposed to baseline or nadir) CD4 cell count has been found to be inversely related to lung cancer incidence [26,31,32]. Thus, for the purpose of understanding the relationship between immunodeficiency and lung cancer risk among HIV-infected patients, we plan to conduct additional more sophisticated analyses with time-updated modeling of CD4 cell count.

Our descriptive univariate analysis also revealed a lower median baseline HIV RNA level in HIV-infected patients who developed lung cancer compared with those who

did not. We speculate that a lower HIV RNA level at baseline may be a marker for greater likelihood of survival in our cohort and, therefore, represents greater time to develop lung cancer; however, it may also represent a spurious finding that requires further evaluation in multivariable models. Previous studies have consistently reported no association [6,9,31] or a positive association [26] between HIV RNA levels and lung cancer risk.

The strengths of this study include its large, multicenter design and national range. Importantly, the lung cancer cases were pathologically confirmed, and our HIV-infected and uninfected individuals were demographically similar and drawn from the same national sample. In addition, although predominantly male, our cohort was racially and ethnically diverse.

Our study had several limitations. Incident lung cancer cases were identified using a Veterans Affairs-based cancer registry and, therefore, cases diagnosed and treated outside of the Veterans Affairs system may not have been captured. However, previous data have suggested low rates of utilization of non-Veterans Affairs healthcare, among both HIV-infected and uninfected Veterans [33]. Another limitation, addressed by our multiple imputation analysis, was that smoking prevalence was unknown for 20% of HIV-infected Veterans and 15% of HIV-uninfected Veterans.

As HIV-infected patients are aging on effective cART, lung cancer may become an increasingly common and often fatal diagnosis. The significantly higher overall mortality rate among HIV-infected patients compared with uninfected patients in our cohort denotes a large competing risk for mortality among HIV-infected patients [34]. This suggests that as AIDS-related mortality

decreases with improved treatment, an even greater incidence rate of lung cancer may be noted, and our study may under-represent both the incidence and enhanced risk of lung cancer. Additional investigations are required to understand the mechanisms by which HIV infection may increase the risk for lung cancer.

### Conclusion

In our cohort of demographically similar HIV-infected and uninfected patients followed during the cART-era, HIV infection was an independent risk factor for lung cancer after controlling for major confounders including smoking and age. The fact that stage of cancer did not differ by HIV status suggests that this finding is not a result of surveillance bias.

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### Conflicts of interest

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The remaining authors report no conflicts of interest.

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