Published in final edited form as:
AIDS. 2012 May 15; 26(8): 1017–1025. doi:10.1097/QAD.0b013e328352d1ad.

HIV as an Independent Risk Factor for Incident Lung Cancer

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Keywords

Human Immunodeficiency Virus (HIV); lung cancer; incidence; smoking; immunosuppression; non-AIDS defining malignancy

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 to 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 to uninfected populations.

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Disclaimer: The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs.

Conflicts of Interest Disclosures
The remaining authors report no conflicts of interest.

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 to 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 anti-retroviral 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 (VA) Health Information System databases. The cohort included HIV infected Veterans enrolled in the VA Health System from fiscal year 1997–2008, identified utilizing data from several VA 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 subject, we chose two race/ethnicity-, age-, gender-, and VA 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 six months after each subject's index date and excluded lung cancer cases that occurred in the six months after the index date. Each subject was then followed prospectively until the date of last VA 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 VA 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 VA 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 3 (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 1,359 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 VA administrative databases, we obtained data on age, gender, 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 time 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 VA 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 two months during the baseline window. Nadir CD4 count was determined using the lowest CD4 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 VA Health Factors data, 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 VA 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.

Analysis

All analyses were performed using SAS 9.2 (SAS Institute, Cary NC). We compared baseline characteristics in HIV infected and uninfected members of the cohort using the Wilcoxon rank-sum test for continuous non-normally distributed variables such as viral load and CD4 count, the t-test for normally distributed variables such as age, and the chi-square 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, gender, 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(MI)[24]. An identical adjusted model was also run on the dataset excluding all subjects with missing smoking values ("complete case") and provided a similar result to the imputed model; therefore, we only present the MI 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, gender, 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 subjects 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 (inter-quartile 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 uninfected patients during the observation period with incidence rates of 204 cases per 100,000 person-years (p-yrs) among HIV infected patients (95% CI: 167–249) and 119 cases per 100,000 p-yrs (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 to 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 to 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 non-cases differed by race ($p<0.001$), with cases more likely to be white. Baseline CD4 count and median nadir CD4 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 IRR for Lung Cancer

The adjusted IRR for lung cancer among all study subjects (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, gender, race/ethnicity, smoking, and baseline COPD and bacterial pneumonia. Increasing age was significantly associated with lung cancer incidence. Subjects 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 to 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 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 subjects 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 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 ALIVE cohort, a single site cohort of injection drug users with HIV infected and uninfected subjects. 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 subjects 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 to 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 SEER 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 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 develop 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 patents, in univariate analyses we also compared HIV infected patients who developed incident lung cancer to HIV infected patients who did not develop lung cancer with respect to baseline CD4 cell count, nadir CD4 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 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 represent greater time to develop lung cancer; however, it may also represent a spurious finding that requires further evaluation in multivariate 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, multi-center design and national range. Importantly, the lung cancer cases were pathologically confirmed, and our HIV infected and uninfected subjects 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 VA-based cancer registry, and therefore cases diagnosed and treated outside of the VA system may not have been captured. However, previous data have suggested low rates of utilization of non-VA 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 to 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.

Acknowledgments

Funding

This study was supported by the National Center for Research Resources (KL2RR029885 to KS), National Institute on Alcohol and Alcohol Abuse (3U01 AA 13566), National Institute of Aging (K23 AG00826), Robert Wood Johnson Generalist Faculty Scholar Award, an Inter-agency Agreement between National Institute on Aging, National Institute of Mental Health and the Veterans Health Administration, and the Veterans Health Administration Office of Research and Development and Public Health Strategic Health Care Group (to ACJ), and National Heart, Lung, and Blood Institute (NIH/NHLBI R01 HL090342 to KC)

JPW reports receiving lecture honorarium from Novartis Pharmaceuticals, and a research grant from GlaxoSmithKline.

We are grateful to the Veterans Affairs Central Cancer Registry (VACCR) for linking the VACS Virtual Cohort with the VACCR database and providing us with a dataset containing the linked records. This study would not have been possible without the VACCR's generous assistance.

Abbreviations

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Syndrome
cART	Combination Anti-retroviral Therapy
COPD	Chronic Obstructive Pulmonary Disease
VACS	Veterans Aging Cohort Study
VACS-VC	Veterans Aging Cohort Study Virtual Cohort
VACCR	Veterans Affairs Central Cancer Registry

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Table 1

Baseline characteristics of cohort.

	HIV infected (n=37,294)		Uninfected (n=75,750)		
Characteristic	**No.**	**%**	**No.**	**%**	**p-value**
Age, years, median (range)	46 (20–92)		46 (20–103)		<0.001
Gender					
Female	879	2	1,771	2	1.00
Male	36,415	98	73,979	98	
Race					
Non-Hispanic white	14,153	39	29,843	38	<0.001
Non-Hispanic black	18,037	48	35,616	48	
Hispanic	2,778	7	5,840	8	
Other	2,326	6	4,451	6	
Smoking status					
Current smoker	17,961	48	34,527	46	<0.001
Former smoker	4,177	11	11,212	15	
Never smoked	7,529	20	18,344	24	
Unknown	7,627	20	11,667	15	
Drug abuse	7,053	19	9,531	13	<0.001
Alcohol abuse	6,010	16	11,068	15	<0.001
Hepatitis C virus infection	12,887	35	11,040	15	<0.001
Chronic obstructive pulmonary disease	1,523	4	2,959	4	0.15
Bacterial pneumonia	2,004	5	624	1	<0.001
Died during follow-up	10,880	29	9,465	13	<0.001

AIDS. Author manuscript; available in PMC 2013 February 24.

Table 2

Baseline characteristics of HIV infected patients, by lung cancer diagnosis.

	HIV infected Lung cancer cases (n=457)		HIV infected No lung cancer (n=36837)		
Characteristic	**No.**	**%**	**No.**	**%**	**p-value**
Age, years, median (range)	51 (34–83)		45	(20–92)	<0.001
Gender					
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	2,754	7	
Other	5	1	2,321	6	
Smoking status					
Current smoker	262	57	17,699	48	<0.001
Former smoker	55	12	4,122	11	
Never smoked	19	4	7,510	20	
Unknown	121	26	7,506	20	
Drug abuse	76	17	6,977	19	0.2
Alcohol abuse	73	16	5,937	16	0.9
Median baseline CD4 count (IQR)	286 (139–448)		282 (119–473)		0.6
Median nadir CD4 count (IQR)	222 (88–386)		229 (110–380)		0.5
Median baseline HIV RNA (IQR)	5124 (409–42,320)		10078 (500–75,000)		0.01
Combination anti-retroviral therapy	94	16	6,576	16	0.08
Hepatitis C virus infection	170	37	12,717	33	0.9
Chronic obstructive pulmonary disease	51	11	1,472	4	<0.001
Pulmonary infections					
PCP	15	3	1,215	3	0.9
Tuberculosis	9	2	544	1	0.4
Bacterial pneumonia	38	8	1,966	5	0.01
Other AIDS defining illnesses					
Kaposi’s sarcoma	3	0.7	298	0.8	0.9

	HIV infected Lung cancer cases (n=457)		HIV infected No lung cancer (n=36837)		
Characteristic	**No.**	**%**	**No.**	**%**	**p-value**
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

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 *	2.3	<0.001	2.2–2.5
Female Gender	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

* 10 year increments

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*	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

*adjusted for age, sex, race, COPD, and previous pneumonia

Table 5

Lung cancer morphology and stage at diagnosis by HIV status.

	HIV infected Lung cancer cases (n=457)		Uninfected Lung cancer cases (n=614)		
Characteristic	**No.**	**%**	**No.**	**%**	**p-value**
Morphology					
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	
Stage at diagnosis					
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	