HIV As a Risk Factor for Lung Cancer in Women: Data From the Women's Interagency HIV Study

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ABSTRACT

Purpose

Prior reports of an increased risk of lung cancer in HIV-infected individuals have not always included control groups, nor considered other risk factors such as tobacco exposure. We sought to determine the role of HIV infection and highly active antiretroviral therapy (HAART) on lung cancer incidence in 2,651 HIV-infected and 898 HIV-uninfected women from the Women's Interagency HIV Study (WIHS).

Methods

A prospective study of the incidence rates of lung cancer was conducted, with cases identified through medical records, death certificates, and state cancer registries. Standardized incidence ratios (SIRs) were calculated to compare lung cancer incidence among HIV-infected and uninfected WIHS participants, with population-based expectations using the Surveillance, Epidemiology, and End Results registry. Behavioral characteristics in the WIHS were compared to US women by age and race adjusting the population-based data from the National Health and Nutritional Examination Survey (NHANES) III.

Results

Incidence rates of lung cancer were similar among HIV-infected and uninfected WIHS women. Lung cancer SIRs were increased in both HIV-infected and -uninfected women compared with population expectations, but did not differ by HIV status. Among HIV-infected women, lung cancer incidence rates were similar in pre-HAART and HAART eras. All WIHS women with lung cancer were smokers; the risk of lung cancer increased with cumulative tobacco exposure. WIHS women were statistically more likely to smoke than US women studied in NHANES III.

Conclusion

HIV infection is strongly associated with smoking behaviors that increase lung cancer risk. The role of HIV itself remains to be clarified.

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INTRODUCTION

Highly active antiretroviral therapy (HAART) has been associated with a remarkable decline in the incidence of AIDS-defining cancers.¹⁻³ However, an increase in certain non-AIDS defining cancers, including lung cancer, has been reported.⁴⁻⁸ The number of HIV-infected persons with lung cancer is relatively small, and not all studies have confirmed an increase in risk.⁹⁻¹¹

Factors associated with development of lung cancer in HIV-infected persons have included history of cigarette smoking, lung disease,⁸ and prolonged duration of HIV infection. The actual role of profound HIV-related immunodeficiency remains unclear.^{6,8,11-13}

Given these uncertainties, we wished to ascertain the incidence of lung cancer among HIV-infected women enrolled in the Women's Interagency HIV Study (WIHS) in the pre-HAART versus HAART eras, comparing incidence data to that from a group of HIV-uninfected WIHS participants, all of whom were observed over prolonged periods, and in whom behavioral characteristics were carefully documented. We also examined risk factors and disease characteristics of lung cancer among HIV-infected versus uninfected participants.

METHODS

Study Cohort

WIHS is a cohort study of women with or at risk for HIV infection, observed at six sites (Bronx/Manhattan,

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NY; Brooklyn, NY; Metropolitan Washington, DC, and surrounds; Northern California; Southern California; and Chicago, IL).^{14,15} The cohort included 3,766 women enrolled during two recruitment waves: October 1994 to November 1995, and October 2001 to September 2002. HIV-infected and -uninfected women were recruited from similar sources and frequency matched on age, race/ethnicity, and risk for HIV acquisition. Semi-annual visits included interviewer-administered questionnaires, physical and gynecological examinations, and collection of biologic specimens. Study protocols were reviewed and approved by each institutional review board; informed consent was obtained from all participants.

The 3,678 women who gave additional written consent for cancer ascertainment through state registries were eligible. We excluded three women with lung cancer before enrollment, and another 126 women without known lung cancer, seen only at baseline. All analyses were conducted using the remaining 3,549 women (94%), and were based on data entered into the database by March 31, 2008; follow-up was censored on September 30, 2006, to allow for lags in reporting and confirmation of incident cancers.

Study Outcome

All incident lung cancers were confirmed through medical record reviews of self-reported lung cancers, and/or through matching to statewide cancer registries (most recently performed in 2008), and the national death index. Lung cancer pathology reports were reviewed.

Exposures and Potential Confounders

The primary independent variables included HIV serostatus, history of tobacco use, and HAART use. HIV serology was tested by enzyme-linked immunosorbent assay with Western blot confirmation. Smoking history was summarized at baseline using a categorical variable indicating never/former/current use; and, among current smokers, quantification of the total cumulative exposure in pack-years (total number of years smoking cigarettes times the average number of packs smoked/day). To account for selection by indication bias resulting from the administration of HAART to women with more advanced HIV, the population effectiveness of HAART at reducing lung cancer incidence was assessed by comparing the incidence rates during the pre-HAART (1994 to 1996) and HAART (1997 to 2006) eras. The onset of the HAART era was set at 1997, since $\geq 25\%$ of HIV-infected participants first reported HAART use at that time. We also evaluated age, sex, race, education, income, employment status, insurance coverage, history of alcohol consumption, body mass index (BMI), CD4 cell count, and HIV RNA levels.

External Comparison Groups

SEER. Surveillance, Epidemiology and End Results (SEER) is an ongoing population-based surveillance program, documenting cancer incidence and survival using selected US state cancer registries.¹⁶ We used age-, sex-, and race-specific cancer incidence data from SEER from 1994 to 2004 to estimate the number of lung cancers expected in WIHS. The SEER "site recode" number 22030 was used to identify lung cancer cases in SEER, including cancers with International Classification of Diseases O-2 site codes C34.0 to C34.9.

National Health and Nutrition Examination Survey III. The third National Health and Nutrition Examination Survey (NHANES III) used a complex multistage cluster sampling of the US civilian, noninstitutionalized population to develop a cohort to investigate risk factors to explain differences in health in the US population.¹⁷ A random sample was selected and interviews were conducted in three waves from 1988 to 1994. We used the NHANES III cohort to obtain population-based estimates of the prevalence of identified lung cancer risk factors.¹⁷⁻¹⁹ The 17,699 women included in NHANES III were used to generate the US population-based control group to which we compared the WIHS women on behavioral characteristics.

Statistical Analyses

Baseline characteristics in WIHS were quantified descriptively. Comparisons between HIV-infected and -uninfected women were performed using χ^2 tests of homogeneity and trend. Lung cancer incidence rates were estimated as the number of incident cancers divided by total number of person-years (PYs) follow-up. Statistical comparisons between HIV-infected and -uninfected women, and between the pre-HAART and HAART eras, assumed a Poisson distribution for lung cancer incidence rates. To compare the observed number

Table 1. Baseline Characteristics of the WIHS Participants at Study Entry by HIV Status (N = 3,549)

Characteristic	HIV Positive		HIV Negative		P
	No.	%	No.	%	
All	2,651	100.0	898	100.0	
Age group, years					
< 30	622	23.5	360	40.1	< .001*
30-39	1,265	47.7	340	37.9	
40-49	651	24.6	176	19.6	
50+	112	4.3	22	2.4	
Race/ethnicity					
Non-Hispanic Black	1,499	56.5	492	54.8	.37
Non-Hispanic White	396	14.9	126	14.0	
Latina/Hispanic	681	25.7	247	27.5	
Other	75	2.8	33	3.7	
Highest education level attained					
Did not graduate from HS	1,014	38.3	316	35.4	.12*
HS graduate	795	30.0	274	30.7	
Post-HS education	838	31.7	302	33.9	
Annual household income, \$					
Fewer than 6,000	698	27.1	271	31.4	.57*
6,000-11,999	862	33.5	236	27.3	
12,000-29,999	698	27.1	212	24.5	
30,000 or greater	315	12.2	145	16.8	
Currently employed	632	23.9	301	33.6	< .001
Medical insurance coverage	2,187	83.2	548	61.5	< .001
Alcohol consumption during past 12 months, drinks per week					
Does not drink alcohol	1,230	47.6	351	38.8	< .001*
Fewer than 3	787	30.4	267	30.3	
3 or more	569	22.0	263	29.9	
Among drinkers, No. of drinks/week					
Mean	7.9		8.9		
SD	19.1		18.3		
Median	1.5		2.5		
IQR	0.5-6.0		1.0-9.0		
Cigarette smoking history					
Never smoked	852	32.3	274	30.6	.001
Former smoker	429	16.3	107	12.0	
Current smoker	1,356	51.4	514	57.4	
Lifetime cigarette consumption among current smokers, pack-years					
Lower than 10	713	53.3	291	58.0	.07*
10-20	383	28.6	133	26.5	
Higher than 20	243	18.2	78	15.5	
Mean	13.0		11.6		
SD	19.7		15.7		
Median	9.0		7.5		
IQR	3.8-16.5		2.5-15.0		
Body mass index, kg/m ²					
Lower than 20.0	225	8.8	74	8.6	.04*
20.0-24.9	871	34.1	271	31.3	
25.0-29.9	758	29.7	247	28.5	
30.0 or higher	697	27.3	274	31.6	
Mean	27.3		28.2		
SD	6.8		7.3		
Median	25.9		26.5		
IQR	22.4-30.5		22.9-32.1		

Abbreviations: WIHS, Women's Interagency HIV Study; HS, high school; SD, standard deviation; IQR, interquartile range.

*Test of trend.

Table 2. Unadjusted Lung Cancer Incidence in the Women's Interagency HIV Study

Parameter	All	Pre-HAART Era:1994-1996	HAART Era:1997-2003	HAART Era v Pre-HAART Era	
				Rate Ratio	95% CI
All					
Observed No. with cancer	14	3	11		
PYs	25,000	4,059	20,941	0.71	0.19 to 3.97
IR per 100,000 PYs	56.0	73.9	52.5		
HIV positive					
Observed No. with cancer	12	2	10		
PYs	18,825	3,221	15,604	1.03	0.22 to 9.69
IR per 100,000 PYs	63.7	62.1	64.1		
HIV negative					
Observed No. with cancer	2	1	1		
PYs	6,175	838	5,337	0.16	0.002 to 12.3
IR per 100,000 PYs	32.4	119.3	18.7		
Rate ratio for HIV positive v HIV negative	1.97	0.52	3.42		
95% CI	0.44 to 18.1	0.03 to 30.7	0.49 to 148.4		

Abbreviations: HAART, highly active antiretroviral therapy; PY, person-years; IR, incidence rate.

of lung cancers in the WIHS to the expected number documented by SEER between January 1, 1994, and December 31, 2004, we computed standardized incidence ratios (SIRs)²⁰ and exact 95% CIs²¹ adjusted for age (5-year categories), sex, and race (African American, Latina/Hispanic, other white, and other). SIRs by HIV serostatus and calendar time were compared using SIR regression. Because of the small number of observed lung cancer cases, all incidence analyses were performed using exact statistical methods. Possible differences in behavioral or demographic characteristics between WIHS and US women were determined comparing baseline characteristics. Data from NHANES III women were directly adjusted to age and race distributions in WIHS, using Longenecker's approach.²² Statistical comparisons of cross-sectional data were performed using Wilcoxon rank-sum and χ^2 tests of homogeneity and trend. All analyses used SAS, version 9.1 (SAS Institute, Cary, NC) or StatXact 8.0 (Cytel Software Corporation, Cambridge, MA). *P* values lower than .05 indicated statistical significance.

RESULTS

WIHS Cohort

Median age at enrollment of all 3,549 WIHS participants was 34.9 years (interquartile range [IQR], 29.3 to 40.4), and was higher in HIV-infected women (35.6 v 32.4 years; *P* < .001; Table 1). The racial/ethnic composition of both groups was similar. At their baseline visit, HIV-infected women were less likely to be currently employed, or to drink alcohol, and were more likely to have medical insurance (including Medicaid) than the HIV-uninfected comparators. The HIV-infected women had lower baseline BMI. Two thirds of WIHS participants reported a history of smoking. While fewer HIV-infected than uninfected women were current smokers, the median lifetime cigarette consumption for current smokers was higher among HIV-infected women. The median lifetime cigarette consumption among all WIHS women who reported smoking at enrollment was 8.4 pack-years (IQR, 3.5 to 16.0).

Lung Cancer Incidence

With 25,000 PYs follow-up, and median follow-up for individual women of 5.8 years (IQR, 4.8 to 12.1), we observed 14 incident lung cancers, yielding an overall lung cancer incidence rate of 56.0 per

100,000 PYs (Table 2). The incidence rates did not differ by HIV status (exact *P* = .58). Further, incidence rates did not differ between pre-HAART and HAART eras in the cohort as a whole (exact *P* = .81) or in the HIV-infected women.

Unadjusted lung cancer incidence rates were significantly associated with older age (Table 3). Further, lung cancer incidence was highest among non-Hispanic blacks when compared with the combined nonblack groups (incidence rate ratio, 10.1; 95% CI, 1.5 to 431; Table 3). Black women were significantly more likely to be current smokers at baseline (59% v 45%; *P* < .001) but among current smokers, black women reported significantly lower pack-years compared to nonblack women (median, 7.5 v 10.0 PYs; *P* = .008).

Comparison of WIHS to the US Population

Fourteen incident lung cancers were observed in WIHS, while between four and five were expected based on population-based age and race-specific rates from SEER (Table 4). Overall, the SIR for lung cancer in WIHS was 3.0 (95% CI, 1.7 to 5.1). The excess lung cancer burden did not vary by HIV status (exact *P* = .85), nor by pre-HAART versus HAART eras (exact *P* = .96).

Because other recognized risk factors for lung cancer might explain the excess incidence rate in WIHS, we compared the WIHS cohort characteristics to those in the age- and race-adjusted US female population, using NHANES III data, reweighted to match the age and race distributions of WIHS. Our adjustment yielded identical age and race distributions in the two cohorts (data not shown). When compared with the NHANES III women, the WIHS participants had significantly (*P* < .05) less education, lower annual household incomes, were less likely to be employed, have medical insurance coverage, or have a BMI higher than 30. A higher percentage of WIHS participants had consumed alcohol during the past 12 months (54.4% v 37.5%). A higher percentage of WIHS participants (both HIV infected and uninfected) had history of smoking cigarettes (68.0% v 37.2%; *P* < .001). Among current smokers at enrollment in the two studies, the cumulative exposure (pack-years) was more than 50% higher in WIHS.

Table 3. Unadjusted Lung Cancer Incidence in WIHS by Age, Race, Smoking History, and HIV Status

Parameter	No. of Lung Cancers	PYs	IR/100,000 PYs
Age ($P < .0001$)			
Younger than 30	0	3,242	0
30-39	1	9,444	10.6
40-49	4	9,247	43.3
50 and older	9	3,067	293.4
Race ($P = .056$)			
Non-Hispanic Black	13	14,047	92.5
Non-Hispanic White	0	3,804	0
Latina	1	6,408	15.6
Other groups	0	741	0
Second race comparison ($P = .007$)			
Non-Hispanic Black	13	14,047	92.5
All others	1	10,953	9.1
Cigarette smoking history			
Overall ($P = .003$)			
Never	0	7,419	0
Former smoker	1	3,889	25.7
Current smoker	13	13,576	95.8
HIV negative ($P = .50$)			
Never	0	1,770	0
Former smoker	0	749	0
Current smoker	2	3,626	55.2
HIV positive ($P = .007$)			
Never	0	5,648	0
Former smoker	1	3,140	31.8
Current smoker	11	9,951	110.5
Lifetime cigarette consumption among women who reported being current cigarette smokers at enrollment, pack-years*			
Overall ($P = .002$)			
< 10	0	6,445	0
10-20	7	3,817	183.4
> 20	6	3,315	181.0
HIV negative ($P = .05$)			
< 10	0	1,841	0
10-20	0	977	0
> 20	2	807	247.8
HIV positive ($P = .005$)			
< 10	0	4,604	0
10-20	7	2,840	246.5
> 20	4	2,508	159.5

Abbreviations: WIHS, Women's Interagency HIV Study; PYs, person-years; IR, incidence rate.

*One incident lung cancer occurred in an HIV positive woman who had stopped smoking prior to being enrolled in the WIHS, and she was excluded from this analysis that was restricted to women who were current smokers at enrollment.

Table 4. Standardized Incidence Ratios for Lung Cancer Incidence in the Women's Interagency HIV Study Compared With the Surveillance, Epidemiology and End Results Program

Parameter	Observed Person-Years	No. of Lung Cancers		Standardized Incidence Ratio	95% CI
		Observed	Expected		
Overall	25,000	14	4.60	3.04	1.66 to 5.10
HIV positive	18,825	12	3.65	3.28	1.70 to 5.74
HIV negative	6,175	2	0.95	2.11	0.25 to 7.61
Pre-HAART era (1994-1996)					
	4,059	3	0.48	6.22	1.28 to 18.19
HIV positive	3,221	2	0.40	4.97	0.60 to 17.95
HIV negative	838	1	0.08	12.57	0.32 to 70.05
HAART era (1997-2006)					
	20,941	11	4.12	2.67	1.33 to 4.78
HIV positive	15,604	10	3.25	3.08	1.47 to 5.66
HIV negative	5,337	1	0.87	1.15	0.03 to 6.40

Abbreviation: HAART, highly active antiretroviral therapy.

significance (Table 3). When stratifying by pack-years, we also found a significant dose-response relationship with lung cancer incidence rates. Among HIV-uninfected women, lung cancers were only observed among women with at least 20 pack-years while the majority of lung cancers in HIV-infected women occurred in those with history of 10 to 20 pack-years of smoking.

The 14 WIHS participants with lung cancer had a median cumulative smoking exposure of 18.9 pack-years, significantly higher than the 9.7 pack-years among the women who smoked but did not develop lung cancer ($P = .002$). Pack-years of smoking did not differ by HIV status among lung cancer cases. There was no difference between age of onset of smoking for either HIV-infected (17.3 years) or HIV-uninfected current smokers (17.9 years), or for WIHS women with or without incident lung cancer.

History of previous injection drug use (IDU) was present in both HIV-uninfected women and three of the 12 HIV-infected women with lung cancer, while three additional HIV infected women reported current IDU. The incidence rate for lung cancer among those with current or prior history of IDU was 96.5/100,000 PYs, versus 36.1/100,000 PYs in those without IDU (incidence rate ratio, 2.67; 95% CI, 0.81 to 9.35), and adjustment for age and pack-years did not statistically alter this result.

Clinical Data Among the WIHS Women With Lung Cancer

The median age at lung cancer diagnosis in the 12 HIV infected women was 53.3 years (range, 36 to 64). All were non-Hispanic black, with a median of 15.5 pack-years smoking exposure (range, 10.0 to 96.3 pack-years). Median CD4 cells and plasma HIV-1 RNA levels at the WIHS visit before lung cancer diagnosis were 376/mm³ (range, 0 to 893/mm³) and 3,400 copies/mL (range, 550 to 310,000 copies/mL). Prior AIDS defining conditions were present in eight (67%). At the visit before diagnosis of lung cancer, two patients were taking HAART, three were on combination ART, and seven were taking no antiretroviral therapy. Pathologic types of lung cancer included adenocarcinoma, poorly differentiated nonsmall cell, and squamous cell carcinoma, all equally distributed. Advanced cancer (stage IIIB or IV) was diagnosed in seven of 14 (50%), while stage I or II was present in

Risk Factors for Lung Cancer

Among the characteristics that differed between the age- and race-adjusted WIHS participants and US female population from NHANES III, only smoking history and pack-years of smoking were significantly associated with lung cancer in WIHS. No lung cancers occurred among WIHS women who had never smoked, and a dose-response relationship between pack-years and lung cancer incidence rate was clearly observed among both HIV-infected and uninfected current smokers, though the latter group did not reach statistical

two; staging information was unavailable in five. Median survival from diagnosis of lung cancer was 14.1 months (range, 3.0 to 62 months) with one woman remaining alive, at 28 months.

The two HIV-uninfected WIHS women with incident lung cancer were 46 and 56 years of age, with 25.0 and 30.9 PYs smoking history. One was non-Hispanic black while the other was Latina. Survival was 1.6 and 8 months from diagnosis.

DISCUSSION

We found a substantially increased risk of lung cancer among both HIV-infected and at-risk uninfected women compared with population-based expectations. A possible explanation is the high rate of cigarette smoking in WIHS women, reported by approximately two thirds, including all women diagnosed with incident lung cancer. Several prior reports have also documented a strong history of tobacco exposure in their HIV-infected patients who developed lung cancer.^{6,8,9,11-13}

As previously noted,²³ we found that WIHS women were almost twice as likely to smoke as age- and race-matched women, studied as part of NHANES III.¹⁷⁻¹⁹ While multiple other behavioral and demographic differences between WIHS and NHANES III women were found, only smoking was significantly associated with incident lung cancer. Thus, when compared to population-based controls, any increase in the incidence of lung cancer among HIV-infected women could be explained by differences in history of tobacco exposure.

When comparing lung cancer incidence rates between HIV-infected women in the WIHS and the internal group of HIV-uninfected women, no differences were apparent. Of importance, all women with lung cancer had strong histories of tobacco exposure, thus serving to explain the equivalent increase in lung cancer among both HIV-infected and uninfected women, when compared with population-based expectations. Of note, both HIV-infected and -uninfected WIHS participants were statistically more likely to smoke than the NHANES III/US female population. Nonetheless, HIV-uninfected women with lung cancer had smoked for 25 and 30 PYs, while those infected with HIV had 10 to 20 PY smoking history. It is possible that HIV may accelerate the development of lung cancer.

Several studies have shown a significant increase in lung cancer among HIV-infected patients after the introduction of HAART.^{6,8,9} The remarkable prolongation in survival due to HAART may have allowed these individuals to live long enough to develop lung cancer. However, we found no difference in the incidence of lung cancer among HIV-infected women in the pre-HAART versus HAART eras. A recent study of 54,780 HIV-infected patients also failed to demonstrate an increase in lung cancer incidence in the HAART era,²⁴ suggesting that the excess risk of lung cancer is not related to use of antiretroviral therapy per se, but rather to other factors, such as pack-years of smoking, in an aging population.

A significant increase in the risk of death due to lung cancer was reported among HIV-infected IDUs,⁸ studied as part of the AIDS Link to the Intravenous Experience Study (ALIVE); 26 of 27 patients had history of smoking. After adjusting for smoking status and other variables, HIV infection was found to be independently associated with an increased risk of lung cancer death. Our data indicate that HIV, per se, was not a risk factor for initial development of lung cancer. While it is plausible that HIV-infected patients with lung

cancer may be more likely to succumb to the malignancy than their HIV-uninfected counterparts, still, this study, and that from ALIVE actually address different issues. It is also possible that lifestyle factors related to IDU may have increased the risk of pre-existing pulmonary disease, possibly predisposing to lung cancer. In this regard, the incidence rate for lung cancer among former or current IDUs in the WIHS was more than twice that of participants without history of IDU, although this difference was not statistically significant.

Similar to this study, locally extensive or metastatic lung cancer has been reported at diagnosis in both pre-HAART¹² and HAART eras,²⁵ despite improvements in immunity associated with HAART. Delays in initial diagnosis of lung cancer among HIV-infected persons may explain the disseminated nature of disease.²⁵ Alternatively, factors related to HIV itself, or to the abnormal immunologic milieu associated with HIV may be operative.

Several studies have reported that adenocarcinomas occur more commonly than expected in HIV-infected individuals,^{4,12,26-29} while others have not.^{6,13,30} Our data demonstrate an equivalent distribution of pathologic types. Brock and colleagues²⁵ noted a change in the pathologic spectrum of lung cancer among 92 HIV-infected patients, when comparing pre-HAART and HAART eras, with 48% of all cancers diagnosed as adenocarcinoma in both time periods, while squamous cell carcinoma increased from 10% to 21%.

The WIHS study followed a large cohort prospectively for up to 12 years, and all cancer diagnoses were confirmed. However, details of treatment or response were not available. Furthermore, despite our large database of more than 3,500 women and 25,000 PYs of follow-up, the small number of incident lung cancers limited the statistical power. Nonetheless, a prospective comparison between HIV-infected women, and HIV-uninfected women with similar lifestyles was possible, augmenting the study design. Further, the careful documentation of tobacco exposure, and the ability to compare our data with behavioral data from age- and race-matched US women (NHANES III) allowed evaluation of the potential role of cigarette smoking as a cause for the increase in lung cancer among WIHS women.

We have demonstrated that WIHS participants, whether HIV-infected or at-risk but uninfected, have a significantly increased risk of lung cancer when compared with the rates expected in the general population, while no difference in lung cancer rates among HIV-infected versus uninfected women was seen. Of importance, both HIV-infected and -uninfected WIHS participants were significantly more likely to have smoked than the NHANES III/US female population. All WIHS women with lung cancer had history of smoking, and the risk of cancer increased with increasing smoking exposure. The development of lung cancer among HIV-infected women appears very strongly correlated with tobacco exposure. As such, the development and implementation of smoking cessation programs aimed at HIV-infected persons will be of increasing importance. The precise role of HIV infection, per se, in terms of the development or progression of lung cancer awaits further clarification.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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