Increased Risk of Radiographic Emphysema in HIV Is Associated With Elevated Soluble CD14 and Nadir CD4

Engi F. Attia, MD; Kathleen M. Akgün, MD; Cherry Wongtrakool, MD; Matthew Bidwell Goetz, MD;
Maria C. Rodriguez-Barradas, MD; David Rimland, MD; Sheldon T. Brown, MD; Guy W. Soo Hoo, MD, FCCP;
Joon Kim, MD; Patty J. Lee, MD; Lynn M. Schnapp, MD; Amir Sharafkhaneh, MD, PhD, FCCP;
Amy C. Justice, MD, PhD; and Kristina Crothers, MD

BACKGROUND: The association between HIV and emphysema remains incompletely understood. We sought to determine whether HIV is an independent risk factor for emphysema severity and whether markers of HIV severity and systemic biomarkers of inflammation (IL-6), altered coagulation (D-dimer), and immune activation (soluble CD14) are associated with emphysema.

METHODS: We performed a cross-sectional analysis of 114 participants with HIV infection and 89 participants without HIV infection in the Examinations of HIV-Associated Lung Emphysema (EXHALE) study. Participants underwent chest CT imaging with blinded semi-quantitative interpretation of emphysema severity, distribution, and type. We generated multivariable logistic regression models to determine the risk of HIV for radiographic emphysema, defined as > 10% lung involvement. Similar analyses examined associations of plasma biomarkers, HIV RNA, and recent and nadir CD4 cell counts with emphysema among participants with HIV infection.

RESULTS: Participants with HIV infection had greater radiographic emphysema severity with increased lower lung zone and diffuse involvement. HIV was associated with significantly increased risk for > 10% emphysema in analyses adjusted for cigarette smoking pack-years (OR, 2.24; 95% CI, 1.12-4.48). In multivariable analyses restricted to participants with HIV infection, nadir CD4 < 200 cells/μL (OR, 2.98; 95% CI, 1.14-7.81), and high soluble CD14 level (upper 25th percentile) (OR, 2.55; 95% CI, 1.04-6.22) were associated with increased risk of > 10% emphysema. IL-6 and D-dimer were not associated with emphysema in HIV.

CONCLUSIONS: HIV is an independent risk factor for radiographic emphysema. Emphysema severity was significantly greater among participants with HIV infection. Among those with HIV, nadir CD4 < 200 cells/μL and elevated soluble CD14 level were associated with emphysema, highlighting potential mechanisms linking HIV with emphysema.

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A leading global cause of morbidity and mortality, COPD is common among individuals with HIV infection.[1,2] In the general population, emphysema-predominant COPD is associated with impaired health status[3,4] and increased risk of pulmonary malignancy,[5] cardiovascular disease, chronic kidney disease, cerebrovascular disease,[6] osteoporosis,[7] and mortality.[8] Cigarette smoking[9] and α_1-antitrypsin deficiency[10] are well-established risk factors for emphysema, with growing evidence linking inflammation and aging to emphysema.[11,12]

An increased risk for bullous emphysema in individuals with HIV infection was reported early in the HIV/AIDS epidemic,[1] yet the link between HIV and emphysema remains incompletely understood. Sequelae of *Pneumocystis* pneumonia, other opportunistic infections, and AIDS-related wasting play a role in destructive lung changes in advanced HIV.[13] Early in the antiretroviral therapy (ART) era, however, increased emphysema was described among individuals with

HIV infection who had no prior opportunistic lung infections.[14]

HIV infection is associated with chronic inflammation, endothelial dysfunction, altered coagulation, and immune activation, which are tightly linked to comorbidities and early mortality in HIV, even among those receiving effective ART[15-20]; whether emphysema is associated with biomarkers reflective of these factors is unknown. Therefore, in the current study, we determined whether HIV infection is a risk factor for radiographic emphysema in the current ART era, characterizing emphysema semiquantitatively on chest CT scans and determining whether differences in the severity, distribution, and type of emphysema by HIV exist. We explored whether radiographic emphysema is associated with markers of HIV severity and systemic biomarkers of inflammation (IL-6), altered coagulation (D-dimer), and immune activation (soluble CD14 [sCD14]).

Materials and Methods

Study Design and Cohort

We performed a cross-sectional analysis of data from 114 participants with HIV infection and 89 participants without HIV infection enrolled from 2009 to 2012 in the Examinations of HIV-Associated Lung Emphysema (EXHALE) study, a substudy of the Veterans Aging Cohort Study.[21] Enrollment was stratified by HIV and smoking status. All participants signed written informed consent. This study was approved by all appropriate institutional review boards. Methodologic details regarding the cohort, data collection, statistical analyses, and institutional review board approval are provided in e-Appendix 1.

Chest CT Scan Examination and Interpretation

Noncontrast CT images were acquired using a standard protocol at enrollment. Supine scans from the lung apices to bases were obtained at end inspiration with multidetector CT scanners calibrated across centers on a standardized lung phantom as part of the research protocol.

Emphysema severity, distribution, and type were determined by a board-certified radiologist trained in thoracic imaging and blinded to clinical history. Emphysema severity was characterized semiquantitatively by visual inspection (Table 1).[5,7] Global severity scores of 0 (no emphysema)

through 5 (> 75% emphysema) were assigned to indicate emphysema severity throughout the entirety of the lungs.

Craniocaudal distribution was assessed by presence of emphysema in upper, middle, and lower lung zones, comprising the upper lobes, middle lobe and lingula, and lower lobes, respectively. Diffuse emphysema was defined as the presence of emphysema in each zone. Emphysema type was categorized as centrilobular, paraseptal, panlobular, and bullous.

Other Data Collection

Plasma biomarker levels, including IL-6 (pg/mL), D-dimer (μg/mL), and sCD14 (ng/mL), were measured at enrollment (Laboratory for Clinical Biochemistry Research, University of Vermont).[22] HIV RNA levels (copies/mL) and CD4 cell counts (cells/μL) within 12 months were obtained from US Veterans Affairs Healthcare System (VA) laboratory data and ART use from VA pharmacy data[21]; nadir CD4 cell counts reflected lowest available VA laboratory values. Standardized questionnaires assessed exposures, including cigarette, marijuana, injection drug, and unhealthy alcohol use.[23] Smoking status was classified as never (< 100 lifetime cigarettes), former (quit > 1 year ago), and current (smoked within the past year). Pack-years were based on average number of cigarettes per day and years smoked. COPD was defined by a postbronchodilator FEV_1/FVC ratio less than the lower limit of normal;

(Drs Rodriguez-Barradas and Sharafkhaneh), Baylor College of Medicine, Houston, TX; Department of Medicine (Drs Brown and Kim), James J. Peters Veterans Affairs Medical Center, Bronx, NY; and Department of Medicine (Dr Brown), Icahn School of Medicine at Mt Sinai, New York, NY.

Dr Schnapp is currently at the Medical University of South Carolina (Charleston, SC).

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CORRESPONDENCE TO: Kristina Crothers, MD, Harborview Medical Center, 325 Ninth Ave, Campus Box 359762, Seattle, WA 98104; e-mail: crothk@uw.edu

TABLE 1] Emphysema Severity Scores

Score	Emphysematous Involvement, %	Severity of Emphysema
0	0	None/negligible
1	1-10	Trace
2	11-25	Mild
3	26-50	Moderate
4	51-75	Severe
5	>75	Very severe

reference populations for spirometry and diffusing capacity of the lung for carbon monoxide (Dlco) were based on National Health and Nutrition Examination Survey III data.[24,25] Pneumonia history was based on *International Classification of Diseases, Ninth Revision* codes from VA administrative databases.

Statistical Analysis

Baseline characteristics were compared by HIV status and emphysema using Wilcoxon rank sum tests for continuous and χ^2 or Fisher exact tests for categorical variables. $P < .05$ was considered statistically significant. Because the median global severity score was 1 (corresponding to 1%-10% emphysema), we used a threshold of >1 (ie, $>10\%$ emphysema) in logistic regression models as the outcome. Elevated biomarker levels were defined as the upper 25th percentile.

To determine the independent risk of emphysema associated with HIV infection and biomarkers, we generated multivariable logistic regression models that included all participants. Pack-years of cigarette smoking are strongly associated with emphysema and demonstrate a dose-response relationship.[14,26,27] In addition, pack-years is a continuous variable, providing more information on smoking history than smoking status alone. As such, pack-years was selected a priori as an important variable to include in all adjusted models. Age was not included due to covariance with pack-years. Biomarkers were retained in multivariable models if they remained statistically significant. Because we could not determine the temporal relationship between emphysema and pneumonia in the data and because pneumonia may be in the causal pathway by which HIV increases emphysema risk, we did not include pneumonia history in the main multivariable model. Nonetheless, to explore this potential association, a model including HIV, pack-years, and pneumonia history was generated. Similar analyses restricted to participants with HIV infection examined the association of HIV severity and biomarkers with emphysema.

Results

Baseline Characteristics

Most participants were black men, and those with HIV infection were slightly older (Table 2). Although there was no significant difference in cigarette smoking, marijuana and injection drug use, prior bacterial pneumonia and TB were significantly more common in participants with HIV infection. Most with HIV infection were receiving ART, had undetectable HIV RNA, and had recent CD4 ≥ 200 cells/μL, although more than one-half had nadir CD4 < 200 cells/μL. sCD14 and IL-6 levels were significantly higher among participants with HIV infection ($P < .001$). Participants with HIV infection had a significantly lower BMI, although few were underweight.

Emphysema Severity, Distribution, and Type

Participants with HIV infection were more likely to have a greater percentage of lung involved with emphysema based on global severity scores (Table 2). Thirty-three percent of those with HIV infection had $>10\%$ emphysema compared with only 17% of those without HIV infection ($P = .01$). Among participants with HIV infection, 41% with nadir CD4 < 200 cells/μL had $>10\%$ emphysema compared with 22% with higher nadir CD4 counts ($P = .04$) (e-Table 1).

Emphysema distribution also differed by HIV (Fig 1). Nearly all participants with emphysema had upper lung zone involvement, but because those with HIV infection also had more lower lung involvement ($P = .05$), they were significantly more likely to have diffuse emphysema compared with those without HIV infection (28% vs 16%, $P = .04$).

However, emphysema type, including bullous emphysema, was similar in participants with and without HIV infection (Table 2). Many had more than one emphysema type. Centrilobular emphysema was the predominant type followed by paraseptal emphysema.

Risk Factors for $>10\%$ Emphysema

When comparing all participants, significantly more individuals with $>10\%$ emphysema had HIV (Table 3). Those with $>10\%$ emphysema were also significantly more likely to have spirometrically diagnosed COPD, lower Dlco, lower BMI, heavier smoking, marijuana use, and prior bacterial pneumonia. Median sCD14 and D-dimer levels were higher in this group (Fig 2).

In bivariate analyses, HIV infection was associated with a significantly increased risk for $>10\%$ radiographic emphysema (unadjusted OR, 2.47; 95% CI, 1.25-4.87) (Table 4). Age, pack-years, ever smoking, prior pneumonia, marijuana use, and elevated sCD14 and D-dimer levels were also important risk factors for $>10\%$ emphysema. Injection drug use was not significantly associated with $>10\%$ emphysema in the sample.

In a logistic regression model adjusting for pack-years, the association with HIV infection remained significant (OR, 2.24; 95% CI, 1.12-4.48) (Table 4). A nested multivariable model additionally adjusting for high sCD14 level markedly attenuated the association between HIV

TABLE 2] Baseline Characteristics of Participants by HIV Status

Characteristic	HIV Infection (n = 114)	No HIV Infection (n = 89)	P Value
Age, y	55 (50-58)	52 (48-57)	.07
Male sex	97	85	.002
Race/ethnicity			.1
Black	67	69	
White	18	24	
Hispanic/other	15	7	
BMI, kg/m^2	25.8 (23.4-29.3)	28.5 (25.9-33.8)	<.001
Cigarette smoking history			.7
Never smoker	16	20	
Former smoker	22	24	
Pack-y	18 (13-43)	18 (1-39)	.5
Current smoker	62	56	
Pack-y	27 (12-41)	22 (11-34)	.3
Other substance abuse, ever			
Marijuana (smoked)	85	72	.04
Alcohol	24	21	.6
Injection drug use	32	10	<.001
COPD (FEV$_1$/FVC<LLN)	20	12	.1
D$_{LCO}$, % predicted	62.5 (53.6-74.4)	67.0 (59.1-76.9)	.07
FEV$_1$, % predicted	91.4 (81.9-103.2)	91.6 (79.2-102.6)	1.0
Prior pneumonia			
Bacterial, community acquired	20	3	<.001
Pneumocystis jirovecii	1	0	1.0
Mycobacterium tuberculosis	8	1	.03
Emphysema severity			.01
None/negligible (0%)	40	46	
Trace (1%-10%)	27	37	
Mild (11%-25%)	19	8	
Moderate (26%-50%)	5	8	
Severe (51%-75%)	9	1	
Very severe (>75%)	0	0	
Emphysema type[a]			
Centrilobular	57	48	.2
Paraseptal	33	30	.7
Panlobular	3	0	.3
Bullous	19	15	.4
Serum biomarkers			
IL-6, pg/mL	1.81 (1.28-3.43)	1.23 (0.94-2.07)	<.001
sCD14, ng/mL	1,671 (1,472-2,128)	1,386 (1,171-1,569)	<.001
D-dimer, μg/mL	0.26 (0.17-0.47)	0.28 (0.17-0.42)	1.0
HIV-related variables[b]			
CD4 count, cells/μL	438 (310-605)	...	...
CD4<200 cells/μL	14	...	...

(Continued)

Characteristic	HIV Infection (n = 114)	No HIV Infection (n = 89)	*P* Value
Nadir CD4 < 200 cells/μL	61	...	...
Detectable HIV RNA ($\geq$ 400 copies/mL)	20	...	...
ART use	93	...	...

Data are presented as median (interquartile range) or %. ART = antiretroviral therapy; D$_{LCO}$ = diffusing capacity of the lung for carbon monoxide; LLN = lower limit of normal; sCD14 = soluble CD14.
[a]Percents do not add to 100 because participants may have had emphysema in more than one lung zone and more than one type of emphysema.
[b]Analyses for HIV-related variables are restricted to participants with HIV infection.

infection and > 10% emphysema (OR, 1.55; 95% CI, 0.71-3.41). In a separate model adjusting for pneumonia history, the association of HIV with emphysema was also attenuated (OR, 1.84; 95% CI, 0.90-3.76).

HIV Severity, Biomarkers, and Emphysema

Among participants with HIV infection, those with > 10% emphysema were significantly more likely to have nadir CD4 < 200 cells/μL than those with ≤ 10% emphysema (74% vs 54%, *P* = .04) (e-Table 2). Significantly more participants with HIV infection and > 10% emphysema had spirometrically diagnosed COPD and were current smokers. When restricted to participants with HIV infection, sCD14 levels were higher among participants with > 10% emphysema than in those with ≤ 10% emphysema (1,883 vs 1,648, *P* = .05); there were no significant differences in IL-6 or D-dimer values by emphysema.

In bivariate analyses restricted to participants with HIV infection, low nadir CD4 cell count was associated with increased odds of > 10% emphysema (OR, 2.39; 95% CI, 1.02-5.62) (Table 5). Age, pack-years, and prior pneumonia were also associated with > 10% emphysema. High sCD14 level was a significant risk factor for radiographic emphysema among participants with HIV but not among those without HIV (data not shown). We did not detect an association of ART use and HIV RNA with emphysema. In a multivariable model restricted to participants with HIV infection adjusting for pack-years, both nadir CD4 < 200 cells/μL (OR, 2.98; 95% CI, 1.14-7.81) and high sCD14 (OR, 2.55; 95% CI, 1.04-6.22) retained a significant association with risk of > 10% emphysema.

Discussion

We found that radiographic emphysema severity was overall significantly greater in individuals with HIV
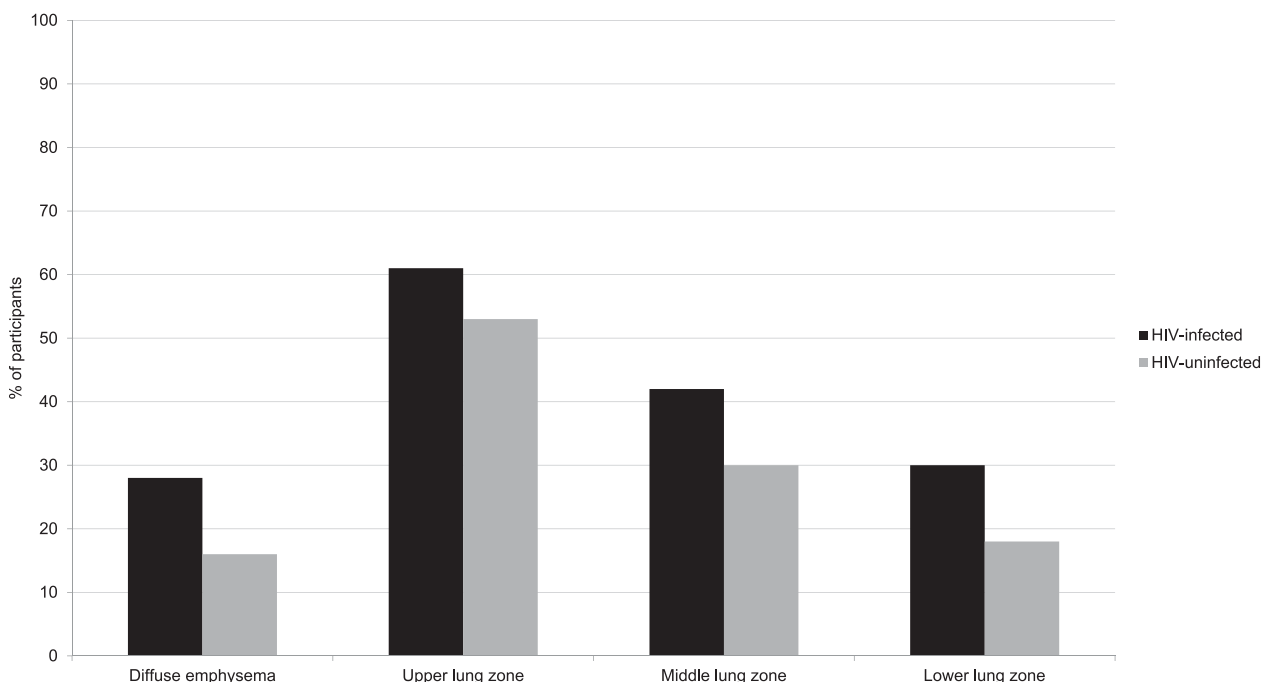

Figure 1 – *Emphysema distribution by HIV status.*

TABLE 3] Baseline Characteristics of Participants by > 10% Emphysema

Characteristic	> 10% Emphysema (n = 53)	≤ 10% Emphysema (n = 150)	P Value
Age, y	57 (52-61)	52 (47-57)	<.001
Male sex	96	91	.2
Race/ethnicity			.3
Black	70	68	
White	25	19	
Hispanic/other	6	13	
BMI, kg/m^2	24.2 (21.2-27.8)	28.1 (25.2-32.3)	<.001
Cigarette smoking history			.001
Never smoker	2	23	
Former smoker	22	23	
Pack-y	41 (15-50)	17 (3-33)	.07
Current smoker	76	54	
Pack-y	36 (18-48)	21 (10 -34)	.002
Other substance abuse, ever			
Marijuana (smoked)	92	75	.007
Alcohol	22	23	.8
Injection drug use	24	22	.7
COPD (FEV$_1$/FVC < LLN)	36	9	<.001
D$_{LCO}$, % predicted	56.9 (47.4-64.2)	68.4 (58.6-78.3)	<.001
FEV$_1$, % predicted	88.4 (75.6-98.3)	92.1 (82-104.7)	.06
Prior pneumonia			
Bacterial, community acquired	22	9	.02
Pneumocystis jirovecii	0	1	1.0
Mycobacterium tuberculosis	9	3	.1
HIV infection	72	51	.008
HIV-related variables (n = 114)[a]			
CD4 count, cells/μL	384 (304-591)	447 (323-633)	.3
CD4 < 200 cells/μL	21	11	.2
Nadir CD4 < 200 cells/μL	74	54	.04
Detectable HIV RNA (≥ 400 copies/mL)	24	18	.6
ART use	92	93	1.0

Data are presented as median (interquartile range) or %. See Table 1 legend for expansion of abbreviations.
[a]Analyses for HIV-related variables are restricted to participants with HIV infection.

infection than in those without HIV infection and that HIV infection was an independent risk factor for emphysema defined by > 10% emphysema on chest CT scan using semiquantitative methods. In the present cohort, the upper lung zone was involved in nearly all participants with emphysema. Interestingly, we found that individuals with HIV infection may be more likely to have diffuse emphysema involving the lower lung in addition to the upper and middle lung zones, with results approaching statistical significance.

We also explored the association between systemic biomarkers and emphysema, focusing on markers known to be elevated in HIV infection, reflecting general inflammation (IL-6), immune activation (sCD14), and altered coagulation (D-dimer). Consistent with prior studies, participants with HIV infection compared with those without had significantly higher median IL-6 and sCD14 values despite the majority receiving ART.[15,22] We found that elevated sCD14 level was strongly associated with radiographic emphysema in participants with HIV infection. Nested models
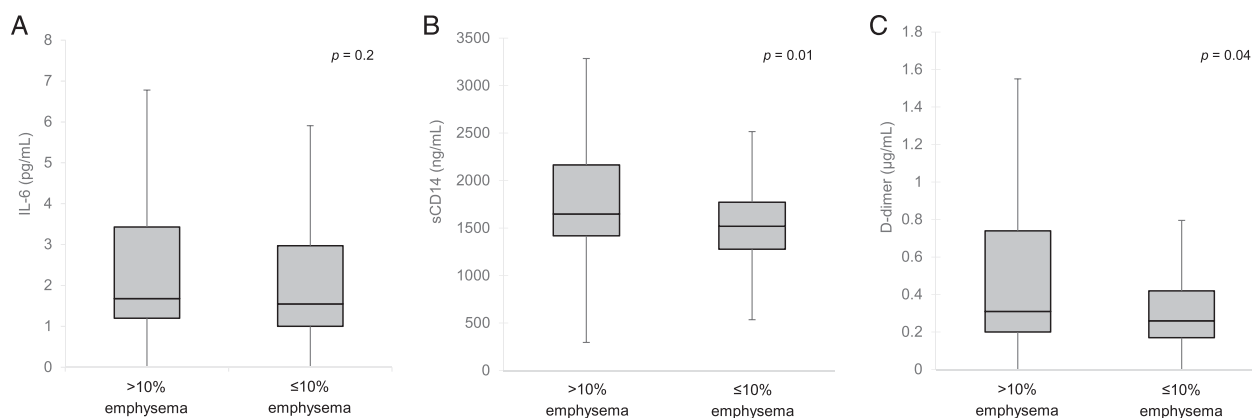
Figure 2 – *Serum biomarkers by radiographic emphysema. A, IL-6 (pg/mL). B, sCD14 (ng/mL). C, D-dimer (μg/mL). sCD14 = soluble CD14.*

adjusting for HIV infection and sCD14 level demonstrated substantial attenuation of the association between HIV and emphysema.

The findings suggest that elevated sCD14 is a marker of radiographic emphysema in HIV infection and support

the hypothesis that increased risk of emphysema in HIV may be mediated by immune activation. Mucosal epithelial leakiness may be an underlying cause of persistent immune activation during suppressive ART, allowing microbial products, including lipopolysaccharide, to leak into the systemic circulation and activate

TABLE 4] ORs for Associations of Baseline Characteristics and > 10% Emphysema on CT Scan Among Participants With and Without HIV Infection

	OR (95% CI) for > 10% Emphysema			
Characteristic	Unadjusted	Adjusted for Pack-y	Adjusted for Pack-y and History of Pneumonia	Adjusted for Pack-y and High sCD14[a]
HIV infection	2.47 (1.25-4.87)[b]	2.24 (1.12-4.48)[b]	1.84 (0.90-3.76)	1.55 (0.71-3.41)
sCD14, upper 25th percentile	2.63 (1.32-5.21)[b]	...	...	2.30 (1.02-5.19)[b]
IL-6, upper 25th percentile	1.41 (0.70-2.84)	...	...	...
D-dimer, upper 25th percentile	2.14 (1.07-4.25)[b]	...	...	...
History of pneumonia	2.85 (1.34-6.07)[b]	...	2.26 (0.96-5.34)	...
Age[c]	2.54 (1.59-4.06)[d]	...	...	...
Male sex	2.63 (0.57-12.0)	...	...	...
Race				
Black	Reference	...	...	...
White	1.28 (0.60-2.74)	...	...	...
Hispanic/other	0.41 (0.12-1.48)	...	...	...
Cigarette smoking, pack-y[e]	1.34 (1.13-1.59)[b]	1.36 (1.13-1.63)[b]	1.35 (1.13-1.62)[b]	1.39 (1.15-1.68)[b]
Smoking status				
Never smoker	Reference	...	...	...
Former smoker	11.3 (1.38-93.0)[b]	...	...	...
Current smoker	16.4 (2.16-125)[b]	...	...	...
Smoking marijuana	3.75 (1.26-11.2)[b]	...	...	...
Injection drug use	1.13 (0.53-2.43)	...	...	...

See Table 1 legend for expansion of abbreviation.
[a]The final multivariable model includes 197 participants (97% of the analytic cohort).
[b]$P < .05$.
[c]10-y increments.
[d]$P < .001$.
[e]Increments of 10 pack-y.

TABLE 5] ORs for Associations of Baseline Characteristics and >10% Emphysema on CT Among Participants With HIV Infection

Characteristic	OR (95% CI) for >10% Emphysema	
	Unadjusted	Adjusted[a]
Nadir CD4 < 200 cells/μL	2.39 (1.02-5.62)[b]	2.98 (1.14-7.81)[b]
sCD14, upper 25th percentile	3.95 (1.20-12.9)[b]	2.55 (1.04-6.22)[b]
IL-6, upper 25th percentile	0.77 (0.32-1.85)	...
D-dimer, upper 25th percentile	2.02 (0.86-4.76)	...
ART use	0.82 (0.18-3.66)	...
Recent CD4 < 200 cells/μL	2.27 (0.77-6.64)	...
Detectable HIV RNA	1.37 (0.53-3.56)	...
History of pneumonia	2.45 (1.04-5.74)[b]	...
Age[c]	2.19 (1.23-3.92)[b]	...
Male sex	1.00 (0.09-11.5)	...
Race		
Black	Reference	...
White	1.52 (0.56-4.13)	...
Hispanic/other	0.25 (0.05-1.17)	...
Cigarette smoking (pack-y)[d]	1.24 (1.02-1.51)[b]	1.29 (1.05-1.59)[b]
Smoking status		
Never smoker	Reference	...
Former smoker	7.00 (0.77-63.8)	...
Current smoker	10.9 (1.36-87.8)[b]	...
Smoking marijuana	4.13 (0.88-19.3)	...
Injection drug use	1.11 (0.47-2.60)	...

See Table 1 legend for expansion of abbreviations.
[a]This final multivariable model includes 111 participants (97% of the analytic cohort with HIV infection).
[b]$P < .05$.
[c]10-y increments.
[d]Increments of 10 pack-y.

the immune system.[28-31] Elevated sCD14 levels may reflect greater immune activation as a result of mucosal bacterial translocation despite ART.[16,20,32] High sCD14 is associated with increased mortality[20] and neurocognitive impairment[33] among individuals with HIV infection. Elevated sCD14 levels have also been identified in BAL fluid of smokers in the general population[34] and in patients with ARDS,[35] supporting a potential link with lung disease. When stratified by HIV, we found that sCD14 was strongly associated with radiographic emphysema in participants with HIV infection but not in those without HIV infection, further suggesting that monocyte activation related to microbial translocation may play a unique role in emphysema in HIV. Given the present sample size, however, we cannot definitively rule out a similar association among individuals without HIV infection.

In addition, we demonstrated that among individuals with HIV infection, nadir CD4 < 200 cells/μL is inde-

pendently associated with >10% emphysema. Nadir CD4 cell count reflects past HIV-related immunosuppression and predicts immune recovery.[36] Low nadir CD4 counts may induce incompletely reversible defects in immune function[37] and correlates with cardiovascular[38] and chronic kidney[39] diseases. Low nadir CD4 is also a marker for increased likelihood of prior opportunistic infections. In the present population, 23% of participants with HIV infection who had nadir CD4 < 200 cells/μL continued to have CD4 < 200 cells/μL at EXHALE enrollment despite most receiving ART with undetectable HIV RNA. Whether low nadir CD4 cell count is a risk factor for emphysema because of greater immune dysfunction, prior pulmonary infections, or other unmeasured confounders is unclear from this cross-sectional study.

Taken together, the present findings point to intriguing differences that may contribute to emphysema in

individuals with HIV infection. First, these data suggest that sCD14 is an important marker of radiographic emphysema in individuals with HIV infection and support the hypothesis that microbial translocation and monocyte activation may be involved in emphysema pathogenesis in HIV. Whether this is mediated by HIV severity remains unknown.[32]

Second, the increased lower lung and, therefore, diffuse emphysema in individuals with HIV infection points to potential vascular-related pathways consistent with the finding that systemic levels of sCD14 are associated with emphysema severity. Because blood flow tends to be greater in basal and dependent lung segments,[40] endothelial dysfunction in the setting of chronic HIV-related immune activation may lead to greater lower lung involvement and diffuse emphysema. Interestingly, this distribution shares features of α_1-antitrypsin deficiency. Low α_1-antitrypsin levels have been associated with HIV infection and elevated plasma sCD14 levels.[41,42]

To assess emphysema severity, we used a validated, semiquantitative approach.[5,7,43] Consistent with other studies, CT scans were scored by a single radiologist.[5,7,43] Studies have reported low interobserver variability for emphysema assessment.[44-46] Although we did not include purely quantitative assessments, other studies suggested a strong correlation between density mask and visual assessment of emphysema.[43,47] Compared with purely quantitative analysis, visual assessment provides important structural information.[48]

We used the median emphysema severity value (corresponding to > 10% involvement) in logistic regression models because the sample size limited utility of statistical methods such as ordinal and multinomial regression. Semiquantitative cut points (> 10% and < 10% emphysema) have been used to differentiate normal and mildly diseased lungs from those with clinically important emphysema.[3,14,49-51] Other studies suggested that any degree of emphysema is associated with worse patient outcomes, including increased incidence of lung cancer,[7] low bone mineral density,[9] and decreased glomerular filtration rate[43]; risk for these outcomes further increases with greater emphysema severity. The clinical significance of varying emphysema thresholds requires further investigation.

Emphysema progression may be linked to latent or subclinical pulmonary infections.[52] We found that prior pneumonia was associated with radiographic emphysema in bivariate analyses. In a multivariable model, pneumonia history attenuated the association of HIV with emphysema, although to a lesser degree than elevated sCD14 level. However, evaluation of the impact of pneumonia on emphysema development and progression is limited in this cross-sectional analysis because we do not know whether emphysema was already established at the time of prior pneumonia or whether pneumonia occurred before and contributed to emphysema development. Further evaluation requires longitudinal studies.

This study has several other limitations. The sample size is relatively small and limits conclusions regarding when significant associations were detected and when they were not; validation within other cohorts is required. Participants were predominantly male veterans, although the cohort was racially diverse and from multiple US sites.[21] Although participants with and without HIV infection were similar in terms of demographics and smoking history and we adjusted for pack-years, residual confounding remains possible. Nonetheless, the results are consistent with work in a larger cohort demonstrating an independent decrease in DLco among men with HIV infection.[53] The present findings suggest that decreased DLco in HIV may be due to greater emphysema severity. Finally, abstracted nadir CD4 cell count may not reflect a participant's true nadir. In the present cohort, however, 61% of participants with HIV infection had nadir CD4 < 200 cells/μL, consistent with a prior observation that 51% of patients establishing HIV care at VA medical centers had CD4 < 200 cells/μL.[54]

In conclusion, we found that HIV infection is an independent risk factor for emphysema in the current ART era. Radiographic emphysema severity was overall significantly greater among individuals with HIV infection. The association of HIV with emphysema appears mediated by elevated sCD14 levels, suggesting an important role for immune activation in emphysema pathogenesis in HIV. Additionally, among those with HIV, nadir CD4 < 200 cells/μL and elevated sCD14 level were associated with radiographic emphysema. The trend toward increased lower lung zone and diffuse emphysema in individuals with HIV infection further suggests that vascular-related mechanisms may be important. Additional studies are needed to investigate mechanisms leading to emphysema and the impact of varying degrees of radiographic emphysema on patient outcomes.

Acknowledgments

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