HHS Public Access

Author manuscript

J Acquir Immune Defic Syndr. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

J Acquir Immune Defic Syndr. 2017 January 01; 74(1): e23–e29. doi:10.1097/QAI.0000000000001133.

The differential impact of emphysema on respiratory symptoms and six-minute walk distance in HIV infection

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Abstract

Background—Emphysema is more prevalent in HIV-infected (HIV+) patients independent of smoking behavior. Nonetheless, health effects of emphysema in this population are poorly understood. We determined whether emphysema is associated with a greater burden of pulmonary symptoms and a lower six-minute walk distance (6MWD) in HIV+ compared to HIV-uninfected (HIV−) subjects.

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Notation of prior abstract publication/presentation: None

Conflicts of interest: Dr. Pipavath reports receiving support from Boehringer Ingelheim as a consultant and expert advisor. Dr. Wongtrakool discloses support from the Department of Veterans Affairs Biomedical Laboratory Research and Development Program, as well as support from Astra-Zeneca as a co-investigator on an industry-sponsored clinical study. Dr. Goetz reports receiving support from the National Institutes of Health during the conduct of this study. Drs. Triplette, Attia, Akgün, Campo, Rodriguez-Barradas, Kim, Soo Hoo, Brown and Crothers, as well as Ms. Shahrir, report no conflicts of interest.

Other contributors: The authors thanks the Veterans who participated in EXHALE and the coordinators who made the study possible. This material is the result of work supported with the resources and the use of facilities at the Veterans Affairs Connecticut Healthcare System, West Haven, CT; Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX; Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA; the Atlanta Veterans Affairs Medical Center, Decatur, GA; and the James J. Peters Veterans Affairs Medical Center, Bronx, NY. We must disclaim that the views expressed in this article are those of the authors and do not necessary reflect the position or policy of the Department of Veterans Affairs.

Methods—We performed a cross-sectional analysis of 170 HIV+ and 153 HIV− subjects in the Examinations of HIV Associated Lung Emphysema (EXHALE) cohort study. Subjects completed a self-assessment of respiratory symptoms, pulmonary function testing, and 6MWD testing as well as a CT scan to determine emphysema severity. We used regression models to determine the association of emphysema with respiratory symptoms and 6MWD in HIV+ subjects and compared this to HIV− subjects.

Results—Models stratified by HIV status demonstrated an association between >10% radiographic emphysema and chronic cough and/or phlegm and 6MWD in HIV+ subjects. These associations persisted among the subset without airflow obstruction: those with emphysema had 4.2 (95% CI 1.3, 14) times the odds of chronic cough and/or phlegm and walked 60m (95% CI 26, 93) less distance than those without emphysema. There was no association between >10% emphysema and symptoms or 6MWD in HIV− subjects.

Conclusions—In our cohort, >10% radiographic emphysema was associated with chronic cough and phlegm and lower 6MWD in HIV+ but not HIV− subjects. These findings were robust even amongst HIV+ subjects with milder forms of emphysema and those without airflow obstruction, highlighting the clinical impact of emphysema in these patients.

Keywords

COPD; Emphysema; HIV; 6-minute walk distance

Introduction

With wide availability of effective antiretroviral therapy (ART), an increasing percentage of HIV-infected (HIV+) patients are surviving to older ages.[1-3] This has been accompanied by an epidemiologic transition in pulmonary disease, characterized by fewer infectious complications but an increasing burden of chronic disease including chronic obstructive pulmonary disease (COPD).[4-7] A high prevalence of tobacco use – between 40-70% [8-10]– is a major factor accounting for the increase in COPD in this group.

However, emphysema is more prevalent and develops at younger ages in HIV+ patients compared to their HIV-uninfected (HIV−) counterparts, even after controlling for differences in smoking behavior.[11-14] The reasons for this remain unclear, but may be related to chronic inflammation that persists despite viremia suppression with ART and relative immunosuppression. [12, 15] Radiographic emphysema can be reflected by the significantly lower diffusion capacity (DLCO) seen in HIV, but there is also a higher burden of respiratory symptoms in HIV+ individuals independent of impairment in pulmonary function when compared to HIV− individuals that is unexplained. [16-21] The impact of emphysema on pulmonary symptoms and functional limitations is largely unexplored in HIV. We hypothesize that emphysema may reflect increased HIV-related inflammatory response, and may, at least partially, account for an increased burden of respiratory symptoms and functional impairment in HIV+ patients.

Therefore, the goals of this study were to understand the clinical impact of emphysema in HIV+ subjects by determining if emphysema is associated with respiratory symptoms and

six-minute walk distance (6MWD) in both HIV+ and HIV− subjects, and to assess different impacts of emphysema in these populations. Our hypothesis was that a higher degree of symptoms and lower 6MWD would be associated with emphysema in both groups, but that the impact of emphysema would be more prominent in those with HIV.

Materials and Methods

Study Design and Population

We performed a cross-sectional analysis of 170 HIV+ and 153 HIV− subjects enrolled in the Examinations of HIV Associated Lung Emphysema (EXHALE) study, a pulmonary substudy of the Veterans Aging Cohort Study (VACS). [20] At the time of the EXHALE study, VACS included a consented cohort of approximately 3500 HIV+ and 3500 age-, race-, sex, and site-of-care matched HIV− Veterans at eight Veterans Affairs (VA) Medical Centers (VAMC) in the US. The EXHALE study enrolled VACS subjects between 2009 and 2012 at four of these VAMC (Atlanta, Bronx, Houston and Los Angeles) to partake in a longitudinal pulmonary substudy. Potential HIV+ and HIV− subjects were identified from VACS participants, who were enrolled during outpatient visits to the General Medicine and Infectious Diseases outpatient clinics. Most of the EXHALE subjects were also recruited and enrolled during clinic visits although some were approached via telephone. Enrollment was stratified by HIV and current vs. non-current smoking status in order to achieve a target sample size of 360 subjects with a similar proportion of current smokers in those with and without HIV infection, mirroring the 50% prevalence of current smoking in HIV+ VACS participants. Exclusion criteria included a history of chronic lung diseases other than COPD or asthma and an acute respiratory infection within the previous month. All subjects provided written informed consent and the study protocol was approved by each center's institutional review board. 385 subjects consented to enroll in EXHALE, and 366 subjects completed any baseline testing. Of these subjects, 24 were found to be ineligible, revoked consent or did not complete other baseline testing. Of the remaining 342 subjects, 323 (94%) completed a baseline chest CT scan that was read by a research radiologist to semi-quantitatively define emphysema, and these subjects form the analytic cohort for the analyses.

Determination of Emphysema

Non-contrast chest CT images were acquired using a standard protocol. All images were obtained at full inspiration in the supine position using multidetector CT scanners calibrated across centers. A single board-certified thoracic radiologist (S.P.) interpreted the scans blinded to the clinical history and HIV status. Emphysema severity was characterized on a semi-quantitative scale. [22, 23] Global severity scores of 0 (no emphysema) through 5 (>75% emphysema) were assigned to each scan. We dichotomized this variable at the median value as trace or no emphysema (≤10% emphysema) or mild or greater emphysema (>10% emphysema) for our main analyses, similar to our prior study using EXHALE data. [24]

Other data collection

Demographic information for subjects was obtained from VA administrative databases. Subjects completed a standard questionnaire at EXHALE enrollment assessing history of

pulmonary disease, smoking, and other exposures using previously published instruments. [5] Smoking was consistently defined and pack-years were calculated based on number of cigarettes smoked per day on average and years smoked. The outcome of chronic cough and/or phlegm was a combination of two previously published questions on respiratory symptoms in the baseline survey. [25] Shortness of breath was quantified using the modified Medical Research Council dyspnea score, a validated scale (1-5) of breathlessness related to activity, and dichotomized to represent any limitation related to dyspnea (those who responded with at least a Grade 2 response: "Short of breath when hurrying on level ground or when walking up a slight hill"). [26, 27] Those who were unable to ambulate were excluded from this measure.

Pre- and post-bronchodilator spirometry and DLCO (corrected for hemoglobin) measurements were obtained on each subject. All spirometry and DLCO measurements were obtained in the clinical pulmonary function laboratories affiliated with each VAMC and were reviewed to ensure that they met American Thoracic Society (ATS) standards; we calculated %-predicted values using reference populations from National Health and Nutrition Examination Survey (NHANES) III data,[28,29] with additional adjustments for racial or ethnic categories not represented in NHANES III, per the current literature (e.g. Asian, n=1, Native Hawaiian or Pacific Islander, n=1, American Indian, n=1).[30-32] 6MWD testing was performed on each subject while breathing ambient air in accordance with ATS guidelines. [33] Laboratory values from within 12 months were obtained from VA laboratory records. ART use was obtained from VA pharmacy data. [20] Other comorbid diseases were based on International Classification of Diseases 9 codes. The VACS Index, a composite risk stratification score, was calculated for each subject, when data were available (missing in n=26). The VACS Index is calculated using age and several routine tests: CD4 cell count, HIV RNA, creatinine, hemoglobin, hepatitis C serostatus and the FIB-4 score for liver function. It is calculated for HIV− subjects assuming normal CD4 cell count and no detectable HIV RNA. The VACS Index correlates with biomarkers of inflammation, and is predictive of hospitalization and mortality. [34, 35] The questionnaire, CT scan, pulmonary function and 6MWD testing, and lab assessment were all completed within a short period after enrollment considered baseline (median time between enrollment and CT scan being 13 [IQR 2-66] days).

Statistical Analysis

We stratified characteristics of subjects by HIV status and severity of emphysema (>10% or ≤10% involvement). We used Wilcoxon rank sum testing for continuous variables and χ^2 testing for categorical variables. We then created a logistic regression model to confirm that HIV status was associated with emphysema independent of smoking and other confounders (including demographics, co-morbid diseases [including chronic heart disease, anemia, hypertension and diabetes], cigarette smoking as pack-years smoked and inhalational and injection drug use).

To determine the independent association between radiographic emphysema with respiratory symptoms, specifically shortness of breath as well as chronic cough and/or phlegm production, we used multiple logistic regression. We determined the independent association

between emphysema and 6MWD using multiple linear regression to estimate difference in 6MWD, with minimal clinically important differences (MCID) in 6MWD being estimated at between 25-35 meters.[36-38] We generated similar models restricted to subjects without airflow obstruction (where airflow obstruction was defined as a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio <0.7), and extended the threshold to 0.75 to determine if near-obstruction was important. Finally, we incorporated all subjects into regression models to determine the association between emphysema and a) shortness of breath, b) cough and/or phlegm and c) 6MWD, and tested multiplicative interaction terms between emphysema and HIV status.

All these models were adjusted for variables selected *a priori* as possible confounders in the relationship between emphysema and symptoms or functional status and included: demographics, body mass index (BMI), co-morbid diseases (chronic heart disease, anemia, hypertension, diabetes), cigarette pack-years, CD4 cell count (if HIV+), and history of injection or inhalational drug use. Those with missing data for these variables were excluded from the models. No models were missing input from more than 10% of eligible subjects.

We conducted sensitivity analyses to assess the impact of the severity and distribution of emphysema by: 1) using the range of emphysema severity categories (scores 0-5) as a predictor in models for each of our outcomes, as well as evaluating the trend of our outcomes over increasing severity of emphysema using Cuzick's non-parametric test of trend; 2) excluding those with emphysema severity >50% to assess whether outliers were driving results; and 3) stratifying by distribution of emphysema (lobar vs. diffuse). We also determined whether the association between emphysema and our outcomes were independent of pulmonary function values that can reflect severity of lung disease (FEV1 %-predicted and DLCO %-predicted).

All results were considered significant at $p<0.05$. Analyses were run using Stata version 14.0 (StataCorp LP, College Station, Texas).

Results

Baseline characteristics

We initially compared subjects by HIV status (**Table 1**). HIV+ subjects were more likely to be male, had lower BMI, and greater history of pulmonary infections and injection drug use. Age, race or ethnic group, and prevalence of several chronic diseases were similar between groups. Smoking status was similar as enrollment was stratified on this variable. Spirometry values were similar, but DLCO was lower in the HIV+ subjects. HIV+ subjects were more likely to report chronic cough and/or phlegm, but the groups had a similar proportion with reported exertional shortness of breath. 6MWD was also similar by HIV status.

Despite similar rates of airflow obstruction, emphysema (of >10% severity) was present in 31% of HIV+ subjects and 16% of subjects without HIV (p=0.003). In unadjusted regression, those with HIV had 2.3 (95% confidence interval [CI] 1.3-3.9) times the odds of >10% emphysema. In multivariable regression adjusted for smoking and other confounders, those with HIV had 2.1 (95% CI 1.1-3.9) times the odds of >10% emphysema. Of note,

other independent predictors of emphysema in this model included age, pack-years of smoking, inhalational and injection drug use.

Grouping HIV+ and HIV− subjects together, we compared those with >10% emphysema to those with ≤10% emphysema (referred to as “with emphysema” and “without emphysema,” respectively) and found several differences (**Table 2**). Those with emphysema were older, had lower BMI and had more extensive pack-year smoking histories than those without emphysema. Those with emphysema also had higher VACS Index scores. Subjects with emphysema had greater prevalence of airflow obstruction compared to those without emphysema (45% vs. 11%; p<0.001) as well as lower FEV1 and DLCO. Those with emphysema were more likely to report cough and/or phlegm but did not have increased exertional shortness of breath. Surprisingly, in the entire cohort, 6MWD was similar between those with emphysema and those without (423m vs. 426m).

Emphysema associations by HIV status

In adjusted models stratified by HIV status, we found that HIV+ subjects with emphysema had 35m (95% CI 6.6, 64) lower 6MWD than those without emphysema (**Table 3**). HIV+ subjects with emphysema also had 2.6 (95% CI 1.0, 6.7) times the odds of chronic cough and/or phlegm compared to those without emphysema. Emphysema was not significantly associated with exertional shortness of breath. Restricting our analysis to subjects without obstruction, among the HIV+ subjects there remained a significant relationship between emphysema and chronic cough and/or phlegm, and with 6MWD (**Table 4**). In adjusted analysis, those with emphysema had 4.2 (95% CI 1.3, 14) times the odds of chronic cough and/or phlegm and walked 60m (95% CI 26, 93) less distance than those without emphysema. Further restricting to the subset with an FEV1/FVC >0.75 did not alter the significance of these results. There was no association seen between emphysema and pulmonary symptoms or 6MWD in the entire group of HIV− subjects (**Table 3**) or the subset without airflow obstruction (**Table 4**). Of note, higher VACS Index score was also associated with >10% emphysema in the HIV+ subjects (median score 34 vs. 28; p=0.04) but no association was seen in the HIV− subjects.

We incorporated all subjects into models for each outcome with interaction terms between HIV status and emphysema. We found the interaction terms in the models for chronic cough and/or phlegm (p=0.03) and 6MWD (p= 0.03) were significant. Using these models to compare by HIV status among those with emphysema, after adjustment, HIV+ subjects with emphysema had 3.8 (95% CI 1.1, 13) times the odds of cough and/or phlegm compared with HIV− subjects with emphysema. HIV+ subjects with emphysema had a 6MWD that was 44m (95% CI 1.9, 85) lower than HIV− subjects with emphysema.

Sensitivity analyses

To determine whether our outcomes (6MWD, increased cough and/or phlegm and exertional shortness of breath) were related to progressive severity of emphysema, we created multivariable models incorporating the emphysema severity score (0-5) as an ordinal predictor variable, otherwise including the other covariates as in the models above. Among the HIV+ subjects, in these multivariable models, each step-wise increase in emphysema

severity was associated with 9.5m (−1.4, 20) lower 6MWD, 1.4 (0.99-2.1) times the odds of exertional shortness of breath, and 1.4 (0.96-1.9) times the odds of cough and phlegm. Using Cuzick's test of trend, there was a significant trend towards lower 6MWD (p=0.04), increased prevalence of exertional shortness of breath (p=0.01) and increased chronic cough and/or phlegm (p=0.01) with increasing severity of emphysema in the HIV+. There were no similar associations or significant trends in the HIV− subjects. We also conducted analysis excluding subjects with >50% emphysema (n=13) to test the association of symptoms and 6MWD among subjects with only mild to moderate radiographic emphysema, and we found similar results to our primary analysis that were again only present for the HIV+ subjects. We also examined differences in the distribution of emphysema by HIV status and these did not account for the observed associations (data not otherwise shown).

Finally, to determine if the radiographic findings of emphysema were associated with the outcomes of cough and/or phlegm and 6MWD independent of the pulmonary function measures reflective of the severity of obstructive lung disease and emphysema (FEV1 %-predicted and DLCO %-predicted), we incorporated these values into our models. In these models, the effect size of the relationship between >10% emphysema and cough and/or phlegm in HIV+ subjects was similar to our main model but was no longer significant: those with emphysema had 2.7 (95% CI 0.94-7.5) times the odds of cough and/or phlegm. Emphysema maintained a similar and significant association with 6MWD in HIV+ subjects: those with emphysema walked 32m (95% CI 2.6-62) less distance. Of note, declining FEV1 had an independent association with outcomes in these models; however, there was no relationship between DLCO and outcomes.

Discussion

Previous studies have shown that respiratory symptoms are more common in HIV+ compared to HIV− patients, and that respiratory symptoms and lower FEV1 are differentially associated with lower 6MWD in HIV+ compared to HIV− patients. [18, 19, 21] In this study, we used the EXHALE cohort of 170 HIV+ and 153 HIV− subjects to determine whether underlying emphysema might account for these differences and to assess the clinical implications of emphysema in those with HIV.

In HIV+ subjects, we found that >10% radiographic emphysema was associated with increased symptoms of chronic cough and/or phlegm as well as decreased 6MWD. There was a lack of association between emphysema and exertional shortness of breath despite the objective functional limitation. Importantly, we found that emphysema continued to be associated with chronic cough and/or phlegm as well as lower 6MWD in the subset of HIV+ subjects without overt airflow obstruction. In the HIV− subjects, there were no associations between >10% radiographic emphysema and the symptoms we assessed or 6MWD.

The extent of the differential association between emphysema and symptoms and functional limitation by HIV status was somewhat surprising. In a cohort with increased severity of radiographic findings, emphysema would likely be associated with respiratory symptoms and lower 6MWD regardless of HIV status. However, in our cohort of subjects with relatively mild disease, there appeared to be a different functional impact of emphysema in

those with HIV. Based on our sensitivity analyses, incorporating robust pulmonary function data, considering borderline airflow obstruction or excluding those with severe forms of emphysema did not appear to account for the association between emphysema and our significant outcomes in the HIV+ subjects, particularly 6MWD.

We speculate that emphysema in HIV+ patients may reflect important pulmonary and extrapulmonary inflammation. In our cohort, emphysema was associated with higher VACS index in HIV+ but not HIV− subjects, and the VACS index is correlated with biomarkers of inflammation. [39] The pathogenesis of emphysema is clearly linked to inflammation, [40, 41] and we postulate that several unique inflammatory mechanisms may result in an increased impact of emphysema in HIV+ individuals. [12] Our previous work demonstrated an association between emphysema and soluble CD14, a biomarker of monocyte immune activation, which was differential by HIV status. [24] Another study has linked biomarkers of inflammation, specifically IL-6, and emphysema with an increased burden of respiratory symptoms in an HIV+ cohort. [42] A recent study illustrating an association between emphysema and coronary calcification in HIV+ subjects demonstrates a link between emphysema and extrapulmonary inflammation in this population. [43] Our study is the first we are aware to examine the differential impact of emphysema on symptoms and functional limitation in HIV+ subjects. This adds to previous literature on the added impact of HIV infection on chronic lung disease, with HIV+ subjects having more clinical symptoms, physiologic differences (lower DLCO), more functional limitation and more radiographic pathology. [13, 17-19, 21] Much of these differences may be related to emphysema.

These results are important because of the burden of smoking and emphysema in individuals with HIV. [8-12] They demonstrate that symptoms and functional limitation may be more prevalent in those HIV+ patients with emphysema, even in those with less severe emphysema and without airflow obstruction, who may not come to clinical attention if evaluation for pulmonary disease stops after obtaining normal spirometry. Based on our analyses the effect of emphysema on outcomes in HIV+ patients may not be entirely reflected in pulmonary function measures that are often used to diagnose and assess the severity of COPD clinically. The effects of emphysema may be particularly important with regards to functional impairment, as the point estimates of differences in 6MWD we found are meaningful based on recent studies, which estimate MCID in 6MWD to be between 25 and 35m.[36-38]

Our cohort is a robust one to determine associations with emphysema in HIV+ subjects and compare this to HIV− subjects. As evident in our initial stratification, the HIV+ and HIV− subjects in our cohort were similar (**Table 1**). In most studies comparing HIV+ to HIV− subjects, those with HIV are younger, more likely to be black, more likely to have chronic diseases and have higher rates of smoking. [8-10, 44, 45] Our cohort of subjects was stratified on current smoking and is made up of Veterans of similar age, which likely accounts for other similarities; this study design reduces confounding as we examine differences by emphysema within these groups.

There are limitations to this study. The sample size of our study is relatively small, which may have limited our ability to detect meaningful differences between the groups,

particularly within HIV− subjects. Limited power also made finer stratification by emphysema severity and other variables (such as cough and/or phlegm and the dyspnea scale) difficult. Given our power limitations, confidence intervals around our estimates are wide, and for measures like the 6MWD, cross the MCID estimate. Also, by recruiting participants at outpatient clinic visits, we may have enrolled a sicker cohort of patients than are represented in the VAMCs as a whole; however, the recruitment was non-differential by HIV status. In addition, our cohort consisted predominantly of male Veterans from urban centers, limiting our understanding of the significance of emphysema in women. However, our cohort was geographically and racially diverse.

Conclusion

In our cohort, >10% radiographic emphysema was associated with chronic cough and/or phlegm and lower 6MWD in HIV+ but not HIV− subjects. These findings were robust even amongst HIV+ subjects with milder forms of emphysema and without airflow obstruction. This highlights the importance of recognition of emphysema in these patients. We speculate that emphysema may reflect pulmonary and extrapulmonary inflammation in HIV+ patients. Future studies are needed to validate these findings in larger cohorts of HIV+ patients, which may be possible with the introduction of automated CT emphysema scoring.[46, 47] This study also highlights the need for further investigations to delineate inflammatory pathways involved in emphysema in HIV and trials to determine whether HIV+ individuals with mild emphysema, in the absence of airflow limitation, would benefit from treatment with therapies traditionally directed against COPD.

Acknowledgments

This work was supported by the National Heart, Lung, and Blood Institute (NHLBI) at the National Institutes of Health (NIH) [R01 HL090342 to Dr. Crothers, T32 HL007287-37 supporting Dr. Triplette under Drs. Robb Glenny and J. Randall Curtis] as well as the National Institute on Alcohol Abuse and Alcoholism at the NIH [U01 AA013566]. This research was funded in part by a 2012 developmental grant from the University of Washington Center for AIDS Research, an NIH-funded program under award number P30-AI-027757, which is supported by the following NIH institutes and centers: National Institute of Allergy and Infectious Diseases, National Cancer Institute, National Institute of Mental Health, National Institute on Drug Abuse, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NHLBI, and National Institute on Aging.

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Table 1

Characteristics of the subjects by HIV status

Characteristic	HIV+ subjects (n=170)	HIV− subjects (n=153)	p-value
Male sex	98%	88%	<0.001
Age, y	55 (50-59)	52 (48-58)	0.16
Race/ethnicity			0.27
Black	72%	63%	
White	15%	21%	
Hispanic	9.4%	13%	
Other	3.5%	2.6%	
BMI (kg/m^2)	26 (23-30)	30 (26-34)	<0.001
Chronic heart disease	17%	15%	0.72
Diabetes	21%	21%	0.94
Hypertension	54%	54%	0.90
Anemia	15%	12%	0.36
VACS index	29(18-42)	18 (10-23)	<0.001
Smoking history			0.57
Current smokers	63%	58%	
Former smokers	21%	25%	
Never smokers	15%	18%	
Pack-years smoked, y	18 (6.8-39)	16 (1.8-33)	0.06
History of injection drug use	31%	15%	0.002
History of inhalational drug use	88%	81%	0.09
History of tuberculosis	7.1%	1.3%	0.01
History of *Pneumocystis*	1.8%	0%	0.10
History of bacterial pneumonia	17%	3.9%	<0.001
Airflow obstruction (post-bronchodilator FEV1/FVC <0.7)	21%	18%	0.61
FEV1, %-predicted	91 (82-107)	92 (78-103)	0.32
DLCO, %-predicted	53 (44-65)	57(49-72)	0.02
Self-reported chronic cough and/or phlegm	66%	55%	0.04
Self-reported exertional SOB	44%	40%	0.46
6MWD, m	427 (376-472)	421 (379-489)	0.67
Emphysema severity			
None	48%	52%	0.09
1-10%	26%	31%	0.33
11-25%	18%	10%	0.04
26-50%	5.9%	5.9%	1.0
50-75%	7.1%	0.7%	0.003
>75%	0	0	
>10% emphysema	31%	16%	0.003

Characteristic	HIV+ subjects (n=170)	HIV− subjects (n=153)	p-value
HIV-specific variables			
CD4 count cells/μL	440 (301-609)		
CD4 count ≤ 200 cells/μL	14%		
HIV viral load ≥50 copies/mL	35%		
Current ART use	72%		

Data are presented in medians (25-75% interquartile range) or %. BMI=body mass index, COPD=chronic obstructive pulmonary disease, PFT=pulmonary function test, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, DLCO=diffusion capacity, SOB=shortness of breath, 6MWD= Six minute walk distance, ART=antiretroviral therapy

Table 2

Characteristics of subjects by >10% emphysema

Characteristic	Emphysema > 10% (n=77)	Emphysema ≤ 10% (n=246)	p-value
HIV-infected	67%	48%	0.003
Male sex	96%	93%	0.29
Age, y	56 (52-61)	52 (47-58)	<0.001
Race/ethnicity			0.11
Black	69%	68%	
White	23%	16%	
Hispanic	7.8%	12%	
Other	0	4.1%	
BMI (kg/m$^{2)}$	24 (22-28)	29 (25-33)	<0.001
Chronic heart disease	17%	16%	0.76
Diabetes	16%	22%	0.20
Hypertension	49%	55%	0.36
Anemia	14%	13%	0.85
VACS Index	28 (22-41)	22 (12-33)	<0.001
Smoking history			0.002
Current smokers	76%	56%	
Former smokers	18%	24%	
Never smokers	5.3%	20%	
Pack-years smoked, y	36 (15-46)	14 (1-30)	<0.001
History of injection drug use	25%	23%	0.65
History of inhalational drug use	93%	81%	0.01
History of tuberculosis	9.1%	2.9%	0.02
History of pneumocystis	2.6%	0.4%	0.08
History of bacterial pneumonia	22%	6.9%	<0.001
Airflow obstruction (post-bronchodilator FEV1/FVC <0.7)	45%	11%	<0.001
FEV1, %-predicted	89 (76-100)	93 (81-105)	0.04
DLCO, %-predicted	48 (40-58)	58 (48-71)	<0.001
Self-reported chronic cough and/or phlegm	71%	58%	0.04
Self-reported exertional SOB	49%	40%	0.19
6MWD, m	423 (375-448)	426 (378-487)	0.14

Data are presented in medians (25-75% interquartile range) or %. BMI=body mass index, COPD=chronic obstructive pulmonary disease, PFT=pulmonary function test, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, DLCO=diffusion capacity for carbon monoxide SOB=shortness of breath, 6MWD= Six minute walk distance, ART=antiretroviral therapy

Table 3

Association between >10% emphysema with symptoms and 6-minute walk distance (6MWD) in HIV-infected (HIV+) and HIV-uninfected (HIV−) subjects

Characteristic	Unadjusted Analysis	Adjusted Analysis[c]
HIV+ (n=169)		
Chronic cough and/or phlegm[a]	2.7 (1.2, 5.9)	2.6 (1.0, 6.7)
SOB[a]	1.8 (0.89, 3.7)	1.5 (0.59, 3.9)
6MWD, m[b]	−33 (−59, −6.2)	−35 (−64, −6.6)
HIV− (n=153)		
Chronic cough and/or phlegm[a]	0.87 (0.37, 2.1)	0.44 (0.15, 1.4)
SOB[a]	0.92 (0.35, 2.4)	0.96 (0.26, 3.5)
6MWD, m[b]	+ 12 (−31, 55)	+27 (−21, 77)

[a]Odds Ratios (95% CI) from separate logistic regression models comparing the association between >10% emphysema with a) chronic cough and/or phlegm, or b) exertional shortness of breath (SOB)

[b]Beta-coefficient from linear regression model comparing the association between >10 emphysema with increase (+) or decrease (−) (95% CI) in 6 minute walk distance (6MWD) in meters

[c]All models adjusted for sex, race, age, BMI, pack years smoking, CD4 count (if HIV+), drug use and chronic illnesses (chronic heart disease, diabetes, hypertension, anemia)

Table 4

Association between >10% emphysema with symptoms and 6-minute walk distance (6MWD) in subjects without airflow obstruction in HIV-infected (HIV+) and HIV-uninfected (HIV−) subjects

Characteristic	Unadjusted Analysis	Adjusted Analysis[c]
HIV+ (n=133)		
Chronic cough and/or phlegm[a]	3.7 (1.3, 10)	4.2 (1.3, 14)
SOB[a]	2.0 (0.78, 4.9)	1.3 (0.40, 4.4)
6MWT distance, m[b]	−56 (−89, −24)	−60 (−93, −26)
HIV− (n=119)		
Chronic cough and/or phlegm[a]	0.97 (0.30, 3.1)	0.74 (0.17, 3.2)
SOB[a]	0.18 (0.02,1.5)	0.29 (0.02, 3.6)
6MW distance, m[b]	+ 18 (−40, 76)	+32.3 (−32, 96)

[a]Odds Ratios (95% CI) from separate logistic regression models comparing the association between >10% emphysema with a) chronic cough and/or phlegm, or b) exertional shortness of breath (SOB)

[b]Beta-coefficient from linear regression model comparing the association between >10 emphysema with increase (+) or decrease (−) (95% CI) in 6 minute walk distance (6MWD) in meters

[c]All models restricted to subjects without airflow obstruction on spirometry, and adjusted for sex, race, age, BMI, pack years smoking, CD4 count (if HIV+), drug use and chronic illnesses (chronic heart disease, diabetes, hypertension, anemia)