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HIV Infection is Independently Associated with Increased CT Scan Lung Density

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Abstract

Rationale and Objectives—Non-infectious pulmonary complications are common among HIV-infected individuals and may be detected early by quantitative CT scan. The association of HIV disease markers with CT lung density measurement remains poorly understood.

Materials and Methods—125 participants free of spirometry-defined lung disease were recruited from a longitudinal cohort study of HIV-infected and HIV negative individuals to undergo standardized CT scan of the chest. Parenchymal densities for the entire lung volumes were calculated using computerized software. Qualitative assessment of CT scans was conducted by two radiologists masked to HIV status. Linear regression models were developed to determine the independent association of markers of HIV infection on inspiratory scan mean lung density (MLD).

Results—HIV-infected participants had a significantly higher MLD (denser lung) compared with HIV-uninfected participants (−815 vs. −837 HU; $p=0.002$). After adjusting for relevant covariates, HIV infection was independently associated with 19.9 HU higher MLD (95% CI 6.04 to 33.7 HU; $p=0.005$). In qualitative assessment, only ground glass attenuation and cysts were noted more commonly among HIV-infected individuals compared with HIV-uninfected individuals [34% versus 17% ($p=0.045$) and 27% versus 10% ($p=0.03$), respectively]. No qualitative radiographic abnormalities attenuated the association between HIV infection and increased MLD.

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MBD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conclusions—HIV infection is independently associated with increased lung density. Although qualitative CT abnormalities were common in this cohort, only ground glass attenuation and cysts were noted more frequently in HIV-infected participants, suggesting that the increased lung density observed among HIV-infected individuals may be associated with subclinical inflammatory lung changes.

Keywords

HIV; respiratory tract disease; lung function; spirometry; tomography; x-ray computed

INTRODUCTION

With the initiation of antiretroviral therapy (ART), non-infectious pulmonary complications of HIV infection including chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, lung cancer and pulmonary hypertension have increasingly been recognized as key contributors to the morbidity and mortality of the HIV infected population.^{1–4} A focus of many studies has been to understand how different tools (i.e., spirometry, diffusing capacity, chest imaging) can detect HIV-associated lung changes earlier in the course of the pulmonary disease.^{3,5,6} Qualitative and quantitative computed tomography (CT) permits the assessment of lung changes which may develop prior to clinically overt lung disease. Several studies have examined the CT findings in HIV-infected individuals from varying populations with different risk factors for lung disease.^{3,7–10} Qualitative abnormalities, including emphysema, nodules, and bronchiectasis are common in HIV-infected individuals, with one study reporting 55% of HIV-infected individuals having a radiographic abnormality.⁷ Quantitative measurements, which use computerized software to calculate the density of each voxel of the lung image, can be employed to determine overall lung density [measured in Hounsfield Units (HU)]. Both decreased lung density (as seen in emphysema) and increased lung density (as seen in fibrotic lung disease) have been reported in HIV-infected populations.^{3,8,10} The association of HIV disease markers (viral load, CD4 cell count) with CT lung density measurement remains poorly understood. As well, the qualitative lung CT changes contributing to quantitative changes in HIV has not been reported.

The Study of HIV Infection in the Etiology of Lung Diseases (SHIELD) is an NIH-funded longitudinal cohort study of HIV-infected and HIV negative participants followed to understand how HIV may enhance susceptibility to lung disease. Within this study, both HIV-infected and uninfected individuals undergo standardized spirometry testing and research lung CT imaging. In this analysis, we determine the independent association of HIV infection with quantitative lung density from 125 SHIELD participants with normal lung function (assessed via spirometry testing). Using a standardized qualitative CT review, we assess the relationship between qualitative and quantitative CT changes to identify processes contributing to lung CT changes in HIV infection.

MATERIALS AND METHODS

Study Cohort

The SHIELD study recruits and enrolls participants from the AIDS Linked to the Intravenous Experience (ALIVE) study. Since 1988, ALIVE has conducted community-based recruitment of residents of Baltimore, MD who were ≥18 years of age and had a history of injection drug use.^{11,12} Both HIV-infected and uninfected individuals are eligible for enrollment into ALIVE. Participants in ALIVE complete twice yearly study visits including standardized interviewer and computerized questionnaires, clinical examination, and blood samples. The SHIELD protocol adds pulmonary-specific assessments including pre-bronchodilator spirometry testing and respiratory specific questionnaires. From February 2010 to August 2013, a subset of 248 SHIELD participants were recruited to complete a CT scan of the chest at a single study visit. In order to minimize the impact of co-existent lung disease on the outcomes of interest, only SHIELD participants completing CT scans of the chest who also had normal spirometry testing (as defined below) were included in this analysis (N=125). The SHIELD study has been continually approved by the IRB. All participants provided written informed consent.

Data collection

Demographic, behavioral, clinical, spirometry measurements and laboratory data were collected at the twice-yearly study visits. Data were selected from the study visit occurring closest to date of completion of the CT scan (median time 20 days). Smoking patterns and ART use were determined by self-report. Duration of smoking was defined using pack-years, calculated by multiplying the self-reported number of packs smoked per day by the number of years smoked. Routine laboratory testing at each visit included HIV serology for HIV-negative participants and, in addition for HIV-infected participants, T-cell subsets and HIV RNA (Roche Molecular Systems, Amplicor HIV-1 Monitor test version 1.5). Pre-bronchodilator spirometry including forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) was performed using KOKO[®] pneumotachometers (nSpire Health Inc, Longmont, CO) in accordance with American Thoracic Society guidelines.¹³ Percent predicted values were calculated using standard formulas.¹⁴ Normal spirometry testing was defined as an FEV1/FVC ratio greater than or equal to 0.70.¹⁵ Lung volumes were measured by body-plethysmography and performed according to ATS guidelines.¹⁶ Single-breath determination of carbon monoxide uptake (DLco) was performed according to American Thoracic Society guidelines.¹⁷

Acquisition of CT data

All subjects underwent a diagnostic chest CT without contrast at full lung inflation after coaching to maximize the inspiratory effort. All scans were performed using the same 64-slice multidetector CT (Siemens Definition 64, Siemens Medical Solutions) with the following settings: tube potential 120kVp, mAs adjusted for body size (small=80, medium=100, large=145), rotation time of 0.5 seconds, spiral pitch of 1.0, slice thickness of 0.75 mm, and slice interval of 0.5 mm. Images were reconstructed using a B35 and B31 algorithm. Parenchymal densities for the entire lung volumes for each subject were calculated using the PW software (VIDA Diagnostic, Coralville, IA). Qualitative assessment

of CT scans was conducted using picture archive and communication systems (Ultraspeed, Emageon, Inc.) by two radiologists (AH and CL) with advanced training in thoracic imaging. Radiologists were masked to all clinical information including HIV status. Data were collected using a standardized electronic data entry form.

Statistical Analysis

Clinical and demographic characteristics between groups are presented as means (standard deviation) for normally distributed data, median values (interquartile range [IQR]) for non-normally distributed data or n (%) for categorical variables. Student's t-test was used to compare continuous variables for normally distributed data and Wilcoxon-Mann-Whitney test for skewed data. The primary outcome of interest was inspiratory scan mean lung density (MLD). The MLD was assessed with quantitative determination of the overall lung Hounsfield units (HU). Lower (more negative) HU represents less dense lung, typically observed in diseases of increased parenchymal destruction such as emphysema while higher HU is typically seen in processes associated with increased parenchymal scarring or fibrosis. Univariable linear regressions were used to identify covariates potentially associated with the outcomes of interest. Adjusted multivariable linear regressions were then developed to determine the independent association of markers of HIV infection on MLD. Initial model construction included demographic and clinical covariates determined to be clinically relevant or associated with difference in MLD from univariable analysis with at a statistical threshold of $p < 0.20$. Race, sex and smoking status were included in all models regardless of statistical significance given the clinical importance of these covariates. In situations where multiple covariates assessed the same parameter of interest (i.e., absolute FEV1 and percent predicted FEV1; history of prior pneumonia and number of prior pneumonias), the variable with the largest point estimate was selected for future inclusion. HIV infection was modeled with HIV serostatus, and separately with viral load and CD4 cell count. Viral load and CD4 cell count were modeled continuously as well as at threshold values approximating median values. The final model was assessed for collinearity with variance inflation factor testing. A p-value of < 0.05 was used to infer statistical significance. Stata version 13.0 (StataCorp LP, College Station, TX) was used for statistical analyses.

RESULTS

Participant Characteristics

A total of 125 participants were included in analysis, comprised of 83 (66%) HIV-infected and 42 (34%) HIV-uninfected individuals (Table 1). The mean age of the cohort was 51 years, with 67% of the cohort being male and 95% identifying as African-American. Tobacco use was prevalent, with 79% reporting current cigarette use and only 7% reporting never having smoked cigarettes. Consistent with selection criteria, spirometric measures were normal in the cohort with the mean FEV1% predicted and FVC% predicted measured at 91% and 93%, respectively. Among HIV-infected participants, the median CD4 cell count was 349 cells/mm³ [interquartile range (IQR) 190–485 cells/mm³]. While 80% of HIV-infected individuals reported ART use in the prior six months, only 56% of participants with HIV had an undetectable viral load. The median viral load among participants with detectable HIV viral RNA was 7547 copies/mL (IQR 779–56,200 copies/mL). The

prevalence of African-American race was higher among HIV-infected participants compared with HIV-uninfected participants (98% versus 88%; $p=0.01$). There were no differences in other demographic, clinical or spirometric characteristics comparing HIV-infected to HIV-uninfected participants.

Current injection drug use remained prevalent in this cohort, with 23% of participants reporting injecting drugs in the prior six months (Table 2). Among current injection drug users, most reported injection frequency less than daily. Current crack cocaine and current other smoked drug use were also prevalent in the cohort (21% and 30%, respectively). There was no difference in drug use patterns between HIV-infected and HIV-uninfected participants. Prior pneumonias were reported in 17% of the cohort, with pneumonia occurring more frequently in HIV-infected individuals than HIV-uninfected (23% vs. 5%; $p=0.01$) (Table 2). All six cases of prior *Pneumocystis* infection occurred in HIV-infected individuals. There was no difference in the total number of pneumonias or *Pneumocystis* infections between HIV-infected and HIV-uninfected participants.

Characteristics associated with Mean Lung Density (MLD)

The MLD for the entire cohort was -822 HU (IQR -840 HU to -799 HU; Range -876 HU to -681 HU). In this cohort of individuals free of obstructive lung disease, emphysema (defined as percent of lung <-950 HU) was rare. The median percent of emphysematous lung was 0.41% (IQR 0.20% to 1.18%; Range 0.006% to 14%). The percent of emphysematous lung <-950 HU was associated with lower MLD (-5.19 HU per % lung <-950 ; 95% CI -6.65 to -3.73 HU; $p<0.001$). Several demographic and clinical covariates were statistically significantly associated with differences in MLD in univariable analysis (Table 3). Male sex was associated with 21.6 HU lower MLD [95% Confidence Interval (CI) -34.3 to -8.83 HU; $p=0.001$]. Higher FEV1 and FVC were associated with lower MLD (-19.0 HU/L and -15.4 HU/L respectively; $p<0.001$). Similarly, for every liter increase in TLC, MLD decreased by 7.77 HU (95% CI -14.0 to -1.55 HU; $p=0.015$). Higher DLco was associated with a small but statistically significant reduction in MLD (-1.76 HU/mL/min/mm Hg; 95% CI -2.8 to -0.72 HU; $p=0.001$). Current smoking, age, race and pack-years smoked were not associated with statistical differences in MLD. Similarly, none of the covariates assessing drug use and pneumonia summarized in Table 2 were associated with differences in mean HU in univariable analysis.

As seen in Figure 1, HIV-infected participants had a significantly higher MLD (denser lung) compared with HIV-uninfected participants (-815 vs. -837 HU; $p=0.002$), resulting in HIV infection being associated with 21.7 HU higher MLD (95% CI for difference 9.09 to 34.4 HU; $p=0.001$). Increased MLD in HIV infection was not restricted to a specific CD4 cell count range. Compared with HIV-uninfected participants, HIV infection with CD4 cell count greater than or equal to 350 cells/mm³ was associated with 29.2 HU higher MLD (95% CI 14.7–43.7 HU; $p<0.001$). HIV infection with CD4 cell count less than 350 cells/mm³ was associated with 14.5 HU higher MLD (95% CI 0.08–28.9 HU; $p=0.049$). Similarly, the association of viral load levels on MLD was not restricted to controlled or uncontrolled viremia. Specifically, compared with HIV-uninfected participants, HIV infection with detectable viral load was associated with 24.4 HU higher MLD (95% CI 10.2–38.6 HU;

p=0.001). HIV infection with undetectable viral load was associated with 18.3 HU higher MLD (95% CI 3.11–33.5 HU; p=0.02) compared with HIV-uninfected individuals. When restricting the analysis to the 85 HIV-infected participants, higher CD4 cell count modeled continuously was associated with higher MLD (2.38 HU per 50 CD4 cells; 95% CI 0.65–4.10 HU; p=0.008). Neither HIV viral RNA level nor current ART use was associated with differences in MLD among HIV-infected participants.

In order to determine the independent association between HIV infection and MLD, multivariable models were constructed using covariates explored in univariable analysis. These covariates included sex, race, current smoking status, FEV1, FVC, TLC, DLco and HIV status. Colinearity was observed between FVC and TLC (both measures of lung volume), and TLC was selected for inclusion given better accuracy as a measure of lung volume. Although no smoking covariates (pack-years smoked, current smoking status) were associated with MLD, current smoking was included in models given the clinical relevance of smoking on CT outcomes. The final model included HIV serostatus, sex, race, current smoking status, FEV1, TLC and DLco (Table 3). As can be seen in the table, the only clinical predictor remaining statistically associated with MLD was HIV serostatus. After adjusting for sex, race, current smoking status, and measures of airflow obstruction, lung volume and emphysema, HIV infection was independently associated with 19.9 HU higher MLD (95% CI 6.04 to 33.7 HU; p=0.005). The independent association between MLD and HIV infection was of greater magnitude than the association between MLD and any other examined covariate. Inclusion of markers of prior pneumonia/Pneumocystis and injection drug use did not attenuate the association between HIV infection and MLD. (see Supplementary Table 1)

The association between HIV infection and increased MLD did not differ across the range of viremia in multivariable analysis. (Table 4) Compared with HIV-uninfected participants, HIV infection with undetectable viral load was associated with 22.2 HU higher MLD (95% CI 6.17 to 38.2 HU; p=0.007). HIV infection with detectable viral load was associated with 17.6 HU higher MLD (95% CI 1.51 to 33.6 HU; p=0.032) compared with HIV-uninfected participants. HIV infection with CD4 cell count greater than or equal to 350 cells/mm³ was associated with 25.0 HU higher MLD (95% CI 9.03 to 41.0 HU; p=0.002) compared with HIV-uninfected participants. HIV infection with CD4 cell count less than 350 cells/mm³ was not associated with difference in MLD (14.6 HU; 95% CI –1.48 to 30.7 HU; p=0.075) compared with HIV-uninfected participants.

Qualitative CT analysis

Qualitative radiographic abnormalities were common in the cohort (Table 5). Emphysema noted by radiologist reviewers was present in 75 (60%) of the total cohort, with most having only trace or mild emphysema. Bronchiectasis was present in 20 (25%) of participants, with nearly all being characterized as minimal in severity. Other findings present in the cohort included ground glass attenuation (28%), mosaic attenuation (56%), cysts, (21%), reticular abnormalities (18%), linear scars (27%) and non-calcified nodules (50%). Neither group had evidence of interstitial pneumonia, giant bulla, lobar/segmental collapse or honeycombing. When comparing the radiographic abnormalities between HIV-infected and HIV-uninfected

individuals, there were few differences. Only ground glass attenuation and cysts were noted more commonly among HIV-infected individuals compared with HIV-uninfected individuals [34% versus 17% ($p=0.045$) and 27% versus 10% ($p=0.03$), respectively]. There were no differences in the prevalence of bronchiectasis, consolidation, mosaic attenuation, reticular abnormalities, linear scars or tree-in-bud pattern between HIV-infected and HIV-uninfected individuals. Participants with ground glass attenuation had higher MLD than those without ground glass attenuation [median(IQR): -814 HU (-834 to -790) versus -828 HU (-842 to -805); $p=0.032$]. There was no difference in MLD comparing participants with cysts to those without cysts [median(IQR): -814 HU (-836 to -801) versus -825 HU (-841 to -799); $p=0.37$]. Incorporating ground glass attenuation and cysts into the multivariable model described in Table 3, HIV infection remained associated with 19.4 HU higher MLD (95% CI 4.53 to 33.1 HU, $p=0.010$) while presence of ground glass attenuation was not associated with MLD difference [5.19 HU (95% CI -9.34 to 19.7 HU; $p=0.48$)].

DISCUSSION

In this analysis of 83 HIV-infected and 42 HIV-uninfected individuals with prevalent tobacco use but free of spirometry-defined airflow obstruction, we have made several key observations. HIV infection is independently associated with increased lung density. The increase in lung density observed with HIV infection is not attenuated by smoking status, lung volumes, injection drug use history or prior pneumonias. While the association between HIV infection and increased lung density was observed across the range of HIV viremia, increased lung density was greatest in individuals with higher CD4 cell counts. Although qualitative CT abnormalities were common in this cohort, only ground glass attenuation and cysts were noted more frequently in HIV-infected participants, suggesting that the increased lung density observed among HIV-infected individuals may be associated with subclinical inflammatory lung changes.

HIV infection is known to increase the risk of chronic lung diseases, including emphysema and fibrosis.^{1,18–21} Several studies have examined the impact of HIV infection on CT findings, demonstrating that HIV infection increases risk of emphysema and fibrosis.^{3,7–10} These publications have focused on populations with prevalent lung disease (defined with spirometry or radiographic criteria), or evaluated imaging with quantitative approaches only. The findings presented here extend these data by selecting a population at-risk but free of significant lung disease, and by evaluating CT findings both qualitatively and quantitatively. To our knowledge, this is the first study to evaluate lung density changes in HIV-infected individuals using continuous measures of lung density, rather than specific thresholds to define emphysema, fibrosis, or normal lung. These approaches permit more sensitive assessment of changes occurring with HIV infection prior to the onset of overt lung disease, as well as determination of the types of radiographic changes contributing to lung density changes.

Leader and colleagues recently reported that HIV infection increases the prevalence of fibrosis-like changes.³ Our findings confirm those observations. However, through concurrent qualitative CT analysis we extend those findings by demonstrating that overt fibrotic changes are not differentially present when comparing HIV-infected to HIV-

uninfected individuals. Rather, the dominant qualitative CT findings potentially contributing to increased lung density is increased ground glass opacification. Ground glass opacification is a radiographic term defined as “hazy increased opacity of lung, with preservation of bronchial and vascular margins”.²² This is a nonspecific CT finding which histologically correlates with partial air space filling, inflammatory infiltration or fibrotic interstitial thickening.²³ The absence of significant consolidation, traction bronchiectasis or honeycombing makes air space filling or fibrotic interstitial thickening less likely explanation for the increased lung density seen with HIV infection in this cohort. While this study cannot definitely determine the cause of increased lung density in HIV infection, the qualitative findings support subclinical inflammatory changes as a potential etiology.²⁴

After adjusting for relevant covariates, HIV infection was associated with an approximately 20 HU increase in lung density. In multivariable analyses, this association was present across the entire range of viral load levels, with both undetectable and detectable viral loads independently associated with increased lung density. However, only higher CD4 cell counts (defined as CD4 ≥ 350 cells/mm³) were associated with increased lung density in multivariable analyses. In the analysis by Leader et al,³ increasing viral load was associated with greater percentage fibrotic lung while no correlation was present with CD4 cell count. Our viral load findings align with those observations. The lack of an association between lower CD4 cell count and increased lung density in our analysis may reflect inadequate sample size to detect the association in this subgroup. Alternatively, this observation supports the hypothesis that an intact immune system is necessary to establish the subclinical inflammatory changes leading to increased lung density. Ultimately, sampling of the lung compartment to measure local inflammatory markers will be necessary to confirm the inflammatory changes supported by radiographic changes.

Although the study cohort was selected for the absence of spirometry-defined airflow obstruction, the prevalence of radiographic abnormalities was strikingly high. Approximately 60% of the cohort had evidence of trace or more severe emphysema, 20% had non-traction bronchiectasis, 56% demonstrated mosaic attenuation, and 50% of scans had non-calcified nodules present. These findings, which did not differ by HIV serostatus, were present at much higher frequencies than previously reported publications of at-risk and HIV-infected populations.^{7,10} In an analysis of 121 HIV-infected individuals, Clausen and colleagues reported prevalence of 26% emphysema, 11% bronchiectasis, 0% mosaic attenuation and 17% nodules. The increased prevalence of radiographic abnormalities in our cohort likely reflects the recruitment criteria for the ALIVE study which included current injection drug use at time of enrollment. Risk behaviors such as injection drug use and smoking are known to increase the prevalence of radiographic abnormalities.²⁵

This study has limitations. The cross-sectional study design does not permit causal inferences regarding the observed association. The ALIVE cohort is a cohort of current and former injection drug users recruited from the community. For these reasons, the findings reported here may not be generalizable to other HIV-infected populations. However, the well matched characteristics of the HIV uninfected comparator group in SHIELD reduces the likelihood of selection bias. Prior studies have identified biomarkers (e.g., soluble CD14, leukocyte telomere length) which may correlate with radiographic changes in HIV.^{10,26} We

do not have biomarker data to determine how levels of lung inflammation correlate with CT findings and HIV status. Currently, longitudinal CT scan data is not available to determine how CT findings may progress over time. Ultimately, these longitudinal data will permit a better understanding of how the HIV-associated CT changes ultimately translate to clinical disease. Despite these limitations, this study represents an important advancement in the knowledge surrounding the impact of HIV on radiographic changes in a cohort free of clinically-significant obstructive lung disease.

Conclusions

In summary, in a cohort of current and former injection drug users without evidence of spirometry-defined lung disease, HIV infection is associated with increased lung density on CT scan. This increase in lung density is not explained by prior respiratory infections, smoking status or severity of immunosuppression. The primary abnormality on qualitative CT review is ground glass opacification, suggesting that HIV infection may increase lung density through a process of subclinical inflammation or early fibrosis. Ultimately, longitudinal evaluation of these early CT findings as well as measurement of lung inflammatory biomarkers will permit an advanced understanding of the mechanisms for lung disease development in HIV infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

ALIVE	AIDS Linked to the Intravenous Experience
ART	Antiretroviral therapy
CD4	Cluster of differentiation 4 T lymphocytes
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
DLco	Single-breath determination of carbon monoxide uptake
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
HIV	Human immunodeficiency virus
HU	Hounsfield units

IQR	Interquartile range
MLD	Mean lung density
SHIELD	Study of HIV Infection in the Etiology of Lung Diseases

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Figure 1. Histograms of Mean Lung Density (MLD) among HIV-infected (upper panel) and HIV-uninfected (lower panel) cohort participants. MLD was higher among HIV-infected versus HIV-uninfected participants ($p=0.001$).

Table 1**Clinical and Demographic Characteristics of Study Participants**

	Total Cohort	HIV-infected	HIV-uninfected	p-value[‡]
N	125	83	42	
Age, years	51.0 (6.5)	51.3 (5.4)	50.3 (8.2)	0.42
Male, n (%)	84 (67)	57 (69)	27 (64)	0.62
Black race, n (%)	119 (95)	82 (98)	37 (88)	0.01
Smoking Status, n (%) [*]				
Current	99 (79)	64 (77)	35 (83)	
Former	17 (14)	12 (14)	5 (12)	
Never	9 (7)	7 (8)	2 (5)	0.67
Smoking, pack years	17 (13–33)	16.5 (12.6–33.0)	19.7 (13.5–37)	0.23
FEV ₁				
Absolute, L	2.74 (0.73)	2.72 (0.72)	2.78 (0.76)	0.69
% Predicted	91.1 (15.1)	90.6 (15.1)	92.0 (15.5)	0.62
FVC				
Absolute, L	3.51 (0.94)	3.48 (0.94)	3.58 (0.96)	0.58
% Predicted	93.4 (15.7)	92.7 (16.1)	94.8 (15.0)	0.48
FEV ₁ /FVC				
Absolute	0.78 (0.05)	0.78 (0.04)	0.78 (0.05)	0.43
Total lung capacity, L	5.53 (1.06)	5.54 (1.07)	5.51 (1.06)	0.89
DLco, mL/min/mm Hg	20.5 (5.92)	19.9 (5.94)	21.8 (5.73)	0.10
HIV markers				
CD4+ cell count, cells/mm ³		349 (190–485)		
Undetectable Viral Load, n (%)		47 (56)		
HIV-1 RNA level, copies/mL [‡]		7547 (779–56200)		
ART use, n (%) [*]		66 (80)		
Mean lung density, HU	–822 (–840 to –799)	–815 (–836 to –792)	–837 (–844 to –809)	0.002

Values presented as mean (SD) or median (IQR) unless indicated otherwise.

^{*} In previous 6 months.

[‡] Among HIV-infected participants with detectable HIV RNA.

[‡] P-value comparing HIV-infected to HIV-uninfected participants

Abbreviations: FEV₁, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; DLco, Diffusion capacity of carbon monoxide; ART, Antiretroviral Therapy; HIV, Human Immunodeficiency Virus; HU, Hounsfield units

Table 2**Drug and Pneumonia Cohort Characteristics**

	Total Cohort	HIV-infected	HIV-uninfected	p-value[‡]
N	125	83	42	
Injection drug use, n (%) [*]	29 (23)	16 (19)	13 (31)	0.14
Injection drug use frequency, n (%) [*]				
None	96 (77)	67 (81)	29 (69)	
Less than daily	21 (17)	11 (13)	10 (24)	
Daily	8 (6)	5 (6)	3 (7)	0.30
Marijuana use, n (%) [*]	19 (15)	12 (14)	7 (17)	0.75
Crack cocaine use, n (%) [*]	26 (21)	16 (19)	10 (24)	0.55
Other smoked drugs, n (%) [*]	37 (30)	23 (28)	14 (33)	0.52
Prior pneumonia, n (%)	21 (17)	19 (23)	2 (5)	0.01
Number of prior pneumonias, n (%)				
0	104 (83)	64 (77)	40 (95)	
1	14 (11)	13 (16)	1 (2)	
2+	7 (6)	6 (7)	1 (2)	0.19
Prior pneumocystis, n (%)	6 (5)	6 (7)	0 (0)	0.07
Number of prior pneumocystis, n (%)				
0	119 (95)	77 (93)	42 (100)	
1	3 (2)	3 (4)	0 (0)	
2+	3 (2)	3 (4)	0 (0)	0.53

Values presented as mean (SD) or median (IQR) unless indicated otherwise.

^{*} In previous 6 months.

[‡] P-value comparing HIV-infected to HIV-uninfected participants

Table 3

Association between Cohort Characteristics and Mean Lung Density

Covariate	Unadjusted Mean HU (95% CI)	p-value	Adjusted* Mean HU (95% CI)	p-value
HIV-infected	21.7 (9.09, 34.4)	0.001	19.9 (6.04, 33.7)	0.005
Male	-21.6 (-34.3, -8.83)	0.001	-10.6 (-28.3, 7.21)	0.24
Black	25.3 (-3.56, 54.2)	0.085	3.35 (-26.4, 33.1)	0.82
Current smoker	10.9 (-4.35, 26.2)	0.16	13.3 (-3.37, 30.1)	0.12
FEV1 (liter)	-19.0 (-26.9, -11.1)	<0.001	-9.44 (-26.9, 8.03)	0.29
TLC (liter)	-7.77 (-14.0, -1.55)	0.015	1.24 (-9.02, 11.5)	0.81
DLeo (ml/min/mm Hg)	-1.76 (-2.80, -0.72)	0.001	-0.33 (-1.75, 1.08)	0.64

* Adjusted for other covariates listed in table.

Abbreviations: FEV1, Forced Expiratory Volume in 1 second; TLC, Total Lung Capacity; DLeo, Diffusion capacity of carbon monoxide; HIV, Human Immunodeficiency Virus; HU, Hounsfield units;

Table 4

Adjusted* association between HIV markers and Mean Lung Density

Covariate	HIV Serostatus Model Adjusted Mean HU (95% CI)	HIV RNA Model Adjusted Mean HU (95% CI)	CD4 Count Model Adjusted Mean HU (95% CI)
HIV Uninfected	Reference	Reference	Reference
HIV Infected	19.1 (6.04, 33.7) [†]		
HIV RNA undetectable		22.2 (6.17, 38.2) [†]	
HIV RNA detectable		17.6 (1.51, 33.6) [†]	
CD4 count ≥350 cells/mm ³			25.0 (9.03, 41.0) [†]
CD4 count <350 cells/mm ³			14.6 (−1.48, 30.7)

* Adjusted for race, sex, current smoking status, absolute forced expiratory volume in 1 second, total lung capacity and diffusion capacity of carbon monoxide;

[†] p<0.05;

Abbreviations: HIV, Human Immunodeficiency Virus; HU, Hounsfield units;

Table 5

Qualitative radiographic abnormalities among cohort participants

	HIV Infected	HIV uninfected	p-value
N	83	42	
Emphysema global severity			
None	29 (35)	21 (50)	
Trace (1–10%)	27 (33)	11 (26)	
Mild (11–25%)	22 (27)	7 (17)	
Moderate (26–50%)	5 (6)	2 (5)	
Severe (51–75%)	0 (0)	1 (2)	
Very severe (>75%)	0 (0)	0 (0)	0.27
Description of Emphysema			
Bullae	9 (11)	1 (2)	0.10
Centrilobular	45 (54)	16 (38)	0.09
Distal acinar/paraseptal	38 (46)	13 (31)	0.11
Bronchiectasis (Non-traction)			
Present	16 (19)	9 (21)	0.78
Minimal	15 (18)	9 (21)	0.22
Bronchial wall thickening	13 (6)	5 (12)	0.57
Traction bronchiectasis	6 (7)	1 (2)	0.27
Pulm artery enlargement	13 (16)	3 (7)	0.18
Diameter if enlarged, mm	33 (32–34)	33 (33–34)	0.72
Consolidation	1 (1)	0 (0)	0.48
Ground glass	28 (34)	7 (17)	0.045
Mosaic attenuation	46 (55)	24 (57)	0.89
Cysts	22 (27)	4 (10)	0.03
Pleural Effusion	1 (1)	0 (0)	0.48
Reticular abnormalities	16 (19)	6 (14)	0.49
Linear scars	26 (31)	8 (18)	0.15
Non-calcified nodules			
Present	44 (53)	18 (43)	0.11
Number			
1	11 (25)	4 (22)	
2	25 (57)	11 (61)	
3+	8 (18)	3 (17)	0.96

	HIV Infected	HIV uninfected	p-value
Mediastinal lymphadenopathy	6 (7)	3 (7)	0.99
Cavitary lesion	1 (1)	0 (0)	0.48
Tree-in-bud	4 (5)	1 (2)	0.51