Original Investigation

HIV Infection Is Independently Associated with Increased CT Scan Lung Density

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Rationale and Objectives: Noninfectious pulmonary complications are common among HIV-infected individuals and may be detected early by quantitative computed tomography (CT) scanning. The association of HIV disease markers with CT lung density measurement remains poorly understood.

Materials and Methods: One hundred twenty-five participants free of spirometry-defined lung disease were recruited from a longitudinal cohort study of HIV-infected and HIV-uninfected individuals to undergo standardized CT scan of the chest. Parenchymal density for the entire lung volume was 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 to HIV-uninfected participants (–815 Hounsfield unit [HU] 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 to HIV-uninfected individuals (34% vs 17% [$P = 0.045$] and 27% vs 10% [$P = 0.03$], respectively). No qualitative radiographic abnormalities attenuated the association between HIV infection and increased MLD.

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.

Key Words: HIV; respiratory tract disease; lung function; spirometry; tomography, x-ray computed.

INTRODUCTION

With the initiation of antiretroviral therapy (ART), noninfectious pulmonary complications of HIV infection including chronic obstructive pulmonary disease, 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 (ie, 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 that 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 unit [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,

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the qualitative lung CT changes contributing to quantitative changes in HIV have not been reported.

The Study of HIV Infection in the Etiology of Lung Diseases (SHIELD) is a National Institutes of Health-funded longitudinal cohort study of HIV-infected and HIV-uninfected 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

SHIELD 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 was recruited to complete a CT scan of the chest at a single study visit. To minimize the impact of coexistent lung disease on the outcomes of interest, only SHIELD participants completing CT scans of the chest who also had normal spirometry testing (as defined next) were included in this analysis ($N = 125$). SHIELD has been continually approved by the Institutional Review Board. 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-uninfected participants and, in addition for HIV-infected participants, T-cell subsets and HIV RNA (Roche Molecular Systems, Pleasanton, CA, Amplicor HIV-1 Monitor test version 1.5). Pre-bronchodilator spirometry including forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) was performed using KOKO pneumotachometers (nSpire Health Inc, Longmont, CO) in accordance with American Thoracic Society (ATS) guidelines (13). Percent predicted values were calculated using standard formulas (14). Normal spirometry testing was defined as an FEV_1/FVC ratio greater than or equal to 0.70 (15). Lung volumes were measured by body plethysmography and performed according to ATS guidelines (16). Diffusion capacity of carbon monoxide (DLco) was performed according to ATS guidelines (17).

Acquisition of CT Data

All subjects underwent a chest CT without contrast at full lung inflation after coaching to maximize the inspiratory effort via established research protocol (18). All scans were performed using the same 64-slice multidetector CT (Siemens Definition 64, Siemens Medical Solutions) with the following settings: tube potential 120 kVp, 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 (Ultravisual, Emageon, Inc.) by two radiologists (AFH and CTL) 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 HUs. Lower (more negative) HU represents less dense lung, typically observed in diseases of increased parenchymal destruction such as emphysema whereas 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 a difference in MLD from univariable analysis at a statistical threshold of $P < 0.20$. Race, sex, and smoking status were included in all models regard-