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Risk Factors Associated with Quantitative Evidence of Lung Emphysema and Fibrosis in an HIV-infected Cohort

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Abstract

Introduction—The disease spectrum for HIV-infected individuals has shifted towards co-morbid non-AIDS conditions including chronic lung disease, but quantitative image analysis of lung disease has not been performed.

Objectives—To quantify the prevalence of structural changes of the lung indicating emphysema or fibrosis on radiographic examination.

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Methods—A cross-sectional analysis of 510 HIV-infected participants in the multi-center Lung-HIV study was performed. Data collected included: demographics, biological markers of HIV, pulmonary function testing, and chest CT examinations. Emphysema and fibrosis-like changes were quantified on CT images based on threshold approaches.

Results—In our cohort: 69% was on antiretroviral therapy, 13% had a current CD4 cell count less than 200 cells/μL, 39% had an HIV viral load greater than 500 copies/mL, 25% had at least a trace level of emphysema (defined as >2.5% of voxels <-950HU). Trace emphysema was significantly correlated with age, smoking, and pulmonary function. Neither current CD4 cell count nor HIV viral load was significantly correlated with emphysema. Fibrosis-like changes were detected in 29% of the participants and were significantly correlated with HIV viral load (Pearson correlation coefficient = 0.210, $p<0.05$); current CD4 cell count was not associated with fibrosis. In multivariable analyses including age, race, and smoking status, HIV viral load remained significantly correlated with fibrosis-like changes (coefficient = 0.107, P = 0.03).

Conclusion—A higher HIV viral load was significantly associated with fibrosis-like changes possibly indicating early interstitial lung disease, but emphysematous changes were not related to current CD4 cell count or HIV viral load.

Keywords

HIV; lung; computed tomography; emphysema; pulmonary fibrosis

Introduction

Pulmonary complications have been associated with human immunodeficiency virus (HIV) infection from the beginning of the acquired immunodeficiency syndrome (AIDS) epidemic.[1-4] Chronic lung diseases and other co-morbid non-AIDS conditions are now associated with a relatively increased number of deaths in persons with HIV as life expectancy increases due to improved HIV treatment and education.[5-9] Numerous publications have provided pictorial essays illustrating common radiographic findings related to the lung and HIV infection or AIDS.[2,10-20] Some of the most common radiographic findings in both the pre-antiretroviral therapy (ART) era and ART era include emphysema,[21-27] focal air trapping,[28] pulmonary infiltrates,[1,10,23,29] alveolar consolidation,[11,30,31] nodules,[10,11,29,31-38] ground glass opacities (GGO),[11,32,39,40] cavitary lesions,[32,35] and bronchial abnormalities.[11,24,34,41] Several early studies described precocious emphysema present in people with HIV infection or AIDS.[21,22,25]

The improved survival of HIV-infected individuals may have shifted the spectrum of chest CT findings to include more manifestations of chronic lung diseases such as chronic obstructive pulmonary diseases (COPD)[42-47] and interstitial inflammation or fibrosis, but only a few large-scale studies of chest CT findings have been performed in the current era.[46,48-52] Furthermore, to our knowledge only two studies performed quantitative CT analyses.[27,52] A quantitative approach may be more sensitive to detect correlations between lung abnormalities on radiographic images and biological/physiological measures as well as to detect lung abnormalities at an earlier stage compared to subjective visual image review.

In our current multi-center study, we quantitatively analyzed chest CT images to determine the prevalence of findings indicative of emphysema and pulmonary fibrosis and to investigate the relation between demographics, lung function, biological markers of HIV infection, and CT image metrics associated with lung disease.

Methods

Subjects

Subjects were participants in the National Heart, Lung, and Blood Institute (NHLBI)-sponsored Lung-HIV study from three Lung-HIV clinical centers: Ohio State University, University of Pittsburgh, and the University of Washington.[53,54] The University of Pittsburgh center had two sub-centers at the University of California Los Angeles and the University of California San Francisco. The University of Washington center recruited participants from four Veterans Affairs centers located in Atlanta, GA, Bronx, NY, Houston, TX, and Los Angeles, CA. The Institutional Review board at each clinical center, the Lung-HIV Data Coordinating Center (Clinical Trials and Surveys Corp, C-TASC), the Lung-HIV Data Safety and Monitoring Board, and the NHLBI approved the study protocol, and all participants signed written informed consent.

Each site recruited HIV-infected adults (≥18 years of age) who were without acute respiratory illness at time of study enrollment. Subjects were not, however, required to have chronic pulmonary disease to participate. At the Ohio State University site, all subjects enrolled were current cigarette smokers, whereas subjects were eligible to enroll in the other two centers regardless of smoking status. The participants completed standardized questionnaires to ascertain demographics, smoking history, illicit drug use, and medical history.[53,54] Participants were defined as never smokers if they reported smoking <100 lifetime cigarettes; as current smokers if they had smoked within the past 12 months; and as former smokers if they had quit more than 12 months prior to enrollment. Smoking pack-years were calculated based upon average number of packs of cigarettes smoked per day and number of years smoked. Current CD4 cell counts (cells/μL) and HIV viral load (copies/mL) were obtained within 12 months of pulmonary function testing.

Pulmonary Function Testing

Pulmonary function tests (PFTs) were performed according to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines at each site's clinical or research pulmonary function laboratory and included pre- and post-bronchodilator spirometry and single breath carbon monoxide diffusion capacity of the lung (DLco).[55,56] Spirometry and DLco predicted normal values (or percent predicted) were computed based on the Hankinson[57] and Neas[58] formulas, respectively. Spirometry measures of lung function evaluated included: percent predicted forced expiratory volume in one second (FEV1%), percent predicted forced vital capacity (FVC%), and the ratio of FEV1 to FVC (FEV1/FVC). Pulmonary function testing data has been previously reported for a subset of this cohort.[53,54]

CT Examinations

The CT examinations were performed at the eight clinical sites using seven scanner models. The CT protocol was standardized across the different scanners to control for scanner differences (see Table S1, Supplemental Digital Content). Quality assurance measures were implemented to evaluate each scanner and each CT scan for protocol compliance (see Supplemental Digital Content). The CT data were acquired without radiopaque contrast at a moderate radiation exposure (100 mAs) with the participants in a supine position and holding their breath at end-inspiration. The image thickness was 0.625 mm, 0.750 mm, and 0.900 mm for General Electric, Siemens, and Phillips scanners, respectively.

CT Image Analysis

The CT data were analyzed using a standardized approach at the University of Pittsburgh by an image analyst who was blinded to all clinical information. The lung was first segmented from the CT images using University of Pittsburgh software.[59] Then we used the density mask technique[60] to quantify the percentage of the lung voxels associated with emphysema using a threshold of -950 Hounsfield units (HU) (Perc950), which is a widely accepted threshold to quantify emphysema on thin section CT images.[61,62] To quantify the presence of interstitial inflammation, fibrosis, or fibrosis-like changes in the lung, we calculated the percentage of the lung voxels with a computed attenuation between -600 and -250 HU or so-called high attenuation areas (PercHAA).[63] This HU value range captures fibrosis-like changes that are more dense than healthy parenchyma (approximate average -750 HU) and less dense than water (0 HU). Both metrics were computed from images reconstructed using either “standard” kernel, “B31f” kernel, or “B” kernel of the General Electric, Siemens, and Phillips scanners, respectively. We classified CT scans as depicting trace levels of “emphysema” and fibrosis-like changes based on 2.5% and 5.0% cutoffs, respectively. These levels are intended to capture early structural changes in lung anatomy that are associated with disease and are mostly likely not clinically significant (e.g., change patient care). For completeness, we also included emphysema and fibrosis cutoffs of 5.0% and 10.0%, respectively.

Statistical Analysis

Subject demographics were described using mean and standard deviation (SD), median and interquartile range (IQR), or numbers and proportions as appropriate. Pearson correlation coefficients (PCC) were computed to quantify the association between quantitative emphysema (Perc950), quantitative fibrosis-like changes (PercHAA), age, smoking history (pack-years), current CD4 cell count, HIV viral load, and lung function with all variables treated as continuous variables. Step-wise, multivariable linear regression analyses were performed with either Perc950 or PercHAA as the dependent variable to further investigate their relation with current CD4 cell count and HIV viral load. Based on both biologic plausibility and prior literature examining lung disease in HIV, we examined a number of potential confounders in stepwise models to determine the effect of adding different covariates *en bloc* to our primary predictors of interest, the current CD4 cell count and HIV viral load. First, demographic variables (age, race, and smoking history) were included in model 1. Next, ART status was added (model 2), and then drug use (marijuana or other

illicit drugs) (model 3). Finally, the history of pertinent lung disease (bacterial pneumonia and *Pneumocystis* pneumonia [PCP]) was added to the analysis (model 4). In both the correlation and multivariable analyses, Perc950 and PercHAA were log transformed, continuous variables. In the multivariable analysis, current CD4 cell count was dichotomized to less than 500 cells/μL and greater than or equal to 500 cells/μL and HIV viral load was dichotomized to less than 500 copies/mL or greater than or equal to 500 copies/mL based on the distribution of the data. Smoking status was defined as current, former or never. Race was defined as white, black, or other. In all statistical tests, a p-value less than 0.05 was considered significant.

Results

Lung HIV CT Study Cohort

The study cohort included 510 HIV-infected individuals of whom 350 (69%) were on ART at the time of enrollment (Table 1). The cohort was 81% male with a mean age (SD) of 48.9 (± 9.5) years. The cohort was racially diverse with 255 (50%) non-Whites. Overall, 77 (15%) of participants were life-long never-smokers, and 325 (64%) were current smokers with a median (IQR) smoking history of 18.4 (29.1) pack-years. Injection drug use, marijuana use, prior bacteria pneumonia, and prior PCP were prevalent. The median (IQR) current CD4 cell count and median (IQR) HIV viral load were 466 (398) cells/μL and 48 (220) copies/mL, respectively. The number of participants with a current CD4 cell count less than 200 cells/μL and an HIV viral load greater than 500 copies/mL were 67 (13%) and 199 (39%), respectively. The mean (SD) values of post-bronchodilator FEV1%, FVC%, and FEV1/FVC were 95.1 (16.5), 98.6 (14.4) 77.0 (10.0), respectively, and the DLco% was 70.6 (17.5).

Emphysema quantified on CT exam

The prevalence of trace (Perc950 > 2.5%) or greater levels of emphysema in the study cohort was 25.1% (Table 1) and was 9.2% for Perc950 > 5.0. There was a positive correlation between emphysema and both age (PCC = 0.283) and smoking history (PCC = 0.164) (Table 2). Neither current CD4 cell count nor HIV viral load was significantly correlated with quantified emphysema. In multivariable analyses using the Perc950 to reflect degree of emphysema as a continuous outcome, there was not a significant relationship between quantitative emphysema and current CD4 cell count, HIV viral load, or ART use in the four linear regression models (see Tables S2-S5, Supplemental Digital Content).

There was a significant positive correlation between lung function and emphysema with FVC% and a negative correlation with FEV1/FVC and quantitative emphysema (Table 2). The association between FEV1/FVC and quantitative emphysema remained when controlling for age and smoking history (see Table S6, Supplemental Digital Content). The correlation between quantitative emphysema and DLco did not reach statistical significance.

Fibrosis quantified on CT exam

Overall, 29.4% of the study cohort had at least a trace level (PercHAA > 5.0%) of fibrosis-like changes in the lung (Table 1) and 5.7% of the cohort had PercHAA > 10.0%.

Correlations between findings of fibrosis were statistically significant with increasing HIV viral load (PCC = 0.210) and decreasing age (PCC= -0.239), but were not significantly correlated with pack-years or current CD4 cell count (Table 2). Age, smoking status, and ART had a significant relation with fibrosis-like changes in the multivariable regression models 1 – 4 (see Tables S7 and S8, Supplemental Digital Content). In multivariable analyses, HIV viral load and smoking status had a significant positive correlation with fibrosis-like changes in the lung (model 1) while age had a significant negative relation with fibrosis-like changes (Table 3). When ART was added to the model, age had significant negative correlation with fibrosis-like changes and participants on ART had significantly lower levels of fibrosis-like changes. These associations remained true as other variables were added to the models (see Tables S9 and S10, Supplemental Digital Content).

Lung function measures (FEV1% and FVC%) had a significant negative correlation with fibrosis-like changes in the lung (Table 2). The association with FVC% remained when controlling for smoking history (see Table S11, Supplemental Digital Content). The correlation between fibrosis-like changes and DLco did not reach statistical significance.

Only 1.2% (6/512) of the subjects were positive for both quantitative emphysema and fibrosis-like changes.

Discussion

The current study is one of the few to investigate the relation between quantitative assessment of CT image metrics associated with lung disease and demographics, biological markers of HIV infection, and pulmonary function. As expected from published studies, we found that a significant number (25%) of HIV-infected individuals have evidence of at least early emphysema. In contrast, an unexpected finding was that a similar proportion (29%) also had fibrosis-like changes in the lung on quantitative analysis as pulmonary fibrosis has been a relatively uncommon chronic lung disease in HIV-infected persons. In addition, higher HIV viral levels were linked to fibrosis-like changes, but not to emphysema.

A novel finding from our study is the significant correlation between HIV viral load and quantified fibrosis-like changes in the lung (PercHAA) depicted on CT images. The histologic correlate of these areas of high computed attenuation (HAA) on CT images has not been established, but it has been hypothesized that regions of increased computed attenuation may indicate areas of the lung affected by subclinical interstitial lung disease or early pulmonary fibrosis.[63] In the Multi-Ethnic Study of Atherosclerosis (MESA) study, Lederer and colleagues performed CT scans for scoring coronary calcium in a population of 2,563 adults without clinical cardiovascular disease or air-flow obstruction and found that increased percentage of high attenuation areas, defined as regions with pixel values between -600 and -250 HU, increased for each 10 pack year cigarette smoking history.[63] When PercHAA was correlated with visual changes on CT scan, the most common findings were ground glass opacities or atelectasis, reticular abnormalities and a possible usual interstitial pneumonitis pattern.[63]

Of note, a recent population-based cohort study in an HIV-uninfected population has shown that CT evidence of subclinical interstitial lung disease (ILD) is an under-recognized phenomenon.[64] Further understanding of the relation between HIV viral load and CT findings suggesting subclinical ILD may inform our understanding of early events in the etiology and pathogenesis of ILD in the general population. Because the precise etiology and natural history of fibrosis-like changes in the lung has not been fully elucidated, the significance of our findings and the relationship between these CT image changes and viral load in HIV remains speculative.

While areas of increased computed attenuation may indicate early ILD, it is also possible that such changes may reflect inflammatory changes which are early events in the pathogenesis of other HIV-related pulmonary disorders. For example, recent data in the general population has demonstrated a significant correlation between fibrosis-like changes and biomarkers of pulmonary vascular endothelial injury, including intercellular adhesion molecule 1 (ICAM-1).[65] Pulmonary vascular abnormalities are well-described in the HIV-infected population, and HIV may have direct effects on the vascular endothelium. Evidence exists that HIV Nef, an accessory HIV protein, may directly affect endothelial function, reducing endothelial vasorelaxation and endothelial nitric oxide synthase (eNOS) expression while increasing oxygen free radical production.[66] Alternatively, there may be direct effects of drugs on pulmonary inflammatory pathways. For example, antiretroviral agents may directly increase leukocyte adhesion to vascular endothelium *in vitro*.[67] Whether HIV-infected individuals with increased findings of fibrosis are at increased risk of developing "vascular–based" clinical abnormalities such as pulmonary diffusion impairment or pulmonary hypertension remains speculative. Finally, it is possible that individuals with areas of increased computed attenuation on CT images may have increased colonization of lung pathogens.

As expected, there was a significant correlation between quantitative findings of emphysema (Perc950) and both age and smoking history (Table 2). A number of studies in both the pre-ART and ART eras have demonstrated a link between HIV status and an increased risk of developing COPD/emphysema.[21,25,27,28,32,46,48,49] While evidence exists that this phenomenon may be related to an interaction between HIV infection and smoking, we did not find a significant correlation between CD4 cell count or HIV viral load and Perc950. Our findings are consistent with Samperiz and colleagues who reported no relation between quantitative assessment of emphysema on CT scan and either HIV viral load or CD4 count.[52] However, they reported that the Center for Disease Control HIV category C was a risk factor for quantitative emphysema and a modest emphysema prevalence (10.5%) using a low emphysema cutoff (greater than 1% of voxels with a value less than -950HU). Three recent studies of HIV-infected cohorts [46,48,52] observed that greater than 30% of the subjects had some evidence of emphysema by visual CT image assessment, which is somewhat higher than our findings of 25.1% by quantitative analysis. However, all three studies reported some significant relation between either nadir or current CD4 count and emphysema.

In the recent studies of emphysema in the HIV-infected population mentioned above, there appears to be some discordance between visual and quantitative assessment of emphysema

prevalence. This discordance has long been discussed in the literature with the reported agreement by kappa statistic ranging from 0.12 to 0.48.[68-73] One hypothesis is that the poor to moderate inter-reader agreement for visual emphysema assessment contributes to the discordance between visual and quantitative assessment with reported agreement kappa ranging from 0.18 to 0.63.[68-73] Some investigators postulated that human observers tend to overestimate emphysema compared to quantitative assessment in subjects with a low level emphysema, but that reader agreement improves as emphysema severity increases.[68] However, poor inter-reader agreement was observed in both subjects without COPD and subjects with severe COPD.[71] One possible component of the discordance is selection of an emphysema threshold (e.g., -950HU) and cutoff for classifying emphysema (e.g., 5% of voxels below the threshold). Investigators have used emphysema cutoff values ranging from 1% - 10% often based on empirical data, lung function data, or clinical outcomes (e.g., mortality).[52,71,74-76] We presented data for cutoff values of 2.5% and 5.0% for emphysema and fibrosis, respectively, and believe those values appropriately capture emphysema and fibrosis-like changes in our cohort based on preliminary visual assessment (unpublished data) and recent reports of other HIV studies. Although the visual and quantitative assessment of emphysema should be concordant, some investigators postulate that the two metrics are complementary with different strengths and weaknesses.[71] Exactly how the two metrics complement each other and how to integrate the two is not quite clear.

A potential limitation to our study is the application of a pre-defined threshold to perform the quantitative assessment of emphysema and fibrosis-like changes in the lung on CT data obtained from different CT scanners. This application may or may not have been appropriate as there is no universal threshold or adjustment to the threshold to account for difference in CT scanners and protocols, but the threshold approach is widely used to quantify emphysema on CT images. Additionally, the values used to dichotomize into categories of emphysema (2.5 % or 5.0%) and fibrosis-like changes (5.0 % or 10.0%) have not been universally validated. However, we believe that our effort to standardize the CT protocols permits an analysis that would detect significant first-order effects, but may be insufficient to detect higher order, more subtle effects limited by the size of our cohort. Another limitation is the cutoff selected for CD4 cell count and HIV viral load in the multivariable models, which can be debated regarding the optimal value. However, our initial multivariable analyses treated CD4 cell count and HIV viral load as continuous variables, but the data did not reach statistical significance (data not shown). Additionally, perhaps nadir CD4 cell count and zenith HIV viral load levels are more appropriate in the context of chronic lung disease, but were not available for these analyses. Finally, our cohort had a high prevalence of smoking, particularly given that all patients from the Ohio State University site were current smokers. Nonetheless, our multi-site study may be more representative of the general HIV-infected population, and we had substantial geographic and racial diversity in our population.

In summary, quantitative CT assessment of the lungs shows that emphysema and fibrosis-like changes were both common in a multi-center cohort of HIV-infected individuals. Fibrosis-like changes were associated with HIV viral load when controlling for age, race, smoking, and ART. In contrast, quantitative assessment of emphysema was not associated with HIV markers. Further investigation and extended follow-up of participants may shed

light on our understanding of HIV-associated pulmonary complications as well as provide new insight into events important in the development of early interstitial lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Cohen BA, Pomeranz S, Rabinowitz JG, et al. Pulmonary complications of AIDS: radiologic features. AJR Am J Roentgenol. Jul; 1984 143(1):115–122. [PubMed: 6610304]
2. Kuhlman JE, Fishman EK, Hruban RH, Knowles M, Zerhouni EA, Siegelman SS. Diseases of the chest in AIDS: CT diagnosis. Radiographics. Sep; 1989 9(5):827–857. [PubMed: 2678294]
3. Murray JF, Mills J. Pulmonary infectious complications of human immunodeficiency virus infection. Part I. Am Rev Respir Dis. May; 1990 141(5 Pt 1):1356–1372. [PubMed: 2187388]
4. Murray JF, Mills J. Pulmonary infectious complications of human immunodeficiency virus infection. Part II. Am Rev Respir Dis. Jun; 1990 141(6):1582–1598. [PubMed: 2190509]
5. Braithwaite RS, Justice AC, Chang CC, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. Am J Med. Aug; 2005 118(8):890–898. [PubMed: 16084183]
6. Crum NF, Riffenburgh RH, Wegner S, et al. Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of the pre-, early, and late HAART (highly active antiretroviral therapy) eras. J Acquir Immune Defic Syndr. Feb 1; 2006 41(2):194–200. [PubMed: 16394852]
7. Lau B, Gange SJ, Moore RD. Risk of non-AIDS-related mortality may exceed risk of AIDS-related mortality among individuals enrolling into care with CD4+ counts greater than 200 cells/mm3. J Acquir Immune Defic Syndr. Feb 1; 2007 44(2):179–187. [PubMed: 17075385]

8. Marin B, Thiebaut R, Bucher HC, et al. Non-AIDS-defining deaths and immunodeficiency in the era of combination antiretroviral therapy. AIDS. Aug 24; 2009 23(13):1743–1753. [PubMed: 19571723]
9. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. AIDS. Aug 16; 2002 16(12):1663–1671. [PubMed: 12172088]
10. Sider L, Gabriel H, Curry DR, Pham MS. Pattern recognition of the pulmonary manifestations of AIDS on CT scans. Radiographics. Jul; 1993 13(4):771–784. discussion 785-776. [PubMed: 8356267]
11. McGuinness G, Scholes JV, Garay SM, Leitman BS, McCauley DI, Naidich DP. Cytomegalovirus pneumonitis: spectrum of parenchymal CT findings with pathologic correlation in 21 AIDS patients. Radiology. Aug; 1994 192(2):451–459. [PubMed: 8029414]
12. McGuinness G, Gruden JF, Bhalla M, Harkin TJ, Jagirdar JS, Naidich DP. AIDS-related airway disease. AJR Am J Roentgenol. Jan; 1997 168(1):67–77. [PubMed: 8976923]
13. Logan PM, Finnegan MM. Pulmonary complications in AIDS: CT appearances. Clin Radiol. Aug; 1998 53(8):567–573. [PubMed: 9744581]
14. Richards PJ, Armstrong P, Parkin JM, Sharma A. Chest imaging in AIDS. Clin Radiol. Aug; 1998 53(8):554–566. [PubMed: 9744580]
15. Kuhlman JE. Imaging pulmonary disease in AIDS: state of the art. Eur Radiol. 1999; 9(3):395–408. [PubMed: 10087106]
16. Padley SP, King LJ. Computed tomography of the thorax in HIV disease. Eur Radiol. 1999; 9(8): 1556–1569. [PubMed: 10525865]
17. Marchiori E, Muller NL, Soares Souza A Jr, Escuissato DL, Gasparetto EL, Franquet T. Pulmonary disease in patients with AIDS: high-resolution CT and pathologic findings. AJR Am J Roentgenol. Mar; 2005 184(3):757–764. [PubMed: 15728594]
18. Allen CM, Al-Jahdali HH, Irion KL, Al Ghanem S, Gouda A, Khan AN. Imaging lung manifestations of HIV/AIDS. Ann Thorac Med. Oct; 2010 5(4):201–216. [PubMed: 20981180]
19. Lichtenberger JP 3rd, Sharma A, Zachary KC, et al. What a differential a virus makes: a practical approach to thoracic imaging findings in the context of HIV infection--part 1, pulmonary findings. AJR Am J Roentgenol. Jun; 2012 198(6):1295–1304. [PubMed: 22623541]
20. Lichtenberger JP 3rd, Sharma A, Zachary KC, et al. What a differential a virus makes: a practical approach to thoracic imaging findings in the context of HIV infection--part 2, extrapulmonary findings, chronic lung disease, and immune reconstitution syndrome. AJR Am J Roentgenol. Jun; 2012 198(6):1305–1312. [PubMed: 22623542]
21. Kuhlman JE, Knowles MC, Fishman EK, Siegelman SS. Premature bullous pulmonary damage in AIDS: CT diagnosis. Radiology. Oct; 1989 173(1):23–26. [PubMed: 2781013]
22. Diaz PT, Clanton TL, Pacht ER. Emphysema-like pulmonary disease associated with human immunodeficiency virus infection. Ann Intern Med. Jan 15; 1992 116(2):124–128. [PubMed: 1727615]
23. Guillemi SA, Staples CA, Hogg JC, et al. Unexpected lung lesions in high resolution computed tomography (HRCT) among patients with advanced HIV disease. Eur Respir J. Jan; 1996 9(1):33–36. [PubMed: 8834330]
24. King MA, Neal DE, St John R, Tsai J, Diaz PT. Bronchial dilatation in patients with HIV infection: CT assessment and correlation with pulmonary function tests and findings at bronchoalveolar lavage. AJR Am J Roentgenol. Jun; 1997 168(6):1535–1540. [PubMed: 9168720]
25. Diaz PT, King MA, Pacht ER, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. Ann Intern Med. Mar 7; 2000 132(5):369–372. [PubMed: 10691587]
26. Diaz PT, Wewers MD, King M, Wade J, Hart J, Clanton TL. Regional differences in emphysema scores and BAL glutathione levels in HIV-infected individuals. Chest. Nov; 2004 126(5):1439–1442. [PubMed: 15539710]
27. Gingo MR, He J, Wittman C, et al. Contributors to diffusion impairment in HIV-infected persons. Eur Respir J. Jan; 2014 43(1):195–203. [PubMed: 23429919]

28. Gelman M, King MA, Neal DE, Pacht ER, Clanton TL, Diaz PT. Focal air trapping in patients with HIV infection: CT evaluation and correlation with pulmonary function test results. AJR Am J Roentgenol. Apr; 1999 172(4):1033–1038. [PubMed: 10587143]
29. Traill ZC, Miller RF, Shaw PJ. CT appearances of intrathoracic Kaposi's sarcoma in patients with AIDS. Br J Radiol. Dec; 1996 69(828):1104–1107. [PubMed: 9135464]
30. Moskovic E, Miller R, Pearson M. High resolution computed tomography of Pneumocystis carinii pneumonia in AIDS. Clin Radiol. Oct; 1990 42(4):239–243. [PubMed: 2225727]
31. Cattamanchi A, Nahid P, Marras TK, et al. Detailed analysis of the radiographic presentation of Mycobacterium kansasii lung disease in patients with HIV infection. Chest. Apr; 2008 133(4): 875–880. [PubMed: 18263685]
32. Hartman TE, Primack SL, Muller NL, Staples CA. Diagnosis of thoracic complications in AIDS: accuracy of CT. AJR Am J Roentgenol. Mar; 1994 162(3):547–553. [PubMed: 8109494]
33. Gruden JF, Huang L, Webb WR, Gamsu G, Hopewell PC, Sides DM. AIDS-related Kaposi sarcoma of the lung: radiographic findings and staging system with bronchoscopic correlation. Radiology. May; 1995 195(2):545–552. [PubMed: 7724781]
34. McGuinness G, Scholes JV, Jagirdar JS, et al. Unusual lymphoproliferative disorders in nine adults with HIV or AIDS: CT and pathologic findings. Radiology. Oct; 1995 197(1):59–65. [PubMed: 7568855]
35. Staples CA, Kang EY, Wright JL, Phillips P, Muller NL. Invasive pulmonary aspergillosis in AIDS: radiographic, CT, and pathologic findings. Radiology. Aug; 1995 196(2):409–414. [PubMed: 7617853]
36. Edinburgh KJ, Jasmer RM, Huang L, et al. Multiple pulmonary nodules in AIDS: usefulness of CT in distinguishing among potential causes. Radiology. Feb; 2000 214(2):427–432. [PubMed: 10671590]
37. Jasmer RM, Edinburgh KJ, Thompson A, et al. Clinical and radiographic predictors of the etiology of pulmonary nodules in HIV-infected patients. Chest. Apr; 2000 117(4):1023–1030. [PubMed: 10767234]
38. Gold JA, Rom WN, Harkin TJ. Significance of abnormal chest radiograph findings in patients with HIV-1 infection without respiratory symptoms. Chest. May; 2002 121(5):1472–1477. [PubMed: 12006431]
39. Richards PJ, Riddell L, Reznek RH, Armstrong P, Pinching AJ, Parkin JM. High resolution computed tomography in HIV patients with suspected Pneumocystis carinii pneumonia and a normal chest radiograph. Clin Radiol. Oct; 1996 51(10):689–693. [PubMed: 8893636]
40. Hidalgo A, Falco V, Mauleon S, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non- Pneumocystis carinii pneumonia in AIDS patients. Eur Radiol. May; 2003 13(5):1179–1184. [PubMed: 12695843]
41. McGuinness G, Naidich DP, Garay S, Leitman BS, McCauley DI. AIDS associated bronchiectasis: CT features. J Comput Assist Tomogr. Mar-Apr;1993 17(2):260–266. [PubMed: 8384223]
42. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med. Feb 1; 2011 183(3):388–395. [PubMed: 20851926]
43. Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. Chest. Dec; 2008 134(6):1287–1298. [PubMed: 19059959]
44. Madeddu G, Fois AG, Calia GM, et al. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? *Infection*. Apr. 2013; 41(2):347–353.
45. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. Dec; 2009 52(5):611–622. [PubMed: 19770804]
46. Guaraldi G, Besutti G, Scaglioni R, et al. The burden of image based emphysema and bronchiolitis in HIV-infected individuals on antiretroviral therapy. PLoS ONE. 2014; 9(10):e109027. [PubMed: 25354261]
47. Drummond MB, Kirk GD, Astemborski J, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. Thorax. Apr; 2012 67(4):309–314. [PubMed: 22090038]

48. Attia EF, Akgun KM, Wongtrakool C, et al. Increased risk of radiographic emphysema in HIV is associated with elevated soluble CD14 and nadir CD4. Chest. Dec 1; 2014 146(6):1543–1553. [PubMed: 25080158]
49. Sigel K, Wisnivesky J, Shahrir S, et al. Findings in asymptomatic HIV-infected patients undergoing chest computed tomography testing: implications for lung cancer screening. AIDS. Apr 24; 2014 28(7):1007–1014. [PubMed: 24401647]
50. Busi Rizzi E, Schinina V, Palmieri F, Girardi E, Bibbolino C. Radiological patterns in HIV-associated pulmonary tuberculosis: comparison between HAART-treated and non-HAART-treated patients. Clin Radiol. Jun; 2003 58(6):469–473. [PubMed: 12788316]
51. Marras TK, Morris A, Gonzalez LC, Daley CL. Mortality prediction in pulmonary Mycobacterium kansasii infection and human immunodeficiency virus. Am J Respir Crit Care Med. Oct 1; 2004 170(7):793–798. [PubMed: 15215152]
52. Samperiz G, Guerrero D, Lopez M, et al. Prevalence of and risk factors for pulmonary abnormalities in HIV-infected patients treated with antiretroviral therapy. HIV Med. Jul; 2014 15(6):321–329. [PubMed: 24314004]
53. Crothers K, Thompson BW, Burkhardt K, et al. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. Proc Am Thorac Soc. Jun; 2011 8(3):275–281. [PubMed: 21653528]
54. Crothers K, McGinnis K, Kleerup E, et al. HIV infection is associated with reduced pulmonary diffusing capacity. J Acquir Immune Defic Syndr. Nov 1; 2013 64(3):271–278. [PubMed: 23979001]
55. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. Aug; 2005 26(2):319–338. [PubMed: 16055882]
56. Macintyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. Oct; 2005 26(4):720–735. [PubMed: 16204605]
57. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. Jan; 1999 159(1):179–187. [PubMed: 9872837]
58. Neas LM, Schwartz J. The determinants of pulmonary diffusing capacity in a national sample of U.S. adults. Am J Respir Crit Care Med. Feb; 1996 153(2):656–664. [PubMed: 8564114]
59. Leader JK, Zheng B, Rogers RM, et al. Automated lung segmentation in X-ray computed tomography: development and evaluation of a heuristic threshold-based scheme. Acad Radiol. Nov; 2003 10(11):1224–1236. [PubMed: 14626297]
60. Muller NL, Staples CA, Miller RR, Abboud RT. “Density mask”. An objective method to quantitate emphysema using computed tomography. Chest. Oct; 1988 94(4):782–787. [PubMed: 3168574]
61. Gevenois PA, de Maertelaer V, De Vuyst P, Zanen J, Yernault JC. Comparison of computed density and macroscopic morphometry in pulmonary emphysema. Am J Respir Crit Care Med. Aug; 1995 152(2):653–657. [PubMed: 7633722]
62. Wang Z, Gu S, Leader JK, et al. Optimal threshold in CT quantification of emphysema. Eur Radiol. Apr; 2013 23(4):975–984. [PubMed: 23111815]
63. Lederer DJ, Enright PL, Kawut SM, et al. Cigarette smoking is associated with subclinical parenchymal lung disease: the Multi-Ethnic Study of Atherosclerosis (MESA)-lung study. Am J Respir Crit Care Med. Sep 1; 2009 180(5):407–414. [PubMed: 19542480]
64. Washko GR, Hunninghake GM, Fernandez IE, et al. Lung volumes and emphysema in smokers with interstitial lung abnormalities. N Engl J Med. Mar 10; 2011 364(10):897–906. [PubMed: 21388308]
65. Podolanczuk A, Sonti R, Kawut SM, et al. Cross-sectional associations of ICAM-1 and HDL with subclinical interstitial lung disease (ILD): The MESA Lung Fibrosis Study. Am J Respir Crit Care Med. 2014; 189:A3928.
66. Duffy P, Wang X, Lin PH, Yao Q, Chen C. HIV Nef protein causes endothelial dysfunction in porcine pulmonary arteries and human pulmonary artery endothelial cells. J Surg Res. Oct; 2009 156(2):257–264. [PubMed: 19540523]

67. Kline ER, Sutliff RL. The roles of HIV-1 proteins and antiretroviral drug therapy in HIV-1-associated endothelial dysfunction. J Investig Med. Jun; 2008 56(5):752–769.

68. Bankier AA, De Maertelaer V, Keyzer C, Gevenois PA. Pulmonary emphysema: subjective visual grading versus objective quantification with macroscopic morphometry and thin-section CT densitometry. Radiology. Jun; 1999 211(3):851–858. [PubMed: 10352615]

69. Cavigli E, Camiciottoli G, Diciotti S, et al. Whole-lung densitometry versus visual assessment of emphysema. Eur Radiol. Jul; 2009 19(7):1686–1692. [PubMed: 19224221]

70. Cederlund K, Bergstrand L, Hogberg S, et al. Visual classification of emphysema heterogeneity compared with objective measurements: HRCT vs spiral CT in candidates for lung volume reduction surgery. Eur Radiol. May; 2002 12(5):1045–1051. [PubMed: 11976845]

71. COPDGene CT, Workshop Group, Barr RG, Berkowitz EA, et al. A combined pulmonary-radiology workshop for visual evaluation of COPD: study design, chest CT findings and concordance with quantitative evaluation. COPD. Apr; 2012 9(2):151–159. [PubMed: 22429093]

72. Hersh CP, Washko GR, Jacobson FL, et al. Interobserver variability in the determination of upper lobe-predominant emphysema. Chest. Feb; 2007 131(2):424–431. [PubMed: 17296643]

73. Mets OM, Smit EJ, Mohamed Hoesein FA, et al. Visual versus automated evaluation of chest computed tomography for the presence of chronic obstructive pulmonary disease. PLoS ONE. 2012; 7(7):e42227. [PubMed: 22848747]

74. Hersh CP, Make BJ, Lynch DA, et al. Non-emphysematous chronic obstructive pulmonary disease is associated with diabetes mellitus. BMC Pulm Med. 2014; 14:164. [PubMed: 25341556]

75. Johannessen A, Skorge TD, Bottai M, et al. Mortality by level of emphysema and airway wall thickness. Am J Respir Crit Care Med. Mar 15; 2013 187(6):602–608. [PubMed: 23328525]

76. Yahaba M, Kawata N, Iesato K, et al. The effects of emphysema on airway disease: correlations between multi-detector CT and pulmonary function tests in smokers. Eur J Radiol. Jun; 2014 83(6):1022–1028. [PubMed: 24703520]

Table 1
Characteristics of HIV-infected participants receiving and not receiving ART

Characteristics	HIV-infected (n=510)	HIV-infected on ART (n=350)	HIV-infected not on ART (n=143)
Male, n (%)	412 (81)	284 (81)	114 (80)
Age, mean yrs. (SD)	48.9 (9.5)	50.7 (9.1)*	44.8 (9.3)
ART use, n (%)	350 (68)		
Race			
White, n (%)	255 (50)	179 (51)	65 (45)
Black, n (%)	236 (46)	157 (45)	74 (52)
Other, n (%)	19 (4)	14 (4)	4 (3)
Smoking status			
Current, n (%)	325 (64)	191 (55) *	117 (82)
Former, n (%)	108 (21)	94 (27)*	14 (10)
Never, n (%)	77 (15)	65 (19)*	12 (8)
Smoking pack-years among ever smokers, median (IQR)	18.4 (29.1)	17.6 (31.3)	19.2 (25.9)
Injection drug use, n (%)	124 (24)	95 (27)	28 (20)
Marijuana use, n (%)	405 (79)	286 (82)	106 (74)
Prior bacterial pneumonia, n (%)	138 (27)	97 (28)	39 (27)
Prior *Pneumocystis* pneumonia, n (%)	55 (11)	39 (11)	12 (8)
CD4 cell count, median cells/μL (IQR)	466 (398)	471 (403)	442 (441)
CD4 cell count < 200 cells/μL, n (%)	67 (13)	45 (13)	21 (15)
HIV viral load, median copies/mL, median (IQR)	48 (220)	48 (11)*	599 (18797)
HIV viral load < 500 copies/mL, n (%)	311 (61)	247 (71)	52 (36)
FEV1%, post-bronchodilator, mean (SD)	95.1 (16.5)	95.1(17.1)	95.9(14.2)
FVC%, post-bronchodilator, mean (SD)	98.6 (14.4)	98.3(14.8)	99.9(13.3)
FEV1/FVC, post-bronchodilator, mean (SD)	77.0 (10.0)	76.0 (9.0)	77.0 (8.0)
DLco%, mean (SD)	70.6 (17.5)	69.4(18.2)*	73.6(15.9)
Perc950, mean (SD)	2.3 (3.6)	2.5 (4.0)	1.9 (2.4)
Perc950 > 2.5%, n (%)	128 (25.1)	94 (26.9)	30 (21.0)
Perc950 > 5.0%, n (%)	47 (9.2)	35 (10.0)	10 (7.0)
PercHAA, mean (SD)	4.8 (2.6)	4.4 (2.3)*	5.7 (3.2)
PercHAA > 5.0%, n (%)	150 (29.4)	78 (22.3)*	65 (45.5)
PercHAA > 10.0%, n (%)	29 (5.7)	12 (3.4)	16 (11.2)

* p-value < 0.05 for difference between subjects on and not on ART

ART – antiretroviral therapy; FEV1% – percent predicted forced expiratory volume in one second; FVC% – percent predicted forced vital capacity; FEV1/FVC – percentage of FEV1 to FVC; DLco% – percent predicted lung diffusion capacity of carbon dioxide; Perc950 – percentage of voxels less than -950HU; PercHAA – percentage of voxels between -600HU and -250HU.

Table 2

Pearson Correlation coefficients between demographics, lung function, and CT image metrics in HIV-infected participants (n = 510)

	Perc950(voxels associated with emphysema)	PercHAA(voxels associated with fibrosis-like changes)
Age	0.283*	-0.239*
Pack-years	0.164*	0.014
CD4 cell count (cells/uL)	-0.018	0.004
HIV viral load (copies/mL)	-0.096	0.210*
FEV1%	-0.054	-0.133*
FVC%	0.146*	-0.173*
FEV1/FVC	-0.301*	0.085
DLco%	0.002	-0.032

* p-value < 0.05

Perc950 – percentage of voxels less than -950HU; PercHAA – percentage of voxels between -600HU and -250HU; FEV1% – percent predicted forced expiratory volume in one second; FVC% – percent predicted forced vital capacity; FEV1/FVC – percentage of FEV1 to FVC; DLco% – percent predicted lung diffusion capacity of carbon dioxide.

Table 3

Step-wise, multivariable linear regression against fibrosis-like changes in the lung (PercHAA) that included HIV viral load for all HIV-infected participants (n=510)

	Model 1		
	Unstandardized coefficients	**T-value**	**p-value**
Constant	-2.986	-16.84	<.0001
HIV viral load			
< 500 copies/ml	0.107	2.24	0.0255
≥ 500 copies/ml	0.000	--	--
Age	-0.009	-3.57	0.0004
Race			
White	0.115	0.97	0.3302
Black	0.072	0.60	0.5461
Other	0.000	--	--
Smoking			
Current	0.141	2.16	0.0317
Ever	0.042	0.54	0.5921
Never	0.000	--	--