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Authors

Crothers, Kristina
McGinnis, Kathleen
Kleerup, Eric
et al.

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HIV Infection is associated with reduced pulmonary diffusing capacity

Kristina Crothers[1], **Kathleen McGinnis**[2], **Eric Kleerup**[3], **Cherry Wongtrakool**[4], **Guy Soo Hoo**[5], **Joon Kim**[6], **Amir Sharafkhaneh**[7], **Laurence Huang**[8], **Zhaoyu Luo**[9], **Bruce Thompson**[9], **Philip Diaz**[10], **Gregory D. Kirk**[11], **William Rom**[12], **Roger Detels**[3], **Lawrence Kingsley**[2], and **Alison Morris**[2]

[1] University of Washington, Seattle, WA

[2] University of Pittsburgh, Pittsburgh, PA

[3] University of California, Los Angeles, Los Angeles, CA

[4] Atlanta VAMC and Emory University, Atlanta, GA

[5] West Greater Los Angeles VAMC and David Geffen School of Medicine at UCLA, Los Angeles, CA

[6] James J. Peters Bronx VAMC, Bronx, NY

[7] Michael E. DeBakey Houston VAMC and Baylor College of Medicine, Houston, TX

[8] University of California, San Francisco, San Francisco, CA

[9] Clinical Trials and Survey Corporation, Bethesda, MD

[10] Ohio State University Medical Center, Columbus, OH

[11] Johns Hopkins University, Baltimore, MD

[12] New York University School of Medicine, New York, NY

Abstract

Rationale: Prior studies comparing abnormalities in pulmonary function between HIV-infected and HIV-uninfected persons in the current era are limited.

Objectives: To determine the pattern and severity of impairment in pulmonary function in HIV-infected compared to HIV-uninfected individuals.

Methods: Cross-sectional analysis of 300 HIV-infected and 289 HIV-uninfected men enrolled from 2009-2011 in two clinical centers of the Lung HIV Study. Participants completed pre- and post-bronchodilator spirometry, diffusing capacity (DLCO) measurement, and standardized questionnaires.

Results: Most participants had normal airflow; 18% of HIV-infected and 16% of HIV-uninfected men had airflow obstruction. The mean percent predicted DLCO was 69% in HIV-infected vs.

Corresponding Author: Kristina Crothers, MD Associate Professor University of Washington Harborview Medical Center 325 9th Avenue PO Box Seattle, WA 98104 Office: (206) 744 9870 Fax: (206) 744.

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76% in HIV-uninfected men (p<0.001). A moderately to severely reduced DLCO of ≤60% was observed in 30% of HIV-infected compared to 18% of HIV-uninfected men (p<0.001), despite the fact that 89% of those with HIV were on antiretroviral therapy. A reduced DLCO was significantly associated with HIV and CD4 cell count in linear regression adjusting for smoking and other confounders. The DLCO was lowest in HIV-infected men with CD4 cell counts <200 compared to those with CD4 cell counts ≥200 and to HIV-uninfected men. Respiratory symptoms of cough, phlegm and dyspnea were more prevalent in HIV-infected patients particularly those with abnormal pulmonary function compared to HIV-uninfected patients.

Conclusions: HIV infection is an independent risk factor for reduced DLCO, particularly in individuals with a CD4 cell count below 200. Abnormalities in pulmonary function among HIV-infected patients manifest clinically with increased respiratory symptoms. Mechanisms accounting for the reduced DLCO require further evaluation.

Keywords

Pulmonary function; FEV1; DLCO; gas exchange; COPD; HIV/AIDS

INTRODUCTION

The aging of the HIV-infected population has resulted in a changing spectrum of disease. Mortality related to AIDS-defining conditions has decreased markedly for those on effective antiretroviral therapy (ART),[1, 2] whereas co-morbid non-AIDS-defining conditions now account for the majority of deaths in recent studies.[2-6] Since the early days of the AIDS epidemic, pulmonary diseases have been among the most frequent complications of HIV.[7-9] Consistent with other co-morbid complications, the spectrum of pulmonary diseases now reflects a substantial burden of non-AIDS defining chronic diseases, especially chronic obstructive pulmonary disease (COPD).[10-15]

While some of the burden of pulmonary disease is explained by the high prevalence of smoking, HIV infection appears to confer an independent increase in the risk for chronic lung diseases, particularly COPD.[10, 11, 16-18] Pulmonary function abnormalities and respiratory symptoms are common in HIV-infected patients, with approximately 20% having irreversible airflow obstruction on spirometry, and >30% reporting cough, phlegm, wheeze or dyspnea.[19-21] However, prior studies directly comparing pulmonary function between HIV-infected and HIV-uninfected persons in the current ART era are limited, and importantly have not assessed post-bronchodilator spirometry or diffusing capacity of the lung for carbon monoxide (DLCO).[12, 19, 20] A low DLCO was first noted in HIV-infected patients prior to the combination ART era,[22, 23] and while recent studies of HIV-infected persons have found that a substantial proportion have an abnormally reduced DLCO,[14, 20] these have not included an HIV-uninfected comparator group.

Therefore, we sought to determine the pattern and severity of impairment in pulmonary function in a large cohort HIV-infected and HIV-uninfected individuals. We also asked whether pulmonary function was associated with markers of HIV severity. These analyses utilized data from HIV-infected and HIV-uninfected men participating in two clinical centers of the Lung HIV Study,[24] a multicenter study of pulmonary disease in HIV infection sponsored by the Lung Division of the National Institutes of Health (NIH), National Heart Lung and Blood Institute (NHLBI). Some of these results have been reported previously in the form of an abstract.[25]

METHODS

Overview of population

We performed a cross-sectional analysis of 300 HIV-infected and 289 HIV-uninfected men enrolled from 2009-2011 in the Lung HIV Study, a longitudinal cross-cohort collaboration examining pulmonary complications in the ART era.[24] Participants from two Lung HIV Clinical Centers that obtained DLCO measurements in HIV-infected and uninfected patients were included, namely the pulmonary substudy of the Multicenter AIDS Cohort (MACS)[26] and the Examinations of HIV Associated Lung Emphysema (EXHALE) Study, a substudy of the Veterans Aging Cohort Study (VACS).[27, 28] The MACS pulmonary study enrolled patients from the Pittsburgh and Los Angeles sites, and the EXHALE study enrolled patients from the Atlanta, Bronx, Houston and Los Angeles VA Medical Centers. Only men were included in these analyses because MACS is an all-male cohort and very few women were enrolled in EXHALE. All participants signed written informed consent, and the study was approved by the Institutional Review Boards at each participating center.

HIV-infected and uninfected outpatients in the MACS and VACS were approached for participation. Those with acute respiratory infections or illnesses in the past 4 weeks were excluded. A history of chronic lung diseases was not required for enrollment. Within the EXHALE study, HIV-infected and uninfected participants were matched by current smoking status; those with a history of lung diseases other than COPD or asthma, including lung cancer, were excluded. In the MACS substudy, consecutive HIV-infected and uninfected participants were selected to reflect the distributions within the parent study of smoking and the presence of respiratory symptoms in order to avoid bias in recruiting primarily smokers or symptomatic individuals who might be more willing to participate in a study of lung function.

Pulmonary function testing

All participants completed pulmonary function tests (PFTs) at study enrollment per American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines,[29, 30] including pre- and post-bronchodilator spirometry and single breath DLCO. Within both studies, PFTs were obtained by certified, trained respiratory technicians or research personnel. PFTS were obtained in the clinical pulmonary function laboratories at the associated medical center in the EXHALE study, and within research pulmonary function laboratories in the MACS substudy. PFT results were reviewed by site pulmonologists or study investigators for quality control; those not meeting ATS criteria for acceptability and reproducibility were not included in these analyses. Airflow obstruction was defined as a ratio of the post-bronchodilator forced expiratory volume in one second (FEV_1) to the forced vital capacity (FVC) below 0.70.[31] In secondary analyses, airflow obstruction was defined as an FEV_1/FVC ratio below the lower limit of normal (LLN); as results were similar, we present the results using a ratio below 0.70. Predicted normal values (% predicted) for spirometry were determined using Hankinson formulas[32], and using Neas formulas for DLCO.[33] Both include adjustments for age, race/ethnicity, gender, and height; % predicted DLCO values were also corrected for hemoglobin. A positive bronchodilator response was present if the FEV_1 and/or FVC increased by at least 12% and 200 mL following bronchodilator administration.[34] Severity of airflow obstruction was graded based on the FEV_1.[31] Impairment in DLCO corrected for hemoglobin was based upon ATS/ERS standards, with a threshold of ≤60% of predicted indicating moderate or greater impairment, and ≤40% of predicted reflecting severe impairment.[34]

Other data collection

Participants completed a standardized questionnaire assessing history of lung diseases, smoking and other exposures using previously published instruments.[24] Similar questions were used in the EXHALE and the MACS substudy. Smoking status and pack-years of smoking were defined consistently. Participants who reported <100 lifetime cigarettes were defined as never smokers; as current smokers if they had smoked within the past 12 months; and as former smokers if they had quit >12 months ago. Pack-years were calculated based upon number of cigarettes smoked per day on average and years smoked; never smokers were considered to have zero pack-years of exposure. Within the MACS substudy, recent drug use was defined as within 6 months, and within EXHALE, recent use was defined as within 12 months. Questions regarding respiratory symptoms of usual cough, usual phlegm, and prior attacks of wheezing that have been associated with shortness of breath were taken from previously published instruments;[35] shortness of breath with activity was quantified using the modified Medical Research Council (MRC) dyspnea score.[36, 37] The MRC dyspnea score was dichotomized at 2 and above as suggested in published guidelines,[31] corresponding to the need to stop for breath when walking at one's own pace on level ground or greater limitation. HIV viral load (copies/ml) and CD4 cell counts (cells/μl) were obtained within 12 months of pulmonary function testing. Recorded nadir CD4 cell count prior to PFTs was dichotomized as ≥ or <200. ART use was captured from the MACS and VACS datasets.[26, 27]

Statistical analysis

To ensure that results were similar within each cohort, analyses were first stratified by cohort. As results were consistent with similar associations and magnitude of difference in PFT results by HIV status, we proceeded with the combined EXHALE and MACS cohort analyses. Baseline characteristics in HIV-infected and HIV-uninfected men were compared using t-tests and Wilcoxon rank-sum tests for parametric or non-parametric continuous variables respectively, and chi-squared tests for categorical variables. To determine the association of HIV with impairment in pulmonary function, potential risk factors were first examined in bivariate models. Then, multivariable linear regression models were used with % predicted DLCO as the outcome, and included HIV, an indicator variable for clinical center, smoking and other potential confounders. Predictors that were significant at $p<0.1$ in bivariate analyses were included in the multivariable models and were retained if statistically significant at $p<0.05$ or if they had a substantive effect on other coefficients.

Because smoking is a major potential confounder, we modeled smoking in several ways, including by deciles of pack-years. The risk of impaired pulmonary function did not increase linearly, but displayed a threshold effect at 35 pack-years; this level was more strongly associated with PFT results than smoking status. Therefore, we modeled smoking exposure as 0 pack-years, 0-34, and ≥35 pack-years in multivariable analysis.

To determine the association of pulmonary function impairment with markers of HIV, we stratified participants by HIV and CD4 cell count, assuming those without HIV to have a CD4 cell count ≥350. HIV-infected participants were divided into groups by CD4 cell count ≥350, 200-349, and <200 cells/μl. Because associations were similar in multivariable regression for those with CD4 cell counts of ≥350 cells/μl and 200-349 cells/μl, these groups were combined in final analysis. We also compared associations with HIV RNA >500 or <500 copies/ml, using HIV-uninfected participants as the referent group. This study was adequately powered at >80% to detect a 7.5% relative difference in means for FEV_1, FVC, FEV_1/FVC and % predicted DLCO between HIV-infected and HIV-uninfected groups. There was also sufficient power to detect an absolute difference of 10% for $FEV_1/FVC<0.70$ and DLCO ≤60% predicted (power of 82% and 79%, respectively).

RESULTS

Demographic and clinical characteristics

Our cohort included 300 HIV-infected and 289 HIV-uninfected men with a mean age of 54 (Table 1); 51% were from VA sites. The VA and MACS patients were comparable, although the VA patients were slightly older and more likely to be current smokers (data not otherwise shown). The combined cohort was racially and ethnically diverse. Overall, more HIV-infected men were current smokers compared to HIV-uninfected men (47% vs. 35%, p=0.007) and had more pack-years of smoking. HIV-infected men were also more likely to have smoked marijuana and used injection drugs (Table 1). As very few participants had used injection drugs recently, current and former use were combined into a composite variable reflecting ever use in subsequent analyses. HIV-infected men were also more likely to report a history of prior bacterial or *Pneumocystis* pneumonia.

Prevalence of PFT abnormalities in HIV-infected compared to HIV-uninfected men

The majority of both HIV-infected and HIV-uninfected men had normal airflow on spirometry (Table 2), with an average FEV_1 post-bronchodilator of >90% of predicted. There was no significant difference in the proportion of HIV-infected compared to HIV-uninfected participants with an $FEV_1/FVC<0.70$ post-bronchodilator or with a positive bronchodilator response. Overall, 18% of HIV-infected and 16% of HIV-uninfected men met criteria for airflow obstruction (p=0.5).

Mean DLCO was significantly lower in HIV-infected compared to HIV-uninfected men (Table 2). Overall, 30% of HIV-infected participants had a DLCO that was ≤60% of predicted compared to 18% of HIV-uninfected participants (p=0.001). HIV-infected participants were also more likely to have greater DLCO impairment across all ATS/ERS severity categories of DLCO (Figure 2). Patients with a DLCO ≤60% predicted were significantly more likely to have ever smoked compared to those with a higher DLCO. Among HIV-infected participants, 92% of those with a DLCO ≤60% vs. 66% of those with a DLCO >60% had ever smoked (p<0.005).

The predominant pulmonary function abnormality observed was an isolated reduction in DLCO. An equal proportion (61%) of HIV-infected and HIV-uninfected participants with a DLCO ≤60% of predicted did not have concomitant airflow obstruction. Among participants with airflow obstruction, the mean % predicted DLCO was substantially lower among those with HIV compared to those without, with a mean (standard deviation (SD)) of 56 (21) vs. 67 (22) respectively, p=0.008. Among participants without airflow obstruction, the mean % predicted DLCO (SD) was also significantly lower among HIV-infected compared to HIV-uninfected men: 73 (17) vs. 77 (17), p=0.005.

PFT results stratified by markers of HIV disease severity

In bivariate analyses stratified by HIV and CD4 cell count, airflow obstruction was present in 36% of HIV-infected men with a CD4 cell count <200 cells/μl compared to 16% with a CD4 cell count 200 to 349, 17% with a CD4 cell count ≥350, and 16% of HIV-uninfected men (p=0.09) (Figure 1). There was no statistically significant relationship in the prevalence of airflow obstruction according to HIV viral load: 24% with HIV viral load >500 had airflow obstruction compared to 17% with viral load ≤500 copies/ml and 16% of HIV-uninfected participants (p=0.4).

However, DLCO was associated with both recent as well as nadir CD4 cell count; the relationship appeared more strongly related to recent CD4 cell count (Supplemental Table 1). HIV-infected men with a recent CD4 cell count <200 as well as those with a CD4

between 200 to 349 had a significantly lower DLCO when compared to HIV-infected men with a CD4 cell count ≥350 and to HIV-uninfected men (Figure 1). The % predicted DLCO (mean (SD)) was 58 (12) in HIV-infected men with CD4 <200 cells/μl; 67 (17) in those with CD4 200 to <350; 72 (19) in those with CD4 ≥350; and 76 (18) in HIV-uninfected men, p=0.001.

DLCO was also significantly associated with HIV viral load (Supplemental Table 1). The mean % predicted DLCO (SD) in HIV-infected participants with a viral load of >500 copies/ml was 66 (18) compared to 71 (19) in the HIV-infected participants who were virally suppressed, and 76 (18) in the HIV-uninfected (p=0.001). Overall, 34% of HIV-infected men with a viral load >500 copies/ml had a DLCO ≤60% of predicted normal, compared to 30% of HIV-infected men with HIV RNA below this level and 18% of HIV-uninfected men, p=0.002.

HIV as an independent risk factor for decreased DLCO

After evaluating factors associated with DLCO in bivariate analyses, we determined independent risk factors for % predicted DLCO, corrected for hemoglobin, in multivariable linear regression (Table 4). Although prior *Pneumocystis* pneumonia, tuberculosis, and injection drug use were significantly associated with DLCO in bivariate analyses, they were no longer significant in multivariable analyses. HIV viral load and CD4 cell count were both associated with DLCO but were collinear; CD4 was chosen because the association with DLCO was stronger. Thus, after adjusting for race-ethnicity, pack-years of smoking and clinical center, we found that HIV status remained significantly associated with a decreased DLCO % predicted. Stratifying participants by HIV and recent CD4 cell count, DLCO was significantly lower in the HIV-infected groups with a CD4 cell count <200 (beta-coefficient −11.6, 95% confidence interval [CI] −18.4 to −4.8) and with a CD4 cell count ≥200 cells/μl (beta-coefficient −3.7, 95% CI −6.4 to −0.88) when compared to those without HIV infection.

Association of PFT results with respiratory symptoms

To assess the clinical significance of abnormal PFT results with patient-reported outcomes, we compared the association between respiratory symptoms and abnormalities in PFTs. Compared to HIV-uninfected participants, HIV-infected participants were significantly more likely to report usual cough (28 vs. 20%, p=0.03) and usual phlegm (33% vs. 24%, p=0.03), whereas the prevalence of wheezing was similar (26% vs 24%, p=0.7). HIV-infected participants tended to have greater dyspnea on exertion (15 vs 10% with MRC dyspnea score of 2 or greater, p=0.058). HIV-infected participants with abnormal lung function defined by an FEV_1/FVC ratio <0.70 or a DLCO ≤60% of predicted were significantly more likely to have usual cough, phlegm and dyspnea compared to HIV-infected participants who did not meet criteria for fixed airflow obstruction or who had a higher DLCO (Table 4). In contrast, the difference between the proportions of HIV-uninfected participants with respiratory symptoms according to PFT results was not as marked. Restricted to those with a DLCO ≤60% predicted, HIV-infected compared to HIV-uninfected participants were more likely to have cough (42% vs. 26%, p=0.04), although the difference in those with phlegm (42% vs. 29%, p=0.1) and dyspnea (29% vs. 16%, p=0.1) was not statistically significant. Restricted to those with an FEV_1/FVC<0.70, HIV-infected compared to HIV-uninfected participants were significantly more likely to have cough (53% vs. 21%, p=0.001), phlegm (58% vs. 20%, p<0.001) and dyspnea (31% vs. 11%, p=0.02), whereas the proportions with wheezing were similar. Among persons without pulmonary function abnormalities, the prevalence of respiratory symptoms was equivalent by HIV status.

DISCUSSION

In the first large-scale and multicenter cohort to examine pulmonary function including DLCO in HIV-infected and HIV-uninfected men in the current ART era, we found that HIV infection was an independent predictor of decreased DLCO after accounting for smoking and other potential confounders. Additionally, markers of greater HIV severity, including higher HIV viral load, recent CD4 cell count, and a nadir CD4 cell count <200 were all associated with lower DLCO. In multivariable models, DLCO was significantly lower in the HIV-infected groups with a CD4 cell count <200 and with a CD4 cell count ≥200 cells/μl when compared to those without HIV infection. Measures of airflow and the likelihood of airflow obstruction were similar in HIV-infected and HIV-uninfected participants, although the proportion with airflow obstruction tended to be greater in those with a CD4 cell count <200. Notably, our cohort had a high prevalence of smoking, even in the HIV-uninfected participants that was substantially higher than the general population.

The prevalence of a decreased DLCO, despite the fact that 89% of the HIV-infected men were on ART, was striking. A DLCO less than 60% of predicted, which is consistent with moderate to severe impairment, was significantly more likely in HIV-infected compared to uninfected men, and was present in 30% of those with HIV. The prevalence of a reduced DLCO is important to consider in light of published guidelines and common clinical practice that often involve only screening spirometry to evaluate for respiratory disease.[31] In our cohort, spirometry alone would have missed a substantial gas exchange abnormality in many of the HIV-infected and uninfected participants; considering HIV-infected individuals, 61% of those with moderate to severely reduced DLCO had an isolated reduction without accompanying airflow obstruction.

These data are significant because both FEV_1 and DLCO are important clinical indicators of patient outcomes. The FEV_1, in particular, is an established measure associated with increased mortality.[31, 38] However, a DLCO <85% predicted, in the absence of other pulmonary impairment, is also associated with increased mortality in the general population.[39] Of PFT measures, DLCO was most closely associated with mortality in a recent study.[40] DLCO has been predictive of morbidity and mortality in a number of specific pulmonary diseases as well.[41-43]

However, the clinical implications of reduced pulmonary function are not fully understood in HIV-infected populations. We found that HIV-infected patients with a low DLCO or airflow obstruction were significantly more likely to have increased respiratory symptoms, including usual cough and phlegm, as well as dyspnea compared to HIV-infected patients with higher DLCO and with no airflow obstruction. Further, respiratory symptoms were notably more prominently expressed among HIV-infected patients with abnormal pulmonary function than among HIV-uninfected patients. A DLCO ≤80% predicted has been associated with a greater prevalence of respiratory complaints in HIV-infected persons in another study.[14] In addition, a reduced DLCO could play a role in the decreased functional capacity[44] and aerobic capacity in HIV-infected persons.[45] Additional longitudinal studies of patient outcomes are required to fully evaluate the significance of our findings.

There are multiple diseases that can contribute to impaired DLCO. The differential diagnosis includes emphysema, interstitial lung diseases (ILD), pulmonary vascular diseases (such as pulmonary arterial hypertension (PAH), chronic thromboembolic disease, or from injection drug use), as well as non-pulmonary diseases, such as congestive heart failure (CHF) with pulmonary edema. Our data suggest that the impairment in DLCO may not be attributable solely to emphysema, given that many participants had an isolated reduction in DLCO with normal airflow. Nonetheless, emphysema may still be a significant contributor, as a greater

prevalence of radiographic emphysema in the absence of airflow obstruction among HIV-infected compared to uninfected persons has been reported early in the combination ART era.[16, 46, 47] An increased risk of ILD,[10] PAH,[13, 48] and CHF[49] have also been reported in HIV-infected persons. Combined emphysematous and interstitial changes, as a consequence of smoking may also occur, [50] although the extent to which this manifests among HIV-infected persons has not been explored. Of note, patients in the EXHALE study were more likely to have a lower DLCO compared to MACS participants; this finding may reflect unmeasured confounding related to socioeconomic status, occupational or environmental exposures, and extent of drug use that Veterans may share in common, but that differ from MACS participants. Additional work understanding which disease processes are causing the decrease in DLCO will have significant implications for appropriate management of HIV-infected persons.

The pathologic mechanisms by which HIV may contribute independently to a decrease in DLCO are uncertain. The increased inflammation observed in HIV-infected individuals, particularly when more severely immunosuppressed,[51, 52] may play a significant role. Higher circulating peripheral neutrophil counts, reflective of greater inflammation, have been associated with a reduced DLCO in the general population.[33] Lymphocytic alveolitis in HIV-infected persons may play a role in reduced DLCO, particularly among those with lower CD4 cell counts.[53] Upregulation of matrix metalloproteinase expression in alveolar macrophages may be particularly important in HIV-associated emphysema.[54] In addition, the presence of subacute infection or greater likelihood of colonization with microorganisms may contribute to the pathogenesis of increased lung inflammation and impaired DLCO. While prior studies have found that a declining DLCO in HIV-infected patients with acute respiratory symptoms is suggestive of PCP,[55] it is important to note that our population consisted of stable HIV-infected outpatients without a recent change in respiratory symptoms.

The association of HIV infection with airflow obstruction remains controversial. Although we have previously shown that COPD prevalence is increased in HIV-infected persons based on ICD-9 or self-reported diagnoses,[56] there was no difference in the prevalence of airflow obstruction defined by spirometry when comparing HIV-infected to HIV-uninfected men in our current cohort. These results are similar to work by Drummond and colleagues,[12] although these authors did find an association between airflow obstruction and substantially higher HIV viral load, defined as >200,000 copies/ml, suggesting a potential pathogenetic role of HIV. There were too few participants with an HIV viral load >200,000 copies/ml (n=2) in our cohort to use this stratification, which may account for the differences between these two studies. Other studies have found an association between airflow obstruction and ART use.[14, 20] Because 89% of the HIV-infected patients were on ART, we had limited power to examine the relationship between ART and pulmonary function.

In contrast to our results and those of Drummond, Madeddu and colleagues from Italy found a lower FEV_1, FEV_1/FVC ratio, and increased prevalence of airflow obstruction in HIV-infected individuals compared to age and smoking-matched HIV-uninfected controls (23% vs. 8%, p=0.008) that remained significant in multivariable analysis.[15] The majority of these patients had undetectable viral load. While residual confounding or other unmeasured factors between our cohorts may explain these differences, the Italian cohort was significantly younger, with a mean age of 42. One possible explanation is that HIV infection may contribute to a decline in lung health through accelerated cellular senescence, resulting in an earlier presentation of COPD that was more pronounced in their younger cohort. It is also possible that in our older cohort, men with more severely compromised lung function have already died, minimizing differences between those with and without HIV, as the mortality rate among HIV-infected individuals still exceeds that of the uninfected.

Our study has a number of strengths. This is the first study to compare results of pre- and post-bronchodilator spirometry and DLCO in HIV-infected and uninfected men in the current era. The participants were enrolled from the MACS and VACS, two large and multicenter ongoing HIV cohort studies with carefully characterized clinical data. PFTs were measured systematically in a standardized fashion. Our cohort was also racially and geographically diverse, with centers located throughout the US.

Our study has certain limitations. Due to technical issues, we were unable to systematically obtain measures of carboxyhemoglobin at all sites and therefore were unable to adjust the DLCO for carboxyhemoglobin. However, all participants were asked to refrain from smoking for at least 6 hours prior to testing, DLCO was corrected for hemoglobin, and adjusted for other potential confounders in multivariable models. Pulmonary function testing was of necessity performed at multiple labs, but all laboratories operated per ATS standards, trained personnel obtained PFTs at each site, and we included an adjustment for clinical center.[29, 30, 57] Finally, our results may not be generalizable to other studies or populations, as our cohort was a research cohort restricted to men.

In summary, HIV-infected men had a significantly decreased DLCO compared to HIV-uninfected men even after adjusting for smoking and other potential confounders, and despite widespread use of ART. Overall, 30% of HIV-infected men had a DLCO ≤60% of predicted normal, with the majority having an isolated reduction in diffusing capacity. Furthermore, a lower CD4 cell count was associated with a greater likelihood of a decreased DLCO. An impaired DLCO and fixed airflow obstruction were also more likely to be associated with chronic cough, phlegm and dyspnea in HIV-infected compared to uninfected participants. Whether the decreased DLCO is due to emphysema or other processes such as pulmonary vascular disease or interstitial lung disease requires further evaluation, and will have significant implications for patient care and for our understanding of the pathogenesis of HIV-related lung disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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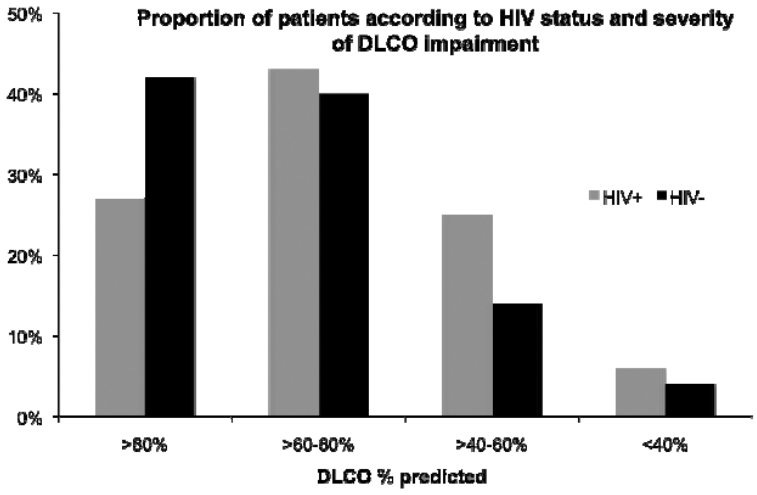
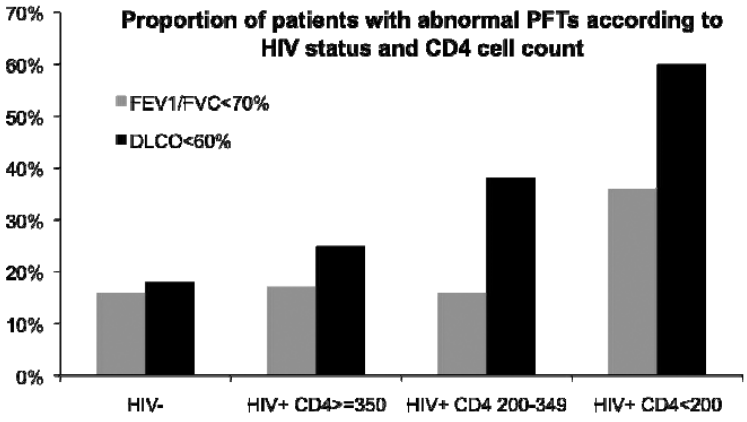


Panel A.

1. .



Panel B.

2. .

Table 1

Characteristics of HIV-infected compared to HIV-uninfected participants

Characteristics	HIV+, N=300	HIV−, N=289	p-value
Age, mean years. (SD)	54 (8)	54 (9)	0.8
Race/ethnicity			0.3
White	43%	50%	
Black	47%	40%	
Hispanic	9%	9%	
Other	1%	1%	
Smoking status			0.007
Current	47%	35%	
Former	27%	30%	
Never	26%	35%	
Smoking pack-years among ever smokers, median (SD)	26 (13-40)	20 (8-37)	0.07
Injection drug use			0.001
Current	3%	0%	
Former	23%	15%	
Never	74%	85%	
Marijuana use			0.05
Current	32%	24%	
Former	50%	50%	
Never	26%	18%	
Prior bacterial pneumonia	28%	16%	<0.001
Prior *Pneumocystis* pneumonia	10%	2%	<0.001
Prior tuberculosis	6%	5%	0.6
CD4 cell count, median (IQR)	493 (354-698)	--	
CD4 cell count <200 cells/μl	8%	--	
HIV viral load ≤500 copies/ml	84%	--	
On Antiretroviral therapy	89%	--	
Hemoglobin, mean (SD)	14.3 (1.5)	14.7 (1.2)	0.002

Table 2

PFT results by HIV status

PFT results	HIV+	HIV−	p-value
FEV_1 in L, pre-BD, mean (SD)	3.16 (0.8)	3.23 (0.8)	0.4
FEV_1, %predicted pre-BD, mean (SD)	90 (19)	91 (19)	0.5
FEV_1 in L, post-BD, mean (SD)	3.31 (0.8)	3.39 (0.8)	0.3
FEV_1, %predicted post-BD, mean	95 (19)	96 (19)	0.4
FVC in L, pre-BD, mean (SD)	4.28 (0.9)	4.35 (0.9)	0.6
FVC, %predicted pre-BD, mean (SD)	95 (16)	96 (18)	0.9
FVC in L, post-BD, mean (SD)	4.34 (0.9)	4.39 (0.9)	0.7
FVC, %predicted post-BD, mean (SD)	97 (15)	97 (16)	0.9
FEV_1/FVC post-BD, mean (SD)	0.76 (0.1)	0.78 (0.1)	0.4
FEV_1/FVC<0.70	18%	16%	0.5
Bronchodilator responsiveness*	16%	13%	0.2
Raw DLCO, mean (SD)	21.9 (6.2)	23.9 (6.3)	0.001
DLCO**, %predicted, mean (SD)	69 (19)	76 (18)	<0.001
DLCO ≤60% predicted, n%	30%	18%	<0.001

BD = Bronchodilator; DLCO = diffusing capacity of the lung for carbon monoxide; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; SD = standard deviation

*Bronchodilator responsiveness was present if the FEV_1 and/or FVC increased by at least 12% and 200 mL following bronchodilator administration.

**Percent predicted DLCO values are corrected for hemoglobin.

Table 3

Multivariable linear regression model for risk factors associated with percent predicted DLCO

Risk factor	Beta coefficient	95% CI	p-value
Race/ethnicity			
Black	1.0	−4.4 to 6.6	0.7
Hispanic/other	−5.8	−9.4 to −2.1	0.002
HIV status and CD4 cell count			
HIV uninfected (referent)	--	--	--
HIV infected, CD4 ≤200	−3.7	−6.5 to −0.88	0.01
HIV infected, CD4 <200	−11.6	−18.4 to −4.8	0.001
Smoking exposure			
Never (referent)	--		
>0 to <35 pack-years	−4.8	−8.1 to −1.5	0.004
≥35 pack-years	−15.3	−19.3 to −11.3	<0.001
EXHALE (VACS) site	−7.3	−10.9 to −3.7	<0.001

Percent predicted DLCO values were also corrected for hemoglobin.

CI = confidence interval

Table 4

Prevalence of respiratory symptoms according to HIV status and PFT results

	HIV-infected			HIV-uninfected		
Respiratory symptom	**DLCO≤60%**	**DLCO>60%**	**p-value**	**DLCO≤60%**	**DLCO>60%**	**p-value**
Usual cough	43%	21%	<0.001	26%	18%	0.2
Usual phlegm	42%	28%	0.02	29%	22%	0.3
Wheeze	26%	25%	0.8	29%	23%	0.3
MRC dyspnea≥2	29%	9%	<0.001	16%	9%	0.17
	$FEV_1/FVC<0.70$	**$FEV_1/FVC\geq0.70$**	**p-value**	**$FEV_1/FVC<0.70$**	**$FEV_1/FVC\geq0.70$**	**p-value**
Usual cough	53%	22%	<0.001	21%	19%	0.8
Usual phlegm	59%	27%	<0.001	20%	25%	0.5
Wheeze	43%	22%	0.001	33%	22%	0.1
MRC dyspnea≥2	31%	11%	<0.001	11%	10%	0.7

p-values represent comparisons by PFT strata within HIV-infected or within HIV-uninfected participants.

DLCO results are presented as above or below 60% of predicted normal.