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HIV Is Associated With Impaired Pulmonary Diffusing Capacity Independent of Emphysema

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Background: HIV is associated with accelerated decline in lung function and increased risk for chronic obstructive pulmonary disease (COPD). Recently, there has been growing attention toward the impairment in the diffusing capacity of the lungs for carbon monoxide (DLCO), a marker of pulmonary gas exchange, observed among persons living with HIV. Although increased emphysema can contribute to the DLCO impairment observed, other factors may drive this association.

Methods: Using cross-sectional data from the Study of HIV in the Etiology of Lung Disease, we studied the association between HIV and DLCO independent of emphysema. We also analyzed the joint influence of HIV and COPD on DLCO impairment. An analysis was conducted among 339 participants (229 with HIV) with lung function and chest CT imaging data. Multivariable regression models were generated with percent predicted DLCO and odds of DLCO impairment as outcomes.

Results: After adjusting for confounders, including emphysema severity, HIV was associated with lower DLCO (β −4.02%; $P = 0.020$) and higher odds of DLCO impairment (odds ratio 1.93; $P = 0.017$). Even among those without COPD, HIV was independently associated with lower DLCO (β −3.89%; $P = 0.049$). Compared with HIV-uninfected participants without COPD, those with both HIV and COPD experienced the greatest impairment in DLCO (β −14.81; $P < 0.001$).

Conclusions: HIV is associated with impaired pulmonary gas exchange independent of emphysema severity. Our data also suggest a potentially additive influence between HIV and COPD on DLCO impairment. Further studies should investigate the other factors, including pulmonary vascular disease, which may contribute to DLCO impairment among persons living with HIV.

Key Words: pulmonary function, chronic obstructive pulmonary disease, emphysema, lung disease, comorbidities

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INTRODUCTION

The impact of chronic respiratory diseases for persons living with HIV (PLWH) has received growing attention in recent years.[1,2] Previous research suggested that HIV is associated with accelerated lung function decline and an increased incidence of chronic obstructive pulmonary disease (COPD) with emphysema.[3–5] Although HIV has been associated with accelerated decline in spirometric measurements, notably the forced expiratory volume in 1 second (FEV_1), there has been increasing focus on the diffusing capacity of the lungs for carbon monoxide (DLCO), a key measurement of pulmonary gas exchange.[6,7] Evidence has suggested that HIV is linked to lower DLCO and greater odds of severe impairment in pulmonary gas exchange, even with the advent of combination antiretroviral therapy.[8] Although studies suggest an increased prevalence of emphysematous changes may contribute to the impairment in DLCO observed, the etiology behind this lung function impairment is still being studied. DLCO remains a complex lung function measurement, with emphysema, pulmonary vascular disease, and interstitial lung disease serving as factors that contribute to DLCO impairment.[7,9,10] Many studies of HIV-related lung disease focused more on following spirometry measurements over time and less on DLCO, related in part to the complexities associated with measuring DLCO.[2] To date, the relationship between HIV and DLCO impairment, distinct from emphysema, has not been fully disentangled.

The Study of HIV Infection in the Etiology of Lung Disease (SHIELD) is a longitudinal cohort study, consisting of epidemiologically matched PLWH and HIV-uninfected participants, followed to understand how HIV increases susceptibility to lung disease. The prevalence of cigarette smoking and COPD has notably been high in this cohort.[11] The cohort provided a platform to study the relationship

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between HIV and DLCO, in individuals both with and without COPD. Within this study, participants undergo spirometry measurements along with detailed clinical, laboratory, and patient-reported data collection. In a subset of participants, matched according to COPD status, research lung CT imaging and expanded lung function testing (DLCO and spirometry) were conducted.[12] Using data from SHIELD, we aimed to (1) describe the relationship between HIV and pulmonary gas exchange (DLCO) independent of emphysema and (2) identify the influence of HIV on DLCO impairment for participants with and without COPD.

METHODS

Study Cohort

The SHIELD study recruits participants from the Johns Hopkins Clinical HIV Cohort and the AIDS Linked to the Intravenous Experience (ALIVE) study. ALIVE recruits were residents of Baltimore, MD, who were aged ≥18 years and had a history of injection drug use. From 2012 to 2015, participants within the SHIELD COPD study completed DLCO measurements and a CT scan of the chest. The SHIELD COPD substudy aimed to characterize factors unique to HIV-associated COPD and recruited PLWH and uninfected participants both with and without COPD. To disentangle the impact of coexistent lung disease on outcomes of interest, both participants with COPD and normal spirometry were recruited, with oversampling of COPD among HIV-uninfected participants. For this study, COPD was defined using the modified GOLD classification of FEV_1 to forced vital capacity (FVC) (FEV_1/FVC) ratio of <0.70 from postbronchodilator spirometry.[13] This study was approved by the IRB of Johns Hopkins University, and all participants provided written informed consent.

Data Collection

Patient demographic data were selected from the study visit that correlated with the date of the DLCO measurements. Smoking patterns and ART use were determined by self-report. Routine laboratory testing at each visit included HIV serology for HIV-negative participants, in addition of PLWH; T-cell subsets; and HIV RNA (Roche Molecular Systems, Amplicor HIV-1 Monitor test version 1.5). Of note, detailed data on injection drug use and chronic hepatitis C infection (assessed by antibodies to hepatitis C) were only available for participants from the ALIVE cohort (227 participants). Spirometry (FEV_1 and FVC) and single-breath determination of DLCO were performed in accordance with the American Thoracic Society (ATS) guidelines and overread by a trained reader.[14] Percent predicted values for DLCO were determined using standardized reference equations and corrected for hemoglobin.[15]

CT Protocol and Determination of Emphysema

Noncontrast chest CTs were performed at full lung inflation. 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, and 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 Pulmonary Workstation software (VIDA Diagnostics, Coralville, IA). Percentage of emphysema was evaluated quantitatively by the calculated percentage of lung volume occupied by low-attenuation areas (voxels with attenuation of −950HU or less).[16] All CTs were reviewed by a single reader (RHB).

Statistical Analysis

Summary statistics of demographic characteristics were assessed for the overall cohort and by HIV status. To examine the contribution of HIV to DLCO impairment, multivariable linear regression models were generated with DLCO % predicted as the primary outcome. Models were adjusted for confounders including demographics, FEV_1/FVC ratio (to account for disproportionate sampling of HIV-uninfected participants with COPD), smoking (current smoking and pack-years), percent emphysema (modeled continuously), and education. Covariates were selected based on relevance from the clinical literature and exploratory data analysis. We additionally generated logistic regression models to describe the association between HIV and the odds of moderate-to-severe DLCO impairment (DLCO <60% predicted) with adjustment for the same covariates as listed above. We also compared associations with DLCO by HIV and COPD status (PLWH with COPD, HIV uninfected with COPD, and PLWH without COPD), with HIV-uninfected participants without COPD as the reference group. These models did not adjust for the FEV_1/FVC ratio as COPD status was accounted for. A secondary analysis modeled HIV by disease stage (nadir $CD4^+$ T-cell count and HIV RNA levels). HIV viral load (<400 copies/mL vs ≥400 copies/mL) and nadir CD4 cell count (<350 vs ≥350 cells/mL^3) were modeled categorically at clinical thresholds. We conducted a sensitivity analysis among ALIVE participants in SHIELD, after adjusting for injection drug use and chronic hepatitis C. A final sensitivity analysis was conducted in the full cohort that adjusted for mean lung density, a surrogate marker that may account for interstitial lung disease and emphysema, instead of emphysema alone.

RESULTS

Participant Characteristics

A total of 350 participants completed DLCO and CT scan measurements, with 11 participants excluded from the final analysis because of DLCO measurements that did not meet ATS quality standards, leaving 339 DLCO measurements available for analysis. Two hundred twenty-nine (67%) were PLWH, and 131 (39%) had COPD. Two hundred thirty-five participants (69%) were male with a median age of 50.9 (IQR 46.1–55.8) years. Demographics were similar between

PLWH and uninfected participants; however, the median pack-years was higher among HIV-uninfected participants [22 (15.0–36.5)] than in PLWH [17 (9.0–34.0)] along with current smoking status [95 (86%) vs 176 (78%)]. Among PLWH, 72 (33%) had detectable viremia, with a median CD4 T-cell count of 375 (247–571).

A high percentage of the participants had impaired DLCO. The median DCLO % predicted value was 63.2 (52.1–70.3), with 140 participants (41%) having moderate-to-severe impairment in DLCO. FEV_1 was preserved for most participants, with a median FEV_1% predicted value of 85.5 (71.0–96.3). As mentioned, a higher percentage of HIV-uninfected participants recruited for this study had COPD [71 (64%)] compared with among PLWH [60 (26%)].

Relationship Between Markers of HIV and DLCO Impairment

After adjusting for relevant covariates, including demographics, smoking (both current smoking and pack-years), and percent emphysema, HIV was associated with a significant decrease in DLCO % predicted (mean difference −4.02; $P = 0.020$) (Table 1). HIV was also associated with greater odds of DLCO impairment (DLCO <60% predicted) [odds ratio (OR) 1.93; $P = 0.017$]. When we performed a sensitivity analysis among ALIVE participants, there was still an association between HIV and decreased DLCO after adjusting for current injection drug use and hepatitis C (mean difference −5.68; $P = 0.008$).

We next aimed to understand the relationship between HIV and DLCO impairment for participants with and without COPD. A higher percentage of those with HIV and COPD [36 (60.0%)] had significant DLCO impairment vs COPD alone [34 (47.9%)] ($P < 0.001$). In adjusted models, even among those without COPD, PLWH still had greater odds of moderate-to-severe DLCO impairment (OR 2.47; $P = 0.028$) and lower DLCO % predicted values (mean difference −3.89; $P = 0.049$) than HIV-uninfected participants (Figure 1). There also seemed to be an additive effect of HIV and COPD on DLCO impairment. We observed lower DLCO values in PLWH with COPD (mean difference −14.81; $P < 0.001$) than those with COPD alone (mean difference −8.85; $P = 0.001$), when compared with the reference group of HIV-uninfected participants without COPD.

We also analyzed the relationship between markers of HIV status and DLCO impairment. When nadir $CD4^+$ T-cell counts were modeled categorically, there was lower DLCO noted for PLWH with low $CD4^+$ T-cell counts. HIV status was associated with a greater decrease in DLCO for individuals with a CD4 T-cell count of <350 (mean difference −6.16; $P = 0.005$) than in those with a CD4 T-cell count of ≥350 (mean difference = −2.58; $P = 0.209$) (Table 1). HIV status for both those with detectable (mean difference −4.63; $P = 0.130$) and undetectable viral loads (mean difference −4.26; $P = 0.035$) was associated with similar decreases in DLCO % predicted, although the difference seen among those with detectable viremia was not significant.

DISCUSSION

We demonstrate in a cohort with significant risk factors for both lung disease and HIV that HIV was associated with

TABLE 1. Characteristics Associated With Percent Predicted DLCO and Odds of DLCO Impairment

	Change in % Predicted DLCO*		Odds of Impairment Moderate-to-Severe DLCO Impairment (DLCO <60% Predicted)†	
Predictor	**Mean Difference (95% CI)**	***P***	**Odds Ratio (95% CI)**	***P***
HIV status				
HIV-positive	−4.02 (−7.59 to −0.68)	**0.020**	1.93 (1.13 to 3.32)	**0.017**
HIV status and CD4 T-cell count				
HIV-positive, CD4 >350	−2.58 (−6.62 to 1.46)	0.209	1.60 (0.86 to 2.93)	0.132
HIV-positive, CD4 <350	−6.16 (−10.45 to −1.86)	**0.005**	2.58 (1.36 to 4.87)	**0.007**
HIV status and viral load				
HIV-positive, viral load <400	−4.26 (−8.14 to −0.33)	**0.035**	2.19 (1.18 to 3.79)	**0.012**
HIV-positive, viral load >400	−4.63 (−9.35 to −1.39)	0.130	2.70 (0.86 to 4.65)	0.127
Demographics				
Age (per 5 yrs)	−1.02 (−2.11 to 0.24)	0.077	1.22 (1.03 to 1.45)	**0.025**
Female gender	−3.12 (−6.74 to 0.49)	0.090	1.40 (0.82 to 2.38)	0.21
Black race	−8.58 (−14.08 to −3.09)	**0.002**	2.38 (0.94 to 6.04)	0.068
High school education	−0.73 (−4.15 to 2.69)	0.68	0.81 (0.49 to 1.33)	0.41
Current smoker	−4.88 (−9.42 to −0.35)	**0.035**	2.13 (1.06 to 4.30)	**0.034**
Smoking pack-yrs	−0.04 (−0.14 to 0.05)	0.40	1.01 (0.99 to 1.02)	0.56
Pulmonary characteristics				
FEV_1 to FVC ratio (per 0.10 decrease)	−4.72 (−2.61 to −6.83)	**<0.001**	1.52 (1.39 to 1.99)	**0.001**
Percentage of emphysema	−0.42 (−1.06 to 0.23)	0.202	1.12 (1.00 to 1.26)	0.050

*Adjusted for age, sex, race, education, smoking status (current smoking and pack-yrs), FEV_1 to FVC ratio, and percentage of emphysema (continuous).
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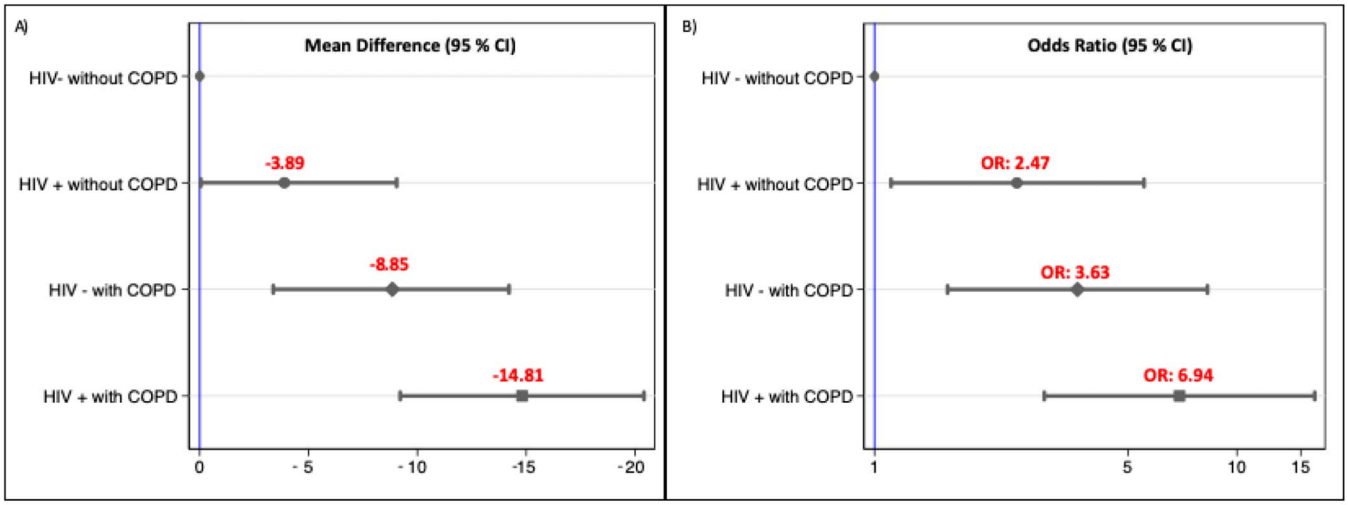

FIGURE 1. The relationship between HIV,COPD status and DLCO impairment A) represents mean difference (95% CI) in DLCO % predicted for differing groups and B) represents odds ratio (OR [95% CI]) of moderate to severe DLCO impairment (<60% predicted) compared to HIV negative participants without COPD. Note panel B is displayed with a log scale. full color online

impaired pulmonary gas exchange independent of underlying emphysema and COPD. By separating out the impact of emphysema in PLWH and matched HIV-uninfected participants, this study builds on previous research that demonstrated the association between HIV and DLCO impairment. The results are also consistent with recent findings that PLWH often face impaired DLCO, even with preserved spirometry.[17] We additionally described a potentially additive effect of HIV and COPD on DLCO impairment, suggesting that those living with HIV and COPD may face a greater disease burden than the general population living with COPD, even after accounting for smoking and traditional risk factors.

DLCO reflects abnormalities at the alveolar–capillary surface of the lungs, and there are several proposed pathways by which HIV may lead to abnormalities in DLCO, including accelerated emphysema, chronic inflammation from HIV, the development of pulmonary vascular disease, early interstitial lung disease, and recurrent infections.[9,18,19] As emphysema does not fully explain DLCO impairment among PLWH, research is required to better define other pathways to DLCO impairment among PLWH. A history of opportunistic infections may be a larger contributor to long-term lung injury, given that the greatest DLCO impairment was observed among those with low $CD4^+$ T-cell counts. Our study did not have detailed physician-adjudicated data on previous pneumonias for every participant, and as a result, we were unable to fully describe the association between respiratory infections and lower DLCO among PLWH. Previous studies have also looked at the contribution of pulmonary vascular disease and pulmonary hypertension among PLWH and DLCO impairment.[7] More work needs to be performed to understand whether PLWH and COPD face a greater burden of pulmonary vascular disease than HIV-uninfected individuals with COPD. A previous study from the SHIELD cohort also noted that HIV was associated with increased lung density in individuals without COPD, which may suggest that individuals with HIV may have subclinical inflammatory lung changes and interstitial lung abnormalities that contribute to the DLCO impairment.[12,20] We adjusted for mean lung density in a sensitivity analysis and found a persistent but mitigated association between HIV and DLCO (mean difference −3.74; $P = 0.040$); however, more detailed characterization of interstitial lung disease was not available. Future studies of HIV and DLCO impairment among PLWH should include more in-depth phenotyping of interstitial lung disease in addition to measurements of pulmonary vascular disease (ie, echocardiography, cardiac MRI, or right heart catheterization data).

Our study does include some limitations. The generalizability of our results may be limited by the inner-city population, with a high percentage of active smokers with concomitant lung disease. Although less reflective of the general population, the study population includes individuals often underrepresented in research and at increased risk for HIV and concomitant lung disease; allowing us to define the combined influence of COPD and HIV on DLCO impairment. Our study population, including PLWH and matched controls with similar risk factors, may reduce the risk of unmeasured confounders. We recognize that active smoking leads to reduced DLCO measurements, unrelated to intrinsic lung disease, and although we were able to correct for hemoglobin and adjust for current smoking, we were unable to correct for carboxyhemoglobin to fully account for the effects of smoking on DLCO. Given that the rate of active smoking was slightly higher among HIV-uninfected participants, there was a chance we underestimated the effect of HIV on DLCO impairment. Finally, we defined COPD based on the GOLD definition of airflow obstruction, instead of the ATS definition which defines airflow obstruction based on FEV_1/FVC less than the lower limit of normal. We note

recent literature demonstrates that the GOLD definition performs well in predicting COPD outcomes, and if the ATS criteria were applied to our cohort, only 3 additional participants would have been classified as COPD.[13]

In summary, we demonstrate that HIV is independently associated with impairment in pulmonary gas exchange after accounting for emphysema. We additionally note a potentially additive influence between HIV and COPD on DLCO impairment. Further studies should investigate the other factors, including pulmonary vascular disease, which may contribute to DLCO impairment among PLWH.

REFERENCES

1. Gingo MR, Nouraie M, Kessinger CJ, et al. Decreased lung function and all-cause mortality in HIV-infected individuals. *Ann Am Thorac Soc.* 2018;15:192–199.
2. Raju S, McCormack MC, Drummond MB, et al. Association of lung function with HIV-related quality of life and health care utilization in a high-risk cohort. *J Acquir Immune Defic Syndr.* 2020;85:219–226.
3. Attia EF, Akgün KM, Wongtrakool C, et al. Increased risk of radiographic emphysema in HIV is associated with elevated soluble CD14 and nadir CD4. *Chest*. 2014;146:1543–1553.
4. Drummond MB, Merlo CA, Astemborski J, et al. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS*. 2013;27:1303–1311.
5. 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.* 2011;183:388–395.
6. Crothers K, McGinnis K, Kleerup E, et al. HIV infection is associated with reduced pulmonary diffusing capacity. *J Acquir Immune Defic Syndr.* 2013;64:271–278.
7. Gingo MR, He J, Wittman C, et al. Contributors to diffusion impairment in HIV-infected persons. *Eur Respir J.* 2014;43:195–203.
8. Kunisaki KM, Nouraie M, Jensen RL, et al. Lung function in men with and without HIV. *AIDS*. 2020;34:1227–1235.
9. Cribbs SK, Crothers K, Morris A. Pathogenesis of HIV-related lung disease: immunity, infection, and inflammation. *Physiol Rev.* 2019;100:603–632.
10. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. Diffusing capacity of carbon monoxide in assessment of COPD. *CHEST*. 2019;156:1111–1119.
11. Drummond MB, Kirk GD, Astemborski J, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax*. 2012;67:309–314.
12. Drummond MB, Lambert AA, Hussien AF, et al. HIV infection is independently associated with increased CT scan lung density. *Acad Radiol.* 2017;24:137–145.
13. Bhatt SP, Balte PP, Schwartz JE, et al. Discriminative accuracy of FEV1:FVC thresholds for COPD-related hospitalization and mortality. *JAMA*. 2019;321:2438–2447.
14. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J.* 2005;26:319–338.
15. Stanojevic S, Grham B, Cooper B, et al. Global lung function initiative: reference equations for the transfer factor for carbon monoxide (TLCO). *Eur Respir J.* 2016;48(suppl 60):OA283.
16. Leader JK, Crothers K, Huang L, et al. Risk factors associated with quantitative evidence of lung emphysema and fibrosis in an HIV-infected cohort. *J Acquir Immune Defic Syndr.* 2016;71:420–427.
17. Jan AK, Moore JV, Wang RJ, et al. Markers of inflammation and immune activation are associated with lung function in a multi-center cohort of persons with HIV. *AIDS*. 2021;35:1031–1040.
18. Fitzpatrick ME, Nouraie M, Gingo MR, et al. Novel relationships of markers of monocyte activation and endothelial dysfunction with pulmonary dysfunction in HIV-infected persons. *AIDS*. 2016;30:1327–1339.
19. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. *Am J Respir Crit Care Med.* 2000;162:612–616.
20. Ronit A, Benfield T, Lundgren J, et al. Interstitial lung abnormalities in people with HIV infection and uninfected controls. *J Infect Dis.* 2020;221:1973–1977.