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RESPIRATORY PHYSIOLOGY

Association Between CD4$^+$, Viral Load, and Pulmonary Function in HIV

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Abstract
Purpose The antiretroviral therapy era has shifted the epidemiology of HIV-associated diseases, increasing the recognition of non-infectious pulmonary complications secondary to HIV. We aimed to determine the association between CD4$^+$, viral load, and pulmonary function in individuals with uncontrolled HIV, and determine how changes in these parameters are associated with pulmonary function longitudinally.
Methods This is a retrospective observational study of individuals with HIV who underwent pulmonary function testing in an urban medical center between August 1997 and November 2015.
Results Of the 146 participants (mean age 52 ± 10 years), 49% were Hispanic, 56% were men, and 44% were current smokers. CD4$^+$ <200 cells/μl was associated with significant diffusion impairment compared to CD4$^+$ ≥200 cells/μl (DL_{CO} 56 vs. 70%, $p = <0.01$). VL (viral load) ≥75 copies/ml was associated with significant diffusion impairment compared to VL <75 copies/ml (DL_{CO} 60 vs. 71%, $p = <0.01$). No difference in FEV1, FEV1/FVC, or TLC was noted between groups. In univariate analysis, CD4$^+$ and VL correlated with DL_{CO} ($r = +0.33$; $p = <0.01$; $r = -0.26$; $p = <0.01$) and no correlation was noted with FEV_1, FEV_1/FVC, or TLC. Current smoking and history of AIDS correlated with DL_{CO} ($r = -0.20$; $p = 0.03$; $r = -0.20$; $p = 0.04$). After adjusting for smoking and other confounders, VL ≥75 copies/ml correlated with a 11.2 (CI 95% [3.03–19.4], $p = <0.01$) decrease in DL_{CO}. In Spearman's Rank correlation, there was a negative correlation between change in VL and change in DL_{CO} over time ($\rho = -0.47$; $p = <0.01$).
Conclusion The presence of viremia in individuals with HIV is independently associated with impaired DL_{CO}. Suppression of VL may allow for recovery in diffusing capacity over time, though the degree to which this occurs requires further investigation.

Keywords HIV · AIDS · Pulmonary function test · Antiretroviral therapy · Non-infectious complications

Introduction

Pulmonary diseases have been a major cause of morbidity and mortality in individuals with HIV [1]. Prior to antiretroviral therapy (ART), individuals with HIV demonstrated a higher prevalence of emphysema, decreased diffusing capacity for carbon monoxide (DL_{CO}), increased prevalence of respiratory symptoms, and faster declines in lung function compared to HIV-negative cohorts [3, 5]. The ART era has seen a shift in the epidemiology of HIV-associated lung disease, with a drop in opportunistic infections and an increased recognition of various non-infectious pulmonary complications affecting this aging population [2, 4].

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The HIV virus has been implicated in the dysregulation of various inflammatory processes associated with chronic lung disease: increased endothelin-1 expression in HIV-associated pulmonary hypertension; pulmonary infiltration of upregulated $CD8^+$ cells in lymphocytic interstitial pneumonitis; impaired humoral immunity causing recurrent bacterial pneumonias; and upregulated metalloproteinases accelerating emphysema. The spectrum of HIV-associated pulmonary complications is diverse, and may relate to obstructive spirometric patterns and impaired DL_{CO} reported by the recent literature [6–8].

The current literature is limited in the reporting of pulmonary function abnormalities in the ART era. Crothers and colleagues in 2006 showed an increased prevalence of chronic obstructive pulmonary disease (COPD) in veterans with HIV, which persisted after adjusting for smoking. The study however did not directly measure pulmonary function and instead relied on self-reported and ICD-9 diagnoses of COPD [6]. George and colleagues in 2009 determined history of smoking, bacterial pneumonia, and ART use to be significant predictors of obstructive lung disease by spirometry, while Drummond in 2012 showed an association between significant viremia and obstructive lung disease in individuals with HIV [7, 8]. In 2015, Drummond and colleagues reported abnormal spirometry in 40% of patients with HIV [9]. They however did not study DL_{CO} [7–9]. Furthermore, few cross-sectional studies have evaluated for lung function longitudinally, leaving the effect of HIV on pulmonary function over time largely unknown.

The current study aims to expand on the existing literature by investigating the association of $CD4^+$ and viral load with spirometry, and DL_{CO} in individuals with poorly controlled HIV. The study also aims to determine how changes in $CD4^+$ or viral load associate with changes in pulmonary function over time.

Methods

Study Population

A retrospective observational study was performed on HIV patients receiving care from the Peter Krueger Center of Immunological Disorders, an HIV clinic affiliated with an urban academic medical center. The study was approved by the Institutional Review Board of the participating center. A complete list of patients with HIV was provided by the center. Electronic medical records (EMR) were reviewed from August 1997 to November 2015. Individuals included in the study had pulmonary function tests (PFTs) and $CD4^+$, and viral load (VL) drawn within 6 months of PFTs. Demographics, smoking history, cardiopulmonary disease, and infectious disease history were obtained. Demographics included age, gender, ethnicity, and body mass index (BMI). History of cigarette smoking was obtained through self-report. Chronic lung disease included asthma (confirmed by post-bronchodilator FEV_1 >12% and >200 cc to pre-bronchodilator measure), COPD (confirmed by FEV_1/FVC <70%), pulmonary hypertension, and interstitial lung disease (ILD). Pulmonary hypertension was defined by either positive right heart catheterization, transthoracic echocardiography (TTE), computed tomography (CT), or physician diagnosis per EMR. ILD was defined by either CT or EMR. History of chronic heart disease included heart failure with and without preserved ejection fraction defined by TTE (Table 1).

Infectious disease history included history of acquired immune deficiency syndrome (AIDS), opportunistic infections, and prevalence of ART during the time of PFTs. AIDS was diagnosed by history of $CD4^+$<200 cells/μl or history of an opportunistic infection (Table 1). All individuals were ≥18 years old.

Pulmonary Function Testing

Individuals included in the study sample had PFTs performed per the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [12], including pre- and post-bronchodilator spirometry and single-breath DL_{CO}. Airflow obstruction was defined as a ratio of post-bronchodilator forced expiratory volume in one second (FEV_1) to forced viral capacity (FVC) below 0.70. Predicted normal values (% predicted) for spirometry were adjusted for age, race/ethnicity, gender, and height [10, 11]. Percent predicted DL_{CO} values were corrected for hemoglobin [14]. To evaluate quality of DL_{CO} measurement, the inspiratory vital capacity (IVC)/FVC ratio was determined for each PFT [13]. Severity of airflow obstruction was determined by FEV_1, while impairment in DL_{CO} was based on ATS/ERS standards [13].

Statistical Analysis

Our analysis compared PFTs associated with the nadir $CD4^+$ and zenith VL within 6 months of PFT performance, to best assess for an association between poorly controlled HIV and pulmonary function. PFTs were analyzed by dichotomizing groups into $CD4^+$ ≥200 and <200 cells/μl and VL ≥75 and <75 copies/mL. The lower limit of detection for HIV RNA was <75 copies/mL. We performed tests for normality for PFT parameters to ensure normal distribution. Only FEV_1/FVC deviated from normality; thus, we performed a Mann–Whitney *U* test which showed no difference between the groups. Differences in the mean PFT values between $CD4^+$ and VL were

Table 1 Demographics and clinical data of study sample

	$CD4^+$<200	$CD4^+$≥200	*p*	VL ≥ 75	VL < 75	*p*	Total
Age (years)	50.39 ± 9.58	52.45 ± 9.56	0.24	48.43 ± 8.15	53.05 ± 9.43	0.55	51.87 ± 9.61
Gender							
Male	21 (51.2)	61 (58.1)	0.51	24 (51.1)	54 (59.3)	0.37	82 (56.2)
Race							
Caucasian	8 (19.5)	20 (19.0)	0.99	9 (19.1)	17 (18.7)	0.76	28 (19.2)
Black	14 (34.1)	31 (29.5)	0.64	18 (38.3)	24 (26.4)	0.12	45 (30.8)
Hispanic	19 (46.3)	52 (49.5)	0.81	20 (42.6)	48 (52.7)	0.25	71 (48.6)
Asian	0 (0)	2 (1.9)	0.36	0 (0)	2 (2.2)	0.26	2 (1.4)
BMI	28.42 ± 8.65	28.04 ± 7.19	0.92	27.46 ± 7.61	28.04 ± 6.46	0.43	28.38 ± 7.63
Reason for PFT referral							
New respiratory symptoms	18 (43.9)	35 (33.3)	0.27	21 (38.2)	32 (35.2)	0.79	53 (36.3)
Asthma	9 (21.9)	28 (26.7)	0.52	15 (27.3)	22 (24.2)	0.73	37 (25.3)
COPD	7 (17.1)	19 (18.1)	0.84	10 (18.2)	16 (17.6)	0.98	26 (17.8)
Pulmonary hypertension	2 (4.9)	8 (7.6)	0.53	3 (5.5)	7 (7.7)	0.58	10 (6.9)
Miscellaneous[a]	5 (12.2)	15 (14.3)	0.71	6 (10.9)	14 (15.4)	0.42	20 (13.7)
Smoking history							
Non-smoker	13 (36.1)	38 (42.7)	0.49	15 (32.6)	36 (45.6)	0.15	51 (40.1)
Pack-years 1–20	12 (33.3)	27 (30.3)	0.74	16 (34.8)	23 (29.1)	0.51	39 (31.2)
Pack–years >20	11 (30.1)	24 (26.9)	0.69	15 (32.6)	20 (25.3)	0.38	35 (28.0)
Smoking during PFT	18 (47.4)	43 (42.6)	0.61	27 (50.9)	34 (40.0)	0.19	61 (43.9)
HIV history							
History of AIDS	41 (100)	53 (65.4)	0.00	42 (84.0)	52 (72.2)	0.13	94 (77.0)
History of OIs[b]	6 (23.1)	19 (23.8)	0.94	10 (25.6)	15 (22.7)	0.79	25 (23.6)
On ART during PFT	20 (74.1)	68 (82.9)	0.31	30 (71.4)	58 (86.6)	0.06	88 (80.1)
Chronic lung disease							
Asthma	13 (31.7)	30 (29.7)	0.81	18 (33)	25 (28.4)	0.54	43 (29.5)
COPD	8 (20.0)	28 (27.4)	0.36	17 (32.1)	19 (21.3)	0.16	36 (24.7)
Pulmonary hypertension	4 (9.8)	15 (14.3)	0.26	3 (5.5)	10 (11.5)	0.22	13 (8.9)
Interstitial lung disease	0 (0.0)	5 (4.8)	0.15	1 (1.8)	4 (4.5)	0.39	5 (12.3)
Congestive heart failure							
Reduced ejection fraction	2 (4.9)	5 (4.8)	0.99	3 (5.5)	4 (4.5)	0.79	7 (4.8)
Preserved ejection fraction	5 (12.2)	12 (11.4)	0.93	7 (12.7)	10 (11.2)	0.79	17 (11.6)

Continuous variables are expressed as the mean ± standard deviation (SD), and categorical data are presented as counts with percentages in parentheses

COPD chronic obstructive pulmonary disease, *PFT* pulmonary function test, *AIDS* acquired immunodeficiency syndrome, *OI* opportunistic infection, *PFT* pulmonary function test

[a] Miscellaneous: pre-operative evaluation, history of cancer, sarcoidosis, pulmonary embolism, idiopathic pulmonary fibrosis, or *pneumocystis jirovecii* infection

[b] Opportunistic infections: *mycobacterium tuberculosis, mycobacterium avium complex, Kaposi's sarcoma-associated herpes virus, pneumocystis jirovecii, candida albicans, toxoplasma gondii, cryptococcus neoformans, cryptosporidium*

computed using a two-sample *t* test. Pearson correlation was then computed using continuous raw assay values of $CD4^+$ and VL, smoking and HIV history, and history of chronic lung disease and congestive heart failure against each of the PFT variables. Statistical significance was set at two-tailed *p*-values <0.20 and significant correlations were inputted into a stepwise regression model to establish quantitative correlations for independent predictors of pulmonary function.

Data from a subset of patients were used to assess for changes in lung function with HIV control over time. This analysis investigated how changes in $CD4^+$ and VL associated with changes in FEV_1, FEV1/FVC, TLC, and DL_{CO} over time. Due to variation in a number of PFTs performed

with available serology for any one individual, paired PFTs were chosen for comparison. To best detect changes in lung function with HIV control, paired PFTs were selected by whether they were associated with the greatest change in $CD4^+$ and VL. Measurement of change in PFT parameters was determined by the Spearman's Rank correlation, where change in VL was correlated with change in DL_{CO} over time. A Spearman's Rank correlation was used to limit the impact of large quantitative changes in VL on DL_{CO}; significant changes in VL occurring over time for any individual would not significantly influence the correlation coefficient when compared with individuals experiencing smaller changes in VL. The Spearman's Rank correlation negated absolute quantitative differences in VL, and considered changes in VL relative to other changes amongst individuals. All statistical analyses were performed using the SPSS software.

Results

Demographics and Clinical Characteristics

Nine hundred thirty-two patients with HIV were screened, and 146 individuals met the inclusion criteria (Fig. 1). The average age of the study sample was 51.87 ± 9.61 years, with no significant difference between $CD4^+$ and VL groups. Hispanic individuals were of highest prevalence in the study sample (48.6%), and race was evenly distributed between study groups. Thirty-six percent of PFTs were performed to evaluate new respiratory symptoms. There was no significant difference between reasons for PFT referral between groups (Table 1). Ninety-one percent of PFTs had an IVC/FVC ≥85%.

Univariate and Stepwise Regression Analysis

Using the two-sample *t*-test, a $CD4^+$ <200 cells/μl was associated with significant diffusion impairment when compared to $CD4^+$ ≥200 cells/μl (DL_{CO} 56 ± 17 vs. 70 ± 21%, $p = <0.01$). VL ≥75 copies/ml was associated with significant diffusion impairment when compared to VL <75 copies/ml (DL_{CO} 59 ± 19 vs. 71 ± 21%, $p = <0.01$). No significant difference in FEV_1, FEV_1/FVC, or TLC was found in $CD4^+$ and VL groups. Individuals with both $CD4^+$ <200 cells/μl and VL ≥75 copies/ml experienced the highest diffusion impairment when compared to individuals with both $CD4^+$ ≥200 cells/μl and VL <75 copies/ml (DL_{CO} 52 ± 15 vs. 71 ± 21%, $p = <0.01$) (Fig. 2; Table 2).

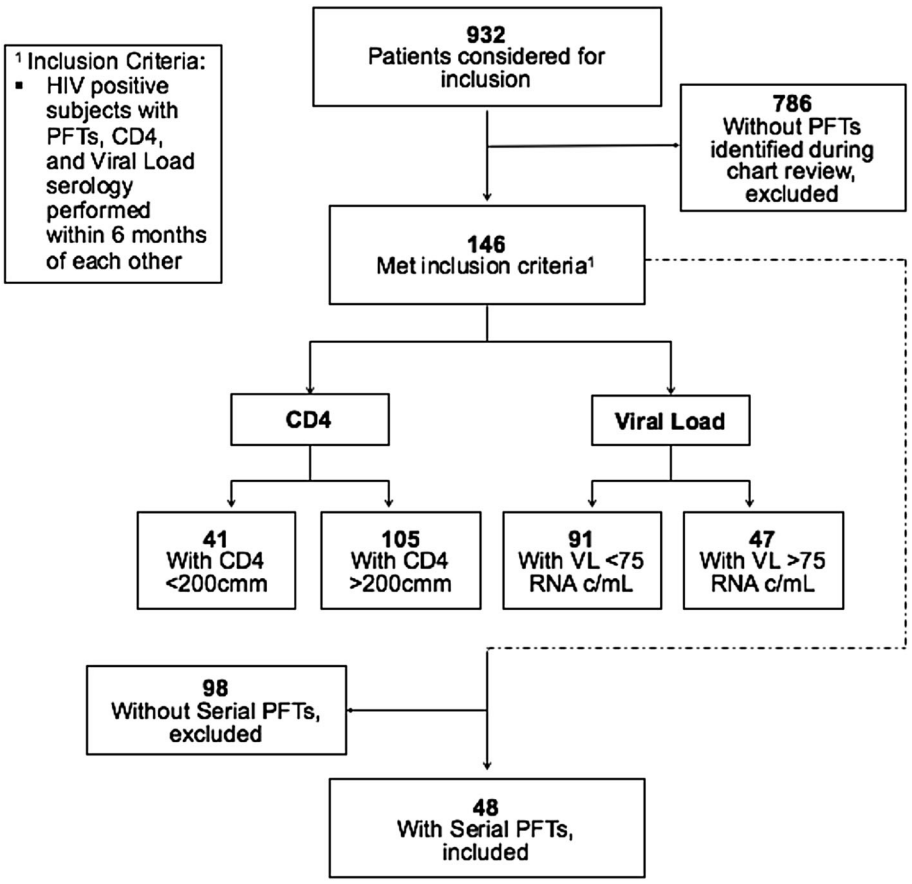

Fig. 1 Flow diagram of the study sample

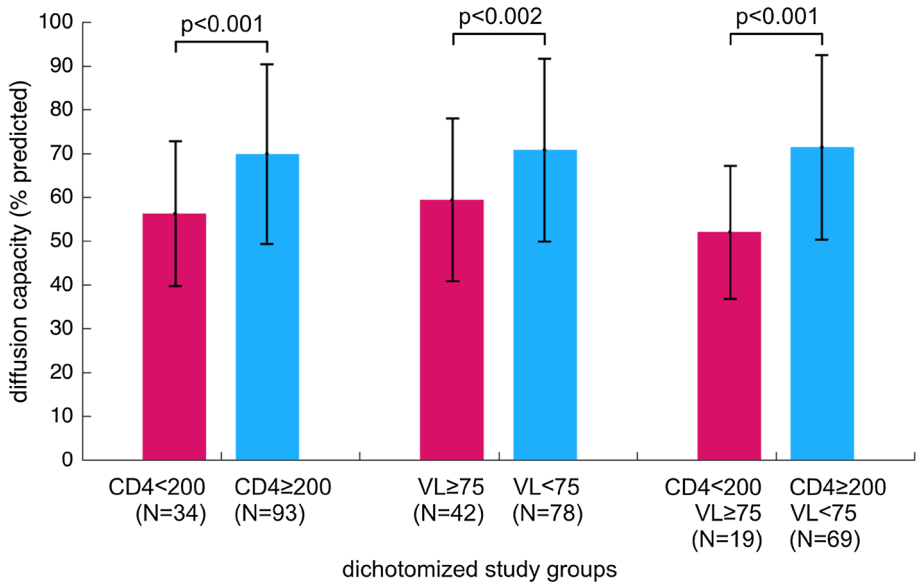

Fig. 2 Association between $CD4^+$ and Viral load and DL_{CO}. Two-sample *t*-test comparing means of PFT variables between $CD4^+$ < and ≥200 cells/μl, viral load ≥ and <75 RNA copies/mL, and individuals with both $CD4^+$ <200 cells/μl and VL ≥75 RNA copies/ml and $CD4^+$ ≥200 cells/μl and VL <75 RNA copies/ml

Table 2 HIV and smoking history and PFT variables: two-sample *t*-test comparing mean PFT variables and HIV control between dichotomized groups

t-tests	$CD4^+$ <200	$CD4^+$ ≥200	*p*	VL ≥ 75	VL < 75	*p*	$CD4^+$<200 VL ≥ 75	$CD4^+$≥200 VL < 75	*p*
FEV_1, (%)	75.47 ± 18.87	75.38 ± 21.91	0.93	72.59 ± 18.52	77.37 ± 22.05	0.12	73.90 ± 17.13	77.17 ± 22.42	0.39
FEV_1/FVC	74.25 ± 11.12	71.63 ± 12.08	0.30	71.04 ± 11.66	72.99 ± 12.14	0.40	73.19 ± 11.75	72.35 ± 12.26	0.68
TLC, (%)	84.12 ± 14.83	89.34 ± 17.64	0.36	86.53 ± 16.18	89.41 ± 17.29	0.48	82.81 ± 14.31	89.02 ± 17.90	0.39
DL_{CO}, (%)	56.31 ± 16.57	69.87 ± 20.58	<0.01	59.46 ± 18.58	70.80 ± 20.89	<0.01	52.04 ± 15.19	71.44 ± 21.06	<0.01

In univariate analysis, $CD4^+$ had a significant positive correlation with DL_{CO} ($r = +0.33$; $p = <0.01$), while VL had a significant negative correlation with DL_{CO} ($r = -0.26$; $p = <0.01$). FEV_1, FEV_1/FVC, and TLC did not significantly correlate with $CD4^+$ or VL (Table 3). Absence of smoking positively correlated with DL_{CO} ($r = +0.26$; $p = <0.01$), whereas history of any smoking negatively correlated with DL_{CO} ($r = -0.27$; $p = <0.01$). Higher pack-years negatively correlated with DL_{CO} though this did not reach statistical significance. Smoking during PFT performance negatively correlated with DL_{CO} ($r = -0.20$; $p = 0.03$). History of AIDS negatively correlated with DL_{CO} ($r = -0.20$; $p = 0.04$), while ART during PFT performance positively correlated with DL_{CO} ($r = +0.13$; $p = 0.01$) (Table 4).

In the stepwise regression model for independent predictors of DL_{CO}, VL ≥75 copies/ml correlated with a 11.2 (CI 95% [3.04–19.4], $p = <0.01$) decrease in DL_{CO}; an increase in one percent predicted of FEV_1 correlated with a 0.33 (CI 95% [0.15–0.52], $p = <0.01$) increase in DL_{CO}; and the presence of ILD correlated with a 22.59 (CI 95% [2.78–42.38], $p = 0.03$) decrease in DL_{CO} (Table 5).

Longitudinal Analysis

Forty-eight individuals were identified for the longitudinal analysis (Fig. 1). On average, 3.27 ± 2.90 years elapsed between paired PFTs. In Spearman's correlation, a change in $CD4^+$ was not significantly associated with a change in FEV_1, FEV_1/FVC, TLC or DL_{CO} over time. A change in

Table 3 HIV and smoking history and PFT variables: Pearson correlation comparing PFT variables and continuous raw assay values of $CD4^+$ and viral load

Pearson correlation	*r*	*p*	Pearson correlation	*r*	*p*
$CD4^+$ versus FEV_1 (%)	+0.076	0.37	Viral load versus FEV_1 (%)	−0.107	0.22
$CD4^+$ versus FEV_1/FVC	−0.016	0.85	Viral load versus FEV_1/FVC	−0.098	0.26
$CD4^+$ versus TLC (%)	+0.104	0.34	Viral load versus TLC (%)	−0.039	0.73
$CD4^+$ versus DL_{CO} (%)	+0.326	<0.01	Viral load versus DL_{CO} (%)	−0.262	<0.01

Table 4 HIV and smoking history and PFT variables: Pearson correlation comparing smoking and HIV history and percent predicted DL_{CO}

Pearson correlation	*r*	*p*
Smoking history		
Non-smoker versus DL_{CO} (%)	+0.264	<0.01
Ever-smoker versus DL_{CO} (%)	−0.267	<0.01
Pack-years 1–20 versus DL_{CO} (%)	−0.108	0.27
Pack-years >20 versus DL_{CO} (%)	−0.170	0.08
Smoking during PFT versus DL_{CO} (%)	−0.199	0.03
HIV history		
History of AIDS versus DL_{CO} (%)	−0.199	0.04
History of OIs versus DL_{CO} (%)	−0.065	0.54
On ART during PFT versus DL_{CO} (%)	+0.126	0.01

OIs opportunistic infections

VL demonstrated a significant association with a change in DL_{CO} over time ($\rho = -0.47$, $p = <0.01$). No significance was appreciated with changes in FEV_1, FEV_1/FVC, or TLC over time (Table 6).

Discussion

Our investigation demonstrates that markers of HIV severity are significantly associated with DL_{CO}, without any association with obstructive or restrictive patterns among individuals with HIV. In dichotomizing our sample into $CD4^+$ <200 or ≥200 cells/μl, individuals with markedly depleted $CD4^+$ cells were found to have significantly greater impairment in diffusing capacity compared to those with intact $CD4^+$ levels, with mean DL_{CO} of 56%. Similarly, individuals with detectable VL had a mean DL_{CO} of 59%, compared to a DL_{CO} of 71% in individuals without viremia. Diffusion impairment was most pronounced with both profound immunosuppression and detectable VL, with a mean DL_{CO} of 52%. Given that a DL_{CO} of <60% is considered moderate impairment [14], and impaired DL_{CO} has been associated with increased respiratory symptoms and mortality [3, 26], the reduced diffusion capacity in our poorly controlled HIV cohort is clinically significant, though correlation with symptomology was not made in our cohort. Our univariate analysis demonstrated a positive correlation between $CD4^+$ and DL_{CO}, and a negative correlation between VL and DL_{CO}, both of which were significant. After adjusting for smoking and other confounders, a detectable VL and the presence of ILD were shown to have significant independent negative correlations with DL_{CO}. While smoking history and history of AIDS had significant correlations in our univariate analysis, they were not significant in our final regression model.

Table 6 Spearman's Rank (ρ) correlation for the longitudinal analysis

	$\Delta CD4^+$		ΔViral load	
	ρ (rho)	*p*-value	ρ (rho)	*p*-value
ΔFEV_1 (%)	−0.047	0.76	−0.083	0.59
ΔFEV_1/FVC	−0.166	0.27	+0.208	0.17
ΔDL_{CO} (%)	+0.023	0.89	−0.469	<0.01

Spearman's correlations (ρ) determining the correlation between change (Δ) in $CD4^+$ and change in PFTs, and change in viral load and change in PFTs over time

Longitudinally, our findings demonstrated a decrease in viral load to significantly correlate with improvement in DL_{CO} over time, suggesting that reversibility in diffusion impairment may result from long-term suppression of HIV viremia. Improvements in $CD4^+$ did not correlate significantly with DL_{CO} in the Spearman's correlation, suggesting that the basis of diffusion impairment may be related more to the direct cytotoxic effects of the HIV virus itself, rather than the host response of depleted $CD4^+$ levels. Mitchell and colleagues in 1992 reported lower baseline DL_{CO} in individuals with more severe HIV, but reported no significant change in DL_{CO} during serial PFTs over 18 months. In a subgroup analysis however, they noted individuals with *pneumocystis jirovecii* infection had reduced DL_{CO}, which improved with treatment during the study period [27]. While we did not assess for *pneumocystis* infection and its association with DL_{CO} specifically, we did assess for change in DL_{CO} following change in HIV control, which may reflect DL_{CO} following recovery from opportunistic infections. Drummond and colleagues in 2013 demonstrated faster declines in annual FEV_1 and FVC in individuals with significant viremia and depleted

Table 5 HIV and smoking history and PFT variables: multivariate linear regression model for risk factors associated with percent predicted DL_{CO}

Risk factor	Beta coefficient	95% CI	*p*
Viral load ≥75 copies/ml	−11.22	−19.41 to −3.04	<0.01
FEV_1	0.33	0.15–0.52	<0.01
Presence of ILD	−22.58	−42.38 to −2.78	0.03

ILD interstitial lung disease

$CD4^+$. They also noted that optimal ART with viral suppression may diminish the rate of accelerated loss of lung function in individuals with poorly controlled HIV [15]. Together, our studies emphasize the need for optimizing ART, with our investigation suggesting the potential for reversing diffusion impairment through sustained viral suppression.

While our study suggests that a relationship between HIV control and DL_{CO} exist, no such association was apparent with respect to obstructive or restrictive impairments. These findings are in accordance with Crothers et al., who in 2013 compared pulmonary function testing between individuals with and without HIV [16]. They demonstrated lower DL_{CO} in individuals with $CD4^+$ <200 cells/μl compared to $CD4^+$ 200–349 and >350 cells/μl, and individuals without HIV (DL_{CO} 58 vs. 67, 72, and 76%, $p = <0.01$). Furthermore, they noted uncontrolled viremia to also be associated with reduced DL_{CO} when compared with adequate viral suppression (DL_{CO} 66 vs. 71%), with a DL_{CO} of 76% in individuals without HIV ($p = <0.01$) [16]. Our findings are in accordance with Drummond as well, who in 2012 reported no association between $CD4^+$ and obstructive lung disease. The study did note however a 3.4-fold increase in the odds of obstruction in individuals with HIV with markedly elevated VL (>200,000 copies/mL) [17]. Furthermore, Drummond in 2013 also noted that accelerated annual FEV_1 declines longitudinally in individuals with VL ≥75,000 copies/ml [15]. While these thresholds may impart an increased risk for obstructive lung disease, our study did not have sufficient individuals with such significant viremia to corroborate these findings.

Attia and colleagues in 2014 demonstrated an increased prevalence of radiographic emphysema in individuals with $CD4^+$ <200 cells/μl, which persisted after adjusting for smoking pack-years [18]. While they did not assess for DL_{CO} directly, emphysema is associated with impaired diffusing capacity through the destruction of pulmonary capillaries, and may explain our finding of impaired DL_{CO} in individuals with $CD4^+$ <200 cells/μl. While we did not assess for radiographic emphysema, it is increasingly recognized that HIV and cigarette smoking share a pathogenic synergy, by increasing cytotoxic lymphocytes in alveoli and upregulating destructive matrix metalloproteinases causing emphysema [19, 20]. Our study demonstrated significant positive correlations between smoking history and presence of spirometric obstruction, as well as negative correlations between smoking and DL_{CO}.

In addition to HIV-associated emphysema, several potential mechanisms exist to explain the relationship between VL and impaired DL_{CO}. Increased inflammatory markers have been associated with reduced diffusing capacity in the general population [21], with HIV implicated in the expression of various contributory pro-inflammatory makers [22]. Endothelin-1 for example has been linked to vascular inflammation and pulmonary vasoconstriction, and is upregulated in HIV-associated pulmonary hypertension [23]. HIV-associated ILDs like lymphocytic interstitial pneumonitis and sarcoidosis may also present with impaired DL_{CO}, with the latter associated with immune reconstitution following ART initiation [20]. HIV can also dysregulate humoral immunity, predisposing to recurrent bacterial pneumonias causing permanent declines in lung function [24]. *Pneumocystis jirovecii* in particular has been shown to significantly impair DL_{CO} following infection [25].

Our study is not without limitations. While common lung diseases and tobacco smoking were accounted for, other potentially relevant medical comorbidities (history of venous thromboembolic disease, bacterial pulmonary infections, occupational exposures, or injection drug abuse) were incomplete. The interval between PFT and serology comparison was not standardized between individuals in the longitudinal analysis. More than one-third of PFTs were performed to evaluate new respiratory symptoms, which increase the likelihood of selection bias. While the study sample is racially diverse and with similar distribution in gender, it is from a single-center population which may limit the study's generalizability.

Conclusion

In summary, we found the presence of viremia in individuals with HIV to be independently associated with impaired DL_{CO}, even after adjusting for smoking and other potential confounders. Suppression of VL may allow for recovery in diffusing capacity over time, though the degree to which this occurs requires further investigation. Depleted $CD4^+$ cells and uncontrolled viremia are associated with impaired DL_{CO}, without associated airflow limitation or restrictive spirometry. The reduction in DL_{CO} may occur from a number of HIV-associated lung diseases, and continued research is required to better understand their mechanisms and impact on the pulmonary function of individuals living with HIV.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

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