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ORIGINAL RESEARCH

Pulmonary Function Trajectories in People with HIV
Analysis of the Pittsburgh HIV Lung Cohort

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Abstract

Rationale: Human immunodeficiency virus (HIV) infection is associated with chronic lung disease and impaired pulmonary function; however, longitudinal pulmonary function phenotypes in HIV are undefined.

Objectives: To identify pulmonary function trajectories, their determinants, and outcomes.

Methods: We used data from participants with HIV in the Pittsburgh HIV Lung Cohort with three or more pulmonary function tests between 2007 and 2020. We analyzed post-bronchodilator forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC, and diffusing capacity of the lung for carbon monoxide (D_{LCO}) using group-based trajectory modeling to identify subgroups of individuals whose measurements followed a similar pattern over time. We examined the association between participant characteristics and trajectories using multivariable logistic regression. In exploratory adjusted analyses restricted to individuals with available plasma cytokine data, we investigated the association between 18 individual standardized cytokine concentrations and trajectories. We compared mortality, dyspnea prevalence, respiratory health status, and 6-minute-walk distance between phenotypes.

Results: A total of 265 participants contributed 1,606 pulmonary function measurements over a median follow-up of 8.1 years. We identified two trajectories each for FEV_1 and FVC: "low baseline, slow decline" and "high baseline, rapid decline." There were three trajectory groups for FEV_1/FVC: "rapid decline," "moderate decline," and "slow decline." Finally, we identified two trajectories for D_{LCO}: "baseline low" and "baseline high." The low baseline, slow decline FEV_1 and FVC, rapid decline, and moderate decline FEV_1/FVC, and baseline low D_{LCO} phenotypes were associated with increased dyspnea prevalence, worse respiratory health status, and decreased 6-minute-walk distance. The baseline low D_{LCO} phenotype was also associated with worse mortality. Current smoking and pack-years of smoking were associated with the adverse FEV_1, FEV_1/FVC, and D_{LCO} phenotypes. Detectable viremia was the only HIV marker associated with the adverse D_{LCO} phenotype. C-reactive protein and endothelin-1 were associated with the adverse FEV_1 and FVC phenotypes, and endothelin-1 trended toward an association with the adverse D_{LCO} phenotype.

Conclusions: We identified novel, distinct longitudinal pulmonary function phenotypes with significant differences in characteristics and outcomes. These findings highlight the importance of lung dysfunction over time in people with HIV and should be validated in additional cohorts.

Keywords: human immunodeficiency virus; pulmonary function; group-based trajectory modeling

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In the era of effective antiretroviral therapy (ART), people with human immunodeficiency virus (PWH) experience growing morbidity and mortality burden because of noninfectious comorbidities, including chronic lung disease. Although smoking is more prevalent among PWH, human immunodeficiency virus (HIV) infection independently predicts airflow obstruction (1, 2), gas exchange limitation (3–5), and emphysema (3, 6). Among PWH, airflow and gas exchange abnormalities have been identified as independent risk factors for increased respiratory symptoms (7), worse respiratory health status (8), decreased functional capacity (6, 9, 10), and increased mortality (11–13).

Longitudinal studies have suggested lung function decline may be accelerated among PWH compared with seronegative control subjects (14–16), and incident chronic obstructive pulmonary disease (COPD) is increased (17–19). In cohorts of PWH, median decline of forced expiratory volume in 1 second (FEV_1) ranges from 30 to 60 ml/yr and that of forced vital capacity (FVC) is between 9 and 67 ml/yr (14, 15, 20, 21). Although this variability may be partly attributed to confounders related to cohort characteristics, it likely also represents the heterogeneity of HIV-associated lung disease. Thus, identifying longitudinal pulmonary function phenotypes may provide insights into lung disease pathogenesis in PWH and help guide assessment, risk factor modification, and potential therapies.

Group-based trajectory modeling (GBTM) is an application of finite mixture modeling used to identify groups of individuals following similar trajectories for a particular variable over time (22, 23). GBTM has been used to characterize pulmonary function trajectories in the general population (24–27). In this analysis, we applied GBTM to describe longitudinal trajectories of pulmonary function among PWH. We hypothesized that there are distinct trajectory groups differing in demographics, HIV infection markers, and plasma cytokine concentrations as well as mortality, symptom burden, respiratory health status, and functional capacity.

Methods

Study Participants

We included 265 participants with HIV at study entry and three or more acceptable pulmonary function tests (PFTs) between 2007 and 2020 from the Pittsburgh HIV Lung Cohort (16, 21). As previously reported, individuals in the Pittsburgh HIV Lung Cohort were recruited from the Pittsburgh Area Center for Treatment (Pittsburgh, PA), Multicenter AIDS Cohort Study (Pittsburgh, PA, and Los Angeles, CA), and Women's Interagency HIV Study (San Francisco, CA). Institutional review boards at the University of Pittsburgh, the University of California, San Francisco, and the University of California, Los Angeles, approved the study protocol. All participants provided informed consent.

Covariates

Demographic and baseline clinical data were determined from structured interviews and medical record review. Data included age, sex, race/ethnicity, height, weight, smoking status, pack-years of smoking, regular marijuana and cocaine use, history of hepatitis C, *Pneumocystis jirovecii* pneumonia, bacterial pneumonia, and tuberculosis, years living with HIV, current ART use, current and nadir CD4 counts, and currently detectable viremia.

PFTs

Participants performed post-bronchodilator spirometry, including FEV_1 and FVC, and diffusing capacity of the lung for carbon monoxide (D_{LCO}) according to American Thoracic Society/European Respiratory Society standards (28, 29). Only tests meeting standards or deemed acceptable by a trained pulmonologist were included. We determined percent predicted values of spirometry and D_{LCO} using Hankinson and Neas equations (30, 31). D_{LCO} was corrected for hemoglobin and carboxyhemoglobin (30).

*These authors share senior authorship.

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Plasma Cytokines

We selected 18 cytokines on the basis of previously shown associations with HIV-associated lung disease and to represent potential mechanistic pathways (16, 32): interleukin (IL)-2, IL-12, and interferon-γ (Th1 cytokines); IL-4, IL-5, IL-10, and IL-13 (Th2 cytokines); IL-17a (Th17 cytokine); IL-1b, IL-6, IL-8, granulocyte colony-stimulating factor, granulocyte–macrophage colony–stimulating factor, monocyte chemoattractant protein-1, macrophage inflammatory protein-1b, tumor necrosis factor-α, and C-reactive protein (CRP) (systemic inflammation); and endothelin-1 (ET-1) (endothelial dysfunction). Peripheral blood samples were obtained at the baseline visit, stored at −80°C, and measured by ELISA or Luminex assays as previously described (32).

Clinical Outcomes

We assessed dyspnea using the modified Medical Research Council (mMRC) dyspnea scale (33) and respiratory health status using the St. George's Respiratory Questionnaire (SGRQ) (34), completed by 243 and 218 participants, respectively, at their final PFT. Standardized 6-minute-walk distance (6MWD) was measured according to American Thoracic Society guidelines to assess functional capacity at final PFT by 152 participants (35). Survival status as of September 3, 2020, was determined by medical record review among Pittsburgh Area Center for Treatment participants, and active surveillance and National Death Registry matching were determined among Multicenter AIDS Cohort Study/Women's Interagency HIV Study participants (11), with the last death occurring in 2019.

Statistical Analysis

We tested two-, three-, and four-group models using linear, quadratic, and cubic modeling terms for each group and censored normal distribution. We used the Bayesian information criterion and null hypothesis test (against zero) to select the most parsimonious model. To assess model fit, we ensured that *1*) the average of posterior probabilities of group membership for participants in each group exceeded 0.7, *2*) the odds of correct classification based on the posterior probabilities of group membership exceeded 5, and *3*) there was correspondence between estimated and assigned probabilities of group membership (23). After model selection, participants were assigned to a group based on their highest estimated group membership probabilities. These categorical variables were used in subsequent analyses. These steps were performed for each pulmonary function parameter separately. GBTM incorporating participant attrition was performed using the *traj* package in Stata (StataCorp) (36).

Baseline demographics, clinical characteristics, plasma cytokine concentrations, and clinical outcomes were compared between trajectory groups for each pulmonary function parameter using the *t* test and one-way analysis of variance for normally distributed data, the Wilcoxon rank-sum test and Kruskal-Wallis test for nonnormally distributed data, and the chi-square test or Fisher's exact test for categorical data as appropriate.

We evaluated the independent association of the aforementioned baseline characteristics with group membership through multivariable logistic regression. Covariates were selected on the basis of biological plausibility and prior studies of longitudinal pulmonary function among PWH (14, 15, 20, 21, 37–39). Collinearity was assessed with the variance inflation factor. In exploratory analyses among participants with available plasma cytokine data, we investigated the association between individual standardized cytokine concentrations in models adjusting for variables identified in the multivariable models. In addition, we performed bivariate regression to evaluate the association of group membership with clinical outcomes. Finally, we examined Bayesian information criterion values to compare fit statistics of bivariate regression with trajectory group, baseline measurement, or rate of change (calculated using a mixed-effects model with random effect as described in the data supplement) as the independent variable and individual clinical outcomes as the dependent variable. Because findings using absolute lung function values and percent predicted values determined by Hankinson (31) and Global Lung Function Initiative equations (40) to perform GTBM and outcomes analyses were consistent, we present only absolute lung function results to improve comparability with prior literature (14, 15, 20, 37, 38). Statistical analyses were performed using Stata version 16.0.

Results

Baseline Cohort Characteristics

We included 265 PWH in GBTM (*see* Table E1 in the online supplement). We excluded 134 PWH for having one or two PFT measurements. Excluded individuals were older and more frequently coinfected with hepatitis C; had lived longer with HIV; and had a greater proportion with undetectable viremia, higher percent predicted $D_{L_{CO}}$, and lower proportion with gas exchange impairment. Among included PWH, the median age was 48 years, 66.8% were men, 50.2% were White, and 48.3% were Black. At baseline, participants had been living with HIV for a median of 14.5 years. The median baseline CD4 count was 524 cells/ml. Although 80.3% were receiving ART, 121 (49.8%) participants had undetectable viremia at baseline. Smoking was prevalent because 194 (73.3%) participants were current or former smokers with a median of 17.3 pack-years of smoking. Forty-four (16.9%) participants had FEV_1/FVC <0.7 and 81.9% had $D_{L_{CO}}$ $<80\%$. Plasma cytokine concentrations were available for 207 (78.1%) participants (Table E2).

Trajectories of Pulmonary Function

Participants contributed 1,606 PFT measurements (median, 5; interquartile range [IQR], 4–8 per participant) during a median follow-up of 8.1 (IQR, 5.8–9.6) years. The median interval between PFT measurements was 526 days (IQR, 311–590 d). GBTM identified two FEV_1 trajectory groups with a linear shape: participants with low baseline FEV_1 that declined slowly over time ("low baseline, slow decline"; $n = 150$; 57.0%) and participants with high baseline FEV_1 that declined more rapidly over time ("high baseline, rapid decline"; $n = 113$; 43.0%). Similarly, we identified two linear-shaped trajectories for FVC with 136 (51.7%) participants assigned to low baseline, slow decline and 127 (48.3%) participants assigned to high baseline, rapid decline. There were three linear-shaped trajectories for FEV_1/FVC differing in the rate of decline, but not the baseline value: "rapid decline" ($n = 21$; 8%), "moderate decline" ($n = 66$; 25.1%), and "slow decline" ($n = 176$; 66.9%). Finally, we identified two linear-shaped trajectories for $D_{L_{CO}}$ differing in the baseline value, but not the rate of decline: "baseline low" ($n = 148$; 57.4%) and "baseline high"

($n = 110$; 42.6%) (Figure 1). Each trajectory model performed well on tests of model adequacy (Table E3). Cross-tabulation of pairwise group membership is shown in Table E4. Participant characteristics by trajectory group for each pulmonary function parameter are summarized in Tables E5–E8.

Trajectory Predictors

Female sex, Black race, shorter height, current smoking, and more pack-years of smoking were associated with the low baseline, slow decline FEV_1 trajectory. Female sex, Black race, shorter height, greater weight, and younger age were associated with the low baseline, slow decline FVC trajectory. Current smoking and more pack-years of smoking were predictors of moderate decline and rapid decline FEV_1/FVC trajectories. Finally, factors associated with the baseline low D_{LCO} trajectory were female sex, Black race, older age, shorter height, lower weight, current smoking, more pack-years of smoking, and detectable viremia (Table 1). Among standardized cytokines, CRP and ET-1 were associated with the low baseline, slow decline FEV_1 and FVC trajectories, and ET-1 trended toward association with the baseline low D_{LCO} trajectory (Table E9).

Outcome Comparisons between Trajectories

Specific phenotypes were associated with adverse outcomes (Table 2). Participants in the low baseline, slow decline FEV_1 trajectory had shorter 6MWD (mean difference [MD], 56.1; 95% confidence interval [CI], 29.6–82.5 m), worse SGRQ score (MD, 9.1; 95% CI, 4.9–13.3), and a greater proportion with mMRC ⩾2 (40% vs. 13.3%) than the high baseline, rapid decline FEV_1 group without a difference in mortality.

Individuals in the low baseline, slow decline FVC trajectory had a shorter 6MWD (MD, 51; 95% CI, 24.4–77.6 m) and a greater proportion with mMRC ⩾2 (34.1% vs. 18.8%) than the high baseline, rapid decline FVC group without differences in mortality and SGRQ scores.

Participants in the moderate decline and rapid decline FEV_1/FVC trajectories had a shorter 6MWD than the slow decline FEV_1/FVC group with MD 29.9 (95% CI, 3.1–62.9) and 75.2 (95% CI, 26.5–123.8) meters, respectively. They also had worse SGRQ scores with MD 10.3 (95% CI, 5.6–15.1) and 23.1 (95% CI, 15–31.4), respectively. The mortality rate and proportion with mMRC ⩾2 increased across the slow decline, moderate decline, and rapid decline FEV_1/FVC groups (19% vs. 36.7% vs.

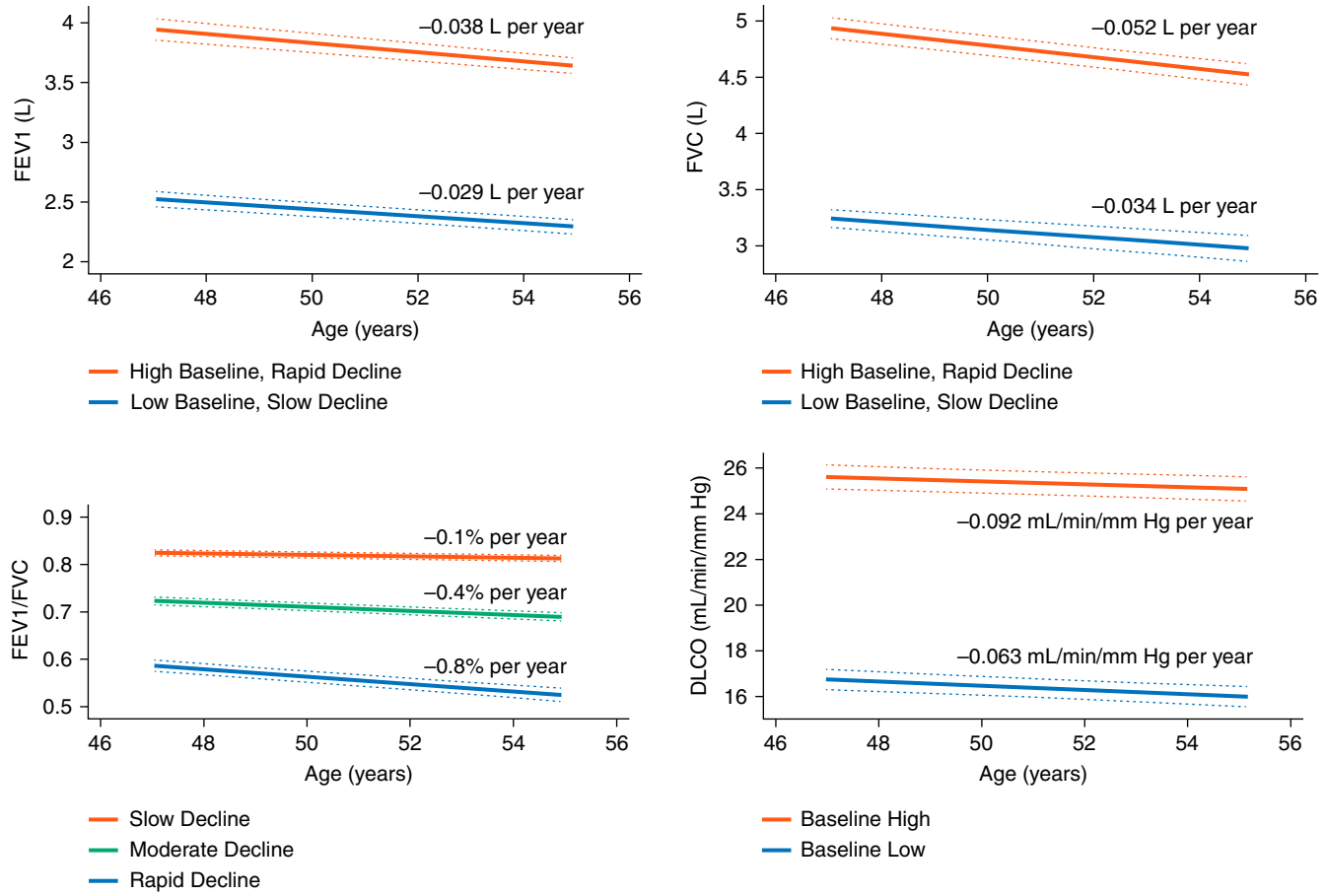

Figure 1. Trajectories of forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC, and diffusing capacity for carbon monoxide (D_{LCO}) among PWH in the Pittsburgh HIV Lung Cohort. Solid lines indicate predicted mean pulmonary function measurements in each trajectory group and dotted lines indicate 95% confidence intervals. *P* values for difference in baseline values were <0.001 for FEV_1, FVC, and D_{LCO}, and 0.21 for FEV_1/FVC. *P* values for difference in slopes were 0.001 for FEV_1, <0.001 for FVC and FEV_1/FVC, and 0.25 for D_{LCO}. PWH = people with human immunodeficiency virus.

Table 1. Baseline characteristics associated with trajectories in multivariable logistic regression

Characteristic	FEV_1 Low Baseline, Slow Decline	FVC Low Baseline, Slow Decline	FEV_1/FVC Moderate Decline vs. Slow Decline and vs. Rapid Decline*	D_{LCO} Baseline Low
Age (per 10-yr increase)	0.80 (0.48–1.35)	0.32 (0.17–0.62)	0.97 (0.66–1.43)	2.17 (1.18–3.98)
Female	9.20 (2.39–35.39)	9.12 (2.24–37.08)	1.20 (0.49–2.98)	14.08 (3.68–67.80)
Black (vs. White)	11.38 (4.49–28.88)	7.64 (2.90–20.14)	1.19 (0.62–2.31)	4.31 (1.45–12.80)
Height (per 1-inch increase)	0.73 (0.62–0.87)	0.57 (0.45–0.71)	0.97 (0.87–1.09)	0.75 (0.62–0.91)
Weight (per 10-pound increase)	1.09 (0.97–1.23)	1.28 (1.10–1.49)	0.97 (0.90–1.05)	0.79 (0.68–0.92)
Years with HIV infection (per 10-yr increase)	1.04 (0.58–1.85)	1.50 (0.78–2.89)	1.00 (0.64–1.56)	0.58 (0.29–1.15)
ART use	2.59 (0.75–8.87)	1.72 (0.45–6.58)	0.82 (0.35–1.96)	2.39 (0.58–9.81)
CD4 count (per 100-cell increase)	0.80 (0.32–2.00)	0.92 (0.76–1.10)	0.97 (0.86–1.09)	0.87 (0.72–1.05)
Nadir CD4 count (per 100-cell increase)	1.09 (0.87–1.35)	1.06 (0.83–1.34)	1.11 (0.94–1.31)	1.05 (0.81–1.37)
Detectable viremia	0.86 (0.73–1.01)	1.41 (0.51–3.86)	0.61 (0.31–1.18)	5.48 (1.78–16.84)
Hepatitis C infection	0.66 (0.22–1.96)	1.58 (0.50–4.98)	0.62 (0.27–1.39)	2.18 (0.53–9.04)
History of PCP	0.82 (0.17–3.98)	1.85 (0.31–10.94)	2.15 (0.72–6.46)	0.49 (0.08–2.88)
History of tuberculosis	0.73 (0.06–8.43)	1.06 (0.78–1.44)	0.81 (0.13–5.13)	0.33 (0.18–6.02)
History of bacterial pneumonia	0.60 (0.26–1.37)	0.40 (0.16–1.04)	1.10 (0.60–2.01)	2.39 (0.90–6.32)
Smoking status (vs. never)				
Current	3.28 (1.49–6.91)	2.10 (0.58–7.58)	1.91 (1.01–3.63)	5.44 (1.20–24.76)
Former	0.62 (0.17–2.23)	0.89 (0.23–3.42)	0.78 (0.28–2.20)	0.60 (0.13–2.88)
Pack-years smoking (per 10-yr increase)	1.53 (1.14–2.06)	0.99 (0.76–1.32)	1.17 (1.03–1.42)	2.13 (1.35–3.36)
Regular marijuana use	1.70 (0.73–3.94)	0.85 (0.32–2.26)	2.08 (0.85–5.12)	0.47 (0.18–1.26)
Regular cocaine use	0.36 (0.09–1.52)	0.99 (0.22–4.49)	0.71 (0.25–2.02)	0.37 (0.06–2.08)

Definition of abbreviations: ART = antiretroviral therapy; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; PCP = *Pneumocystis jirovecii* pneumonia.
Data are presented as odds ratio (95% confidence interval).
*Results of ordinal logistic regression.

60% and 8.5% vs. 10.6% vs. 23.8%, respectively), although the former was not statistically significant.

Compared with participants in the baseline high D_{LCO} group, those in the baseline low group had a higher mortality rate (14.2% vs. 4.6%; odds ratio, 3.47; 95% CI, 1.27–9.52), shorter 6MWD (MD, 41.1; 95% CI, 14.1–68.1 m), worse SGRQ score (MD, 7.5; 95% CI, 3.2–11.8), and greater proportion with mMRC ⩾2 (34.6% vs. 16.4%).

Comparison of fit statistics for regression models of outcomes on trajectories, baseline measurements, and rate of change indicated overall more robust statistical associations for GBTM than other parameters. For example, the regression of mortality using D_{LCO} trajectory as the independent variable had superior fit statistics compared with models using

Table 2. Outcome comparisons between trajectories

	Death	*P* Value	6MWD	*P* Value	SGRQ	*P* Value	mMRC Score ⩾2	*P* Value
FEV_1								
Low baseline, slow decline	18 (12.0%)	0.31	393.8 (109.7)	<0.001	12.7 (22.8)	<0.001	51 (40.0%)	<0.001
High baseline, rapid decline	9 (8.0%)		466.6 (102.9)		3.9 (8.8)		14 (13.3%)	
FVC								
Low baseline, slow decline	15 (11.0%)	0.69	392.3 (112.2)	<0.001	10.2 (19.3)	0.11	43 (34.1%)	0.009
High baseline, rapid decline	12 (9.5%)		451.7 (113.4)		4.7 (16.5)		22 (18.8%)	
FEV_1/FVC								
Rapid decline	5 (23.8%)	0.09	365.8 (57.9)	0.01	32.8 (34.5)	<0.001	12 (60.0%)	<0.001
Moderate decline	7 (10.6%)		426.1 (129.2)		17.4 (27.4)		22 (36.7%)	
Slow decline	15 (8.5%)		436.8 (109.7)		4.5 (14.6)		31 (19.0%)	
D_{LCO}								
Baseline low	21 (14.2%)	0.01	399.3 (109.7)	0.001	10.6 (21.4)	<0.001	47 (34.6%)	0.002
Baseline high	5 (4.6%)		460.9 (122.8)		4.2 (15.6)		17 (16.4%)	

Definition of abbreviations: 6MWD = 6-minute-walk distance; D_{LCO} = diffusing capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; mMRC = modified Medical Research Council dyspnea scale; SGRQ = St. George's Respiratory Questionnaire.
Categorical data are presented as count (percent), and continuous data are presented as median (interquartile range).

baseline D_{LCO}, baseline gas exchange impairment, or annual D_{LCO} rate of change (Table E10).

Discussion

We report a novel, data-driven method to characterize longitudinal pulmonary function phenotypes in PWH. We found significant demographic, clinical, and plasma cytokine differences between trajectory groups for each pulmonary function parameter and significant differences in mortality, dyspnea prevalence, respiratory health status, and functional capacity. In multivariable analyses, current smoking and pack-years of smoking were predictors of adverse FEV_1, FEV_1/FVC, and D_{LCO} phenotypes, and detectable viremia was the only HIV infection marker associated with the adverse D_{LCO} phenotype.

This study defines distinct phenotypes for pulmonary function trajectories in PWH. We identified three trajectories for FEV_1/FVC differing significantly in rate of decline, but not in baseline value. We found two declining trajectories of D_{LCO} differing significantly in baseline value, but not in rate of decline. Finally, we identified two trajectories each for FEV_1 and FVC characterized by faster rate of decline in participants with higher baseline lung function. These findings are consistent with observations in population-based (41) and COPD cohorts (42, 43), and they differ from the "horse-racing effect" for FEV_1 described in other studies (44, 45), whereby worse baseline FEV_1 impairment predicts faster FEV_1 decline. Our study thus provides important data about the natural history of lung function in PWH and suggests that distinct mechanistic pathways lead to airflow obstruction and gas exchange impairment in this population.

We found that baseline current smoking and more pack-years of smoking were associated with the low baseline, slow decline FEV_1 trajectory, moderate decline and rapid decline FEV_1/FVC trajectories, and baseline low D_{LCO} trajectory. Current smoking and pack-years of smoking have been identified as independent predictors of airflow and diffusion impairment in cross-sectional studies (4, 7, 21, 37, 46–48) and of faster decline in pulmonary function in longitudinal cohorts (14, 21, 37, 38). Our study, which integrates baseline and longitudinal data to identify lung function trajectories and has longer follow-up (median, 8.1 yr vs. 1.5–6.3 yr in earlier cohorts), provides additional evidence on the detrimental relationship between smoking and lung function in PWH.

The effects of length of HIV infection, ART use, viremia, and baseline and nadir CD4 counts on pulmonary function have been evaluated in cross-sectional studies with conflicting findings (1, 2, 7, 37, 46–49). Although a longitudinal cohort of PWH in the pre-ART era found that lower baseline CD4 count was a risk factor for D_{LCO} (but not FEV_1 or FVC) decline (38), two studies in the ART era did not report a significant association between these factors and lung function decline (20, 21). Our analysis identified detectable viremia as a risk factor for the adverse D_{LCO} phenotype, suggesting greater importance of optimized viral suppression versus CD4 count and duration of HIV infection in determining the trajectory of D_{LCO}.

Our data suggest that systemic inflammation and endothelial dysfunction may be important contributors to lung function impairment in PWH. In exploratory multivariable analyses, we found that elevated CRP was associated with the adverse FEV_1 and FVC phenotypes, consistent with previous reports of an association between increased CRP with cross-sectional and longitudinal spirometry abnormalities (14, 32, 37, 46, 50, 51). Whether the observed effect of CRP partly reflects ongoing viral replication, contemporaneous smoking, or pulmonary infections (all of which were prevalent in our cohort) or another factor is unknown. In addition, we found that elevated ET-1 concentration was associated with the adverse FEV_1 and FVC phenotypes and trended toward association with the adverse D_{LCO} phenotype, adding to the literature on the relationship between endothelial damage and abnormal lung function (16, 32). Interestingly, we did not observe associations between any cytokines and the adverse FEV_1/FVC, unlike prior studies linking inflammatory cytokines with airflow obstruction (16, 32, 37, 46, 50, 51).

Decreased D_{LCO}, FEV_1, FVC, and FEV_1/FVC and rapidly declining FEV_1 are associated with mortality in population-based cohorts (52–54). Three studies have examined pulmonary function and mortality in PWH. In the Pittsburgh HIV Lung Cohort, participants with moderate gas exchange limitation or airflow obstruction had increased risk of mortality, with the Kaplan-Meier curve diverging earlier in those with diffusion impairment (11). The Examinations of HIV-associated Lung Emphysema study demonstrated that decreased D_{LCO} and FEV_1 and airflow obstruction were independent predictors of mortality (12). Finally, incident airflow obstruction was a risk factor for mortality in the AIDS Linked to the Intravenous Experience study (13). Our finding that only the adverse D_{LCO} phenotype was associated with increased mortality further supports diffusion impairment as a marker of excess mortality risk in HIV.

Shorter 6MWD is associated with decreased therapeutic response and increased mortality in COPD (55). The minimal clinically important difference in 6MWD in severe COPD is estimated at 25–35 meters (56, 57). Studies have shown that HIV infection is an independent predictor of shorter 6MWD (6, 10), with lower percent predicted D_{LCO} and FEV_1 identified as risk factors for decreased 6MWD in PWH (6, 9). We found that adverse phenotypes for D_{LCO}, FEV_1, FVC, and the rapid decline phenotype for FEV_1/FVC were associated with clinically significant decrements in 6MWD (ranging from 41 to 75 m), indicating meaningful functional exercise limitation in these individuals.

Dyspnea is more prevalent and respiratory health status is impaired in PWH than in uninfected control subjects (1, 9, 49). Among PWH, airflow obstruction is a predictor of breathlessness (58), and poorer respiratory health status has been linked to airflow limitation (8, 47) and rapidly declining FEV_1 (20). In our study, breathlessness was significantly more prevalent in each adverse lung function phenotype. Moreover, participants with adverse lung function trajectories had statistically and clinically significant differences in SGRQ scores compared with referent trajectories, ranging from 7.5 to 23.2 points (compared with the minimal clinically important difference of 4 units) (59), suggesting consequential impairment of respiratory health status.

Strengths and Limitations

A major strength of this study is the use of GBTM for pulmonary function in PWH, which represents a data-driven, unsupervised classification technique, thereby allowing assessment of potential longitudinal pulmonary function phenotypes not based

on *a priori* hypotheses. In addition, we had comprehensive pulmonary function data for a large multicenter sample of PWH with a long duration of follow-up. Finally, we were able to make inferences for associations between phenotypes and several clinical outcomes.

This study has certain limitations. First, pulmonary function measurements may represent different temporal stages of pathology in addition to possible interindividual differences due to different risk profiles for abnormal lung function. Moreover, abnormal lung function was highly prevalent at baseline. However, our comparison of trajectory groups (which incorporate baseline and longitudinal data) with cross-sectional and rate-based pulmonary function parameters indicated that the association of trajectory groups with most clinical outcomes was statistically more robust than previously used parameters. Second, there may be uncontrolled confounding from factors for which we lacked baseline data (e.g., comorbidities, frailty, environmental exposures) or longitudinal data (e.g., smoking, HIV infection markers, pulmonary infections), which may have affected pulmonary function trajectories and clinical outcomes. We did not have information on cause of death, which limits inferences between phenotypes and mortality. Because we had assessments of circulating cytokines for a subset of participants, we were limited to exploratory analyses incorporating these variables and likely had insufficient power to detect significant associations. Finally, survivor and selection bias and recall bias for self-reported data are possible.

In summary, we identified novel longitudinal pulmonary function trajectories in a large sample of PWH with significantly different clinical outcomes. Future work should focus on validating these findings in additional cohorts, examining the influence of time-updated variables and possible confounders and further investigating the inflammatory pathways involved in the pathogenesis of clinical and subclinical lung disease in PWH. Because smoking and detectable viremia were associated with adverse phenotypes, risk modification via smoking cessation and optimizing viral control should remain cornerstones of therapy in PWH. ■

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