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Factors associated with progression of lung function abnormalities in HIV-infected individuals

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Abstract

Background: HIV is an independent risk factor for chronic obstructive pulmonary disease (COPD); however, baseline risk factors for lung function decline remain largely unknown in this population.

Methods: —HIV-infected participants in the Pittsburgh Lung HIV Cohort with at least three pulmonary function measurements between 2007–2016 were included. Pulmonary function testing (PFT) including post-bronchodilator (BD) spirometry and diffusion capacity for carbon monoxide (DLco) was performed every 18 months. We used a mixed effect linear model to evaluate factors associated with PFT and DLco decline and logistic regression models to evaluate factors associated with rapid FEV1 decline (defined as >80ml per year) and any DLco decline.

Results: 285 HIV-infected participants were included. Median baseline CD4 cell count was 521 cells/μl, 61.9% had an undetectable HIV viral load at baseline, and 78.5% were receiving ART. Approximately 20% of participants met Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria for a diagnosis of COPD at baseline. Older age and baseline GOLD stage 1 compared with stage 0 were associated with faster decline in post-BD FEV1%, while female sex was associated with slower decline. Similarly, female sex was associated with slower decline in DLco%. HIV-related factors including CD4 cell count, viral load and ART use were not significantly associated with pulmonary function decline.

Conclusion: Older age, male sex and higher baseline GOLD stage were associated with more rapid Post-BD FEV1% decline in HIV-infected individuals.

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Conflicts of Interest

No conflicts of interest.

Keywords

HIV; chronic obstructive pulmonary disease; pulmonary function test; sex difference

Introduction

In the era of antiretroviral therapy (ART), human immunodeficiency virus (HIV) has become a chronic disease, but mortality and morbidity associated with non-AIDS-defining diseases has increased [1]. Among these non-AIDS-defining conditions, lung diseases, including chronic obstructive pulmonary disease (COPD), malignancy, pulmonary hypertension, and pulmonary fibrosis, are increasing causes of morbidity and mortality [2]. These diseases may contribute to a substantial excess health burden in HIV-infected individuals. COPD, which can include phenotypes of fixed airway obstruction or impaired diffusing capacity for carbon monoxide, is a common cause of chronic lung disease in HIV-infected populations [3].

Despite the rising awareness of chronic lung diseases in the HIV-infected population, the trajectory of lung function decline as well as the risk factors that predict lung function decline remain largely unknown in this population. In the AIDS Linked to the Intravenous Experience (ALIVE) cohort study, plasma HIV RNA > 75,000 copies/ml and CD4 cell count <100 cells/μl were associated with greater decline in pre-bronchodilation forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) when compared to HIV-uninfected individuals[4]. However, participants in this study were intravenous drug users (IDU), which is an independent factor for COPD people with HIV [5]; also, only pre-bronchodilation pulmonary function were measured, which cannot distinguish reversible airway disease such as asthma from incompletely reversible disease such as COPD. Study follow-up duration was also relatively short (median follow-up duration 2.75 years). Studies focusing on long-term follow-up of post-bronchodilation pulmonary function test (PFT) in the general HIV-infected population are lacking. To this end, we utilized data from Pittsburgh HIV Lung Cohort to evaluate the trajectory of lung function decline and the characteristics associated with lung function decline in an HIV-infected cohort.

Methods

Subjects

Subjects from the Pittsburgh HIV Lung Cohort (previously reported in [6, 7]) were selected for this analysis. Inclusion criteria for the parent study included HIV-1 infection and ages 18 to 80 years. Exclusion criteria included pregnancy or breast-feeding; contraindication to pulmonary function testing; increasing respiratory symptoms or fevers (temperature>38°C) within 4 weeks of study entry; hospitalization within 4 weeks prior to study entry (excluding mental health); uncontrolled hypertension at screening visit (systolic >180 mmHg or diastolic >100 mmHg); current systemic chemotherapy or radiation for cancer; or current infection of the lungs, brain, or abdomen. Individuals in the Pittsburgh HIV Lung Cohort were recruited from the Pittsburgh AIDS Clinical Trial Unit, the Multicenter AIDS Cohort Study (MACS), and the Women's Interagency HIV Study (WIHS) in Pittsburgh, San

Francisco and Los Angeles [7, 8]. All participants provided written, informed consent approved by institutional review boards at the sponsoring institutions.

For the current study, individuals with three or more pulmonary function tests available between 2007–2016 were included to evaluate change in lung function over time. Pulmonary function testing was conducted approximately every eighteen months. Baseline clinical data including age, sex, race/ethnicity, cigarette smoking, recreational drug use, history of pneumonia, CD4 cell count, viral suppression, and antiretroviral therapy use were determined by participant interview, medical record review, and data collected at MACS and WIHS study visits [7, 8]. Individuals with fewer than three acceptable pulmonary function tests between 2007 and 2016 were excluded.

Pulmonary function testing

PFT was performed by trained personnel per American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines[9, 10]. Lung function was evaluated by post-bronchodilation (post-BD) percent predicted forced expiratory volume in one second (FEV1%), absolute post-BD FEV1, post-BD percent predicted FVC (post-BD FVC%), absolute post-BD FVC, as well as carbon monoxide diffusion capacity of the lung percent predicted (DLco). All tests were reviewed by a trained pulmonologist and were included if they met ATS acceptability criteria (Grade A, B, or C) and/or were deemed acceptable on review. Hankinson and Neas predicted equations were used to determine percent predicted values of spirometry and DLco, respectively with DLco corrected for hemoglobin and carboxyhemoglobin [10, 11]. COPD is defined as FEV1/FVC<70%.

Statistical Analysis

Continuous variables were summarized by median and interquartile range (IQR). We used a chi square test to compare proportions for categorical variables. Univariate analyses included baseline age, sex, smoking history, recreational drug use, and baseline Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage [12]. In order to account for potential influence from menopause, we further stratified women into age group <50 years old and ≥50 years old. We used mixed effect linear models (with random slope) to evaluate factors associated with post-BD FEV1%, post-BD FEV1, post-BD FVC%, post-BD FVC and DLco % changes. In these models, the effects of baseline variables on these baseline PFT measures as well as the interaction between variable and time (to measure the effect on annual rate of PFT change) were calculated. For each individual, we also calculated a rate of decline for absolute post-BD FEV1 and DLco for the entire follow-up time using mixed effect models. Logistic regression models were then applied to evaluate the effect of baseline factors on rapid post-BD FEV1 decline (defined as >80ml per year, or greater than the third tertile of the magnitude of annual decline in post-BD FEV1, consistent with previous reports [13, 14]). We also used logistic regression to evaluate factors associated with DLco decline (any decline in DLco vs. no decline in DLco). We also assessed smoking as a time-varying covariate with three different approaches. First, we assessed the relationship between smoking status and FEV1%, FVC%, DLco% at each visit. Then, we assessed the effect of change of smoking status at each visit from the last visit on pulmonary measures in subsequent visit (lag time analysis). Finally, we assessed the effect of smoking status at the

prior visit on pulmonary measures in each visit (adjusted for smoking status on same visit). We used Stata 14.0 (StataCorp., College Station, TX) for statistical analyses.

Results

Baseline characteristics

285 HIV-infected participants were included (Table 1). Most participants were 40 to 50 years old, male (67.7%), current (51.1%) or former smokers (22.3%) and had a history of marijuana use (82.5%). 35.5% of women were over 50 years old. 47.7% of participants were Caucasian and 46.3% African-American. Of note, female sex was associated with higher proportion of African-American ethnicity (female vs. male, 66.3% vs. 36.8%, p< 0.001) and lower rate of marijuana use (female vs. male, 75.6% vs. 85.6%, p= 0.042), but otherwise similar proportions of current smoking status, smoking pack year, age, baseline CD4 cell count, viral suppression rate, ART use and GOLD stage. Current smoking rate was higher in marijuana users compared to marijuana nonusers (56.6% vs. 25.0%, p<0.001). We also compared baseline characteristics between participants who were included and excluded in this analysis. In the exclusion group, there were more females (included vs. excluded 32.3% vs. 45.7%, p=0.020), African-Americans (46.3% vs. 60.9%, p=0.024), and individuals who had used intravenous drugs (19.7% vs. 35.6%, p=0.002). Median post-BD FVC was slightly lower in exclusion group (4.2 vs. 3.8 L, p=0.029) and median DLco% slightly higher (67.5% vs. 73.0%, p=0.003) (Supplementary Table S1).

Baseline lung function

Post-BD PFTs in most participants (82.8%) did not demonstrate evidence of COPD at the time of enrollment, and median FEV1% predicted was 97.5% (IQR 85.1%−109.5%). In contrast, 79.0% of individuals had a clinically abnormal diffusion capacity (defined as DLco<80%[5]), with median DLco 67.5% predicted (Table 1).

Several baseline variables were associated with post-BD PFT. Current smoking (median baseline post-BD FEV1% 94.7% in current smokers versus 101.3% in non-smokers, p<0.001) and greater pack-year smoked (median baseline post-BD FEV1% 93.0% in subjects with ≥20 pack-year versus 101.3% in never-smokers, p<0.001) were significantly associated with low baseline post-BD FEV1% in univariate analysis. CD4 cell count, viral suppression, and ART use were not correlated to baseline post-BD FEV1% (Table 2). Similarly, greater smoking pack-years was associated with lower baseline absolute post-BD FEV1 and post-BD FVC (Supplementary Table S2 and Supplementary Table S3).

In univariate analyses, factors associated with low baseline DLco predicted included older age, female older than 50 years old, current smokers, smoking >10 pack year, IDU, crack cocaine use, history of pneumonia, and high GOLD stage (Table 2).

Factors associated with Post-BD FEV1% and Post-BD FEV1 decline

The median duration of follow-up in HIV-infected participants was 6.3 (IQR 3.6–7.7) years. Post-BD FEV1% rate of change was −1.0% per year (IQR, −1.7 to −0.1). In a mixed effects model with random coefficient, baseline age 41–50 years old (excess change −0.56% per

year, p=0.041) and age 51–60 (−0.72% per year, p=0.020) compared to age 19–40 were associated with faster decline, as was baseline GOLD stage 1 compared to stage 0 (−0.81% per year, p=0.024). Female sex (0.66% per year, p=0.004), specifically female younger than 50 years old (0.75% per year, p=0.004), was associated with slower decline (Table 3). Absolute median change in post-BD FEV1 was −62 ml per year (IQR −23 to −91). In a mixed effect with random coefficient model, only female sex (0.04L per year, p<0.001) was significantly associated with slower absolute decline (Supplementary Table S2).

We also evaluated factors associated with rapid Post-BD FEV1 decline, defined as >80ml per year decline. In univariate analyses, age 41–50 (odds ratio [OR] 1.97, p=0.046) and marijuana use (OR 2.47, p=0.018) were independent risk factors for rapid pulmonary function decline, while female sex was a protective factor for rapid pulmonary function decline (OR 0.30, p<0.001). There was no relationship between baseline DLco and risk of rapid decline (OR = 1.00, P = 0.71). The odds ratio for participants to develop new obstruction during the follow-up if they had baseline DLco%<0.8 was 8.1 (P=0.15). After adjusting for age and sex, marijuana use (OR 2.28, p=0.037) was the only significant risk factor associated with rapid decline, while smoking 10–19.9 pack year compared to non-smokers was marginally associated with rapid decline (OR 2.05, p=0.06) (Table 4). HIV-related factors or GOLD stage were not associated with rapid Post-BD FEV1 decline.

Factors associated with Post-BD FVC and Post-BD FVC% decline

Median change in post-BD FVC% predicted was −0.96% per year (IQR −1.63 to −0.15) and absolute median change in post-BD FVC was −67 ml per year (IQR −24 to −105). In univariate analysis, older age (age 41–50 year-old compared to 19–40 year-old, excess change −0.54% per year, p= 0.038; age 51–60 year-old compared to 19–40 year-old, −0.78% per year, p= 0.008), any history of pneumonia (−0.46% per year, p=0.029), and GOLD stage 1–3 (stage 1 compared to stage 0, −0.81% per year, p=0.016; stage 2–3 compared to stage 0, −1.43% per year, p<0.001) were associated with faster post-BD FVC% decline. Female sex (compared to male, 0.58% per year, p=0.009), especially women younger than 50 years old (0.65%, p=0.009), was associated with slower decline (Supplementary Table S3). In univariate analysis of absolute decline in FVC, older age (age 51–60 years-old compared to 19–40 years-old, excess change −0.03L per year, p=0.004), and GOLD stage 1 (compared to stage 0, −0.03L per year, p=0.025) and stage 2–3 (excess change −0.06L per year, P<0.001) were associated with faster post-BD FVC decline. Female sex (0.05L per year, p<0.001) was associated with slower absolute decline, with no differences in <50 years old and ≥50 years old age groups (Supplementary Table S4).

Factors associated with DLco decline

There was no decline in the cohort overall in DLco percent predicted over time with median rate of DLco% change of 0.7% (IQR 0.2–1.7, p<0.001 compared to 0%) per year. Fifty-six participants (21%) had a decline in DLco% during the follow-up period. In univariate analysis, female sex was significantly protective for DLco% decline (excess change 0.77% per year, p=0.003), while other factors including HIV-related factors were not significantly associated with change in DLco% (Table 5). In multivariate analysis adjusted for age and sex, history of pneumonia was significantly associated with DLco% decline (OR 1.95,

p=0.030), and current smokers tended to be associated with DLco% decline (OR 2.18, p=0.051) (Supplementary Table S5).

Smoking as a time-varying covariate

When smoking status at each visit was included in the model, current and former smokers had significantly lower FEV1% (β=−4.6, 95% CI=−8.1- −1.1, p=0.010 for current; β=−4.7, 95% CI=−8.2- −1.2, p=0.008 for former) and DLco% (β=−7.6, 95% CI=−10.8- −4.5, p<0.001 for current; β=−5.4, 95% CI=−8.6- −2.2, p=0.001 for former). We did not find an effect of change in smoking status on pulmonary function by either lag-time analysis or in examining the effect of change from prior visit on the subsequent visit although only 10% of the cohort changed smoking status.

Discussion

This study examined progression of pulmonary function measurements in a varied HIV-infected cohort over a period of six years. We discovered that older age and higher baseline GOLD stage were associated with more rapid post-BD FEV1%, post-BD FVC and post-BD FVC% decline, while history of pneumonia was significantly associated with DLco% decline. Female sex was a protective factor against post-BD FEV1%, post-BD FEV1, post-BD FVC, post-BD FVC% and DLco% decline. Marijuana use was found to be a risk factor for rapid post-BD FEV1 decline. We did not find that HIV-related factors were significantly associated with pulmonary function decline.

Post-BD FEV1% change and post-BD FEV1 change in our study were comparable with previous studies in HIV-infected and uninfected populations. In the HIV-uninfected population, average change rate in FEV1 is quite variable, ranging from −80ml per year to −20ml per year [15, 16]. Of note in these prior studies, the HIV-uninfected participants all had a diagnosis of COPD, were older, and had a greater pack-year smoking history, and therefore had lower baseline FEV1% compared to our participants. Both HIV-uninfected studies discovered great variability in FEV1 change among individuals, including many individuals with stable or improving measurements over time, indicating that COPD evolvement is a heterogeneous process [15, 16].

Few studies have investigated longitudinal change in HIV-infected individuals. The pre-ART era Pulmonary Complications of HIV Infection Study, a large multicenter cohort study with median follow-up 3.7 years, demonstrated that FEV1 change was −27.4 ml per year [17]. In a study of the AIDS Linked to the Intravenous Experience (ALIVE) cohort, which enrolled participants during 2007–2010 in the ART era with median follow-up 2.75 years, pre-BD FEV1 change was −35.8 ml per year (95% CI −51.2 to −20.3) and pre-BD FVC change was −9.29 ml per year, somewhat less than we found in our cohort [4]. Paradoxically, the ALIVE cohort had more current smokers (85% compared to 51% in our study), more IDU (39% compared to 20% in our study) and lower ART use at baseline (55% compared to 79% in our study) which might lead to faster rather than slower decline compared to our study. In the Strategic Timing of Antiretroviral Treatment (START), FEV1 change slope was around −30 ml per year in baseline smokers and −25 in baseline nonsmokers [18]. In an HIV study from South Africa, average FEV1 decline was −7 ml per year[19]. The difference between

other studies and our study (−62 ml per year) could be due to length of follow-up or other unmeasured differences between the cohorts. In addition, we measured post-BD FEV1 while in the ALIVE study, only pre-BD FEV1 was measured, which may assess both asthma and COPD. The greater rate of decline in our population may also reflect the older age of the cohort and the greater prevalence of risk factors such as smoking in the cohort. In addition, duration of HIV is much longer than other studies such as the START study which may impact results as well.

We discovered that older age and baseline airway obstruction are risk factors for post-BD FEV1% decline while female sex is a protective factor. These results have some similarities and differences to findings in the HIV-uninfected population. In an analysis from multicenter COPDGene study, GOLD stage 1 was associated with faster FEV1 decline compared to GOLD stage 0, similar to our findings [20]. In contrast to our findings, female sex was associated with rapid FEV1 decline in the COPDGene study, although this study was not designed to assess sex difference [20]. Similarly, in the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, female sex was also associated with progression of emphysema, although all subjects were diagnosed with COPD [21]. In another study evaluating sex difference in airway obstruction in smokers (HIV status unknown), both sexes had similar FEV1, but male sex was associated with greater pack-year smoking history and more severe emphysema based on high-resolution CT scan [22]. In our current study, female sex was also associated with higher proportions of African-American race and lower rate of marijuana use, which may potentially influence the sex difference in pulmonary function decline. It is unclear why female sex has a different association with FEV1 decline in HIV-infected and HIV-uninfected populations, as smoking status, social economic status etc. could be different in people with and without HIV infection [23].

Changes over time in DLco in HIV have not been examined in the ART era, but DLco abnormalities are common in HIV-infected individuals [24]. We found little change in DLco over time, consistent with data from the pre-ART era. For example, a prospective, 18-month study found that DLco did not show decline during the follow-up in the overall cohort; however, DLco decline was observed in a subset of participants with clinical deterioration due to *Pneumocystis* pneumonia and in those with a smoking history [25]. In contrast, the Pulmonary Complications of HIV Infection Study demonstrated a significant decline in DLco (−0.4ml/min/mmHg per year) in HIV-infected men [17]. No studies have examined DLco longitudinally in the ART era. Competing mortality may explain some of the lack of decline as we have previously found DLco to be a predictor of mortality[26], and there was an increased risk of death in individuals with rapid DLco decline in this study. However, the absolute numbers of deaths were small and unlikely to have significantly impacted the findings. A pilot study from our group also found no change in DLco over six months in the placebo arm of the trial [27]. These findings suggest that impairment of DLco occurs early in the course of HIV infection and may be stabilized by ART use or other factors.

We did not find an association between HIV-related factors with decline in FEV1, FVC or DLco. This finding is consistent with the START trial, which showed that timing of ART initiation based on CD4 cell count was not associated with decrease in FEV1 over a median follow-up duration of two years [18]. In contrast, the ALIVE study demonstrated that poorly

controlled HIV with HIV viral levels greater than 75,000 copies/ml was associated with accelerated decline in FEV1 when compared with HIV-uninfected participants [4], while in our study, most participants had viral load lower than 75,000 copies/ml. In addition, the national Veterans Aging Cohort Study, a large-scale longitudinal cohort study, demonstrated that HIV infection, especially with lower CD4 cell counts, was associated with acute exacerbations of COPD [28]. In comparison, another study enrolling participants with drug use found that high CD4 cell count was associated with increased acute exacerbation of COPD [29]. It is possible that cohort differences including degree of immunosuppression, age, baseline viral load and other risk factors for obstructive lung disease could explain these discrepancies. We also did not examine other HIV-related markers including CD4/CD8 ratio, which has been demonstrated to be related to lower COPD rate in a geriatric population [30].

We focused on a sub-population of individuals with “rapid decline” of 80 ml per year as these individuals are the most clinically at risk. Baseline risk factors for rapid post-BD FEV1 decline included age and sex. Smoking pack years were marginally associated with rapid decline. In a previous study to evaluate baseline factors associated with rapid post-BD FEV1 decline (defined as decline >60 ml per year) in subjects exposed to biomass (HIV status unknown), rapid decline was associated with higher proportion of male sex (94% in rapid decline group and 70% in slow decline group) while age was similar in different decline groups [13]. Interestingly, marijuana use was also a significant risk factor for rapid decline. A systematic review suggested that long-term marijuana use is associated with airway obstruction symptoms including cough, phlegm production, and wheeze [31]; however, data regarding marijuana use and PFT change are mixed. Of the 14 studies cited by the review, eight studies showed association between marijuana use and evidence of airway obstruction (measured by FEV1, FVC, FEV1/FVC, specific conductance or airway obstruction reversibility); however, after adjusting for smoking tobacco, the association became non-significant in two of the larger studies [32, 33]. Similarly, in our cohort, marijuana use was significantly associated with cigarette smoking, with 91% of current smokers and 84% of former smokers using marijuana, compared with 64% of non-smokers using marijuana ($P<0.001$). There may be synergistic effects between cigarette smoking, marijuana use and HIV infection including effects on lung inflammation and muco-ciliary dysfunction [34].

Our findings have important clinical implications for patients with HIV and airway obstruction, supporting following pulmonary function more closely in individuals with baseline airway obstruction given that it is associated with accelerated pulmonary function decline. Increased efforts at smoking cessation should target this group of patients. Future studies should also consider novel therapies, such as inflammatory modulators (i.e. statin) in this group of patients with HIV and COPD to mitigate lung function decline [27].

There are several strengths to this study. It is a multicenter and longitudinal study, with a long follow-up duration (median follow-up 6.3 years). Most individuals were either current or former smokers, similar to the overall HIV-infected population [35]. Limitations of this study include a relatively small number of participants with baseline airway obstruction on enrollment, which limits the power in this group. Individuals were also enrolled from a variety of different HIV cohorts which may have diluted effects in particular risk groups, but

also improves the generalizability of the results. Our ability to determine smoking as a risk factor for decline may have been limited by the sample size or study duration. We were also unable to evaluate the correlation between PFT decline and nadir CD4 cell count which may play a role in subsequent lung function.

In conclusion, this multicenter, longitudinal cohort study evaluated factors associated with pulmonary function decline in HIV-infected individuals over six years. We found that HIV-infected individuals had a significant degree of decline in post-BD FEV1 and post-BD FVC, but DLco was relatively conserved despite baseline low values. These findings suggest that different risk factors influence these two aspects of lung function and that certain risk groups may benefit from more intensive screening with pulmonary function testing and smoking cessation to prevent further loss of lung function.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points:

In HIV-infected participants, excess pulmonary function decline was associated with older age, male sex and higher baseline Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage. HIV-related factors were not associated with excess pulmonary function decline.

Table 1.

Baseline characteristics of the cohort.

	N	
Age, median years (IQR)	285	47 (41–53)
Female, n (%)	285	92 (32.3)
Female ≥50 years old, n (%)	285	33 (11.6)
Race, n (%) Caucasian African-American Other	285	 136 (47.7) 132 (46.3) 17 (6.0)
Smoking history, n (%) Non-smoker Current Former	274	 73 (26.6) 140 (51.1) 61 (22.3)
Pack year history, median pack-years (IQR)	267	12.0 (0–26.6)
Ever used IV drug, n (%)	273	54 (19.7)
Ever used marijuana, n (%)	274	226 (82.5)
Ever used crack cocaine, n (%)	261	106 (40.6)
History of pneumonia, n (%)	274	95 (34.7)
History of *Pneumocystis* pneumonia, n (%)	274	16 (5.8)
CD4 cell count, median cells/μl (IQR)	281	521 (342–765)
VL detectable, n (%)	281	107 (38.1)
VL in participants with detectable VL, median copies/ml (IQR)	107	5130 (470–50400)
On ART, n (%)	274	215 (78.5)
Ever used bronchodilator, n (%)	285	65 (22.8)
Ever used ICS, n (%)	285	20 (7.0)
Post-BD FEV1% predicted, median% (IQR)	285	97.5 (85.1–109.4)
Post-BD FEV1, median liter (IQR)	285	3.2 (2.6–4.0)
Post-BD FVC, median liter (IQR)	285	4.2 (3.4–5.0)
Post-BD FEV1/FVC, median% (IQR)	285	79.4 (73.8–83.5)
DLco% predicted, median% (IQR)	277	67.5 (57.3–76.6)
GOLD Stage 0 1 2 3	285	 236 (82.8) 26 (9.1) 22 (7.7) 1 (0.4)

Abbreviation: IQR, interquartile range; IV, intravenous; VL, viral load; ART, antiretroviral therapy; ICS, inhaled corticosteroid; BD, bronchodilation; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; DLco, carbon monoxide diffusion capacity of the lung; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Table 2.

Baseline factors associated with baseline Post-BD FEV1% and DLco%.

	Effect on baseline FEV1%		Effect on baseline DLco%	
	Beta (95% CI)	**P**	**Beta (95% CI)**	**P**
Age 19–40 41–50 51–60 60+	Ref 1.85 (−3.08– 6.78) −2.14 (−7.68– 3.39) −2.92 (−11.08– 5.23)	0.5 0.5 0.5	Ref −6.15 (−10.25- −2.05) −9.21 (−13.82- −4.61) −5.86 (−12.65– 0.93)	0.003 <0.001 0.09
Female sex	−0.54 (−4.70– 3.62)	0.8	−0.86 (−4.41– 2.69)	0.6
Sex Male Female <50 years old Female ≥50 years old	Ref 0.50 (−4.35– 5.35) −2.45 (−8.76– 3.80)	0.8 0.4	Ref 2.83 (−1.22– 6.88) −7.94 (−1.32- −2.66)	0.17 0.003
Smoking status Non-smoker Current smoker Former smoker	Ref −7.62 (−12.09 - −3.14) −3.15 (−8.58– 2.28)	<0.001 0.3	Ref −9.62 (−13.38- −5.87) −4.81 (−9.36- −0.27)	<0.001 0.037
Pack year 0 0.1–9.9 10.0–19.9 20+	Ref −3.74 (−9.50– 2.02) −4.29 (−9.65– 1.06) −9.81 (−14.81- −4.81)	0.2 0.12 <0.001	Ref −3.11 (−7.91– 1.69) −9.43 (−13.90- −4.97) −10.56 (−14.73- −6.38)	0.2 <0.001 <0.001
IDU *	3.63 (−1.17– 8.43)	0.14	−5.38 (−9.44- −1.31)	0.010
Marijuana *	1.16 (−3.98– 6.29)	0.7	0.60 (−3.80– 5.00)	0.8
Crack cocaine *	0.27 (−3.72– 4.26)	0.9	−3.47 (−6.89- −0.05)	0.047
History of pneumonia	−3.36 (−7.41– 0.69)	0.10	−3.57 (−7.02- −0.11)	0.043
History of *Pneumocystis* pneumonia	−4.80 (−13.47– 3.88)	0.3	−5.4 (−12.6– 1.8)	0.14
CD4 cell count (per 10 cell/μl increase)	0.02 (−0.04– 0.08)	0.6	0.04 (−0.01–0.09)	0.15
VL detectable	0.17 (−3.83– 4.17)	0.9	−1.2 (−4.7– 2.3)	0.5
On ART	−0.49 (−5.10– 4.12)	0.8	−0.27 (−3.71– 3.18)	0.9
GOLD 0 1 2–3	Ref −9.78 (−15.54- −4.03) −33.31 (−39.38- −27.23)	0.001 <0.001	Ref −6.98 (−12.65- −1.32) −13.66 (−19.65- −7.66)	0.016 <0.001

Abbreviation: CI, confidence interval; IDU, intravenous drug use; VL, viral load; ART, antiretroviral therapy; BD, bronchodilation; FEV1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

* ever had substance use versus never had substance use (reference group).

Table 3.

Baseline factors associated with Post-BD FEV1% decline in HIV-infected individuals (interaction term with time, % per year) based on a mixed effect with random coefficient model.

	Effect on annual rate of FEV% change	
	Beta (95% CI)	**P**
Age 19–40 41–50 51–60 60+	 Ref −0.56 (−1.09- −0.02) −0.72 (−1.32- −0.11) −0.07 (−1.01– 0.88)	 0.041 0.020 0.9
Female sex	0.66 (0.21–1.11)	0.004
Sex Male Female <50 years old Female ≥50 years old	 Ref 0.75 (0.24–1.26) 0.45 (−0.28– 1.18)	 0.004 0.2
Smoking status Non-smoker Current smoker Former smoker	 Ref −0.31 (−0.81– 0.19) 0.11 (−0.47– 0.70)	 0.2 0.7
Pack year 0 0.1–9.9 10.0–19.9 20+	 0.49 (−0.16– 1.15) −0.47 (−1.04– 0.09) −0.27 (−0.81– 0.27)	 0.14 0.10 0.3
IDU *	0.12 (−0.39– 0.64)	0.6
Marijuana *	−0.48 (−1.04– 0.07)	0.09
Crack cocaine *	−0.26 (−0.70– 0.17)	0.2
History of pneumonia	−0.29 (−0.72– 0.14)	0.18
History of *Pneumocystis* pneumonia	0.64 (−0.23– 1.51)	0.15
CD4 cell count (per 10 cell/μl increase)	−0.001 (−0.006– 0.007)	0.8
VL detectable	−0.23 (−0.66– 0.20)	0.3
On ART	0.08 (−0.42– 0.58)	0.7
GOLD 0 1 2–3	 Ref −0.81 (−1.51- −0.11) −0.69 (−1.49– 0.12)	 0.024 0.10

Abbreviation: CI, confidence interval; IDU, intravenous drug use; VL, viral load; ART, antiretroviral therapy; BD, bronchodilation; FEV1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

* ever had substance use versus never had substance use (reference group).

Table 4.

Baseline risk factors associated with FEV1 decline>80 ml/year (from baseline) in HIV-infected individuals in the last follow-up visit.

	Crude		Age-, sex-adjusted	
	OR (95% CI)	**P**	**OR (95% CI)**	**P**
Age 19–40 41–50 51–60 60+	Ref 1.97 (1.01–3.85) 1.83 (0.88–3.83) 2.16 (0.78–6.00)	0.046 0.11 0.14	NA	NA
Female sex	0.30 (0.17–0.55)	<0.001	NA	NA
Sex Male Female <50 years old Female ≥50 years old	Ref 0.27 (0.13–0.57) 0.36 (0.15–0.86)	0.001 0.022	NA	NA
Smoking status Non-smoker Current smoker Former smoker	Ref 1.21 (0.67–2.18) 0.94 (0.46–1.93)	0.5 0.9	Ref 1.46 (0.77–2.76) 1.02 (0.48–2.18)	0.2 0.9
Pack year 0 0.1–9.9 10.0–19.9 20+	Ref 0.52 (0.22–1.21) 1.54 (0.77–3.07) 1.37 (0.72–2.63)	0.13 0.2 0.3	Ref 0.67 (0.27–1.63) 2.05 (0.97–4.37) 1.38 (0.70–2.73)	0.4 0.06 0.3
IDU *	0.85 (0.45–1.60)	0.6	0.92 (0.46–1.81)	0.8
Marijuana *	2.47 (1.17–5.20)	0.018	2.28 (1.05–4.94)	0.037
Crack cocaine *	1.05 (0.62–1.75)	0.9	1.44 (0.81–2.60)	0.2
History of pneumonia	1.29 (0.77–2.15)	0.3	1.26 (0.73–2.15)	0.4
History of *Pneumocystis* pneumonia	0.79 (0.27–2.35)	0.7	0.64 (0.21–1.98)	0.4
CD4 cell count (per 10 cell/μl increase)	0.997 (0.989-1.004)	0.4	0.996 (0.988–1.004)	0.4
VL detectable	0.71 (0.43–1.19)	0.19	0.85 (0.49–1.48)	0.6
On ART	1.38 (0.74–2.56)	0.3	1.20 (0.662–2.32)	0.6
GOLD 0 1 2–3	Ref 1.49 (0.65–3.39) 1.86 (0.78–4.40)	0.3 0.16	Ref 1.40 (0.58–3.35) 1.88 (0.76–4.67)	0.5 0.17

Abbreviation: OR, odds ratio; CI, confidence interval; IDU, intravenous drug use; VL, viral load; ART, antiretroviral therapy; BD, bronchodilation; FEV1, forced expiratory volume in one second; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

* ever had substance use versus never had substance use (reference group).

Table 5.

Baseline factors associated with DLco (%) change in HIV-infected individuals (interaction term with time, percent per year).

	Effect on annual rate of DLco % change	
	Beta (95% CI)	**P**
Age 19–40 41–50 51–60 60+	Ref 0.18 (−0.44– 0.81) −0.27 (−1.00– 0.40) −0.03 (−1.13– 1.07)	0.6 0.4 >0.9
Female sex	0.77 (0.26– 1.29)	0.003
Sex Male Female <50 years old Female ≥50 years old	Ref 0.69 (0.10– 1.28) 0.96 (0.12–1.80)	0.022 0.025
Smoking status Non-smoker Current smoker Former smoker	Ref 0.02 (−0.56– 0.60) 0.20 (−0.48– 0.89)	0.9 0.6
Pack year 0 0.1–9.9 10.0–19.9 20.0+	Ref 0.03 (−0.74– 0.80) 0.09 (−0.58– 0.78) 0.09 (−0.56– 0.73)	0.9 0.8 0.8
IDU *	0.27 (−0.32– 0.87)	0.4
Marijuana *	0.21 (−0.43– 0.85)	0.5
Crack cocaine *	0.01 (−0.51– 0.53)	>0.9
History of pneumonia	−0.16 (−0.66– 0.34)	0.5
History of *Pneumocystis* pneumonia	0.5 (−0.5– 1.5)	0.3
CD4 cell count (per 10 cell/μl increase)	0.003 (−0.004– 0.011)	0.4
VL detectable	−0.1 (−0.6– 0.4)	0.6
On ART	−0.01 (−0.52– 0.49)	>0.9
GOLD 0 1 2–3	Ref 0.48 (−0.36– 1.31) −0.39 (−1.38– 0.60)	0.3 0.4

Abbreviation: CI, confidence interval; IDU, intravenous drug use; VL, viral load; ART, antiretroviral therapy; DLco, carbon monoxide diffusion capacity of the lung; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

* ever had substance use versus never had substance use (reference group).