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The Association of Lung Function with HIV Related Quality of Life and Healthcare Utilization in a High-Risk Cohort

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Abstract

Background: Chronic respiratory disease represents an important comorbidity for persons living with HIV(PLWH). HIV itself is associated with greater impairment in lung function. We aimed to determine the association between declining lung function and both quality of life(QOL) and healthcare utilization for PLWH.

Methods: Using longitudinal data from the Study of HIV in the Etiology of Lung Disease (SHIELD) 2009–2017, we studied the association between changes in lung function and both QOL and acute care events(ED visit or hospitalization). The Medical Outcomes Studies-HIV Questionnaire provided QOL domains. Multivariable regression models were performed with generalized estimating equations accounting for 1499 participants, 485 with HIV, contributing 10,825 spirometry visits.

Results: Among PLWH, decreased FEV₁ was associated with worse physical health for those with higher viral load(β -1.66, 95% CI -3.11 to -0.39) compared to those with viral suppression(β -0.58, 95% CI -1.06 to -0.162), even in those without airflow obstruction. Lower FEV₁ was also associated with increased odds of both ED(OR 1.21, 95% CI 1.09 to 1.34) and inpatient(OR 1.26, 95% CI 1.12 to 1.42) hospitalizations for PLWH. Lung function was not associated with increased odds of acute care events for HIV-uninfected participants.

Conclusions: FEV₁ declines represent an independent predictor of QOL and acute care events among PLWH. Though the generalizability of these results may be limited, due to the high-risk population included, findings suggest that care for PLWH should involve monitoring FEV₁ over time, especially in those with poor virologic control, with emphasis on the development and implementation of interventions to mitigate lung function decline.

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INTRODUCTION

With increases in the effectiveness of combination antiretroviral therapy (cART) for treating HIV, age-related diseases, such as chronic obstructive pulmonary disease (COPD), have emerged as significant comorbidities^{1,2}. To date, multiple studies have demonstrated that people living with HIV (PLWH) are at increased risk for development of COPD compared to uninfected individuals with similar risk factors^{3,4}. Notably, HIV is associated with an accelerated decline in lung function, including spirometric measurements and diffusing capacity (DLCO)⁵⁻⁷. Obstructive lung disease has been associated with both decreased quality of life (QOL) and increased all-cause mortality for PLWH^{8,9}. Several studies have demonstrated the association between spirometric measures, notably forced expiratory volume in 1 second (FEV₁), and health related QOL amongst HIV-uninfected individuals¹⁰⁻¹². In the general population, FEV₁ predictably declines with age, while the incidence of obstructive lung disease rises¹³. Among PLWH, those with higher HIV RNA levels have even greater rates of FEV₁ decline, with increased risk for the early development of obstructive lung disease¹⁴. The independent impact of spirometric impairment monitored over time, including decreased FEV₁ and forced vital capacity (FVC), on patient centered outcomes, including quality of life and healthcare utilization, in PLWH has not been fully established. For high-risk individuals with HIV in particular, it has been challenging to separate the impact of lung function from behaviors, including smoking and injection drug use, which may contribute to other comorbidities, QOL and healthcare utilization.

Since 2007, the Study of HIV Infection in the Etiology of Lung Disease (SHIELD) has routinely performed spirometry measurements along with detailed clinical, laboratory and patient-reported data collection every 6 months on a large cohort of HIV-infected and similar HIV-uninfected participants with a history of injection drug use in Baltimore, Maryland. The prevalence of cigarette smoking and respiratory symptoms has been notably high in this cohort. Using longitudinal data from SHIELD, we aimed to 1) analyze the associations between declining FEV₁ and airflow obstructions on both QOL and acute care events; 2) determine if FEV₁ or the presence of obstructive lung disease was a stronger predictor of these outcomes among PLWH versus HIV-uninfected participants; and 3) describe the relationship between markers of HIV disease (i.e., HIV status, viral suppression), lung function, and patient-centered health outcomes (QOL and healthcare utilization).

METHODS

Study Participants

Participants included in this analysis were restricted to SHIELD recruits from the AIDS Linked to the Intravenous Experience (ALIVE) cohort (which had serial QOL data available) above the age of 30 years (recognizing that lung function will generally continue to rise among healthy adults until the age of 30 before subsequently declining with further aging)¹⁵(see Supplemental Figure 1 for STROBE diagram). As part of routine study visits, HIV-infected and uninfected participants complete standardized interviewer- and computer-administered questionnaires, clinical examination, and spirometry. We analyzed spirometry, QOL and health care utilization data collected between February 2009 and June 2017. The

study was approved by the Institutional Review Board of Johns Hopkins University (NA_00020295); all participants provided written informed consent.

Data Collection

Pre-Bronchodilator Spirometry data was collected using KoKo pneumotachometers (Pulmonary Data Services, Louisville, Colorado, USA) in accordance with American Thoracic Society guidelines^{5,16}. Percent predicted values were calculated using Global Lung Initiative (GLI) reference equations. The presence of airflow obstruction in our analysis was determined based on a pre-bronchodilator FEV₁/FVC ratio below the lower limit of normal (LLN), based on the GLI mixed-ethnic reference equations¹⁷.

Quality of life scores were determined using the Medical Outcomes Study-HIV (MOS-HIV) questionnaire, conducted by trained interviewers at study visits concurrent with spirometry measurement. The MOS-HIV questionnaire is a 35-item survey that assesses ten dimensions of health to measure functional status and well-being in PLWH¹⁸. Physical health (MOS PHS) and mental health (MOS MHS) summary scores are generated using regression-based weights of individual domains¹⁹. Summary scores are standardized with a mean of 50 among the study population, with higher scores indicating better health status. The physical and mental health summary scores have been demonstrated to correlate with survival in longitudinal studies of HIV infection, with a one point increase or decrease in either summary score linked to a clinically significant change in mortality risk, when compared to other participants in the study population²⁰.

Medical conditions, such as respiratory infections or clinical AIDS events, including emergency department (ED) and inpatient visits, occurring in the prior six months were identified through self-report and confirmed via review of medical records. Information on smoking status, injection drug use, education, respiratory medications and anti-retroviral therapy were determined by self-report. During each visit, laboratory testing included HIV RNA levels, CD4+ T-cell counts, and antibodies to HIV-1 (on HIV-uninfected persons); antibodies to hepatitis C virus (anti-HCV) and HCV RNA was performed at study entry.

Statistical Analysis

Summary statistics of clinical and demographic characteristics were assessed for the overall cohort and stratified by HIV status. Data are presented as mean (SD) for normally-distributed data and median [IQR] for non-normally distributed data. Normally-distributed continuous variables were compared using the t-test, while categorical variables were compared with Pearson's chi-squared and Fisher's exact tests. In parallel, we analyzed two lung function abnormalities as exposures of interest including significant declines in FEV₁ (based on change from baseline assessment) or the presence of airflow obstruction (either at baseline or follow-up assessment). Decreases in percent predicted FEV₁ were modeled continuously, with results displayed for a 15-point change in percent predicted FEV₁. A 15-point change was selected as it approximated the median decrease in FEV₁% predicted (15.3 [7.3–21.7]) for PLWH in our study and provided ease of interpretation. This value also approximated the 5-year decrease observed in population based studies of smokers, and has additionally been used as the targeted meaningful difference for absolute change of FEV₁%

predicted in interventional trials for COPD^{21–23}. Our primary analysis focused on FEV₁ and airflow obstruction, given the established associations between FEV₁, obstructive lung disease and QOL in the general population. Models for FVC using similar methods are presented here as a secondary analysis, while analyses with a decline in the FEV₁ to FVC ratio modeled continuously are presented separately in an online supplement. To determine the independent influence of lung function abnormalities on QOL, we utilized multivariable linear regression models of the MOS PHS and MHS scores, with generalized estimating equations (GEE) of population aggregate data to account for the correlation arising from repeated measures amongst participants, adjusted for age, sex, race, education, recent injection drug use, smoking history, HCV status, health insurance, and the presence of self-reported comorbid conditions (diabetes, hypertension, cerebrovascular accident, cardiovascular disease, renal disease, obesity). To evaluate the effect of lung function on acute care events (both ED and inpatient visits), we utilized logistic regression models with GEE and robust estimation of variance, adjusted for similar covariates. Models for acute care events were constructed with a lag structure designed to look at the relationship between lung function at the current study visit and odds of reporting acute care events at the next six-month follow-up visit. Models of QOL scores were designed without a lag structure as our hypothesis was that lung function would influence QOL contemporaneously. HIV-related markers (HIV serostatus, viral load, CD4+ T-cell count) were analyzed as time-varying covariates, updated every six months. HIV viral load was modelled continuously, and categorically at different clinical thresholds (<400 copies/ml, >400–100,000 copies/ml, >100,000 copies/ml); 400 copies/ml was considered the lower limit of detection for the viral load assay. CD4+ T-cell counts were also modeled categorically at clinical thresholds (<200, 200–499, >500 cells/uL; supplemental digital content). For all analyses we performed a separate sensitivity analysis that limited data to participants with 5 years of follow-up data, to evaluate any biases that may be introduced by differential follow-up time among cohort participants. These results are provided in an online supplement.

STATA 15.0 (Stata Corp, College Station, TX) was utilized for statistical analyses. A P-value of <0.05 was considered as significant for our primary analysis and <0.10 for interaction terms and effect modification²⁴.

RESULTS

Participant Characteristics

A total of 1499 participants contributed 10,825 spirometry measurements over a median follow-up time of 5.2 (IQR 1.0–7.5) years. Of these, 465 participants (31.0%) were HIV-infected and 1264 (84.6%) were current smokers (Table 1). Participants were a median of 49.5 years old at baseline, and predominantly African American (84.1%) and male (67.1%). Demographics and exposures were relatively similar between HIV-infected and uninfected participants. HIV-infected participants were less likely to be active injectors but had similar pack-years of smoking and levels of comorbidity. Healthcare utilization was common with 656 (43.8%) having at least one inpatient hospitalization and 997 (66.0%) having an ED visit during the entire study follow-up period. The number of ED visits over the entire study follow-up period did not vary by HIV status, though HIV-infected participants were more

likely to have been hospitalized (48.9% v 41.5%, $p=0.004$). At baseline, 186 (40.6%) of HIV-infected participants had HIV RNA levels ≥ 400 copies/ml, with a median (IQR) HIV RNA (log copies/ml) of 4.26 (3.45–4.75) for those with detectable virus. The median CD4 count of HIV-infected participants was 379 cell/mm³ (IQR 234–569). 325 (21.1%) participants had airflow obstruction during baseline pre-bronchodilator spirometry, the presence of airflow obstruction did not substantially differ by HIV status (20.8% for HIV-infected participants compared to 21.3% for HIV-uninfected). The overall mean FEV₁% predicted was 87.9%, and lower amongst HIV-infected participants (85.6%) compared to HIV-uninfected (88.8%) ($p<0.001$). The mean FVC% predicted was also lower for HIV-infected compared to HIV-uninfected participants (91.9% v 95.0%, respectively) ($p<0.001$).

Associations between Lung Function and Quality of Life Scores

In multivariable models, a 15 point decrease in percent predicted FEV₁ was independently associated with lower MOS physical health scores (mean difference -0.51 , 95% CI -0.75 to -0.26 , $p<0.001$) but not mental health scores (mean difference -0.08 , 95% CI -0.15 to 0.30 , $p=0.50$), after adjusting for HIV status, age, gender, race, education, current injection drug use, smoking, comorbid conditions, health insurance status, and HCV (Table 2). The presence of airflow obstruction alone was not associated with a statistically significant change in either MOS summary score. In our overall model HIV was similarly associated with worse physical health (mean difference -1.80 , 95% CI -2.80 to -0.81 , $p<0.001$) but not mental health (mean difference -0.26 , 95% CI -1.29 to 0.76 , $p=0.61$). Female gender, recent injection drug use, lack of a high school education, and an increased number of comorbid conditions were all associated with lower physical and mental health scores.

In continuous models, the association between physical health scores and cross-sectional assessment of FEV₁ % predicted was linear for both PLWH and HIV-uninfected participants (Figure 1). Stratified by HIV status, declines in FEV₁ appeared more strongly associated with worse physical health for PLWH (mean difference -0.75 , 95% CI -1.14 to -0.34 , $p<0.001$) than in HIV-uninfected participants (mean difference -0.38 , 95% CI -0.69 to -0.09 , $p=0.011$), although we did not detect a statistically significant interaction (p interaction= 0.374).

Among PLWH, the level of HIV viremia strongly modified the association between FEV₁ and physical health (p interaction= 0.010). The association between FEV₁ declines and physical health scores demonstrated a dose-response increase with poorer virological control (Table 3). Declines in FEV₁ appeared to be associated with a greater change in physical health for those with viral load $>100,000$ copies/ml (mean difference -1.66 , 95% CI -3.11 to -0.39 , $p=0.020$) compared to those with an undetectable VL (mean difference -0.58 , 95% CI -1.06 to -0.12 , $p=0.014$; Table 3). Of note, the impact of FEV₁ was seen even in models that adjusted concurrently for both decline in FEV₁ and the presence of airflow obstruction (Supplemental Table 1). In contrast, the presence of airflow obstruction was only independently associated with a significant decrease in physical health for those with the highest levels of HIV RNA (mean difference -4.70 , 95% CI -8.60 to -0.80 , $p=0.018$ (Table 3). A similar pattern was observed when decreases in the FEV₁/FVC ratio were modeled

continuously, with a statistically significant association only observed for those with the poorest virologic control (Supplemental Table 3).

Associations between Lung Function and Acute Care Events

For the overall cohort, a 15-point decrease in percent predicted FEV₁ was associated with increased odds of ED visits (OR 1.09, 95% CI 1.03 to 1.16, $p=0.005$) and hospitalization (OR 1.15, 95% CI 1.07 to 1.25, $p<0.001$) in adjusted models. The presence of airflow obstruction was associated with increased odds of hospitalization (OR 1.26, 95% CI 1.05 to 1.51, $p=0.011$) but not ED visits ($p=0.175$). These associations appeared to be driven by HIV, with HIV status notably modifying the effect of FEV₁ on odds of both ED visits (p -interaction=0.019) and hospitalizations (p -interaction=0.048).

For HIV-uninfected participants, neither changes in FEV₁ nor the presence of airflow obstruction were associated with a statistically significant change in the odds of acute care events (Table 4). In contrast among PLWH, a 15-point decline in percent predicted FEV₁ was associated with increased odds of experiencing an ED visit (OR 1.21, 95% CI 1.09 to 1.34, $p<0.001$) and hospitalization (OR 1.26, 95% CI 1.12 to 1.42, $p<0.001$; Figure 2). Airflow obstruction was also associated with increased odds of hospitalization (OR 1.56, 95% CI 1.15 to 2.11, $p=0.004$) but not ED visits amongst PLWH. HIV RNA levels did not further modify the effect of lung function on acute care events in PLWH.

Associations between FVC, quality of life, and acute care events

Similar to patterns observed for FVC declines, a 15-point change in percent predicted FVC was associated with reduced physical health in a dose response manner (Table 3); with the caveat that the strata with HIV RNA levels $>100,000$ copies/ml was not statistically significant. A statistically significant association for those with an undetectable VL (mean difference -0.76 , 95% CI -1.26 to -0.25 , $p=0.003$) was observed after controlling for similar covariates.

We additionally looked at the relationship between changes in FVC and odds of reporting acute care events (Supplemental Figure 2). For PLWH individuals there was increased odds of both ED visits (OR 1.22, 95% CI 1.10 to 1.37, $p<0.001$) and hospitalization (OR 1.26, 95% CI 1.12 to 1.42, $p<0.001$) associated with a 15-point decline in percent predicted of FVC (Supplemental Table 4). Much like in models of FEV₁, we did not detect a statistically significant association between changes in FVC and acute care events for HIV-uninfected participants.

DISCUSSION

We demonstrate, in a large cohort with significant risk for comorbid lung disease and HIV, followed for a median of 5 years with 10,000 spirometry measurements, that declines in lung function are linked to both worsened physical health and increased risk of healthcare utilization, even after adjusting for multiple high-risk behaviors and HIV related comorbidities. Our analyses indicate that the potential impact of declining lung function is greater for those with uncontrolled viremia than uninfected individuals. This study also suggests that substantial declines in FEV₁ may be more important than the presence of

airflow obstruction alone. Our results further speak to the importance of monitoring lung function over time in the care of PLWH and developing interventions that influence the trajectory of lung function, particularly for those with poor virologic control.

This study demonstrates a clinically meaningful impact associated with changes in both FEV₁ and FVC over time for PLWH. Studies have reported that a one point decrease in physical or mental health summary scores was associated with a 4% increase in the likelihood of death, compared to others in that study population^{18,20}. This suggests that, even amongst a cohort with a high prevalence of comorbid conditions and healthcare utilization, the decrease of 1.04 units in the MOS PHS seen for individuals with viral load >400 copies/ml, or 1.66 units for patients with high viral loads, associated with a decrease in FEV₁ percent predicted, is of clinical importance and could be linked to worse outcomes. For the cohort as a whole, the impact of declining lung function on QOL was also notably greater than the underlying behaviors, such as smoking, that contribute to disease. We do note that for those who experience a slower rate of lung function decline over time, changes in FEV₁ are still associated with lower physical health scores, but the clinical impact of this may be less profound.

Of note, a previous cross-sectional study from the SHIELD cohort that focused on the presence of COPD and its impact on HIV associated quality of life, demonstrated a link between COPD and lower MOS mental health scores⁸. Our study however did not find this association. These contrasting results may be related to multiple factors including a longer follow-up time and adjusting for the development of additional comorbidities. This study does help expand previous work by demonstrating the impact of impaired spirometric measures on physical health, even without the presence of airflow obstruction. In recent years there has been increased recognition of a population of smokers with Preserved Ratio and Impaired Spirometry (PRISm), defined as a reduced FEV₁ in the setting of a preserved FEV₁/FVC ratio^{25,26}. This phenomenon has been associated with increased respiratory symptoms and decreased quality of life in the COPDGene cohort²⁷. Similarly in our cohort, declines in FEV₁ may also represent a transitional state associated with increased physical impairment prior to the development of overt airflow obstruction. Declines in FVC may suggest the development of restrictive lung disease over time. Previous studies have demonstrated that respiratory infections in PLWH lead to permanent declines in FVC and worsened restriction among PLWH²⁸.

Our analysis of acute care events highlights that decreased lung function is associated with worse health outcomes for PLWH than for uninfected participants, where no association was seen. These results prompt consideration of potential explanations as to why declining lung function may have a greater impact on those with uncontrolled HIV than uninfected participants. One theory may be that those with lower lung function have increased susceptibility to lower respiratory tract infections or exacerbations of underlying lung disease for PLWH²⁹. It is also possible that the decreases in lung function observed were driven by preceding respiratory illnesses and acute care events, as observed in prior studies, but we were unable to definitively determine this based on the data available. We do have concerns that lung disease remains undertreated among PLWH, as previous studies from SHIELD demonstrated that nearly 25% of those with severe COPD were not even aware of

their diagnosis of COPD³⁰. Previous studies have also suggested that worsened pulmonary disease goes hand and hand with progression of other HIV related comorbidities^{31,32}. While we did adjust for the presence of several comorbidities, our analysis was unable to account for severity of disease in a number of important comorbidities, including cardiovascular disease and renal failure. The differing associations between declining lung function and acute care visits, seen by HIV status, may also reflect behavioral issues rather than biologic factors. HIV-infected participants with higher viral load may represent those more likely to participate in high risk behavior and be less engaged with medical care. Our study was not able to determine if variation in acute care utilization was related to lack of follow-up, under treatment of intrinsic lung disease or poor medication adherence. However, the number of ED visits reported for participants in our cohort did not differ by HIV status and adjusting for variables that may introduce this bias (education, injection drug use, and health insurance status) did not affect our overall results.

The study does have a number of other limitations worth noting. Generalizability of our study results may be limited by our inner-city population with a history of injection drug use, in which smoking was nearly ubiquitous. We are unable to assess whether our results can easily be translated to other practice settings. However, the cohort represents an important population, often under-represented in research, that is representative of an inner-city HIV population, with epidemiologically matched HIV-uninfected controls to provide appropriate comparison. The shared risk factors across the HIV-subgroups in the cohort additionally attenuates the risk of unmeasured exposures accounting for the differences observed. We do note the differential follow-up time among participants as a potential limitation; however, the results were consistent in sensitivity analyses limited to participants with 5-years of follow-up data (Supplemental Tables 7 and 8). The analysis of certain health outcomes was limited in our studies. We did not have complete data surrounding the etiology of each acute care event. As a result, we were not able to determine if hospitalizations were specifically related to pulmonary complications. In a supplemental analysis we did observe an association between decreases in FEV₁ and pneumonia, which may suggest that lower respiratory tract infections contribute to the acute care events and lung function decline observed, however this association did not significantly differ by HIV status (Supplemental Table 6). Our study may also underestimate the association between airflow obstruction and quality of life, as those with airflow obstruction and COPD in our cohort tended to have mild disease. Modified Medical Research Council (mMRC) dyspnea scores were available in a smaller subset that noted those with airflow obstruction had a mean mMRC score 0.93, which indicates mild dyspnea at baseline. The milder nature of COPD in this cohort may have underestimated the potential impact of obstructive lung disease. In terms of our measurements of pulmonary function, the absence of longitudinal data on DLCO is a limitation of our study. Previous studies of HIV associated lung disease have noted that DLCO impairment was an independent predictor of dyspnea, and that over half of individuals with moderate to severe DLCO impairments³³ had no evidence of airflow obstruction^{34,35}. Longitudinal analysis of the impact of DLCO impairments on HIV related quality of life remains a key area for future study. Many of these limitations are countered by the large-scale nature of our study, with over 10,000 spirometry measurements and QOL assessments, which allows us to dissect the independent impact of impaired lung function.

In summary, we demonstrate that lung function remains an important marker of both physical health and healthcare utilization among people living with HIV. The association appears strongest in those with uncontrolled HIV disease and poor virologic control. Our study suggests that as the prevalence of HIV-related lung disease grows, monitoring lung function over time is of notable importance. Further work should be undertaken to help determine if changes in lung function also correlates with progression of other HIV related comorbidities. In screening for HIV related lung disease, clinicians should evaluate for longitudinal changes in lung function, as measured by declines in FEV₁ or FVC, rather than relying on single measurements of obstructive lung disease. Our work suggests that established interventions that have the potential to decrease the rate of lung function decline should be pursued among PLWH; such as smoking cessation programs, efforts to mitigate air pollutant exposure, early introduction of long-acting bronchodilators, and therapies to decrease the incidence of recurrent lower respiratory tract infections and exacerbations of underlying respiratory disease^{36–40}. Interventions with the potential to slow the rate of lung function decline, could ultimately have a significant impact on improving QOL and reducing healthcare utilization in this at-risk population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lerner AM, Eisinger RW, Fauci AS. Comorbidities in Persons With HIV: The Lingering Challenge. *JAMA*. Published online 12 11, 2019. doi:10.1001/jama.2019.19775
2. Althoff KN, Gebo KA, Moore RD, et al. Contributions of traditional and HIV-related risk factors on non-AIDS-defining cancer, myocardial infarction, and end-stage liver and renal diseases in adults with HIV in the USA and Canada: a collaboration of cohort studies. *The Lancet HIV*. 2019;6(2):e93–e104. doi:10.1016/S2352-3018(18)30295-9 [PubMed: 30683625]
3. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. *Chest*. 2006;130(5):1326–1333. doi:10.1378/chest.130.5.1326 [PubMed: 17099007]
4. Drummond MB, Kunisaki KM, Huang L. Obstructive Lung Diseases in HIV: A Clinical Review and Identification of Key Future Research Needs. *Seminars in Respiratory and Critical Care Medicine*. 2016;37(2):277–288. doi:10.1055/s-0036-1578801 [PubMed: 26974304]
5. Drummond MB, Merlo C a, Astemborski J, et al. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS (London, England)*. 2013;27(8):1303–1311. doi:10.1097/QAD.0b013e32835e395d
6. Rosen MJ, Lou Y, Kvale PA, et al. Pulmonary function tests in HIV-infected patients without AIDS. Pulmonary Complications of HIV Infection Study Group. *American journal of respiratory and critical care medicine*. 1995;152(2):738–745. doi:10.1164/ajrccm.152.2.7633736 [PubMed: 7633736]
7. Verboeket SO, Wit FW, Kirk GD, et al. Reduced Forced Vital Capacity Among Human Immunodeficiency Virus-Infected Middle-Aged Individuals. *The Journal of Infectious Diseases*. Published online November 12, 2018;jiy653–jiy653.

8. Drummond MB, Kirk GD, McCormack MC, et al. HIV and COPD: Impact of risk behaviors and diseases on quality of life. *Quality of Life Research*. 2010;19(9):1295–1302. doi:10.1007/s11136-010-9701-x [PubMed: 20617387]
9. Gingo MR, Nouraie M, Kessinger CJ, et al. Decreased lung function and all-cause mortality in HIV-infected individuals. *Annals of the American Thoracic Society*. 2018;15(2):192–199. doi:10.1513/AnnalsATS.201606-492OC [PubMed: 29313714]
10. Berry CE, Drummond MB, Han MK, et al. Relationship between lung function impairment and health-related quality of life in COPD and ILD. *Chest*. Published online 2012. doi:chest.11-1332 [pii]n10.1378/chest.11-1332 [PubMed: 22796832]
11. Weatherall M, Marsh S, Shirtcliffe P, Williams M, Travers J, Beasley R. Quality of life measured by the St George's respiratory questionnaire and spirometry. *European Respiratory Journal*. 2009;33(5):1025–1030. doi:10.1183/09031936.00116808 [PubMed: 19164350]
12. Ståhl E, Lindberg A, Jansson S-A, et al. Health-related quality of life is related to COPD disease severity. *Health and quality of life outcomes*. 2005;3:56. doi:10.1186/1477-7525-3-56 [PubMed: 16153294]
13. Fowler RW, Pluck RA, Hetzel MR. Maximal expiratory flow-volume curves in Londoners aged 60 years and over. *Thorax*. Published online 1987. doi:10.1136/thx.42.3.173
14. Drummond MB, Kirk GD, Astemborski J, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. *Thorax*. 2012;67(4):309–314. doi:10.1136/thoraxjnl-2011-200702 [PubMed: 22090038]
15. Knudson RJ, Burrows Lebowitz B, Holberg CJ. Changes in the Normal Maximal Expiratory Flow-Volume Curve with Growth and Aging. *RESPIR DIS*. Published online 1983. doi:10.1164/arrd.1983.127.6.725
16. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26(2):319. doi:10.1183/09031936.05.00034805 [PubMed: 16055882]
17. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: The global lung function 2012 equations. *European Respiratory Journal*. Published online 2012. doi:10.1183/09031936.00080312
18. Wu AAW, Jacobson DL, Frick KD, et al. Validity and Responsiveness of the EuroQol as a Measure of Health-Related Quality of Life in People Enrolled in an AIDS Clinical Trial. *Quality of Life Research*. 2016;11(3):273–282.
19. Wu AW, Hays RD, Kelly S, Malitz F, Bozzette SA. Applications of the medical outcomes study health-related quality of life measures in HIV/AIDS. In: *Quality of Life Research*. Vol 6; 1997:531–554. doi:10.1023/A:1018460132567 [PubMed: 9330553]
20. Jacobson DL, Wu AW, Feinberg J. Health-related quality of life predicts survival, cytomegalovirus disease, and study retention in clinical trial participants with advanced HIV disease. *Journal of clinical epidemiology*. 2003;56(9):874–879. [PubMed: 14505773]
21. Yuan R, Hogg JC, Paré PD, et al. Prediction of the rate of decline in FEV(1) in smokers using quantitative Computed Tomography. *Thorax*. 2009;64(11):944–949. doi:10.1136/thx.2008.112433 [PubMed: 19734130]
22. Sciurba FC, Ernst A, Herth FJF, et al. A Randomized Study of Endobronchial Valves for Advanced Emphysema. *N Engl J Med*. 2010;363(13):1233–1244. doi:10.1056/NEJMoa0900928 [PubMed: 20860505]
23. Criner GJ, Sue R, Wright S, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (LIBERATE). *Am J Respir Crit Care Med*. 2018;198(9):1151–1164. doi:10.1164/rccm.201803-0590OC [PubMed: 29787288]
24. Selvin S *Statistical Analysis of Epidemiologic Data*. Oxford University Press; 2004.
25. Wan ES, Castaldi PJ, Cho MH, et al. Epidemiology, genetics, and subtyping of preserved ratio impaired spirometry (PRISm) in COPD. *Gene*. Respiratory Research. Published online 2014. doi:10.1186/s12931-014-0089-y
26. K.A. Y, G.L. K, P. C, et al. Increased subclinical atherosclerosis among preserved ratio impaired spirometry (PRISm) subjects relative to smokers with normal spirometry in the copdgene study. *American Journal of Respiratory and Critical Care Medicine*. Published online 2015.

27. Wan E, Fortis S, Hokanson J, DeMeo D, Crapo J, Silverman E. Longitudinal lung function and mortality in preserved ratio impaired spirometry (PRISM) in the COPD gene study. American journal of respiratory and critical care medicine Conference: american thoracic society international conference, ATS 2017 United states. Published online 2017. doi:10.1164/ajrccm-conference.2017.C22
28. Morris AM, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group American journal of respiratory and critical care medicine. Published online 2000. doi:10.1164/ajrccm.162.2.9912058
29. Lambert AA, Kirk GD, Astemborski J, Mehta SH, Wise RA, Drummond MB. HIV Infection Is Associated With Increased Risk for Acute Exacerbation of COPD. Journal of acquired immune deficiency syndromes (1999). 2015;69(1):68–74. doi:10.1097/QAI.0000000000000552 [PubMed: 25942460]
30. Drummond MB, Kirk GD, Astemborski J, et al. Prevalence and risk factors for unrecognized obstructive lung disease among urban drug users. International Journal of COPD. Published online 2011. doi:10.2147/COPD.S15968
31. Morris A Heart-lung interaction via infection. Annals of the American Thoracic Society. 2014;11(SUPPL. 1). doi:10.1513/AnnalsATS.201306-157MG
32. Besutti G, Raggi P, Zona S, et al. Independent association of subclinical coronary artery disease and emphysema in HIV-infected patients. HIV Medicine. 2016;17(3):178–187. doi:10.1111/hiv.12289 [PubMed: 26268373]
33. Perez T, Burgel PR, Paillasseur JL, et al. Modified medical research council scale vs baseline dyspnea index to evaluate dyspnea in chronic obstructive pulmonary disease. International Journal of COPD. Published online 2015. doi:10.2147/COPD.S82408
34. Crothers K, McGinnis K, Kleerup E, et al. HIV infection is associated with reduced pulmonary diffusing capacity. Journal of acquired immune deficiency syndromes (1999). Published online 2013. doi:10.1097/QAI.0b013e3182a9215a
35. Gingo MR, He J, Wittman C, et al. Contributors to diffusion impairment in HIV-infected persons. European Respiratory Journal. Published online 2014. doi:10.1183/09031936.00157712
36. Wedzicha JA. Airway Infection Accelerates Decline of Lung Function in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2001;164(10):1757–1758. doi:10.1164/ajrccm.164.10.2108049a [PubMed: 11734418]
37. Zhou Y, Zhong N, Li X, et al. Tiotropium in Early-Stage Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017;377(10):923–935. doi:10.1056/NEJMoa1700228 [PubMed: 28877027]
38. Willemse BW, Postma DS, Timens W, ten Hacken NHT. The impact of smoking cessation on respiratory symptoms, lung function, airway hyperresponsiveness and inflammation. Eur Respir J. 2004;23(3):464. doi:10.1183/09031936.04.00012704 [PubMed: 15065840]
39. Siddharthan T, Grigsby MR, Goodman D, et al. Association between Household Air Pollution Exposure and Chronic Obstructive Pulmonary Disease Outcomes in 13 Low- and Middle-Income Country Settings. Am J Respir Crit Care Med. 2018;197(5):611–620. doi:10.1164/rccm.201709-1861OC [PubMed: 29323928]
40. Morris AM, Huang L, Bachetti P, et al. Permanent Declines in Pulmonary Function Following Pneumonia in Human Immunodeficiency Virus-Infected Persons. Am J Respir Crit Care Med. 2000;162(2):612–616. doi:10.1164/ajrccm.162.2.9912058 [PubMed: 10934095]

Figure 1.

Predicted MOS-Physical Health Scores with 95% Confidence Intervals for A) PLWH and B) HIV-uninfected participants.

*Adjusted for age, sex, African American Race, Smoking Status (current smoking and pack years), comorbidities (cardiac disease, hypertension, stroke, obesity, renal disease, diabetes), HCV status, insurance status, injection drug use, education

Figure 2.

Odds of Acute Care Events Associated with A) a 15% Decline in Percent Predicted of FEV₁. B). presence of Airflow Obstruction (FEV₁/FVC <LLN). (Presented as Odds Ratio [95% CI]), stratified by HIV and viral suppression status (Presented as Odds Ratio [95% CI])

*Adjusted for age, sex, African American Race, Smoking Status (current smoking and pack years), comorbidities (cardiac disease, hypertension, stroke, obesity, renal disease, diabetes), HCV status, insurance status, injection drug use, education

Table 1.

Participant Characteristics at Baseline Spirometry Visit *

<i>N</i>	Overall Cohort (n=1499)	HIV Infected (465)	HIV Uninfected (1034)	p Value
Demographics				
Age, year	49.5 (9.2)	50.5 (7.0)	49.1 (8.7)	0.003
Male, n (%)	1006 (67.1)	310 (66.7)	696 (67.3)	0.82
Race/ethnicity, n (%)				
Black	1261 (84.1)	427 (91.8)	834 (80.6)	<0.001
Smoking Status, n (%)				0.012
Current	1264 (84.6)	374 (80.6)	890 (86.3)	
Former	133 (8.9)	52 (11.2)	81 (7.9)	
Never	98 (6.6)	38 (8.2)	60 (5.8)	
Smoking, pack-years	23.7 (17.7)	23.0 (18.9)	23.9 (17.1)	0.89
High School Education, n (%)	656 (43.8)	181 (39.1)	475 (45.9)	0.007
Recent Injection Drug Use (IDU),n (%) [†]	871 (58.1)	248 (53.3)	623 (60.3)	0.004
# Comorbid Conditions [‡]				0.57
1	467 (31.2)	143 (30.9)	324 (31.4)	
2	384 (25.6)	126 (27.2)	258 (25.0)	
3	288 (19.3)	80 (17.3)	208 (20.1)	
HIV Characteristics[§]				
HIV RNA <400 copies/ml, n (%)		186 (40.6)		
HIV RNA (copies/mL)		18,121 [2,820–56,440]		
HIV RNA (log ₁₀ copies/ml)		4.26 [3.45–4.75]		
CD4 count (cells/mm ³)		379 [234–569]		
Lung Function				
FEV ₁				
Absolute (L)	2.61 (0.76)	2.51 (0.72)	2.65 (0.78)	<0.001
% Predicted	87.9 (18.3)	85.6 (19.0)	88.8 (17.9)	
Decline in % Predicted	13.7 [6.2–18.8]	15.3 [7.3–21.7]	13.1 [5.6–18.0]	0.45
FVC				
Absolute (L)	3.52 (0.98)	3.39 (0.89)	3.57 (1.01)	<0.001
% Predicted	94.1 (17.1)	91.9 (16.9)	95.0 (17.0)	
FEV ₁ /FVC Ratio	74.7 (8.7)	74.7 (9.4)	74.7 (8.4)	0.91
Airflow Obstruction, n (%) ^{**}	356 (24.1)	108 (23.8)	248 (24.3)	
Acute Care Events During Study Period				
Inpatient Hospitalization, n (%)	656 (43.8)	227 (48.9)	429 (41.5)	0.004
ED Visit, n (%)	997 (66.0)	314 (67.5)	683 (66.2)	0.46

* Values presented as mean (S.D) or median [IQR] unless indicated otherwise

[†] Indicates reporting exposure within prior 6 months

[‡] History of non-pulmonary comorbidities (diabetes, hypertension, cerebrovascular accident, cardiovascular disease, renal disease, obesity)

[§] Among HIV-infected only

^{||} Among HIV-infected participants with detectable viral load only

^{**} Participants meeting criteria for airflow obstruction at first spirometry visit

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Table 2.

Association of a 15% Decline in FEV₁% predicted with MOS Physical Health and Mental Health Quality of Life Scores

Predictor	Change in PHS		Change in MHS	
	Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	p-value
Decrease in FEV ₁	−0.52 (−0.75 to −0.26)	<0.001	−0.08 (−0.15 to 0.30)	0.50
Age (per 10 year)	−2.97 (−3.58 to −2.36)	<0.001	−0.18 (−0.76 to 0.39)	0.53
Female Gender	−3.27 (−4.31 to −2.22)	<0.001	−2.20 (−3.24 to −1.16)	<0.001
Black Race	3.78 (2.32 to 5.24)	<0.001	5.35 (3.82 to 6.88)	<0.001
High School Education	1.53 (0.55 to 2.51)	0.002	2.24 (1.27 to 3.20)	<0.001
Current Smoker	−0.14 (−1.10 to 0.83)	0.78	0.88 (−0.16 to 1.94)	0.098
Current Injection Drug Use	−1.47 (−1.96 to −0.98)	<0.001	−2.31 (−2.82 to −1.80)	<0.001
# Comorbid Conditions	−1.40 (−1.71 to −1.09)	<0.001	−0.64 (−0.94 to −0.36)	<0.001
HIV Status	−1.80 (−2.80 to −0.81)	<0.001	−0.26 (−1.29 to 0.76)	0.61

* Adjusted for age, sex, African American Race, HIV status, current smoking status, pack years, comorbidities (cardiac disease, hypertension, stroke, obesity, renal disease, diabetes), HCV status, health Insurance Status, injection drug use

Table 3.

The Association of Changes in Lung Function and MOS Physical Health Score Stratified by HIV Status^{*}

HIV Strata	Per 15% Decrease in FEV₁ % Predicted		Presence of Airflow Obstruction		Per 15% Decrease in FVC₁ % Predicted	
	<i>Mean Change in PHS (95 % CI)</i>	<i>p-value</i>	<i>Mean Change in PHS (95 % CI)</i>	<i>p-value</i>	<i>Mean Change in PHS (95 % CI)</i>	<i>p-value</i>
HIV Negative	-0.38 (-0.69, -0.09)	0.011	0.11 (-0.51, 0.73)	0.72	-0.61 (-0.93, -0.29)	<0.001
HIV Positive (Viral Load <400)	-0.58 (-1.06, -0.12)	0.014	-1.15 (-2.34, 0.05)	0.061	-0.76 (-1.26, -0.25)	0.003
HIV Positive (Viral Load >400-1000000)	-1.04 (-1.71, -0.21)	0.012	-0.04 (-1.76, 1.69)	0.97	-1.17 (-1.95, -0.41)	0.003
HIV Positive (Viral Load >1000000)	-1.66 (-3.11, -0.39)	0.020	-4.70 (-8.60, -0.80)	0.018	-1.06 (-2.81, 0.68)	0.233

^{*} Adjusted for age, sex, African American Race, Smoking Status (current smoking and pack years), comorbidities (cardiac disease, hypertension, stroke, obesity, renal disease, diabetes), HCV status, injection drug use, health insurance coverage, education

Table 4.

Association of Changes in Lung Function and Odds of Healthcare Utilization Stratified by HIV Status

HIV Strata	Per 15% Decrease in FEV % Predicted		Presence of Airflow Obstruction	
	OR (95% CI)	P Value	OR (95% CI)	P Value
Odds of ED Visit				
Overall Cohort	1.09 (1.03, 1.16)	0.005	1.10 (0.96, 1.26)	0.175
HIV Negative	1.03 (0.96, 1.11)	0.416	1.01 (0.84, 1.21)	0.73
HIV Positive	1.21 (1.09, 1.34)	<0.001	1.26 (0.98, 1.61)	0.070
Odds of Hospitalization				
Overall Cohort	1.15 (1.07, 1.25)	<0.001	1.26 (1.05, 1.51)	0.011
HIV Negative	1.07 (0.97, 1.18)	0.170	1.10 (0.86, 1.41)	0.33
HIV Positive	1.26 (1.12, 1.42)	<0.001	1.56 (1.15, 2.11)	0.004

* Adjusted for age, sex, African American Race, Smoking Status (current smoking and pack years), comorbidities (cardiac disease, hypertension, stroke, obesity, renal disease, diabetes), HCV status, health insurance coverage, injection drug use, education