Published in final edited form as:
AIDS. 2013 May 15; 27(8): 1303–1311. doi:10.1097/QAD.0b013e32835e395d.

The Effect of HIV Infection on Longitudinal Lung Function Decline Among Injection Drug Users: A Prospective Cohort

M. Bradley DRUMMOND, MD[1], **Christian A. MERLO, MD**[1], **Jacquie ASTEMBORSKI**[2], **Mariah M. MARSHALL**[3], **Annamarie KISALU**[2], **John F. MCDYER**[4], **Shruti H. MEHTA, PhD**[2], **Robert H. BROWN, MD**[1,5], **Robert A. WISE, MD**[1], and **Gregory D. KIRK, MD**[1,2]

[1]Department of Medicine, School of Medicine, Johns Hopkins University, Baltimore, MD

[2]Department of Epidemiology, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

[3]Department of Epidemiology, School of Public Health and Health Services, George Washington University, Washington DC

[4]Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA

[5]Department of Environmental Health Sciences, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD

INTRODUCTION

The advancement of anti-retroviral therapy (ART) has led to improved survival and longer life expectancy for persons living with human immunodeficiency virus (HIV) infection.[1-3] Subsequently there is increased recognition of development of age-associated chronic diseases (e.g., cardiovascular, metabolic, renal, neurological) and non-AIDS-defining malignancies occurring in these individuals.[4-8] Emerging data suggests an increased prevalence of chronic lung disease in HIV-infected individuals, the spectrum of which includes both chronic airflow obstruction and restrictive lung disease.[9-12] HIV-infection has been shown to increase the diagnosis of self-reported and administratively diagnosed COPD.[13, 14] We have previously shown that the odds of airflow obstruction were increased >3-fold among HIV-infected individuals with the highest plasma viral load independent of smoking compared to epidemiologically similar HIV-negative individuals.[15] Respiratory infections, increased in HIV-infected individuals, are associated with restrictive lung disease.[12] Beyond these cross-sectional reports, few studies have evaluated longitudinal lung function decline among HIV-infected persons.[12, 16] Because earlier studies were prior to widespread ART availability and recent studies were limited by small numbers of persons, short duration of follow-up, and lack of HIV-negative comparator groups, the independent effect of HIV disease markers on lung function decline remains unanswered.

The AIDS Linked to the Intravenous Experience (ALIVE) study is a longitudinal cohort of persons with a history of injecting drugs with or at-risk for HIV infection followed in Baltimore, Maryland since 1988.[17] The ALIVE study collects behavioral, clinical, and laboratory data at regular six-month intervals and recently instituted serial spirometric measures into the data collection protocol. With nearly ubiquitous cigarette smoking and substantial prevalence of respiratory symptoms and obstructive lung disease (OLD),[18-20]

Corresponding Author/Reprint Requests: M. Bradley Drummond, MD Division of Pulmonary and Critical Care Medicine 5501 Hopkins Bayview Circle, JHAAC 4B.70 Baltimore, MD 21224 mdrummo3@jhmi.edu Phone: 410-550-0545 Fax: 410-537-7259.

ALIVE represents an appropriate population to examine the effect of HIV infection on changes in lung function. In the current study, we use longitudinal data from ALIVE to determine the independent association of HIV infection on lung function decline over almost three years of observations. We hypothesized that HIV infection, particularly more advanced HIV disease, would be associated with accelerated lung function decline. Some of these results have been previously presented at the 19th Conference on Retroviruses and Opportunistic Infections and published in abstract form.[21]

METHODS

Study Cohort

As described previously,[17, 22] since 1988, ALIVE has recruited residents of Baltimore, MD who were ≥18 years of age and had a history of injection drug use into biannual follow-up. At each study visit, both HIV-infected and uninfected participants complete standardized interviewer and computerized questionnaires, a clinical examination, and provide blood samples. Since 2007, participants performed pre-bronchodilator spirometry testing at each study visit. We performed a longitudinal analysis of 1064 participants who contributed at least two spirometry measurements between January 2007 and December 2010. The study was approved by the IRB of Johns Hopkins University. All participants provided written informed consent.

Data Collection

Demographic, behavioral, clinical, and laboratory data were collected contemporaneously with spirometry measurements. Smoking patterns, injection drug use, and ART use were determined by self-report. Respiratory infections were identified through standardized medical record review and were classified as bacterial, *Pneumocystis*, or other (e.g., viral, tuberculosis or multi-factorial). Pre-bronchodilator spirometry forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) was performed using KOKO® pneumotachometers (nSpire Health Inc, Longmont, CO). All spirograms were automatically assessed by computer software for accordance with American Thoracic Society guidelines.[23] Any spirogram identified as potentially of poor quality was reviewed by two pulmonologist and excluded if effort and reproducibility criteria were not met. Percent predicted values were calculated using standard formulas.[24] OLD was defined as an FEV1/FVC ratio less than 0.70.[25]

Statistical Analysis

All data are presented as mean (standard deviation) for normally distributed data and median (interquartile range [IQR]) for non-normally distributed data. To determine the independent association of markers of HIV infection on longitudinal lung function decline, linear regression models of FEV1, FVC and FEV1/FVC ratio with generalized estimating equations[26] with an exchangeable correlation structure and robust estimation of variance were used. Predictors were selected based on association with FEV1 decline in univariate analysis and by relevance based on literature review. Final models included age, race, sex, body mass index, baseline pack-years smoking (defined as the reported number of years smoked throughout life * average packs per day smoked), time varying current smoking status (current vs. non-smoker updated biannually), time varying injection drug use updated biannually, and prior respiratory infection updated biannualy. Markers of HIV disease (HIV serostatus, viral load, CD4 cell count) and ART use were modeled as time varying covariates, updated at biannual visits. Annual change in lung function decline (ml/year) was assessed via the interaction of the spirometric measure and time. HIV viral load was modeled categorically at clinical thresholds (<400 copies/ml vs. 400-75,000 copies/ml vs. >75,000 copies/ml). CD_4 cell count was also considered categorically (<100, 100-200, >200

cells/mm^3). Models evaluated HIV-infected persons overall and stratified by disease markers compared to HIV-uninfected persons as the reference group; similar analysis was also performed among HIV-infected persons only. For data presentation, graphs of modeled absolute FEV1 and FVC decline (expressed in ml) versus follow-up time were generated after centering values for the covariates of a typical participant (50 year old African-American male current smoker with 20 pack-year smoking history, BMI 25 kg/m^2, and no history of pneumonia) as well as time updated HIV serum viral load and CD_4 cell count. A p-value of <0.05 was used to infer statistical significance. Stata version 12.0 (Stata Corp, College Station, TX) and SAS software was used for statistical analyses.

RESULTS

Participant Characteristics

A total of 97% of eligible ALIVE participants completed spirometry testing, with 1064 participants contributing 4555 spirometry measurements over a median follow-up time of 2.75 years (range 0.5 to 3.9 years). We found no differences in distribution of sex, race, HIV status, viral load category, current injection drug use or current smoking comparing those with and without spirometry measurements. Age was different between those who did and did not complete spirometry (median 51.6 years for those without spirometry; p=0.04). For the cohort with spirometry data, at baseline, the mean age was 48±7 years, nearly two-thirds were male and 91% were black (Table 1). Almost all participants reported ever smoking cigarettes (94%) and most were current cigarette smokers (85%). Although all participants had a history of injecting drugs, 40% reported active injection drug use in the prior six months. Nearly 40% reported ever smoking cocaine, heroin, or marijuana. At baseline, 169 (16%) met spirometric criteria for OLD. The proportion of individuals with OLD increased to 23% at last visit, with 109(10%) of the 895 without OLD at baseline meeting spirometric criteria at final visit. At baseline, the FEV1/FVC was 0.77 ±0.08, baseline FEV1 was 92% predicted and FVC 3.65±0.94L. At baseline, 316 (30%) were HIV-infected with 230 (74%) having a CD4 cell count>200 cells/mm^3, 55% were currently receiving highly-active anti-retroviral therapy (HAART), and 148 (47%) had an HIV RNA viral load<400 copies/mL. At baseline, a total of 129 clinically-confirmed respiratory infections had occurred. During follow-up, 60 respiratory infections occurred, with 28 (47%) occurring in HIV-negative individuals, 20 (33%) in HIV-infected individuals with CD_4>200 cell/mm^3, 7(11%) in HIV-infected individuals with CD_4 between 100-199 cells/mm^3 and 5(8%) in HIV-infected individuals with CD_4<100 cells/mm^3.

Effect of HIV Infection on Absolute FEV1 and FVC Levels

Female sex, older age, black race and higher BMI were independently associated with lower absolute FEV1 and FVC (see Table, Supplemental Digital Content 1, which displays the adjusted effect of demographic, behavioral and clinical factors on absolute FEV1 and FVC). In this group of nearly ubiquitous smokers and after adjusting for age (collinear with pack-years), increasing pack-years of smoking history and smoking status were not independently associated with lower absolute FEV1 or FVC. Prior respiratory infection resulted in 106 ml lower absolute FEV1 (95% CI -162 to -48.8 ml; p<0.001) and 96.5 ml lower absolute FVC (95% CI -167 to -26.4 ml; p=0.007). Each year of time from initial spirometry was associated with a lower FEV1 but not lower FVC. After adjusting for these demographic, behavioral and clinical factors, HIV infection was independently associated with a 154 ml lower absolute FEV1 (95% CI -221 to -86 ml) and 210 ml lower absolute FVC (95% CI -288 to -132 ml) compared to HIV uninfected individuals (p<0.001 for both estimates).

Markers of HIV Disease and Annual Rate of Decline of FEV1 and FVC

In order to assess the association of advanced HIV disease on annual FEV1 and FVC decline, we incorporated HIV disease markers into adjusted models (Table 2). The annual rate of FEV1 decline in HIV-infected individuals was -35.8 ml/yr (95% CI -51.2 to -20.3 ml/yr) compared with -23.6 ml/yr (95%CI -32.6 to -14.7 ml/yr) among HIV-uninfected participants, with a difference in slopes of 12.2 ml/yr (95% CI -28.1 to 3.78 ml/yr; p=0.135). The annual rate of FVC decline in HIV-infected persons was -9.29 ml/yr (95%CI -25.1 to 6.5 ml/yr), in HIV-uninfected persons +8.0 ml/yr (95% CI -26.4 to 18.7 ml/yr) with the difference in slopes of 17.3 ml/yr (95% CI -34.3 to -0.33 ml/yr; p=0.05). Figure 1 graphically represents the impact of HIV infection on modeled FEV1 and FVC over time by centering the other covariates to represent the typical participant in this cohort (50 year old African-American current smoker with a 20 pack-year smoking history, BMI of 25, and no history of respiratory infection). While HIV-infected persons had a lower absolute FEV1 and FVC at study entry, the annual rate of FEV1 decline did not differ compared to HIV-uninfected individuals.

Recognizing that HIV status alone does not accurately model the range of severity of HIV disease in this cohort, additional models were examined that incorporated HIV viral load and CD_4 cell count levels (Table 2). Compared to HIV-uninfected individuals, HIV-infected individuals with a plasma viral load ≤75,000 copies/ml had a similar adjusted annual FEV1 decline (-23.5 vs. -29.9 ml/yr; p=0.44). However, HIV-infected participants with a viral load >75,000 copies/ml experienced a substantially greater adjusted annual FEV1 decline compared with HIV-uninfected individuals (-99.1 vs. -23.5 ml/yr; p=0.004), with a difference of 75.6 ml/yr (95% CI 23.8 to 127 ml/yr). The difference in annual FEV1 decline between HIV-infected individuals with viral load ≤75,000 copies/ml and HIV-infected individuals with viral load >75,000 copies/ml was also significantly greater (69.2 ml/yr; 95% CI 15.3 to 123 ml/yr; p=0.012). Similar results were observed when examining the effect of HIV viral load level on annual FVC decline (Table 2). HIV-infected participants with a viral load >75,000 copies/ml demonstrated a greater adjusted annual FVC decline compared with HIV-uninfected individuals (-74.0 vs. 8.24 ml/yr; p=0.008), with a difference of 85.7 ml/yr (95% CI 35.8 to 136 ml/yr; Figure 2).

When stratifying HIV-infected persons by the degree of immunodeficiency, individuals with lower CD_4 cell counts experienced a more rapid decline in FEV1 and FVC (Table 2 and Figure 3). While HIV-infected individuals with CD_4 >200 cells/mm^3 had similar adjusted annual FEV1 and FVC decline compared to HIV-uninfected persons, HIV-infected participants with CD_4 cell counts between 100 and 200 cells/mm^3 experienced a 34.4 ml/year (95% CI 1.63 to 67.1 ml/yr; p=0.04) greater decline in FEV1 and 34.3 ml/yr (95% CI -1.5 to 70.1 ml/yr; p=0.06) greater decline in FVC compared to HIV-uninfected individuals. HIV-infected individuals with the lowest CD_4 cell counts (<100 cells/mm^3) had the most rapid adjusted annual FEV1 and FVC decline. There was no difference in annual FEV1 or FVC decline comparing HIV-infected individuals with CD4 between 100 and 200 cell/ml^3 to HIV-infected individuals with CD_4>200 cells/ml^3. However, HIV-infected individuals with CD_4<100 cells/ml^3 experienced a greater decline in FEV1 and FVC than HIV-infected individuals with CD4>200 cells/ml^3 (p=0.031 and p=0.003, respectively). There were no differences in the annual rates of decline of FEV1 or FVC comparing HIV-infected participants with CD_4<100 cells/ml^3 to HIV-infected persons with CD_4 between 100 and 200 cells/ml^3.

To differentiate whether higher viral load or lower CD_4 cell count may represent the primary contributor to FEV1 and FVC decline, we evaluated models incorporating groups classified by combined CD_4/viral load levels (Table 2). While a dose-response relationship in annual FEV1 decline was observed with lower CD_4 cell counts, this relationship was not

significantly different from HIV-uninfected persons if HIV-infected individuals had HIV RNA levels ≤75,000 copies/ml. In contrast, HIV-infected persons with viral load >75,000 copies/ml had significantly more rapid annual FEV1 decline compared to HIV-uninfected persons irrespective of CD_4 count (-90.8 ml/yr for CD_4>100 cells/mm^3; 95% CI -145 to -36.2 ml/yr; p=0.017 and -125 ml/yr for CD4<100 cells/mm^3; 95% CI -220 to -30.4 ml/yr; p=0.037). In contrast, when examining the effect of combined CD_4/viral load levels on FVC decline, strata with CD_4<100 cell/mm3 had more rapid annual decline compared to HIV-uninfected persons. This association was present irrespective of viral load level.

Sensitivity analyses were performed to determine the effect of incorporating other potential confounders of relationship between HIV and lung function decline. The association between markers of HIV disease and annual decline in FEV1 or FVC did not change when including history of smoked drugs, time varying ART use or hepatitis C antibody status into models. To explore whether specific types of respiratory infections (bacterial, *Pneumocystis*) differentially impacted our findings, we performed sensitivity analyses with models including only bacterial or only *Pneumocystis* infections, and found no difference from our primary findings. When incorporating CD_4% rather than absolute CD_4 cell count, similar associations with lung function decline were observed. There was no association between markers of HIV infection and annual rate of change in FEV1/FVC ratio (see Table, Supplemental Digital Content 2, which displays the adjusted effect of markers of HIV infection on annual FEV1/FVC ratio).

DISCUSSION

In this analysis of 4555 spirometry measurements obtained on 1064 individuals with or at-risk for HIV infection over a median of 2.75 years, we found a strong effect of poorly controlled HIV disease independently contributing to accelerated lung function decline. Specifically, HIV-infected individuals with plasma viral load exceeding 75,000 copies/ml had a more rapid annual decline in FEV1 and FVC compared to those with controlled HIV disease or without HIV infection. Similarly, the annual loss in FEV1 and FVC of HIV-infected individuals with CD_4 cell counts less than 100 cells/mm^3 was greater than HIV-infected individuals with CD4 exceeding 200 cell/mm^3 or HIV-uninfected individuals. Importantly, the effect of poorly controlled HIV disease was independent of factors known to contribute to longitudinal lung function decline, including age, smoking habits and respiratory infections. As well, while there were decrements in both FEV1 and FVC over time associated with HIV infection, the magnitude of effect on FEV1 decline exceeded that of FVC. These observations provide further evidence to the emerging body of literature that accelerated lung disease is a complication of HIV infection. Both obstructive and restrictive processes are implicated in chronic lung disease associated with poorly controlled HIV infection. Additionally, these findings highlight the need for optimizing HIV treatment among HIV-infected individuals with tobacco dependence and suggest a potential benefit of maintaining lung function through achieving viral suppression.

Our findings of accelerated longitudinal lung function decline in poorly controlled HIV infection extend the previously described cross-sectional associations between HIV infection and obstructive lung disease.[11, 13, 14] Previously we demonstrated that higher plasma viral load was independently associated with the presence of airflow obstruction.[27] In this analysis, we again see a strong independent effect of higher viral load on adverse lung outcomes. As well, we observed that low CD_4 cell counts predicted accelerated FEV1 and FVC decline over time, although the viral load effect appeared to be the dominant factor associated with accelerated FEV1 decline while CD_4 effects contribute to FVC decline. In addition to predicting AIDS progression and death,[22] our findings suggest that CD4 count and viral load can also predict lung function decline in the setting of HIV.

While the highly prevalent tobacco use among ALIVE participants does not allow for robust modeling of potential additive effects of smoking and HIV infection on lung function decline, this characteristic of the ALIVE cohort does allow for isolation of the effects of HIV infection independent of smoking. In this analysis, HIV-infected individuals with elevated viral load or reduced CD_4 cell counts had a more rapid annual FEV1 decline on the order of 55-76 ml/yr compared to those with controlled HIV infection or without HIV. Studies comparing the rates of decline of FEV1 in the general population have reported that current smoking results in an annual FEV1 decline of approximately 35-45 ml compared to former or non-smokers.[28, 29] Thus, the effect of uncontrolled HIV infection on FEV1 decline in this analysis was of greater magnitude than the impact of smoking reported in the general population. Our findings demonstrate that uncontrolled HIV infection is at least as powerful a contributor to lung function decline as cigarette smoking in HIV-uninfected populations, and may even exceed the deleterious effects of current tobacco use.

There are potential immune mechanisms to explain the association between HIV disease severity and accelerated lung function decline. Systemic immune activation has been correlated with HIV progression and may play an important role in lung disease progression similar to that described in the gastrointestinal tract.[30] The HIV-specific adaptive immune T cell response may contribute to injurious pulmonary $CD8^+$ T-cell alveolitis.[27, 31, 32] Additionally, behavioral effects may contribute to this association, including differential access to medical care or engagement in high risk behaviors among those persons with uncontrolled HIV infection. The unique strength of the ALIVE cohort is that the HIV-negative comparator group is similar in other measured and unmeasured confounders, allowing for HIV associations with lung function decline. While epidemiological studies such as the one presented cannot ultimately determine causal pathways, the findings we describe highlight the need for increased exploration of the role of HIV in chronic lung disease, increased awareness of potential for undiagnosed lung disease during HIV clinical encounters and targeted smoking cessation in this high-risk cohort.

Another potential explanation for the association between more severe HIV infection and accelerated lung function decline is the increased risk of respiratory infections in this population. Prior studies have established that lung function decline in HIV is accelerated in the setting of bacterial and *Pneumocystis* respiratory infections.[12, 16] In an HIV-infected cohort followed for an average of 3.7 years, it was shown that bacterial pneumonia and *Pneumocystis* infections resulted in a 109-264 ml fall in FEV1 and 117-254 ml fall in FVC, which was not regained over time.[12] We observed a similar magnitude of association with prior respiratory infections. Because of the standardized medical record abstraction of respiratory infections in the ALIVE cohort, we are able to account for this confounding factor in analyses. Our observations of more rapid annual decline in FEV1 and FVC with worse HIV control persisted after adjusting for bacterial and *Pneumocystis* infections, suggesting that accelerated decline is largely attributable to HIV infection, rather than a secondary consequence of respiratory infections. Despite this, respiratory infections may predispose to progressive restrictive lung disease, resulting in decrements of both FEV1 and FVC. The observation that the FVC is not falling at a greater rate than FEV1 suggests this is not simply a restrictive process resulting in secondary FEV1 fall. In this cohort, decrements in FEV1 and FVC observed with HIV disease are likely multifactorial, related to obstructive ventilatory defects from tobacco use as well as restrictive defects related to prior infection.

This study has some limitations. The ALIVE cohort is comprised of predominantly urban, African American smokers who currently or previously engaged in injection drug use. Thus, these findings may not be generalizeable to other populations. Post-bronchodilator spirometry testing was not obtained, nor was bronchodilator use prior to spirometry assessed. Variable bronchodilator use could impact lung function measurements.

Respiratory infections are abstracted and standardized case definitions employed during systematic medical records review. As higher quality records were obtained from hospitalizations, it is possible that milder respiratory infections were not fully captured. However, our approach ensures that standardized clinical criteria are met and identifies the severe infections most likely to substantially impact FEV1.

In summary, through longitudinal observation of a large HIV-infected and HIV-uninfected cohort, we describe a strong association of advanced HIV disease, particularly among those with poor virological control, with accelerated lung function decline. The effect of uncontrolled HIV infection on FEV1 decline may exceed the effect of smoking on lung function decline observed in the general population, and is independent of prior respiratory infections and other risk factors. These findings provide longitudinal evidence supporting the observation that chronic lung disease is an emerging complication of HIV infection. In response, smoking cessation assumes greater priority in the care of persons living with HIV. All HIV-infected individuals with active tobacco use should receive aggressive counseling and assistance to help them abstain from tobacco use. Beyond smoking cessation, our data suggest that optimal antiretroviral therapy with HIV virological control may diminish the accelerated lung function decline associated with HIV-infected smokers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors wish to thank the ALIVE study participants and the clinic staff for their contributions to this work. MD had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The funding agency (National Institutes of Health) had no role in the study design, data collection, analysis, or writing of the manuscript. MD contributed to study design, analysis plan, interpretation and writing and editing of the report. CM contributed to study design, analysis plan, interpretation and editing of the report. JA contributed to the analysis plan, interpretation and was responsible for data analysis. MM contributed to study design, analysis plan, interpretation and editing of the report. AK contributed to data collection, interpretation of results, and editing of the report. JM contributed to study design, analysis, interpretation and editing of the report. SM contributed to study design, interpretation and editing of the report. RB contributed to study design, interpretation and editing of the report. RW contributed to study design, analysis plan, interpretation and editing of the report. GK contributed to study design, analysis plan, interpretation and writing and editing of the report. The authors declare that there are no conflicts of interest for any author as it pertains to this manuscript.

Funding: National Institutes of Health

REFERENCES

1. Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, et al. The survival benefits of AIDS treatment in the United States. J Infect Dis. 2006; 194:11–19. [PubMed: 16741877]
2. Braithwaite RS, Justice AC, Chang CC, Fusco JS, Raffanti SR, Wong JB, et al. Estimating the proportion of patients infected with HIV who will die of comorbid diseases. Am J Med. 2005; 118:890–898. [PubMed: 16084183]
3. Wood E, Hogg RS, Lima VD, Kerr T, Yip B, Marshall BD, et al. Highly active antiretroviral therapy and survival in HIV-infected injection drug users. JAMA. 2008; 300:550–554. [PubMed: 18677027]
4. Effros RB, Fletcher CV, Gebo K, Halter JB, Hazzard WR, Horne FM, et al. Aging and infectious diseases: workshop on HIV infection and aging: what is known and future research directions. Clin Infect Dis. 2008; 47:542–553. [PubMed: 18627268]

5. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD. HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. Clin Infect Dis. 2011; 53:1256–1264. [PubMed: 21976463]
6. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. J Acquir Immune Defic Syndr. 2009; 52:611–622. [PubMed: 19770804]
7. Barnett CF, Hsue PY, Machado RF. Pulmonary hypertension: an increasingly recognized complication of hereditary hemolytic anemias and HIV infection. JAMA. 2008; 299:324–331. [PubMed: 18212317]
8. Fitch KV, Looby SE, Rope A, Eneh P, Hemphill L, Lee H, et al. Effects of aging and smoking on carotid intima media thickness in HIV-infection. AIDS. 2012
9. Crothers K, Thompson BW, Burkhardt K, Morris A, Flores SC, Diaz PT, et al. HIV-associated lung infections and complications in the era of combination antiretroviral therapy. Proc Am Thorac Soc. 2011; 8:275–281. [PubMed: 21653528]
10. Gingo MR, George MP, Kessinger CJ, Lucht L, Rissler B, Weinman R, et al. Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. Am J Respir Crit Care Med. 2010; 182:790–796. [PubMed: 20522793]
11. Diaz PT, Clanton TL, Pacht ER. Emphysema-like pulmonary disease associated with human immunodeficiency virus infection. Ann Intern Med. 1992; 116:124–128. [PubMed: 1727615]
12. Morris AM, Huang L, Bacchetti P, Turner J, Hopewell PC, Wallace JM, et al. Permanent declines in pulmonary function following pneumonia in human immunodeficiency virus-infected persons. The Pulmonary Complications of HIV Infection Study Group. Am J Respir Crit Care Med. 2000; 162:612–616. [PubMed: 10934095]
13. Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Nagaraja HN, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. Ann Intern Med. 2000; 132:369–372. [PubMed: 10691587]
14. 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; 130:1326–1333. [PubMed: 17099007]
15. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. Thorax. 2012; 67:309–314. [PubMed: 22090038]
16. Mitchell DM, Fleming J, Pinching AJ, Harris JR, Moss FM, Veale D, et al. Pulmonary function in human immunodeficiency virus infection. A prospective 18-month study of serial lung function in 474 patients. Am Rev Respir Dis. 1992; 146:745–751. [PubMed: 1519857]
17. Vlahov D, Anthony JC, Munoz A, Margolick J, Nelson KE, Celentano DD, et al. The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. NIDA Res Monogr. 1991; 109:75–100. [PubMed: 1661376]
18. Marshall MM, Kirk GD, Caporaso NE, McCormack MC, Merlo CA, Hague JC, et al. Tobacco use and nicotine dependence among HIV-infected and uninfected injection drug users. Addict Behav. 2011; 36:61–67. [PubMed: 20875704]
19. Drummond MB, Kirk GD, Ricketts EP, McCormack MC, Hague JC, McDyer JF, et al. Cross sectional analysis of respiratory symptoms in an injection drug user cohort: the impact of obstructive lung disease and HIV. BMC Pulm Med. 10:27. [PubMed: 20459792]
20. Drummond MB, Kirk GD, Astemborski J, McCormack MC, Marshall MM, Mehta SH, et al. Prevalence and risk factors for unrecognized obstructive lung disease among urban drug users. Int J Chron Obstruct Pulmon Dis. 2011; 6:89–95. [PubMed: 21407821]
21. Drummond, MB.; Merlo, C.; Astemborski, J.; Mehta, SH.; Wise, R.; Brown, RH., et al. The impact of HIV infection on longitudinal lung function decline.. 19th Conference on Retroviruses and Opportunistic Infections; Seattle, WA, USA. 2012;
22. Vlahov D, Graham N, Hoover D, Flynn C, Bartlett JG, Margolick JB, et al. Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4+ cell count. JAMA. 1998; 279:35–40. [PubMed: 9424041]
23. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005; 26:319–338. [PubMed: 16055882]

24. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. Am J Respir Crit Care Med. 1999; 159:179–187. [PubMed: 9872837]

25. Knaupp AS, Bottomley SP. Serpin polymerization and its role in disease--the molecular basis of alpha1-antitrypsin deficiency. IUBMB Life. 2009; 61:1–5. [PubMed: 18785256]

26. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. Biometrics. 1986; 42:121–130. [PubMed: 3719049]

27. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF, et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. Thorax. 2011

28. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. Am J Respir Crit Care Med. 2002; 166:675–679. [PubMed: 12204864]

29. Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977; 1:1645–1648. [PubMed: 871704]

30. Brenchley JM, Schacker TW, Ruff LE, Price DA, Taylor JH, Beilman GJ, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med. 2004; 200:749–759. [PubMed: 15365096]

31. Saetta M, Turato G, Maestrelli P, Mapp CE, Fabbri LM. Cellular and structural bases of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001; 163:1304–1309. [PubMed: 11371392]

32. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest. 2008; 118:3546–3556. [PubMed: 18982161]

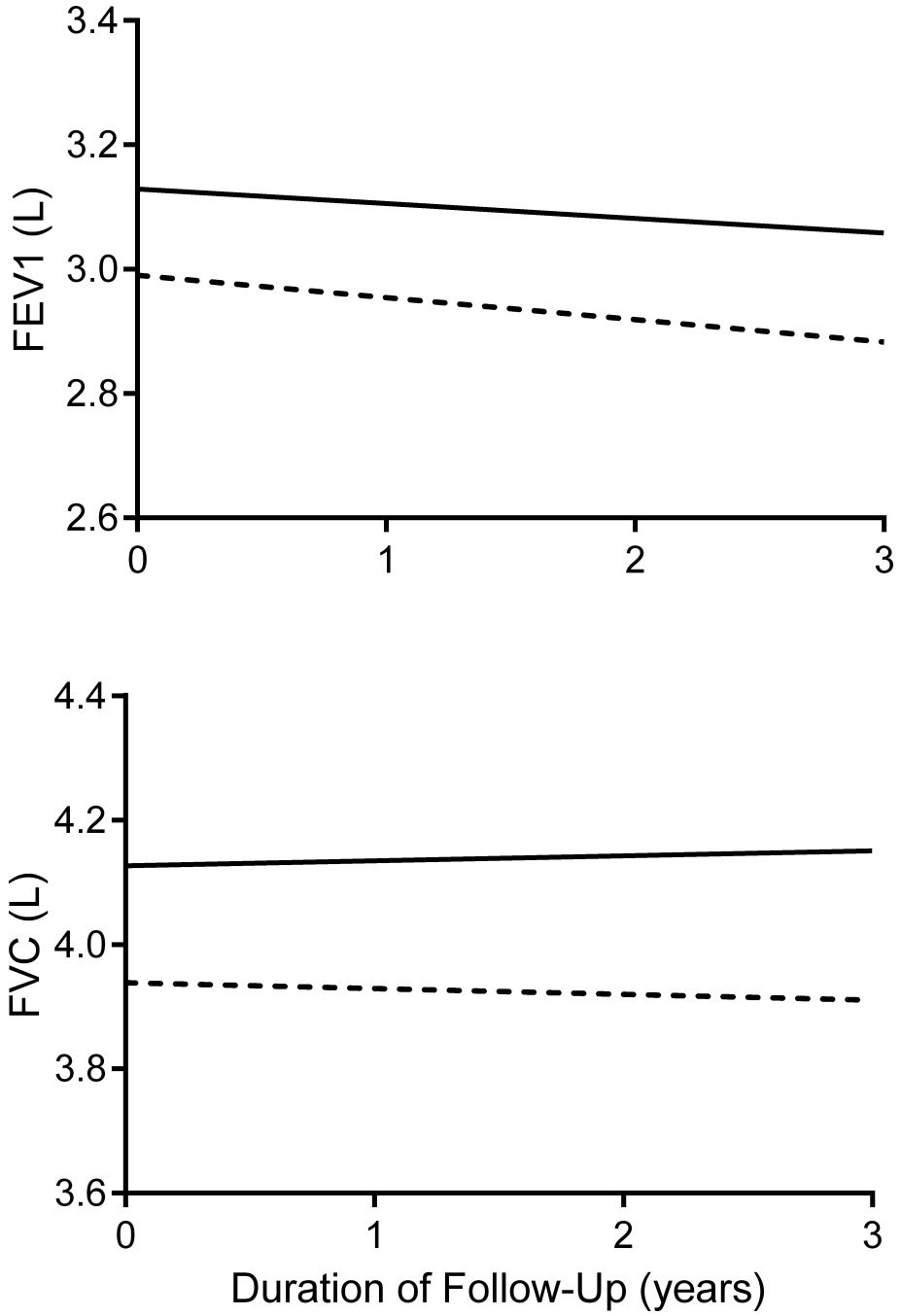

Figure 1.
Effect of HIV infection on adjusted annual FEV1 (upper panel) and FVC (lower panel) decline. Lines represent the modeled change in absolute FEV1 (or FVC) after centering other covariates in model to represent the typical cohort participant (50 year old African-American male current smoker with 20 pack-year smoking history, BMI 25 kg/m^2 and no history of pneumonia). (Solid line = HIV negative participants, Dashed line = HIV-infected participants).

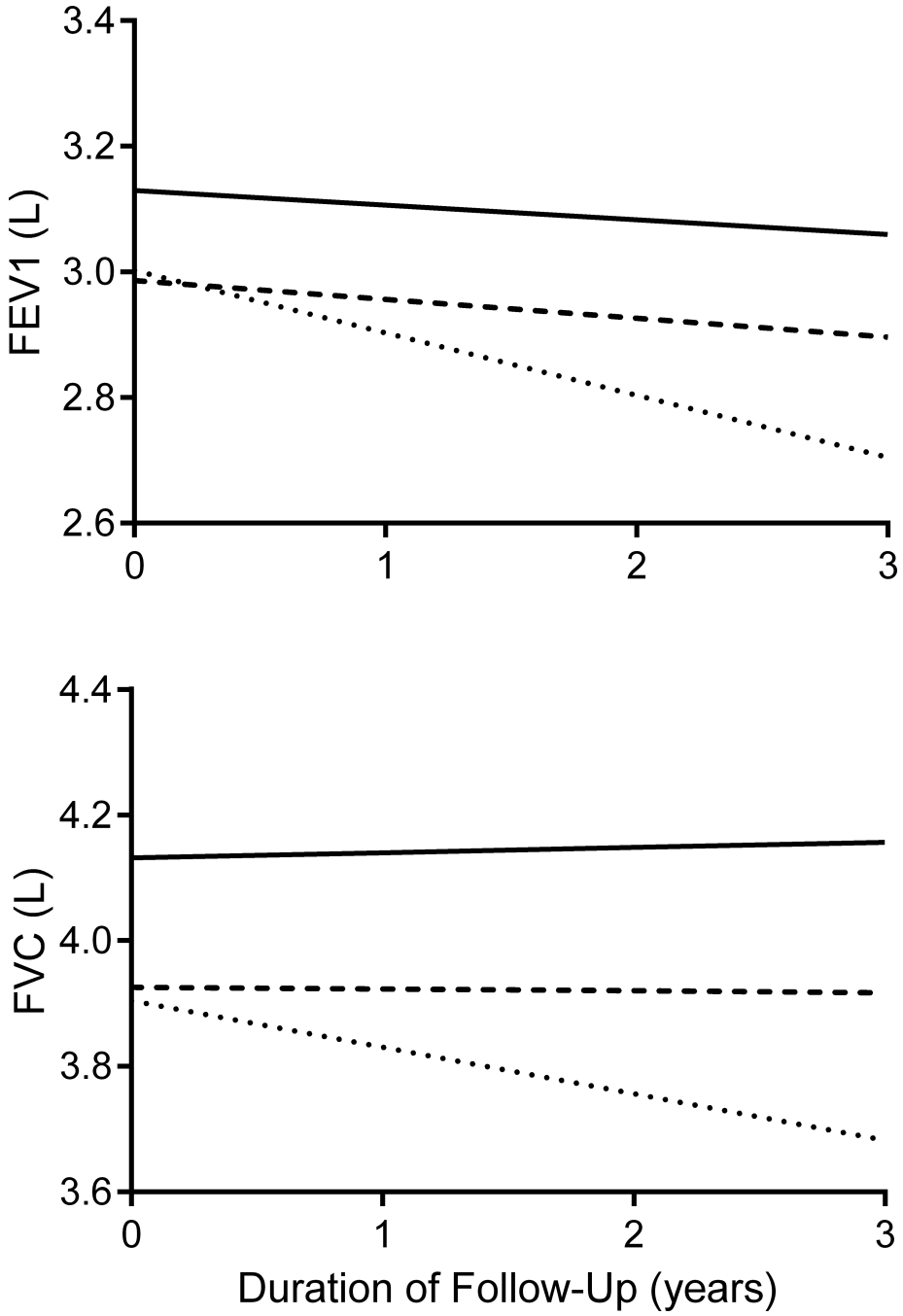

Figure 2.

Effect of HIV viral load on adjusted annual FEV1 (upper panel) and FVC (lower panel) decline. Lines represent the modeled change in absolute FEV1 (or FVC) after centering other covariates in model to represent the typical cohort participant (50 year old African-American male current smoker with 20 pack-year smoking history, BMI 25 kg/m^2 and no history of pneumonia). (Solid line = HIV negative participants; Dashed line = HIV-infected participants with viral load≤75,000 copies/ml; Dotted line = HIV-infected participants with viral load>75,000 copies/ml).

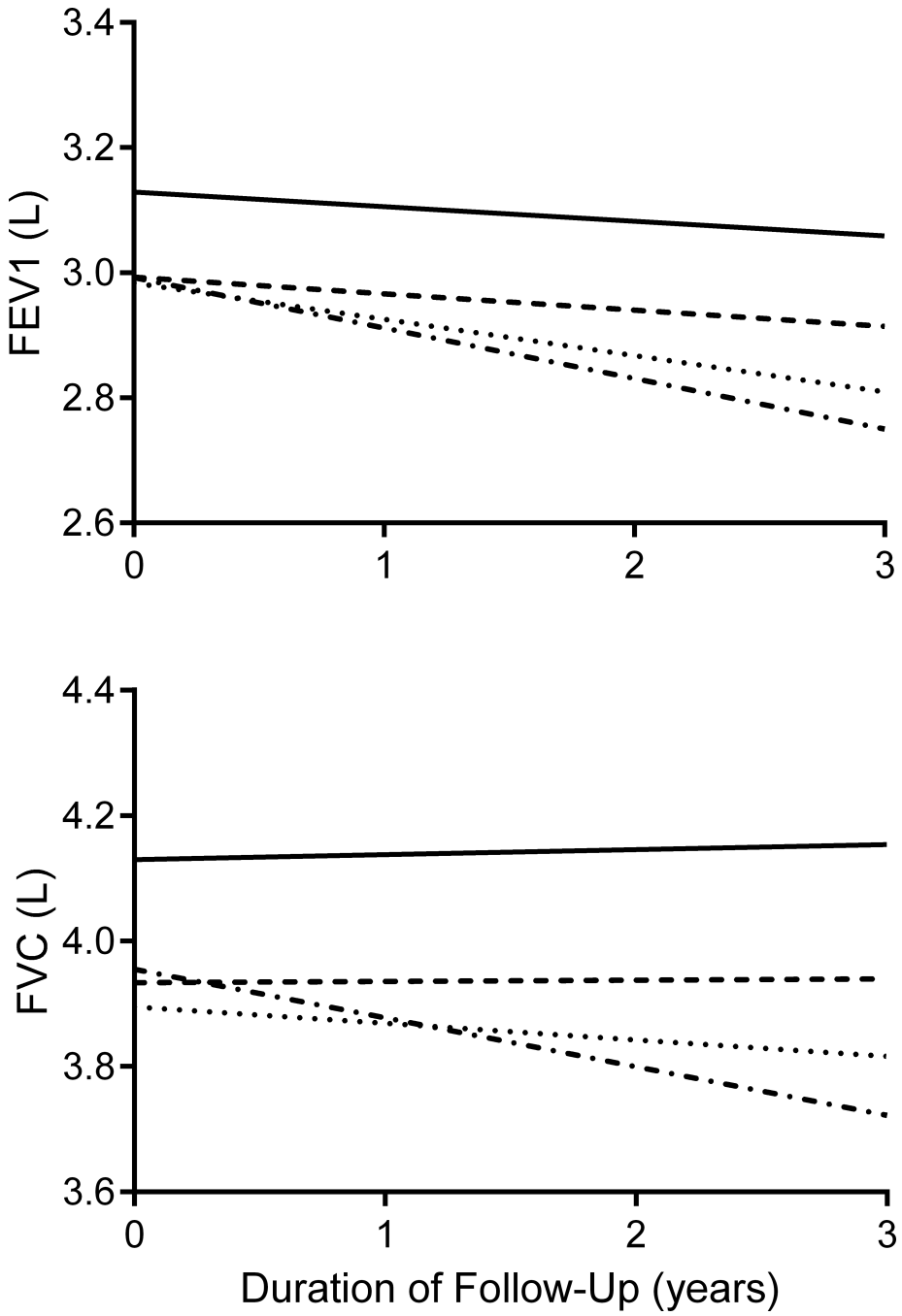

Figure 3.

Effect of CD_4 cell count on adjusted annual FEV1 (upper panel) and FVC (lower panel) decline. Lines represent the modeled change in absolute FEV1 (or FVC) after centering other covariates in model to represent the typical cohort participant (50 year old African-American male current smoker with 20 pack-year smoking history, BMI 25 kg/m^2 and no history of pneumonia). (Solid line = HIV negative participants; Dashed line = HIV-infected participants with CD_4 cell count>200 cells/mm^3; Dotted line = HIV-infected participants with CD_4 cell count 100-200 cells/mm^3; Dotted-Dashed line = HIV-infected participants with CD_4 cell count <100 cells/mm^3).

Table 1

Baseline demographic, behavioral, and clinical characteristics

	Total Cohort	HIV infected	HIV uninfected
N	1064	316	748
Age, yr	48.6 (7.2)	48.0 (6.5)	48.8 (7.5)
Male, n(%)	695 (65)	208 (66)	487 (65)
Black race, n(%)	969 (91)	298 (94)	671 (90)
BMI, (kg/m^2) (median, IQR)	25.5 (22.5-30.0)	24.7 (21.6-28.5)	25.8 (22.8-30.5)
Smoking status, n(%)*			
Current	904 (85)	266 (84)	638 (85)
Former	100 (9)	30 (9)	70 (9)
Never	60 (6)	20 (6)	40 (5)
Smoking, pack-yrs	23.9 (17)	23.5 (18)	24.0 (17)
Current IDU, n(%)*	420 (39)	106 (34)	314 (42)
Ever smoked cocaine or heroin, n(%)	399 (38)	101 (32)	298 (40)
FEV1			
Absolute (L)	2.80 (0.75)	2.72 (0.74)	2.83 (0.75)
% predicted	92.1 (18.2)	90.3 (19.6)	92.8 (17.5)
FVC, (L)			
Absolute (L)	3.65 (0.94)	3.54 (0.90)	3.70 (0.95)
% predicted	96.7 (16.6)	94.9 (17.3)	97.4 (16.2)
FEV1/FVC ratio	0.77 (0.08)	0.76 (0.09)	0.77 (0.07)
OLD present, n(%)	169 (16)	52 (16)	117 (16)
Respiratory infection, n±			
All	129	78 (25)	51 (7)
Bacterial	125	74 (23)	51 (7)
Pneumocystis	17	17 (5)	0 (0)
CD4 count, n(%)†			
<100 cells/ mm^3	31 (10)	31 (10)	
100-199 cells/ mm^3	50 (16)	50 (16)	
>200 cells/ mm^3	230 (74)	230 (74)	
HIV RNA level, n(%)†			
<400 copies/ml	148 (47)	148 (47)	
400-75,000 copies/ml	131 (42)	131 (42)	
>75,000 copies/ml	33 (11)	33 (11)	
HAART use, n(%)†*	172 (55)	172 (55)	

All values mean (S.D.) unless otherwise indicated.

BMI= body mass index; FEV1= forced expiratory volume in 1 sec; FVC= forced vital capacity; OLD= obstructive lung disease; HIV=human immunodeficiency virus; HAART= highly active anti-retroviral therapy; IDU= injection drug use.

†Among HIV-infected individuals.

*In last 6 months.

±Number of infections from initial ALIVE enrollment to entry into spirometry cohort (some participants had multiple diagnoses).

Table 2

Effect of markers of HIV infection on annual lung function decline*

	FEV1 (ml/yr)		FVC (ml/yr)	
Predictor	**Adjusted change**	**p-value†**	**Adjusted change**	**p-value†**
Serostatus				
HIV negative	−23.6 (−32.6, −14.7)		8.04 (−2.60, 18.7)	
HIV positive	−35.8 (−51.2, −20.3)	0.135	−9.29 (−25.1, 6.5)	0.05
Plasma viral load (copies/ml)				
HIV negative	−23.5 (−32.4, −14.6)		8.24 (−2.43, 18.9)	
HIV positive, viral load≤75,000	−29.9 (−45.8, −14.0)	0.443	−2.93 (−18.7, 12.8)	0.20
HIV positive, viral load >75,000	−99.1 (−151, −47.4)	0.004	−74.0 (−134, −13.6)	0.008
CD_4 cell count (cells/ml^3)				
HIV negative	−23.5 (−32.5, −14.6)		8.12 (−2.56, 18.8)	
HIV positive, CD_4>200	−26.3 (−43.5, −9.00)	0.763	2.06 (−15.1, 19.2)	0.52
HIV positive, CD_4 100-200	−57.9 (−90.2, −25.6)	0.04	−26.2 (−61.4, 9.11)	0.06
HIV positive, CD_4<100	−80.8 (−128, −33.2)	0.018	−77.6 (−128, −27.6)	0.001
Combined viral load/CD_4 levels				
HIV negative	−24.3 (−33.2, −15.4)		7.50 (−3.16, 18.2)	
HIV pos, CD_4≥100, VL≤75,000	−31.7 (−47.7, −15.6)	0.385	−2.76 (−18.6, 13.1)	0.243
HIV pos, CD_4<100, VL≤75,000	−58.8 (−108, −9.73)	0.167	−60.2 (−110, −9.94)	0.008
HIV pos, CD_4≥100, VL>75,000	−90.8 (−145, −36.2)	0.017	−59.6 (−126, 7.22)	0.05
HIV pos, CD_4<100, VL>75,000	−125 (−220, −30.4)	0.037	−111 (−218, −4.13)	0.030

*Models adjusted for sex, age, race, baseline pack-years smoked, current smoking status, body mass index and history of prior respiratory infections.

†P-value comparing HIV parameter to HIV negative. See text for additional details regarding comparisons between HIV infected groups.