Pulmonary Function Abnormalities in HIV-Infected Patients during the Current Antiretroviral Therapy Era

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***Rationale*: Before the introduction of combination antiretroviral (ARV) therapy, patients infected with HIV had an increased prevalence of respiratory symptoms and lung function abnormalities. The prevalence and exact phenotype of pulmonary abnormalities in the current era are unknown. In addition, these abnormalities may be underdiagnosed.**

***Objectives*: Our objective was to determine the current burden of respiratory symptoms, pulmonary function abnormalities, and associated risk factors in individuals infected with HIV.**

***Methods*: Cross-sectional analysis of 167 participants infected with HIV who underwent pulmonary function testing.**

***Measurements and Main Results*: Respiratory symptoms were present in 47.3% of participants and associated with intravenous drug use (odds ratio [OR] 3.64; 95% confidence interval [CI], 1.32–10.046; $P = 0.01$). Only 15% had previous pulmonary testing. Pulmonary function abnormalities were common with 64.1% of participants having diffusion impairment and 21% having irreversible airway obstruction. Diffusion impairment was independently associated with ever smoking (OR 2.46; 95% CI, 1.16–5.21; $P = 0.02$) and *Pneumocystis* pneumonia prophylaxis (OR 2.94; 95% CI, 1.10–7.86; $P = 0.01$), whereas irreversible airway obstruction was independently associated with pack-years smoked (OR 1.03 per pack-year; 95% CI, 1.01–1.05; $P < 0.01$), intravenous drug use (OR 2.87; 95% CI, 1.15–7.09; $P = 0.02$), and the use of ARV therapy (OR 6.22; 95% CI, 1.19–32.43; $P = 0.03$).**

***Conclusions*: Respiratory symptoms and pulmonary function abnormalities remain common in individuals infected with HIV. Smoking and intravenous drug use are still important risk factors for pulmonary abnormalities, but ARV may be a novel risk factor for irreversible airway obstruction. Obstructive lung disease is likely underdiagnosed in this population.**

Keywords: HIV; respiratory function tests; smoking; antiretroviral therapy, highly active; AIDS

Pulmonary complications have been a major cause of morbidity and mortality in patients with HIV infection (1, 2). With the development of combination antiretroviral (ARV) therapy and improvements in prophylaxis for *Pneumocystis* pneumonia (PCP) and other opportunistic infections, the incidence of infectious pulmonary complications has decreased drastically in patients with HIV infection (1, 3, 4). Changes in noninfectious pulmonary complications, such as chronic obstructive pulmonary disease (COPD) and asthma, are less clear, and these diseases may actually be increasing. Studies before the introduction of combination ARV demonstrated that persons with HIV infection had a higher prevalence of impaired diffusing capacity for carbon monoxide (D_{LCO}), increased emphysema, accelerated airway obstruction and small airways disease, and more frequent respiratory symptoms than subjects not infected with HIV (2, 5–8).

Limited data exist regarding the extent and types of pulmonary function abnormalities in the current era. In one recent study, veterans with HIV infection had an increased risk of COPD compared with veterans not infected with HIV even after adjusting for smoking (9), but this finding was based on patient self-report or International Classification of Disease-9 codes and not direct assessment of pulmonary function. This study also did not include women, a group that comprises an increasing proportion of the HIV population and has a high prevalence of smoking (10, 11). Another recent study performed spirometry in outpatients infected with HIV and found that 7% had clinical obstruction and that the ratio of FEV_1 to FVC was lower in those subjects who smoked, had a history of bacterial pneumonia, or were receiving combination ARV therapy (12). This study did not measure post-bronchodilator spirometry or D_{LCO}; thus, the exact "phenotype" of pulmonary abnormalities associated with HIV infection is currently unknown.

Underdiagnosis of COPD is common in the non–HIV-infected population, and it may be even more of a problem in those with HIV (13–18). Smoking prevalence is higher in the HIV-infected population (19), yet there is decreased recognition of smoking behavior and lack of confidence in smoking cessation counseling among primary care providers of patients with HIV infection (20). It is currently unknown whether diagnosis of smoking-related diseases is similarly decreased.

In this study, we determined the extent and nature of respiratory symptoms and pulmonary function abnormalities in a cohort of outpatients with HIV infection. We identified factors associated with particular phenotypes (i.e., diffusion impairment, irreversible airway obstruction, bronchodilator response) and assessed the frequency of pulmonary function testing (PFT) for respiratory disease in a primary care setting.

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Before highly active combination antiretroviral (ARV) therapy, respiratory symptoms and pulmonary function abnormalities were common among individuals infected with HIV. The prevalence of symptoms and pulmonary function abnormalities has not been thoroughly investigated in individuals infected with HIV in the era of combination ARV therapy.

What This Study Adds to the Field

Respiratory symptoms and pulmonary function abnormalities are still very common in individuals infected with HIV even with combination ARV therapy. Diffusion impairment is also common, even in those with HIV infection who have never smoked.

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METHODS

Study Population

Subjects with documented HIV infection who were 18 years of age or older were recruited from the University of Pittsburgh Medical Center HIV/AIDS clinic between July 1, 2007, and May 15, 2009. Recruitment was performed using posted advertisements and by contacting patients in a research registry. All participants signed written informed consent, and the University of Pittsburgh Institutional Review Board approved the protocol. Participants were excluded if they had new or increasing respiratory symptoms (cough, shortness of breath, or dyspnea) or fevers within the past 4 weeks.

Data Collection

Clinical data were collected by participant interview and medical record review. Comparable clinical data were obtained for the overall clinic (*see* online supplement). Participants were determined to be on ARV if they were using at least three ARV agents from at least two classes of medications. All available $CD4^+$ T-lymphocyte (CD4) counts and serum HIV RNA levels were obtained from medical record review to determine the concurrent (most recent level within 3 months), average, minimum, and maximum levels, and rate of change in CD4 counts. The lower limit of detection for the HIV RNA assay was less than 50 copies/ml. Respiratory symptoms were assessed using a modified version of the St. George's Respiratory Questionnaire (21, 22). Performance of prior PFTs was determined both by subject report and by electronic medical record review.

Pulmonary Function Testing

All participants performed pre-bronchodilator and post-bronchodilator spirometry and measurement of D_{LCO} in accordance with American Thoracic Society standards (23, 24). Crapo and coworkers' (25) (spirometry) and Miller and coworkers' (26) (D_{LCO}) reference equations were used for predicted values. D_{LCO} was corrected for hemoglobin and carboxyhemoglobin.

Statistical Analysis

Statistical analyses were performed using Stata version 10 (StataCorp, College Station, TX). Participant characteristics, respiratory symptoms, and respiratory medication use were described using mean and SD, median and range, or frequencies as appropriate. Percentage of subjects who had previous PFTs was determined. Pulmonary functions variables included FEV_1 percent predicted, FVC percent predicted, FEV_1/FVC, and D_{LCO} percent predicted. Means and SD were computed for the entire cohort and compared between ever smokers and never smokers by *t* tests. We defined four PFT phenotypes: (*1*) diffusion impairment (D_{LCO} corrected for hemoglobin and carboxyhemoglobin <80% predicted [26]); (*2*) irreversible airway obstruction (post-bronchodilator FEV_1/FVC ratio <0.70 or the FEV_1/FVC below the lower limit of normal for age [27]) with or without diffusion impairment; (*3*) irreversible airway obstruction with diffusion impairment; and (*4*) bronchodilator response (increase of at least 12% and 200 ml in either FEV_1 or FVC [28]). Participant characteristics were determined for each PFT phenotype and controls and compared by *t* tests, Wilcoxon rank sum (Mann-Whitney) test, and chi-square or Fisher exact test where appropriate. Multivariable modeling was used to determine independent predictors of respiratory symptoms, inhaler use, and PFT phenotypes using a step-up/step-down procedure (*see* online supplement) (29). Clinically relevant variables significant at a *P* value of 0.10 were entered into the model in order of increasing univariable logistic regression *P* values. The likelihood ratio test was used to compare hierarchical models, and those variables reaching a significance level of *P* less than or equal to 0.10 were retained in the model. Step-down regression was then performed by removing variables in order of decreasing *P* value. Variables were retained in the model if the likelihood ratio test was significant at a level of *P* less than or equal to 0.05. Interactions were identified by comparing the main effects model with a model containing interaction terms. If variables were related (i.e., smoking status and pack-year history), the variable with the strongest univariable relationship to the outcome was included, and the multivariable models were assessed by variance inflation factors to check for colinearity. Fit of the model was assessed using the Hosmer-Lemeshow goodness of fit test (30). The results of multivariable modeling were similar when using the lower limit of normal of FEV_1/FVC or a FEV_1/FVC below 0.70 to define obstruction; therefore, we only present results using an FEV_1/FVC less than 0.70.

Two subjects did not have CD4 cell counts or HIV RNA levels at the time of the study and eight did not have prior CD4 cell counts or HIV RNA levels, one subject did not have acceptable spirometry, and one subject did not have D_{LCO} testing. The subjects were not included in analyses for those variables.

RESULTS

Participant Characteristics

Of 177 participants recruited, six failed screening, three did not attend their study visit, and one had PFT that did not meet criteria. A total of 167 participants with HIV infection completed the study (Table 1). Median age was 46 years (range, 20–70 years). About one-quarter of participants (26.4%) were female and approximately half were African American (49.7%). Over three-fourths (76.1%) were ever smokers and 52.7% were current smokers. Most (80.7%) were receiving ARV. There were no subjects who were receiving ARV regimens with fewer than three agents. Median CD4 count was 479 cells/μl (range, 22–1,390), and 62.3% had an undetectable serum HIV viral level. Participants' CD4 counts and HIV RNA levels were available for a median of 7 years (range, <1–18.4 years), which was the average length of time that study subjects were followed in the clinic. Study participants were similar to the general HIV clinic population in age, sex, ARV use, current PCP prophylaxis use, CD4 count, and serum HIV RNA levels (data not shown). There were a greater proportion of African-American participants in the study cohort (49.7% vs. 36.1%; $P < 0.001$); fewer men who had sex with men (47.7% vs. 59.7%; $P = 0.01$); and more current smokers (52.7% vs. 38.2%; $P = 0.002$).

Respiratory Symptoms and Inhaler Use

Respiratory symptoms were present in almost two-thirds of subjects (63.5%), and ever smokers were more likely to have symptoms than never smokers (68.5% vs. 47.5%; $P = 0.02$) (Figure 1). The most common symptoms were dyspnea (43.7%) and having a usual cough (37.1%). Fewer complained of more severe symptoms, such as shortness of breath at rest (6.6%) or coughing more than four times a day on at least 4 days a week (7.2%). Subjects with respiratory symptoms were less likely to have an HIV risk factor of men who have sex with men (odds ratio [OR] 0.50; 95% confidence interval [CI], 0.26–0.94; $P = 0.03$) and were more likely to have ever smoked (OR 2.40; 95% CI, 1.16–4.16; $P = 0.02$) or to have ever used intravenous (IV) drugs (OR 3.64; 95% CI, 1.32–10.06; $P = 0.01$) (*see* Table E1). Multivariable modeling found IV drug use (OR 3.64; 95% CI, 1.31–10.12; $P = 0.01$) was independently associated with having respiratory symptoms (Table 2). About one-quarter of participants (27.5%) reported using respiratory inhaler medications.

PFT Abnormalities

For the entire cohort, average pre-bronchodilator and post-bronchodilator FEV_1 percent predicted, FVC percent predicted, and FEV_1/FVC were normal (Figure 2). In contrast, average D_{LCO} percent predicted was low (72.3% ± 17.6%). The average FEV_1/FVC (0.76 ± 0.10 vs. 0.82 ± 0.60; $P < 0.001$) and D_{LCO} percent predicted (69.4% ± 17% vs. 81.4% ± 16.5%; $P < 0.001$) were lower in ever smokers than in never smokers (Figure 2).

Diffusion impairment (D_{LCO} <80% predicted) was the most common pulmonary function phenotype and was identified in 64.1% of participants. A greater proportion of ever smokers

TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS INFECTED WITH HIV

	Study Subjects (*n = 167*)	Diffusion Impairment (*n = 107*)	Obstruction (*n = 35*)	Diffusion Impairment and Obstruction (*n = 27*)
Age, median years (range)	46 (20–70)	47 (20–67)	49 (35–61)	50 (40–61)
Female, n (%)	44 (26.4)	29 (27.1)	8 (22.9)	7 (25.9)
African-American, n (%)	83 (49.7)	54 (50.5)	20 (57.1)	16 (59.3)
Men who have sex with men, n (%)	83 (49.7)	48 (44.9)	13 (37.1)	9 (33.3)
Current smoker, n (%)	88 (52.7)	65 (60.8)	26 (74.3)	20 (74.1)
Ever smoker, n (%)	127 (76.1)	88 (82.2)	34 (97.1)	26 (96.3)
Pack-year history, median (range)	10 (0–105)	15 (0–100)	20 (0–75)	20 (0–75)
Intravenous drug use, n (%)	31 (18.6)	24 (22.4)	13 (37.1)	10 (37)
Marijuana use, n (%)	129 (77.3)	86 (80.4)	30 (85.7)	24 (88.9)
Cocaine use, n (%)	65 (42.7)	43 (46.2)	15 (51.7)	12 (57.4)
History of hepatitis B or C, n (%)*	51 (33.6)	36 (38.7)	15 (51.7)	11 (52.4)
History of PCP or BP, n (%)	74 (44.3)	53 (49.5)	18 (51.4)	15 (55.6)
On antiretroviral therapy, n (%)	134 (80.7)	86 (80.4)	32 (94.1)	25 (92.6)
On PCP prophylaxis currently, n (%)	33 (19.8)	27 (25.2)	10 (28.6)	10 (37)
CD4 cells/μl, median (range)	479 (22–1,390)	434 (22–1,390)	481 (60–1,091)	425 (60–1,091)
HIV RNA, median ln copies/ml (range)	3.89 (3.89–14.3)	3.89 (3.89–13.8)	3.89 (3.89–12.7)	3.89 (3.89–12.7)
Duration of HIV infection, median years, (range)	13.0 (0.1–27)	13.1 (0.1–24.7)	14.8 (2.8–24.4)	15.0 (2.8–22.1)
Any respiratory symptom, n (%)	106 (63.5)	76 (71)	26 (74.3)	21 (77.8)
PFT before enrollment, n (%)	25 (15)	17 (15.9)	7 (20)	5 (18.5)

Definition of abbreviations: BP = bacterial pneumonia; ln = natural logarithm; PCP = *Pneumocystis* pneumonia; PFT = pulmonary function testing.

had diffusion impairment than never smokers (69.3% vs. 47.5%; $P = 0.01$), but diffusion impairment was also common in those who had never smoked (Figure 3). Diffusion impairment was associated with a greater number of pack-years smoked (OR per pack-year, 1.03; 95% CI, 1.01–1.05; $P = 0.02$); use of PCP prophylaxis (OR, 2.47; 95% CI, 1.23–4.98; $P = 0.01$); and CD4 cell count less than 200 cells/μl (OR, 4.34; 95% CI, 1.23–15.29; $P = 0.02$) (*see* Table E1). Ever smoking (OR, 2.46; 95% CI, 1.16–5.21; $P = 0.02$) and use of PCP prophylaxis (OR, 2.94; 95% CI, 1.10–7.86; $P = 0.03$) were independently associated with diffusion impairment (Table 2).

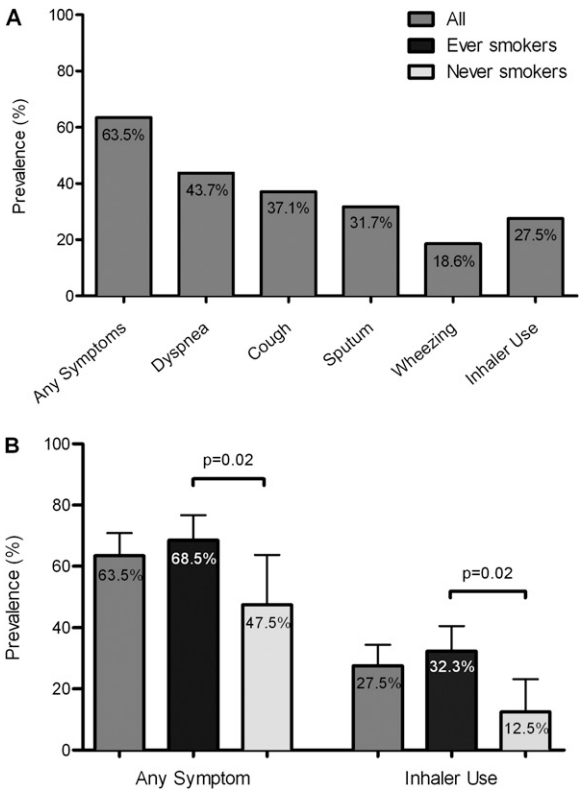

Figure 1. (*A*) Frequency of respiratory symptoms. (*B*) Frequency of having any symptoms or using inhaler medication for all participants (*All*), those who have ever smoked (*Ever smokers*), and those who have never smoked (*Never smokers*). Whiskers represent the 95% confidence interval.

Twenty-one percent of participants had irreversible airway obstruction based on a post-bronchodilator FEV_1/FVC ratio less than 0.70, and this phenotype was more common in ever smokers than never smokers (26.8% vs. 2.5%; $P = 0.001$) (Figure 3). Nineteen percent of the cohort had irreversible airway obstruction based on a post-bronchodilator FEV_1/FVC ratio below the lower limit of age-adjusted normal. In univariable analysis, irreversible airway obstruction (post-bronchodilator FEV_1/FVC ratio <0.70) was associated with higher age (OR per 10 yr, 1.74; 95% CI, 1.15–2.63; $P = 0.01$); ever smoking (OR, 14.30; 95% CI, 1.88–107.80; $P = 0.01$); greater number of pack-years smoked (OR per pack-year, 1.03; 95% CI, 1.01–1.05; $P = 0.001$); IV drug use (OR, 3.74; 95% CI, 1.60–8.73; $P = 0.002$); hepatitis B or C (OR, 2.59; 95% CI, 1.13–5.91; $P = 0.02$); and ARV therapy (OR, 4.71; 95% CI, 1.07–20.80; $P = 0.04$) (*see* Table E1). Inhaler use was also more common in those with irreversible airway obstruction (51.4% vs. 28.2%; $P < 0.001$) (*see* Table E2). Multivariable modeling demonstrated that increased number of pack-years smoked (OR, 1.03; 95% CI, 1.01–1.05; $P = 0.008$), IV drug use (OR, 2.87; 95% CI, 1.15–7.09; $P = 0.02$), and the use of ARV therapy (OR, 6.22; 95% CI, 1.19–32.43; $P = 0.03$) were independently associated with irreversible airway obstruction (Table 2). To determine if the association of ARV therapy and airway obstruction was the result of changes in CD4 cell counts or HIV RNA levels, we examined the relationship of nadir and average CD4 cell count and maximum and average HIV RNA level with airway obstruction, but did not find any significant relationships.

There were 27 participants (16.2%) who had diffusion impairment in combination with irreversible airway obstruction (Figure 3). In univariable analysis, having both diffusion impairment and irreversible airway obstruction was associated with older age (OR per 10 yr, 1.78; 95% CI, 1.13–2.80; $P = 0.01$); ever smoking (OR, 11.06; 95% CI, 1.45–84.15; $P = 0.02$); greater number of pack-years smoked (OR per pack-year, 1.03; 95% CI, 1.01–1.05; $P = 0.001$); IV drug use (OR, 4.3; 95% CI, 1.78–10.39; $P = 0.001$); and use of PCP prophylaxis (OR, 2.52; 95%

TABLE 2. MULTIVARIABLE LOGISTIC REGRESSION MODELING. ODDS RATIOS (95% CONFIDENCE INTERVALS) FOR FACTORS INDEPENDENTLY ASSOCIATED WITH OUTCOMES

	Any Symptom*	*P* Value	Diffusion Impairment†	*P* Value	Obstruction (*ratio <0.7*)†	*P* Value	Diffusion Impairment and Obstruction	*P* Value
Smoking, ever smoked			2.46 (1.16–5.21)	0.02				
Pack-year, per yr					1.03 (1.01–1.05)	0.008	1.03 (1.01–1.04)	0.009
Intravenous drug use	3.64 (1.31–10.12)	0.01			2.87 (1.15–7.09)	0.02		
PCP prophylaxis, current use			2.94 (1.10–7.86)	0.03				
On antiretroviral therapy					6.22 (1.19–32.43)	0.03		

Definition of abbreviations: HIV = human immunodefieciency virus; PCP = *Pneumocystis* pneumonnia.
* Controlling for sex.
† Controlling for age and HIV risk factor.

CI, 1.10–5.78; $P = 0.03$). Multivariable analysis found a greater number of pack-years smoked (OR, per pack-year 1.03; 95% CI, 1.01–1.04; $P = 0.009$) to be independently associated with having diffusion impairment and irreversible airway obstruction (Table 2).

A bronchodilator response was the least common phenotype and occurred in 14 (8.4%) subjects (Figure 3). Bronchodilator response was not associated with any patient characteristics.

Prior PFTs

Twenty-five participants (15.0%) had PFTs in the past. Nearly two-thirds of participants who had not previously had PFTs (61.3%) reported respiratory symptoms; one-fourth of them (24.7%) had been prescribed inhalers, and over three-fourths (76.1%) had ever smoked. Subjects who had not had PFTs before enrollment had a high prevalence of PFT abnormalities (irreversible airway obstruction, 19.7%; diffusion impairment, 72.7%; and bronchodilator response, 8.5%) (*see* Table E2). The participants who had PFTs before enrollment had a lower post-bronchodilator FEV_1 percent predicted (88.8% vs. 96.5%; $P = 0.04$) than those who had never had PFTs, and they tended to have a lower D_{LCO} percent predicted (66.2% vs. 73.4%; $P = 0.06$). However, there were no significant differences between the groups for post-bronchodilator FVC percent predicted (95.4% vs. 101%; $P = 0.06$) and post-bronchodilator FEV_1/FVC (0.76 vs. 0.77; $P = 0.4$).

DISCUSSION

The current study documents prevalence of respiratory symptoms in HIV and is the first conducted during the era of combination ARV therapy that directly tests pulmonary function in patients with HIV infection with both pre-bronchodilator and post-bronchodilator spirometry and diffusing capacity. Respiratory symptoms and inhaler use were quite prevalent. Pulmonary function abnormalities were very common, with diffusion impairment being the most common phenotype and present in about 65% of the cohort, including a large number of never smokers. Irreversible airway obstruction was also common and found to be independently associated with ARV use. Bronchodilator reversibility was less common. Despite the high burden of respiratory symptoms, smoking, and pulmonary function abnormalities in this population, few participants had undergone PFT as part of their primary care.

Studies of pulmonary function in individuals with HIV infection before potent ARV therapy documented a high prevalence of respiratory abnormalities (8, 31, 32). A study of respiratory symptoms from the pre-ARV era found a greater prevalence of sputum production (41% vs. 31.7%) and wheezing (approxi-

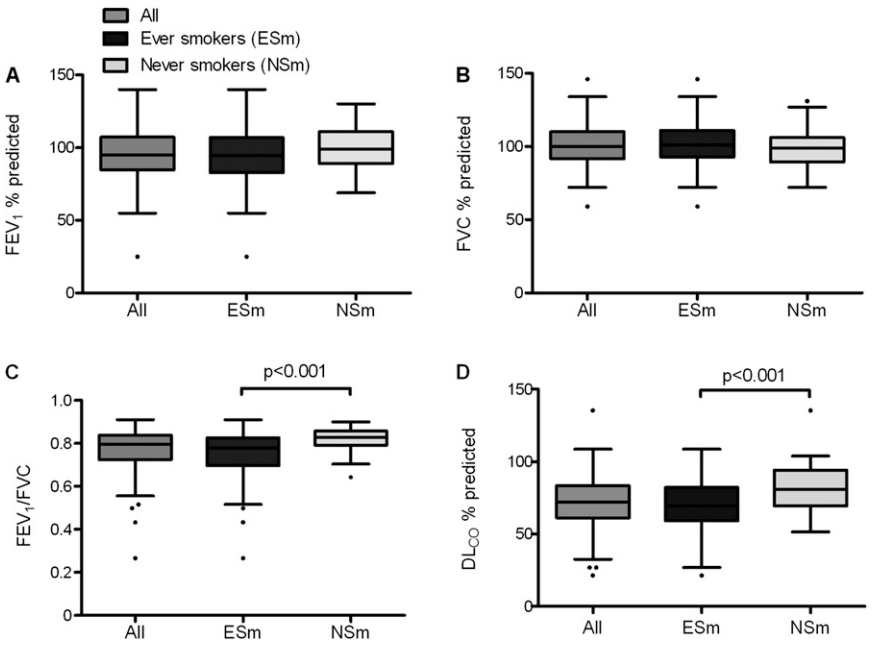

Figure 2. Distribution of results of pulmonary function testing. Boxplots show the median and interquartile range. (*A*) Post-bronchodilator FEV_1 % predicted. (*B*) Post-bronchodilator FVC % predicted. (*C*) Post-bronchodilator FEV_1/FVC. (*D*) Corrected D_{LCO} % predicted. All = all participants; D_{LCO} = diffusing capacity for carbon monoxide; ESm = ever smokers, those who have ever smoked; NSm = never smokers, those who have never smoked.

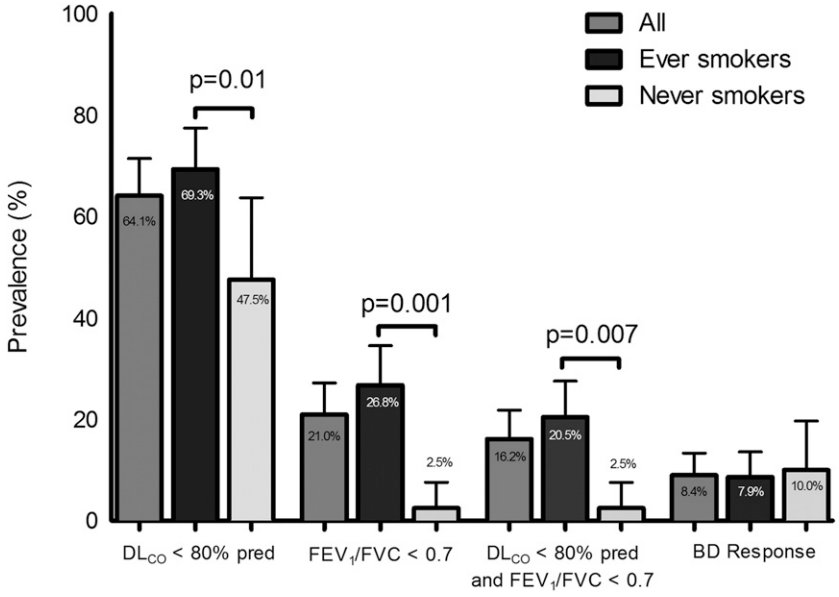

Figure 3. Frequency of pulmonary function phenotypes of all participants (*All*), those who have ever smoked (*Ever smokers*), and those who have never smoked (*Never Smokers*). Whiskers represent the 95% confidence interval. BD = bronchodilator; D_{LCO} = diffusing capacity for carbon monoxide.

mately 39% vs. 18.6%) compared with our population, but similar prevalence of shortness of breath (41.6% vs. 43.7%) and cough (40% vs. 37.1%). The only study in the combination ARV era found a lower prevalence of overall symptoms (31.5%), but was performed in a younger cohort with a lesser smoking history (12).

Prior studies have also documented a high prevalence of abnormalities in spirometry and diffusion (8, 31, 32). Before combination ARV, lung function impairment was worse with more advanced HIV disease, and similar to our study, abnormally low diffusing capacity was the most prominent finding (31, 32). The D_{LCO}% predicted in pre-ARV cohorts of HIV-infected outpatients was somewhat higher than in our cohort (78.5–84.8% vs. 72.3%) and was associated with cigarette smoking, IV drug use, CD4 cell count, PCP, and Kaposi sarcoma (7, 8, 32–34). Although we also found an association of diffusing capacity with smoking and IV drug use, we did not find an independent association with CD4 cell count and none of our subjects reported a history of Kaposi sarcoma. Strikingly, almost half of our never smokers also had diffusion impairment, and most of these were also not using IV drugs, suggesting that another mechanism is responsible for this finding. Diffusion impairment in HIV might be secondary to emphysema, pulmonary vascular disease, HIV-induced inflammation, prior pneumonia, or interstitial lung disease (7, 35–37). Further investigation is needed to determine the causes and clinical significance of impaired diffusing capacity in HIV-infected individuals.

Airway obstruction was also commonly reported in the pre-ARV era of HIV. The mean FEV_1 percent predicted in our cohort was similar to a pre-ARV cohort (91.1–91.8% predicted vs. 92.6% predicted prebronchodilator) (7, 8). A recent study in the combination ARV era found a lower prevalence of airway obstruction (8.6% by FEV_1/FVC less than lower limit of normal and 6.8% by a FEV_1/FVC <0.7) than reported here, but in a younger cohort with less smoking. The current study is the second to report an independent association of airway obstruction with ARV use. George and colleagues recently reported an independent association of combination ARV with airway obstruction, findings repeated in our study in a cohort from a different geographic region and with different demographic characteristics (12). We found no link between ARV use and the phenotypes of diffusion impairment and bronchodilator responsiveness. The biologic link, if any, between ARV therapy and airway obstruction is unknown. ARV therapy may be a confounder for severity of HIV disease before starting ARV therapy or duration of HIV infection. To assess these possibilities, we examined prior CD4 cell counts and HIV RNA levels over time and history of prior bacterial pneumonias or PCP, but did not find that these factors explained the association of airway obstruction and ARV. We also examined reported time infected with HIV, but we found no association between this factor and airway obstruction. Several mechanisms might link ARV use and airway obstruction. Airway obstruction may be a result of direct effects of the ARV drugs. For example, ARV-associated cardiovascular disease and metabolic syndrome are thought to occur because of ARV-associated decreased expression of peroxisome-proliferator–activated receptor. This receptor is an important transcription factor in lipid and cytokine metabolism and provides an antiinflammatory effect in the lungs and airways; therefore, decreased levels might contribute to development of airway obstruction after ARV initiation (38–41). Abnormal immune restoration similar to that in the immune reconstitution inflammatory syndrome may result in response to occult infection or colonization in the respiratory tract and lead to airway obstruction (12, 42, 43). Individuals with HIV infection are noted to have organ-specific autoimmune complications with ARV therapy, and another possibility is that autoimmunity may occur in response to lung antigens after ARV treatment (43–46).

Although bronchodilator response was the least common phenotype seen, it still may be more prevalent in HIV than in the non–HIV-infected population. A population cohort of non–HIV-infected subjects reported 2% of people age 47 to 48 years and 4.1% of those age 71 to 73 years had a bronchodilator response (47), lower than the 8.4% in our HIV cohort. It is possible that bronchodilator responsiveness, although still higher in those with HIV, has decreased when compared with the pre-ARV era. A study of bronchodilator response in individuals infected with HIV before combination ARV therapy found a prevalence of 31% with no relationship to smoking (48), suggesting this phenotype might be less common in the current era.

Underdiagnosis of obstructive lung disease is frequent in the non–HIV-infected population. In this study, we demonstrated that few patients had previous PFT despite a high prevalence of

respiratory symptoms, prescription of inhalers, and abnormal lung function. Consensus guidelines from the American Thoracic Society/European Respiratory Society task force and Global Initiative for Chronic Obstructive Lung Disease recommend spirometry screening for COPD in high-risk groups, such as smokers, and it seems that individuals infected with HIV should be considered a high-risk group in this context (49, 50). PFT is especially important in those with HIV infection because respiratory symptoms can be caused by a wide range of etiologies.

There are several limitations of our study. The study is a cross-sectional assessment of a cohort recruited from a single HIV clinic, and it is possible that patients were more likely to participate if they were experiencing symptoms or less likely to participate if they were already being treated effectively, but CD4 cell counts and ARV use were similar in our cohort to the overall clinic population. Also, the results may not be applicable to all HIV populations. This cohort had a higher prevalence of smoking and IV drug use compared with prior studies (7, 8, 12), and the smoking prevalence of the cohort studied was higher than the clinic from which they were recruited. Smoking and IV drug use, however, are much more common among individuals with HIV infection than the general population (17, 51); therefore, the results of the study are likely applicable to many individuals with HIV infection. In addition, we found a high prevalence of respiratory symptoms and lung function abnormalities in our nonsmoking, non–IV drug using subjects. Although we performed pre-bronchodilator and post-bronchodilator spirometry, we might have also uncovered more bronchodilator responsiveness if we had performed methacholine challenge. We also were not able to measure lung volumes, which would have helped determine if restrictive lung disease was present concomitantly with obstruction or was a factor accounting for the diffusion impairment seen. An additional limitation was that CD4 cell counts and serum HIV RNA levels were gathered by chart review, not prospectively.

Conclusions

Our study is one of the first to describe respiratory symptoms and pulmonary function including post-bronchodilator spirometry and diffusing capacity in individuals with HIV infection during the era of combination ARV therapy. We have found a high prevalence of symptoms, diffusion impairment, and persistent airway obstruction. Diffusion impairment was the most common type of pulmonary function abnormality seen and was common even among nonsmokers. As was reported in the pre-ARV era, smoking and IV drug use are major risk factors associated with both symptoms and pulmonary function abnormalities. We extend the findings of a previous report documenting the association of ARV use and a higher risk of airway obstruction by confirming this association in a different population and demonstrating that ARV use is associated with persistent airway obstruction, but not with diffusing capacity or bronchodilator responsiveness. Finally, we found that PFT is likely underused in these symptomatic, high-risk patients with HIV infection. The HIV population may be more susceptible to diseases, such as COPD and lung cancer, and to mortality associated with smoking (7, 8, 12, 52–57), and smoking cessation counseling is of great importance in this population.

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