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HIV infection is associated with diffusing capacity impairment in women

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Abstract

Respiratory dysfunction is common in HIV, but few studies have directly assessed whether HIV remains an independent risk factor for pulmonary function abnormalities in the antiretroviral therapy era. Additionally, few studies have focused on pulmonary outcomes in HIV+ women.

We tested associations between risk factors for respiratory dysfunction and pulmonary outcomes in 63 HIV+ and 36 HIV-uninfected women enrolled in the Women's Interagency HIV Study. Diffusing capacity (DL_{CO}) was significantly lower in HIV+ women (65.5% predicted vs. 72.7% predicted, p=0.01), and self-reported dyspnea in HIV+ participants was associated with both DL_{CO} impairment and airflow obstruction. Providers should be aware that DL_{CO} impairment is common in HIV and that either DL_{CO} impairment or airflow obstruction may cause respiratory symptoms in this population.

Keywords

HIV; Pulmonary function; Pulmonary diffusing capacity; AIDS; Hepatitis C, chronic

INTRODUCTION

With combination antiretroviral therapy (ART), HIV has become a chronic disease in people with access to treatment, and new challenges have arisen in describing and managing the complications of long-term HIV infection. One emerging concern for treated HIV patients is

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the increased occurrence of chronic pulmonary dysfunction[1–3]. HIV is a risk factor for both prevalent and incident diagnosis of chronic obstructive pulmonary disease (COPD)[1, 2]. Several cross-sectional studies of pulmonary function testing (PFT) in HIV-infected cohorts have demonstrated a higher than expected prevalence of obstructive lung disease (ranging from 8–21% in mid-life adults)[3–6] and impaired diffusing capacity for carbon monoxide (DL_{CO}) which is strikingly prevalent (64% overall and 48% of never-smokers)[3]. Past studies measuring DLco are limited by the absence of an HIV-uninfected control group. Whether HIV is independently associated with impaired DLco in the current era is unknown.

Pulmonary complications in HIV-infected women, who comprise approximately 25% of the HIV-infected population in the United States[7], are understudied. Most current-era investigations examining lung function or respiratory symptoms have been primarily focused on men (66–100% male)[1–6, 8–10], and no studies have specifically compared pulmonary outcomes between HIV-infected and HIV-uninfected women. Characterizing pulmonary dysfunction among HIV-infected women is important since pulmonary risk behaviors are common in this group; for example, approximately 56% and 72% of HIV-infected women are current or former smokers, respectively[11]. Additionally, sex differences occur in the natural history of lung disease; female smokers may be more susceptible to COPD than males[12]. Improved understanding of the contributions of HIV infection to pulmonary outcomes and interactions between HIV and other pulmonary risk factors among females will help guide assessment, risk factor modification, and potential treatment approaches.

In this study, we assessed the effects of HIV infection on pulmonary function measures in women. We measured lung function in HIV-infected and HIV-uninfected women from a site of the Women's Interagency HIV Study (WIHS) and examined predictors of pulmonary function abnormalities and dyspnea among HIV-infected women.

METHODS

Participants

The WIHS cohort has been previously described and includes both HIV-infected women and HIV-negative controls with a similar high-risk profile and exposure history for HIV infection[13]. For this study, a subset of women were selected to match the overall cohort prevalence in HIV status, smoking history, and prevalence of respiratory symptoms in the WIHS cohort[13, 14] at the University of California, San Francisco. This matching was performed to avoid a bias in assessing the population if, for example, more smokers or more individuals with respiratory complaints volunteered for this pulmonary study, thus biasing the results. Participants were enrolled between April 2009 and November 2011 and were excluded if there were contraindications to pulmonary function testing, they were pregnant, or they were experiencing new or increasing respiratory symptoms in the past four weeks. Participants provided written informed consent, and study protocols were approved by the University of California, San Francisco Institutional Review Board.

Data collection

Demographic and clinical data in WIHS participants are collected at 6 month standardized assessments, as previously described[14]. We extracted data including age, race, ethnicity, self-reported alcohol use (any amount of alcohol during the previous 6 month period, or heavy alcohol use if >3 drinks per week), illicit drug use (ever-use or use in the 6 months before the WIHS visit that preceded pulmonary function testing), use and adherence to antiretroviral drugs, and history of bacterial and *Pneumocystis* pneumonia. Hepatitis C RNA positivity results were available at entry into WIHS, and CD4 count and plasma HIV RNA

level were available from each completed 6-month visit. Current smoking status and pack-years of smoking were determined from participant report at the time of pulmonary function testing. Dyspnea was assessed using a standardized questionnaire[15].

Spirometry and DL_{CO} measurements were performed per ATS/European Respiratory Society (ERS) standards and were adjusted for hemoglobin and carboxyhemoglobin[16, 17]; reference values that adjusted for race, age, and height were uses to determine percent predicted[18, 19]. Abnormal forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and DL_{CO} were defined as <80% predicted values, and moderately severe diffusing capacity impairment was defined by a DL_{CO} <60% predicted value[20].

Statistical Analysis

Statistical analyses were performed using Stata version 12 (StataCorp, College Station, TX). Characteristics of participants, pulmonary function variables, and dyspnea symptoms were compared between HIV-infected and HIV-uninfected women using t-tests, rank-sum, chi-squared, or Fisher exact tests where appropriate. To determine the independent association of HIV with pulmonary function values, linear regression models were created. Variables were selected for inclusion in the models if they had a univariate association to the pulmonary function parameter with $p<0.1$. Because spirometry and DL_{CO} prediction equations adjust for age and race, these variables were not included in these PFT models, but age and race were included in models for FEV_1/FVC ratios (which are not based on prediction equations). Multivariable model selection was done by a stepwise up/stepwise down process as previously described[21]. Excessive covariance was assessed using variance inflation factors. To assess for confounding by smoking, pack-years of smoking was added to the final models, and no significant effect was found (data not shown). To assess for HIV-related factors associated with lung function, similar modeling procedures were performed comparing HIV-infected women with CD4 counts ≤200 cells/μL and >200 cells/μL vs. HIV-uninfected women. Additionally, associations were modeled using data limited to HIV-infected participants including the following variables: ART use, current CD4 count, and current plasma HIV RNA copy level.

RESULTS

One hundred six WIHS participants were screened, but seven participants were not able to complete pulmonary function testing per ATS/ERS standards. Pulmonary function testing was completed by 63 HIV-infected and 36 HIV-uninfected participants (Table 1).

Spirometry

Overall, mean spirometry values were within normal limits for the cohort, and did not differ between HIV-infected and HIV-uninfected participants (Table 1). In multivariable analyses, several factors were associated with spirometry outcomes for the entire cohort (HIV-infected and HIV-uninfected) (Table 2); however, HIV was not identified as a risk factor.

Among the HIV-infected women, hepatitis C positivity was associated with lower post-bronchodilator FEV_1% predicted ($p=0.03$) and lower post-bronchodilator FVC% predicted ($p=0.04$), and history of bacterial or *Pneumocystis* pneumonia was associated with lower FEV_1/FVC, both pre- ($p=0.01$) and post-bronchodilator ($p=0.03$). Marijuana use was associated with greater pre-bronchodilator FVC% predicted ($p=0.045$) and post-bronchodilator FEV_1% predicted ($p=0.03$).

Diffusing capacity

Diffusing capacity was abnormal on average in this cohort and to a greater degree in HIV-infected compared to HIV-uninfected participants (p=0.01) (Table 1). Impaired diffusing capacity (DL_{CO} <80% predicted) was present similarly in HIV-infected and HIV-uninfected participants (p=0.27), but moderately impaired diffusing capacity (DL_{CO} <60% predicted) was more common in HIV-infected vs. HIV-uninfected participants (p=0.04). HIV-infected participants with a current CD4 count ≤200cells/μL had significantly worse DL_{CO}% predicted compared to HIV-uninfected women (59.5% [7.2%] vs. 72.7% [13.3%], p<0.001). Multivariable modeling demonstrated that worse DL_{CO}% predicted was associated with HIV infection (p=0.03) and hepatitis C RNA positivity (p=0.009) (Table 2A). Pack years of smoking did not influence DL_{CO} in this cohort. Although DL_{CO} <60% predicted was much more likely in those with airflow obstruction (FEV_1/FVC<0.7), 51.7% of participants with a DL_{CO} <60% predicted had no evidence of airflow obstruction.

In HIV-infected participants, DL_{CO} was associated with the current CD4 cell count (unadjusted coefficient per increase in 100 cells/μl, 0.0128; p=0.03), and lower DL_{CO} was independently associated with a history of bacterial or *Pneumocystis* pneumonia (p=0.007) and cocaine use (p=0.003), while better DL_{CO} was associated with marijuana use (p=0.03).

Dyspnea

Dyspnea was present in 33 (33.3%) participants and did not differ between HIV-infected and HIV-uninfected groups (34.9% vs. 30.6%, p=0.66). Dyspnea in HIV-infected participants was associated with pre- and post-bronchodilator airflow obstruction and presence of moderate diffusing capacity impairment (DL_{CO} <60% predicted) and tended to be more common in those with a history of pneumonia, use of intravenous drugs, and those with higher plasma HIV RNA copy numbers. In multivariable models, moderate diffusing impairment (OR, 3.6; p=0.03) remained significantly associated with dyspnea.

DISCUSSION

The current study is the first to compare spirometry and diffusing capacity in a cohort of HIV-infected and HIV-uninfected women. While spirometry values were similar between HIV-infected and HIV-uninfected participants, diffusing capacity was significantly lower among women infected with HIV, independent of other contributory variables.

This study confirms the high prevalence of impaired diffusing capacity among HIV-infected persons[3, 22], and it is the first to report that HIV infection is an independent risk factor for impaired DL_{CO} in women. We found that the impairment in diffusing capacity is related to HIV-associated immune impairment (CD4 count <200cells/μL) independent of other covariates (including smoking). Both prior post-ART studies found a strikingly high prevalence of HIV-associated diffusing capacity impairment (42–64%)[3, 22], but with no comparable HIV-uninfected control group. Inclusion of HIV-uninfected participants whose demographics and risk exposures were fairly comparable to the HIV-infected participants is a particular strength of the current study.

This study also describes contributors to DL_{CO} impairment among HIV-infected women in the ART era. Pre-ART era predictors of DL_{CO} reduction among HIV-infected persons included AIDS and associated conditions[23], and in the ART era, greater cumulative smoking history and use of *Pneumocystis* prophylaxis have been associated with worse diffusing capacity[3]. Among HIV-infected women in the current study, the majority of whom were on ART, history of bacterial or *Pneumocystis* pneumonia and cocaine use were associated with

worse DL_{CO}. There was also a positive correlation between DL_{CO} and current CD4 cell count among HIV-infected participants, suggesting a possible role of immunosuppression.

The mechanisms of impaired diffusing capacity associated with HIV remain unclear. Low diffusing capacity may be related to emphysema, which is overall increased in HIV-infected smokers[8]. In the current study, diffusing capacity impairment was strongly associated with airflow obstruction; however, impaired diffusing capacity was frequently present without obstruction. The latter pattern may represent early emphysema, but may also represent pulmonary vascular disease, interstitial lung disease, or primary cardiac dysfunction – all of which are reported to be more common in HIV-infected persons[2, 24–28].

An additional novel finding of this study is the association of HCV and worse airflow obstruction in HIV-infected participants. We also report HCV to be associated with lower diffusing capacity and obstruction in the overall cohort. Previous investigations have described deleterious effects of HCV on respiratory outcomes in the general population[29–31], theorized to be related mechanistically to systemic and pulmonary inflammation[30, 32–35]. The role of HCV on lung function may be important in the HIV population, as HCV/HIV co-infection is common,[36] and HCV viremia in the setting of HIV is associated with a state of immune activation[37, 38]. Intravenous drug use is a potential confounder of the relationship between HCV and respiratory function that we did not find in multivariable modeling, likely because ever-use of intravenous drugs was highly prevalent in the cohort, and we could not account for other unmeasured confounders associated with intravenous drug use. Examination of the associations of HCV, intravenous drug use, the precise drug(s) injected, and respiratory outcomes in cohorts with less pervasive intravenous drug exposure may help illuminate the differential effects of each exposure on pulmonary outcomes.

To evaluate the clinical impact of pulmonary dysfunction in this cohort, we also assessed the participants' respiratory symptoms. Other ART era studies report that respiratory symptoms are common in HIV,[3, 4, 10] and HIV is independently associated with increases in moderate dyspnea[10]. Although dyspnea was not more common in HIV-infected participants in our study, greater dyspnea was present in HIV-infected women with airflow obstruction and reduced DL_{CO}. These findings indicate that lung function abnormalities in HIV-infected women are not incidental findings, but are clinically relevant, with impact on symptoms and potentially quality of life[9].

The study has several limitations. Assessment of pulmonary outcomes was cross-sectional, and therefore could not address changes in respiratory function over time. The data generated from this cohort, which has a particularly high frequency of intravenous drug use and active HCV, may not be applicable to all populations. There was also a relatively low level of cumulative cigarette smoking in this cohort, which may explain the lack of association of pulmonary function with smoking. Finally, lung volumes, which may be helpful in elucidating causes of DL_{CO} reduction, were not measured.

This study provides the first analysis of pulmonary function abnormalities in a female cohort and is the first to report HIV as an independent risk factor for DL_{CO} impairment in women. Abnormal diffusing capacity and airflow obstruction were both associated with symptoms of shortness of breath among HIV-infected women, reinforcing the clinical relevance of the findings. Pulmonary function testing has been reported to be underutilized in the HIV-infected population[3], and previous studies have found that diffusing capacity abnormalities in HIV are related to emphysema, airflow obstruction, and echocardiographic evidence of pulmonary hypertension. This study provides further support for advocating appropriate diagnostic pulmonary testing, including diffusing capacity measurements, for patients with

respiratory symptoms. Future respiratory research in HIV will benefit from efforts to determine underlying causes and appropriate treatment of pulmonary dysfunction among persons with chronic HIV infection.

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Table 1

Participant characteristics by HIV status

	HIV-infected (n=63)	HIV-uninfected (n=36)	p-value
Age, mean years (SD)	49.1 (8.9)	43.7 (9.3)	0.005
African-American, n (%)	41 (65.1)	24 (66.7)	0.87
Hispanic, n (%)	4 (6.4)	4 (11.1)	0.46
Smoking status, n (%)			0.10
Never	16 (25.4)	14 (38.9)	
Former	18 (28.6)	4 (11.1)	
Current	29 (46.0)	18 (50.0)	
Pack-years smoking, median (range)	10.0 (0–78)	4.2 (0–38)	0.054
Alcohol use, any, n (%)	25 (39.7)	20 (55.6)	0.13
Heavy alcohol use, n (%)	9 (14.3)	6 (16.7)	0.75
Marijuana smoking, n (%)			
In the past 6 months	16 (25.4)	11 (30.6)	0.58
Ever	52 (82.5)	31 (86.1)	0.64
Cocaine use, n (%)			
In the past 6 months	1 (1.6)	2 (5.6)	0.30
During study enrollment	23 (36.5)	18 (50.0)	0.19
Intravenous drug use, n (%)			
In the past 6 months	6 (9.5)	2 (5.6)	0.49
Ever	34 (54.0)	11 (30.6)	0.02
Illicit drug use in the past 6 months, n (%)	25 (39.7)	14 (38.9)	0.94
Bacterial pneumonia, ever, n (%)	11 (17.5)	4 (11.8)	0.72
Pneumocystis pneumonia, ever, n (%)	4 (6.4)	0	--
Hepatitis C RNA positive, n (%)	21 (33.3)	6 (16.7)	0.07
Currently on HAART, n (%)	51 (81.0)		
CD4 T-cell counts			
Within past 6 months, median (range)	426 (3–1220)		
Nadir during study, median (range)	159 (0–797)		
Mean during study, median (range)	392 (68–1214)		
Plasma HIV RNA level (log copies/mL), median (range)	4.6 (3.9–12.2)		
Pre-BD FEV_1 % predicted, mean (SD)	97.0 (15.1)	92.4 (12.1)	0.12
Pre-BD FVC % predicted, mean (SD)	106.1 (15.5)	101.2 (14.5)	0.13
Pre-BD FEV_1/FVC, mean (SD)	0.74 (0.08)	0.75 (0.08)	0.48
Post-BD FEV_1 % predicted, mean (SD)	101.9 (14.2)	97.6 (12.9)	0.14
Post -BD FVC % predicted, mean (SD)	104.9 (15.2)	101.3 (14.8)	0.26
Post -BD FEV_1/FVC, mean (SD)	0.78 (0.07)	0.79 (0.08)	0.62
DL_{CO} % predicted, mean (SD)	**65.5 (13.7)**	**72.7 (13.3)**	**0.01**

BD – bronchodilator; DL_{CO} – diffusing capacity for carbon monoxide; FEV_1 – forced expiratory volume in the first second; FVC – forced vital capacity; HIV – human immunodeficiency virus; n – number; SD – standard deviation; RNA – ribonucleic acid

Table 2

Multivariable regression for factors independently associated with pulmonary function in the entire cohort (HIV-infected and HIV-uninfected)

	Linear regression	**coefficient**	**p-value**
Pre-BD FEV_1 % predicted	Hepatitis C RNA positive	−0.0678	0.03
Pre-BD FEV_1/FVC	Age at visit (per year)	−0.0028	0.001
Post-BD FEV_1 % predicted	Hepatitis C RNA positive	−0.0867	0.005
Post-BD FEV_1/FVC	Age at visit (per year)	−0.0028	<0.001
	Pack-years smoking (per 10)	−0.0108	0.04
DL_{CO} % predicted	HIV infection	−0.0586	0.03
	Hepatitis C RNA positive	−0.0812	0.009
B. Multivariable regression for factors independently associated with pulmonary function in HIV-infected participants only			
	Linear regression	coefficient	p-value
Pre-BD FVC % predicted	Marijuana use (ever)	0.1027	0.045
Pre-BD FEV1/FVC	History of bacterial or *Pneumocystis* pneumonia	−0.0613	0.01
Post-BD FEV1 % predicted	Marijuana use (ever)	0.0999	0.03
	Hepatitis C RNA positive	−0.0799	0.03
Post-BD FVC % predicted	Hepatitis C RNA positive	−0.0851	0.04
Post-BD FEV1/FVC	History of bacterial or *Pneumocystis* pneumonia	−0.0482	0.03
	Age at visit (per year)	−0.0021	0.04
DLco % predicted	History of bacterial or *Pneumocystis* pneumonia	−0.1026	0.007
	Cocaine use (during enrollment)	−0.0968	0.003
	Marijuana use (ever)	0.0930	0.03

BD – bronchodilator; DLco - diffusing capacity for carbon monoxide; FEV1 - forced expiratory volume in the first second; FVC - forced vital capacity