



## Pulmonary Function in HIV-Infected Recreational Drug Users in the Era of Anti-Retroviral Therapy

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### Abstract

**Background:** Individuals with HIV infection commonly have pulmonary function abnormalities, including airflow obstruction and diffusion impairment, which may be more prevalent among recreational drug users. To date, the relationship between drug use and pulmonary function abnormalities among those with HIV remains unclear.

**Objective:** To determine associations between recreational drug use and airflow obstruction, diffusion impairment, and radiographic emphysema in men and women with HIV.

**Methods:** Cross-sectional analysis of pulmonary function and self-reported recreational drug use data from a cohort of 121 men and 63 women with HIV. Primary outcomes were the presence (yes/no) of: 1) airflow obstruction, (pre- or post-bronchodilator forced expiratory volume in 1 second/forced vital capacity <0.70); 2) moderate diffusion impairment (diffusing capacity for carbon monoxide <60% predicted); and 3) radiographic emphysema (>1% of lung voxels <-950 Hounsfield units). Exposures of interest were frequency of recreational drug use, recent (since last study visit) drug use, and any lifetime drug use. We used logistic regression to determine associations between recreational drug use and the primary outcomes.

**Results:** HIV-infected men and women reported recent recreational drug use at 56.0% and 31.0% of their study visits, respectively, and 48.8% of men and 39.7% of women reported drug use since their last study visit. Drug use was not associated with airflow obstruction or radiographic emphysema in men or women. Recent crack cocaine use was independently associated with moderate diffusion impairment in women (odds ratio 17.6; 95% confidence interval 1.3-249.6, p=0.03).

**Conclusions:** In this cross-sectional analysis, we found that recreational drug use was common among HIV-infected men and women and recent crack cocaine use was associated with moderate diffusion impairment in women. Given the increasing prevalence of HIV infection, any relationship between drug use and prevalence or severity of chronic pulmonary diseases could have a significant impact on HIV and chronic disease management.

**Keywords:** HIV; COPD; Emphysema; Diffusion impairment; Drug use; Pulmonary function; Cocaine

### Introduction

As advances in HIV treatment have led to longer life expectancies for those with access to recommended care [1-3], chronic pulmonary diseases (e.g., chronic obstructive pulmonary disease, pulmonary arterial hypertension) have become more prevalent [4,5]. Respiratory symptoms are common in persons with HIV infection [6], as are

airflow obstruction and pulmonary diffusion impairment [7,8]. A recent analysis of 167 HIV-infected individuals found that 1 in 5 had irreversible airflow obstruction while 2 in 3 had diffusion impairment [6].

Recent studies have demonstrated associations between tobacco and antiretroviral therapy (ART) use and airflow obstruction in those with HIV [6,7]. HIV infection is also an independent risk factor for impaired diffusion capacity in both men and women; though causes of this impairment remain unclear [9,10]. Potential mechanisms for these abnormalities include lung injury from opportunistic infections and

altered microbial colonization, aberrant inflammatory responses associated with HIV infection and/or other pathogens, and the effects of chronic ART [6,7,11,12].

Behavioral risk factors such as recreational drug use may also be important, as HIV-infected populations have a high prevalence of drug use [13-15]. Estimates of drug use among HIV-infected populations have varied significantly, depending on the time period and specific subgroup sampled [16-18]. Data from the National Survey of Drug Use and Health suggest that approximately 80% of HIV-infected persons in the U.S. have used a recreational drug at some point in their life, including 16% who reported using an intravenous drug [16]. Estimates of current marijuana use among HIV-infected persons in the U.S. have ranged from 12-23% [19-21] and among a recent sample of HIV-infected men, more than 20% reported recent use of stimulants, including crack cocaine and methamphetamines [22].

Among the HIV-uninfected, a number of acute and chronic pulmonary complications of recreational drug use have been identified [23,24]. Heroin use is associated with an increased risk for pneumonia, as well as acute, non-cardiogenic pulmonary edema. Stimulant use, such as amphetamines, cocaine and crack cocaine, can cause pulmonary barotrauma and acute pulmonary edema or hemorrhage when used by inhalation. When used intravenously, the same drugs may lead to the development of pulmonary arterial hypertension or granulomatous responses due to reactions from particulate matter that often contaminate the injected drug. Though marijuana use is associated with acute bronchodilation and long-term side effects, such as chronic cough, wheezing, and sputum production [25,26], no clear association between its use and serious pulmonary conditions has been identified [25].

Despite the relationship between recreational drug use and pulmonary complications in HIV-uninfected persons, the relationship between drug use and pulmonary function in those with HIV remains ill-defined [25-28]. Recent studies have identified a relationship between cocaine and marijuana use and reduced diffusing capacity in HIV-infected women [9], and a relationship between intravenous drug use and airflow obstruction in HIV-infected men and women [6]. Another study demonstrated that lung function decline among intravenous drug users may disproportionately affect those with low CD4 counts and high HIV RNA levels [29]. However, in-depth studies of drug use and lung function in HIV have not been done; nor has the relationship between drug use and radiographic emphysema been evaluated. The aim of this study was to determine associations between recreational drug use and airflow obstruction, diffusion impairment, and radiographic emphysema in men and women with HIV.

## Methods

We conducted a cross-sectional analysis of 121 men and 63 women 18 years of age or older with documented HIV infection who were followed longitudinally within the Multicenter AIDS Cohort Study (MACS) [30] and the Women's Interagency HIV Study (WIHS) [31] cohorts. Participants were outpatients without acute respiratory illness who were recruited from the University of Pittsburgh, University of California Los Angeles, and University of California San Francisco to participate in the University of Pittsburgh Lung HIV Cohort. Participants were selected to reflect the distributions of tobacco use and prevalence of respiratory symptoms within the MACS and WIHS

parent studies [4,9,10,30]. Participants completed questionnaires at the time of enrollment and at study follow-up appointments (approximately every 6 months), and completed pulmonary function testing (PFTs) and computed tomography (CT) examination between January 1, 2009 and February 15, 2012. Institutional review boards at each site approved this study, and all subjects provided written, informed consent.

## Participant characteristics

We abstracted sociodemographic data from study questionnaires, including: age, gender, race/ethnicity, and marital and educational statuses. We used questionnaire data to identify tobacco use, alcohol consumption per week, history of bacterial or *Pneumocystis jirovecii* pneumonia, and use of ART, defined as use of three or more drugs from two or more categories [32]. We used self-reported data collected during study visits to identify comorbid asthma diagnosis and bronchodilator use in the previous 3 months. We identified a history of hepatitis C infection by questionnaire and serologic data collected during study visits, and abstracted HIV-specific clinical data from MACS and WIHS, including nadir and current CD4 counts, and current HIV RNA level.

## Recreational drug use

We used questionnaire responses to characterize recent (since last study visit) or any lifetime use of recreational drugs, including: any intravenous drug, marijuana, crack (alkaloid cocaine), cocaine, and heroin. Drug use survey questions differed between cohorts; thus, we characterized methamphetamine use in women, and use of "uppers" (i.e., stimulants, including methamphetamines) and "poppers" (amyl nitrites) in men. We then created a proxy variable to estimate frequency of drug use by calculating the percentage of all study visits in which a participant reported recent drug use.

## Pulmonary function testing and computed tomography

Participants completed PFTs according to American Thoracic Society guidelines to obtain pre- and post-bronchodilator spirometry, and diffusing capacity for carbon monoxide (DLCO) [33,34]. Hankinson [35] and Neas [36] equations were used for spirometry and DLCO percent predicted values, respectively. Both equations adjust for age, gender, height and race. Predicted DLCO was additionally adjusted for hemoglobin and carboxyhemoglobin.

Helical, non-contrast, CT examinations were performed at the three institutions under similar protocols using 64-detector scanners with the subjects supine and holding their breath at end-inspiration. CT data were acquired at 120-peak kilovoltage and 100-milliampere seconds with images reconstructed using General Electric's "standard" or Siemens' "B31f" kernel at 0.625 mm or 0.75 mm section thickness. Voxels depicting the lung were segmented from the CT images [37]. Those with a Hounsfield unit (HU) value less than -950 were considered to represent emphysema based on the density mask approach [38,39].

## Statistical analysis

We analyzed participants from each cohort separately because of significant baseline differences in sociodemographic, clinical and recreational drug use characteristics. Primary outcomes were the presence of: 1) airflow obstruction, defined as a pre- or post-

bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.70; 2) moderate diffusion impairment defined as DLCO <60% predicted; and 3) radiographic emphysema (>1% of lung voxels < -950 HU). We selected moderate diffusion impairment as an outcome because mild impairment (DLCO <80% predicted) is highly prevalent in HIV-infected populations [6,11]. Independent variables of interest were frequency of recreational drug use, recent (yes/no) drug use, and any lifetime (yes/no) drug use. We used logistic regression to determine associations between sociodemographic, clinical, and drug use characteristics and the primary outcomes. In multivariable models, we included ART use and cumulative pack-years of tobacco use as covariates based on their a priori clinical significance. We selected all other covariates based on significance in bivariate analyses (p<0.2). For all significant outcomes, we tested whether the association between drug use and the outcomes differed based on CD4 count and HIV RNA level by testing an interaction term that included current CD4 count, log HIV RNA level, and the independent variable.

Assuming an alpha level of 0.05 and 80% power, the minimum effect size required to detect a statistically significant result in the outcome was 11% and 16% in the MACS and WIHS cohorts, respectively. We analyzed all data using SAS Version 9.2 (SAS, Inc., Cary, NC).

## Results

### Participant characteristics

Of 121 HIV-infected men enrolled from the MACS cohort, the mean age was 53 and 78.5% reported current or former tobacco use (Table 1). Men had a median CD4 count of 575 cells/microliter (IQR 440-794), median HIV RNA level of <40 copies/mL, and 86.0% reported taking ART since their previous visit.

Of 63 HIV-infected women enrolled from the WIHS cohort, the mean age was 49 and 80.9% reported current or former tobacco use (Table 1). Women had a median CD4 count of 426 cells/microliter (IQR 264-677), median HIV RNA level of 102 copies/mL, and 81.0% reported taking ART since their previous visit.

### Recreational Drug Use

Men reported recent recreational drug use at 56.0% of all study visits and 48.8% reported using at least 1 drug since their previous visit (Table 1). A large proportion of men reported some lifetime use of marijuana (81.0%), poppers (71.1%), cocaine (62.8%), and uppers (38.8%), and 14.9% reported some lifetime use of intravenous drugs (Table 2).

Women reported recent recreational drug use at 31.0% of all study visits and 39.7% reported using at least 1 drug since their previous visit (Table 2). A large proportion of women reported some lifetime use of marijuana (82.5%) and intravenous drugs (54.0%) (Table 2).

Characteristic	(Men's Multicenter AIDS Cohort Study (n=121))	Women's Interagency HIV Study (n=63)
Age, mean (SD)	53.1 (7.5)	49.1 (8.9)
Female, n (%)	0 (0)	63 (100)
<b>Race, n (%)</b>		

White	100 (82.6)	23 (36.5)
Black	21 (17.4)	40 (63.5)
Hispanic, n (%)	3 (2.5)	5 (7.9)
Completed high school, n (%)	114 (94.2)	47 (74.6)
<b>Marital status, n (%)</b>		
Never married	--	21 (33.3)
Married	--	22 (34.9)
Divorced or widowed	--	20 (31.8)
<b>Alcohol consumption, n (%)</b>		
None	69 (57.0)	38 (60.3)
1-2 drinks per week	22 (18.2)	16 (25.4)
>2 drinks per week	30 (24.8)	9 (14.3)
<b>Clinical History</b>		
Number of study visits attended, mean (SD)	35 (16.0)	26 (6.3)
<b>Tobacco use, n (%)</b>		
Never	26 (21.5)	12 (19.1)
Former	58 (47.9)	23 (36.5)
Current	37 (30.6)	28 (44.4)
Cumulative pack-years tobacco use, median (IQR)	8.2 (0-33.2)	3.0 (0.04-12.4)
Asthma diagnosis, n (%)	15 (12.4)	22 (34.9)
Bronchodilator use in previous 3 months, n (%)	12 (9.9)	11 (17.5)
Hepatitis C infection, n (%)	13 (10.7)	30 (47.6)
History of bacterial or Pneumocystis jirovecii pneumonia, n (%)	40 (33.1)	14 (22.2)
ART use since last visit, n (%)	104 (86.0)	51 (81.0)
Current CD4 (cells/μL), median (IQR)	575 (440-794)	426 (264-677)
Nadir CD4 (cells/μL), median (IQR)	269 (155-358)	159 (65-286)
Current HIV RNA level (copies/mL), median (IQR)	<40 (40-40)	102 (48-727)
<b>Recreational Drug Use</b>		
Percentage of total visits reporting recent drug use, median % (IQR)	56 (18-87)	31 (3-75)
Any drug use since last visit, n (%)	59 (48.8)	25 (39.7)
<b>Pulmonary Function</b>		
<b>Airflow obstruction</b>		

Post-BD FEV1/FVC ratio <0.70, n (%)	16 (13.2)	7 (11.1)
Post-BD FEV1/FVC ratio, mean (SD)	0.78 (0.08)	0.78 (0.07)
<b>Diffusion impairment</b>		
DLCO % predicted <80%, n (%)	65 (53.7)	53 (84.1)
DLCO % predicted <60%, n (%)	16 (13.2)	23 (36.5)
DLCO % predicted, mean (SD)	79 (19.0)	65 (14.0)
Radiographic emphysema, n (%)	64 (65.3)	9 (15.3)

**Table 1:** HIV: Human Immunodeficiency Virus; SD: Standard Deviation; IQR: Interquartile Range; ART: Antiretroviral Therapy;  $\mu$ L: Microliter; BD: Bronchodilator; FEV1: Forced Expiratory Volume in 1 second; FVC: Forced Vital Capacity; DLCO: Diffusing Capacity for Carbon Monoxide. aSurvey questions differ between MACS and WIHS. Unavailable data represented with "--". bCT data available for 98 men and 59 women. Radiographic emphysema defined as >1% of lung voxels <-950 Hounsfield units.

### Recreational drug use and airflow obstruction

Airflow obstruction was present in 13.2% of men and 11.1% of women (Table 1). In bivariate and multivariable analyses, there were no statistically significant associations between recent, frequent or lifetime recreational drug use and airflow obstruction in men or women (Table 2). In multivariable analyses, men who reported recent marijuana use were somewhat more likely to have airflow obstruction (odds ratio [OR] 2.8; 95% confidence interval [CI] 0.9-8.0;  $p=0.06$ ).

### Recreational drug use and moderate diffusion impairment

Moderate diffusion impairment was present in 13.2% of men and 36.5% of women (Table 1). In bivariate analyses, there were no statistically significant associations between recent, frequent or lifetime recreational drug use and moderate diffusion impairment in men (Table 2). Women who reported any lifetime use of intravenous drugs were somewhat more likely to have moderate diffusion impairment (OR 2.8; 95% CI 0.9-8.3;  $p=0.06$ ) and women who reported recent crack use were more likely to have moderate diffusion impairment (OR 20.8; 95% CI 2.4-180.8;  $p<0.01$ ).

In multivariable analyses, there were no statistically significant associations between recent, frequent or lifetime recreational drug use and moderate diffusion impairment in men (Table 2). In multivariable analyses that adjusted for ART use, cumulative pack-years of tobacco use, marital status, hepatitis C infection, and history of bacterial or *Pneumocystis pneumonia*, women who reported recent crack use were more likely to have moderate diffusion impairment (OR 17.6; 95% CI 1.3-249.6;  $p=0.03$ ). There was no statistically significant interaction between recent crack use and current CD4 count and log HIV RNA levels.

### Recreational drug use and radiographic emphysema

Radiographic emphysema was present in 65.3% of 98 men and 15.3% of 59 women with available CT data (Table 1). In bivariate and multivariable analyses, there were no statistically significant associations between recent, frequent or lifetime recreational drug use and radiographic emphysema in men or women (Table 2).

### Discussion

In this cross-sectional analysis of 121 men and 63 women with HIV, we found that recreational drug use, and lung function abnormalities, such as airflow obstruction, moderate diffusion impairment, and radiographic emphysema were all common. Overall, approximately 1 in 10 had clinical airflow obstruction, while 13% of men and 37% of women had moderate diffusion impairment, and 65% of men and 15% of women had radiographic evidence of emphysema. We also observed an independent association between recent crack cocaine use and moderate diffusion impairment in women, and no relationship between drug use and airway obstruction or radiographic emphysema in either cohort.

While the causes of diffusion impairment in HIV-uninfected persons have been well documented (e.g., emphysema, pulmonary vascular disease), the mechanism by which diffusion impairment develops in those with HIV remains unclear. We have previously shown that cocaine use is associated with a worse absolute diffusing capacity in women, but the relationship was not examined in detail, nor had this relationship been evaluated in men with HIV [9]. This study adds to a growing body of evidence suggesting that cocaine exposure has a unique impact on diffusion abnormalities in HIV-infected persons [11,40]. However, whether cocaine exposure accelerates or independently causes these diffusion abnormalities remains unclear. *In vitro* models have suggested that cocaine exposure has an additive effect on endothelial injury and dysfunction in persons with HIV [41]. Pulmonary vascular disease, which is more common among women and those with HIV, may have contributed to the diffusion impairment in this cohort [42], and perhaps, cocaine exposure causes diffusion impairment through an additive or synergistic relationship with HIV-induced pulmonary hypertension. Additionally, cocaine exposure through smoking crack cocaine may cause this damage through direct toxicity. Importantly, crack cocaine use was not associated with radiographic emphysema in this study, suggesting that the diffusion abnormalities in this group were not secondary to emphysema. Notably, the association between cocaine use and diffusion impairment remains unclear even in HIV-uninfected populations [27,43-45].

There are several limitations of this study. First, we analyzed a relatively small, gender-stratified sample of participants who had a high prevalence of multi-substance use, which limited our ability to detect the independent effects of individual drugs. Second, the cross-sectional nature of these analyses limits our ability to make causal inferences regarding the relationship between recreational drug use and the primary outcomes. Third, using available data, we created a proxy variable to estimate frequency of drug use. Given the complexity of drug use in this cohort, future analyses would benefit from detailed questionnaire data that precisely quantify frequency and quantity of drug use and delineate the complicated exposure histories of multi-substance users. Fourth, we did not account for duration or history of *Pneumocystis prophylaxis*, which may affect pulmonary function by altering microbial colonization and inflammation within pulmonary



tissue. Finally, most participants had relatively controlled HIV and more than 80% were on ART. These characteristics may have masked an interaction between drug use and lung function that differentially affects those with poorly controlled HIV, as a recent study of intravenous drug users showed that markers of poorly controlled HIV

were associated with accelerated decline in both FEV1 and FVC [29]. Though we tested whether the relationship between drug use and the primary outcomes was dependent on CD4 cell count and viral load, this analysis was limited by our sample size.

Recreational Drug Use Characteristic	(Men's) Multicenter AIDS Cohort Study				Women's Interagency HIV Study			
	n=121				n=63			
	Drug Use	Airflow Obstruction	Moderate Diffusion Impairment	Radiographic Emphysema	Drug Use	Airflow Obstruction	Moderate Diffusion Impairment	Radiographic Emphysema
	%	OR (95% CI)	OR (95% CI)	OR (95% CI)	%	OR (95% CI)		
Percentage of total visits reporting recent drug use	56	1.41 (1.00-1.98)	1.04 (0.77-1.40)	1.07 (0.85-1.36)	31	1.19 (0.78-1.82)	1.17 (0.88-1.55)	1.07 (0.72-1.59)
Since last visit	n (%)				n (%)			
Any drug	59 (48.8)	1.91 (0.65-5.62)	1.41 (0.49-4.08)	1.53 (0.66-3.53)	25 (39.7)	2.22 (0.45-10.9)	2.27 (0.79-6.49)	0.91 (0.22-3.78)
Any intravenous drug	1 (0.8)	§	§	§	6 (9.5)	1.70 (0.17-17.1)	4.0 (0.67-23.8)	0.89 (0.09-8.65)
Marijuana	36 (29.8)	2.75 (0.94-8.03)	2.04 (0.70-5.98)	0.79 (0.30-2.06)	16 (25.4)	2.48 (0.49-12.5)	1.06 (0.33-3.43)	0.70 (0.15-3.22)
Crack	8 (6.7)	§	0.92 (0.11-8.05)	2.95 (0.47-18.6)	9 (14.3)	1.00 (0.11-9.44)	20.8 (2.4-180.8)	1.52 (0.17-13.9)
Cocaine	13 (10.8)	1.21 (0.24-6.03)	0.51 (0.06-4.22)	2.54 (0.64-10.2)	1 (1.6)	§	§	§
Heroin	1 (0.8)	§	§	§	6 (9.5)	1.70 (0.17-17.1)	4.0 (0.67-23.8)	0.89 (0.09-8.65)
"Poppers"	25 (20.7)	1.33 (0.39-4.56)	0.87 (0.23-3.33)	1.41 (0.53-3.75)	---	---	---	---
"Uppers"	6 (5.0)	§	1.32 (0.14-12.1)	0.92 (0.16-5.31)	---	---	---	---
Methamphetamine	---	---	---	---	2 (3.2)	§	§	§
Any lifetime use	n (%)				n (%)			
Any intravenous drug	18 (14.9)	2.37 (0.65-8.62)	1.04 (0.21-5.19)	1.25 (0.41-3.84)	34 (54.0)	1.16 (0.24-5.65)	2.79 (0.94-8.27)	0.54 (0.12-2.41)
Marijuana	98 (81.7)	§	1.67(0.35-7.93)	0.80 (0.28-2.30)	52 (82.5)	0.48(0.08-2.86)	0.41 (0.11-1.52)	§
Crack	38 (60.3)	2.16 (0.40-11.6)	1.96 (0.47-8.22)	0.70 (0.23-2.13)	---	---	---	---
Cocaine	76 (62.8)	1.61 (0.48-5.40)	2.44 (0.65-9.18)	1.52 (0.62-3.72)	---	---	---	---
Crack, cocaine or heroin	---	---	---	---	51 (80.9)	0.26 (0.05-1.34)	1.94 (0.47-8.03)	0.50 (0.06-4.47)
"Poppers"	86 (71.1)	1.90 (0.51-7.13)	0.47 (0.16-1.37)	1.63 (0.61-4.38)	---	---	---	---
"Uppers"	47 (38.8)	1.38 (0.46-4.10)	1.01 (0.33-3.05)	0.80 (0.34-1.89)	---	---	---	---
Methamphetamine	---	---	---	---	4 (6.4)	§	0.56 (0.06-5.73)	§

**Table 2:** HIV: Human Immunodeficiency Virus; AIDS: Acquired Immunodeficiency Syndrome; OR: Odds Ratio; CI: Confidence Interval; poppers: Amyl Nitrites; uppers: Stimulants, Including Methamphetamines. aAirflow obstruction defined as a pre- or post-bronchodilator forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) <0.70; moderate diffusion impairment defined as diffusing capacity for carbon monoxide (DLCO) <60% predicted; radiographic emphysema defined as >1% of lung voxels < -950 Hounsfield units. bSurvey questions differ between MACS and WIHS. Unavailable data represented with "---". cOdds ratio represents the increase in odds of the primary outcome for each 20% increase in the percentage of total study visits reporting recent drug use. § No observations available for analysis

## Conclusions

In summary, we investigated recreational drug use characteristics and pulmonary function among HIV-infected men and women in the era of antiretroviral therapy, and observed an independent association

between recent crack cocaine use and moderate diffusion impairment in women. Recreational drug use is common among those with HIV. Given the increasing prevalence of HIV, any potential relationship between drug use and the prevalence of chronic pulmonary diseases

could have a significant impact on HIV and chronic disease management. Future studies aimed at addressing this question would benefit from detailed information regarding frequency and quantity of recreational drug use and the complicated exposure histories of multi-substance users.

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