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Lung Function in Women With and Without Human Immunodeficiency Virus

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Background. Prior studies have found that human immunodeficiency virus (HIV) infection is associated with impaired lung function and increased risk of chronic lung disease, but few have included large numbers of women. In this study, we investigate whether HIV infection is associated with differences in lung function in women.

Methods. This was a cross-sectional analysis of participants in the Women's Interagency HIV Study, a racially and ethnically diverse multicenter cohort of women with and without HIV. In 2018–2019, participants at 9 clinical sites were invited to perform spirometry. Single-breath diffusing capacity for carbon monoxide (DL_{CO}) was also measured at selected sites. The primary outcomes were the post-bronchodilator forced expiratory volume in 1 second (FEV_1) and DL_{CO}. Multivariable regression modeling was used to analyze the association of HIV infection and lung function outcomes after adjustment for confounding exposures.

Results. FEV_1 measurements from 1489 women (1062 with HIV, 427 without HIV) and DL_{CO} measurements from 671 women (463 with HIV, 208 without HIV) met standards for quality and reproducibility. There was no significant difference in FEV_1 between women with and without HIV. Women with HIV had lower DL_{CO} measurements (adjusted difference, –0.73 mL/min/mm Hg; 95% confidence interval, −1.33 to −.14). Among women with HIV, lower nadir CD4 + cell counts and hepatitis C virus infection were associated with lower DL_{CO} measurements.

Conclusions. HIV was associated with impaired respiratory gas exchange in women. Among women with HIV, lower nadir CD4 + cell counts and hepatitis C infection were associated with decreased respiratory gas exchange.

Keywords. HIV; hepatitis C; pulmonary function testing; lung disease; comorbidity.

Human immunodeficiency virus (HIV) infection is associated with increased risk for comorbidities, including chronic lung disease [1–4]. Persons with HIV (PWH) experience increased occurrence of chronic obstructive pulmonary disease (COPD), pulmonary hypertension, and lung cancer [5–7]. How HIV contributes to the pathogenesis of comorbid respiratory illnesses is an area of active investigation [8]. Studies of respiratory physiology, that is, lung function, among PWH are vital to understanding how HIV affects respiratory health.

There is accumulating evidence that HIV infection adversely affects aspects of respiratory physiology including expiratory airflow, vital capacity, and respiratory gas exchange, but studies of lung function among PWH have included far fewer women than men [9–17]. Because sex differences influence susceptibility to and the natural history of lung diseases [18–21], there is uncertainty whether effects of HIV on respiratory physiology are accentuated or attenuated by sex. Since women comprise 52% of all PWH worldwide, there is an urgent and unmet need to include women in studies of HIV and lung function [22].

The Women's Interagency HIV Study (WIHS) is one of the largest prospective cohort studies of women with and without HIV. An earlier study of lung function in 99 WIHS participants (63 with HIV, 36 without HIV) at the San Francisco research site found that HIV infection was associated with impaired respiratory gas exchange [11]. However, the small sample size of this study limited capacity for adjustment of confounding exposures, and the single-center design increased uncertainty

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regarding external validity. As such, lung function was measured across the entire WIHS cohort in 2018 and 2019. The results of this effort are reported here. The primary objective was to investigate whether, in women, HIV infection is associated with impairment in 2 key clinical dimensions of lung function: expiratory airflow and respiratory gas exchange. Among women with HIV, the relationships between measures of HIV disease severity and hepatitis C virus (HCV) infection with lung function outcomes were also evaluated.

METHODS

Participants and Study Design

The WIHS, now a part of the Multicenter AIDS Cohort Study (MACS)-WIHS Combined Cohort Study, was established in 1993 and has been described in prior publications [23, 24]. From 1 April 2018 to 30 September 2019, WIHS participants at all 9 clinical sites were invited to complete spirometry measurements and, at a subset of 5 sites with the necessary equipment, measurements of single-breath diffusing capacity. Participants were excluded if they were pregnant or had contraindications to lung function testing, such as a recent respiratory infection. Local institutional review boards approved the protocol, and participants provided informed consent.

Measurements

Spirometry

Key spirometric measurements include the forced expiratory volume in 1 second (FEV_1), which is the volume of gas expelled in the first second of a maximal forced exhalation maneuver, and the forced vital capacity (FVC), which is the total volume of gas expelled in a maximal forced exhalation maneuver. Participants performed spirometry before and after inhaling 360 µg of albuterol via metered-dose inhaler. Measurements were made using an Easy on-PC or EasyOne Pro device (ndd Medizintechnik AG, Zurich, Switzerland). Quality was assessed in accordance with published standards [25]. Further details regarding quality control are described in the Supplementary Methods. Reference values were calculated from published equations derived from the Third National Health and Nutrition Examination Survey [26].

Single-Breath Diffusing Capacity for Carbon Monoxide

The single-breath diffusing capacity for carbon monoxide (DL_{CO}), also referred to as the transfer factor for carbon monoxide, is a measurement of carbon monoxide uptake by the lungs during a single breath held for 10 seconds. Measurements were made using an EasyOne Pro device and were adjusted for hemoglobin and carboxyhemoglobin concentrations. Quality was assessed in accordance with international standards, and reference values were calculated from published equations derived from the First National Health and Nutrition Examination Survey [27, 28].

Demographic, Exposure, and Clinical Data

Data were collected from WIHS participants at semiannual visits using standardized instruments. Key exposures included cigarette smoking (measured in lifetime pack-years) and substance use; marijuana, cocaine, methamphetamine, and heroin exposures were categorized as never use, current use (any use reported in the 6 months prior), and former use (any lifetime use, but no use reported in the 6 months prior). HCV infection was defined as HCV seropositivity upon cohort enrollment or at any time up to lung function testing.

Statistical Analyses

The primary exposure of interest was HIV infection. The coprimary outcomes of interest were the post-bronchodilator FEV_1 and the DL_{CO}. Because the FEV_1 and DL_{CO} are affected by age, sex, height, and race, these measurements are compared to standardized reference values and reported as a percentage of the predicted value for age, sex, height, and race. Secondary outcomes include the FVC and the post-bronchodilator FEV_1-to-FVC ratio.

In addition to their analyses as continuous variables, FEV_1 and DL_{CO} were also analyzed as dichotomous variables (less than 80% and 60% of predicted for mild and moderate impairment, respectively). The FEV_1-to-FVC ratio was analyzed as a dichotomous variable (greater than or equal to vs less than 0.7, the threshold for diagnosis of COPD) as well.

Characteristics of participants with and without HIV were compared using *t* tests for continuous variables and the Fisher exact test for categorical variables.

Linear and logistic regression models were used to compare the primary outcomes between participants with and without HIV. A causal model (see the directed acyclic graph in Supplementary Figure 1) identified possible confounding exposures in published literature: cigarette smoking [29], marijuana use [29], cocaine use [30, 31], heroin or injection drug use [32], years of education [33, 34], and HCV infection [11]. Adjusted regression models included these exposures as covariates.

A secondary analysis restricted to participants with HIV examined the relationship between indicators of HIV severity and lung function outcomes. Exposure variables of interest were the CD4 + cell count at the time of lung function testing, lifetime nadir CD4 + cell count, lifetime peak HIV RNA, and cumulative years of exposure to antiretroviral therapy (ART).

Informed by prior research suggesting that HCV infection may affect respiratory gas exchange [11, 35–39], additional secondary analyses compared DL_{CO} between HCV seropositive and seronegative participants. For this analysis, the participants with and without HIV were analyzed separately. Unadjusted

and adjusted regression models estimated the association of HCV infection with DL_{CO}.

RESULTS

Of the 2022 women who attended at least 1 study visit during the lung function testing window, 1736 met eligibility criteria and consented to study participation. Post-bronchodilator spirometry measurements from 1489 participants (1062 with HIV, 427 without HIV) and DL_{CO} measurements from 671 participants (463 with HIV, 208 without HIV) met standards for data quality (see Supplementary Figures 2 and 3 for participant flow diagrams).

Characteristics of Participants With Spirometry Measurements

The median age was 52 years (interquartile range, 44 to 58). Two-thirds (66%) were current or former cigarette smokers (Table 1). Participants with HIV were older, less likely to report ever smoking or using illicit substances, and more likely to be HCV seropositive but were otherwise similar to participants without HIV. Among participants with HIV, nearly all (92%) reported current ART, 69% had undetectable HIV RNA, and the median current CD4 + cell count was 700 cells/mm^3.

The characteristics of the 671 participants with valid DL_{CO} measurements were similar to those of the 1489 participants with valid spirometry data (Supplementary Table 1).

Association Between HIV Infection and Spirometric Outcomes

Among the 1489 participants with valid post-bronchodilator spirometry data, the median percent predicted FEV_1 was similar for participants with and without HIV (90.3% vs 91.8%; Table 2). The difference in FEV_1 between participants with and without HIV was not statistically significant in either unadjusted or adjusted analyses.

Participants with HIV had a lower percent predicted FVC than participants without HIV (unadjusted mean difference, −1.8). However, after adjustment for confounding exposures, the confidence intervals did not exclude the possibility of no effect.

The median FEV_1-to-FVC ratio was the same for participants with and without HIV (0.82). The prevalence of COPD, defined as an FEV_1-to-FVC ratio of less than 0.7, was not significantly different between participants with and without HIV (10% vs 11%). Using an alternative criterion to define COPD as an FEV1-to-FVC ratio less than the lower limit of normal yielded similar results.

Association Between HIV Infection and Respiratory Gas Exchange

Participants with HIV had lower DL_{CO} measurements than participants without HIV (Table 2). After adjustment for confounding exposures, HIV infection was associated with a lower percent predicted DL_{CO} of 4.8 (95% confidence interval [CI], −7.7 to −1.9; $P = .001$).

In a sensitivity analysis, the inclusion of study site and enrollment cohort in the regression model did not appreciably change the estimate of effect of HIV infection on DL_{CO} (−4.9; 95% CI, −7.6 to −2.1; $P = .001$).

A sensitivity analysis that modeled the diffusing capacity outcome in native units (mL/min/mm Hg) while adjusting for both confounding exposures as well as factors known to affect the outcome (age, height, and race) confirmed the association of HIV infection with lower DL_{CO}. On average, the DL_{CO} for participants with HIV was 0.73 mL/min/mm Hg less than for participants without HIV (95% CI, −1.33 to −.14; $P = .02$).

When DL_{CO} was modeled as a dichotomous outcome, participants with HIV had 1.47 times the odds of having mild diffusion impairment or worse (DL_{CO} less than 80% of predicted) compared with participants without HIV, after adjustment for confounding exposures (95% CI, 1.02 to 2.12; $P = .04$). We did not find that participants with HIV were significantly more likely to have moderate diffusion impairment or worse (DL_{CO} less than 60% of predicted) compared with participants without HIV (adjusted odds ratio, 1.37; 95% CI, .69 to 2.72; $P = .37$). However, the small number of participants with this degree of diffusion impairment may have limited statistical power to evaluate this threshold.

Participants who underwent diffusing capacity measurements had spirometry results that were similar to those for participants who did not (see Supplementary Table 2).

Indicators of HIV Severity and Lung Function

Among participants with HIV, a greater cumulative number of years of ART was associated with a larger FEV_1 (Table 3); for every 10 years of ART, the percent predicted FEV_1 was higher by 2.5 (95% CI, .8 to 4.2; $P = .004$). For diffusing capacity, a lower lifetime nadir CD4 + cell count was associated with a lower DL_{CO}; for every decrease in 100 cells/μL, the percent predicted DL_{CO} was lower by 1.0 (95% CI, −.3 to −1.7; $P = .004$).

Hepatitis C and Respiratory Gas Exchange

In multivariable regression modeling of the association between HIV and DL_{CO}, HCV infection was associated with lower percent predicted DL_{CO} (adjusted mean difference, −7.4; 95% CI, −11.4 to −3.3). Secondary analyses stratified participants by HIV status to model the relationship between HCV infection and DL_{CO} among participants with HIV and participants without HIV separately (Table 4). Among participants with HIV, HCV infection was associated with a lower percent predicted DL_{CO} by 8.3 after adjustment for confounding exposures, including cigarette smoking and heroin use (95% CI, −13.3 to −3.3; $P = .001$). Among participants without HIV, the point estimate for the effect of HCV infection on percent predicted DL_{CO} was of similar magnitude (−6.3; 95% CI, −13.4 to .9; $P = .09$).

To investigate whether any effect of HCV on impaired DL_{CO} was mediated by the development of liver fibrosis, a sensitivity

Table 1. Characteristics of Participating Women With and Without Human Immunodeficiency Virus at the Time of Pulmonary Function Testing

Characteristic	With HIV (n = 1062)	Without HIV (n = 427)	*P* Value
Age, median (Q1–Q3), y	52 (45–58)	50 (42–57)	.01
Body mass index, median (Q1–Q3), kg/m^2	31.2 (26.5–37.9)	32.6 (26.9–38.3)	.66
Race			.11
American Indian or Alaskan Native	14 (1)	7 (2)	
Asian	4 (0)	5 (1)	
Native Hawaiian or Pacific Islander	1 (0)	0 (0)	
Black	699 (66)	285 (67)	
White	114 (11)	33 (8)	
Other	74 (7)	21 (5)	
Multiracial	155 (15)	76 (18)	
Education			.46
12th grade or less	677 (64)	257 (60)	
1–3 years of college	301 (28)	132 (31)	
4+ years of college	84 (8)	37 (9)	
Monthly household income			.18
$12 000 or less	474 (45)	183 (43)	
$12 001–$24 000	251 (24)	88 (21)	
$24 001–$36 000	122 (11)	49 (11)	
More than $36 000	175 (16)	93 (22)	
Smoking			.005
Never	379 (36)	122 (29)	
Former	320 (30)	123 (29)	
Current	363 (34)	182 (43)	
Smoking pack-years, median (Q1–Q3), cumulative[a]	8.8 (3.4–16.8)	9.5 (3.1–18.4)	.62
Substance use			
Marijuana use			
Current	228 (21)	109 (26)	.17
Ever	712 (67)	322 (75)	.002
Cocaine or crack use			
Current	63 (6)	37 (9)	.07
Ever	444 (42)	224 (52)	< .001
Heroin or injection drug use			
Current	8 (1)	10 (2)	.02
Ever	202 (19)	106 (25)	.01
Methamphetamine use			
Current	5 (1)	3 (1)	.70
Ever	5 (1)	3 (1)	.70
Any of the above			
Current	244 (23)	119 (29)	.05
Ever	743 (70)	336 (79)	.001
Liver disease			
Hepatitis B infection, baseline	28 (3)	9 (2)	.43
Hepatitis C infection, baseline or during follow-up	196 (18)	48 (11)	.001
Aspartate aminotransferase to platelet ratio index, (Q1–Q3), median	0.18 (0.14–0.26)	0.16 (0.12–0.72)	.01
Fibrosis-4 index, (Q1–Q3), median	0.94 (0.7–1.36)	0.84 (0.61–1.12)	.001
HIV characteristics			
CD4+ cell count nadir, median (Q1–Q3), cells/mm^3	231 (101–362)		
CD4+ cell count current, median (Q1–Q3), cells/mm^3	700 (495–938)		
Peak HIV RNA (1000 copies/mL), (Q1–Q3), median	45 (9.6–140)		
HIV RNA undetectable	728 (69)		
Currently on ART	979 (92)		
Cumulative ART years, (Q1–Q3), median	5.9 (3.8–15)		
History of AIDS	310 (29)		
History of *Pneumocystis* pneumonia	65 (6)		
Cohort of enrollment			
1994–1995	298 (28)	101 (24)	.001
2001–2002	205 (19)	120 (28)	
2011–2012	129 (12)	60 (14)	
2013–2015	430 (40)	146 (34)	
Site			.12
Brooklyn, New York	171 (16)	62 (14)	
Bronx, New York	48 (5)	24 (6)	
Washington, District of Columbia	146 (14)	65 (15)	
San Francisco, California	118 (11)	63 (15)	
Chicago, Illinois	136 (13)	60 (14)	
Chapel Hill, North Carolina	111 (10)	35 (8)	
Atlanta, Georgia	129 (12)	60 (14)	
Miami, Florida	66 (6)	20 (5)	
Birmingham, Alabama / Jackson, Mississippi	133 (13)	38 (9)	

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus; Q1, first quartile; Q3, third quartile.

[a]For current and former smokers only.

analysis excluded participants with HCV who had ever reported a diagnosis of cirrhosis or had an aspartate aminotransferase-to-platelet ratio (APRI) greater than 0.5, a parameter that correlates with moderate liver fibrosis [40]. Excluding participants with HCV infection and a history of cirrhosis or a high APRI value (4 with HIV and 8 without HIV) did not substantially change the association between HCV infection and DL_{CO} (a lower percent predicted DL_{CO} by 9.6 among participants with HIV and 5.9 among participants without HIV).

DISCUSSION

In this racially, ethnically, and geographically diverse cohort of women with and without HIV, we found that HIV infection

Table 2. Differences in Lung Function Between Participating Women With and Without Human Immunodeficiency Virus

Spirometry Outcomes	With HIV (n = 1062)	Without HIV (n = 427)	Unadjusted Comparisons	Adjusted Comparisons
	Median (Q1–Q3)	Median (Q1–Q3)	Unadjusted mean difference (95% CI), *P* value	Adjusted mean difference (95% CI), *P* value
Post-BD FEV_1% predicted	90.3 (79.6–102.6)	91.8 (80.3–105.1)	−1.3 (−3.3 to .6) .20	−1.1 (−3.2 to .9)[a] .29
Post-BD FVC % predicted	90.4 (80.1–100.5)	92.5 (81.1–103.0)	−1.8 (−3.6 to −.02) .047	−1.3 (−3.2 to .5)[a] .14
Post-BD FEV_1/FVC ratio	0.82 (0.77–0.86)	0.82 (0.77–0.86)	0.002 (−.007 to .011) .70	−0.0004 (−.01 to .009)[a] .92
	n (%)	n (%)	Unadjusted OR (95% CI), *P* value	Adjusted OR (95% CI), *P* value
Post-BD FEV_1 < 80% predicted	276 (26)	102 (24)	1.11 (.86 to 1.45) .40	1.10 (.84 to 1.44)[a] .49
Post-BD FEV_1 < 60% predicted	51 (5)	26 (6)	0.78 (.48 to 1.27) .31	0.81 (.49 to 1.34)[a] .42
COPD (FEV_1/FVC < 0.7)	106 (10)	46 (11)	0.91 (.64 to 1.32) .65	0.98 (.67 to 1.44)[a] .94
COPD (FEV_1/FVC < lower limit of normal)	109 (10)	52 (12)	0.82 (.58 to 1.17) .28	0.88 (.61 to 1.26)[a] .48
Diffusion Outcomes	With HIV (n = 463)	Without HIV (n = 208)	Unadjusted Comparisons	Adjusted Comparisons
	Median (Q1–Q3)	Median (Q1–Q3)	Unadjusted mean difference (95% CI), *P* value	Adjusted mean difference (95% CI), *P* value
DL_{CO} % predicted	84 (73–94)	89 (76–101)	−4.9 (−7.8 to −2.0) .001	−4.8 (−7.7 to −1.9)[a] .001
DL_{CO} (mL/min/mm Hg)	16.9 (14–19.3)	17.6 (15.1–21.0)	−1.10 (−1.81 to −.38) .003	−0.73 (−1.33 to −.14)[b] .02
	n (%)	n (%)	Unadjusted OR (95% CI), *P* value	Adjusted OR (95% CI), *P* value
DL_{CO} < 80% predicted	191 (41)	69 (33)	1.41 (1.00 to 1.99) .047	1.47 (1.02 to 2.12)[a] .040
DL_{CO} < 60% predicted	39 (8)	13 (6)	1.38 (.72 to 2.64) .33	1.37 (.69 to 2.72)[a] .37

Abbreviations: BD, bronchodilator; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DL_{CO}, single-breath diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HIV, human immunodeficiency virus; OR, odds ratio; Q1, first quartile; Q3, third quartile.

[a]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), marijuana use (current, former, or never), and hepatitis C infection.

[b]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), marijuana use (current, former, or never), hepatitis C infection, race (Black, White, multiracial, or other), height, and age.

Table 3. Relationship Between Human Immunodeficiency Virus (HIV) Disease Variables and Pulmonary Function Outcomes Among Participating Women With HIV

Outcome	Current CD4 + cell Count (per 100 Cells/μL)	Nadir CD4 + cell Count (per 100 Cells/μL)	Years of ART Exposure (per 10 Years of ART)	Peak Human Immunodeficiency Virus RNA Viral Load (log10 Transformed)
	Adjusted mean difference (95% CI), *P* value[a]			
Post-BD FEV_1 % predicted	0.0 (−0.3 to 0.3), .87	0.0 (−0.6 to 0.6), .98	2.5 (0.8 to 4.2), .004	−0.2 (−1.3 to 1.0), .79
DL_{CO} % predicted	0.3 (−0.1 to 0.8), .09	1.0 (0.3 to 1.7), .004	−1.8 (−4.6 to 1.1), .22	−0.8 (−2.2 to 0.8), .34
	Adjusted odds ratio (95% CI), *P* value[a]			
Post-BD FEV_1 < 80% predicted	1.0 (0.96 to 1.04), .87	1.0 (0.92 to 1.08), .95	0.76 (0.59 to 0.97), .03	0.98 (0.85 to 1.14), .84
DL_{CO} < 80% predicted	0.95 (0.91 to 1.01), .12	0.89 (0.81 to 0.99), .03	1.12 (0.77 to 1.66), .54	1.05 (0.85 to 1.31), .62

Abbreviations: ART, antiretroviral therapy; BD, bronchodilator; CI, confidence interval; DL_{CO}, single-breath diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second.

[a]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), marijuana use (current, former, or never), and hepatitis C infection.

was associated with lower DL_{CO}. We did not observe an association between HIV infection and lower FEV_1. Among women with HIV, lower lifetime nadir CD4 + cell counts and HCV infection were associated with lower DL_{CO}.

In this cohort, women with HIV had lower FEV_1 measurements (the median value being 90.3% of predicted) than expected for age, height, sex, and race, indicating increased expiratory airflow obstruction when compared to a reference population. However, when compared to WIHS participants without HIV—a sample of women with similar demographic characteristics and, in some cases, with increased prevalence of exposures known to cause airflow obstruction such as cigarette smoking—there was no significant difference in FEV_1, even after adjustment for confounding exposures. There was also no difference in the prevalence of COPD among participants with and without HIV.

In contrast to our findings, prior work in men has suggested an adverse impact of HIV on FEV_1 [2, 10, 12, 13, 15, 16]. It is possible that the effect of HIV infection on expiratory airflow obstruction is specific to male sex. However, our results may be subject to survival bias as a result of the cross-sectional study design. Longitudinal lung function testing is underway in this cohort to determine whether women with HIV have accelerated decline in FEV_1 as has been observed in other populations [41, 42].

We found that HIV infection is associated with lower DL_{CO} measurements, which is consistent with an earlier study of lung function among WIHS participants at the San Francisco clinical site [11] and with other studies of mostly men, both in the pre-ART and the ART eras [9, 14, 32]. We note that this is the largest study of diffusing capacity in women with HIV to date. Strengths of this study include a sample population that is demographically representative of women with HIV in the United States, as well as detailed longitudinal data on confounding exposures. The effect estimate we observed was greater than in an earlier multicenter study of men in the MACS, suggesting the

Table 4. Relationship Between Hepatitis C Infection and Diffusing Capacity Among Participating Women With and Without Human Immunodeficiency Virus

Outcome	Hepatitis C Positive	Hepatitis C Negative	Unadjusted comparisons	Adjusted comparisons
	Median (Q1–Q3)	Median (Q1–Q3)	Unadjusted mean difference (95% CI), *P* value	Adjusted mean difference (95% CI), *P* value
Overall	n = 127	n = 543		
DL_{CO} % predicted				−7.4 (−11.4 to −3.3)[a] <.001
With HIV only	n = 92	n = 370		
DL_{CO} % predicted	75 (63–85)	86 (77–96)	−11.1 (−14.7 to −7.4) <.001	−8.3 (−13.3 to −3.3)[b] .001
Without HIV only	n = 35	n = 173		
DL_{CO} % predicted	80 (70–94)	90 (79–102)	−7.6 (−14.2 to −1.0) .02	−6.3 (−13.4 to .9)[c] .09

Abbreviations: CI, confidence interval; DL_{CO}, single-breath diffusing capacity for carbon monoxide; HIV, human immunodeficiency virus; Q1, first quartile; Q3, third quartile.

[a]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), marijuana use (current, former, or never), and HIV infection.

[b]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), marijuana use (current, former, or never), and nadir CD4 + cell count (log transformed).

[c]Adjusted for smoking (pack-years), education, ever heroin or injection drug use, cocaine use (current, former, or never), and marijuana use.

possibility of differential sex-specific effects on DL_{CO} [14]. However, our estimate was smaller than among WIHS participants in San Francisco only (4.8 vs 5.8) [11], possibly due to differences in sample characteristics and analytic approach.

The mechanism by which HIV infection affects DL_{CO} is not fully understood. DL_{CO} is decreased in pathologic processes that reduce the surface area and volume of the pulmonary vascular bed. Whether diffusion impairment among PWH reflects incipient, preclinical emphysema; interstitial lung disease; pulmonary vascular disease; or some combination of these is uncertain. Also, it is not known whether diffusion impairment is a direct effect of HIV infection in lung tissue or if it is mediated by systemic immunosuppression or immune activation [43, 44]. Nevertheless, DL_{CO} is an important marker of lung disease among those with and without HIV and has been associated with decreased quality of life and increased risk of mortality [45, 46]. Our study highlights the need to understand the pathologic processes by which HIV infection might cause impaired respiratory gas exchange.

In analyses limited to participants with HIV, a lower nadir CD4 + cell count was associated with decreased DL_{CO}, which is consistent with prior studies among men with HIV in the MACS and among US veterans with HIV who obtain care at Veterans Affairs medical centers [9, 14]. We also found that a greater number of years of cumulative ART was associated with higher FEV_1. However, this finding has not been observed elsewhere and should be considered provisional since cross-sectional studies such as this may be subject to survival bias.

We observed a robust association between HCV infection and DL_{CO} in this cohort, which was also observed by Fitzpatrick et al [11]. In the earlier study of WIHS participants in San Francisco, however, key exposures, such as injection drug use, were not included in multivariable regression modeling due to sample size limitations (27 HCV seropositive women). In this larger multicenter study of WIHS participants, the relationship between HCV infection and DL_{CO} persisted among women with HIV, even after adjustment for cigarette smoking and injection drug use.

Other than Fitzpatrick et al, prior studies have found that persons with HCV infection have a higher than expected prevalence of diffusion impairment (ranging from 10% to 76%), but these studies were small, mostly without seronegative comparison groups, and not directly comparable due to differences in target populations and measurement methods [35–39]. Our analysis provides further evidence of a relationship between HCV infection and diffusion impairment.

How HCV may adversely affect respiratory gas exchange is uncertain. Liver cirrhosis is a known cause of diffusion impairment, mediated in part by the hepatopulmonary syndrome [47, 48]. However, advanced liver disease is unlikely to explain the observed relationship between HCV infection and diffusion impairment in the study population, since few participants had cirrhosis and their exclusion did not affect the results. Alternatively, the effect of HCV on diffusing capacity may be mediated by cryoglobulins, low levels of which are common among persons with chronic HCV infection [49], which may cause a subclinical pulmonary vasculitis that could interfere with respiratory gas exchange [50].

Particular features of the WIHS cohort make this analysis a unique contribution to the literature on comorbidities associated with HIV. The WIHS is comprised of women, who are underrepresented in the scientific literature on HIV and lung function. Semiannual participant follow-up enabled frequent measurement of key exposure variables, such as cigarette smoking. The enrollment of participants without HIV who have similar demographic characteristics to participants with HIV may reduce unmeasured confounding.

Limitations of this analysis include the cross-sectional study design, which is subject to known biases. The lack of detailed echocardiographic, lung imaging, or right heart catheterization data limits mechanistic understanding of how HIV and HCV may cause diffusion impairment. Data on the prevalence of chronic bronchitis were not collected. Last, the small number of HCV-seropositive participants without HIV (n = 35) may have reduced power to detect a significant association between HCV and DL_{CO} among persons without HIV.

CONCLUSIONS

HIV infection is associated with lower DL_{CO} in women. Among women with HIV, a lower nadir CD4 + cell count and HCV infection are associated with lower DL_{CO}. Further research is needed to understand the mechanisms by which HIV and HCV may affect DL_{CO}.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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