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Decreased Lung Function and All-Cause Mortality in HIV-infected Individuals

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Abstract

Rationale: Human immunodeficiency virus (HIV) infection is associated with pulmonary disease and worse lung function, but the relationship of lung function with survival in HIV is unknown.

Objectives: To determine whether lung function is associated with all-cause mortality in HIV-infected individuals.

Methods: HIV-infected participants from cohorts in three locations underwent pre- and post-bronchodilator spirometry and determination of single-breath diffusing capacity of the lung for carbon monoxide (D_{LCO}) in 2008–2009, computed tomographic (CT) scanning of the chest for quantitative emphysema and airway measures, and echocardiography for estimated left ventricular systolic and diastolic function and tricuspid regurgitant velocity. Bivariate analysis and multivariable Cox proportional hazards models were used to determine whether decreased lung function was independently associated with increased all-cause mortality. Models were adjusted for covariates including age, sex, body mass index, smoking status, self-reported hepatitis C status, HIV viral levels, $CD4^+$ T-cell counts, hemoglobin, antiretroviral therapy, and illicit drug use.

Results: Overall, 396 HIV-infected participants underwent pulmonary function testing. Thirty-two participants (8%) died during a median follow-up period of 69 months. A post-bronchodilator FEV_1-to-FVC ratio less than 0.7 (hazard ratio [HR], 2.47; 95% confidence interval [CI], 1.10–5.58) and a D_{LCO} less than 60% (HR, 2.28; 95% CI, 1.08–4.82) were independently associated with worse mortality. Also, hepatitis C (HR, 2.68; 95% CI, 1.22–5.89) and baseline plasma HIV RNA level (HR per ln RNA copies/ml, 1.50; 95% CI, 1.22–1.86) were associated with mortality in HIV-infected participants. The only CT or echocardiographic measure associated with greater mortality in univariate analysis was greater wall thickness of medium-sized airways (HR for wall area percent, 1.08; 95% CI, 1.00–1.18; $P = 0.051$), but none of the CT or echocardiogram measures were associated with mortality in multivariable analysis.

Conclusions: Airflow obstruction and impaired diffusing capacity appear to be associated with all-cause mortality in HIV-infected persons over an average of 6 years of follow-up. These data highlight the importance of lung dysfunction in HIV-infected persons and should be confirmed in larger cohorts and with extended follow-up periods.

Clinical trial registered with www.clinicaltrials.gov (NCT00869544, NCT01326572).

Keywords: HIV; acquired immunodeficiency syndrome; chronic obstructive pulmonary disease

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Improvements in treatment and care of human immunodeficiency virus (HIV)-infected individuals have led to decreased acquired immunodeficiency syndrome (AIDS)–related complications and prolonged survival; however, excess mortality continues to occur among the HIV-infected population (1–3). In noninjection drug–using HIV-infected adults in Denmark, all-cause mortality was 15.5 per 1,000 person-years and the mortality rate was 2.9 per 1,000 person-years in HIV-uninfected persons matched to the HIV cohort on sex and year of birth. Smoking tripled the excess risk of death and doubled the population attributable risk of death in HIV-infected compared with HIV-uninfected persons.

Smoking-related lung disease is an important morbidity and contributor to mortality in the general population. Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide (4). Pulmonary function is also an independent predictor of increased mortality in HIV-uninfected populations. In the First National Health and Nutrition Examination Survey (NHANES I), decreases in forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), FEV_1/FVC, and single-breath diffusion capacity of the lung for carbon monoxide (D_{LCO}) were each associated with increased risk of all-cause mortality (5). In National Health and Nutrition Examination Survey III, low FVC and FEV_1 were associated with increased mortality after adjustment for the Framingham risk score (6). These findings suggest lung disease may play an important role in excess mortality in HIV.

HIV infection has been independently associated with respiratory symptoms, respiratory diagnoses, and abnormal lung function. Respiratory symptoms and diagnoses, particularly those related to COPD, are common in HIV-infected individuals (7, 8). Reduced diffusing capacity is also common in HIV infection and is likely the most significant lung function abnormality associated with HIV infection (9, 10).

The relationship between abnormal lung function and mortality among HIV-infected individuals is not known. We determined whether abnormalities of spirometry and diffusing capacity were independently associated with all-cause mortality in a large cohort of HIV-infected persons.

Methods

Participants

HIV-infected individuals over 18 years of age were recruited from three cohorts (Pittsburgh AIDS Center for Treatment [PACT], Multicenter AIDS Cohort Study [MACS], and Women's Interagency HIV Study [WIHS]) from three cities (Pittsburgh, Pittsburgh and Los Angeles, and San Francisco, respectively) to form the Pittsburgh HIV lung cohort. Participants were recruited from the PACT by posted advertisements and by contacting patients in a research registry (8). Participants matching the age and smoking distribution of the overall cohorts were recruited from the MACS and WIHS. All participants signed written informed consent forms, and protocols were approved by institutional review boards at participating institutions.

Measures

Participants were seen in 2008–2009, when the following baseline data were collected. Demographic and clinical data were obtained from structured interviews, chart review, or examination to determine age, sex, race/ethnicity, body mass index, systolic and diastolic blood pressure, hemoglobin (measured at the time of pulmonary function testing), smoking history, recreational drug use, accepted combination antiretroviral treatment (11), $CD4^+$ T-cell counts, baseline plasma HIV RNA levels, and history of hypertension, diabetes, self-reported history of hepatitis C, prior pneumonia or respiratory illnesses, and respiratory medication use. Nadir $CD4^+$ T-cell counts were not used because they could not be reliably determined. Participants underwent pre- and post-bronchodilator spirometry and D_{LCO} determination, based on American Thoracic Society standards (12). Percent predicted lung function was determined using predicted values from NHANES III and Miller and colleagues (13, 14). D_{LCO} was adjusted for hemoglobin and carboxyhemoglobin. Standardized noncontrast computed tomographic (CT) scans of the entire thorax at end-inspiration were obtained in individuals who had less than approximately 10-rad exposure to radiation in the prior year. Percentage of lung voxels associated with emphysema defined as voxels below –950 or –910 Hounsfield units (HU) and global emphysema severity score were calculated (15). CT of the chest was used to determine airway wall area percentage (WA%) in the smallest one-third of measurable airways. We used a fully automated computer scheme to detect and quantify airway sections depicted in axial section of the CT examination as previously described (16). Echocardiography was performed to determine peak tricuspid regurgitant velocity (TRV), estimated pulmonary artery systolic pressure (17, 18), left ventricular (LV) ejection fraction, LV hypertrophy, and diastolic dysfunction. Echocardiograms were added to the study protocol as of July 1, 2009 and were available in 228 participants.

Data in this article were collected by the Multicenter AIDS Cohort Study (MACS) and/or the Women's Interagency HIV Study (WIHS). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the National Institutes of Health (NIH). MACS (Principal Investigators): University of California, Los Angeles (Roger Detels), U01-AI35040; University of Pittsburgh (Charles Rinaldo), U01-AI35041; the Center for Analysis and Management of MACS, Johns Hopkins University Bloomberg School of Public Health (Lisa Jacobson), UM1-AI35043. The MACS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional cofunding from the National Cancer Institute (NCI). Targeted supplemental funding for specific projects was also provided by the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute on Deafness and Communication Disorders (NIDCD). MACS data collection is also supported by UL1-TR000424 (JHU CTSA).

WIHS (Principal Investigators): Connie Wofsy Women's HIV Study, Northern California (Ruth Greenblatt, Bradley Aouizerat, and Phyllis Tien), U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub). The WIHS is funded primarily by the National Institute of Allergy and Infectious Diseases (NIAID), with additional cofunding from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the National Cancer Institute (NCI), the National Institute on Drug Abuse (NIDA), and the National Institute on Mental Health (NIMH). Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Alcohol Abuse and Alcoholism (NIAAA), the National Institute on Deafness and other Communication Disorders (NIDCD), and the NIH Office of Research on Women's Health. WIHS data collection is also supported by UL1-TR000004 (UCSF CTSA) and UL1-TR000454 (Atlanta CTSA).

Survival time was calculated from the baseline visit when pulmonary function testing was performed until the time of death or censoring. Death was determined by active surveillance and National Death Registry matching in the MACS and WIHS per study protocols (19–22). The follow-up time was censored at the time each participant was last seen for the 6-month MACS or WIHS visit unless death was recorded after that visit and before data-freeze. Deaths in the PACT cohort were determined by medical record review, and alive status was confirmed by participant contact at the time of the dataset creation.

Statistical Analysis

Demographic and clinical data were summarized and compared between participants who had a post-bronchodilator FEV_1/FVC ratio less than 0.7 and those with an FEV_1/FVC ratio equal to or exceeding 0.7, and between those with a D_{LCO} less than 60% and a D_{LCO} equal to or exceeding 60% predicted (*see* the online supplement). Hazard ratios and *P* values for survival were determined for each variable including pulmonary function as continuous variables for FEV_1 % predicted, FVC % predicted, FEV_1/FVC, and D_{LCO} % predicted and as dichotomous variables for airflow obstruction (post-bronchodilator $FEV_1/FVC < 0.7$) and impaired diffusing capacity ($D_{LCO} < 60\%$ predicted) (8, 23). Continuous variables were used for percentage of voxels less than –910 and –950 HU, emphysema global severity score, WA%, LV ejection fraction, TRV, and estimated pulmonary artery systolic pressure. Dichotomous variables were used for the presence of LV hypertrophy, diastolic dysfunction, and a TRV greater than 2.5 m/min.

Clinical and pulmonary function variables with a bivariate *P* value not exceeding 0.2 were entered into multivariable Cox proportional hazards models to determine whether worse lung function was independently associated with all-cause mortality. Considering lower sample size for the CT and echocardiographic variables, we then tested whether any of these variables with bivariate *P* value not exceeding 0.2 could be entered into the final model. The model was tested with the cohort/site as a random effects variable to control for overall differences in the three cohorts, and there were no important differences in the estimates when considering the cohort as a random or a fixed effect in the model. Model assumptions were checked by assessing scaled Schoenfeld residuals, proportional hazards, martingale residual, Cox–Snell residual, and leverage (DFbeta). One outlier was removed for high scaled residual and one for high leverage. Models using the continuous variable for FEV_1/FVC and D_{LCO} were unstable because of the nonlinear relationship of these variables and survival; therefore, dichotomous variables were used for the Cox proportional hazards model. There was a high degree of correlation between FEV_1/FVC and D_{LCO}, and separate models were therefore created. An additional model was created with the addition of smoking status to create estimates for the effect of lung function on mortality controlling for smoking. An additional model was created with smoking status added to estimate the effect of lung function on mortality controlling for smoking.

Given that the percent predicted formulas account for age, sex, height, and ethnicity and that there were a limited number of deaths in the cohort, we selected the most parsimonious models as the main models. We also calculated two separate propensity scores based on potential confounders (one for $FEV_1/FVC < 0.7$ and one for $D_{LCO} < 60\%$ using "psmatch2" in the STATA software [StataCorp]). In two separate Cox models, we adjusted the effect of FEV_1/FVC less than 0.7 and D_{LCO} less than 60% on mortality for these scores. Population attributable risk was calculated for FEV_1/FVC less than 0.7 and D_{LCO} less than 60% predicted (24). The effect of undiagnosed COPD was also assessed with Cox proportional hazards ratios. Statistical analyses were performed with STATA 14.0.

Results

The cohort included 396 HIV-infected participants. Participants had a median age of 49 years, 32% were female, and 44% were African American. The median (interquartile range [IQR]) follow-up time was 69 (59–80) months, and there were 32 deaths (8%) with a corresponding mortality rate of 7.0 per 1,000 person-years. Smoking was prevalent (only 26% were never smokers), as was cocaine use (40%) and injection drug use (25%). The median body mass index was 25.8 and systolic/diastolic blood pressures were 126/77 mm Hg. Of the participants, 81% were receiving an accepted antiretroviral therapy regimen at the time of pulmonary function testing; the median (IQR) $CD4^+$ T-lymphocyte count was 514 (341–743) cells/μl and baseline plasma HIV RNA was below the level of assay detection in 257 participants (65%).

Participants reported having been told by their medical provider that they had asthma 21% and COPD 10% of the time. Twenty-three participants (6%) had a history of *Pneumocystis* pneumonia, 35% reported having had bacterial pneumonia, and 22% had a self-report of hepatitis C infection.

Spirometric results were normal on average with a median (IQR) post-bronchodilator FEV_1 % predicted of 98 (88–109); however, diffusing capacity was low on average with a median (IQR) D_{LCO} % predicted of 69 (57–81). The median (IQR) percentage of voxels < –910 HU was 7 (3–16), WA% was 46 (42–49), tricuspid regurgitation velocity was 2.4 (2.2–2.6), and estimated pulmonary artery systolic pressure was 33 (29–37).

There were differences in baseline variables between those with an FEV_1/FVC less than 0.7 and an FEV_1/FVC equal to or greater than 0.7. Participants with an FEV_1/FVC less than 0.7 were older, smoked more, were more likely to have been told they have asthma or COPD, and were more likely to die (Table 1; and *see* Table E1 in the online supplement). Differences in baseline variables between those with a D_{LCO} less than 60% predicted and a D_{LCO} equal to or greater than 60% predicted are shown in Table E2.

In univariate analysis of survival, a greater number of pack-years of smoking was associated with increased all-cause mortality (hazard ratio [HR] per square root of pack-years of smoking, 1.18; 95% confidence interval [CI], 1.03–1.36; $P = 0.02$) (Table E3). Cocaine use demonstrated a trend toward increased mortality (HR, 2.0; 95% CI, 1.0–4.0; $P = 0.06$). History of hepatitis C infection by self-report was associated with greater mortality among HIV-infected

Table 1. Distribution of demographic and clinical variables between those with and without $FEV_1/FVC \geq 0.7$

	$FEV_1/FVC \geq 0.7$		$FEV_1/FVC < 0.7$		*P* Value
	n	Results	*N*	Results	
Age, median (IQR), yr	320	48 (41–54)	66	51 (46–55)	<0.001
Female sex	320	102 (32%)	66	16 (24%)	0.2
Race	320	175 (55%)	66	34 (52%)	0.3
White (Hispanic and non-Hispanic)		136 (42%)		32 (48%)	
Black (Hispanic and non-Hispanic)		9 (3%)		0	
Other					
Study	320	173 (54%)	66	46 (70%)	0.064
PACT		91 (28%)		13 (20%)	
MACS		56 (18%)		7 (10%)	
WIHS					
Deaths	320	20 (6%)	66	10 (15%)	0.014
Pack-years of smoking, median (IQR)	320	10 (0–20)	66	26 (0–40)	<0.001
Smoking status	320	92 (29%)	66	8 (12%)	0.006
Never		142 (44%)		42 (64%)	
Current		86 (27%)		16 (24%)	
Former					
Ever use cocaine	311	119 (38%)	62	28 (45%)	0.3
Ever use marijuana	320	251 (78%)	66	55 (83%)	0.4
Ever use injection drugs	320	70 (22%)	66	22 (33%)	0.047
Body mass index, median (IQR)	320	25.9 (23.5–29.5)	66	25.0 (22.3–29.8)	0.9
Accepted combination antiretroviral treatment	320	256 (80%)	66	58 (88%)	0.2
$CD4^+$ T-lymphocytes/μl, median (IQR)	320	514 (341–758)	66	545 (359–672)	0.7
Plasma HIV RNA copies/ml,* median (IQR)	320	49 (49–617)	66	49 (49–879)	>0.9
Asthma diagnosis	320	57 (18%)	65	22 (34%)	0.004
COPD diagnosis	318	23 (7%)	65	17 (26%)	<0.001
Post-BD FEV_1 % predicted, median (IQR)	320	101 (91–111)	66	82 (70–91)	<0.001
D_{LCO} < 60% predicted	320	72 (23%)	66	40 (61%)	<0.001
Bronchodilator response†	320	15 (5%)	66	18 (27%)	<0.001
Global emphysema score, median (IQR)	264	0 (0–0)	53	0 (0–1)	<0.001
WA%, large, median (IQR)	251	44 (41–47)	45	46 (43–50)	0.006
TRV > 2.5 m/min	159	41 (26%)	40	18 (45%)	0.017

Definitions of abbreviations: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; HIV = human immunodeficiency virus; IQR = interquartile range; MACS = Multicenter AIDS Cohort Study; PACT = Pittsburgh AIDS Center for Treatment; TRV = tricuspid regurgitant velocity; WA% = wall area percent; WIHS = Women's Interagency HIV Study.

Results are presented as *n* (%) unless otherwise identified.

*Performed at baseline. Lower limit of detection of plasma HIV RNA level is 49 copies/ml for MACS and WIHS.

†Bronchodilator response was defined as more than a 12% and 200-ml increase in either FEV_1 or FVC.

individuals (HR, 2.7; 95% CI, 1.3–5.6; $P = 0.006$). Lower $CD4^+$ T-lymphocyte counts were associated with worse mortality (HR, 0.95; 95% CI, 0.90–0.99; $P = 0.041$), and higher quantities of baseline plasma HIV RNA were associated with increased mortality (HR per log RNA copies/ml, 1.19; 95% CI, 1.08–1.31; $P < 0.001$).

Impaired lung function ($FEV_1/FVC < 0.7$ and $D_{LCO} < 60\%$ predicted) was associated with increased all-cause mortality (Figure 1). CT emphysema measures were not associated with mortality, but greater WA% of the largest tertile of airways was associated with increased mortality (HR, 1.08; 95% CI, 1.00–1.18; $P = 0.051$). A TRV greater than 2.5 m/min was the only echocardiogram data that had a trend with mortality (HR, 2.88; 95% CI, 0.88–9.45; $P = 0.08$).

In a multivariable Cox proportional hazards model, the factors independently associated with all-cause mortality were baseline plasma HIV RNA level (HR per ln RNA copies/ml, 1.50; 95% CI, 1.22–1.86; $P < 0.001$), hepatitis C infection (HR, 2.68; 95% CI, 1.22–5.89; $P = 0.014$), and D_{LCO} less than 60% predicted (HR, 2.28; 95% CI, 1.08–4.82; $P = 0.03$) (Table 2). Because of colinearity between D_{LCO} less than 60% predicted and FEV_1/FVC less than 0.7 (percent agreement was 74.6%; κ [95% CI] was 0.30 [0.20–0.40]; χ^2 $P < 0.001$) and because the model became unstable with both variables, we replaced D_{LCO} less than 60% predicted with FEV_1/FVC less than 0.7. FEV_1/FVC less than 0.7 was also independently associated with mortality (HR, 2.47; 95% CI, 1.10–5.58; $P = 0.03$). Adjusting for smoking did not significantly change the effect of decreased lung function on mortality (Table 2, model 2).

Population attributable risk fraction (95% CI) for having an FEV_1/FVC less than 0.7 was 0.18 (0.08–0.28) and 0.30 (0.09–0.46) for D_{LCO} less than 60% predicted. Only 17 participants (26%) with a post-bronchodilator FEV_1/FVC less than 0.7 had physician-diagnosed COPD (Table 1). All-cause mortality was greater in participants who did not have physician-diagnosed COPD, but who had

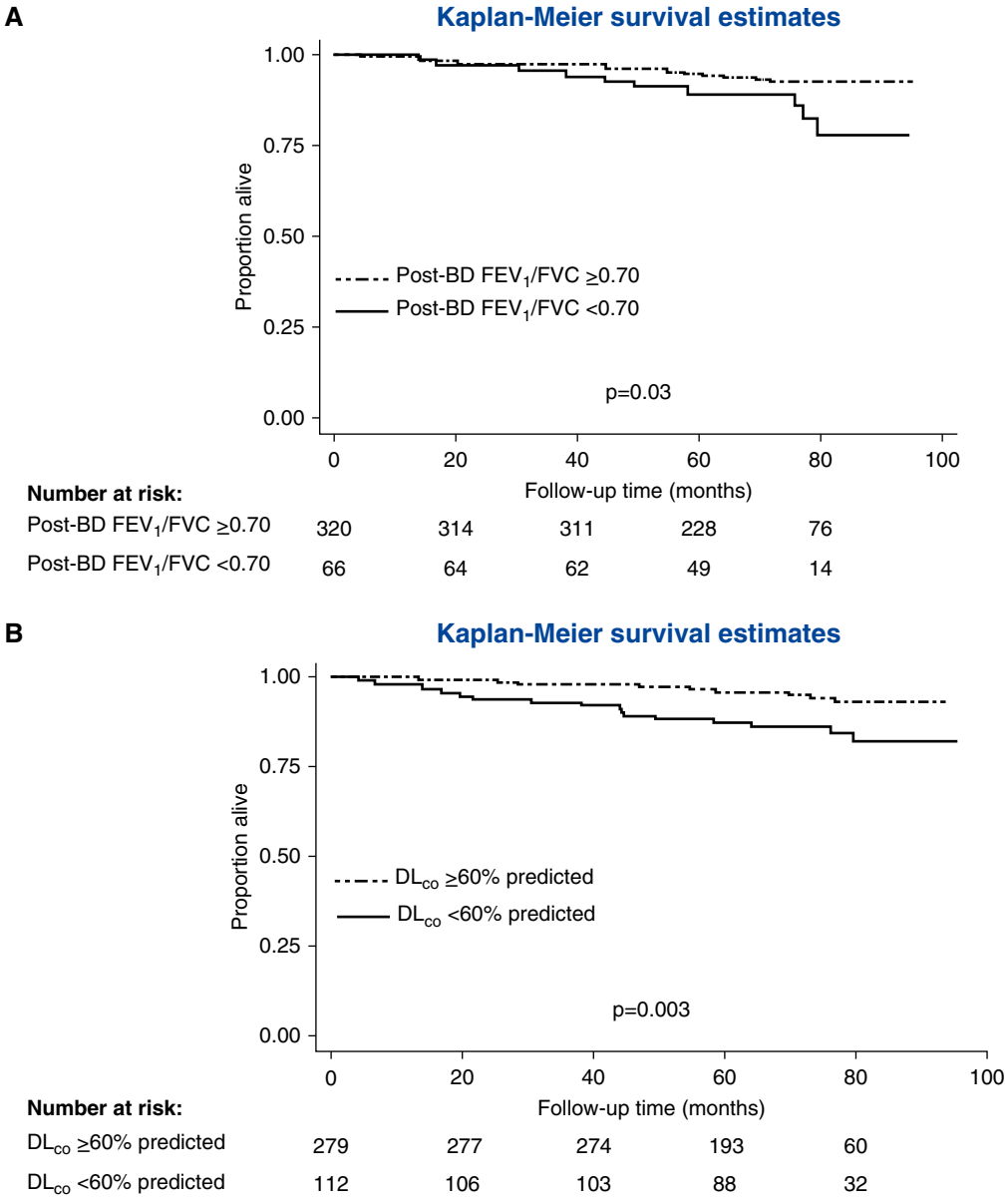

Figure 1. (*A*) Kaplan–Meier survival estimates for post-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) < 0.7 versus $FEV_1/FVC \geq 0.7$ in human immunodeficiency virus (HIV)-infected participants, and (*B*) Kaplan–Meier survival estimates for single-breath diffusion capacity for carbon monoxide (D_{LCO}) < 60% predicted versus $D_{LCO} \geq 60\%$ predicted in HIV-infected participants. BD = bronchodilator.

a post-bronchodilator FEV_1/FVC less than 0.7 (HR, 2.56; *P* value, 0.03) (Tables E4 and E5).

Discussion

In a multicenter cohort, airflow obstruction and impaired diffusing capacity were associated with increased all-cause mortality in HIV-infected participants. These findings were independent of smoking history and presence of emphysema, elevated pulmonary artery pressures, or left ventricular dysfunction. In addition to poor lung function, increased mortality was independently associated with HIV viral load and self-reported hepatitis C coinfection.

Our findings suggest that abnormal or impaired lung function is a marker of mechanisms that influence morbidity and mortality in people with HIV infection. HIV infection has been shown to be an independent predictor of COPD, emphysema, airflow obstruction, and diffusion impairment (7, 9, 10, 25–27). We now find that airflow obstruction and diffusion impairment are independently associated with all-cause mortality, supporting COPD/emphysema as an important manifestation of lung dysfunction in HIV. In addition, the Kaplan–Meier curve (Figure 1) appears to diverge earlier in those with diffusion impairment than in those with and without airflow obstruction, suggesting diffusing impairment may be an earlier or potentially

Table 2. Mortality rates and unadjusted and adjusted Cox regression estimate of all-cause mortality by pulmonary function

	Post-BD $FEV_1/FVC \geq 0.7$	Post-BD $FEV_1/FVC < 0.7$	$D_{LCO} \geq 60\%$ Predicted	$D_{LCO} < 60\%$ Predicted
Number at risk	320	66	279	112
Number of deaths	20	10	14	17
Person-years of observation	1,810	375	1,573	642
Mortality per 1,000 person-years	11.0	26.4	8.9	26.4
		HR (95% CI)*		HR (95% CI)*
Unadjusted	Ref	2.36 (1.11–5.05)[1]	Ref	2.92 (1.43–5.92)[2]
Multivariate adjusted†				
Model 1	Ref	2.47 (1.10–5.58)[1]	Ref	2.28 (1.08–4.82)[1]
Model 2	Ref	2.36 (1.03–5.38)[3]	Ref	2.19 (1.03–4.67)[3]
Model 3	Ref	2.37 (1.10–5.10)[1]	Ref	2.09 (1.001–4.35)[4]
Model 4	Ref	2.68 (1.18–6.10)[5]	Ref	2.17 (1.06–4.45)[2]
Propensity score adjusted‡	Ref	2.54 (1.09–5.91)[1]	Ref	2.15 (0.94–4.94)[6]

Definition of abbreviations: BD = bronchodilator; CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1/FVC = forced expiratory volume in 1 second/forced vital capacity; HR = hazard ratio; Ref = reference group.
*P values: [1]$P = 0.03$; [2]$P = 0.003$; [3]$P = 0.04$; [4]$P = 0.050$; [5]$P = 0.02$; [6]$P = 0.070$.
†Multivariate adjustments: model 1—adjusted for viral load and hepatitis C; model 2—adjusted for viral load, self-reported history of hepatitis C, and smoking status; model 3—adjusted for age, sex, body mass index, hepatitis C, baseline HIV viral load; model 4—adjusted for smoking, hepatitis C, baseline HIV viral load, CD4, hemoglobin, HIV treatment, illicit drug use.
‡Propensity score was calculated from age, race, sex, self-reported hepatitis C, viral load, and smoking status (beside hemoglobin in D_{LCO} model).

a more important marker although definition of diffusing impairment may impact this finding. Previous studies in the general population have found diffusing impairment to be a predictor of mortality (5, 6). These studies also found that a restrictive pattern on spirometry was associated with mortality. Because we found an association of mortality with FEV_1/FVC, we expected there to be an association with one or both components of the ratio. In those with obstruction, the FEV_1 was significantly lower, but the FVC was also slightly, although not statistically significantly, lower. This relationship may explain why we see an association with FEV_1/FVC, but not with either of the components. We also do not find a threshold level of FEV_1 or FVC associated with all-cause mortality. We were not able to show an association between CT measures of emphysema and airway remodeling or echocardiographic measures of left ventricle function and right heart pressures and mortality. The poor correlation between mortality and CT or echocardiogram measures suggests the factors influencing all-cause mortality are better reflected in pulmonary function, which itself is a more physiologic measure compared with CT images or echocardiographic measures.

Unrecognized obstructive lung disease is common in the general population and is an important public health concern. The prevalence of unrecognized COPD and its association with increased mortality in this cohort could suggest a lack of access to care in these participants, that the presence of obstructive lung disease is not frequently considered by medical providers, or that unrecognized COPD has significant impact on survival. It will be important to understand how improved recognition of and care for obstructive lung disease can impact morbidity and mortality in the HIV-infected population.

The relative impact of abnormal pulmonary function on mortality in this study of HIV-infected participants is substantially greater than in prior studies of the general population. This finding may be a result of increased risk factors common to both lung dysfunction and mortality (smoking, drug use, poor socioeconomic status, etc.) in these cohorts compared with the general population. Hepatitis C infection is an indicator of past injection drug use, and thus injection of foreign substances may contribute to pulmonary function abnormalities, or the effect may be related to hepatic injury or other effects of the hepatitis C virus itself. There is also good evidence that lung dysfunction is more common in HIV-infected persons (9, 10). With the advent of effective antiretroviral therapy, obstructive lung disease has become a more prominent cause of morbidity and mortality (28). Lung disease may be a larger contributor to the absolute risk of death in the HIV-infected population; however, because other comorbidities that contribute to increased mortality are also more prevalent in HIV-infected persons, there may be competition among the contributors to the higher mortality rate in HIV, which may obscure the impact of lung dysfunction on death in the HIV population in some studies (1, 29, 30). In our data, the population attributable risk for low diffusing capacity is striking considering that the abnormal lung function and mortality we found in these cohorts occur at a young age in the HIV-infected participants (mean age at death, 55 yr).

Although associations do not prove causality, there are several mechanistic connections that may explain our findings. COPD and asthma are inflammatory diseases associated with increased systemic inflammation in the general population, and in the case of COPD, that inflammation predicts mortality (31, 32). In HIV, chronic inflammation is increased and associated with increased mortality (33–35). We have previously shown that pulmonary dysfunction is associated with increased systemic inflammation in HIV-infected persons (23, 36–38). In addition, immune activation is associated with multimorbidity in HIV that can lead to increased mortality. Similarly, COPD is associated with markers of accelerated aging in the general population and the HIV-infected population (38–40). In conjunction with

other comorbidities, COPD leads to increased frailty in the HIV-infected population, a known marker for increased mortality (41).

There are also several disease processes that have been associated with abnormal lung function and greater mortality. Increased risk of cardiovascular disease has been linked to COPD and exacerbations of COPD (42–46). If these disease processes are related mechanistically, then it is possible that lung dysfunction or COPD in the HIV-infected population may contribute to the increased risk of cardiovascular disease in HIV. COPD and COPD severity are also associated with lung cancer (47), which is common among HIV-infected individuals and associated with high mortality (48, 49). In addition, we find that hepatitis C is associated with mortality in our cohort. Hepatitis C and cirrhosis are associated with lung function impairment and decline and may be a link between abnormal lung function and mortality in this population (50–53).

There are several limitations to our study. Lack of cause of death limits inferences that we can make about how airflow obstruction and diffusion impairment are linked to mortality in HIV-infected persons. We also use only baseline data in our modeling of survival; thus, we may have missed confounding variables that longitudinal data may capture. The cohort and small number of death events may not be large enough to completely assess for important confounders of association of lung function and mortality including cardiovascular disease. There may also be confounding by factors that we were unable to capture from the cohort data such as nadir $CD4^+$ T-lymphocyte count and subclinical cardiovascular disease. We also cannot rule out an impact on mortality of other variables such as smoking, illicit drug use, and HIV viral levels. It would be informative to determine whether the association of lung function with survival remains independent or adds to the predictive ability of known risk scores such as the Framingham index or Veterans Aging Cohort Study Index specifically in HIV infection. We also did not have lung volume measures to confirm restriction versus air trapping. We were unable to test specifically for mortality by COPD severity to determine whether there is a dose-dependent effect of lung dysfunction on mortality. We used CT and echocardiogram measures that are commonly cited in the literature for cardiopulmonary assessment, but more sophisticated measures may better correlate with disease morbidity and mortality. The CT and echocardiographic measures are only available from a subset of the cohort, which may not reflect an unbiased sample of the entire cohort.

To our knowledge, this study is the first to demonstrate that abnormal or impaired lung function is independently associated with increased all-cause mortality in HIV-infected persons. This finding is particularly important as HIV infection is an independent risk factor for a greater degree of airflow obstruction and impaired diffusing capacity and diagnosis of several pulmonary diseases, and HIV-infected individuals are diagnosed with lung disease at an earlier age (7, 9, 10). These data also highlight the importance of determining the causes of lung disease in HIV-infected persons, which may be independent of smoking, and to identify treatments for preventing lung dysfunction in this population. ■

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References

1 Helleberg M, Afzal S, Kronborg G, Larsen CS, Pedersen G, Pedersen C, *et al*. Mortality attributable to smoking among HIV-1–infected individuals: a nationwide, population-based cohort study. *Clin Infect Dis* 2013;56:727–734.
2 Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, *et al*.; HIV Outpatient Study Investigators. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006;43:27–34.
3 Walensky RP, Paltiel AD, Losina E, Mercincavage LM, Schackman BR, Sax PE, *et al*. The survival benefits of AIDS treatment in the United States. *J Infect Dis* 2006;194:11–19.
4 World Health Organization. The top 10 causes of death. 2016 [updated 2017 Jan; accessed 2016 Mar 10]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.
5 Neas LM, Schwartz J. Pulmonary function levels as predictors of mortality in a national sample of US adults. *Am J Epidemiol* 1998; 147:1011–1018.
6 Lee HM, Le H, Lee BT, Lopez VA, Wong ND. Forced vital capacity paired with Framingham risk score for prediction of all-cause mortality. *Eur Respir J* 2010;36:1002–1006.
7 Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, *et al*. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med* 2011;183:388–395.
8 Gingo MR, George MP, Kessinger CJ, Lucht L, Rissler B, Weinman R, *et al*. Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. *Am J Respir Crit Care Med* 2010;182:790–796.
9 Crothers K, McGinnis K, Kleerup E, Wongtrakool C, Hoo GS, Kim J, *et al*. HIV infection is associated with reduced pulmonary diffusing capacity. *J Acquir Immune Defic Syndr* 2013;64:271–278.
10 Fitzpatrick ME, Gingo MR, Kessinger C, Lucht L, Kleerup E, Greenblatt RM, *et al*. HIV infection is associated with diffusing capacity impairment in women. *J Acquir Immune Defic Syndr* 2013;64: 284–288.
11 Department of Health and Human Services; Henry J. Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents [23 Mar 2004; accessed 2008 Nov 3]. Available from: http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf.
12 Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis* 1981;123:659–664.
13 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179–187.
14 Miller A, Thornton JC, Warshaw R, Anderson H, Teirstein AS, Selikoff IJ. Single breath diffusing capacity in a representative sample of the population of Michigan, a large industrial state: predicted values, lower limits of normal, and frequencies of abnormality by smoking history. *Am Rev Respir Dis* 1983;127:270–277.
15 Leader JK, Zheng B, Rogers RM, Sciurba FC, Perez A, Chapman BE, *et al*. Automated lung segmentation in X-ray computed tomography: development and evaluation of a heuristic threshold-based scheme. *Acad Radiol* 2003;10:1224–1236.

16 Zheng B, Leader JK, McMurray JM, Park SC, Fuhrman CR, Gur D, *et al*. Automated detection and quantitative assessment of pulmonary airways depicted on CT images. *Med Phys* 2007;34:2844–2852.
17 Hsue PY, Deeks SG, Farah HH, Palav S, Ahmed SY, Schnell A, *et al*. Role of HIV and human herpesvirus-8 infection in pulmonary arterial hypertension. *AIDS* 2008;22:825–833.
18 Kircher BJ, Himelman RB, Schiller NB. Noninvasive estimation of right atrial pressure from the inspiratory collapse of the inferior vena cava. *Am J Cardiol* 1990;66:493–496.
19 Bacon MC, von Wyl V, Alden C, Sharp G, Robison E, Hessol N, *et al*. The Women's Interagency HIV Study: an observational cohort brings clinical sciences to the bench. *Clin Diagn Lab Immunol* 2005;12: 1013–1019.
20 Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P, *et al*.; WIHS Collaborative Study Group. The Women's Interagency HIV Study. *Epidemiology* 1998;9:117–125.
21 Detels R, Jacobson L, Margolick J, Martinez-Maza O, Muñoz A, Phair J, *et al*. The multicenter AIDS Cohort Study, 1983 to…. *Public Health* 2012;126:196–198.
22 Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987;126: 310–318.
23 Gingo MR, He J, Wittman C, Fuhrman C, Leader JK, Kessinger C, *et al*. Contributors to diffusion impairment in HIV-infected persons. *Eur Respir J* 2014;43:195–203.
24 Greenland S, Drescher K. Maximum likelihood estimation of the attributable fraction from logistic models. *Biometrics* 1993;49: 865–872.
25 Diaz PT, King MA, Pacht ER, Wewers MD, Gadek JE, Nagaraja HN, *et al*. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;132:369–372.
26 Diaz PT, Wewers MD, Pacht E, Drake J, Nagaraja HN, Clanton TL. Respiratory symptoms among HIV-seropositive individuals. *Chest* 2003;123:1977–1982.
27 Drummond MB, Merlo CA, Astemborski J, Kalmin MM, Kisalu A, Mcdyer JF, *et al*. The effect of HIV infection on longitudinal lung function decline among IDUs: a prospective cohort. *AIDS* 2013;27: 1303–1311.
28 Louie JK, Hsu LC, Osmond DH, Katz MH, Schwarcz SK. Trends in causes of death among persons with acquired immunodeficiency syndrome in the era of highly active antiretroviral therapy, San Francisco, 1994–1998. *J Infect Dis* 2002;186:1023–1027.
29 Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, *et al*. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* 2013;173:614–622.
30 Freiberg MS, Chang CC, Skanderson M, McGinnis K, Kuller LH, Kraemer KL, *et al*.; Veterans Aging Cohort Study. The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circ Cardiovasc Qual Outcomes* 2011;4:425–432.
31 Ford ES, Cunningham TJ, Mannino DM. Inflammatory markers and mortality among US adults with obstructive lung function. *Respirology* 2015;20:587–593.
32 Min KB, Min JY. Reduced lung function, C-reactive protein, and increased risk of cardiovascular mortality. *Circ J* 2014;78:2309–2316.
33 Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, *et al*.; INSIGHT SMART Study Group. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med* 2008;5:e203.
34 McDonald B, Moyo S, Gabaitiri L, Gaseitsiwe S, Bussmann H, Koethe JR, *et al*. Persistently elevated serum interleukin-6 predicts mortality among adults receiving combination antiretroviral therapy in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses* 2013;29:993–999.
35 Tien PC, Choi AI, Zolopa AR, Benson C, Tracy R, Scherzer R, *et al*. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. *J Acquir Immune Defic Syndr* 2010;55:316–322.
36 Morris A, Gingo MR, George MP, Lucht L, Kessinger C, Singh V, *et al*. Cardiopulmonary function in individuals with HIV infection in the antiretroviral therapy era. *AIDS* 2012;26:731–740.
37 Fitzpatrick ME, Nouraie M, Gingo MR, Camp D, Kessinger CJ, Sincebaugh JB, *et al*. Novel relationships of markers of monocyte activation and endothelial dysfunction with pulmonary dysfunction in HIV-infected persons. *AIDS* 2016;30:1327–1339.
38 Fitzpatrick ME, Singh V, Bertolet M, Lucht L, Kessinger C, Michel J, *et al*. Relationships of pulmonary function, inflammation, and T-cell activation and senescence in an HIV-infected cohort. *AIDS* 2014;28: 2505–2515.
39 Mui TS, Man JM, McElhaney JE, Sandford AJ, Coxson HO, Birmingham CL, *et al*. Telomere length and chronic obstructive pulmonary disease: evidence of accelerated aging. *J Am Geriatr Soc* 2009;57:2372–2374.
40 Savale L, Chaouat A, Bastuji-Garin S, Marcos E, Boyer L, Maitre B, *et al*. Shortened telomeres in circulating leukocytes of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2009;179:566–571.
41 Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, *et al*.; Multicenter AIDS Cohort Study. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. *J Gerontol A Biol Sci Med Sci* 2007;62:1279–1286.
42 Donaldson GC, Hurst JR, Smith CJ, Hubbard RB, Wedzicha JA. Increased risk of myocardial infarction and stroke following exacerbation of COPD. *Chest* 2010;137:1091–1097.
43 Mapel DW, Dedrick D, Davis K. Trends and cardiovascular co-morbidities of COPD patients in the Veterans Administration Medical System, 1991–1999. *COPD* 2005;2:35–41.
44 Rothnie KJ, Yan R, Smeeth L, Quint JK. Risk of myocardial infarction (MI) and death following MI in people with chronic obstructive pulmonary disease (COPD): a systematic review and meta-analysis. *BMJ Open* 2015;5:e007824.
45 Sin DD, Man SF. Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proc Am Thorac Soc* 2005;2:8–11.
46 Sin DD, Wu L, Man SF. The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 2005;127:1952–1959.
47 Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, *et al*. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008;178: 738–744.
48 Gingo MR. The changing landscape of HIV-related lung disease: non-AIDS lung malignancy as a player in the field. *Respirology* 2014;19: 300–302.
49 Sigel K, Wisnivesky J, Gordon K, Dubrow R, Justice A, Brown ST, *et al*. HIV as an independent risk factor for incident lung cancer. *AIDS* 2012;26:1017–1025.
50 Hourani JM, Bellamy PE, Tashkin DP, Batra P, Simmons MS. Pulmonary dysfunction in advanced liver disease: frequent occurrence of an abnormal diffusing capacity. *Am J Med* 1991;90: 693–700.
51 Kanazawa H, Hirata K, Yoshikawa J. Accelerated decline of lung function in COPD patients with chronic hepatitis C virus infection: a preliminary study based on small numbers of patients. *Chest* 2003; 123:596–599.
52 Silva DR, Stifft J, Cheinquer H, Knorst MM. Prevalence of hepatitis C virus infection in patients with COPD. *Epidemiol Infect* 2010;138: 167–173.
53 Yigit IP, Hacievliyagil SS, Seckin Y, Oner RI, Karincaoglu M. The relationship between severity of liver cirrhosis and pulmonary function tests. *Dig Dis Sci* 2008;53:1951–1956.