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Lung Function, Coronary Artery Disease, and Mortality in HIV

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Abstract

Rationale: Impaired lung function is a potent independent predictor of coronary artery disease (CAD) in individuals without human immunodeficiency virus (HIV) infection; however, the relationship between lung function and CAD in HIV remains undefined.

Objectives: To examine the relationship between lung function, CAD, mortality, and circulating biomarkers in HIV.

Methods: Spirometry, diffusing capacity of the lung for carbon monoxide (D_{LCO}), emphysema, coronary artery calcium, mortality, cause of death, and biomarkers were examined in HIV-infected and uninfected individuals enrolled in a cohort study at the University of Pittsburgh. Results were then validated in the Multicenter AIDS Cohort Study (MACS) cohort.

Results: We examined data on 234 participants in the Pittsburgh cohort. The mean ± standard deviation age was 49.5 ± 10.2 years old, 82.1% were male, and 67.5% were ever smokers. Among the 177 of 234 individuals with HIV infection, lower D_{LCO} (not forced expiratory volume in 1 second or emphysema) was independently associated with greater coronary artery calcium (odds ratio, 1.43 per 10% lower D_{LCO}; 95% confidence interval, 1.14–1.81). HIV-infected individuals with both reduced D_{LCO} and coronary artery calcium had a much higher mortality than those with either low D_{LCO} or coronary calcium alone or with neither condition. Endothelin-1, a circulating biomarker of endothelial dysfunction, was associated with both lower D_{LCO} and greater coronary artery calcium in those with HIV infection. Results were reproducible in 144 individuals enrolled in the MACS cohort; intercellular adhesion molecule 1 was the biomarker of endothelial dysfunction assessed in the MACS cohort.

Conclusions: Impaired D_{LCO} and CAD were associated with each other and with higher mortality in individuals with HIV infection.

Keywords: HIV; coronary artery disease; mortality; endothelial dysfunction

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Coronary artery disease (CAD) is among the top five causes of death in persons with human immunodeficiency virus (HIV) infection, and its prevalence is increasing as these individuals live longer with modern antiretroviral therapy (ART) (1–3). Nonetheless, understanding of the determinants and risk factors for CAD in HIV remains incomplete.

In those without HIV infection, expiratory airflow limitation is a potent

independent predictor of CAD (4–6). For example, reduced forced expiratory volume in 1 second (FEV_1) was associated with a 77% increase in cardiovascular mortality compared with normal FEV_1 independent of smoking and other shared risk factors (pooled risk ratio, 1.77; 95% confidence interval [CI], 1.56–1.97) in a meta-analysis that included 83,330 individuals (7). Also, one-fourth of the attributable risk for mortality in ischemic heart disease was due to reduced FEV_1 in the Renfrew and Paisley community-based prospective cohort study (8). The findings of these studies have prompted greater awareness regarding the high morbidity and mortality due to CAD in those with chronic obstructive pulmonary disease (COPD) (9), efforts to incorporate FEV_1 into CAD risk stratification (10), and investigation into shared mechanisms between lung and coronary vascular injury (4). The latter has provided insight into the pathogenesis of both lung disease and atherosclerosis by novel inflammatory pathways as well as endothelial dysfunction (11, 12).

In contrast, despite the rising prevalence of lung disease and CAD with modern ART, it remains unclear if lung function and CAD are associated with each other in the HIV-infected population. On the one hand, there are differences in the epidemiology and pathogenesis of lung disease and CAD in individuals with versus without HIV infection (13–15). For example, COPD may occur at a younger age than in those without HIV infection and is associated with the degree of immunodeficiency (14, 16–19). Also, impaired diffusing capacity of the lung for carbon monoxide (D_{LCO}) is a more common lung function abnormality than airflow obstruction in those with HIV infection (20). Similarly, atherosclerosis occurs at an earlier age, and HIV Tat, gp120, and Nef proteins may play a unique role in its pathogenesis, unlike in those without HIV (21, 22). Despite these differences, an association between lung function and CAD in HIV is plausible because immune dysregulation and endothelial dysfunction occur in individuals with HIV infection similarly to uninfected individuals. Identification of such an association could have multiple implications, including potential inclusion of lung function in CAD risk prediction models in HIV and identification of shared mechanisms that may be targeted with novel multisystem therapies to simultaneously mitigate lung and atherosclerotic vascular injury in HIV.

In the present study, we examined the relationship between lung function and CAD and how such a relationship may be associated with mortality and with a panel of circulating biomarkers in a cohort of individuals with and without HIV infection at the University of Pittsburgh. To determine if the results were reproducible, we examined data from a second multicenter cohort, despite the use of different methodologies in the second cohort (the Multicenter AIDS Cohort Study [MACS]). We hypothesized that impaired lung function and CAD would be associated with each other and with increased mortality in individuals with HIV.

Methods

Study Cohort

Enrollment criteria for the University of Pittsburgh and MACS cohorts have been described in detail previously (23, 24). In brief, the Pittsburgh cohort recruited men and women with and without HIV from outpatient clinics who were free of acute respiratory symptoms in the prior 4 weeks, whereas the MACS enrolled homosexual and bisexual men older than 18 years of age and without clinical acquired immunodeficiency syndrome at enrollment at four metropolitan centers in the United States. MACS participants who had been enrolled in both the pulmonary and cardiovascular substudies at Pittsburgh and Los Angeles MACS sites were included in the current analysis. If a participant was enrolled in both the Pittsburgh cohort and the MACS cohort, the individual was analyzed as part of the MACS cohort to maximize sample size in the MACS dataset. Both studies were approved by the institutional review boards at all participating sites, and written informed consent was obtained from each participant.

Coronary Artery Calcium

In the Pittsburgh cohort, coronary artery calcium (CAC) was measured using non–EKG-gated noncontrast thoracic computed tomographic (CT) scans by Weston score (25), whereas in the MACS cohort, it was assessed using electrocardiogram (EKG)-gated cardiac noncontrast CT scans by Agatston score (26). We have previously validated the Weston score as an excellent surrogate for the Agatston score in individuals with and without HIV infection who were enrolled in the Pittsburgh and MACS cohorts (27), as have other investigators using data from other cohorts (25, 28, 29). Summed for the four coronary arteries, the total Weston score increases from 0 to 12 with increasing CAC. The Weston score was subcategorized using previously validated thresholds (i.e., none = 0; mild = 1, 2; moderate = 3–7; and severe = 8–12) (25, 27). Agatston scores were calculated using the area density method as described previously (26) and divided into four categories because of their skewed distribution per convention (i.e., none = 0; mild = 1–100; moderate = 101–400; and severe = >400) (30–32). Further details regarding CAC scoring are included in the online supplement.

The clinical interpretation of CAC scores has been discussed in detail previously in the general population (33), although data in individuals with HIV infection is not available, to our knowledge. A score of 0 is associated with a very low risk of future CAD events, and the risk for future CAD events increases with greater concentrations of CAC.

Lung Function, D_{LCO}, and Emphysema

In both cohorts, post-bronchodilator spirometry and D_{LCO} were assessed per American Thoracic Society guidelines (34) (*see* online supplement for details). D_{LCO} was defined as normal if it was greater than 80% of predicted in both cohorts.

Emphysema was assessed using density mask analysis of chest CT images as described previously (23). Two commonly used thresholds for quantifying emphysema (i.e., voxels depicting the lung with a Hounsfield unit [HU] value less than −950 [percentage low-attenuation area {LAA%} −950] or less than −910 [LAA% −910]) were used (35).

In the Pittsburgh cohort, pulmonary function tests and chest CT scanning were performed during the same study visit. In MACS participants, the median gap between pulmonary function and CAC assessments was 190 days (interquartile range [IQR], 102–400 d).

Cardiovascular Risk Factors

Established cardiovascular risk factors were assessed in both cohorts (*see* online supplement for details).

HIV Status

In both cohorts, HIV serostatus was defined during the same visit at which the CT scan was obtained. CD4 cell count, HIV viral level, and use of combination ART were assessed in individuals with HIV infection in both cohorts as described previously (23, 24).

Biomarkers

In the Pittsburgh cohort, concentrations of circulating markers of inflammation (interleukin [IL]-6 and IL-8), monocyte activation (sCD163 and sCD14), activation of coagulation and fibrinolytic systems (D-dimer), acute-phase response (high-sensitivity C-reactive protein), and endothelial dysfunction (endothelin-1) were measured by enzyme-linked immunosorbent assay or Luminex assay with samples collected during the same visit at which CT scanning and pulmonary function testing were performed, as described previously (36).

In the MACS cohort, levels of circulating biomarkers of systemic inflammation (IL-6), monocyte activation (sCD163 and sCD14), activation of coagulation and fibrinolytic systems (D-dimer), acute-phase response (fibrinogen and high-sensitivity C-reactive protein), tumor necrosis factor–mediated immune cell activation (soluble tumor necrosis factor-α receptor I [sTNFαRI] and receptor II [sTNFαRII]), and endothelial dysfunction (intercellular adhesion molecule 1 [ICAM-1]) were measured during the same visit that the CT scan was obtained, as described previously (37, 38).

Survival and Cause of Death

Survival in both cohorts was assessed via the Social Security Death Index and the National Death Index, supplemented by additional sources of information, such as physician or family report, obituaries, and medical record review. The methodology for determination of cause of death is described in the online supplement.

Statistical Analyses

Baseline characteristics were compared across severity of CAC. The association between lung function (predictor/independent variable) and CAC score (none/mild/moderate/severe as the outcome/dependent variable) was examined using ordinal logistic regression models. The proportional odds assumption was tested using the Brant test. To further ensure that results were not dependent on the use of ordinal regression models, analyses were repeated with presence/absence of any CAC as the outcome variable. Because calcium scores have skewed distributions with many zero values, transformations such as logarithms or square roots do not normalize their distributions and were not attempted. Established cardiovascular risk factors as well as lung function variables were adjusted for as confounders. It was specified *a priori* that all models would be stratified by the presence or absence of HIV infection. Because the MACS cohort included data from two centers, we also examined the impact of adjusting for study site.

Kaplan-Meier survival curves were plotted to examine survival, whereas Cox proportional hazards models were used to estimate hazard ratios (HRs) adjusted for covariates. Survival time was ascertained from the date of the CT scan.

The chi-square test was used to compare categorical variables, and the Kruskal-Wallis test was used for continuous variables. *Post hoc* power analyses and multiple imputation for missing data were performed (*see* online supplement for details). Analyses were performed using Stata MP version 14.1 (StataCorp). A two-tailed P value less than 0.05 was defined as statistically significant. Adjustment for multiple comparisons by estimation of false discovery rates was not considered necessary, because the number of predictors for a given outcome was modest (e.g., various measures of pulmonary function as predictors of CAC and six or seven biomarkers as predictors of D_{LCO} and CAC).

Results

Participant Characteristics, Lung Function, and CAC in the Pittsburgh Cohort

We included 234 participants after excluding 109 who were enrolled in both cohorts, 48 with missing blood pressure measurements, 27 with missing emphysema assessment, 5 without D_{LCO} assessment, and 13 with missing information for various other variables. The 109 individuals enrolled in both the Pittsburgh and MACS cohorts were included in the MACS dataset rather than in the Pittsburgh cohort to preserve statistical power in the MACS dataset ($n = 161$, including the 109 coenrolled). Included participants tended to be younger (49.6 ± 10.2 vs. 55.2 ± 8.8 yr), were more frequently current smokers (43.2% vs. 28.6%), had lower D_{LCO} (71.8 ± 14.7% vs. 86.8 ± 18.0% predicted), and were more frequently HIV infected (75.6% vs. 56.8%) than excluded participants.

Participants in the Pittsburgh cohort were 49.6 ± 10.2 years of age, 82.1% male, 59.8% non-Hispanic white, and 67.5% ever smokers. One hundred seventy-seven had HIV infection (75.6%) and had mostly preserved CD4 counts (median, 602 cells/μl; IQR, 390–811 cells/μl) and low HIV viral levels (undetectable in 71.2%). Expiratory airflow limitation was on average mild, although individuals with a wide range of severity were enrolled (post-bronchodilator FEV_1, 93.2 ± 18.3; range, 34.4–139.4%; FEV_1/forced vital capacity [FVC], 0.80 ± 0.08; range, 0.45–0.97; 15.4% met the spirometric definition of airflow limitation [i.e., $FEV_1/FVC < 0.7$]). Similarly, D_{LCO} was mildly impaired on average (71.8 ± 14.7% predicted); however, individuals with a wide range of D_{LCO} values were enrolled (range, 20.8–112.8%).

Fifty-six percent of participants had no CAC, whereas 23.9% had mild, 7.7% had moderate, and 12.4% had severe CAC (Table 1). The median CAC score was 0 (IQR, 0–3) in all comers, 0 (IQR, 0–6) in those without HIV, and 0 (IQR, 0–3) in those with HIV infection ($P = 0.42$ comparing those with and without HIV infection). D_{LCO} and FEV_1/FVC ratio both decreased significantly with increasing CAC in unadjusted analyses (Table 1) per 10% decrease in D_{LCO} percent predicted (odds ratio [OR], 1.25; 95% CI, 1.05–1.48) and per 10% lower FEV_1/FVC (OR, 1.40; 95% CI, 1.06–1.85). In contrast, we did not detect an association between either lower FEV_1 percent predicted or emphysema measures with CAC (Table 1) per 10% decrease in FEV_1 percent predicted (OR, 1.13; 95% CI, 0.98–1.30) and per 10% greater LAA% −910 HU (OR, 1.01; 95% CI, 0.98–1.04). We did not detect an association between CAC and HIV serostatus, CD4 count, viral load, or use of ART. Expected associations between CAC and older age, male sex, white race, and higher systolic blood pressure were present (Table 1).

Participant Characteristics, Lung Function, and CAC in the MACS Cohort

In the MACS cohort, 161 participants underwent measurement of lung function

and CAC. Four were excluded because of missing D_{LCO} values, one was excluded because of missing CAC score, and 12 were excluded because of missing data for other variables. The remaining 144 participants were 54.3 ± 7.0 years old, all men, 82.1% non-Hispanic white, and 77.6% ever smokers. Eighty-one (56.2%) had HIV infection, with mostly preserved CD4 counts (median, 644 cells/μl; IQR, 399 cells/μl) and low HIV viral levels (undetectable in 77.4%). Similarly to the Pittsburgh cohort, airflow limitation and D_{LCO} were minimally impaired, on average, but with a wide range of severity (FEV_1, 101.4 ± 18.3; range, 43.3–132.9% predicted; FEV_1/FVC, 0.80 ± 0.08; range, 0.48–0.90; with 12.5% meeting the spirometric definition of airflow limitation [i.e., FEV_1/FVC <0.7; D_{LCO}, 85.0 ± 21.1; range, 27.4–138.3% predicted).

No CAC was present in 43.1% of participants, whereas 25.0% had mild, 23.6% had moderate, and 8.3% had severe CAC (Table 1). The median CAC score was 12.5 (IQR, 0–139.9) in all comers, 14.8 (IQR, 0–184.2) in those without HIV, and 9.1 (IQR, 0–131.23) in those with HIV infection (P = 0.90 comparing those with and without HIV infection). Findings in the Pittsburgh cohort were also present in MACS (1): Reduced D_{LCO} and FEV_1/FVC values were associated with higher CAC scores per 10% less D_{LCO} percent predicted (OR, 1.28; 95% CI, 1.07–1.51) and per 10% lower FEV_1/FVC (OR, 1.47; 95% CI, 1.04–2.01) (2). Neither FEV_1 per 10% less FEV_1 percent predicted (OR, 1.11; 95% CI, 0.93–1.34) nor emphysema per 10% higher LAA% −910 HU (OR, 0.90; 95% CI, 0.72–1.15) was associated with CAD (3), HIV infection (OR, 1.13; 95% CI, 0.62–2.08), CD4 count per 100/ml lower CD4 count (OR, 0.98; 95% CI, 0.93–1.11; n = 81), viral load per 1,000/ml higher viral load (OR, 0.98; 95% CI, 0.95–1.02; n = 81), and use of ART (OR, 2.03; 95% CI, 0.62–6.67; n = 81) were not associated with CAC scores (Table 2).

Multivariate Analyses

Because D_{LCO} demonstrated a statistically significant association with CAC in both cohorts, unlike FEV_1 percent predicted and measures of emphysema severity, it was further examined in adjusted models. Also, impairment in D_{LCO} is the most common lung function abnormality in individuals with HIV infection and is associated with inflammation and pulmonary vascular disease (20, 39).

Participant characteristics stratified by D_{LCO} are summarized in Tables E1 and E2 in the online supplement. In the Pittsburgh cohort, each 10% lower D_{LCO} was associated with a 43% increase in the odds of being in one higher category of severity of CAC score (OR, 1.43; 95% CI, 1.14–1.81) (Figure 1) after adjustment for age, sex, race, pack-years of smoking, systolic blood pressure,

Table 1. Characteristics of the participants in the University of Pittsburgh cohort, stratified by severity of coronary artery calcium

	None	Mild	Moderate	Severe
n (%)	131 (56.0)	56 (23.9)	18 (7.7)	29 (12.4)
Age, yr	45.7 (9.7)	51.9 (7.9)	55.8 (9.6)	58.6 (8.2)
Male sex, *n* (%)	98 (74.8)	50 (89.3)	18 (100.0)	26 (89.7)
Race				
Non-Hispanic white, *n* (%)	62 (47.3)	40 (71.4)	15 (83.3)	23 (79.3)
Non-Hispanic black, *n* (%)	69 (52.7)	16 (28.6)	3 (16.7)	6 (20.7)
Blood pressure				
Systolic, mm Hg	125.3 (15.7)	130.4 (14.8)	128.0 (17.2)	131.6 (14.6)
Diastolic, mm Hg	76.7 (10.8)	79.8 (8.8)	81.1 (6.6)	77.7 (10.6)
Diabetes mellitus, *n* (%)	6 (4.6)	0 (0.0)	1 (5.6)	4 (13.8)
BMI, kg/m^2	28.2 (6.3)	27.1 (6.2)	26.0 (4.9)	28.6 (4.9)
Smoking status				
Never smoker, *n* (%)	36 (27.5)	23 (41.1)	8 (44.4)	9 (31.0)
Prior smoker, *n* (%)	36 (27.5)	11 (19.6)	3 (16.7)	7 (24.1)
Current smoker, *n* (%)	59 (45.0)	22 (39.3)	7 (38.9)	13 (44.8)
Pack-years of smoking (n = 158)*	14.3 (15.7)	17.2 (22.3)	16.1 (17.3)	21.6 (24.8)
FEV_1, % predicted	96.0 (18.3)	93.1 (17.0)	90.9 (18.9)	90.6 (20.3)
FEV_1/FVC	0.79 (0.07)	0.77 (0.09)	0.75 (0.11)	0.76 (0.10)
D_{LCO}, % predicted	73.8 (14.5)	71.0 (14.8)	64.8 (15.0)	68.5 (14.3)
LAA% −950 HU	1.7 (4.1)	2.0 (3.2)	1.4 (1.1)	1.6 (1.5)
LAA% −910 HU	9.5 (10.0)	11.7 (9.7)	10.0 (8.3)	10.4 (7.5)
HIV infected, *n* (%)	100 (76.3)	47 (83.9)	11 (61.1)	19 (65.5)
CD4 count, hundreds/ml (n = 177)†‡	6.2 (3.9–8.6)	6.0 (4.6–7.7)	4.1 (2.1–6.9)	6.2 (3.5–7.2)
Viral load undetectable, % (n = 177)†	69.0	70.2	63.6	89.5
Viral load, thousands/ml (n = 51)‡§	4.6 (0.3–37.4)	0.3 (0.09–1.9)	0.6 (0.3–8.1)	16.5 (0.7–32.2)
ART, *n* (%) (n = 177)†	88 (67.20)	37 (66.1)	10 (55.6)	19 (65.5)

Definition of abbreviations: ART = antiretroviral therapy; BMI = body mass index; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HIV = human immunodeficiency virus; LAA% −910 HU = percentage low-attenuation area at values less than −910 Hounsfield units; LAA% −950 HU = percentage low-attenuation area at values less than −950 Hounsfield units; SD = standard deviation. Severity of coronary artery calcium is scored for the Weston score as follows: none = 0; mild = 1–2; moderate = 3–7; and severe = 8–12. Continuous variables are summarized as mean ± SD, unless noted otherwise.

*Pack-years are reported only for the 158 current and prior smokers.

†CD4 count, viral load undetectable, and ART use are reported only for the 177 HIV-seropositive individuals.

‡Reported as median (interquartile range) because of the highly skewed distribution.

§Reported in the 51 of 177 HIV-positive patients with detectable viral load.

Table 2. Characteristics of the participants in the Multicenter AIDS Cohort Study cohort, stratified by severity of coronary artery calcium

	None	Mild	Moderate	Severe
n (%)	62 (43.1)	36 (25.0)	34 (23.6)	12 (8.3)
Age, yr	51.5 (6.6)	56.7 (6.9)	56.6 (6.5)	58.9 (4.9)
Race, *n* (%)				
Non-Hispanic white	42 (67.7)	31 (86.1)	29 (85.3)	12 (100.0)
Non-Hispanic black	15 (24.2)	5 (13.9)	5 (14.7)	0 (0.0)
Other	5 (8.1)	0 (0.0)	0 (0.0)	0 (0.0)
BMI, kg/m^2	26.3 (4.2)	27.1 (4.6)	28.2 (5.8)	28.3 (6.9)
Smoking status				
Pack-years of smoking, *n* (*n* = 95)*	10.6 (15.2)	13.5 (19.0)	23.6 (23.6)	21.1 (18.7)
Ever smoker, *n* (%)	44 (71.0)	28 (77.8)	28 (84.8)	11 (91.7)
Diabetes mellitus, *n* (%)	4 (6.6)	0 (0.0)	7 (23.3)	1 (10.0)
Hypertension, *n* (%)	21 (36.8)	20 (58.8)	20 (66.7)	9 (75.0)
Hyperlipidemia, *n* (%)	47 (75.8)	29 (80.6)	28 (87.5)	12 (100.0)
FEV_1, % predicted	99.8 (15.1)	100.3 (16.5)	97.6 (16.9)	92.2 (26.6)
FEV_1/FVC	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)
D_{LCO}, % predicted	89.7 (19.6)	86.6 (14.7)	80.1 (19.2)	78.0 (21.2)
LAA% −950 HU	18.8 (15.7)	17.0 (12.1)	16.1 (11.6)	18.0 (10.9)
LAA% −910 HU	3.3 (6.2)	2.3 (2.3)	2.9 (4.4)	2.6 (2.3)
HIV seropositive, *n* (%)	34 (54.8)	21 (58.3)	17 (50.0)	9 (75.0)
CD4 count, hundreds/ml (*n* = 81)†‡	6.7 (3.9–8.5)	5.8 (4.8–7.4)	6.4 (4.3–8.5)	7.0 (5.9–9.0)
Viral load undetectable, % (*n* = 81)†	64.7	90.5	94.1	66.7
Viral load, thousands/ml (*n* = 21)†‡§	1.2 (0.6–17.4)	0.05 (0.02–0.08)	40.4 (40.4–40.4)	3.7 (0.8–35.1)
Duration of ART, yr (*n* = 81)†	8.2 (11.2)	11.1 (7.4)	8.5 (5.3)	12.9 (5.8)

Definition of abbreviations: ART = antiretroviral therapy; BMI = body mass index; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HIV = human immunodeficiency virus; LAA% −910 HU = percentage low-attenuation area at values less than −910 Hounsfield units; LAA% −950 HU = percentage low-attenuation area at values less than −950 Hounsfield units; SD = standard deviation.
Severity of coronary artery calcium is scored for the Agatston score as follows: none = 0; mild = 1–100; moderate = 101–400; and severe = >401.
Continuous variables are summarized as mean ± SD, unless noted otherwise.
*Pack-years are reported only for the 95 current and prior smokers.
†CD4 count, viral load, and ART use are reported only for the 81 HIV-seropositive individuals.
‡Reported as median (interquartile range) because of the highly skewed distribution.
§Reported in the 21 of 81 HIV-positive patients with detectable viral load.

diabetes mellitus, LAA% −910 HU, and FEV_1 percent predicted. The association was statistically significant only in those with HIV infection, although the sample size (and hence statistical power) was lower in the HIV-uninfected subgroup and *P* value for interaction due to HIV status was nonsignificant (*P* = 0.24) (Figure 1).

The presence and magnitude of this association was reproduced in the MACS cohort: Each 10% lower D_{LCO} percent predicted level was associated with a 48% increase in the odds of being in one higher category of severity of CAC score (OR, 1.44; 95% CI, 1.12–1.90) (Figure 1) after adjusting for age, race, pack-years of smoking, hypertension, diabetes, hyperlipidemia, LAA% −910 HU, and FEV_1 percent predicted. Similarly to the Pittsburgh cohort, the fully adjusted association appeared stronger in those with HIV infection, although the sample size (and hence statistical power) was lower in the HIV-uninfected subgroup and the *P* value for interaction due to HIV status was nonsignificant (*P* = 0.46) (Figure 1).

When analyses were repeated with presence or absence of CAC as the outcome variable, the results were unchanged (*see* online supplement). Also, the Brant test for the proportional odds assumption generated a nonsignificant *P* value, suggesting that the proportional odds assumption had not been violated (*P* = 0.46 in the Pittsburgh cohort and *P* = 0.82 in MACS data). Finally, adjustment for study site in the MACS cohort did not impact the results, and study site was not a significant predictor of CAC score (*P* = 0.98) (*see* online supplement)

Impaired D_{LCO}, CAC, and Mortality

Because the association between D_{LCO} and CAC was significant only in those with HIV infection in both cohorts (Figure 2), further examination of this association was performed in the participants with HIV infection in both cohorts. To understand the clinical significance of the association between reduced D_{LCO} and increased CAC in the HIV-infected cohort, we examined mortality in those with both reduced D_{LCO} and presence of calcium compared with those with only reduced D_{LCO}, only presence of calcium, and absence of both low D_{LCO} and calcium (Tables E3 and E4). Those with a low D_{LCO} and presence of CAC had significantly higher mortality than those in either of the other subgroups (Figure 2).

In the Pittsburgh cohort, over a median follow-up of 5.9 years (IQR, 5.2–7.1 yr), mortality was 21.6% in those with low D_{LCO} and presence of calcium (HR, 6.3; 95% CI, 1.3–29.7), 12.5% in those with normal D_{LCO} and presence of calcium (HR, 3.3; 95% CI, 0.6–17.4), 10.4% in those with low D_{LCO} and no calcium (HR, 2.6; 95% CI, 0.5–13.3), and 3.8% in those with normal D_{LCO} and no calcium (reference group). Adjustment for age, sex, race, pack-years of smoking, CD4 count, and viral load had minimal impact on these findings. Specifically, those with low D_{LCO} and presence of calcium had increased mortality compared with those with normal D_{LCO} and no calcium (adjusted HR, 6.7;

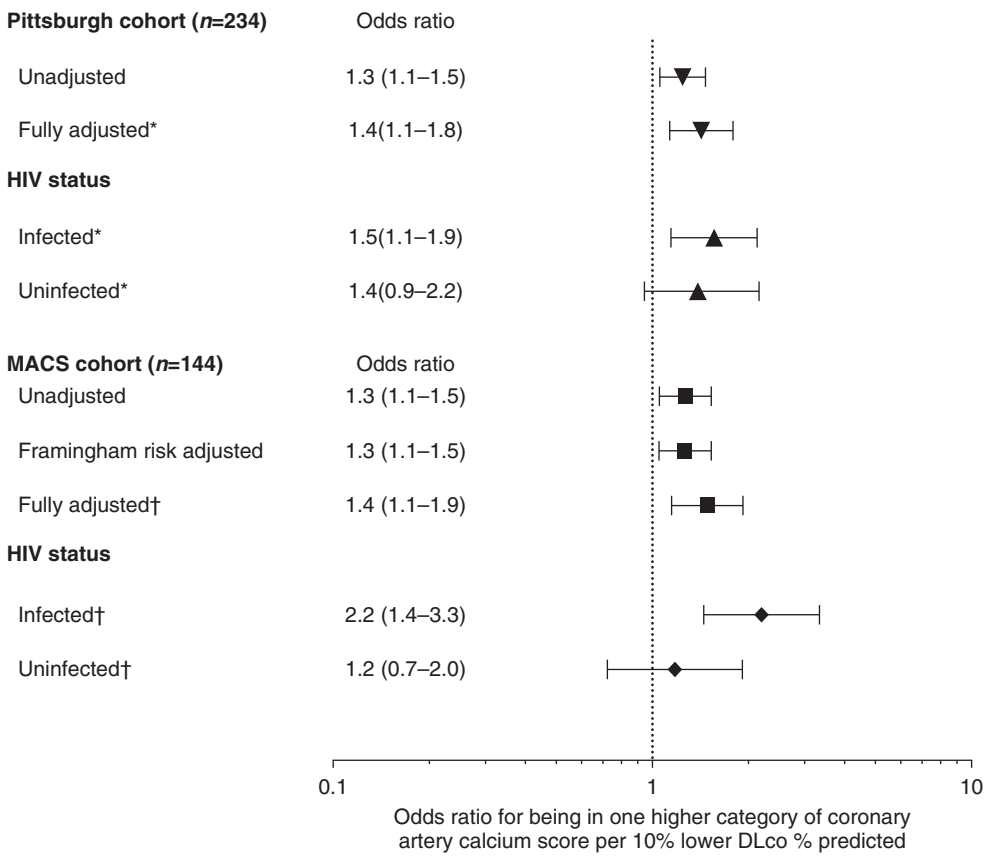

Figure 1. The unadjusted and adjusted odds ratios for the associations between diffusing capacity of the lung for carbon monoxide (D_{LCO}) and coronary artery calcium score among 234 participants in the Pittsburgh cohort and 144 participants in the Multicenter AIDS Cohort Study (MACS) cohort. The fully adjusted associations were further stratified by the presence or absence of human immunodeficiency virus (HIV) infection. *Variables adjusted for: age, sex, race, pack-years of smoking, systolic blood pressure, history of diabetes mellitus, LAA% −910 HU, and FEV_1 % predicted. †Variables adjusted for: age, race, pack-years of smoking, presence of hypertension, presence of diabetes, presence of hyperlipidemia, LAA% −950 HU, and FEV_1 % predicted. FEV_1 = forced expiratory volume in 1 second; LAA% −910 HU = percentage low-attenuation area at values less than −910 Hounsfield units; LAA% −950 HU = percentage low-attenuation area at values less than −950 Hounsfield units.

95% CI, 1.2–36.0), whereas there was no statistically significant difference in mortality in the other subgroups (normal D_{LCO} and presence of calcium, and low D_{LCO} and no calcium) compared with those with normal D_{LCO} and no calcium.

Results were similar in the MACS cohort: Mortality was 26.3% in those with low D_{LCO} and CAC compared with 10.7% in those with normal D_{LCO} and CAC, 0% in those with low D_{LCO} and no coronary calcium, and 0% in those with normal D_{LCO} and no coronary calcium ($P = 0.009$) over a median follow-up of 6.6 years (IQR, 5.5–7.1 yr).

Examination of the cause of death in the Pittsburgh cohort revealed that only one death was related to immunodeficiency (Table E5). Although the number of deaths was low, liver disease was a frequent cause of death in those with low D_{LCO} and CAC. Similarly, in the MACS cohort, deaths occurred for various reasons unrelated to immunodeficiency (Table E6). Therefore, these data suggested that the presence of impaired D_{LCO} and CAC was associated with worse survival due to non–immunodeficiency-related causes.

Impaired D_{LCO}, CAC, and Biomarkers

Next, to gain insight into pathological processes associated with both D_{LCO} impairment and CAD, we sought biomarkers associated with both reduced D_{LCO} and increased CAC in individuals with HIV infection. In the Pittsburgh cohort, the only such biomarker was endothelin-1, a marker of endothelial dysfunction (Figure 3). Although endothelin-1 had not been assessed in MACS, the related biomarker of endothelial dysfunction, ICAM-1, showed the same associations with decreasing D_{LCO} and increasing coronary calcium (Figure 3). Further details of the biomarker analyses are included in the online supplement.

Missing Data, Power, and Sample Size

Analyses performed to determine the impact of missing data did not suggest significant bias due to missing data (*see* online supplement). Power and sample size calculations suggested that in individuals without HIV, the ability to detect an association between D_{LCO} and CAC was limited by the small sample size (*see* online supplement and Figure E1). Therefore, the absence of an association between D_{LCO} and CAC in individuals without HIV infection in our analyses may have resulted from inadequate power rather than from the true absence of an association.

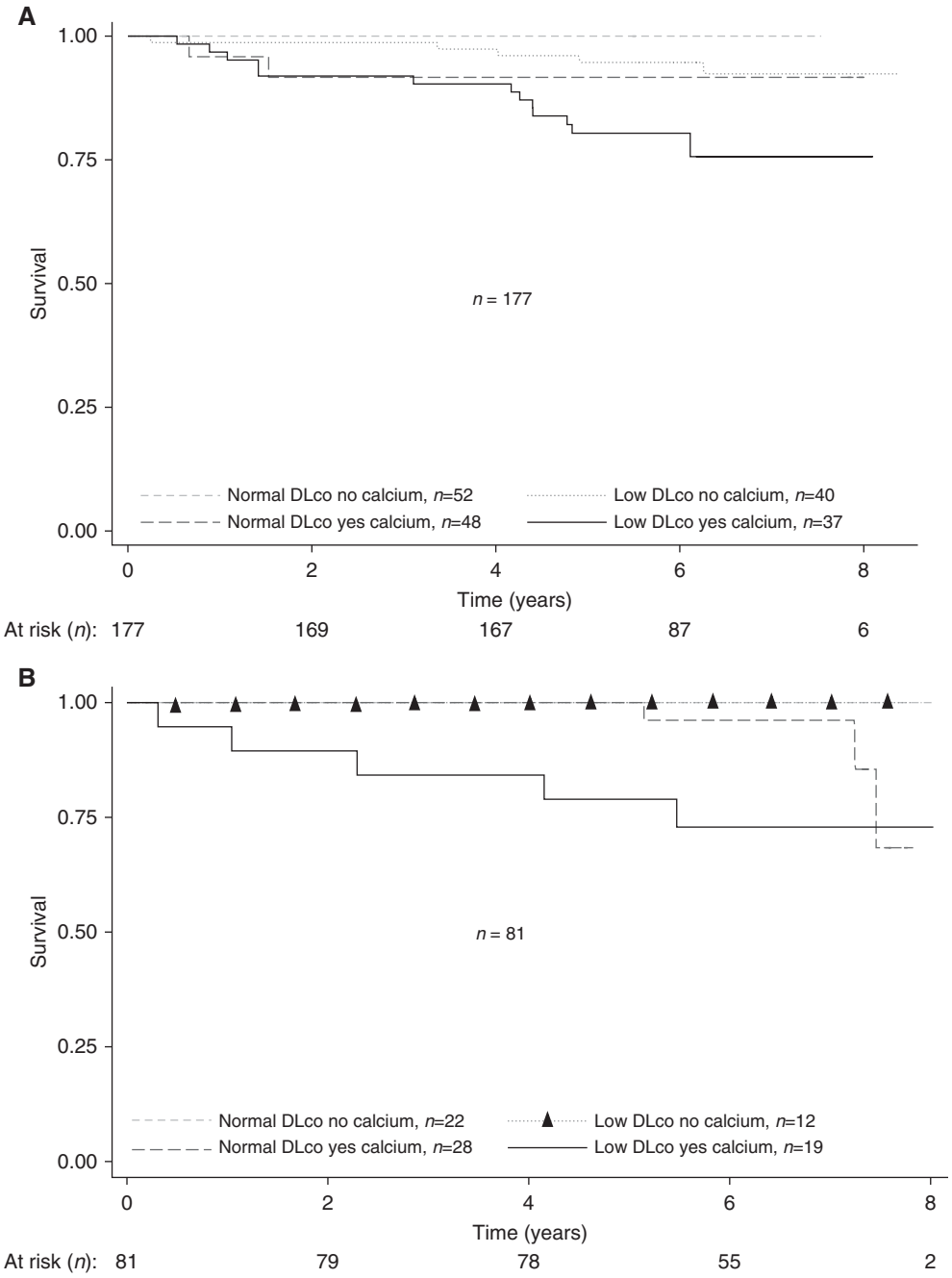

Figure 2. Kaplan-Meier survival curves stratified by presence/absence of coronary artery calcium and presence/absence of reduced diffusing capacity of the lung for carbon monoxide (D_{LCO}) among (*A*) 177 participants with human immunodeficiency virus (HIV) infection in the Pittsburgh cohort and (*B*) 81 participants with HIV infection in the Multicenter AIDS Cohort Study.

Discussion

We examined the association between lung function and CAD in individuals with and without HIV. Our results suggest that impaired D_{LCO}, rather than airflow limitation or emphysema, is independently associated with greater CAC in individuals with HIV infection. Furthermore, this association appeared to be clinically meaningful because individuals with HIV infection with reduced D_{LCO} and presence of CAC were at increased risk of death compared with those with only D_{LCO} impairment, only coronary artery calcification, or neither. Biomarkers of endothelial dysfunction were associated with both impaired D_{LCO} and increased CAC scores in the individuals with HIV infection. These results were reproducible in an unrelated cohort of individuals enrolled in a multicenter study.

In individuals without HIV, the association between impaired FEV_1 and CAD is well established (4, 7, 11). This association has led to increased awareness regarding the morbidity and mortality of

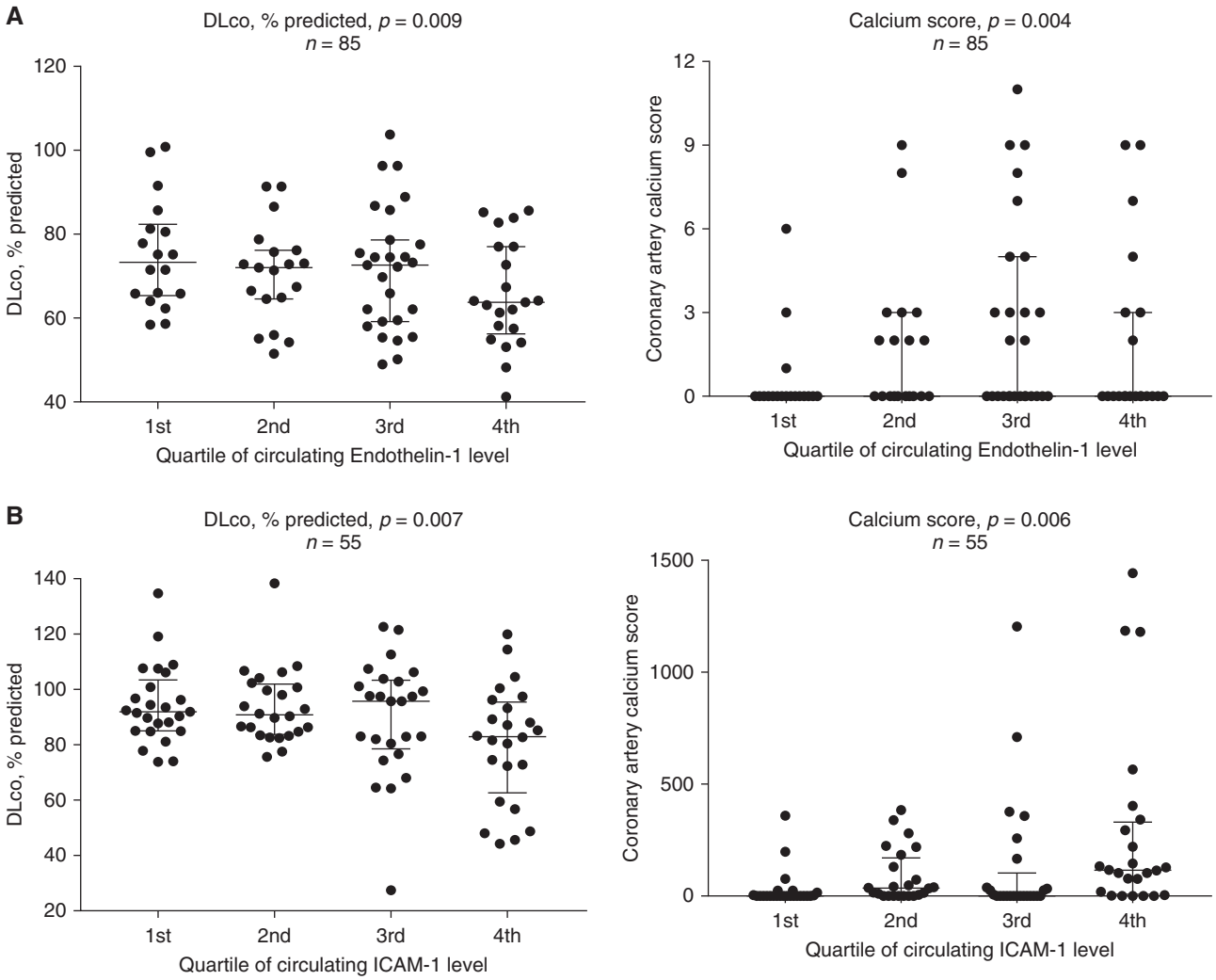

Figure 3. The diffusing capacity of the lung for carbon monoxide (D_{LCO}) percent predicted and coronary artery calcium score (median with interquartile range) in participants with human immunodeficiency virus infection, grouped by quartile of circulating endothelin-1 level in (*A*) the Pittsburgh cohort and by quartile of circulating intercellular adhesion molecule 1 (ICAM-1) level in (*B*) the Multicenter AIDS Cohort Study.

CAD in COPD, efforts to screen for CAD in those with COPD, and efforts to incorporate airflow limitation in CAD risk prediction models in COPD (9, 10). Also, a number of shared mechanisms for lung and coronary atherosclerosis have been identified, and it is now widely accepted that lung disease and CAD may be manifestations of shared underlying biological processes.

One such biological process is systemic endothelial dysfunction (40, 41). Endothelial dysfunction often refers to reduced bioavailability and impaired vasodilatory effects of endothelium-derived relaxing factors such as nitric oxide, prostacyclin, or endothelium-derived hyperpolarizing factors (42). Endothelial dysfunction in systemic arteries is a precursor to atherosclerosis and has also been linked to pulmonary emphysema in those without HIV (41). Nonetheless, the role of endothelial dysfunction as a physiological abnormality linking lung disease and CAD in those without HIV infection remains controversial (4).

In individuals with HIV, impaired D_{LCO} rather than airflow limitation appeared to be associated with CAD in our cohorts. Possible explanations for this finding include the underlying pathophysiology of lung impairment and CAD being different in individuals with HIV than in the general population. As discussed above, COPD occurs at a younger age than in those without HIV infection and is associated with the degree of immunodeficiency in individuals with HIV infection. Similarly, atherosclerosis occurs at an earlier age, and HIV-specific mechanisms and mediators (HIV Tat, gp120, Nef proteins) may play a unique role. Alternatively, this finding may be due to chance or may be related to inadequate power to detect an association between FEV_1 and CAC, despite adequate power to detect an association between D_{LCO} and CAC.

Only one prior study has examined the relationship between lung disease and CAD, to our knowledge (43). In this study, Agatston CAC scores and visual emphysema scores were assessed using EKG-gated cardiac CT scans. The presence of emphysema was associated with the

presence of CAC (OR, 1.34; 95% CI, 1.08–1.88; $P = 0.01$) independent of age, sex, smoking status, pack-years of smoking, visceral adiposity, and duration of HIV infection. Assessment of lung function, D_{LCO}, mortality, and biomarkers was not performed. Unlike the prior study, in our examination of the Pittsburgh and the MACS cohorts, quantitative assessments of emphysema were not associated with CAC scores. Therefore, it is possible that had spirometry and D_{LCO} been measured in the previous study, they would have been more closely associated with CAC than with emphysema. Nonetheless, as interest in assessment of CAC and emphysema using lung cancer screening CT scans continues to increase, it is likely that more data regarding a possible association between emphysema and CAC in HIV will become available in the future (44).

Multiple studies show that endothelial dysfunction occurs in individuals with HIV infection regardless of ART and is a risk factor for accelerated atherosclerosis (45–48). Our biomarker data suggest that endothelial dysfunction is associated not only with atherosclerosis but also with pulmonary vascular dysfunction as assessed by D_{LCO}. In a previous analysis of data from the Pittsburgh cohort, we reported that higher IL-6 and endothelin-1 were associated with lower FEV_1 percent predicted; higher sCD163 was associated with worse FEV_1/FVC; and higher IL-6, TNF-α, lipopolysaccharide, sCD163, IL-2 receptor, and endothelin-1 were associated with lower D_{LCO}. The present results suggest that among these biomarkers, endothelin-1 may be unique because it is also associated with CAD. Although the biomarker results are intriguing, they should be considered preliminary pending independent replication because different biomarkers were examined in the two cohorts.

Examination of the cause of death suggested that mortality was largely unrelated to immunodeficiency. The causes appeared variable with no obvious connection to CAD, impaired D_{LCO}, or endothelial dysfunction. Although the numbers are small, it is possible that death caused by liver disease was more frequent in those with low D_{LCO}, possibly because liver disease can be associated with impaired D_{LCO}.

To integrate the various findings of our analyses, we present a hypothetical conceptual diagram (Figure 4). In this model, HIV infection induces pulmonary and systemic endothelial dysfunction. The resulting pulmonary endothelial injury propagates pulmonary vascular dysfunction manifesting as impaired D_{LCO} (46), whereas coronary endothelial dysfunction leads to coronary atherosclerosis manifesting as increased CAC score (47). Impairment of D_{LCO} and CAD, in turn, contributes to increased mortality. This model is hypothetical because we did not examine the causality or underlying mechanisms of the associations presented; however, it represents one possible framework for integration of the associations described in the present study.

Our findings may have multiple implications. First, addition of lung function to CAD risk prediction models may help improve the calibration and tendency of these models to underestimate CAD risk in HIV (49, 50). Furthermore, identification of shared mechanisms for lung disease and CAD in HIV may provide avenues to develop novel multisystem therapies. For example, statins are known to reduce endothelial dysfunction and CAD in HIV (51, 52). In a recent pilot study, we found that statin therapy also improves lung function, including D_{LCO}, in individuals with HIV infection and also decreases circulating endothelin-1 concentrations (53). Therefore, it is plausible that statins may be an effective multisystem therapy in HIV that can simultaneously reduce pulmonary disease and CAD by targeting the shared underlying mechanism of endothelial dysfunction.

The present study has limitations. First, CAC was assessed using non–EKG-gated CT scans in the Pittsburgh cohort. However, this technique has been validated by multiple independent investigators (25, 27–29), and results were the same for CAC assessed by EKG-gated cardiac CT scans in the MACS cohort (Agatston scores). Although it is possible to perform Agatston scoring on the non–EKG-gated CT scans, this technique requires proprietary cardiac imaging software and specialized expertise, making it time and cost prohibitive for our study. Similarly, lipid panels and fasting blood glucose were not measured in the Pittsburgh cohort, but these were assessed in the MACS cohort, and the same independent associations between D_{LCO} and CAD were identified. Second, in the MACS cohort, emphysema assessment was performed using different CT scanners at the two centers. However, adjustment for study site did not alter our findings, suggesting that use of different CT equipment did not introduce significant bias in our results. Third, related but different biomarkers for endothelial dysfunction were assessed in the two cohorts. Also, we did not have data on pulmonary artery systolic pressure, right ventricular function, or interstitial abnormalities that can all impact D_{LCO} and mortality (54). Furthermore, owing to the methodological differences between the two cohorts, we decided not to merge the two datasets into one statistical analysis. Therefore, findings from the two cohorts stand alone and do not confound each other. Although differences in methodology between cohorts complicate the presentation and interpretation of data, replication of results in a second multicenter cohort that used different methods strengthens the validity of the results.

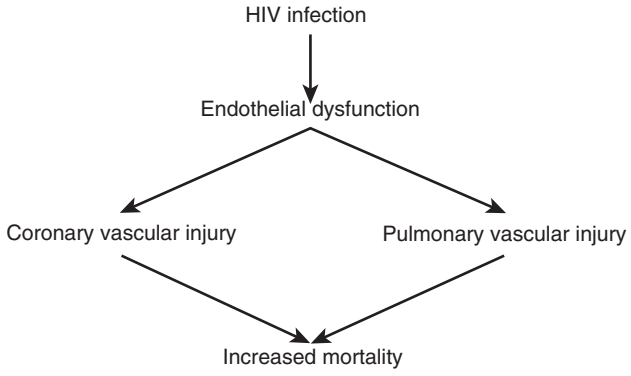

Figure 4. A hypothetical conceptual diagram based on the various associations identified in the present study. HIV = human immunodeficiency virus.

Finally, statistical power was limited for some comparisons, particularly in individuals without HIV infection, and multiple biomarkers were analyzed, raising the risk of false-negative and false-positive results, respectively.

In conclusion, we identified a novel independent association between impaired D_{LCO} and CAD in individuals with HIV infection. Pulmonary vascular and coronary vascular injury should be further investigated as potentially related processes that may be associated with markers of endothelial dysfunction and higher mortality in HIV. Future studies should also examine if addition of D_{LCO} improves CAD risk prediction models in HIV and explore shared mechanisms for lung and coronary vascular injury that may provide insight into the pathogenic mechanisms of lung and cardiovascular disease in HIV. ■

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