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Systemic Inflammation, Immune Activation and Impaired Lung Function among People Living with HIV in Rural Uganda

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Abstract

Background—Although both chronic lung disease and HIV are inflammatory diseases common in sub-Saharan Africa, the relationship between systemic inflammation and lung function among people living with HIV (PLWH) in sub-Saharan Africa is not well described.

Methods—We measured lung function (using spirometry) and serum high sensitivity C-reactive protein, IL-6, sCD14 and sCD163 in 125 PLWH on stable antiretroviral therapy and 109 age and sex-similar HIV-uninfected controls in rural Uganda. We modeled the relationship between lung function and systemic inflammation using linear regression, stratified by HIV serostatus, controlled for age, sex, height, tobacco and biomass exposure.

Results—Half of subjects (46%, [107/234]) were women and the median age was 52 years (IQR 48–55). Most PLWH (92%, [115/125]) were virologically suppressed on first-line antiretroviral therapy. Median CD4 count was 472 cells/mm^3. In multivariable linear regression models stratified by HIV serostatus, an interquartile range increase in IL-6 and sCD163 were each inversely associated with lung function (mL, 95% confidence interval) among PLWH (IL-6: FEV_1 −18.1 (−29.1, −7.1), FVC −17.1 (−28.2, −5.9); sCD163: FVC −14.3 (−26.9, −1.7)). hsCRP (>3mg/L *vs.* <1mg/L) was inversely associated with lung function among both PLWH and HIV-uninfected controls (PLWH: FEV_1 −39.3 (−61.7, −16.9), FVC −44.0 (−48.4, −6.4); HIV-uninfected: FEV_1 −37.9 (−63.2, −12.6), FVC −58.0 (−88.4, −27.5)). sCD14 was not associated with lung function, and all interaction terms were insignificant.

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AUTHOR CONTRIBUTIONS

CMN conceived of the study design, conducted the data analysis and wrote the first draft of the manuscript. DCC and MJS provided methodological guidance. SO, MJS, BK and ACT led study procedures and data collection. RT and DSK led biomarker-related testing. All authors reviewed and critiqued the final manuscript.

Conclusions—Macrophage activation and systemic inflammation are associated with lower lung function among PLWH on stable antiretroviral therapy in rural Uganda. Future work should focus on underlying mechanisms and public health implications.

Keywords

AIDS; Spirometry; Respiratory; Africa; Biomarker

INRODUCTION

People living with HIV (PLWH) are at increased risk for chronic obstructive pulmonary disease (COPD)[1–3] through various poorly understood mechanisms including direct virus-related pulmonary toxicity, persistent systemic inflammation, and accelerated immune senescence. The lungs are an HIV reservoir, even among PLWH with undetectable viral loads.[4,5] HIV-infected pulmonary macrophages, lymphocytes and airway epithelial cells cause lymphocytic alveolitis, cellular apoptosis and lung parenchymal damage,[6–9] which are associated with pulmonary complications among PLWH.[10] Although alveolar viral load and inflammation decrease with antiretroviral therapy (ART),[11] the parenchymal damage may be irreversible. Concurrently, intestinal barrier dysfunction and microbial translation are associated with systemic inflammation and immune activation[12] that persists despite ART, [13–15] although the causality of this relationship has not been fully elucidated. Lastly, accelerated immune senescence may result from continuous, low-grade immune activation due to repeated antigenic stimulation among PLWH.[16] Indices of immune senescence, including markers of T cell activation and telomere shortening, are similarly associated with lung function abnormalities.[17,18]

Among patients with COPD, systemic inflammation is associated with disease severity, exacerbations and overall mortality.[19,20] Biomarkers of macrophage activation and systemic inflammation have also been associated with impaired lung function and parenchymal abnormalities in U.S. and European HIV cohorts.[17,21–23] However, these findings may not be applicable to sub-Saharan Africa, where PLWH present for HIV care at advanced disease stages [24] and air pollution rather than smoking is the major chronic lung disease risk factor[25–28]

To address this knowledge gap, we measured lung function, systemic inflammation (high sensitivity C-reactive protein (hsCRP), interleukin 6 (IL-6)) and macrophage activation (soluble CD14 (sCD14) and soluble CD163 (sCD163)) among a mixed cohort of older-age PLWH and population-based, HIV-uninfected controls in rural Uganda. We hypothesized that systemic inflammation and macrophage activation would be associated with lower lung function, the effect of which would be the greatest among PLWH.

METHODS

Participants were enrolled in the Uganda Non-Communicable Diseases and Aging Cohort (UGANDAC; NCT02445079), a mixed cohort of PLWH and population-based HIV-uninfected controls described in detail previously.[29,30] In brief, a convenience sample of PLWH were recruited from the HIV outpatient clinic at the Mbarara Regional Referral

Hospital who were at least 40 years of age and had been on antiretroviral therapy for at least three years. HIV-uninfected controls were recruited from the complete population census of a cluster of 8 villages approximately 20 kilometers from the HIV clinic, were sex- and age-matched (by age quartile) to PLWH, and were confirmed to be HIV negative prior to study visits. We collected data on demographics, medical history, socioeconomic status (SES)[31], tobacco exposure[32] and respiratory symptoms.[33] We measured serum concentrations of hsCRP by latex immunoturbidimetry (LabCorp, Burlington, NC) and plasma concentrations of IL-6 (MesoScale Discovery, Rockville, MD), sCD14 and sCD163 (R&D Systems, Minneapolis, MN) with ELISA according to manufacturer instructions at the Laboratory for Clinical Biochemistry Research at the University of Vermont. We defined HIV viral suppression as a viral load below the assay detection limit (plasma: <40 copies/uL; dried blood spot: <550 copies/uL; Roche Cobas® assay, Pleasanton, CA; assay limitations changed due to local clinical practice modification).

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were measured by trained research assistants using the EasyOne® Plus handheld spirometer (ndd Medical Technologies Inc., Andover MA) in accordance with American Thoracic Society (ATS) guidelines.[34,35] Four puffs of albuterol (Ventolin, GlaxoSmithKline, Philadelphia, PA) were administered to participants with $FEV_1/FVC<0.7$ and spirometry was repeated after 10 minutes. Spirometry was interpreted by two pulmonologists (CMN, DCC) using National Health and Nutrition Examination Survey III (NHANES III) prediction equations with African American correction factors,[36] given their similarity to East African prediction equations.[37] COPD was defined as post-bronchodilator $FEV_1/FVC<0.7$, and obstruction severity was defined using Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[38]

Statistical Analysis

Cohort characteristics were compared by HIV serostatus using parametric and non-parametric tests as indicated by covariate distributions. To evaluate for selection bias, demographics were compared between those who completed and those who declined spirometry, and between those with and without ATS-acceptable spirometry.

Our primary outcome of interest was lung function (in mL), as measured by FEV_1 and FVC. Secondary outcomes of interest included self-reported respiratory symptoms, defined as self-reported cough, phlegm production, wheezing or dyspnea. Our explanatory variables of interest were systemic inflammation and macrophage activation, which included blood levels of hsCRP, IL-6, sCD14 and sCD163. Serum biomarkers were log transformed and divided by the interquartile range (IQR) of the distribution,[39] except for hsCRP, which was categorized according to clinical risk (<1 mg/L, 1–3 mg/L, or >3 mg/L) as previously described.[40] We fit multivariable linear regression models to evaluate the relationship between our outcomes of interest and an IQR increase in IL-6, sCD14 or sCD163, and hsCRP risk category. Models were stratified by HIV serostatus and adjusted for predicted confounders, which were selected *a priori* based on scientific plausibility and included age, sex, height, smoking, biomass (cooking fuel) exposure and SES. Cooking fuel and SES were collinear ($p<0.001$), so cooking fuel was preferentially included in regression models.

Sensitivity analyses were conducted in which lung function outcomes were modeled as percent predicted using both NHANES III and Global Lung Initiative equations[41] and statistical significance was defined with more conservative Bonferroni-corrected *P* values to account for multiple testing ($p < 0.0125$). Data were analyzed using Stata 13 (StataCorp, College Station, TX).

All participants gave written informed consent, and all study procedures were approved by the institutional review boards of Mbarara University of Science and Technology and Partners Healthcare.

RESULTS

Of the 287 consented study participants, 269 (94%) completed spirometry, 239 (89%) of whom met ATS acceptability criteria. There were no differences between those who completed or declined spirometry, or between those with or without ATS-acceptable spirometry. Among the 239 participants with ATS-acceptable spirometry, 5 participants (2%) declined phlebotomy.

Of the 234 participants included in the analysis, 53% (n=125) were PLWH, 46% (n=107) were women, and the median age was 52 years (IQR 48–55) (Table 1). Compared to HIV-uninfected participants, PLWH were more likely to be never smokers (57% [71/125] *v.* 44% [48/109], p=0.01), to live in homes using charcoal rather than firewood for cooking (26% [32/125] *v.* 1% [1/109], p<0.001), and to have higher socioeconomic status (p<0.001). Most PLWH (92%, [115/125]) were virally suppressed with a median CD4 count of 472 cells/mm^3 (IQR 374–622). Median time on ART was 9 years (IQR 8–10) and 93% (116/125) were on first-line non-nucleoside reverse transcriptase inhibitor-based therapy.

There was no difference in mean FEV_1 or FVC percent predicted (%pred) by HIV serostatus (FEV_1: 103 %pred, 95% confidence interval [95%CI] 101–105; FVC: 104 %pred, 95%CI 102–106; FEV_1/FVC: 98 %pred, 95%CI 97–99). Four percent (9/234) met criteria for COPD, most of whom (89%, [8/9]) were PLWH. COPD severity was mild (33% [3/9]) or moderate (56% [5/9]) in most cases. COPD prevalence was unchanged when defined as FEV_1/FVC < lower limit of normal. Respiratory symptoms were reported by 25% (n=58) of participants, with no difference by HIV serostatus. Of the 20 participants (9%) who reported prior pneumonia and 16 participants (7%) who reported prior tuberculosis, most were PLWH (80% [16/20], p=0.02 & 100% [16/16], p<0.001, respectively). There were no associations between respiratory symptoms and prior pneumonia or tuberculosis (p=0.03).

Median hsCRP and sCD14 concentrations were higher among PLWH as compared to HIV-uninfected participants (p<0.001 for both), while median IL-6 and sCD163 concentrations were similar (p=0.1 and 0.37, respectively; Supplemental Figure 1). Median hsCRP concentrations were also higher among those who lived in homes using charcoal as compared to firewood for cooking (p=0.003), while median IL-6, sCD14 and sCD163 concentrations were no different by cooking fuel type (p=0.52, 0.29 and 0.44, respectively; Supplemental Figure 2).

In multivariable linear regression models adjusted for predicted confounders, among PLWH, higher IL-6 was associated with lower FEV_1 and FVC while higher sCD163 was associated only with lower FVC (IL-6: FEV_1 −18.1 (−29.1 to −7.1), FVC −17.1 (−28.2 to −5.9); sCD163: FVC −14.3 (−26.9 to −1.7)). Higher hsCRP (>3 *vs* <1mg/L) was associated with lower FEV_1 and FVC among both PLWH and HIV-uninfected participants (FEV_1: −39.3 (−61.7 to −16.9) and −37.9 (−63.2 to −12.6), respectively; FVC: −44.0 (−48.4 to −6.4) and −58.0 (−88.4 to −27.5), respectively) (Table 2, Supplemental Figures 3 & 4). There were no associations between sCD14 and lung function, or between these biomarkers and either FEV_1/FVC or respiratory symptoms. Interaction terms between HIV serostatus and each biomarker were not statistically significant. In sensitivity analyses, relationships between hsCRP, IL-6 and sCD14 were unchanged, while the relationship between sCD163 and FVC lost statistical significance (Supplemental Table 1).

DISCUSSION

This study is the first to report that biomarkers of macrophage activation (sCD163) and systemic inflammation (hsCRP, IL-6) are associated with lower lung function among older aged PLWH on antiretroviral therapy in Uganda, and joins just one other study in the region that identifies an association between systemic inflammation and COPD among PLWH in urban South Africa.[42] The magnitude of the change in lung function associated with the systemic biomarkers in the current study is similar to that observed in cross-sectional studies of cigarette smoking and air pollution exposure,[43,44] both of which are leading causes of chronic lung disease globally.

Similar relationships between lung function, inflammation and macrophage activation have been described in U.S. and European HIV cohorts. In a mixed cohort of male PLWH and HIV-uninfected men, Fitzpatrick and colleagues found that PLWH with higher sCD163 had lower lung function, while IL-6 was associated with lower lung function in both PLWH and HIV-uninfected controls.[21] Differences in associations between IL-6 and lung function between our cohorts may be due to more prevalent smoking across HIV serotypes in Fitzpatrick's cohort, which has been associated with both IL-6 and lower lung function.[45] hsCRP was also associated with lower lung function in an HIV cohort with higher tobacco exposure and more severe lung dysfunction,[17] although there was no HIV-uninfected group for comparison. Attia *et al.* found that sCD14 was associated with increased risk of radiographic emphysema among PLWH, while no association was present among HIV-uninfected controls.[22] Lung function was lower and COPD prevalence higher compared to the current study, which may explain the difference in relationships between sCD14 and lung disease. Alternatively, spirometry more readily identifies airways abnormalities rather than parenchymal disease, which is more thoroughly assessed with radiographic imaging.[46] Thus, sCD14 may be indicative of parenchymal destruction rather than airways disease in PLWH. In a population-based registry of PLWH on ART, Danish investigators found that baseline sCD163 levels were associated with increased risk of incident chronic lung disease, although spirometry was not completed nor was there an HIV-uninfected population for comparison.[23]

In contrast to hsCRP and IL-6, which were associated with both FEV_1 and FVC, sCD163 was associated only with FVC among PLWH in this cohort. Activated macrophages, identified by CD163, are central to the pathophysiology of lung fibrosis.[47,48] Additionally, there is increasing recognition of the coexistence of interstitial lung abnormalities in people with obstructive lung disease.[49] Therefore, the association between sCD163 and FVC observed in this cohort may identify a more fibrotic-predominant pattern of HIV-associated lung disease, although imaging studies are required to corroborate this hypothesis.

hsCRP was the only biomarker associated with lung function in both PLWH and HIV-uninfected participants in this cohort. One potential explanation for the effect of hsCRP across HIV serotypes may lie in ubiquitous regional biomass smoke exposure.[50] While several inflammatory biomarkers have been associated with biomass exposure, biomass-associated hsCRP has also been associated with impaired lung function.[26,51] All participants in this cohort live in homes where firewood or charcoal is used for cooking, and hsCRP levels differed by home cooking fuel type while the other measured biomarkers (IL-6, sCD14, sCD163) did not. Thus, biomass smoke exposure may drive elevated hsCRP concentrations across HIV serotypes. Although we were not powered to assess for such effects, these data provide rationale for future studies investigating the possibility of interactive effects of HIV and air pollution-associated lung disease.

The main strength of this analysis is the inclusion of an HIV-uninfected comparator group, which allowed us to estimate associations by HIV serostatus. We also conducted spirometry in accordance with international standards and utilized rigorous quality control procedures. Our study also has several limitations. Firstly, the cross-sectional nature of the analysis prevents any determination of causality between systemic inflammation and lung function. To address this, we are repeating spirometry and biomarker measurements annually to investigate the longitudinal relationship between systemic inflammation and lung function trajectory. Second, we may have been underpowered to identify smaller differences in lung function by inflammatory biomarkers. Also, biomarkers were measured systemically rather than in bronchoalveolar lavage fluid, which could change the observed relationship between inflammation and lung function. However, we would expect this to bias our results towards the null, further emphasizing our significant findings. Also, DLCO (diffusion capacity for carbon monoxide) measurements were not available locally due to infrastructure constraints and chest imaging was not obtained, thus we cannot comment on parenchymal abnormalities that were not severe enough to impair lung function. Finally, there were no biomass-unexposed participants in the cohort, thus we cannot estimate the independent effect of biomass exposure on systemic inflammation or lung function.

In conclusion, systemic inflammation and macrophage activation are associated with lower lung function among PLWH on stable ART in rural Uganda. As AIDS-related mortality decreases and life expectancy increases across SSA, identifying the leading causes of preventable morbidity among PLWH will be critical. Future work should focus on developing the pathophysiologic framework to explain contributions of HIV infection to lung health in SSA, identifying low-cost, locally available biomarkers to identify those at risk for lung disease, and spur interventional studies to reduce the burden of COPD in the region.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Cohort Characteristics

	Total Cohort (n = 234)	HIV+ (n = 125)	HIV− (n = 109)
Age, years	52 [48, 55]	52 [49,56]	52 [48, 55]
HIV positive	125 (53)		
Female gender	107 (46)	56 (45)	51 (47)
Smoking History			
Current	35 (15)	11 (9)	24 (22)
Former	80 (34)	43 (34)	37 (34)
Never	119 (51)	71 (57)	48(44)
Smoking years *	0 [0, 18]	0 [0, 15]	5 [0, 26]
Biomass			
Firewood	199 (86)	91 (74)	108 (99)
Charcoal	33 (14)	32 (26)	1 (1)
Asset Index, quartile			
Poorest	51 (22)	22 (18)	29 (27)
Poorer	61 (26)	25 (20)	36 (33)
Richer	59 (25)	31 (25)	28 (26)
Richest	62 (27)	47 (38)	15 (14)
Education level			
Less than Primary school	128 (55)	62 (50)	66 (61)
Completed Primary school	79 (34)	47 (38)	32 (29)
Completed Secondary school	27 (12)	16 (13)	11 (10)
HIV Characteristics			
CD4 count, cells/mm^3			
< 350		23 (18)	
350 – 499		47 (38)	
≥ 500		55 (44)	
Viral Load, copies/μL			
Undetectable		115 (92)	
Detectable, ≤ 10,000		5 (4)	
Detectable, > 10,000		1 (1)	
ART duration, years		9 [8, 10]	
ART regimen †			
AZT/3TC/NVP or EFV		101 (81)	
TDF/3TC/NVP or EFV		15 (12)	
TDF/3TC/LPV/r		8 (6)	
AZT/3TC/ABC		1 (1)	

Median [IQR] or n (%) unless otherwise noted

*Among current or former smokers only

†AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; TDF, tenofovir; EFV, efavirenz; LPV/r, lopinavir/ritonavir, ABC, abacavir

Table 2

Associations between lung function (mL) and serum inflammatory biomarkers

	HIV+ (*n=122*[†])		HIV− (*n=108*[†])		Interaction Term *p* values[‡]	
	FEV_1	**FVC**	**FEV_1**	**FVC**	**FEV_1**	**FVC**
IL-6, *per IQR increase*	−18.1 (−29.1 to −7.1) **	−17.1 (−28.2 to −5.9) **	−6.2 (−16.0 – 3.5)	−8.7 (−20.8 – 3.5)	0.44	0.74
sCD14, *per IQR increase*	2.3 (−11.7 – 16.3)	7.0 (−6.9 – 21.0)	6.2 (−4.3 – 16.6)	8.9 (−4.1 – 21.8)	0.74	0.94
sCD163, *per IQR increase*	−11.4 (−24.0 – 1.2)	−14.3 (−26.9 to −1.7) *	−3.7 (−13.8 – 6.3)	−6.5 (−19.0 – 6.1)	0.41	0.48
hsCRP, >3mg/L *vs.* <1mg/L	−39.3 (−61.7 to −16.9) **	−44.0 (−48.4 to −6.4) ***	−37.9 (−63.2 to −12.6) **	−58.0 (−88.4 to −27.5) ***	0.75	0.38

All models adjusted for age, gender, height, smoking (current/former/never), smoking duration (years) and cooking fuel use (firewood vs charcoal)

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; mL: milliliters; HIV: human immunodeficiency virus; IL-6: interleukin 6; sCD14: soluble CD14; sCD163: soluble CD163; hsCRP: high sensitivity C-reactive protein

* $p < 0.05$,

** $p < 0.01$,

*** $p<0.001$

[†] hsCRP model sample sizes: n=120 (HIV+) & n=107 (HIV-)

[‡] *p* values for HIV*biomarker interaction terms

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