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Sex Modifies the Risk of HIV-associated Obstructive Lung Disease in Ugandans Post-Pneumonia

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Author contributions:

In addition to the below, all listed co-authors drafted the manuscript or reviewed it critically for important intellectual content.

Rebecca A. Abelman: Dr. Abelman developed the research question, conducted the analysis with the assistance of Dr. Jessica Fitzpatrick and Dr. Laurence Huang, and wrote and revised the manuscript.

Jessica Fitzpatrick: Dr. Fitzpatrick performed the statistical analysis and guided the interpretation of the results for the manuscript.

Josephine Zawedde: Ms. Zawedde is the study nurse in Uganda who enrolled patients, obtained clinical data, and performed spirometry for this project.

Ingvar Sanyu: Mr. Sanyu is the clinical manager in Uganda who also enrolled patients, obtained clinical data, and performed spirometry for this project.

Patrick Byanyima: Mr. Byanyima is the laboratory supervisor in Uganda who obtained blood and respiratory specimens and performed HIV testing and TB testing (e.g., Xpert) for this project.

Sylvia Kaswabuli: Ms. Kaswabuli is a lab technician in Uganda who obtained blood and respiratory specimens and performed HIV testing and TB testing (e.g., Xpert) for this project.

Emmanuel Musisi: Just received his PhD. At the time of the study, Mr. Musisi was a lab technician for the study in Uganda. He obtained blood and respiratory specimens and performed HIV testing and TB testing (e.g., Xpert) for this project.

Jenny Hsieh: Ms. Hsieh is a respiratory therapist and trained to over-read spirometry. She over-read all spirometry tests for this project for acceptability and reproducibility according to ATS/ERS guidelines.

Kendall Gardner: Ms. Gardner is a clinical research coordinator for Dr. Huang. She collated all Uganda spirometry results, assisted Ms. Hsieh, and curated this dataset for analysis.

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Katerina Byanova: Dr. Byanova is a pulmonary research fellow under Dr. Huang's mentorship and oversees the performance of spirometry, troubleshoots issues related to spirometry in Uganda (and the US) and updates our Spirometry SOP for the overall I AM OLD Study. She also participated in the interpretation of the results.

Abdul Sessolo: Dr. Sessolo is the study coordinator in Uganda and was responsible for the day-to-day conduct and coordination of the study in Uganda.

Peter W. Hunt: Dr. Hunt is a Co-Investigator on I AM OLD and guides the performance and analysis of inflammatory biomarkers in the study. He contributed to the interpretation of data.

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William Worodria: Dr. Worodria is a Co-Investigator and is the Uganda site PI for I AM OLD. He helped establish the Uganda cohort in 2005 and oversees the implementation of the study in Uganda. He contributed to the interpretation of data.

Laurence Huang: Dr. Huang is the Principal Investigator of I AM OLD and established the Uganda cohort in 2005. He assisted with refining the research question, data management, analysis, and the interpretation of the study results in addition to providing input on the preparation of this manuscript.

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Abstract

Objectives—Spirometric abnormalities are frequent and obstructive lung disease (OLD) is a common comorbidity among people with HIV (PWH). HIV increases the risk of many comorbidities to a greater degree in women than in men. Few studies have evaluated whether sex modifies the HIV-associated risk of OLD.

Design and Methods—To evaluate the associations between sex and HIV with abnormal lung function, women and men with and without HIV underwent spirometric testing after completing therapy for pneumonia, including tuberculosis (TB), in Kampala, Uganda. OLD was defined as a post-bronchodilator forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) ratio <0.70. Associations between sex, HIV, and lung function were evaluated using multivariable regression models including sex-by-HIV interaction terms after adjusting for age, body mass index (BMI), smoking status, and TB status.

Results—Among 348 participants, 147 (42%) were women and 135 (39%) were HIV positive. Sixteen (11%) women and 23 men (11%) had OLD. The HIV-sex interaction was significant for obstructive lung disease (p=0.04). In the adjusted stratified analysis, women with HIV had 3.44 (95% CI 1.11, 12.0; p=0.04) increased odds of having OLD compared to men with HIV. Women without HIV did not have increased odds of having OLD compared to men without HIV.

Conclusions—HIV appears to increase the risk of OLD to a greater degree in women than in men in an urban Ugandan setting. The mechanistic explanation for this interaction by sex remains unclear and warrants further study.

Keywords

HIV; sex-based differences; obstructive lung disease; comorbidities; tuberculosis

Introduction

People with HIV (PWH) are at an increased risk for the development of medical comorbidities, including obstructive lung disease (OLD) [1–3]. Chronic lung disease represents the second most common comorbidity among PWH [4], among which OLD serves as an important cause of morbidity and mortality [2,5–7]. Two lung function abnormalities, airflow obstruction measured by spirometry and impaired diffusing capacity, are frequently abnormal in PWH and have been associated with increased symptom burden [8–10]. Other lung function abnormalities, such as spirometric restriction, are also seen frequently in PWH and are associated with increased respiratory symptoms [11]. HIV infection is independently associated with OLD. Studies have demonstrated PWH have higher rates of OLD as well as an earlier onset and a more rapid decline in lung function than the general population, even after controlling for cigarette smoking [1,3,12,13]. The exact mechanisms of HIV-associated OLD are incompletely known, although heightened immune activation and inflammation, environmental exposures, the lung microbiome, and a predilection for the development of pneumonia likely play a role [14–16].

Sex-based differences may also modify the risk of HIV-associated OLD. Evidence suggests that, compared to men with HIV, women with HIV (WWH) are at increased risk of development and progression of some aging-associated comorbidities, such as cardiovascular disease [17–19]. Women with HIV may be particularly vulnerable to developing OLD [20]; studies in the general population suggest that women, when accounting for cigarette smoke exposure, have increased susceptibility to OLD when compared to men [21–26]. While studies in a large North American cohort of women with and without HIV have not found HIV-associated differences in spirometric abnormalities [27,28], a recent study in Uganda found that WWH had an accelerated rate of forced expiratory volume in the first one second (FEV_1) decline over time compared to women without HIV [29]. Similar findings were not seen among men with and without HIV. Importantly, compared to women in higher-income settings, women in sub-Saharan Africa have distinct risk factors for the development of abnormal lung function and OLD, including biomass fuel exposure and higher rates of pulmonary tuberculosis (TB), which is now being increasingly recognized as a risk factor in OLD development [30,31].

To determine whether women in a low-income, high TB-incidence area are at increased risk for OLD and other spirometric abnormalities compared to their male counterparts and whether there is an interaction by HIV status, we conducted a longitudinal study among adults in Uganda after treatment for pneumonia evaluating the associations of sex and lung function abnormalities as stratified by HIV status. The primary objective of this study was to investigate whether sex-based differences in OLD were present after treatment for pneumonia among PWH as measured by the FEV_1, the forced vital capacity (FVC), and their ratio (FEV_1/FVC). Secondary objectives were to evaluate the association between sex and spirometric restriction among PWH and to assess the impact of TB on the associations of sex and lung function abnormalities.

Methods

The I AM OLD study

The Inflammation, Aging, Microbes, and Obstructive Lung Disease (I AM OLD) Study is a prospective, longitudinal cohort study that enrolls participants in the United States (San Francisco and Seattle) and Kampala, Uganda. The study aims to evaluate the progression and development of lung function abnormalities in adults with and without HIV after resolution of acute pneumonia. After enrolling participants at the time of acute pneumonia, the study performs longitudinal lung function testing and collects serial immune activation and telomere biology markers at the end of pneumonia treatment and annually thereafter. The study protocols between the US and Uganda cohorts are identical, but the demographics and clinical characteristics of the enrolled participants differ.

Uganda cohort

We enroll non-pregnant patients ages 18–60 at the time of acute pneumonia, including pulmonary TB. Participants are enrolled from inpatient wards or the outpatient TB clinic if they have presented with suspected pneumonia (including TB) at the China-Uganda Friendship Hospital Naguru in Kampala, Uganda. Patients are eligible for inclusion if they have had a cough for less than six months. All participants are tested for HIV at enrollment and at their first spirometry visit. For participants with HIV, CD4 counts are measured and antiretroviral therapy status is assessed, but HIV RNA measurements are not available.

After enrollment, participants receive a chest radiograph and undergo protocolized evaluation for pulmonary TB using AFB fluorescence smear microscopy x2, Xpert x1, sputum LJ culture x 2, and sputum MGIT x2. A participant was considered TB positive if any microbiological test (smear, Xpert, LJ, and/or MGIT) returned positive. A participant was considered TB negative if at least two tests (Xpert, LJ, and/or MGIT) were negative and no tests were positive. If TB positive, participants receive TB therapy followed by baseline post-treatment pre- and post-bronchodilator spirometry after completion of TB therapy. If TB testing is negative, participants are treated for pneumonia followed by baseline post-treatment pre- and post-bronchodilator spirometry at least three months after therapy completion. Participants continue to undergo pre- and post-bronchodilator spirometry testing and respiratory symptom assessment annually.

Ethical Approvals

Ethical approval was obtained from the Makerere University School of Medicine Research and Ethics Committee (REC REF No. 2006–017) and the University of California San Francisco Committee on Human Research (IRB #10–02633). All study participants were informed about the study by a nurse or physician and provided written informed consent prior to participation in the study.

Study population and procedures

This current secondary analysis from Uganda spanned visits from February 2016 to March 2022. At follow-up visits after completion of pneumonia therapy, pre- and post-bronchodilator spirometry was performed according to the 2005 American Thoracic Society/

European Respiratory Society (ATS/ERS) guidelines [32]. Spirometry was performed by trained study personnel using an Easy on-PC (February 2016-October 2021) or EasyOne Pro device (October 2021-March 2022) (ndd Medizintechnik AG, Zurich, Switzerland). Each spirometry maneuver was over-read by a trained respiratory therapist to confirm acceptability and reproducibility of test results. Using the 2005 ATS/ERS spirometry quality grading system, tests with grades A through C were included in the analysis [32].

Classification of lung function patterns

Spirometry results were classified according to GOLD criteria with lung function abnormalities categorized into obstructive lung disease (OLD), spirometric restriction, or undefined [33,34]. OLD was defined as a post-bronchodilator FEV_1/FVC ratio <0.70. Spirometric restriction was defined as a post-bronchodilator FEV_1/FVC ratio ≥0.70 with an FVC <80% predicted and any FEV_1 whereas an undefined pattern was a post-bronchodilator FEV_1/FVC ratio ≥0.70, FVC ≥80% predicted, and FEV_1 <80% predicted. Normal spirometry was defined as a post-bronchodilator FEV_1/FVC ratio ≥0.70 with an FEV1 and FVC both ≥80% predicted.

Analysis

Participants included in this analysis had acceptable spirometry results and known TB status. In this analysis, all variables from the time of enrollment were used except for age and body mass index (BMI) which were obtained at the time of spirometry. Demographics, clinical characteristics, and lung function were compared by sex. Univariate analyses were performed examining the associations between demographic parameters, including age and BMI, as well as important clinical factors, including ever smoking status (self-report yes/no), biomass fuel exposure (self-report yes/no), HIV status, and TB status and the two spirometric outcomes, OLD and spirometric restriction. Variables with a $p<0.20$ in the univariate analysis were included in the multivariable models. In the multivariable analyses, a two-tailed p-value was used with cutoff $p\leq0.05$ for statistical significance. The associations between sex and lung function were evaluated using multivariable logistic regressions adjusting for age, BMI, smoking status, HIV status, and TB status. Biomass fuel was not included as it did not reach statistical significance in the univariate analysis. Odds for the presence of OLD or spirometric restriction were calculated compared to those with normal lung function. Interactions between sex and HIV were assessed and given the significant interaction between sex and HIV, these models were then stratified by HIV status.

To evaluate the contribution of TB in modifying the sex association with abnormal lung function, a sub-analysis was performed among participants who were found to have pulmonary TB. Multivariable models adjusted for age, smoking status, BMI, and HIV status were developed in addition to a stratified analysis by HIV status.

Results

Cohort and participant characteristics

Overall, 388 participants were enrolled at the time of acute pneumonia and underwent spirometry at the completion of therapy (Figure 1). Sex was similarly distributed between

those who were lost to follow-up prior to receiving baseline post-treatment spirometry and those who were included in the analysis. Among the 388 participants who underwent spirometry, ten participants had unknown or indeterminate TB status and another 30 had spirometry that failed to meet ATS/ERS criteria and were excluded from the analysis. Characteristics were similar among the 348 included and the 40 excluded individuals except the median CD4 count was higher among excluded participants (328 versus 128 cells/mm^3, p=0.02) (Supplementary Table 1).

Among the 348 remaining participants, 147 (42%) were women and 201 (58%) were men; 135 (39%) were HIV positive and 213 (61%) were HIV negative (Table 1). Among those without HIV, 78 were women and 135 were men. Among those with HIV, 69 were women and 66 were men. Median CD4 counts were 156 cells/mm^3 (IQR 45, 289) for WWH and 91 cells/mm^3 (IQR 37, 302) for men with HIV (p=0.44). More HIV positive women reported current ART use compared to HIV positive men (52% versus 29%, p<0.001). Overall, the women in the cohort were younger than the men (median 31 versus 34 years, p=0.04) and had a higher median BMI than men (21.6 versus 20.5 kg/m^2, p<0.001). Compared to men, women were less likely to report a history of tobacco smoking (4% versus 33%, p<0.001) or current smoking (1% versus 12%, p<0.001), but were more likely to report biomass fuel exposure at home (91% versus 60%, p<0.001). Most pneumonia cases were confirmed to be TB for both women (80%) and men (87%). The median time between initial enrollment and the baseline post-treatment spirometry visit was 6.4 months (IQR: 5.9, 7.9) without a statistically significant difference by sex (p=0.47). Among the 292 participants with TB, 90 (31%) had HIV.

When stratified by HIV status, those with HIV were older than their seronegative counterparts (37 versus 29 years) and had lower rates of smoking and TB (Table 1).

Prevalence of spirometric abnormalities

Overall, 205 (59%) had normal spirometry, 39 (11%) had OLD, 91 (26%) had spirometric restriction, and 13 (3.7%) had undefined abnormal spirometry (Table 1). There were no significant differences in lung function findings by sex. In total, 58% of women and 60% of men had normal lung function (p=0.74). In terms of abnormal lung function, 11% of women and men had obstruction (p=0.90) and 27% of women compared to 25% of men had spirometric restriction (p=0.70). When stratified by HIV status, 16% of those with HIV had OLD compared to 8% of those without HIV (p=0.29). Spirometric restriction was less common among those with HIV when compared to their seronegative counterparts (18% versus 31%, respectively, p=0.01).

Risk factors for lung function abnormalities

In the univariate analyses, age, BMI, smoking status, and HIV status were associated with one or more lung function abnormalities. In the multivariable analyses, smoking was significantly associated with increased odds of OLD and a higher BMI and HIV-positive status were associated with decreased odds of spirometric restriction. No other covariates, including biomass fuel exposure, reached statistical significance. In the multivariable

analysis, there were non-significant associations of female sex with OLD (aOR 1.91; 95% CI 0.81, 4.65; p=0.14) and spirometric restriction (aOR 1.59; 95% CI 0.90, 2.85; p=0.11).

Heterogeneity of effect was assessed by including a multiplicative interaction term between sex and HIV status in the adjusted models. In the overall group, the interaction between sex and HIV in association with OLD was statistically significant (p=0.04), but the interaction between sex and HIV in association with spirometric restriction did not reach statistical significance (p=0.28).

Association of sex and lung function abnormalities stratified by HIV status

In the adjusted stratified analysis among those with HIV, women had a 3.44-fold higher adjusted odds of obstructive lung disease than men (95% CI 1.11, 12.0; p=0.04) (Table 2, Figure 2). Interestingly, among those without HIV, there was no evidence for an association between female sex and OLD (aOR 0.72, 95% CI 0.14, 3.15; p=0.67). Both among those with and without HIV, women tended to have higher odds of spirometric restriction than men (aOR 2.41 and 1.28, respectively), but these results did not reach statistical significance (Table 2, Figure 2).

When restricting to those with TB, women had nominally greater odds of obstruction (aOR 1.15) and spirometric restriction (aOR 1.48), respectively, than men, but these differences were not significant (Table 3). Bootstrapping was attempted to get the standard error estimates and the results were similar. In the analyses stratified by HIV status, HIV and TB co-infected women demonstrated a non-significant association with obstructive lung disease with an aOR 2.06 (95% CI 0.49, 9.12; p=0.32) but HIV-uninfected women with TB did not (aOR 0.72). Unlike the overall analysis, the interaction term of sex and HIV status did not reach statistical significance when restricted to TB positive participants (p=0.08).

Biomass fuel was added to the model as an *a priori* variable to determine whether differences in amount of biomass fuel exposure was driving the sex-specific differences seen in the analysis. The magnitude and direction of the associations of sex and OLD were similar but attenuated, with WWH demonstrating higher odds of OLD whereas women without HIV did not have higher odds of OLD (aOR 3.11 versus 0.76) compared to men. Similarly, when including factors related to pneumonia severity such as baseline heart rate and oxygen saturation level, WWH continued to demonstrate higher odds of OLD (aOR 3.58), a finding that was not seen in their seronegative counterparts (aOR 0.75).

Discussion

In this cohort of adults who recovered from pneumonia in Kampala, Uganda, women had a greater than three-fold increased odds of OLD than men, but only among those with HIV. Among those without HIV, there was no evidence for an association between sex and OLD. These results persisted, albeit attenuated, among participants with TB and when adjusting for biomass fuel exposure and pneumonia severity measures. Together, these findings suggest that sex modifies HIV-associated drivers of OLD among adults who have recovered from pneumonia. Further investigation into the interplay between sex and

HIV in OLD could provide mechanistic insights that promote the development of targeted, sex-specific interventions for PWH.

Sex-specific differences in OLD prevalence have been described in the general population, with studies suggesting that women are more susceptible to the development of OLD and more vulnerable to the deleterious effects of cigarette smoking compared to men [22–25]. In a large US-based cohort evaluating factors associated with early-onset severe chronic obstructive pulmonary disease (COPD), female sex was a significant risk factor and was associated with increased odds of development of severe, early-onset COPD (aOR 3.1, 95% CI 1.1–8.7; p=0.03) [22]. In high-income countries, OLD prevalence has risen more rapidly for women than men [35,36], thought to be partially due to increased rates of cigarette smoking. For example, in a study by Amaral *et al*, the smoking-associated odds of airflow obstruction was higher in women (aOR 3.45) than in men (aOR 3.06) [25]. While differences in smoking intensity may have partially explained this observed interaction, these findings suggest that sex may modify the association between risk factors and OLD.

Sex-based differences in other aging-associated comorbidities have been seen among PWH, including abnormal lung function. In a study evaluating longitudinal spirometry among PWH in India, WWH demonstrated a 7-fold increased odds of a restrictive spirometry pattern and a 22-fold increase in preserved ratio impaired spirometry (PRISm, FEV_1/FVC ratio ≥0.70 and FEV_1<80% of the predicted value) compared to men with HIV, even when controlling for smoking and biomass fuel exposure [37]. While no sex differences in OLD were noted, only five total patients in the cohort were classified as having OLD [37]. These findings, taken with our own, suggest that WWH may be particularly vulnerable to the development of abnormal lung function compared to men with HIV, although further study is needed.

In this study, the HIV-associated odds of OLD in adults recovered from pneumonia was substantially higher in women than in men. While studies have investigated whether there are HIV-related differences in spirometric abnormalities among women in the US, they have not found higher rates of OLD in WWH compared to women without HIV [27,28]. Nevertheless, women in Uganda demonstrate distinct environmental exposures and sociodemographic factors compared to women in the US, including high rates of biomass fuel exposure, high incidence of TB, and lower rates of smoking. Notably, the Global Burden of Disease Chronic Respiratory Disease collaborators performed a systematic analysis and found that household air pollution from biomass fuel serves as the leading risk factor for OLD development among women in sub-Saharan Africa [36]. Given these discordant exposures, drivers for the development of HIV-associated pulmonary disease may differ in sub-Saharan Africa compared to the US, emphasizing the need for continued study in geographically diverse settings. This need is corroborated by a study evaluating longitudinal lung function in a Ugandan cohort where WWH demonstrated an accelerated FEV_1 decline compared to women without HIV, a finding that was not observed in their male counterparts [29].

Many other aging-related comorbidities among PWH have demonstrated both increased HIV-attributable risk as well as sex-based differences [18,38,39]. For example, within

cardiovascular disease, PWH have a 1.5- to 2-fold increase in myocardial infarction compared to their seronegative counterparts [18]. In another US-based study, after adjusting for cardiovascular risk factors, WWH had a relative risk of 2.98 for myocardial infarction as compared to women without HIV, whereas men with HIV had a relative risk of 1.4 compared to their seronegative counterparts [19]. Thus, sex appears to modify the HIV-associated risk of cardiovascular disease, with HIV increasing the risk more in women than in men, a strikingly concordant finding to our OLD results reported here. Similarly, compared to women without HIV, US-based WWH have been found to have a higher burden of aging-related comorbidities compared to women without HIV, such as dyslipidemia, liver disease, bone disease, CKD, and non-AIDS cancers [28]. Collectively, these observations may suggest a common mechanistic pathway by which female sex exacerbates the impact of HIV on comorbidity risk.

Elevated immune activation may play a role in the development of aging-related comorbidities in HIV. Women with HIV have demonstrated higher levels of immune activation markers when compared to their male counterparts, even when on ART [40–43]. Similar biomarkers found at higher levels among WWH have also been associated with lung function abnormalities, particularly decreased diffusion capacity for carbon monoxide (DL_{CO}) [16,44,45]. For example, sCD163 levels, a marker of macrophage and monocyte activation, have been found to be higher among WWH when compared to women without HIV, as well as to men with and without HIV [40,42,43]. Higher sCD163 levels have been associated with decreased DL_{CO} as well as decreased FVC among PWH [16,45]. Sex-specific differences in immune activation levels among PWH provides a plausible mechanism for our results. Why sex-based differences in inflammation may be more dramatic in those with HIV than in those without HIV has not been fully elucidated but may be important to understanding the development and progression of lung disease among PWH. One potentially important factor may be incomplete silencing of the X-linked TLR7 gene in women, resulting in a more robust innate immune response to viral RNAs (including HIV) in women than in men [46–49]. Hormonal factors may also play a role.

Limitations of this analysis include the lack of longitudinal data available for this study as lung function testing was primarily available at only one time point. Longitudinal lung function testing is currently ongoing, which will allow for the monitoring of changes in lung function over time as the cohort ages. As some of the associations were moderate and similarly sized but not statistically significant, it is possible that some of the analyses are underpowered. As the study is ongoing, future analyses will be better positioned to address these associations with greater precision. Given the absence of definitive diagnostics for the participants without pulmonary TB, it is possible that some participants without acute pneumonia were included in the analysis, although there were overall low numbers of TB negative participants due to our enrollment approach. Further, our current questionnaire does not account for the degree of biomass fuel exposure, which almost certainly differs by sex. Given the absence of total lung capacity measurements, pulmonary restriction could not be definitively diagnosed. While spirometric restriction was used as a proxy measurement, this has lower diagnostic accuracy. Whether these results can be generalized to PWH who have not had recent pneumonia merits further study.

Our study was strengthened by the nature of the cohort, which includes participants both with and without HIV and is highly enriched in women, paralleling the epidemiology of HIV in Uganda and sub-Saharan Africa. The presence of adults with and without HIV makes the cohort well-positioned for our comparisons by sex and HIV status. Despite representing over half of the world population of people with HIV, WWH remain under-represented in clinical and translational research [50]. In addition, most of the studies evaluating the development of aging-related comorbidities among WWH have not been conducted in sub-Saharan Africa, where the majority of WWH reside. This analysis provides an important contribution to the literature as it focuses on a key, understudied population with results that may guide future screening for OLD and subsequent therapeutic decisions.

Conclusions

The impact of HIV on OLD is greater among women than men among Ugandans who have recovered from pneumonia. Further research is needed to elucidate sex-specific mechanisms in OLD risk among PWH.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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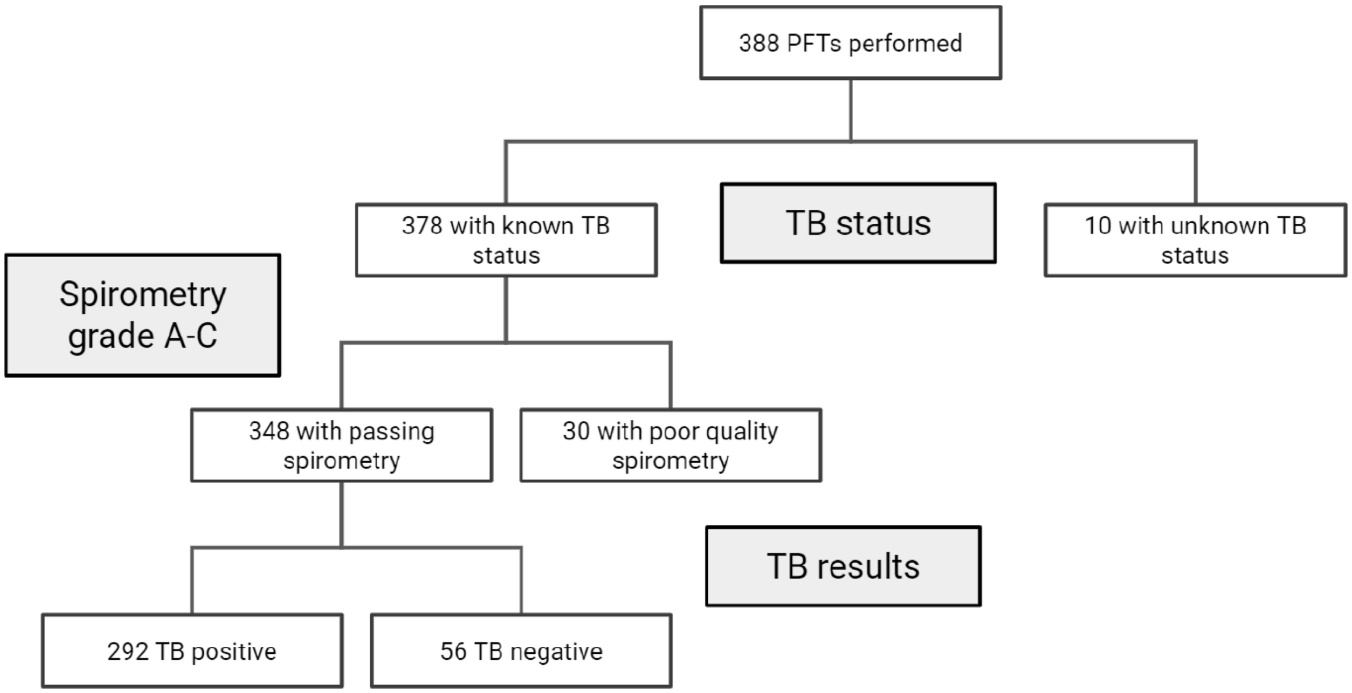

Figure 1.
Flow Diagram of Participant Inclusion in the Analysis

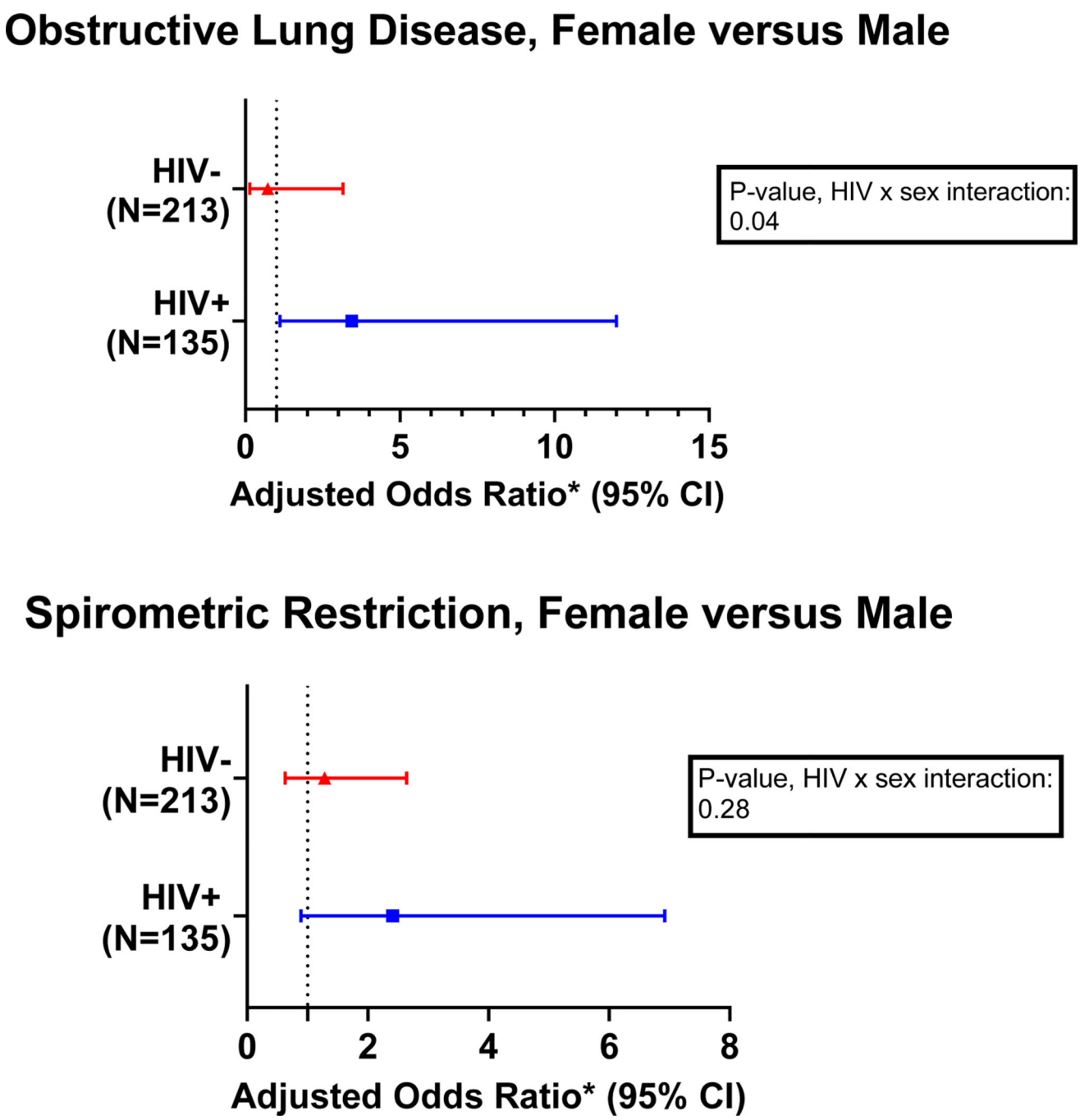

Figure 2: Odds of obstructive lung disease and spirometric restriction by sex, stratified by HIV status

* Adjusted for age, smoking status, BMI, and TB status

Table 1.

Baseline participant characteristics (N=348)

	Mean ± SD, Median (IQR), or N(%)					
	Women (N=147)	**Men (N=201)**	**P-value**	**HIV+ (N=135)**	**HIV- (N=213)**	**P-value**
Age, years	31 (25, 40)	34 (27, 41)	0.04	37 (31, 44)	29 (24, 38)	<0.001
BMI, kg/m^2	21.6 (19.7, 24.6)	20.5 (15.3, 22.3)	<0.001	21.1 (19.0, 23.4)	20.8 (19.4, 22.8)	0.66
Ever cigarette smoker	6 (4.0)	66 (33)	<0.001	26 (19)	46 (22)	0.68
Current cigarette smoker	1 (1)	25 (12)	<0.001	5 (4)	21 (10)	0.04
Exposure to biomass fuel at home	132 (91)	118 (60)	<0.001	101 (78)	149 (70)	0.17
HIV Status			0.01			
HIV Positive	69 (47)	66 (33)		-	-	-
HIV Negative	78 (53)	135 (67)		-	-	-
CD4 count †	156 (45, 289)	91 (37, 302)	0.44	128 (41, 293)	-	-
Current ART use †	36 (52)	19 (29)	<0.001	57 (42)	-	-
TB Status			0.08			<0.001
Positive TB status	117 (80)	175 (87)		90 (67)	202 (95)	
Negative TB status	30 (20)	26 (13)		45 (33)	11 (5)	
Baseline clinical presentation						
Heart rate	106 ± 22	103 ± 20	0.17	107 ± 23	102 ± 19	0.047
Respiratory rate	24 (20, 26)	24 (20, 28)	0.49	24 (20, 28)	22 (20, 26)	0.07
Oxygen saturation	96 (94, 98)	96 (93, 97)	0.009	96 (94, 97)	96 (93, 98)	0.86
Bedbound	15 (10)	15 (7)	0.44	19 (14)	11 (5)	0.01
Lung function						
Normal	85 (58)	120 (60)	0.74	87 (64)	118 (55)	0.12
Obstructed	16 (11)	23 (11)	0.90	21 (16)	18 (8)	0.29
Spirometric restriction	40 (27)	51 (25)	0.70	24 (18)	67 (31)	0.01
Undefined	6 (4)	7 (3)	0.77	3 (3)	10 (5)	0.25

Lung function definitions: normal = post-BD $FEV_1/FVC \geq 0.70$ and post-BD $FEV_1 \geq 80\%$ predicted and post-BD FEVC ≥ 80% predicted; obstructed = post-BD $FEV_1/FVC < 0.70$; restricted = post-BD $FEV_1/FVC \geq 0.70$ and post-BD FVC < 80% predicted; undefined = post-BD $FEV_1/FVC \geq 0.70$, FVC≥0.80, and FEV_1<80

Abbreviations: BMI = body mass index; TB = tuberculosis; HIV = human immunodeficiency virus; IQR = interquartile range; BD = bronchodilator; FEV1%predicted = forced expiratory

volume in 1 second as percentage of predicted reference value; FEV1/FVC ratio = ratio of forced expiratory volume in 1 second to forced vital capacity; FVC% predicted = forced vital capacity as percentage of predicted reference value

† Among those with HIV (N=135)

Table 2.

Sex Differences in Lung Function Abnormalities by HIV Status

	Obstructed		Spirometric restriction	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Overall (N=348)				
Unadjusted	0.98 (0.48, 1.96)	0.96	1.11 (0.67, 1.82)	0.69
Adjusted[a]	1.91 (0.81, 4.65)	0.14	1.59 (0.90, 2.85)	0.11
Among HIV+ (N=135)				
Unadjusted	2.5 (0.90, 7.7)	0.09	1.38 (0.54, 3.62)	0.50
Adjusted[b]	**3.44 (1.11, 12.0)**	**0.04**	2.41 (0.89, 6.92)	0.09
Among HIV- (N=213)				
Unadjusted	0.32 (0.07, 1.04)	0.08	1.01 (0.54, 1.88)	0.96
Adjusted[b]	0.72 (0.14 3.15)	0.67	1.28 (0.63, 2.64)	0.49

[a]Model adjusted for age, smoking status, HIV, BMI, and TB status

[b]Model adjusted for age, smoking status, BMI, and TB status

Lung function definitions: normal = post-BD FEV1/FVC ≥ 0.70 and post-BD FEV1 ≥ 80% predicted and post-BD FEVC ≥ 80% predicted; obstructed = post-BD FEV1/FVC < 0.70; restricted = post-BD FEV1/FVC ≥ 0.70 and post- BD FVC < 80% predicted

Abbreviations: BMI = body mass index; TB = tuberculosis; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval; BD = bronchodilator; FEV1%predicted = forced expiratory volume in 1 second as percentage of predicted reference value; FEV1/FVC ratio = ratio of forced expiratory volume in 1 second to forced vital capacity; FVC%predicted = forced vital capacity as percentage of predicted reference value

Table 3.

Sex differences in lung function abnormalities by HIV status among TB+ Ugandans

	Obstructed		Spirometric restriction	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Overall (N=292)				
Unadjusted	0.65 (0.27, 1.46)	0.31	1.06 (0.62, 1.81)	0.22
Adjusted[a]	1.15 (0.43, 3.06)	0.77	1.48 (0.80, 2.78)	0.21
Among HIV+ (N=90)				
Unadjusted	1.41 (0.38, 5.38)	0.59	1.33 (0.45, 3.98)	0.61
Adjusted[b]	2.06 (0.49, 9.12)	0.32	1.85 (0.57, 6.33)	0.31
Among HIV- (N=202)				
Unadjusted	0.32 (0.07, 1.04)	0.09	1.06 (0.56, 1.98)	0.87
Adjusted[b]	0.72 (0.14, 3.17)	0.67	1.34 (0.64, 2.83)	0.43

[a]Model adjusted for age, smoking status, HIV, and BMI

[b]Model adjusted for age, smoking status, and BMI

Lung function definitions: normal = post-BD FEV1/FVC ≥ 0.70 and post-BD FEV1 ≥ 80% predicted and post-BD FEVC ≥ 80% predicted; obstructed = post-BD FEV1/FVC < 0.70; restricted = post-BD FEV1/FVC ≥ 0.70 and post- BD FVC < 80% predicted

Abbreviations: BMI = body mass index; TB = tuberculosis; HIV = human immunodeficiency virus; OR = odds ratio; CI = confidence interval; BD = bronchodilator; FEV1%predicted = forced expiratory volume in 1 second as percentage of predicted reference value; FEV1/FVC ratio = ratio of forced expiratory volume in 1 second to forced vital capacity; FVC%predicted = forced vital capacity as percentage of predicted reference value