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Sex and HIV Differences in Preserved Ratio Impaired Spirometry (PRISm) Among Ugandans Postpneumonia

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Background. Preserved ratio impaired spirometry (PRISm), defined as a normal ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (≥ 0.70) with low FEV_1 ($<80\%$ predicted), has been associated with increased mortality in the general population. Female sex has been associated with increased odds of PRISm in people without HIV. People with HIV (PWH) are at increased risk for lung function abnormalities, but whether HIV modifies the effect of sex on PRISm development is largely unknown.

Methods. Adults with and without HIV underwent baseline followed by serial spirometry after completing therapy for pneumonia, predominantly tuberculosis (TB), in Kampala, Uganda. Using generalized estimating equations adjusted for age, body mass index, smoking, biomass fuel exposure, HIV, and TB status, we compared individuals with PRISm with those with normal spirometry. These models were stratified by HIV status.

Results. Of 339 baseline participants, 153 (45%) were women; 129 (38%) had HIV, of whom 53% were women. Overall, 105/339 participants (31%) had PRISm at baseline. HIV was associated with lower odds of PRISm (adjusted odds ratio [aOR], 0.38; 95% CI, 0.21–0.68; $P = .001$). Female sex trended toward increased odds of PRISm among all participants (aOR, 1.65; 95% CI, 0.99–2.75; $P = .052$). The association between female sex and PRISm tended to be stronger among PWH (aOR, 3.16; 95% CI, 1.14–8.76; $P = .03$) than among those without HIV (aOR, 1.34; 95% CI, 0.73–2.45; $P = .34$); this study was underpowered to detect an HIV–sex interaction of this magnitude ($P = .30$).

Conclusions. Among Ugandan adults who recovered from pneumonia, female sex was associated with increased odds and HIV with decreased odds of PRISm, suggesting independent sex and HIV effects on PRISm pathogenesis.

Keywords. HIV; preserved ratio impaired spirometry; sex differences; tuberculosis.

Chronic respiratory disease is a leading cause of death globally [1]. The most commonly diagnosed chronic lung disease is chronic obstructive pulmonary disease (COPD), which is characterized by airflow obstruction and diagnosed by a decreased ratio of forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) on postbronchodilator spirometry [2]. Airflow obstruction serves as an important cause of both morbidity and mortality worldwide [2, 3].

Nonobstructive lung function abnormalities are increasingly being recognized as harbingers of mortality or respiratory disease–associated morbidity. Preserved ratio impaired spirometry (PRISm), which is defined as a normal FEV_1/FVC ratio but with an abnormal FEV_1, has been independently associated with increased mortality [4–6] and a higher respiratory symptom burden [7–9]. Patients with PRISm also demonstrate increased frequency in progression from normal FEV_1/FVC ratio to airflow obstruction over time [7, 10, 11]. For example, a large UK-based study found an 11% prevalence of PRISm, with 12% of individuals with PRISm at baseline subsequently developing COPD over a median of 9 years of follow-up [7]. Studies in the general population have found that female sex is associated with increased odds of PRISm development [4, 7, 12]. Other risk factors include high and low body mass index (BMI), cigarette smoking, exposure to biomass fuel, and tuberculosis (TB) [12–15].

Women with HIV may be at particular risk for developing PRISm. A cross-sectional study in India evaluating lung function among people with HIV (PWH) demonstrated that female sex was independently associated with a 22-fold higher odds of having PRISm compared with male sex, even when controlling for TB status and biomass fuel exposure [16]. Notably, this cohort had low rates of airflow obstruction and did not find HIV-related factors, such as HIV viral load, to be significantly associated with the presence of abnormal lung function. In a Uganda-based cohort, longitudinal FEV_1 decline was noted only among women with HIV, a finding that was not seen among women without HIV or among men with and without HIV [17]. While there are several potential explanations for these findings, such as sex serving as a biologic risk factor or sex serving as a confounder for unmeasured exposures, these findings suggest that both sex-specific drivers and HIV-associated factors may play a role in PRISm development.

To determine whether women with HIV in urban Uganda have higher odds of PRISm after acute pneumonia compared with men with and without HIV and women without HIV, we conducted a longitudinal study among Ugandan adults evaluating the associations of HIV and sex with PRISm, FEV_1, and FVC overall, and then subsequently stratified by HIV status. Our primary objective was to investigate whether sex-based differences in PRISm prevalence exist when compared with normal spirometry among PWH after acute pneumonia, predominantly pulmonary TB. Given the recommendation to use the lower limit of normal (LLN) for the diagnosis of abnormal lung function by the American Thoracic Society/European Respiratory Society (ATS/ERS) [18], we then performed a sensitivity analysis using the LLN as the cutoff value for PRISm, FEV_1, and FVC.

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 evaluates the development and progression 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 to elucidate potential mechanistic insights into lung function abnormalities among PWH. This analysis focuses on participants enrolled in Uganda.

Uganda Cohort

We enroll nonpregnant patients aged 18–60 at the time of acute pneumonia, including pulmonary TB. Participants are enrolled from the inpatient wards or the outpatient TB clinic if they have presented with suspected pneumonia at the China-Uganda Friendship Hospital Naguru in Kampala, Uganda. Patients are eligible for inclusion if they have had a cough for <6 months. All participants are tested for HIV at enrollment and at each follow-up visit. For participants with HIV, CD4 counts are checked and antiretroviral therapy status is assessed, but HIV RNA levels are not available.

After enrollment, participants receive a chest radiograph and undergo protocolized evaluation for pulmonary TB, as described previously [19–21]. If TB-positive, participants receive TB therapy followed by baseline post-treatment pre- and postbronchodilator spirometry after completion of TB therapy. Participants then receive follow-up spirometry 3 months after the baseline visit to assess the stability of the spirometry results in the immediate post-TB period. If TB testing is negative, participants are treated for pneumonia followed by baseline post-treatment pre- and postbronchodilator spirometry at least 3 months after therapy completion. All participants continue to undergo pre- and postbronchodilator spirometry testing 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 Institutional Review Board (IRB #10-02633). All study participants were informed about the study by a nurse or physician and provided written informed consent before participation in the study.

Study Population and Procedures

This current secondary longitudinal analysis from Uganda spans visits from February 2016 to October 2022. Pre- and postbronchodilator spirometry was performed by trained study personnel using an Easy on-PC (February 2016–October 2021) or an EasyOne Pro device (October 2021–October 2022; ndd Medizintechnik AG, Zurich, Switzerland) according to ATS/ERS guidelines [18, 22]. Each spirometry maneuver was overread by a trained respiratory therapist to confirm acceptability and reproducibility of test results. Using the ATS/ERS spirometry quality grading system, tests with grades A through C were included in the analysis [18, 22].

Classification of Lung Function Patterns

PRISm was defined as a postbronchodilator FEV_1/FVC ratio ≥ 0.70 and a postbronchodilator FEV_1 <80% predicted (the fixed ratio definition), as defined in prior studies [4, 5, 10]. An abnormal FVC was defined as <80% predicted. Normal spirometry was defined as a postbronchodilator FEV_1/FVC ratio ≥ 0.70 with an FEV_1 and FVC both $\geq 80\%$ predicted. In recognition of the ATS/ERS guidelines, a sensitivity analysis was

performed with PRISm defined as FEV$_1$/FVC ratio ≥ LLN with an FEV$_1$ < LLN (the LLN definition) [18]. Normal spirometry was defined as FEV$_1$/FVC ratio ≥ LLN with an FEV$_1$ and FVC both ≥ LLN [18]. Participants with COPD or spirometric restriction were not included in the analysis to avoid heterogeneity between comparison groups and potential overlap of PRISm with spirometric restriction. The Global Lung Initiative African American equations were used for both the fixed ratio and LLN definitions, per the ATS/ERS guidelines [18, 23].

Statistical Analysis

Participants included in this analysis had acceptable spirometry results and known TB status. In this analysis, time-independent variables were used at the time of initial enrollment with pneumonia, with age, BMI, and smoking status used at each respective visit. Tertiles were used for BMI as the models would not converge when using clinical BMI cutoffs due to few obese participants in the cohort, and trend with increasing BMI was assessed. Demographics and clinical characteristics were compared between those with PRISm and those with normal spirometry. Multivariable analyses were performed at the baseline spirometry visit examining the associations between demographic parameters, including sex, 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 with PRISm, FEV$_1$ <80% predicted, and FVC <80% predicted. A sensitivity analysis was performed using the LLN definitions for PRISm, FEV$_1$, and FVC. These models were then stratified by HIV status to examine whether the associations differed among people with and without HIV. Generalized estimating equations (GEEs) with a log link and binomial distribution were subsequently used across all spirometry visits, controlling for biologically important predictors (age, BMI, smoking status, biomass fuel exposure, HIV, and TB status). Repeated measures were used at each available spirometry visit (ie, baseline and subsequent visits) for participants with either PRISm or normal spirometry without censoring. All observations where a participant's spirometry demonstrated PRISm or was classified as normal were included in the analysis. As using age as a continuous variable led to convergence issues in the GEE models, age was dichotomized to the sample median. The models were stratified by HIV status due to biologic plausibility and our a priori study question. As there were only 13 participants with HIV who did not have TB, TB status was excluded from the stratified model.

RESULTS

Baseline Participant Characteristics

Overall, 1013 participants were enrolled in I AM OLD during an episode of acute pneumonia. Of the 392 participants with passing spirometry, 339 had PRISm or normal spirometry at baseline (Figure 1). There were 43 participants with known TB status who never had PRISm or normal spirometry and were therefore excluded from the longitudinal analysis. Of those 43 participants, 22 were PWH, of whom 19 had obstruction and 3 had spirometric restriction. Of the 339 included baseline participants, 153 (45%) were women and 129 (38%) were PWH (Table 1). Among those with HIV, 68 (53%) were women. Of those who were lost to follow-up, 322 had HIV (54%) as compared with 271 (46%) without HIV. However, the proportion of women who were lost to follow-up was similar to those included in the analysis (48% of those lost to follow-up were female vs 53% included in the analysis).

At baseline, 105 (31%) individuals had PRISm and 234 (69%) had normal spirometry using the fixed ratio definitions for FEV$_1$/FVC and FEV$_1$. Demographic characteristics were similar between the PRISm and normal spirometry groups, except that those with normal spirometry were slightly older (median, 32 vs 29 years; $P = .005$) and had a slightly higher median BMI (median, 21.6 vs 20.0 kg/m^2; $P < .001$). Prevalence of cigarette smoking and biomass fuel exposure were similar between groups. There was a higher proportion of PWH in the normal spirometry group than among those with PRISm (44% vs 25%; $P < .001$), but among those with HIV, those with PRISm were more likely to be on ART (54% vs 39%; $P = .03$). The median time between ART initiation and the baseline visit (interquartile range) was 177 (155–201) days. TB positivity was similar between groups (82% with PRISm vs 79% with normal spirometry). When the LLN was used as the cutoff definition, the demographic characteristics were similar between the PRISm and normal spirometry groups and mirrored those of the fixed ratio definition (Table 1).

Longitudinal Associations of Participant Characteristics With PRISm

Of the 339 baseline participants, 19 individuals had unknown or indeterminate TB status at baseline and were excluded from the GEE models (Figure 1). Seven individuals who had initially been excluded at the baseline visit subsequently developed either normal spirometry or PRISm during follow-up and were included in the longitudinal analysis, leading to a total of 327 participants across 560 visits included in the GEE models (Table 2). Overall, female sex trended toward increased odds of PRISm in the adjusted analysis (adjusted odds ratio [aOR], 1.65; 95% CI, 0.99–2.75; $P = .052$). In both the unadjusted and adjusted models, HIV was associated with lower odds of PRISm (aOR, 0.38; 95% CI, 0.21–0.68; $P = .001$). The study was underpowered to detect an HIV–sex interaction of this magnitude ($P = .30$).

Longitudinal Associations of Sex With PRISm Stratified by HIV Status

In the adjusted stratified analysis among those with HIV, women had 3.16-fold higher adjusted odds of PRISm than men (95% CI, 1.14–8.76; $P = .03$) (Table 2) using the fixed ratio definition.
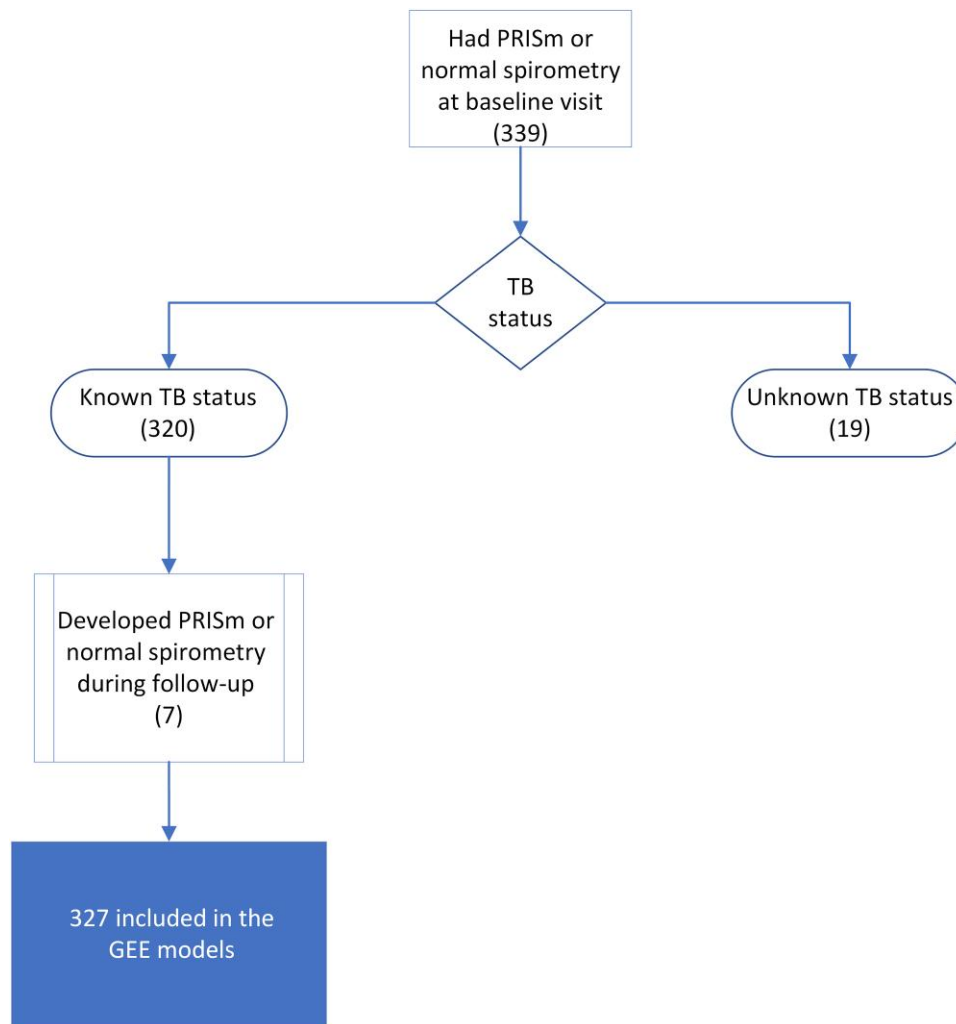
Figure 1. Flow diagram of participant inclusion in the analysis. Abbreviations: GEE, generalized estimating equation; PRISm, preserved ratio impaired spirometry; TB, tuberculosis.

Among those without HIV, however, there was no evidence of an association between female sex and PRISm (aOR, 1.34, 95% CI, 0.73–2.45; $P = .34$). When time was included in the models, the inferences were similar. Overall, women had non–statistically significantly higher odds of PRISm (aOR, 1.56; 95% CI, 0.90–2.70; $P = .11$), whereas women with HIV had 3.62 higher odds of PRISm compared with normal spirometry (95% CI, 1.32–9.90; $P = .01$, results not shown). Women without HIV did not demonstrate higher odds of PRISm (aOR, 1.10).

In Figure 2, the predicted probabilities of PRISm for women and men with and without HIV as a function of time using the models described above are pictured. Over time, men with and without HIV have a lower mean probability of developing PRISm. Women without HIV start with a higher mean probability of PRISm than women with HIV as well as compared with men with and without HIV, but the mean probability decreases over time. In contrast, women with HIV start with a lower mean probability for PRISm at baseline but develop a higher mean probability for PRISm than all other groups by month 21.

Longitudinal Associations of Sex With Abnormal FEV$_1$ and FVC Stratified by HIV Status

When evaluating the overall presence of abnormal FEV$_1$ during follow-up, female sex was associated with 1.68 higher odds of having an FEV$_1$ <80% predicted (95% CI, 1.05–2.69; $P = .03$) (Table 3). As expected from the PRISm results, HIV was associated with lower odds of having an FEV$_1$ <80% predicted (aOR, 0.50; 95% CI, 0.30–0.83; $P = .01$).

In the stratified analysis, among those with HIV, women had 3.20 times higher odds of having a low FEV$_1$ than men with HIV (95% CI, 1.39–7.36; $P = .006$); women without HIV did not demonstrate higher odds of an abnormal FEV$_1$ when compared with their male counterparts. Similar patterns were seen for those with an FVC <80% predicted over follow-up (Table 3).

Table 1. Participant Characteristics Among Those With and Without PRISm at Baseline

	Fixed Ratio Definition			Lower Limit of Normal Definition		
	PRISm[a] No. (%) or Median (IQR) n = 105	Normal[a] No. (%) or Median (IQR) n = 234	P Value	PRISm[b] No. (%) or Median (IQR) n = 81	Normal[b] No. (%) or Median (IQR) n = 242	P Value
Age, y	29 (23–38)	32 (27–41)	**.005**	31 (23–38)	32 (27–41)	**.01**
Female sex	49 (47)	104 (44)	.72	37 (46)	107 (44)	.89
BMI, kg/m^2	20.0 (18.7–21.9)	21.6 (20.0–24.0)	**<.001**	19.6 (18.5–21.5)	21.5 (19.8–24.0)	**<.001**
Ever cigarette smoker	22 (21)	38 (16)	.36	19 (23)	43 (18)	.25
Exposure to biomass fuel at home	76 (74)	168 (73)	.89	58 (73)	175 (73)	.89
HIV status	…	…	**<.001**	…	…	**<.001**
Positive	26 (25)	103 (44)	…	18 (22)	104 (43)	…
Negative	79 (75)	131 (56)	…	63 (78)	138 (57)	…
CD4 count[a]	150 (65–297)	112 (32–293)	.47	143 (65–313)	120 (35–303)	.50
CD4 <200 cells/mm^3	7 (33)	27 (35)	.90	3 (21)	27 (35)	.37
CD4 ≥200 cells/mm^3	14 (67)	50 (65)	…	11 (79)	50 (65)	…
Current ART use[a]	14 (54)	40 (39)	**.03**	9 (50)	41 (20)	**.03**
TB status	…	…	.67	…	…	.42
Positive TB status	86 (82)	185 (79)	…	69 (85)	188 (78)	…
Negative TB status	15 (14)	34 (15)	…	9 (11)	39 (16)	…
Unknown TB status	4 (4)	15 (6)	…	3 (4)	15 (6)	…

The bold values are those that reached statistical significance.

Abbreviations: BMI, body mass index; FEV$_1$%predicted, forced expiratory volume in 1 second as percentage of predicted reference value; FEV$_1$/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; IQR, interquartile range; PRISm, preserved ratio impaired spirometry; TB, tuberculosis.

[a]PRISm defined as FEV$_1$/FVC ≥0.70 and FEV$_1$ <80% predicted, and normal defined as FEV$_1$/FVC ≥0.70 and FEV$_1$ ≥80% predicted and FVC ≥80% predicted.

[b]PRISm defined as FEV$_1$/FVC ≥ LLN and FEV$_1$ < LLN, and normal defined as FEV$_1$/FVC ≥ LLN and FEV$_1$ ≥ LLN and FVC ≥ LLN.

[c]Among those with HIV.

Longitudinal Associations of Sex and Abnormal Lung Function Using the Lower Limit of Normal

In the models evaluating the associations of participant characteristics during follow-up with PRISm using the LLN definition, female sex was associated with 1.88 higher odds of PRISm (95% CI, 1.09–3.24; P = .02) (Supplementary Table 1). In the stratified model, among those with HIV, female sex was non–statistically significantly associated with increased odds of PRISm (aOR, 1.77; 95% CI, 0.66–4.71; P = .26). Women without HIV had similar non–statistically significant associations of increased odds of PRISm (aOR, 1.71; 95% CI, 0.90–3.23; P = .10). Using the LLN as the cutoff value, similar inferences were observed with FEV$_1$ and FVC during follow-up (Supplementary Table 2).

DISCUSSION

In this longitudinal cohort of adults who recovered from pneumonia in Kampala, Uganda, the odds of PRISm among women with HIV were up to 3 times higher than the odds for men with HIV. Similar to prior studies, there was an overall association of female sex with PRISm [4, 7]. Overall, 31% of participants in this selected cohort had PRISm at baseline using the fixed ratio definition, whereas 25% of participants had PRISm at baseline when using the LLN definition. Regardless of the definition used, HIV

was associated with lower odds of PRISm development. Participants with HIV demonstrated a >60% reduction in odds of PRISm compared with their seronegative counterparts. Taken together, these findings suggest that both sex and HIV-associated factors may contribute to PRISm development.

Our findings of a sex difference in HIV are similar to but of a smaller magnitude than a study by Baidya et al. of women (n = 121) and men (n = 89) with HIV [16]. This study found that female sex was independently associated with 22-fold higher odds of having PRISm when compared with males, even after adjusting for BMI, smoking, diabetes, TB status, and HIV-associated factors (95% CI, 7.42–69.92; P < .001). Similar to our analysis, female sex was also associated with lower FEV$_1$ and FVC. Differences in the magnitude of our results could be attributed to differences in our cohort, which is younger (median age, 32 vs 40) and has a higher burden of tuberculosis (∼80% as compared with 40%), perhaps leading to higher rates of post-tuberculosis airflow obstruction or spirometric restriction. Furthermore, in the Baidya cohort, 46% of participants were categorized as having PRISm, whereas only 3% had airflow obstruction as compared with 19% with airflow obstruction among those with HIV in our cohort. Despite these differences, the findings from the Baidya study are in the same direction as observed in this analysis and in the general

Table 2. The Longitudinal Adjusted Associations of Participant Characteristics With PRISm Using the Fixed Ratio Definition[b]

...	Overall (n_participants = 327; n_obs = 560)				HIV+ (n_participants = 120; n_obs = 211)		HIV- (n_participants = 207; n_obs = 349)	
	Unadjusted PRISm[a] vs Normal OR (95% CI)	P Value	Adjusted PRISm[a] vs Normal aOR (95% CI)	P Value	PRISm[a] vs Normal aOR (95% CI)	P Value	PRISm[a] vs Normal aOR (95% CI)	P Value
Age >32 y	0.83 (0.51–1.34)	.45	1.23 (0.71–2.14)	.45	1.59 (0.46–5.55)	.46	1.05 (0.59–1.87)	.89
Female sex	1.19 (0.77–1.85)	.43	1.65 (0.99–2.75)	.052	**3.16 (1.14–8.76)**	**.03**	1.34 (0.73–2.45)	.34
BMI, tertile 2 vs 1[c]	**0.62 (0.39–0.99)**	**.046**	**0.55 (0.34–0.89)**	**.01**	**0.23 (0.07–0.76)**	**.02**	0.73 (0.45–1.19)	.21
BMI, tertile 3 vs 1	**0.35 (0.20–0.61)**	**<.001**	**0.29 (0.16–0.53)**	**<.001**	**0.21 (0.07–0.63)**	**.005**	**0.34 (0.17–0.68)**	**.002**
P_trend	...	**<.001**	...	**<.001**	...	**.05**	...	**.03**
Ever cigarette smoker	1.43 (0.79–2.57)	.24	1.27 (0.62–2.55)	.51	1.23 (0.36–4.21)	.74	1.27 (0.55–2.92)	.57
Exposure to biomass fuel at home	0.99 (0.59–1.68)	.99	0.86 (0.48–1.53)	.61	0.52 (0.16–1.78)	.30	0.96 (0.50–1.86)	.91
HIV+ vs HIV-	**0.48 (0.29–0.80)**	**.005**	**0.38 (0.21–0.68)**	**.001**	-	-	-	-
TB+ vs TB-	0.92 (0.48–1.75)	.80	0.55 (0.27–1.10)	.10	-	-	-	-

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; FEV_1%predicted, forced expiratory volume in 1 second as percentage of predicted reference value; FEV_1/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; IQR, interquartile range; OR, odds ratio; PRISm, preserved ratio impaired spirometry; TB, tuberculosis.

n_participants = the number of participants included in the analysis; n_obs = the number of unique observations included in the analysis. The bold values are those that reached statistical significance.

[a]PRISm defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 <80\%$ predicted, and normal defined as $FEV_1/FVC \geq 0.70$ and $FEV_1 \geq 80\%$ predicted and FVC $\geq 80\%$ predicted.

[b]Adjusted for age, BMI, smoking status, biomass fuel exposure, HIV, and TB status.

[c]BMI was divided into tertiles to facilitate model convergence. For clinical interpretation, trend was also assessed.
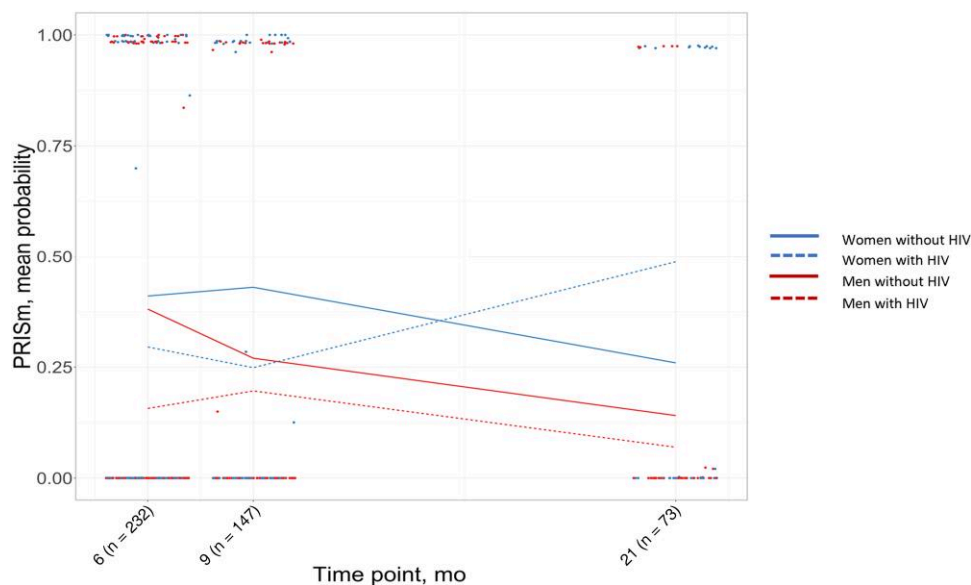
Figure 2. Mean probability of PRISm by HIV status and sex over time. Abbeviation: PRISm, preserved ratio impaired spirometry.

population, in which female sex has been identified as a risk factor for PRISm development [4, 7].

Among those with HIV, women demonstrated increased odds for PRISm development as well as a low FEV_1 and FVC, with women with HIV demonstrating statistically significantly higher odds of PRISm when using the fixed ratio definition for FEV_1/FVC. When using the LLN as the cutoff, overall, female sex was associated with higher odds of PRISm, but an HIV-associated difference was not seen in the stratified

analysis. While the seminal papers by Wan et al. define PRISm using the fixed definition (a fixed ratio of $FEV_1/FVC \geq 0.70$ with an $FEV_1 <80\%$ predicted) [4, 10, 24], the ATS/ERS recommends use of the LLN for the diagnosis of airflow obstruction given that changes in lung function over time are dependent on many factors, including age and sex [18]. Due to sex differences in the dysanaptic growth of the airways as compared with the lungs, the FEV_1/FVC ratio is typically higher in women [25]. While it is possible that using the LLN was

Table 3. The Longitudinal Adjusted Associations of Participant Characteristics With FEV_1 <80% Predicted and FVC <80% Predicted Using the Fixed Ratio Definition[a]

	FEV_1 <80% Predicted vs Normal aOR (95% CI)	P Value	FVC <80% Predicted vs Normal aOR (95% CI)	P Value
Overall	$n_{participants}$ = 358; n_{obs} = 617		$n_{participants}$ = 341; n_{obs} = 575	
Age >32 y	1.34 (0.85–2.11)	.21	1.16 (0.72–1.89)	.54
Female sex	**1.68 (1.05–2.69)**	**.03**	1.53 (0.93–2.50)	.09
BMI, tertile 2 vs 1[b]	**0.60 (0.41–0.87)**	**.01**	**0.48 (0.33–0.69)**	**<.001**
BMI, tertile 3 vs 1	**0.33 (0.21–0.54)**	**<.001**	**0.25 (0.16–0.41)**	**<.001**
P_{trend}	…	**<.001**	…	**<.001**
Ever cigarette smoker	1.49 (0.82–2.72)	.19	1.32 (0.69–2.49)	.40
Exposure to biomass fuel at home	0.87 (0.51–1.47)	.59	0.75 (0.44–1.29)	.31
HIV+ vs HIV-	**0.50 (0.30–0.83)**	**.01**	**0.58 (0.33–0.94)**	**.03**
TB+ vs TB-	0.54 (0.29–1.00)	.05	0.75 (0.38–1.49)	.41
HIV+	$n_{participants}$ = 137; n_{obs} = 239		$n_{participants}$ = 130; n_{obs} = 221	
Female sex	**3.20 (1.39–7.36)**	**.006**	**3.20 (1.26–8.13)**	**.02**
HIV-	$n_{participants}$ = 221; n_{obs} = 378		$n_{participants}$ = 211; n_{obs} = 354	
Female sex	1.26 (0.72–2.23)	.42	1.23 (0.68–2.25)	.49

$n_{participants}$ = the number of participants included in the analysis; n_{obs} = the number of unique observations included in the analysis. The bold values are those that reached statistical significance.

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; FEV_1%predicted, forced expiratory volume in 1 second as percentage of predicted reference value; FVC% predicted, forced vital capacity as percentage of predicted reference value; TB, tuberculosis.

[a]Adjusted for age, BMI, smoking status, biomass fuel exposure, HIV, and TB status.

[b]BMI was divided into tertiles to facilitate model convergence. For clinical interpretation, trend was also assessed.

therefore more accurate in our cohort, thereby demonstrating that female sex alone is associated with higher odds of PRISm, as has been seen in prior studies [4, 7, 12], this is belied by the FEV_1 results. Specifically, we found that women with HIV uniquely demonstrated significantly higher odds of an abnormal FEV_1 under both definitions. Prior studies have also demonstrated an HIV-specific, sex-specific FEV_1 decline. A study by McNeill et al. conducted in a rural Ugandan cohort (n = 278) with low rates of TB similarly found an accelerated rate of decline in FEV_1 over time among women with HIV as compared with women without HIV, a finding that was not seen among men with and without HIV [17]. These findings suggest that despite differences in odds of PRISm depending on the cutoff definition used, sex-specific and HIV-specific factors appear to play a role in the development of abnormal lung function, particularly FEV_1 decline.

Despite PWH being at higher risk for COPD [26–29], there have been few data on rates of nonobstructive lung function abnormalities, such as PRISm, among PWH. Chronic lung disease represents the second most common comorbidity among PWH [26]; HIV infection is independently associated with COPD, even when controlling for cigarette smoking [28, 30]. PWH have also been found to have an earlier onset and a more rapid decline in lung function than the general population [28, 31, 32]. Interestingly, in our analysis, we found that HIV was associated with lower odds of PRISm when compared with normal spirometry. This is in contrast to a cross-sectional analysis in a Nigerian cohort of adults with and without HIV by Fink et al.

in which there was no HIV-associated difference in PRISm prevalence [33]. Notably, in the Fink analysis, a history of TB was significantly higher among those with HIV when compared with those without HIV (28.8% vs 0.7%), and the median FEV_1 and FVC were both lower among PWH than among their seronegative counterparts. Given the parent study's design, our participants were recruited after an episode of acute pneumonia, whereas the participants in the Fink study were recruited from outpatient clinics. Our discrepant results may also be related to selection bias as participants with PRISm were compared with those with normal spirometry alone, with participants with HIV exhibiting a higher prevalence of abnormal lung function than their seronegative counterparts. For example, the prevalence of obstructive lung disease in this cohort was slightly higher in PWH (19%, or 21 individuals) as compared with those without HIV (13%, or 18 individuals), suggesting that the association of HIV with lower odds of PRISm in this analysis could be due to higher rates of HIV-associated COPD or spirometric restriction. In addition, different definitions were used in the Fink study, which may have contributed to our different results. In the Fink study, the LLN was used for FEV_1, FVC, and their ratio, whereas PRISm was defined using the fixed cutoff definition, allowing for overlap between PRISm and other lung function abnormalities.

Our study has several limitations. As our participants underwent spirometry after recovery from pneumonia, it is uncertain whether these results are generalizable to PWH without recent pneumonia. There were overall low numbers of TB-negative

participants given our enrollment strategy, thereby reducing the power of the analysis to evaluate the association of non-TB pneumonia with abnormal lung function. We were similarly underpowered to detect an HIV–sex interaction in this study. While we had longitudinal lung function testing, many of our enrolled participants were lost to follow-up, and most of our participants did not have pulmonary function testing beyond 9 months of follow-up at the time of this analysis, limiting our ability to determine the durability of PRISm and its potential progression to COPD over time. We do not have the amount of biomass fuel exposure or cigarette smoking intensity as part of our data collection, which may have introduced measurement error into our analysis. Additional data to better evaluate socioeconomic status were not collected, and, among women, menopausal status was not determined. In the general population, early menopause has been associated with lower FEV_1/FVC [34], and a prior study found that women with amenorrhea for >6 months had lower FEV_1 and FVC than women with a normal menstrual flow [35]. Longitudinal lung function is currently being measured, and additional metrics on biomass fuel exposure, socioeconomic factors, and menstrual status data among female participants are currently being collected.

The strengths of this study include the nature of the cohort, which includes participants both with and without HIV and is highly enriched with women, which parallels the epidemiology of HIV in Uganda and in Sub-Saharan Africa. To date, there have been no studies evaluating the relationship between biologic sex and the development of PRISm among women with HIV despite the association of PRISm with increased mortality [4–6]. Evidence suggests that women with HIV are at higher risk for developing aging-related comorbidities compared with men [36, 37]; the progression and development of lung function abnormalities within this group merit further study.

CONCLUSIONS

Among Ugandans with HIV who have recovered from pneumonia, female sex increases the odds of PRISm while HIV decreases the odds of PRISm, consistent with potential independent sex and HIV effects on PRISm pathogenesis. Given the known increased mortality associated with PRISm, studies to elucidate underlying mechanistic pathways are warranted.

Supplementary Data

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

References

1. World Health Organization. Global health estimates: leading causes of death. Available at: https://www.who.int/data/gho/data/themes/mortality-and-global-health-estimates/ghe-leading-causes-of-death. Accessed January 19, 2022.
2. Global Initiative for Chronic Obstructive Lung Disease. Global strategy for prevention, diagnosis, and management of COPD: 2023 report. 2023. Available at: https://goldcopd.org/2023-gold-report-2/. Accessed January 19, 2022.
3. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. Lancet 2022; 399:2227–42.
4. Wan ES, Balte P, Schwartz JE, et al. Association between preserved ratio impaired spirometry and clinical outcomes in US adults. JAMA 2021; 326:2287.
5. Marott JL, Ingebrigtsen TS, Çolak Y, Vestbo J, Lange P. Trajectory of preserved ratio impaired spirometry: natural history and long-term prognosis. Am J Respir Crit Care Med 2021; 204:910–20.
6. Schwartz A, Arnold N, Skinner B, et al. Preserved ratio impaired spirometry in a spirometry database. Respir Care 2021; 66:58–65.
7. Higbee DH, Granell R, Davey Smith G, Dodd JW. Prevalence, risk factors, and clinical implications of preserved ratio impaired spirometry: a UK Biobank cohort analysis. Lancet Respir Med 2022; 10:149–57.
8. Heo IR, Kim HC, Kim TH. Health-related quality of life and related factors in persons with preserved ratio impaired spirometry: data from the Korea National Health and Nutrition Examination Survey. Medicina (B Aires) 2020; 57:4.
9. Park HJ, Byun MK, Rhee CK, Kim K, Kim HJ, Yoo KH. Significant predictors of medically diagnosed chronic obstructive pulmonary disease in patients with preserved ratio impaired spirometry: a 3-year cohort study. Respir Res 2018; 19:185.
10. Wan ES, Fortis S, Regan EA, et al. Longitudinal phenotypes and mortality in preserved ratio impaired spirometry in the COPDGene study. Am J Respir Crit Care Med 2018; 198:1397–405.
11. Fortis S, Comellas A, Kim V, et al. Low FVC/TLC in preserved ratio impaired spirometry (PRISm) is associated with features of and progression to obstructive lung disease. Sci Rep 2020; 10:5169.
12. Mukherjee S, Roychoudhury S, Siddique S, et al. Respiratory symptoms, lung function decrement and chronic obstructive pulmonary disease in premenopausal Indian women exposed to biomass smoke. Inhal Toxicol 2014; 26:866–72.
13. Amaral AFS, Coton S, Kato B, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. Eur Respir J 2015; 46:1104–12.
14. Lee JY, Hwang YI, Park YB, et al. Prevalence of spirometrically-defined restrictive ventilatory defect in Korea: the fourth-2, 3, and fifth Korean National Health and Nutrition Examination Survey, 2008–2012. J Korean Med Sci 2015; 30:725–32.
15. Pefura-Yone EW, Balkissou AD, Kengne AP. Determinants of restrictive spirometric pattern in a Sub-Saharan urban setting: a cross-sectional population-based study. Open Respir Med J 2016; 10:86–95.
16. Baidya A, Sangle S, Marbaniang I, et al. Clinical and immunological markers of pulmonary impairment among people with HIV in India. Open Forum Infect Dis 2022; 9:1–11.
17. McNeill J, Okello S, Sentongo R, et al. Chronic HIV infection is associated with accelerated FEV_1 decline among women but not among men: a longitudinal cohort study in Uganda. Ann Am Thorac Soc 2022; 19:1779–83.
18. Stanojevic S, Kaminsky DA, Miller M, et al. ERS/ATS technical standard on interpretive strategies for routine lung function tests. Eur Respir J 2021; 60:2101499.
19. Abelman RA, Fitzpatrick J, Zawedde J, et al. Sex modifies the risk of HIV-associated obstructive lung disease in Ugandans postpneumonia. AIDS 2023; 37:1683–92.
20. Wang RJ, Moore J, Moisi D, et al. HIV infection is associated with elevated biomarkers of immune activation in Ugandan adults with pneumonia. PLoS One 2019; 14:e0216680.
21. Cattamanchi A, Davis JL, Worodria W, et al. Sensitivity and specificity of fluorescence microscopy for diagnosing pulmonary tuberculosis in a high HIV prevalence setting. Int J Tuberc Lung Dis 2009; 13:1130–6.
22. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J 2005; 26:319–38.
23. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3–95-yr age range: the Global Lung Function 2012 equations. Eur Respir J 2012; 40:1324–43.
24. Wan ES. The clinical spectrum of PRISm (preserved ratio impaired spirometry). Am J Respir Crit Care Med 2022; 206:524–5.
25. Townsend EA, Miller VM, Prakash YS. Sex differences and sex steroids in lung health and disease. Endocr Rev 2012; 33:1–47.
26. Kunisaki KM. Recent advances in HIV-associated chronic lung disease clinical research. Curr Opin HIV AIDS 2021; 16:156–62.
27. Byanova K, Kunisaki KM, Vasquez J, Huang L. Chronic obstructive pulmonary disease in HIV. Expert Rev Respir Med 2021; 15:71–87.
28. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest 2006; 130:1326–33.
29. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. Lancet Respir Med 2014; 2:583–92.
30. Bigna JJ, Kenne AM, Asangbeh SL, Sibetcheu AT. Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis. Lancet Glob Health 2018; 6:e193–202.
31. Crothers K, Huang L, Goulet JL, et al. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. Am J Respir Crit Care Med 2011; 183:388–95.
32. Drummond MB, Huang L, Diaz PT, et al. Factors associated with abnormal spirometry among HIV-infected individuals. AIDS 2015; 29:1691–700.
33. Fink DL, Oladele DA, Slack AJ, et al. A multi-centre observational study of HIV, tuberculosis and risk of chronic lung disease in urban West Africa. AIDS 2022; 36:1987–95.
34. Zhai T, Diergaarde B, Wilson DO, et al. Early natural menopause is associated with poor lung health and increased mortality among female smokers. Am J Obstet Gynecol 2022; 227:885.e1–12.
35. Real FG, Svanes C, Omenaas ER, et al. Lung function, respiratory symptoms, and the menopausal transition. J Allergy Clin Immunol 2008; 121:72–80.e3.
36. Pond RA, Collins LF, Lahiri CD. Sex differences in non-AIDS comorbidities among people with human immunodeficiency virus. Open Forum Infect Dis 2021; 8:1–19.
37. Collins LF, Palella FJ, Mehta CC, et al. Aging-related comorbidity burden among women and men with or at-risk for HIV in the US, 2008–2019. JAMA Netw Open 2023; 6:e2327584.