Association Between HIV and Prevalence and Manifestations of Asthma: Analysis of the Multicenter AIDS Cohort Study and Women's Interagency HIV Study

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Background: The association between HIV and asthma prevalence and manifestations remains unclear, with few studies including women.

Setting: A retrospective observational cohort study from the Multicenter AIDS Cohort Study and Women's Interagency HIV Study.

Methods: Asthma was defined in 2 ways: (1) self-report and (2) robust criteria requiring all the following: lack of fixed airflow obstruction, presence of wheeze on the St. George's Respiratory Questionnaire (SGRQ), and report of asthma therapies. Estimates of asthma prevalence and asthma-related manifestations were compared by HIV serostatus.

Results: A total of 1815 men and 2122 women were included. Asthma prevalence did not differ between people with HIV (PWH) and people without HIV regardless of definition: self-report (men, 12.0% vs. 11.2%; women, 24.3% vs. 27.5%) and robust criteria (men, 5.0% vs. 3.4%; women, 12.8% vs. 13.2%). Among men with asthma, worse respiratory symptom burden was reported among those with HIV, regardless of asthma definition. Among women with self-reported asthma, those with HIV had less respiratory symptom burden. Regardless of serostatus, women with robust-defined asthma had similar respiratory symptoms across SGRQ domains and similar frequencies of phlegm, shortness of breath, and wheezing.

Conclusions: Among PWH and people without HIV, asthma prevalence was 2-fold to 3-fold higher using self-reported definition rather than robust definition. In men and women, HIV was not associated with increased asthma prevalence. In men, HIV was associated with more respiratory symptoms when asthma was self-reported; the relationship was attenuated with the robust criteria. Further studies are needed to explore asthma phenotypes among PWH.

Key Words: asthma, HIV, lung diseases

INTRODUCTION

Since the introduction of effective antiretroviral therapy (ART), people with HIV (PWH) have experienced increased life expectancy.[1] With this increase, there has been recognition of increased multimorbidity among PWH, with the prevalence of at least 2 comorbid chronic illnesses now approaching 65%.[2] Chronic lung diseases, the spectrum of which includes asthma and chronic obstructive pulmonary disease (COPD), are conditions associated with substantial morbidity and mortality in the United States (US) general population.[3–5] Several studies have described an increased prevalence of chronic lung disease among PWH, with most studies focused on COPD.[6–13] There are few studies exploring the relationship between HIV and asthma prevalence and symptom burden.[9,14] Importantly, existing studies of asthma and HIV are limited largely to men and define asthma solely through self-report.

The Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS) are 2 longitudinal, observational cohort studies of individuals with or at risk for HIV.[15–19] Both cohorts have collected biannual self-reported respiratory diagnoses, data on inhaled and oral treatments, and standardized respiratory symptom assessments. Pulmonary function testing (PFT), including prebronchodilator and postbronchodilator spirometry, has been recently collected in both cohorts. These data afford the unique opportunity to determine the relationship between HIV and prevalence and burden of asthma in each cohort using 2 different definitions: (1) self-report and (2) robust criteria incorporating spirometry, symptoms, and medication history. Some of these results have been previously reported in abstract form.[20]

METHODS

Study Population

We used data from MACS and WIHS cohorts before their integration into the MACS/WIHS Combined Cohort Study in 2019. Beginning in 1984, MACS enrolled gay and bisexual men with or at risk for HIV at sites in 5 US cities; WIHS started a decade later and has now enrolled women with or at risk for HIV at sites in 11 US cities. Participants attended semiannual study visits for physical examinations, collection of biological specimens, and self-reported questionnaires on sociodemographic and health information, including histories of asthma and other respiratory conditions, along with related symptoms and medication use. In 2017–2018 (MACS) and 2018–2020 (WIHS), individuals completed a separate PFT visit including prebronchodilator and postbronchodilator spirometry.

For this analysis, we constructed 2 distinct population subsets separately in both MACS and WIHS. In subset 1, we compared the manifestations of asthma defined by using self-report between PWH and people without HIV. In this subset, we included individuals who answered the question "Have you ever been diagnosed with asthma?" Subset 1 included men who attended at least 1 visit between 2008 and 2010 and between 2017 and 2018 when PFT was performed in the cohort and women who attended a study visit from March-September 2018. In MACS, data for self-reported asthma were selected from the completed PFT visit. However, if a participant did not complete a PFT visit, then data were selected from the latest attended visit at which *cohort-level* PFT was performed. In MACS, the temporal gap between classification of self-reported asthma ("Have you ever been diagnosed with asthma?" was last asked in 2008–2010) and more recent characteristics (2017–2018) was necessary because data from PFT, and other asthma-related domains were only available in the latter period. In WIHS, data for self-reported asthma were from the March-September 2018 study visit. In subset 2, we compared the manifestations of asthma as defined by using the robust criteria between PWH and people without HIV. For this subset, we included individuals within each cohort who had completed prebronchodilator and postbronchodilator spirometry measurements and the St. George's Respiratory Questionnaire (SGRQ).[21] When defining asthma using the robust criteria, the sociodemographic, clinical, laboratory, and other asthma-related data collected at the PFT visit were used.

Individuals in subset 1 met the self-reported asthma definition if they reported ever being diagnosed with asthma. Individuals in subset 2 met the robust asthma definition if all the following criteria were met: (1) PFT with no fixed obstruction (obstruction defined as postbronchodilator forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio <0.7), (2) reported any wheeze on the SGRQ, and (3) reported inhaled or oral asthma therapies at the PFT visit or any earlier visit. Wheeze was selected as the symptom domain because it is the most common symptom element used in epidemiological definitions[22] and has high diagnostic value to define asthma.[23,24] Asthma therapies included inhaled bronchodilators, inhaled corticosteroids, leukotriene receptor or histamine antagonists, and theophylline.

After classifying individuals within each of subsets 1 and 2 into 4 mutually exclusive groups (HIV+/asthma+, HIV+/asthma−, HIV−/asthma+, and HIV−/asthma−), we then restricted further analyses to individuals who were classified as having asthma, regardless of HIV serostatus.

Measures and Analyses

Participants completed the modified Medical Research Council (mMRC) dyspnea scale and assigned a discrete score ranging from grade 0 ("I only get breathless with strenuous exercise") to grade 4 ("I am too breathless to leave the house,

or I am breathless when dressing").[25] The SGRQ was used to assess symptom burden using a 0–100 scale over 3 subdomains (symptoms, activity, and impact), with higher scores representing worse symptoms.[21] Spirometry before and after the administration of 4 puffs of albuterol (360 μg) was performed using a spirometer (EasyOne Pro or Easy-on-PC, ndd Medical Technologies, Zurich/Switzerland) with quality assessment per American Thoracic Society/European Respiratory Society standards.[26] Reference values were derived from the third National Health and Nutrition Examination Survey.[27] Bronchodilator responsiveness was defined as a ≥200 mL absolute increase and a ≥12% increase in either FEV1 or FVC.[28]

To compare groups (eg, HIV serostatus and asthma definition), we used unadjusted binomial regression with an identity link to estimate prevalence differences (PDs) and 95% confidence intervals (CIs) for categorical variables and linear regression to calculate means and mean differences with 95% CIs for continuous variables. As this analysis was descriptive and not designed for causal inference, adjusted analyses were not performed. Trained personnel at MACS and WIHS sites obtained informed consent from all participants to use their data in research analyses, which were approved by relevant institutional review boards. All analyses were conducted in SAS version 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Composition and Characteristics of Populations When Asthma is Defined by Using Self-Report Compared With the Robust Criteria

In MACS, the analysis of asthma as defined by using self-report (subset 1) included 1572 men: 96 HIV+/asthma+ (6.1%), 648 HIV+/asthma− (41.2%), 93 HIV−/asthma+ (5.9%), and 735 HIV−/asthma− (46.8%). Overall, the mean age of subset 1 was 60.6 years; 72.5% were White and 50.8% currently smoked. When asthma was defined using the robust criteria (subset 2), the analysis included 1117 men: 32 HIV+/asthma+ (2.9%), 588 HIV+/asthma− (52.6%), 20 HIV−/asthma+ (1.8%), and 477 HIV−/asthma− (42.7%). Subset 2 was younger (mean age: 55.8 years; mean difference: −4.8; 95% CI: −5.6 to −4.0); smaller proportions were White (61.3%; PD: −11.2%; 95% CI: −14.8% to −7.6%) and reported current smoking (44.6%; PD: −6.2%; 95% CI: −10.0% to −2.4%).

In WIHS, the analysis of asthma as defined by using self-report (subset 1) included 2075 women: 354 HIV+/asthma+ (17.1%), 1103 HIV+/asthma− (53.2%), 170 HIV−/asthma+ (8.2%), and 488 HIV−/asthma− (23.5%). In this subset, the mean age was 51.4 years, 75.4% were Black, and 37.8% currently smoked. When asthma was defined by using the robust criteria (subset 2), the analysis included 1523 women: 139 HIV+/asthma+ (9.1%), 944 HIV+/asthma− (62.0%), 58 HIV−/asthma+ (3.8%), and 382 HIV−/asthma− (25.1%). The mean age of 50.9 years was similar to that of the self-reported asthma subset (mean

difference: −0.5; 95% CI: −1.1 to 0.2), as were the proportions of women who were Black (78.1%; PD: 2.7%; 95% CI: −0.1% to 5.5%) and who currently smoked (36.7%; PD: −1.1%; 95% CI: −4.3% to 2.1%).

Impact of Asthma Definitions on Prevalence Estimates

Figure 1 shows asthma prevalence estimates by definition, sex, and HIV serostatus. In men, the overall prevalence of asthma when defined using self-report was 12.0%. The prevalence did not differ comparing men with HIV (12.9%) with men without HIV (11.2%) (PD: 1.7%; 95% CI: −1.6% to 4.9%). When asthma was defined using the robust criteria, the prevalence of asthma among men was lower (4.7%) than self-report and similarly did not differ between men with and without HIV (5.2% and 4.0%, respectively; PD: 1.1%; 95% CI: −1.3 to 3.6%). In women, similar to men, the prevalence of asthma was higher when defined by using self-report compared with the robust criteria. Specifically, the overall prevalence of asthma when defined using self-report was 25.3% among women, 24.3% among women with HIV compared to 27.5% among women without HIV (PD: −3.2%; 95% CI: −7.4%, 0.9%). With the robust criteria, the overall prevalence was lower (12.9%) and did not differ between women with HIV (12.8%) and women without HIV (13.2%) (PD: −0.4%; 95% CI: −4.1% to 3.4%).

Asthma Manifestations Among Men With HIV vs. Men Without HIV

Asthma Defined by Using Self-Report in MACS

Among 189 men with self-reported asthma (Table 1), 96 (50.8%) had HIV. Men with HIV and self-reported asthma were younger and more likely to be Black than those without HIV; smoking status and intensity were similar in the 2 groups. Men with HIV more commonly used bronchodilators and had more substantial respiratory symptoms than those without HIV; however, pulmonary function measurements, bronchodilator responsiveness, and eosinophil count did not differ between groups. Specifically, the total SGRQ score and
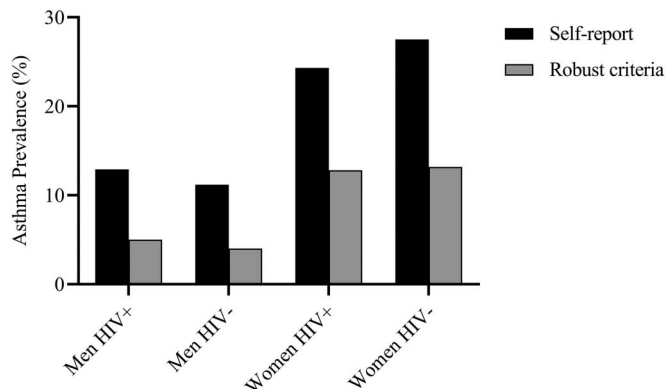

FIGURE 1. Asthma prevalence by HIV serostatus, sex, and definition (self-report or robust criteria) among participants of the MACS and WIHS cohorts.

TABLE 1. Characteristics of MACS Men With Asthma by Definition (Self-Report or Robust Criteria) and HIV Status

	Self-Report			Robust		
	HIV+ (n = 96)	HIV− (n = 93)	Difference (95% CI)*	HIV+ (n = 32)	HIV− (n = 20)	Difference (95% CI)*
Age in years, mean (SD)	57.1 (8.7)	60.0 (10.3)	−2.9 (−5.6 to −0.1)	54.1 (9.8)	58.1 (12.7)	−4.0 (−10.3 to 2.3)
Race, n (%)						
White	60 (62.5)	72 (77.4)	−14.9 (−27.8 to −2.0)	21 (65.6)	11 (55.0)	10.6 (−16.7 to 37.9)
Black	30 (31.3)	17 (18.3)	13.0 (0.8 to 25.1)	8 (25.0)	9 (45.0)	−20.0 (−46.5 to 6.5)
Others	6 (6.3)	4 (4.3)	2.0 (−4.4 to 8.3)	3 (9.4)	0 (0.0)	9.4 (−0.7 to 19.5)
Body mass index, mean (SD)	26.4 (5.0)	27.9 (6.4)	−1.4 (−3.1 to 0.2)	28.1 (5.0)	30.1 (4.5)	−2.0 (−4.7 to 0.8)
Body mass index, n (%)						
<30	76 (79.2)	67 (72.0)	7.1 (−5.1 to 19.3)	23 (71.9)	12 (60.0)	11.9 (−14.7 to 38.4)
30–<35	14 (14.6)	14 (15.1)	−0.5 (−10.6 to 9.7)	7 (21.9)	6 (30.0)	−8.1 (−32.8 to 16.5)
35–<40	4 (4.2)	7 (7.5)	−3.4 (−10.1 to 3.3)	0 (0.0)	1 (5.0)	−5.0 (−14.6 to 4.6)
≥40	2 (2.1)	5 (5.4)	−3.3 (−8.7 to 2.1)	2 (6.3)	1 (5.0)	1.3 (−11.5 to 14.0)
Self-report of COPD, n (%)	2 (2.1)	3 (3.2)	−1.1 (−5.7 to 3.5)	0 (0.0)	0 (0.0)	0.0
Smoking history, n (%)						
Current	54 (56.3)	55 (59.1)	−2.9 (−17.0 to 11.2)	16 (50.0)	10 (50.0)	0.0 (−27.9 to 27.9)
Former	16 (16.7)	12 (12.9)	3.8 (−6.3 to 13.9)	6 (18.8)	4 (20.0)	−1.3 (−23.4 to 20.9)
Never	26 (27.1)	26 (28.0)	−0.9 (−13.6 to 11.9)	10 (31.3)	6 (30.0)	1.3 (−24.5 to 27.0)
Pack-years smoked if ever, mean (SD)	18.8 (20.2)	16.8 (19.5)	1.9 (−4.9 to 8.7)	16.6 (16.4)	22.0 (22.4)	−5.4 (−18.9 to 8.2)
Annual income <$20,000, n (%)	35 (36.5)	21 (22.6)	13.9 (1.0 to 26.7)	20 (62.5)	7 (35.0)	27.5 (0.7 to 54.3)
Less than high school education, n (%)	5 (5.2)	3 (3.2)	2.0 (−3.7 to 7.7)	4 (12.5)	0 (0.0)	12.5 (1.0 to 24.0)
HIV-related markers						
Viral load not detected, n (%)	82 (85.4)	N/A	N/A	28 (87.5)	N/A	N/A
CD4 count, mean (SD)	686 (320)	N/A	N/A	706 (273)	N/A	N/A
Nadir CD4 count, mean (SD)	279 (199)	N/A	N/A	321 (217)	N/A	N/A
On ART, n (%)	91 (94.8)	N/A	N/A	30 (93.8)	N/A	N/A
Years since ART initiation, mean (SD)†	15.8 (5.2)	N/A	N/A	14.3 (6.2)	N/A	N/A
Years since the first visit with HIV, mean (SD)	20.8 (8.1)	NA	NA	18.3 (10.0)	NA	NA
History of pneumocystis pneumonia, n (%)	4 (4.2)	N/A	N/A	2 (6.3)	N/A	N/A
Inhaled/oral asthma therapies in the past 6 mo, n (%)	22 (22.9)	7 (7.5)	15.4 (5.4 to 25.4)	12 (37.5)	4 (20.0)	17.5 (−6.8 to 41.8)
St. George's Respiratory Questionnaire‡						
Total score, mean (SD)	21.8 (16.9)	11.2 (14.1)	10.6 (4.8 to 16.5)	29.8 (16.3)	22.1 (16.5)	7.8 (−1.6 to 17.1)
Symptoms score, mean (SD)	35.5 (25.0)	18.6 (16.5)	16.9 (8.9 to 24.8)	49.7 (16.6)	40.4 (19.7)	9.3 (−0.9 to 19.5)
Activity score, mean (SD)	28.3 (25.1)	15.7 (22.2)	12.6 (3.8 to 21.4)	36.9 (26.2)	26.3 (23.8)	10.6 (−3.9 to 25.1)
Impact score, mean (SD)	14.1 (14.2)	6.5 (10.9)	7.6 (2.9 to 12.4)	19.9 (16.1)	14.2 (14.1)	5.7 (−3.1 to 14.6)
Cough most/several days/week, n (%)	26 (43.3)	13 (24.1)	19.3 (2.3 to 36.2)	14 (43.8)	7 (35.0)	8.8 (−18.3 to 35.8)
Phlegm most/several days/week, n (%)	18 (30.0)	4 (7.4)	22.6 (9.1 to 36.1)	8 (25.0)	5 (25.0)	0.0 (−24.2 to 24.2)
Shortness of breath most/several days/week, n (%)	19 (31.7)	7 (13.0)	18.7 (3.9 to 33.5)	12 (37.5)	6 (30.0)	7.5 (−18.7 to 33.7)
Wheeze most/several days/week, n (%)	12 (20.0)	1 (1.9)	18.2 (7.4 to 28.9)	7 (21.9)	3 (15.0)	6.9 (−14.3 to 28.1)
mMRC dyspnea scale score‡						
Total, mean (SD)	1.02 (1.20)	0.59 (1.07)	0.42 (−0.00 to 0.85)	1.47 (1.34)	0.79 (1.13)	0.68 (−0.06 to 1.42)
mMRC ≥2, n (%)	15 (25.0)	10 (18.5)	6.5 (−8.6 to 21.6)	15 (46.9)	6 (31.6)	15.3 (−11.8 to 42.4)
FEV1 % predicted, prebronchodilator, mean (SD)‡	0.93 (0.22)	0.89 (0.15)	0.03 (−0.05 to 0.11)	0.90 (0.22)	0.91 (0.20)	−0.01 (−0.13 to 0.12)
FEV1/FVC ratio, prebronchodilator, mean (SD)‡	0.74 (0.08)	0.75 (0.07)	−0.01 (−0.04 to 0.02)	0.76 (0.05)	0.75 (0.08)	0.01 (−0.03 to 0.05)
FEV1 % predicted, postbronchodilator, mean (SD)‡	0.97 (0.18)	0.93 (0.16)	0.03 (−0.04 to 0.10)	0.92 (0.14)	0.95 (0.17)	−0.02 (−0.11 to 0.07)

TABLE 1. (*Continued*) Characteristics of MACS Men With Asthma by Definition (Self-Report or Robust Criteria) and HIV Status

	Self-Report			Robust		
	HIV+ (n = 96)	HIV− (n = 93)	Difference (95% CI)*	HIV+ (n = 32)	HIV− (n = 20)	Difference (95% CI)*
FEV1/FVC ratio, postbronchodilator, mean (SD)‡	0.77 (0.09)	0.77 (0.07)	−0.00 (−0.03 to 0.03)	0.79 (0.05)	0.77 (0.06)	0.02 (−0.00 to 0.05)
Bronchodilator responsiveness, n (%)‡	4 (8.7)	1 (2.2)	6.5 (−2.7 to 15.7)	2 (6.9)	2 (10.0)	−3.1 (−19.2 to 13.0)
Eosinophil count, mean (SD)‡	171 (112)	197 (159)	−27 (−67 to 14)	184 (128)	186 (168)	−2 (−86 to 82)

*Prevalence difference for categorical variables (denoted by "n" in column 1) or mean difference for continuous variables (denoted by "mean" in column 1).

†Among individuals on ART.

‡Percent of cohort with data for listed domain for HIV+ self-report, HIV− self-report, HIV+ robust, and HIV− robust, respectively: St. George's Respiratory Questionnaire and mMRC—63%, 58%, 100%, and 100%; both prebronchodilator and postbronchodilator FEV1 % predicted and FEV1/FVC ratio—48%, 48%, 91%, and 100%; and eosinophil count—93%, 95%, 97%, and 100%. Bronchodilator responsiveness defined as a ≥200 mL absolute increase and a ≥12% increase in either FEV1 or FVC.

all 3 subdomains (symptoms, activity, and impact) were worse among men with HIV, as were cough, phlegm, shortness of breath, and wheezing.

Asthma Defined by Using the Robust Criteria in MACS

Among 52 men with asthma defined using the robust criteria, 32 (61.5%) had HIV (Table 1). Men with HIV were similar to men without HIV in age, race/ethnicity, smoking status, and smoking intensity. Compared with men without HIV, men with HIV had increased but not statistically different respiratory symptoms across all SGRQ domains, and similar proportions reported cough, phlegm, shortness of breath, and wheezing. Pulmonary function measurements and eosinophil count did not differ by HIV serostatus.

Asthma Manifestations Among Women With HIV vs. Women Without HIV

Asthma Defined by Using Self-Report in WIHS

Among 524 women with asthma defined using self-report, 354 (67.6%) had HIV, with no differences by HIV serostatus in demographic characteristics, smoking histories, or bronchodilator use (Table 2). Women with HIV and women without HIV had similar scores across all domains of the SGRQ except for the symptom domain, where women with HIV had a lower (better) score. Women with HIV were less likely to report phlegm and had lower eosinophil counts than women without HIV. Pulmonary function measurements including bronchodilator responsiveness did not differ by HIV serostatus.

Asthma Defined by Using the Robust Criteria in WIHS

Among 197 women with asthma defined using the robust criteria, 139 (70.6%) had HIV; demographic characteristics and smoking histories were similar in these groups (Table 2). Women with HIV and women without HIV had similar respiratory symptoms across all SGRQ domains, and similar proportions reported phlegm, shortness of breath, and wheezing. Cough was more often reported among women with HIV than women without HIV. The prebronchodilator FEV1/FVC ratio was higher in women with HIV than in women without HIV, although this difference was likely not clinically significant [mean difference 0.02 (95% CI: 0.00 to 0.04)].

Impact of Asthma Definition on Asthma Manifestations by HIV Serostatus

There were differences in the associations between HIV serostatus and asthma domains by asthma definition. In men, the association between HIV and worse respiratory symptoms observed when defining asthma using self-report was attenuated when asthma was defined using the robust criteria. In women, the association between HIV serostatus and lower SGRQ symptom score (better symptom burden) when defining asthma by using self-report was attenuated when using the robust criteria. Cough, which did not differ by HIV serostatus when defining asthma using self-report, was more prevalent among women with HIV when using the robust criteria. In both men and women, pulmonary function measurements did not differ by HIV serostatus regardless of asthma definition.

DISCUSSION

This analysis, which included nearly 4000 participants from 2 multisite, longitudinal, cohort studies, provides several key findings regarding asthma prevalence and manifestations among men and women with and without HIV. First, estimates of asthma prevalence differed based on the epidemiological definition used to define disease, with a 2-fold to 3-fold higher prevalence using a self-report definition compared with a more robust definition incorporating spirometry, self-reported symptoms, and medication history. Second, irrespective of definition used, asthma prevalence did not differ between PWH and people without HIV of the same sex. Third, among men with asthma, HIV was associated with greater symptom burden despite similar lung function metrics, with these differences attenuated when asthma was defined using the robust criteria. Finally, among women with asthma, there was no difference in symptom burden between women with and women without HIV. Through analysis of a cohort with extensive asthma-related data collection and epidemiologically appropriate comparator groups, these findings greatly expand our understanding of asthma among PWH.

TABLE 2. Characteristics of WIHS Women With Asthma, by Definition (Self-Report or Robust Criteria) and HIV Status

	Self-Report			Robust		
	HIV+ (n = 354)	HIV− (n = 170)	Difference (95% CI)*	HIV+ (n = 139)	HIV− (n = 58)	Difference (95% CI)*
Age in years, mean (SD)	52.7 (7.9)	51.6 (9.0)	1.1 (−0.4 to 2.6)	52.3 (7.9)	51.3 (8.6)	1.0 (−1.5 to 3.5)
Race, n (%)						
White	51 (14.4)	17 (10.0)	4.4 (−1.4 to 10.2)	22 (15.8)	5 (8.6)	7.2 (−2.2 to 16.6)
Black	256 (72.3)	135 (79.4)	−7.1 (−14.8 to 0.6)	104 (74.8)	42 (72.4)	2.4 (−11.2 to 16.0)
Others	47 (13.3)	18 (10.6)	2.7 (−3.1 to 8.5)	13 (9.4)	11 (19.0)	−9.6 (−20.8 to 1.6)
Body mass index, mean (SD)	33.6 (10.2)	32.7 (9.2)	0.8 (−1.0 to 2.6)	35.0 (10.8)	36.3 (10.3)	−1.3 (−4.6 to 2.0)
Body mass index, n (%)						
<30	159 (44.9)	73 (42.9)	2.0 (−7.1 to 11.0)	53 (38.1)	16 (27.6)	10.5 (−3.5 to 24.6)
30–<35	57 (16.1)	29 (17.1)	−1.0 (−7.8 to 5.9)	28 (20.1)	13 (22.4)	−2.3 (−14.9 to 10.4)
35–<40	50 (14.1)	29 (17.1)	−2.9 (−9.7 to 3.8)	19 (13.7)	9 (15.5)	−1.9 (−12.8 to 9.1)
≥40	88 (24.9)	39 (22.9)	1.9 (−5.8 to 9.7)	39 (28.1)	20 (34.5)	−6.4 (−20.8 to 7.9)
Self-report of COPD, n (%)	57 (16.1)	37 (21.8)	−5.6 (−13.0 to 1.6)	22 (15.8)	10 (17.2)	−1.4 (−12.9 to 10.1)
Smoking history, n (%)						
Current	155 (43.8)	89 (52.4)	−8.6 (−17.7 to 0.6)	66 (47.5)	33 (56.9)	−9.4 (−24.6 to 5.8)
Former	129 (36.4)	49 (28.8)	7.6 (−0.8 to 16.1)	47 (33.8)	19 (32.8)	1.1 (−13.4 to 15.5)
Never	70 (19.8)	32 (18.8)	1.0 (−6.2 to 8.1)	26 (18.7)	6 (10.3)	8.4 (−1.8 to 18.5)
Pack-years smoked if ever, mean (SD)	15.1 (23.8)	15.9 (14.4)	−0.8 (−4.5 to 2.9)	11.8 (10.9)	14.5 (12.8)	−2.8 (−6.7 to 1.2)
Annual income <$18,000, n (%)	273 (77.1)	122 (71.8)	5.4 (−2.7 to 13.4)	96 (69.1)	43 (74.1)	−5.1 (−18.7 to 8.6)
Less than high school education, n (%)	142 (40.1)	67 (39.4)	0.7 (−8.2 to 9.7)	50 (36.0)	23 (39.7)	−3.7 (−18.6 to 11.2)
HIV-related markers						
Viral load not detected, n (%)	226 (63.8)	N/A	N/A	92 (66.2)	N/A	N/A
CD4 count, mean (SD)	733 (378)	N/A	N/A	777 (404)	N/A	N/A
Nadir CD4 count, mean (SD)	246 (197)	N/A	N/A	252 (200)	N/A	N/A
On ART, n (%)	326 (92.1)	N/A	N/A	129 (92.8)	N/A	N/A
Years since ART initiation, mean (SD)†	13.1 (6.4)	N/A	N/A	13.1 (6.1)	N/A	N/A
Years since the first positive HIV test, mean (SD)	18.9 (8.1)	N/A	N/A	18.3 (8.2)	N/A	N/A
History of pneumocystis pneumonia, n (%)	52 (14.7)	N/A	N/A	21 (15.1)	N/A	N/A
Inhaled/oral asthma therapies in the past 6 mo, n (%)	247 (69.8)	117 (68.8)	1.0 (−7.5 to 9.4)	84 (60.4)	37 (63.8)	−3.4 (−18.2 to 11.4)
St. George's Respiratory Questionnaire‡						
Total score, mean (SD)	27.4 (18.2)	28.6 (20.2)	−1.2 (−5.2 to 2.8)	35.7 (17.2)	34.2 (16.5)	1.5 (−3.8 to 6.8)
Symptoms score, mean (SD)	26.7 (20.2)	32.1 (23.6)	−5.3 (−10.2 to −0.5)	46.1 (18.6)	43.6 (17.8)	2.5 (−3.1 to 8.2)
Activity score, mean (SD)	46.7 (27.3)	44.3 (29.4)	2.5 (−3.5 to 8.4)	54.9 (25.9)	51.8 (25.8)	3.1 (−4.9 to 11.1)
Impact score, mean (SD)	16.5 (16.7)	18.6 (18.2)	−2.1 (−5.8 to 1.5)	21.4 (17.2)	21.2 (15.7)	0.3 (−4.9 to 5.4)
Cough most/several days/week, n (%)	88 (32.5)	42 (33.9)	−1.4 (−11.4 to 8.6)	72 (51.8)	20 (34.5)	17.3 (2.5 to 32.1)
Phlegm most/several days/week, n (%)	48 (17.7)	34 (27.4)	−9.7 (−18.8 to −0.1)	44 (31.7)	15 (25.9)	5.8 (−7.9 to 19.5)
Shortness of breath most/several days/week, n (%)	73 (26.9)	42 (33.9)	−6.9 (−16.8 to 2.9)	55 (39.6)	27 (46.6)	−7.0 (−22.2 to 8.2)
Wheeze most/several days/week, n (%)	30 (11.1)	21 (16.9)	−5.9 (−13.5 to 1.7)	51 (36.7)	17 (29.3)	7.4 (−6.8 to 21.6)
mMRC dyspnea scale score‡						
Total, mean (SD)	1.90 (1.31)	1.81 (1.33)	0.09 (−0.19 to 0.37)	2.09 (1.26)	2.09 (1.20)	0.01 (−0.38 to 0.39)
mMRC ≥2, n (%)	156 (57.8)	66 (53.2)	4.6 (−6.0 to 15.1)	89 (64.0)	36 (62.1)	2.0 (−12.9 to 16.8)
FEV1 % predicted, prebronchodilator, mean (SD)‡	0.81 (0.19)	0.83 (0.21)	−0.02 (−0.06 to 0.03)	0.83 (0.16)	0.81 (0.19)	0.02 (−0.03 to 0.07)
FEV1/FVC ratio, prebronchodilator, mean (SD)‡	0.76 (0.09)	0.75 (0.10)	0.01 (−0.01 to 0.03)	0.79 (0.06)	0.77 (0.06)	0.02 (0.00 to 0.04)

TABLE 2. (*Continued*) Characteristics of WIHS Women With Asthma, by Definition (Self-Report or Robust Criteria) and HIV Status

	Self-Report			Robust		
	HIV+ (n = 354)	HIV− (n = 170)	Difference (95% CI)*	HIV+ (n = 139)	HIV− (n = 58)	Difference (95% CI)*
FEV1 % predicted, postbronchodilator, mean (SD)‡	0.85 (0.18)	0.87 (0.19)	−0.02 (−0.06 to 0.03)	0.86 (0.16)	0.86 (0.18)	−0.00 (−0.05 to 0.05)
FEV1/FVC ratio, postbronchodilator, mean (SD)‡	0.79 (0.07)	0.78 (0.10)	0.01 (−0.01 to 0.03)	0.81 (0.05)	0.80 (0.04)	0.01 (−0.01 to 0.02)
Bronchodilator responsiveness, n (%)‡	44 (19.4)	24 (24.5)	−5.1 (−15.1 to 4.8)	20 (14.9)	14 (25.5)	−10.5 (−23.5 to 2.5)
Eosinophil count, mean (SD)‡	145 (120)	176 (144)	−31 (−55 to −7)	155 (130)	182 (124)	−26 (−66 to 14)

*Prevalence difference for categorical variables (denoted by "n" in column 1) or mean difference for continuous variables (denoted by "mean" in column 1).

†Among individuals on ART.

‡Percent of cohort with data for listed domain for HIV+ self-report, HIV− self-report, HIV+ robust, and HIV− robust, respectively: St. George's Respiratory Questionnaire and mMRC—77%, 73%, 100%, and 100%; both prebronchodilator and postbronchodilator FEV1 % predicted and FEV1/FVC ratio—64%, 58%, 96%, and 95%; and eosinophil count—98%, 95%, 100%, and 95%. Bronchodilator responsiveness defined as a ≥200 mL absolute increase and a ≥12% increase in either FEV1 or FVC.

Defining asthma in epidemiological studies is not straightforward. Because the penetrance of symptom and airflow abnormalities are variable in asthma, multiple definitions of asthma have been used in clinical studies, ranging from self-report of asthma diagnosis to self-report combined with the presence of symptoms and treatment.[29–31] Sa-Sousa et al[22] examined 117 articles incorporating questions to define asthma in epidemiological studies. Lifetime asthma, diagnosed asthma, and current asthma were defined in 8, 12, and 29 different ways, respectively. Applying these varied definitions to the 2005–2006 National Health and Nutrition Examination Survey, the prevalence of asthma ranged from 1% to 17%. In this analysis, we defined asthma using 2 different approaches to determine the impact of definitions on prevalence estimates in a cohort of PWH and people without HIV. Defining asthma using self-report yielded a 2-fold to 3-fold higher asthma prevalence estimate than when asthma was defined using the robust criteria. These findings suggest that studies of HIV and HIV at-risk cohorts using self-report to define asthma without incorporating symptoms, physiologic, and treatment factors into the definition may overestimate the actual asthma prevalence. This observation may be explained by the lack of specificity and the low predictive value of self-report. Conversely, it is possible that our robust definition may have been too restrictive because reports of wheezing and prior medication use are susceptible to recall bias. In addition, access to asthma therapies may be a marker of socioeconomic status, which may be lower in MACS and WIHS compared with other HIV populations. Therefore, the true asthma prevalence among MACS and WIHS participants may lie somewhere between those estimated by using the self-report and robust definitions. These findings reinforce the point that providers should obtain additional data to confirm asthma using a rigorous clinical definition rather than relying solely on self-report. By presenting estimates derived from 2 different definitions, this analysis provides reference prevalence estimates for comparison with future cohort studies of asthma among PWH.

Regardless of definition, asthma prevalence did not differ by HIV status in our study. In the general US population, the prevalence of asthma when defined by using self-report was 6.1% for adult men and 9.8% for adult women in 2019.[32] Asthma prevalence when defined by using self-report in MACS and WIHS was 2-fold to 3-fold higher. Previous studies of asthma prevalence comparing PWH with individuals without HIV have inconsistent findings and are often confounded by poorly matched HIV-seronegative comparators. Prevalence studies early in the HIV epidemic demonstrated higher self-reported asthma among men with HIV compared with population-based comparators, with reports ranging from 16% to 17% among PWH and 9%–12% among individuals without HIV.[14,33,34] There are limited data on the prevalence of asthma among PWH in the ART era, despite the finding that asthma defined by using *ICD-9* data was the second most common noninfectious pulmonary disease among male PWH in the Veterans Aging Cohort Study.[6] A cross-sectional prevalence study of self-reported pulmonary diagnoses from MACS and WIHS cohorts using data from 2008 to 2010 found that self-reported asthma was the most prevalent pulmonary diagnosis, reported in 23% of WIHS women and 14% of MACS men, with similar prevalences in participants without HIV.[35] The wide range of prevalence estimates across previous studies highlights the impacts of the asthma definition and the timing (ie, pre-ART vs. post-ART) of the cohort.

Using 2 different definitions, we observed no difference in asthma prevalence comparing PWH with individuals without HIV. There are several reasons why our findings may differ from prior research. Standardized data collection across the cohorts, combined with epidemiologically appropriate comparators, reduces the risk of selection bias confounding comparisons between risk groups. In addition, most MACS and WIHS PWH demonstrate HIV disease control, as indicated by an undetectable viral load and preserved CD4 levels. It is possible that asthma risk among PWH who have well-controlled HIV is similar to that of individuals without HIV. Ultimately, these data suggest that asthma prevalence does not differ between PWH and individuals without HIV in a cohort of PWH and epidemiologically comparable individuals without HIV.

We did observe a higher prevalence of asthma among women with HIV compared with men with HIV, regardless of asthma definition. However, the MACS and WIHS cohorts are quite dissimilar in demographics and other predictors, so interpretation of these findings must be made with caution. For example, MACS participants are majority White, while WIHS participants are majority Black. In addition, smoking intensity, body mass index, and socioeconomic status differed between MACS and WIHS. Key differences such as these between the cohorts limit the ability to assess the relationship between sex and asthma prevalence among PWH.

In our analysis, HIV was associated with greater symptom burden in men with asthma despite similar lung function and atopic measures. Among women with asthma, there was no difference in respiratory symptoms comparing women with HIV with those without HIV. Awareness of increasing chronic lung disease symptom burden among PWH has focused largely on COPD.[36–39] There are few data regarding the relationship between HIV and respiratory symptoms in asthma, making our findings novel. Poirier et al[14] reported that men with HIV had a greater prevalence of wheeze (54% vs. 21%) when compared with men without HIV. Our study expands this observation by exploring symptom burden through validated questionnaires encompassing multiple domains. HIV was associated with worse domains of respiratory symptoms in men, with associations attenuated when asthma was defined by using the robust criteria. The increased symptom burden was present despite no differences in lung function or smoking history. A recent report described elevated fraction of exhaled nitric oxide levels among PWH compared with controls without HIV, suggesting that HIV may be associated with increased eosinophilic airway inflammation.[40] Although we did not observe differences in peripheral markers of atopy (eg, eosinophilia) among men with HIV compared with men without HIV, it is possible that studies of airway inflammation in MACS and WIHS may provide further insight into mechanisms of increased symptom burden in men with HIV and asthma. Another potential etiology for increased symptom burden may be related to comorbidities that differ between groups.

To the best of our knowledge, there are no previous large studies of the associations between HIV and asthma manifestations in women. Regardless of the definition used, we did not observe an association between HIV and respiratory symptom burden among women with asthma. This finding differs from the noted association between HIV and asthma symptoms in men. One could interpret this observation as an HIV-specific asthma phenotype that differs by sex, although as previously highlighted the MACS and WIHS cohorts have substantial, systematic differences which indicate that such a general interpretation should only be made very cautiously. An alternative explanation may relate to the impact of asthma treatment on symptom burden. Notably, bronchodilator use was high in WIHS and similar by HIV status, which could attenuate the association between HIV and respiratory symptoms. Ultimately, although this study cannot establish causal relationships, our findings

highlight the need for focused investigation on the association between HIV and asthma symptoms in women.

This study has limitations. The clinical definition of asthma recommended by respiratory societies[41,42] includes domains not available in MWCCS. Therefore, our robust asthma definition may lack specificity compared with a more rigorous clinical definition. If a provider suspects asthma in a patient with HIV, additional detailed pulmonary evaluation should be obtained to determine whether asthma is present according to a clinically focused definition. We were not able to assess detailed asthma phenotypes. The definitions of asthma relied on participant-reported factors (eg, prior asthma diagnosis, wheeze, and asthma medication use), which are susceptible to recall bias. The temporal gap in MACS between self-reported asthma and sociodemographic, clinical, laboratory, and asthma-related variables may have introduced bias into prevalence estimates, unlike in the WIHS cohort. Despite the use of a standard respiratory symptom assessment tool (SGRQ), future studies should include asthma-specific tools to assess asthma control and symptoms. The robust definition excluded individuals with fixed obstruction. Although this approach excluded participants with COPD, such an approach would also exclude persons with asthma who developed chronic, fixed airflow limitation. Atopy assessments were limited to eosinophil count and did not include more robust measures (eg, allergen sensitization panel, total immunoglobulin E, and exhaled nitric oxide measurements). MACS and WIHS are unique cohorts with differences in sociodemographic and clinical predictors for asthma and HIV, limiting the ability to directly assess sex-related differences. MACS and WIHS are US cohorts, and therefore, the findings should not be extrapolated to PWH living in other parts of the world. Despite these limitations, this analysis leverages large, multisite cohorts with epidemiologically appropriate comparators, along with 2 distinct definitions of asthma, to address key gaps in our understanding of the relationship between HIV and asthma among men and women.

In conclusion, among individuals with or at risk for HIV enrolled in 2 multicenter US cohorts, defining asthma by using self-report increased estimates of asthma prevalence 2-fold to 3-fold compared with defining asthma by using the robust criteria including spirometry, symptoms, and medication history. Regardless of asthma definition, however, HIV was not associated with increased asthma prevalence in these analyses. In men with asthma, HIV was associated with increased respiratory symptoms despite similar physiologic measures. In women with asthma, HIV was not associated with differential symptom burden. Further investigation is warranted on the potentially unique asthma phenotypes in men and women with HIV suggested by this study.

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