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Respiratory Symptoms and Pulmonary Function Among Participants in the MACS/WIHS Combined Cohort Study Using Protease Inhibitors:

A Cross-Sectional Study

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Respiratory Symptoms and Pulmonary Function Among Participants in the MACS/WIHS Combined Cohort Study Using Protease Inhibitors: A Cross-Sectional Study

By

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MD, Vanderbilt University, 2014

Advisors: Sushma Cribbs, M.D., M.Sc. and David Guidot, MD

An abstract of

A thesis submitted to the Faculty of the James T. Laney School of Graduate Studies of Emory University in partial fulfillment of the requirements for the degree of Master of Science in Clinical Research

2021

ABSTRACT

Respiratory Symptoms and Pulmonary Function Among Participants in the MACS/WIHS Combined Cohort Study Using Protease Inhibitors:

A Cross-Sectional Study

By Charles R. Terry, M.D.

Objective: People living with human immunodeficiency virus (PLWH) have higher prevalence of cough, dyspnea, and wheezing than HIV-negative populations. While the mechanisms are unknown, antiretroviral therapy (ART) has been associated with worsened airflow limitation. We sought to estimate the prevalence of respiratory symptoms among PLWH and their association with protease inhibitor (PI) use.

Design: Retrospective cross-sectional study of Multicenter AIDS Cohort Study (MACS) visits from 04/01/2017 to 03/30/2018 and the Women's Interagency Health Study (WIHS) visits from 10/31/2017 to 09/30/2019.

Methods: Participants completed the St. George's Respiratory Questionnaire (SGRQ), modified Medical Research Council (mMRC) dyspnea scale, and pulmonary function testing. Demographic, clinical, laboratory, and pulmonary function data from each visit were compared among PLWH using PIs, PLWH not using PIs, and HIV-negative groups. Logistic regression was used to estimate the association between PI use and the higher scores of SGRQ (defined as SGRQ>10) and mMRC scores after adjusting for potential confounders.

Results: In the MACS and WIHS cohorts respectively, 77/177 (45.3%) and 117/239 (49.0%) PLWH using PIs had SGRQ scores ≥ 10 while 171/501 (34.7%) and 508/956 (52.8%) of PLWH not using PIs and 162/549 (29.9%) and 266/493 (53.6%) of people living without HIV had SGRQ scores ≥ 10 (p=0.001 and p=0.4218). Adjusted models found an association between PI use and SGRQ score ≥ 10 [OR 1.91 (95% CI 1.29-2.82), ref: HIV-negative and OR 1.50 (95% CI 1.01-2.22) ref: PLWH not using PIs] in the MACS cohort but not the WIHS cohort [OR 0.95 (95% CI 0.68-1.34), ref: HIV-negative and OR 0.84 (95% CI 0.62-1.16) ref: PLWH not using PIs]. Similar associations were found with mMRC scores and PI use [OR 1.79 (95% CI 1.21-2.64), ref: HIV-negative and OR 1.53 (95% CI 1.04-2.25), ref: PLWH not using PIs] but not the WIHS cohort [OR 0.94 (95% CI 0.70-1.27), ref: HIV- negative and OR 0.85 (95% CI 0.65-1.12), ref: PLWH not using PIs].

Conclusions: PI use is associated with severe respiratory symptoms and an increased prevalence of pulmonary disease among men; however, this finding could not be replicated in the WIHS cohort, suggesting a sex-specific effect modification or unmeasured confounding.

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Table of Contents

Page

INTRODUCTION

As of 2016, there were 1,008,929 people living with human immunodeficiency virus (HIV) in the United States with increasing prevalence in individuals over 50 years of age (1). While fewer patients are dying from acquired immunodeficiency syndrome (AIDS) and related-illnesses, chronic obstructive lung diseases and treatment-related morbidity are becoming more common and significant causes of debility in people living with HIV (PLWH) (2). Despite antiretroviral therapy (ART), PLWH continue to have more frequent and severe respiratory symptoms than people living without HIV, even after accounting for rates of smoking, drug use, and immunodeficiency (3, 4).

Among ART drug classes, HIV protease inhibitors (PIs) can induce metabolic consequences that lead to obesity, hyperglycemia, and insulin resistance and may increase bronchial reactivity and susceptibility to respiratory infections (5). While current guidelines recommend initiation of ART with integrase strand transfer inhibitors (INSTIs) and nucleoside reverse transcriptase inhibitors (NRTIs), PIs remain an important alternative anchor drug class, with a high barrier to viral resistance and novel application in two-drug therapies (6, 7). However, PIs are known to worsen insulin resistance, hyperglycemia, and lipodystrophy by impairing pancreatic beta-cell function and competitively inhibiting glucose transporter function to varying degrees among specific drugs (8).

While the metabolic consequences of PI use on cardiovascular disease and diabetes risk are well known, their effect on pulmonary function remains unstudied. Impaired glucose metabolism has been associated with increased bronchial hyperreactivity in HIV-positive pediatric populations, but remains unstudied among adult

PLWH (9). Among adults without HIV, the third National Health and Nutrition Examination Survey (NHANES III) found an inverse linear relationship between oral glucose tolerance (OGT) and reduction in forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) with the highest post-OGT plasma glucose levels corresponding to the most severe reductions in lung function (10). These findings suggest that PI use may contribute to metabolic dysregulation, specifically impaired glucose tolerance, which may lead to worsening pulmonary function and may partially explain the higher burden of HIV-related chronic lung disease.

Given the increased risk of insulin resistance and glucose dysregulation from PIs, this study sought to determine whether PLWH using PIs have more impaired glucose metabolism, higher burden of respiratory symptoms, and more severe pulmonary function abnormalities on their initial pulmonary sub-study visit compared with PLWH not using PIs or people without HIV. In this cross-sectional study, we sought to estimate the prevalence of impaired respiratory health and dyspnea among PLWH using data from the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). Secondly, we constructed binary and ordinal logistic univariate and multivariable models to determine the relative association of HIV and PI-status with worsened respiratory symptom burden.

BACKGROUND

The HIV epidemic in the United States has largely shifted from mitigating the complications of AIDS to understanding and controlling the chronic disease and comorbidity burden among PLWH. While the acute pulmonary complications of AIDS have been well-described since the early days of the epidemic the burden of disease has shifted from predominately infectious to non-infectious pulmonary complications. In the early 2000s, Diaz and colleagues found that PLWH were at a higher risk for developing pulmonary symptoms prior to AIDS-related complications (11). Their study only found minor differences in the diffusion capacity of HIV-positive participants versus HIV-negative participants, but only found minor protective effects of ART. Roughly ten years later, beginning with the Veterans Aging Cohort Study, Crothers and colleagues found that veterans living with HIV had higher incidence of chronic obstructive pulmonary disease (COPD), lung cancer, pulmonary hypertension, bacterial pneumonia and tuberculosis (12, 13). In their study ART was found to be protective against COPD, however other cohorts found ART to be a risk factor for irreversible airflow limitation (14, 15). Gingo and colleagues found that 63.5% of PLWH experienced some type of regular pulmonary symptoms (14). Pulmonary function abnormalities were common among participants in their cohort with 64.1% having impaired diffusion capacity and 21% having airflow limitation. While smoking was associated with pulmonary function abnormalities, this was the first study that found a strong association with antiretroviral medication use; however, they did not assess any association with ART and pulmonary symptom burden. Multiple observational studies thereafter found inconsistent associations between ART and airflow limitation albeit in very different populations,

with inconsistent associations between pulmonary function abnormalities and respiratory symptom burden (4). A subsequent meta-analysis found a decrease in respiratory symptoms with ART, but with persistently higher symptom burden among PLWH in well-resourced settings despite access to ART (16). Likewise, a study of the MACS and WIHS found HIV status to be an independent risk factor for different respiratory symptoms in either cohorts, but did not find associations with ART or the incidence of specific respiratory symptoms (3). Instead of using a comprehensive measure of respiratory health or assess dyspnea severity, this study asked participants about the presence or absence of specific symptoms without measuring how they affect their overall quality of life in a more systematic way.

The evidence to date for how ART influences respiratory symptom burden and pulmonary function abnormalities remains inconsistent due to the varied populations used in each observational study and significant confounding from multiple biologic, environmental, and behavioral confounders such as socioeconomic status and tobacco use. Respiratory symptom burden is poorly predictive of pulmonary function abnormalities, suggesting that other variables besides airflow limitation and diffusion capacity are driving the symptom burden in these populations (17).

Chronic inflammation, immune dysregulation, increased oxidative stress, endothelial dysfunction, and dysregulated pulmonary and gastrointestinal microbiomes are thought to be the biologic mediators of non-infectious pulmonary disease observed among PLWH (18). ART has indisputably changed the trajectory of HIV, including partially controlling chronic inflammation related to HIV (19). Nevertheless, adverse effects from long-term ART exposure have become an increasingly important

consideration in HIV care, especially as the population of PLWH ages. Multiple drug classes of ART have been associated with increased cardiovascular events, particularly PIs (20-22). Studies have shown that diabetes risk and insulin resistance increase with each year of exposure to ART (23-25). These early studies focused on the effect of ART on cardiovascular disease; however, they did not consider pulmonary disease or respiratory symptom burden.

Evidence from large epidemiologic studies in HIV-negative adults participating in the third National Health and Nutrition Examination survey (NHANES III) suggests that insulin resistance and hyperglycemia may negatively affect pulmonary function. McKeever and colleagues found an inverse association with plasma glucose two hours following an oral glucose tolerance test and (FEV1) and (FVC) despite adjusting for BMI (10). Disruption of airway glucose homeostasis by systemic hyperglycemia has been associated with bronchial hyper-responsiveness, worsened mortality in community acquired pneumonia, and more frequent infections in COPD (9, 26, 27). These results suggest that metabolic dysregulation may worsen pulmonary function and contribute to poorer overall respiratory health.

PIs have long been associated with similar metabolic dysregulation seen in the HIV-associated lipodystrophy syndrome (8). Given the metabolic dysfunction associated with PI use, we hypothesized a similar mechanism may partially explain the disparate respiratory symptom burden and pulmonary function abnormalities observed among PLWH using ART. Twigg and colleagues found similar drug concentrations of PIs and other classes of ART in bronchoalveolar lavage fluid compared with serum, suggesting that these drugs remain at biologically active concentrations in the alveolar space (28). It

is unknown what influence these drugs may have on local airway glucose homeostasis or systemic metabolic dysregulation, and whether these effects are important for respiratory health or pulmonary function.

The cumulative effect of long-term exposure to ART on pulmonary function or respiratory health remains unclear. A secondary analysis of the "Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection" trial found no difference in longitudinal spirometry decline or respiratory symptom burden in a large sample of ART-naïve individuals with relatively recent HIV infection over a roughly three year follow-up period (29). The investigators did not find any differences in yearly decline of FEV1 among participants started on an INSTI, a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a PI. In addition, no differences in the prevalence of diabetes were reported among trial participants at baseline or during follow-up (30). These results established the importance of ART at the time of diagnosis. However, the conclusions with respect to chronic lung disease and the long-term effects of ART are limited due to the short-term follow-up of the trial and young and generally healthy trial participants. Moreover, their published data did not look at respiratory symptom burden by ART drug class. What remains understudied in the literature is how different ART drug classes in older populations with longer ART exposure influence respiratory symptom burden and pulmonary function. Given the metabolic derangements associated with PI use among PLWH, and the detrimental effect of insulin resistance and hyperglycemia in HIV-negative populations, we hypothesized that similar mechanisms may exist in PLWH and may partially account for the disproportionate pulmonary disease and symptom burden they experience.

METHODS

A. Specific Aims and Hypotheses

- **Specific Aim 1:** Estimate the prevalence of impaired respiratory health (defined as a St. George's Respiratory Questionnaire (SGRQ) score greater than or equal to 10 or modified Medical Research Council (mMRC) score greater than 2) among PLWH using data from the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS).

- **Hypothesis 1:** HIV-positive MACS/WIHS participants will have a higher proportion of participants with SGRQ scores greater than or equal to 10 and higher mMRC scores than HIV-negative MACS/WIHS participants.

- **Specific Aim 2:** Estimate the association between protease inhibitor (PI) use and SGRQ scores greater than or equal to 10 and higher mMRC scores after adjusting for clinically significant covariables among PLWH using data from the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS).

- **Hypothesis 2:** PI-use is associated with SGRQ scores greater than or equal to 10 and higher mMRC scores after adjusting for clinically significant covariables.

B. Study Design

This is a cross-sectional study using data obtained from the MACS, a large longitudinal cohort of men who have sex with men living with and at risk for HIV, and the WIHS, a largely heterosexual cohort of women living with and at risk for HIV (31, 32).

C. Characteristics of the Study Population

The MACS/WIHS combined cohort study is a combined cohort of the MACS and WIHS cohorts. The MACS cohort started early in the HIV epidemic in 1984. It is comprised of men who have sex with men from Los Angeles, Pittsburgh, Chicago, Baltimore. The WIHS cohort was initiated in 1994 and has been enrolling women at risk and diagnosed with HIV in Brooklyn, Bronx/Manhattan, Washington DC, Chicago, San Francisco, and Los Angeles. In 2013, to better represent the evolution of the HIV epidemic in the United States, four new southern sites in Chapel Hill, Atlanta, Birmingham/Jackson, and Miami were added while the Los Angeles site was closed (31, 32).

All MACS and WIHS participants were eligible to participate in the pulmonary sub-study during their regular cohort visit. Participants with pulmonary function testing data, people without HIV seroconversion within one year of pulmonary function testing, and PLWH with ART information were included in the analyses. Participants who were unable to complete study procedures, had uncontrolled hypertension, retinal detachment, recent pneumothorax, myocardial infarction, current pulmonary infection including active tuberculosis, or recent eye, chest, or abdominal surgery were excluded.

D. Measurements

Predictors, Outcomes, and Covariables

The predictor variable for this study was a three-level variable consisting of the following: HIV-negative participants, HIV-positive participants not using PIs since their last visit, and HIV-positive individuals using PIs since their last visit. The primary

outcome of interest was quality of life as measured by the dichotomized SGRQ total score (< 10 vs ≥ 10, as scores less than 10 have been established as normal in healthy subjects) and the mMRC dyspnea scale score (33). Secondary outcomes included predicted percentiles of spirometry values and diffusion capacity measurements. Covariables including demographics, tobacco use, alcohol use, medical history, and medication history were collected during the visit interview. Laboratory testing including $CD4^+$ T-lymphocyte count, HIV viral load, fasting glucose, serum insulin, and hemoglobin a1c was performed at each visit, as well. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was used to approximate insulin sensitivity (34).

Cardiovascular and pulmonary disease history were defined by self-report from participants with any current or previous cardiovascular or respiratory disease diagnosis at the time of visit. Diabetes was defined as a hemoglobin a1c > 6.5%, fasting glucose level > 125 mg/dL or prior diagnosis with current medication use. Hypertension was defined as a systolic blood pressure measurement > 140 mmHg or a diastolic measurement > 90 mmHg or self-reported diagnosis with medication use. Kidney disease in the MACS cohort was defined as an estimated glomerular filtration rate < 60 ml/min or a spot urine protein to creatinine ratio ≥ 200. Kidney disease in the WIHS cohort was defined as an estimated glomerular filtration rate < 60 ml/min only. Current AIDS status in the MACS cohort was defined by a CD4 count ≤ 200 cells per microliter or presence of an AIDS-defining illness, while AIDS status was defined by CD4 count less than or equal to 200 alone in the WIHS cohort.

Data Collection and Measurement

Data from each cohort was obtained from the MACS/WIHS Combined Cohort Study Data Analysis and Collection Center (DACC). MACS cohort data was obtained from regular six-month study visits between April 1st, 2017 and March 30th, 2018. WIHS cohort data was obtained from regular six-month visits between October 31st, 2017 and September 30th, 2019. While most data was obtained at the same visit, pulmonary function testing in the WIHS cohort was delayed and obtained between April 4th, 2018 and January 1st, 2020. During each visit participants completed general medical history interviews, laboratory testing, and pulmonary function testing consisting of respiratory symptom questionnaires, pre- and post-bronchodilator spirometry and diffusion capacity measurements. All pulmonary function tests were conducted and interpreted in accordance with the American Thoracic Society and European Respiratory Society guidelines (35, 36). Spirometry and diffusion capacity data was reported as predicted percentiles according to the National Health and Nutrition Examination Survey (NHANES) III reference values and Neas reference values derived from NHANES I data (37, 38). The quality of each test was reviewed by two pulmonologists and graded accordingly. Respiratory health and dyspnea were measured using the St. George's Respiratory Questionnaire (SGRQ) and modified Medical Research Council (mMRC) dyspnea scale (39, 40).

All MACS participants completed one set of pulmonary function testing and respiratory symptom questionnaires during the data collection period. The majority of WIHS participants had completed one pulmonary function testing session, but 64 participants completed multiple pulmonary function testing sessions in the WIHS cohort. Among these participants, the highest quality spirometry and diffusion capacity

measurements were included in the analysis. The quality of each spirometry and diffusion capacity maneuver was graded A through F for quality and reproducibility according to the American Thoracic Society and European Respiratory Society guidelines (41). Only participants with complete SGRQ and mMRC data were included in analysis for the primary outcomes.

Missing data

Predictor and primary outcome variables had few missing values. Missingness for each covariable was reported in data tables. Among the MACS cohort three records did not have a listed HIV status and four records had no listed PI status. These participants were excluded. Twenty-three participants did not have a listed SGRQ score and twenty-five had no mMRC score. There were twenty MACS participants without spirometry and 138 with missing diffusion capacity measurements.

The WIHS cohort had ten participants with missing SGRQ scores and seventeen participants with missing mMRC scores. There were 29 participants missing spirometry and 1,030 participants missing diffusion capacity measurements. Four participants had diffusion capacity measurements that were over 900% of their predicted value. As these values were highly implausible, these observations were excluded from analysis.

Sample Size and Power Calculations.

As this was an observational cross-sectional study, there were no applicable power calculations for detecting a difference in respiratory health status among PI users and non-PI users. A prior meta-analysis of respiratory symptoms in HIV-seropositive versus HIV-seronegative populations reported an odds ratio of 1.39 for increased

respiratory symptom burden among PLWH, although this was a composite estimate of symptom prevalence and not actually using the SGRQ score. Assuming a similar OR with a baseline prevalence in SGRQ scores greater than or equal to 10 with a proportion of 0.55 in the HIV-seropositive group, we estimated a sample size necessary of 1,318 in each cohort to detect a similar difference in SGRQ scores in each cohort (42). Power calculations for ordinal logistic regression were not feasible as there are no available prior estimates.

Analytic Plan

Participants were classified by HIV status and PI use to create a three-level independent variable of interest: HIV-negative, HIV-positive not using PIs, and HIV-positive using PIs. We defined PI use as any reported PI use since last visit. Analysis using PI use at time of visit was also performed and had similar values and model results. Counts and relative frequencies for categorical characteristics, mean and standard deviation for normally distributed continuous characteristics, and median, Q1, and Q3 for non-normally distributed continuous characteristics were calculated for all groups combined and by HIV/PI use. Association between each characteristic and HIV/PI use was assessed by chi-square for categorical characteristics, two-sample t-test/simple linear regression, and Wilcoxon Rank Sum test for continuous characteristics, as appropriate. Ordinal logistic regression was used to estimate the association between PI use and higher mMRC dyspnea class. Similarly, binary logistic regression was used to estimate the association between PI use and dichotomized SGRQ scores, respectively. Bivariate and multivariate models were constructed to estimate the prevalence odds ratios and confidence intervals for elevated SGRQ and mMRC scores. Each model was assessed

using the HIV-seronegative and HIV-seropositive non-PI using participants as referent groups. Logistic model fit was assessed by Hosmer-Lemeshow Goodness-of-Fit test. Score Test assessed the proportional odds assumption for ordinal logistic regression models. Significance for all analyses was set at $\alpha=0.05$. Analyses were conducted in SAS version 9.4 (Cary, NC).

Model covariates were determined *a priori* based on prior literature and biological importance. Inclusion of covariates for adjusted models was determined based on review of clinical literature, exploratory analysis from univariate models and representativeness of covariates in the cohort. Age, body mass index (BMI), smoking status, self-reported race, self-reported pulmonary and cardiovascular disease were included in both models. Independent variable of interest was a three-level variable of HIV status and current PI use. Covariates included smoking status, self-reported race, self-reported pulmonary and cardiovascular disease. Acquired Immunodeficiency Disease Syndrome (AIDS) diagnosis at visit and aforementioned variables were also examined in models that only included HIV-positive participants using HIV-positive participants not using PIs as the referent. Binary and ordinal logistic model equations are listed in **Figure 3.**

RESULTS

Participant Characteristics

There were 1227 total participants (549 HIV-negative and 678 HIV-positive participants) in the MACS cohort and 1698 participants (496 HIV-negative and 1202 HIV-positive participants) in the WIHS cohort. Among the HIV-positive participants, there were 177 participants using PIs in the MACS cohort and 239 participants using PIs in the WIHS cohort. Age, BMI, race, smoking status, alcohol use, marijuana use, kidney disease, pulmonary disease, diabetes, and hepatitis C status were unequally distributed among all groups in the MACS cohort (**Table 1**). Likewise, age, smoking status, cumulative pack-year exposure, alcohol use, marijuana use, kidney disease, and hepatitis C status were unequally distributed in the WIHS cohort (**Table 6**). Insulin resistance, serum insulin levels, diabetes diagnosis, and diabetes medication use were highest among HIV-positive participants using PIs in the MACS cohort (**Table 1**). There were no differences in diabetes prevalence among the exposure groups in WIHS cohort, although each exposure group was uniformly higher than the prevalence in the corresponding MACS cohort (**Table 10**). Compared to HIV-positive participants not using PIs, MACS participants using PIs had lower mean CD4 counts [637.2 (SD: 280.7) cells/mm^3 vs. 743.1 (SD: 307.3) cells/mm^3] and a higher prevalence of AIDS [28 (15.8%) vs. 25 (5.0%)] (**Table 11**). WIHS participants using PIs also had lower mean CD4 counts [646.0 (SD: 373.2) cells/mm^3 vs. 754.9 (SD: 358.4) cells/mm^3] and a higher prevalence of AIDS [22 (9.2%) vs. 30 (3.1%)] compared with HIV-positive non-PI using participants (**Table 11**).

Respiratory Symptom Burden

Modified Medical Research Council (mMRC) dyspnea scale score frequencies were highest among HIV-positive participants using PIs in the MACS cohort, while mMRC dyspnea scores were uniformly high among the WIHS cohort with no differences among groups (**Table 3; Table 12**). MACS HIV-positive participants using PIs had significantly higher median total SGRQ scores [7.9 (Q1-Q3: 2.4- 21.8)] compared to HIV-positive participants not using PIs [5.5 (Q1-Q3:1.7-15.0) and HIV-negative participants [4.8 (Q1-Q3:1.3-12.1), p= 0.0005] (**Table 3**). In the WIHS cohort all three exposure groups had uniformly high median SGRQ scores with no differences among groups [9.6 (Q1-Q3:2.8-25.3) among HIV-positive participants using PIs; 11.3 (Q1-Q3:2.8-25.3) HIV-positive participants not using PIs; and 11.4 (Q1-Q3:3.7-25.5) among HIV-negative participants, p=0.1893] (**Table 12**). A greater percentage of MACS cohort HIV-positive participants using PIs had SGRQ score ≥ 10 (45.3%) vs. HIV-positive participants not using PIs (34.7%), and HIV-negative participants (29.9%), p=0.001 (**Table 3**). Spirometry and diffusion capacity values were similar across all MACS groups (**Table 3**). In the WIHS cohort diffusion capacity and post-bronchodilator forced vital capacity were lower among the HIV-positive groups, although a substantial proportion of the DLCO data was missing (**Table 12**).

Logistic Modeling

PI use was associated with higher mMRC dyspnea class in unadjusted and adjusted models in the MACS cohort (**Table 4**). Likewise, in the HIV-positive only model, PI use was associated with higher mMRC dyspnea class in adjusted and unadjusted models (**Table 5**). Age, smoking, race, BMI, cardiovascular disease, and

pulmonary disease were significantly associated with higher mMRC dyspnea scores in the model using HIV negative referent group. The adjusted model using the HIV-positive non-PI using cohort had the same covariate association except for age (**Table 6**). WIHS models did not find any significant associations between PI use and higher mMRC dyspnea class in unadjusted or adjusted models (**Tables 13-15**). Age, BMI, AIDS, history of cardiovascular and pulmonary disease, race, and smoking status were all found to be significantly associated with higher mMRC classes (**Table 15**).

PI use was associated with higher SGRQ scores in unadjusted and adjusted models for the MACS cohort (**Tables 7-9**). In the models using HIV-positive participants not using PIs as the referent, PI use and higher SGRQ scores association remained significant (**Table 8; Table 9**). In WIHS models, there were no associations between PI use and higher SGRQ scores in unadjusted or adjusted models (**Tables 16-18**). Age, BMI, smoking status, history of cardiovascular disease and pulmonary disease, and AIDS status were associated with higher SGRQ scores in adjusted models (**Table 18**).

DISCUSSION

This study used two large, prospective cohorts of men and women living with HIV to better understand the long-term effects of ART on respiratory health. In this study, PI users had a higher prevalence of dyspnea and worse respiratory health than HIV-negative and HIV-positive participants not using PIs among MACS participants; however, WIHS participants uniformly had high levels of dyspnea and poor respiratory health without differences among the aforementioned exposure groups. Likewise, PI-use was associated with higher SGRQ scores and mMRC dyspnea scores in both adjusted and unadjusted models using HIV-negative and HIV-positive non-PI users as referents in the MACS cohort, but not the WIHS cohort.

This is the first study to find an association of impaired respiratory health and dyspnea with PIs, despite spirometry and diffusion capacity being similar among all three exposure groups. In an earlier study of respiratory symptoms among PLWH, Diaz and colleagues did not find a difference in respiratory symptom burden among PI users and non-PI users in their single-center cohort (11). However, demographically their cohort and the MACS cohort differ significantly in age and likely duration of ART exposure. Although the authors do not report cumulative years of ART exposure in their paper, their data was collected between 1993 and 1998. Since saquinavir, the first PI, was approved by the FDA in 1997, their cohort likely had very little exposure to PIs. Moreover, the odds ratios for PIs and impaired respiratory health and dyspnea in the MACS logistic models had a statistically significant, albeit relatively weak association. Therefore, given the smaller sample size of their study Diaz and colleagues would be unlikely to find similar associations with ART and respiratory health. Subsequent single-

center studies reported a prevalence of any persistent respiratory symptom between 26% and 47.3% among research participants with access to ART supporting the heterogeneity found between the MACS and WIHS cohorts (14, 15). The populations in these single center cohorts were more similar to the MACS cohort as they were comprised of predominately male participants with decreased diffusion capacity, but without evidence of airflow limitation on spirometry. Smoking, age, HIV viral load, IV drug use and history of bacterial pneumonia were previously associated with higher symptom burden (14, 15, 43). IV drug use and viral load were not included in our models due to a low prevalence of IV drug use and high rates of virologic control among the cohorts. A recent meta-analysis of respiratory symptoms among PLWH found no overall association with cough among resource-rich countries with access to ART and an increased odds of breathlessness among this same group compared with HIV-negative participants (16).

While the MACS cohort showed an association with impaired respiratory health and higher mMRC dyspnea classes and PI use, the WIHS cohort did not have comparable associations. Both crude and adjusted models in each cohort suggested little influence on effect measures from confounders included in models. Nevertheless, unmeasured confounding remains a limitation of this study due to its observational design. The two cohorts are profoundly different in race, smoking prevalence, age, and geographic distribution. The high prevalence of pulmonary disease among the WIHS exposure groups is reflective of existing health disparities that exist among underrepresented minorities (44). Residual confounding from environmental and other community-level risk factors that affect underrepresented minorities, such as socioeconomic status, air quality, and disparities in community health are more consequential to respiratory health

and symptom burden in the WIHS cohort versus the MACS cohort. Given the complex nature of environmental, behavioral, and biological causal factors in HIV-related lung disease, future observational studies particularly in ART among disadvantaged communities, should consider environmental health factors and controlling for community-level respiratory health risk factors to better understand the influence of ART on respiratory health and dyspnea.

While community-level determinants of respiratory health are likely the most important causal factor in explaining the poor respiratory health among WIHS participants, current literature among women and racially diverse research populations suggest differences in treatment efficacy. Forty-eight and 96-week studies of darunavir in a racially diverse study population comprised of mostly women found lower virologic responses among black participants related to treatment disruption and more advanced HIV (45). Women had a higher risk of virologic failure than men, although once adjusted for premature treatment discontinuation there were no differences in virologic control suggesting that there were no biologic differences in drug response. One limitation in our study is the lack of available data on adherence and tolerability among participants. Smith and colleagues found similar adverse events attributable to darunavir among black, Hispanic, and white research subjects; however, black participants had the highest prevalence of cough and hyperglycemia. There were no significant differences in adverse events among black men and women reported in the study (46). In these studies, the investigators did not pre-specify pulmonary symptoms as being adverse events related to darunavir use as prior literature had not described any pulmonary adverse events. Similarly, a retrospective cohort study of HIV-positive women with prior exposure to

ART who were switched to an ART regimen containing ritonavir-boosted atazanavir found higher rates of treatment discontinuation and virologic failure among women and more common adverse effects, although the study did not consider pulmonary symptoms in their analysis (47). The differences in associations between PI use and impaired respiratory health in MACS cohort with the WIHS cohort suggest effect modification by sex as each cohort. As pulmonary adverse effects were not considered related to PI use in prior studies, this hypothesis remains a plausible explanation for respiratory health impairment among HIV-positive exposure groups; however the HIV-negative group had similar impairments in respiratory health. The impaired respiratory health in all three exposure groups suggesting that residual confounding of community-level determinants of health is a more plausible explanation for the severe symptom burden and dyspnea in all three groups.

The MACS cohort had an increase prevalence of diabetes prevalence among HIV-positive PI users, but there was a uniformly higher prevalence of diabetes in the WIHS cohort than the MACS cohort. Hyperglycemia and insulin resistance have been associated with worsened pulmonary function in HIV-negative populations, but the association of ART-induced metabolic dysregulation, pulmonary function, and impaired respiratory health remains uncertain. The higher prevalence of diabetes among exposure groups in either cohort corresponded to the exposure groups with higher SGRQ scores and mMRC dyspnea supporting an influence of diabetes status and insulin resistance in HIV-positive participants on overall respiratory health. Nevertheless, causal inference is limited given the cross-sectional nature of the data. Moreover, diabetes status and insulin resistance did not seem to be influenced by PI exposure in the WIHS cohort suggesting

that there is likely confounding or no relationship between PI use and diabetes status in this population. In future cohort studies, continuous measures of metabolic dysregulation would provide more conclusive evidence of insulin resistance or hyperglycemia contributing to respiratory health impairment and better define the relationship between PI use and diabetes in the WIHS cohort.

These results have several strengths but many limitations. The strengths of this work include its multicenter study design enriched for older PLWH among the MACS cohort and a racially diverse women's cohort among the WIHS cohort. With respect to study design, the current data presented is cross-sectional, limiting possible causal inference. Although this is the first study to find an association between PI use and dyspnea or respiratory health status among PIs in large cohorts of men living with HIV, these findings were not present in the WIHS cohort suggesting that they are likely confounded by more significant environmental and socioeconomic determinants of respiratory health or less likely sex-related effect measure modification. Moreover, while the MACS and WIHS cohorts were recently combined into one cohort, the presented data was collected prior to merger. As such, several covariables had differing definitions for each cohort which prevented pooling data for formally testing interaction between sex and PI use for respiratory symptoms. The number of MACS participants recruited in the study was fewer than what the power analysis in the methods section suggested would be required for an accurate measure of association. While confounding can be a significant limitation in any observational study, in this study, both crude and adjusted models suggested little influence on effect measures from confounders included in the models. Nevertheless, unmeasured confounding remains a potential limitation of this study due to

its observational design. Interaction was not able to be formally compared in a multiplicative model due to the disparate populations in each cohort, risk for residual confounding, and differences in covariable definitions that prevented pooling of data to create a combined multivariable model with interaction. Non-differential misclassification error and recall bias due to self-reported outcomes and covariate data are possible as both cohort studies relied significantly on self-reported data. In addition, our study relied on two health-related quality of life measures, the SGRQ and the mMRC dyspnea scale. While used in general populations, the SGRQ and mMRC were originally designed for use in populations with obstructive lung diseases and have less experience in the general population. Nevertheless, the prevalence of dyspnea and impaired respiratory health and the associations from mMRC and SGRQ data were similar in each cohort suggesting that each measure was valid in these populations. Finally, given the diverse nature of the HIV epidemic, the generalizability of each cohort is likely limited.

In conclusion, notwithstanding its many limitations, this work contributes a robust cross-sectional description of the prevalence and severity of respiratory health impairment and dyspnea in a cohort of men living with and at risk for HIV and a racially diverse cohort of women living with and at risk for HIV. Furthermore, this work offers hypothesis-generating data regarding the class-specific associations of PI-based ART to respiratory health impairment and data to better determine which specific populations among the diverse groups of PLWH may be most at risk for ART-related respiratory health impairment and dyspnea.

As hypothesis-generating data, these results serve to inform future studies in three ways: firstly, longitudinal studies in similar populations are needed to establish a causal

relationship of PIs and impaired respiratory health and better define populations in which the effect is most evident. While biological differences among different communities living with HIV may exist, the disparate results in the MACS and WIHS cohorts suggest that other unknown determinants of dyspnea and respiratory health are likely more important and deserve further study. Secondly, future cohort and translational studies should use continuous glucose homeostasis measures to better define how metabolic dysregulation contributes to HIV-related lung health disparities. Finally, these results underscore the heterogeneity of PLWH and the need for trials and cohorts with representation of women and disadvantaged minorities to understand sex-specific differences in respiratory health with PI use and other ART drug classes.

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TABLES/FIGURES

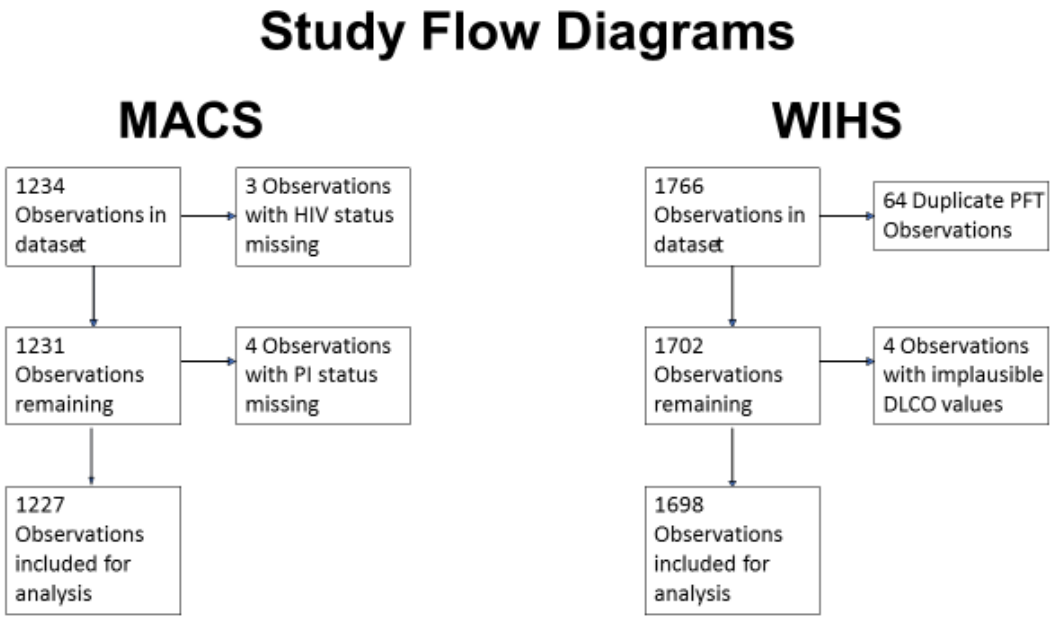


Figure 1. Study Flow Diagrams. Data was obtained from Multicenter AIDS Cohort Study (MACS) visits between 04/01/2017 and 03/31/2018 and Women's Interagency HIV Study (WIHS) visits between 10/31/2017 and 09/30/2019.

Causal Diagram

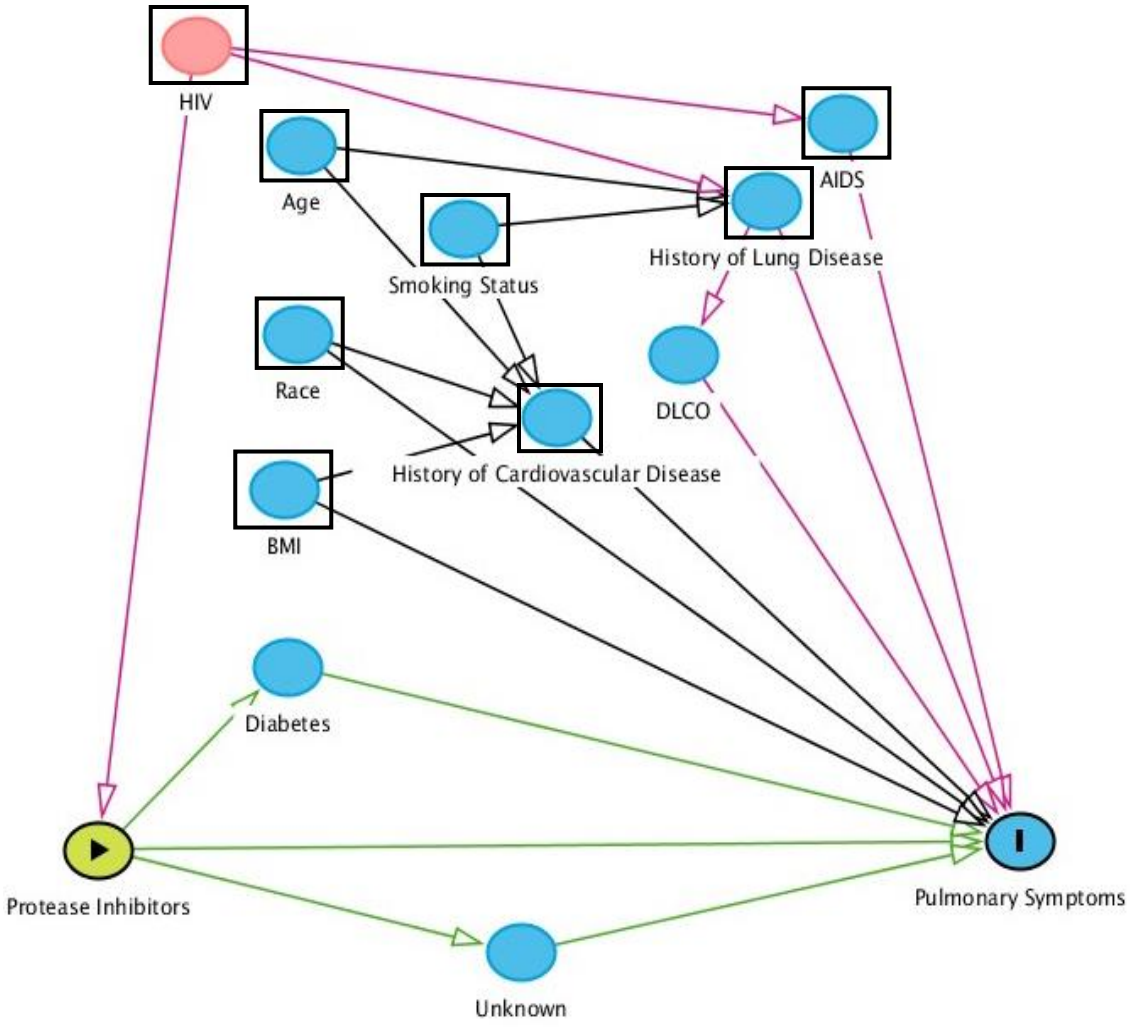


Figure 2. Causal Flow Diagram. A directed acyclic graph was created based on hypothesized relationships between intermediate causal factors and prior literature review.

Multicenter AIDS Center Study (MACS) Data Tables

Table 1. Description of MACS study population, overall, and by HIV serostatus/PI use

Participant Characteristic	**Total N=1227**	**HIV-negative N=549**	**HIV-positive without PI use N=501**	**HIV-positive with PI use N=177**	**P-value**
Age, years					<0.0001
Mean (SD)	56.0 (12.1)	59.0 (12.4)	52.5 (11.3)	56.3 (10.4)	
BMI [kg/m^2] Mean (SD)	27.4 (5.4)	27.8 (5.4)	27.5 (5.6)	26.3 (4.6)	0.0086
Race/Ethnicity n (%)					<0.0001
White	735 (60.0)	384 (70.0)	260 (52.1)	91 (51.4)	
Black	360 (29.4)	124 (22.6)	178 (35.7)	58 (32.8)	
Else	70 (5.7)	19 (3.5)	33 (6.6)	18 (10.2)	
Multi-Racial	60 (4.9)	22 (4.0)	28 (5.6)	10 (5.7)	
Smoking n (%)					0.0169
Never smoked	379 (31.7)	175 (32.7)	139 (28.5)	65 (37.4)	

Former smoker	533 (44.5)	253 (47.2)	212 (43.5)	68 (39.1)	
Current smoker	285 (23.8)	108 (20.2)	136 (27.9)	41 (23.6)	
Cumulative pack-years± Median (Q1-Q3)	9.7 (0.7-27.0)	10.3 (0.2-28.9)	8.8 (1.3-27.0)	10.8 (2.3-23.6)	0.7775
Alcohol Use n (%)					0.0485
None	242 (20.7)	100 (18.8)	104 (22.0)	38 (23.0)	
1 to 3 drinks/week	556 (47.5)	243 (45.7)	225 (47.6)	88 (53.3)	
4 to 13 drinks/week	268 (22.9)	142 (26.7)	96 (20.3)	30 (18.2)	
More than 13 drinks/week	104 (8.9)	47 (8.8)	48 (10.2)	9 (5.5)	
Current Marijuana Use n (%)					0.0014
No	811 (68.9)	394 (74.1)	303 (63.5)	114 (67.9)	
Yes	366 (31.1)	138 (25.9)	174 (36.5)	54 (32.1)	
Cardiovascular disease n (%)					0.1931
No	1015 (82.7)	447 (81.4)	426 (85.0)	142 (80.2)	
Yes	212 (17.3)	102 (18.6)	75 (15.0)	35 (19.8)	
Pulmonary Disease n (%)					0.0006

No	931 (76.0)	442 (80.8)	369 (73.7)	120 (67.8)	
Yes	294 (24.0)	105 (19.2)	132 (26.4)	57 (32.2)	
Hypertension n (%)					0.1564
No	586 (48.7)	247 (45.7)	254 (51.7)	85 (49.1)	
Yes	618 (51.3)	293 (54.3)	237 (48.3)	88 (50.9)	
Kidney Disease n (%)					<0.0001
No	1008 (84.9)	486 (91.4)	385 (79.4)	137 (80.1)	
Yes	180 (15.2)	46 (8.7)	100 (20.6)	34 (19.9)	
Hepatitis C Status n (%)					0.0193
Negative or Cleared	1121 (94.1)	520 (95.8)	435 (91.8)	166 (95.4)	
Chronic Infection	70 (5.9)	23 (4.2)	39 (8.2)	8 (4.6)	
Diabetes Mellitus Diagnosis n (%)					0.0002
No	999 (84.9)	455 (86.3)	415 (87.0)	129 (74.6)	
Yes	178 (15.1)	72 (13.7)	62 (13.0)	44 (25.4)	
Diabetes Medication Use n (%)					0.0053
No	1079 (88.1)	488 (89.2)	448 (89.4)	143 (80.8)	

Yes	146 (11.9)	59 (10.8)	53 (10.6)	34 (19.2)	
HOMA-IR Median (Q1-Q3)	2.8 (1.9-4.5)	2.6 (1.9-4.1)	3.0 (1.8-4.6)	3.7 (2.1-5.9)	0.0003
Fasting Glucose level [mg/dL] Median (Q1-Q3)	92.0 (85.0-101.0)	92.0 (85.0-100.0)	91.0 (85.0-101.0)	94.0 (86.0-108.0)	0.0528
HbA1c [%] Median (Q1-Q3)	5.4 (5.1-5.8)	5.4 (5.2-5.7)	5.4 (5.1-5.8)	5.5 (5.1-6.0)	0.1386
Fasting Insulin Level [µIU/mL] Median (Q1-Q3)	12.4 (8.5-18.5)	11.2 (8.3-17.2)	12.9 (8.6-19.2)	14.6 (9.3-22.5)	0.0002

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; BMI, Body Mass Index, HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; HbA1c, Hemoglobin A1c; PI, Protease Inhibitor.

*Missing data for continuous variables are BMI n=37; HOMA-IR n=241; HbA1c n=16; insulin n=235; glucose n=47

** Missing data for categorical variables are Race/Ethnicity n=2; Hypertension n=23; Kidney Disease n=39; HCV status n=36; Diabetes n=50; Diabetes Medication n=2;

Smoking Status n=30; Alcohol Use n=57; Marijuana Use n=50; and History of Pulmonary Disease n=2

±Calculated among smokers

-Column percentages may not total 100% due to rounding

Table 2. HIV-Specific characteristics among HIV positive MACS participants, overall, and by PI use

Participant Characteristic	**Total N=678**	**HIV-positive without PI use N=501**	**HIV-positive with PI use N=177**	**P-value**
Current AIDS n (%)				<0.0001
No	625 (92.2)	476 (95.0)	149 (84.2)	
Yes	53 (7.8)	25 (5.0)	28 (15. 8)	
Viral Load n (%)				0.3636
Undetectable or <200 copies/mL	618 (92.4)	460 (92.9)	158 (90.8)	
>=200 copies/ml	51 (7.6)	35 (7.1)	16 (9.2)	
CD4 Count [cells/mm^3] Mean (SD)	715.2 (303.9)	743.1 (307.3)	637.2 (280.7)	<0.0001
Type of Therapy at Visit n (%)	625 (92.2)	461 (92.0)	164 (92.7)	0.7853
HAART				

Cumulative HAART years Median (Q1-Q3)	12.5 (5.2-17.1)	11.4 (4.8-16.6)	14.5 (7.8-18.0)	0.0001
Cumulative NRTI years Median (IQR)	13.3 (5.4-18.8)	12.5 (4.8-18.3)	15.7 (9.2-20.0)	<0.0001
Cumulative PI years Median (Q1-Q3)	3.8 (0.0-11.5)	0.5 (0.0-6.3)	13.1 (8.0-18.0)	<0.0001
Cumulative NNRTI years Median (Q1-Q3)	3.8 (0.2-10.1)	4.4 (0.4-11.5)	2.0 (0.0-5.5)	<0.0001
Cumulative II years Median (Q1-Q3)	0.8 (0.0-3.1)	0.9 (0.0-2.9)	0.1 (0.0-4.7)	0.8723

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; AIDS, Acquired Immunodeficiency Syndrome; HAART, Highly Active Antiretroviral Therapy; NRTI, Nucleoside Reverse Transcriptase Inhibitors; PI, Protease Inhibitor; NNRTI, Non-nucleoside Reverse Transcriptase Inhibitors; II, Integrase Inhibitor. *Missing data for continuous variables are CD4 count n=9.

** Missing data for categorical variables are Viral Load n=9;

-Column percentages may not total 100% due to rounding

Table 3. Respiratory Symptoms and Pulmonary Function Among MACS Participants, Overall and by HIV serostatus/PI use

Participant Characteristic	**Total N=1227**	**HIV-negative N=549**	**HIV-positive without PI use N=501**	**HIV-positive with PI use N=177**	**P-value**
mMRC Dyspnea Scale n (%)					0.0214
0 (No Dyspnea)	853 (71.0)	405 (75.3)	343 (69.7)	105 (61.1)	
1 (Slight Dyspnea)	204 (17.0)	77 (14.3)	87 (17.7)	40 (23.3)	
2 (Moderate Dyspnea)	44 (3.7)	19 (3.5)	17 (3.5)	8 (4.7)	
3 (Severe Dyspnea)	81 (6.7)	28 (5.2)	35 (7.1)	18 (10.5)	
4 (Very Severe Dyspnea)	20 (1.7)	9 (1.7)	10 (2.0)	1 (0.6)	
SGRQ Total Scores Median (Q1-Q3)	5.5 (1.7-15.4)	4.8 (1.3-12.1)	5.5 (1.7-15.0)	7.9 (2.4-21.8)	0.0005
SGRQ Total Scores n (%)					0.0010

< 10 points ≥ 10 points	794 (66.0) 410 (34.0)	379 (70.1) 162 (29.9)	322 (65.3) 171 (34.7)	93 (54.7) 77 (45.3)	
Pre-BD FEV1/FVC Mean (SD)	0.77 (0.08)	0.76 (0.08)	0.77 (0.08)	0.77 (0.07)	0.0631
Pre-BD FEV1 (%) Mean (SD)	94.0 (16.6)	93.9 (16.8)	94.1 (16.9)	94.3 (15.3)	0.9737
Pre-BD FVC (%) Mean (SD)	94.8 (14.7)	94.2 (14.4)	95.3 (15.5)	95.3 (13.5)	0.4698
Post-BD FEV1 [%] Mean (SD)	96.3 (16.9)	96.4 (16.8)	96.2 (16.9)	96.1 (17.0)	0.9830
Post-BD FVC [%] Mean (SD)	94.3 (14.7)	94.1 (14.7)	94.5 (15.0)	94.4 (14.3)	0.8676
DLCO [%] Mean (SD)	85.0 (14.8)	85.7 (14.2)	84.9 (15.8)	83.1 (13.7)	0.1479

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; mMRC, Modified Medical Research Council; SGRQ St. George's Respiratory Questionnaire; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; BD, Bronchodilator; DLCO, Diffusion Capacity.

*Missing data for continuous variables are SGRQ n=23; pre-BD FEV1 n=20; pre-BD FVC n=20; post-BD FEV1 n=56; post-BD FVC n=56; FEV1/FVC n=20; DLCO n=138.

-Column percentages may not total 100% due to rounding

Binary SGRQ models

Unadjusted

$$\text{Logit}(Pr(SGRQ\geq 10))=\alpha+\beta_1*(HIV+/PI-)+\beta_2*(HIV+/PI+)\ [\text{HIV-negative as referent}]$$

$$\text{Logit}(Pr(SGRQ\geq 10))=\alpha+\beta_1*(HIV+/PI-)+\beta_2*(HIV+/PI+)\ [\text{HIV-positive without PI-use as referent}]$$

Adjusted

$$\text{Logit}(Pr(SGRQ\geq 10))=\alpha+\beta_1*(HIV+/PI-)+\beta_2*(HIV+/PI+)+\beta_3*(AGE)+\beta_4*(BMI)+\beta_5*(\text{Former Smoker})+\beta_6*(\text{Current Smoker})+\beta_7*(\text{Black Race})+\beta_8*(\text{Other Race})+\beta_9*(\text{Multiracial})+\beta_{10}*(\text{CV disease})+\beta_{11}*(\text{Lung disease})\ [\text{HIV-negative as referent}]$$

$$\text{Logit}(Pr(SGRQ\geq 10))=\alpha+\beta_1*(HIV+/PI-)+\beta_2*(HIV+/PI+)+\beta_3*(AGE)+\beta_4*(BMI)+\beta_5*(\text{Former Smoker})+\beta_6*(\text{Current Smoker})+\beta_7*(\text{Black Race})+\beta_8*(\text{Other Race})+\beta_9*(\text{Multiracial})+\beta_{10}*(\text{CV disease})+\beta_{11}*(\text{Lung disease})+\beta_{12}*(AIDS)\ [\text{HIV-negative as referent}]$$

Ordinal mMRC models

Unadjusted

$$\text{Logit}(Pr(mMRC\geq g))=\alpha+\beta_1*(HIV+/PI-)+\beta_2*(HIV+/PI+)\ [\text{HIV-negative as referent}];\ \text{Where, } g=1,2,3,4$$

$$\text{Logit}(Pr(mMRC\geq g))=\alpha+\beta_1*(HIV+/PI+)\ [\text{HIV-positive without PI-use as referent}];\ \text{Where, } g=1,2,3,4$$

Adjusted

$$\text{Logit}(Pr(mMRC\geq g))=\alpha+\beta_1*(HIV+/PI+)+\beta_2*(AGE)+\beta_3*(BMI)+\beta_4*(\text{Former Smoker})+\beta_5*(\text{Current Smoker})+\beta_6*(\text{Black Race})+\beta_7*(\text{Other Race})+\beta_8*(\text{Multiracial})+\beta_9*(\text{CV disease})+\beta_{10}*(\text{Lung disease})\ [\text{HIV-negative as referent}];\ \text{Where, } g=1,2,3,4$$

$$\text{Logit}(Pr(mMRC\geq g))=\alpha+\beta_1*(HIV+/PI+)+\beta_2*(AGE)+\beta_3*(BMI)+\beta_4*(\text{Former Smoker})+\beta_5*(\text{Current Smoker})+\beta_6*(\text{Black Race})+\beta_7*(\text{Other Race})+\beta_8*(\text{Multiracial})+\beta_9*(\text{CV disease})+\beta_{10}*(\text{Lung disease})+\beta_{11}*(AIDS)\ [\text{HIV-positive without PI-use as referent}];\ \text{Where, } g=1,2,3,4$$

Figure 3. Logistic Regression Modelling Equations for SGRQ and mMRC Data.

The listed equations were used to determine the odds ratio estimates for dichotomized high SGRQ outcome and ordered mMRC ordinal oucome

Table 4. MACS Unadjusted mMRC Ordinal Logistic Model Odds Ratio Estimates [HIV-Negative As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive non-PI users vs HIV-negative group	1.32	1.01	1.73
HIV-positive PI users vs HIV-negative group	1.86	1.30	2.66

Table 5. MACS Unadjusted mMRC Ordinal Logistic Model Odds Ratio Estimates [HIV-Positive Not Using PIs As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive PI users vs. HIV-positive non-PI users	1.42	1.00	2.02

Table 6. MACS Adjusted mMRC Ordinal Logistic Model Odds Ratio Estimates

Participant Characteristic	**Odds Ratio (95% CI)[#]**	**Odds Ratio among HIV-positive participants (95% CI)[§,#]**
Age	1.02 (1.00, 1.03)	1.01 (0.99, 1.03)
BMI	1.07 (1.04, 1.09)	1.06 (1.03, 1.09)
HIV-negative HIV No PI-Based ART HIV PI-Based ART	Ref 1.13 (0.83, 1.53) 1.79 (1.21, 2.64)	-- Ref 1.53 (1.04, 2.25)
Smoking Never smoked Former smoker Current smoker	Ref 1.27 (0.91, 1.76) 2.87 (1.98, 4.15)	Ref 1.09 (0.72, 1.66) 1.87 (1.18, 2.97)
Race White	Ref	Ref

Black Other Multi-Racial	2.21 (1.61, 3.03) 3.43 (1.99, 5.90) 2.21 (1.20, 4.07)	2.25 (1.52, 3.33) 3.59 (1.88, 6.86) 2.43 (1.16, 5.09)
History of Cardiovascular Disease	1.56 (1.10, 2.21)	1.62 (1.03, 2.55)
History of Pulmonary Disease	2.34 (1.75, 3.13)	2.13 (1.47, 3.09)
AIDS at visit (among HIV-positive)*	--	1.17 (0.62, 2.22)

Adjusted OR from ordinal logistic regression model mMRC Dyspnea scale including all covariates listed

§ Population restricted to HIV positive only

-Due to missingness in data, 1139 of 1227 observations were used in the full multivariable model and 625 of 678 observations in the HIV-positive multivariable model.

*Referent group: HIV positive non-PI using participants

Table 7. MACS Unadjusted SGRQ Logistic Model Odds Ratio Estimates [HIV-Negative As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive non-PI users vs HIV-negative group	1.24	0.96	1.61
HIV-positive PI users vs HIV-negative group	1.94	1.36	2.76

Table 8. MACS Unadjusted SGRQ Logistic Model Odds Ratio Estimates [HIV-Positive Not Using PIs As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive PI users vs. HIV-positive non-PI users	1.56	1.10	2.22

Table 9. MACS Adjusted SGRQ Logistic Model Odds Ratio Estimates

Participant Characteristic	**Odds Ratio (95% CI)[#]**	**Odds Ratio among HIV-positive (95% CI)[§,#]**
Age	1.02 (1.01, 1.04)	1.02 (1.00, 1.04)
BMI	1.04 (1.01, 1.06)	1.03 (1.00, 1.06)
HIV-negative HIV No PI-Based ART HIV PI-Based ART	Ref 1.21 (0.90, 1.63) 1.91 (1.29, 2.82)	-- Ref 1.50 (1.01, 2.22)
Smoking Never smoked Former smoker Current smoker	Ref 1.14 (0.84, 1.55) 2.78 (1.92, 4.02)	Ref 1.22 (0.80, 1.85) 2.45 (1.52, 3.95)
Race White Black Other	Ref 1.34 (0.98, 1.84) 3.53 (2.00, 6.22)	Ref 1.32 (0.89, 1.96) 3.98 (1.98, 7.98)

Multi-Racial	1.96 (1.07, 3.57)	2.39 (1.12, 5.07)
History of Cardiovascular Disease	1.60 (1.13, 2.25)	1.58 (0.99, 2.52)
History of Pulmonary Disease	2.23 (1.67, 3.00)	2.23 (1.53, 3.26)
AIDS at visit (among HIV-positive)*	--	1.47 (0.77, 2.80)

Adjusted OR from logistic regression model of SGRQ Scores ≥10 (vs <10) including all covariates listed

§ Population restricted to HIV positive only

-Due to missingness in data, 1141 of 1227 observations were used in the full multivariable model and 624 of 678 observations in the HIV-positive multivariable model.

*Referent group: HIV positive non-PI using participants

Women's Interagency HIV Study (WIHS) Data Tables

Table 10. Description of WIHS Population, Overall, and by HIV Serostatus/PI Use

Participant Characteristics	**Total N=1698**	**HIV-negative N=496**	**HIV-positive without PI use N=963**	**HIV-positive with PI use N=239**	**P-value**
Age, years Median (Q1-Q3)	52 (45-58)	50 (42-57)	52 (45-58)	52 (46-57)	0.0125
BMI [kg/m^2] Mean (SD)	32.8 (9.1)	33.0 (8.83)	32.9 (9.42)	32.0 (8.30)	0.3473
Missing (%)	28 (1.65)	6 (1.21)	17 (1.77)	5 (2.09)	
Race/Ethnicity (%)					0.0956
White	167 (9.84)	39 (7.86)	110 (11.42)	18 (7.53)	
Black	1113 (65.55)	323 (65.12)	624 (64.80)	166 (69.46)	
Other	143 (8.42)	40 (8.06)	80 (8.31)	23 (9.62)	

Multi-Racial	274 (16.14)	94 (18.95)	148 (15.37)	32 (13.39)	
Missing (%)	1 (0.001)		1 (0.1)		
Smoking (%)					0.0006
Never smoked	559 (32.92)	133 (26.81)	333 (34.58)	93 (38.91)	
Former smoker	502 (29.56)	142 (28.63)	288 (29.91)	72 (30.13)	
Current smoker	637 (37.51)	221 (44.56)	342 (35.51)	74 (30.96)	
Cumulative pack-years Median (Q1-Q3)	3.40 (0.0-12.2)	4.29 (0.0-14.2)	2.87 (0.0-11.7)	2.44 (0.0-10.7)	0.0035
Missing (%)	39 (2.30)	11 (2.2)	23 (2.4)	5 (2.09)	
Alcohol Use (%)					<0.0001
None	852 (50.18)	203 (40.93)	527 (54.72)	122 (51.05)	
1 to 7 drinks/week	703 (41.40)	226 (45.56)	377 (39.15)	100 (41.84)	
8 to 12 drinks/week	50 (2.94)	18 (3.63)	26 (2.70)	6 (2.51)	
More than 12 drinks/week	92 (5.42)	49 (9.88)	32 (3.32)	11 (4.60)	

Missing (%)	1 (0.06)		1 (0.1)		
Current Marijuana Use (%)					0.0271
No	1300 (76.56)	360 (72.58)	749 (77.78)	191 (79.92)	
Yes	395 (23.26)	136 (27.42)	212 (22.01)	47 (19.67)	
Missing	3 (0.18)		2 (0.21)	1 (0.42)	
Cardiovascular disease (%)					0.4073
No	1567 (92.29)	453 (91.33)	896 (93.04)	218 (91.21)	
Yes	131 (7.71)	43 (8.67)	67 (6.96)	21 (8.79)	
History of Pulmonary Disease (%)					0.3147
No	1223 (72.03)	349 (70.36)	693 (71.96)	181 (75.73)	
Yes	475 (27.97)	147 (29.64)	270 (28.04)	58 (24.27)	
Hypertension (%)					0.9813

No Yes	363 (21.38) 1335 (78.62)	106 (21.37) 390 (78.63)	207 (21.5) 756 (78.5)	50 (20.92) 189 (79.08)	
Kidney Disease (%) No Yes Missing	 1331 (78.39) 172 (10.13) 195 (11.48)	 306 (61.69) 20 (4.03) 170 (34.27)	 821 (85.25) 122 (12.67) 20 (2.08)	 204 (85.36) 30 (12.55) 5 (2.09)	0.0031
Hepatitis C Status (%) Negative Positive Resolved Unknown	 1402 (82.57) 89 (5.24) 204 (12.01) 3 (0.18)	 427 (86.09) 31 (6.25) 37 (7.46) 1 (0.2)	 775 (80.48) 48 (4.98) 139 (14.43) 1 (0.1)	 200 (83.68) 10 (4.18) 28 (11.72) 1 (0.42)	0.0028
Diabetes Mellitus Diagnosis (%) No Yes	 1298 (76.44) 400 (23.56)	 375 (75.6) 121 (24.4)	 728 (75.6) 235 (24.4)	 195 (81.59) 44 (18.41)	0.1292

Diabetes Medication Use (%)					0.2642
No	1433 (84.39)	418 (84.27)	805 (83.59)	210 (87.87)	
Yes	265 (15.61)	78 (15.73)	158 (16.41)	29 (12.13)	
HOMA-IR median (Q1-Q3)	2.24 (1.23-4.11)	2.00 (1.08-3.76)	2.30 (0.82-4.32)	2.25 (1.19 – 4.08)	0.0165
Missing		1 (0.2)	3 (0.31)		

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; BMI, Body Mass Index, HOMA-IR, Homeostatic Model Assessment-Insulin Resistance; HbA1c, Hemoglobin A1c.

*Categorical variable frequencies were compared using chi-squared testing (P< 0.05 were considered significant) without missing data.

Continuous Variables were compared using ANOVA for parametric variables (P< 0.05 were considered significant).

Kruskal-Wallis testing was used to compare non-parametric variables (P< 0.05 were considered significant).

-All percentages are column percentages

Table 11. HIV-Specific Characteristics Among HIV-Positive WIHS Participants, Overall, and By PI Use

Participant Characteristics	**Total N=1202**	**HIV-positive without PI use N=963**	**HIV-positive with PI use N=239**	**P-value**
Current AIDS (%)				<0.0001
No	846 (70.38)	707 (73.42)	139 (58.16)	
Yes	356 (29.62)	256 (26.58)	100 (41.84)	
Viral Load (%)				0.0771
<200 copies/mL	1014 (84.36)	820 (85.15)	194 (81.17)	
>=200 copies/ml	159 (13.23)	119 (12.36)	40 (16.74)	
Missing	29 (2.41)	24 (2.49)	5 (2.09)	
CD4 Count [cells/mm^3] Mean (SD)	733.2 (363.9)	754.9 (358.4)	646.0 (373.2)	<0.0001
Missing	11 (0.92)	9 (0.93)	2 (0.84)	
Type of Therapy at Visit (%)				0.0194
HAART	1083 (90.10)	858 (89.1)	225 (94.14)	

Cumulative HAART years median (Q1-Q3)	5.9 (3.69-14.83)	5.0 (3.6-13.4)	11.7 (4.3-16.7)	<0.0001
Cumulative NRTI years median (Q1-Q3)	13.0 (7.75-32.25)	10.75 (7.75-29.5)	23.75 (9.25-37.75)	<0.0001
Cumulative PI years median (Q1-Q3)	1.625 (0.0-11.0)	0.0 (0.0-6.5)	13.5 (6.75-23.25)	<0.0001
Cumulative NNRTI years median (Q1-Q3)	1.5 (0.0-5.25)	2.0 (0.0-5.75)	0.75 (0.0-3.25)	0.0010
Cumulative II years median (Q1-Q3)	1.75 (0.0-3.75)	2.0 (0.0-3.75)	0.75 (0.0-4.25)	0.0974

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; AIDS, Acquired Immunodeficiency Syndrome; HAART, Highly Active Antiretroviral Therapy; NRTI, Nucleoside Reverse Transcriptase Inhibitors; PI, HIV Protease Inhibitor; NNRTI, Non-nucleoside Reverse Transcriptase Inhibitors; II, Integrase Inhibitor.

*Categorical variable frequencies were compared using chi-squared testing ($P < 0.05$ were considered significant) without missing data.

Continuous Variables were compared using ANOVA for parametric variables ($P < 0.05$ were considered significant).

Kruskal-Wallis testing was used to compare non-parametric variables ($P < 0.05$ were considered significant).

-All percentages are column percentages

Table 12. Respiratory Symptoms and Pulmonary Function Among WIHS Participants, Overall and by HIV serostatus/PI use

Participant Characteristics	**Total N=1194**	**HIV-negative N=499**	**HIV-positive without PI use N=963**	**HIV-positive with PI use N=239**	**P-value**
mMRC Dyspnea Scale (%)					0.6391
0	669 (39.4)	188 (37.9)	379 (39.36)	102 (42.68)	
1	407 (23.97)	121 (24.4)	230 (23.88)	56 (23.43)	
2	104 (6.12)	35 (7.06)	50 (5.19)	19 (7.95)	
3	457 (26.91)	134 (27.02)	267 (27.73)	56 (23.43)	
4	44 (2.59)	11 (2.22)	27 (2.8)	6 (2.51)	
Missing	17 (1.0)	7 (1.41)	10 (1.04)	0 (0)	
SGRQ Total Scores					0.1893
median (IQR)	11.2 (3.0-25.1)	11.4 (3.69-25.50)	11.34 (2.83-25.34)	9.56 (1.9-22.4)	
Missing	10 (0.01)	3 (0.60)	7 (0.73)		

SGRQ Total Scores (%)					0.4218
< 10 points	797 (46.94)	227 (45.77)	448 (46.52)	122 (51.05)	
≥ 10 points	891 (52.47)	266 (53.63)	508 (52.75)	117 (48.95)	
Missing	10 (0.59)	3 (0.6)	7 (0.73)	0 (0)	
FEV1/FVC Mean (SD)	0.785 (0.088)	0.782 (0.090)	0.786 (0.089)	0.793 (0.078)	0.3190
Missing (%)	29 (1.71)	12 (2.42)	13 (1.35)	4 (1.67)	
Pre-BD FEV1 (%) Mean (SD)	88.9 (18.4)	89.7 (20.0)	88.3 (17.8)	89.6 (17.2)	0.3163
Missing (%)	29 (1.71)	12 (2.42)	13 (1.35)	4 (1.67)	
Pre-BD FVC (%) Mean (SD)	91.0 (17.3)	92.5 (19.1)	90.2 (16.2)	91.0 (17.5)	0.0589
Missing (%)	29 (1.71)	12 (2.42)	13 (1.35)	4 (1.67)	
Post-BD FEV1 [%] Mean (SD)	90.9 (18.3)	92.1 (19.2)	90.0 (17.5)	92.1 (19.4)	0.0929
Missing (%)	182 (10.7)	59 (11.9)	97 (10.07)	26 (10.88)	

Post-BD FVC [%] Mean (SD)	91.2 (17.2)	92.9 (18.8)	90.4 (16.2)	91.2 (17.6)	0.0488
Missing (%)	182 (10.7)	59 (11.9)	97 (10.07)	26 (10.88)	
DLCO [%] Mean (SD)	84.8 (17.2)	88.1 (18.3)	83.1 (16.9)	83.9 (14.1)	0.0033
Missing (%)	1030 (60.7)	290 (58.5)	565 (58.7)	175 (73.22)	

Abbreviations: Q1, quartile 1; Q3, quartile 3; SD, Standard Deviation; mMRC, Modified Medical Research Council; SGRQ St. George's Respiratory Questionnaire; FEV1, Forced Expiratory Volume in 1 Second; FVC, Forced Vital Capacity; BD, Bronchodilator; DLCO, Diffusion Capacity.

*Categorical variable frequencies were compared using chi-squared testing ($P < 0.05$ were considered significant) without including missing data.

Continuous Variables were compared using ANOVA for parametric variables ($P < 0.05$ were considered significant).

Kruskal-Wallis testing was used to compare non-parametric variables ($P < 0.05$ were considered significant).

-All percentages are column percentages

Table 13. WIHS Unadjusted mMRC Ordinal Logistic Model Odds Ratio Estimates [HIV-Negative As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive non-PI users vs HIV-negative group	0.98	0.81	1.20
HIV-positive PI users vs HIV-negative group	0.85	0.64	1.13

Table 14. WIHS Unadjusted mMRC Ordinal Logistic Model Odds Ratio Estimates [HIV-Positive Not Using PIs As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive PI users vs. HIV-positive non-PI users	0.87	0.67	1.13

Table 15. WIHS Adjusted mMRC Ordinal Logistic Model Odds Ratio Estimates

Participant Characteristic	**Odds Ratio (95% CI)[#] Ref: HIV-Negative**	**Odds Ratio among HIV-positive (95% CI)[§,#] Ref: HIV-positive without PI**
Age	1.03 (1.02, 1.04)	1.03 (1.01, 1.04)
BMI	1.04 (1.03, 1.06)	1.04 (1.03, 1.06)
HIV-negative	Ref	--
HIV No PI-Based ART	1.05 (0.85, 1.29)	Ref
HIV PI-Based ART	0.94 (0.70, 1.27)	0.85 (0.65, 1.12)
Smoking		
Never smoked	Ref	Ref
Former smoker	1.18 (0.93, 1.50)	1.07 (0.81, 1.41)
Current smoker	2.12 (1.69, 2.67)	1.85 (1.42, 2.43)
Race		
White	Ref	Ref
Black	1.93 (1.40, 2.68)	2.20 (1.50, 3.21)
Other	1.57 (1.01, 2.43)	1.73 (1.04, 2.88)
Multi-Racial	1.72 (1.18, 2.51)	2.08 (1.33, 3.25)

History of Cardiovascular Disease	1.89 (1.34, 2.68)	1.92 (1.25, 2.93)
History of Pulmonary Disease	2.67 (2.17, 3.28)	2.45 (1.90, 3.14)
AIDS at visit (among HIV-positive)*	--	1.29 (1.01, 1.65)

Abbreviations: mMRC, Modified Medical Research Council; CI, Confidence Interval;

*Referent group: HIV positive non-PI using participants

Adjusted OR from ordinal logistic regression model mMRC Dyspnea scale including all covariates listed

§ Population restricted to HIV positive only

-Due to missingness in data, 1653 of 1698 observations were used in the full multivariable model and 1169 of 1202 observations in the HIV-positive multivariable model.

Table 16. WIHS Unadjusted SGRQ Logistic Models Odds Ratio Estimates [HIV-Negative As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive non-PI users vs HIV-negative group	0.97	0.78	1.20
HIV-positive PI users vs HIV-negative group	0.82	0.60	1.12

Table 17. WIHS Unadjusted SGRQ Logistic Models Odds Ratio Estimates [HIV-Positive Not Using PIs As a Referent Group]

Effect	**Odds Ratio**	**95% Confidence Intervals**	
HIV-positive PI users vs. HIV-positive non-PI users	0.85	0.64	1.12

Table 18. WIHS Adjusted Logistic SGRQ Score Models

Participant Characteristic	**Odds Ratio (95% CI)[#]** **Ref: HIV-Negative**	**Odds Ratio among HIV-positive (95% CI)[§,#]** **Ref: HIV-positive without PI**
Age	1.04 (1.02, 1.05)	1.03 (1.01, 1.04)
BMI	1.05 (1.04, 1.06)	1.04 (1.03, 1.06)
HIV-negative	Ref	--
HIV No PI-Based ART	1.06 (0.83, 1.35)	Ref
HIV PI-Based ART	0.95 (0.68, 1.34)	0.84 (0.62, 1.16)
Smoking		
Never smoked	Ref	Ref
Former smoker	1.12 (0.85, 1.48)	1.129 (0.82, 1.56)
Current smoker	2.28 (1.75, 2.96)	2.121 (1.56, 2.89)
Race		
White	Ref	Ref
Black	1.13 (0.78, 1.64)	1.31 (0.86, 2.01)
Other	1.08 (0.66, 1.79)	1.12 (0.63, 2.00)

Multi-Racial	1.36 (0.88, 2.10)	1.82 (1.09, 3.04)
History of Cardiovascular Disease	2.04 (1.31, 3.19)	2.29 (1.32, 3.99)
History of Pulmonary Disease	4.02 (3.10, 5.20)	3.94 (2.89, 5.37)
AIDS at visit (among HIV-positive)*	--	1.33 (1.00, 1.78)

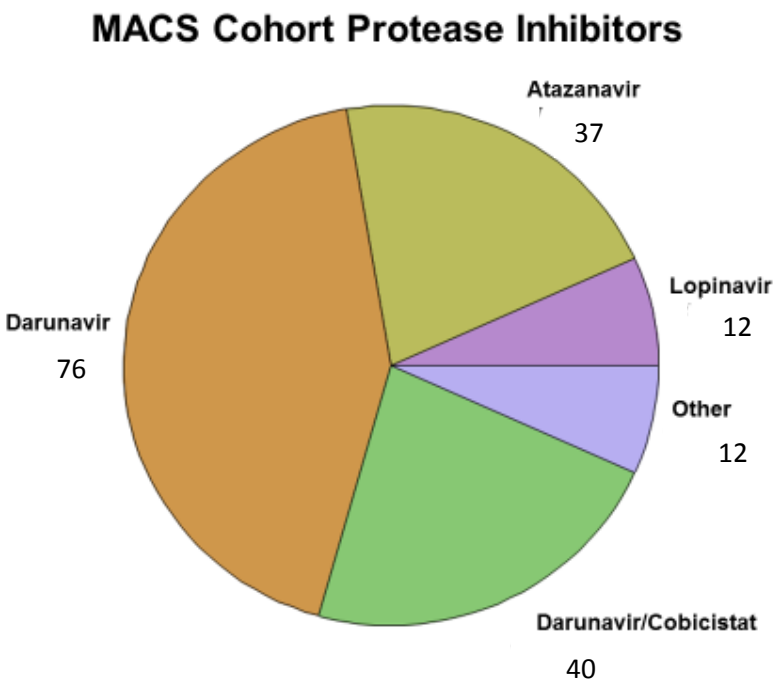
Abbreviations: SGRQ, St. George's Respiratory Questionnaire; CI, Confidence Interval;

*Referent group: HIV positive non-PI using participants

Adjusted OR from logistic regression model of SGRQ Scores ≥10 (vs <10) including all covariates listed

§ Population restricted to HIV positive only

-Due to missingness in data, 1660 of 1698 observations were used in the full multivariable model and 1170 of 1202 observations in the HIV-positive multivariable model.



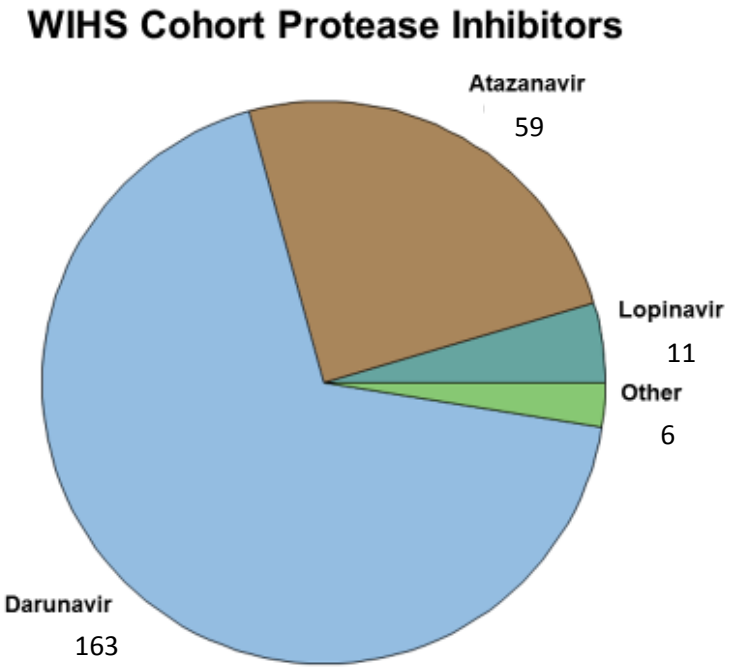


Figure 4. Protease Inhibitors Used in the Multicenter AIDS Cohort Study (MACS) and Women's Interagency HIV Study (WIHS). Pie charts listed above show the absolute number of participants using each specific drug.

St. George's Respiratory Questionnaire Score Boxplots

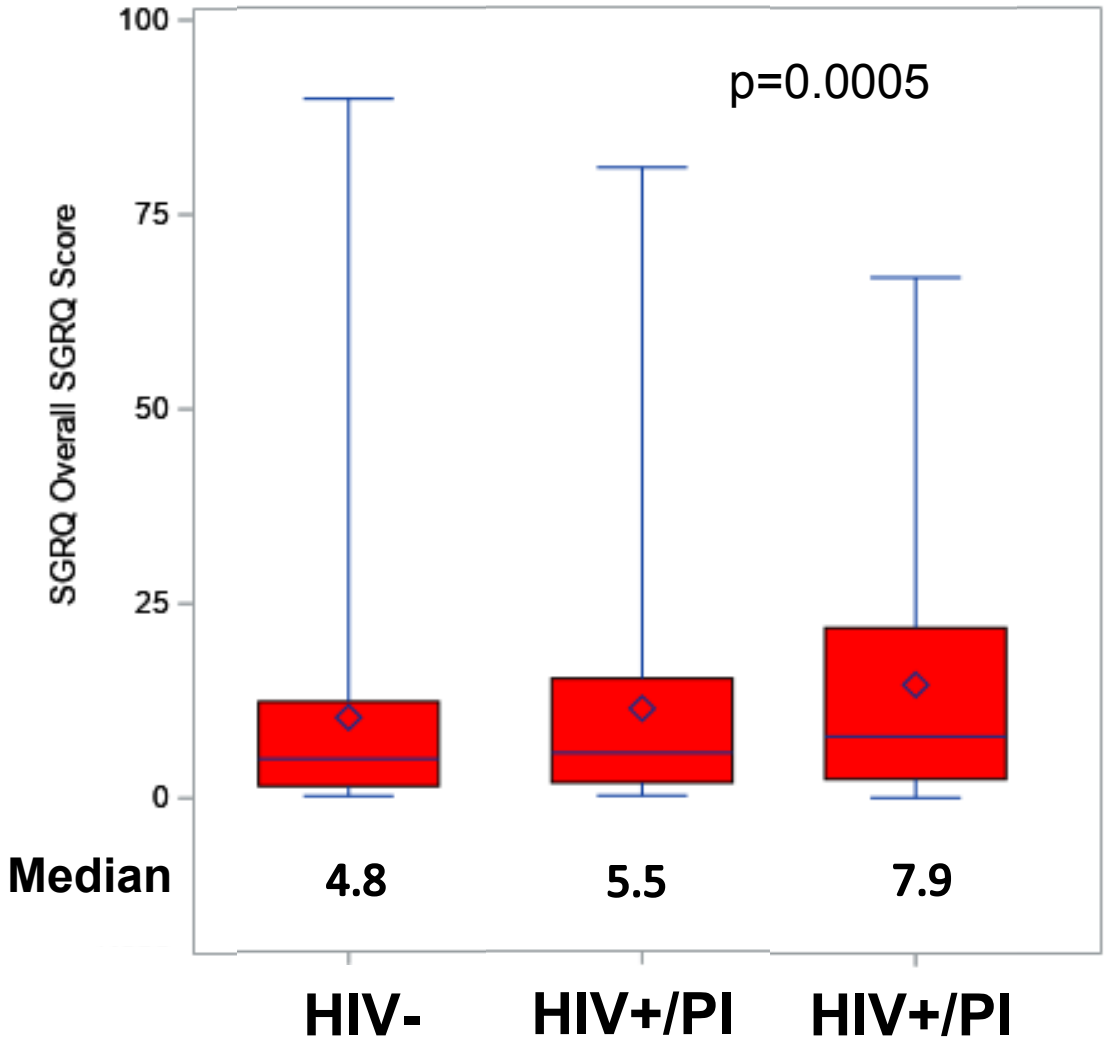


Figure 5. Total St. George's Respiratory Questionnaire Scores Among Multicenter AIDS Cohort Study (MACS) Groups. Among MACS exposure groups there is a steady increase in the median SGRQ scores among each of the exposure groups.

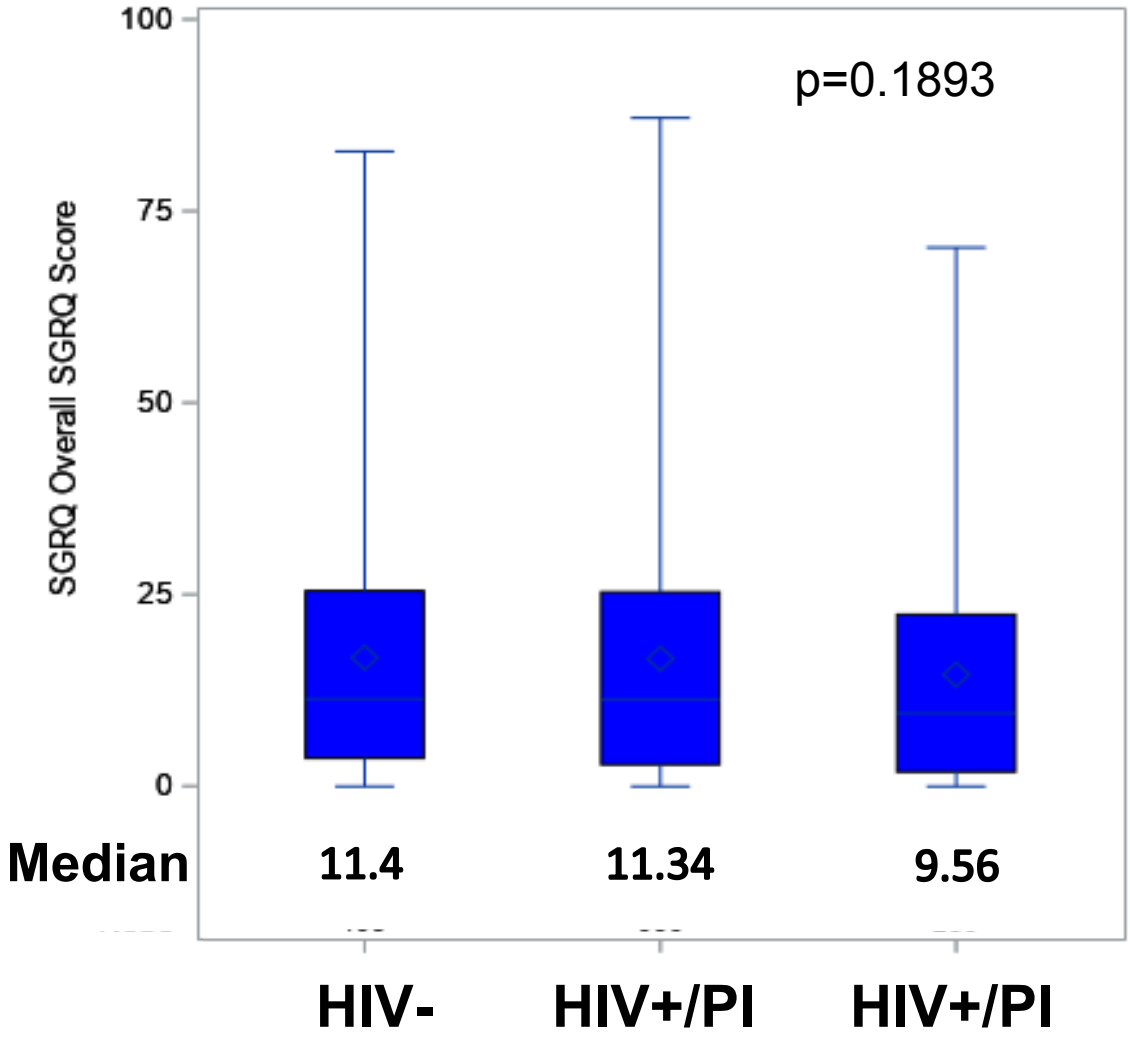


Figure 6. Total St. George's Respiratory Questionnaire Scores Among Women's Interagency HIV Study (WIHS) Groups. Among WIHS exposure groups there are uniformly elevated SGRQ scores indicated of poor respiratory health regardless of HIV status or PI use.

Table 19. Dichotomized SGRQ Scores ≥ 10 and < 10 In Each Cohort

Participant Characteristics	**HIV-negative**		**HIV-positive without PI use**		**HIV-positive with PI use**		**P-value**	
	MACS N=549	**WIHS N=496**	**MACS N=501**	**WIHS N=963**	**MACS N=177**	**WIHS N=239**	**MACS**	**WIHS**
SGRQ Total Scores n (%)*							0.0010	0.4218
< 10 points	379 (70.1)	227 (45.8)	322 (65.3)	448 (46.5)	93 (54.7)	122 (51.1)		
≥ 10 points	162 (29.9)	266 (53.6)	171 (34.7)	508 (52.8)	77 (45.3)	117 (49.0)		

*Percentages not adding to 100% reflect the proportion of missingness in the data

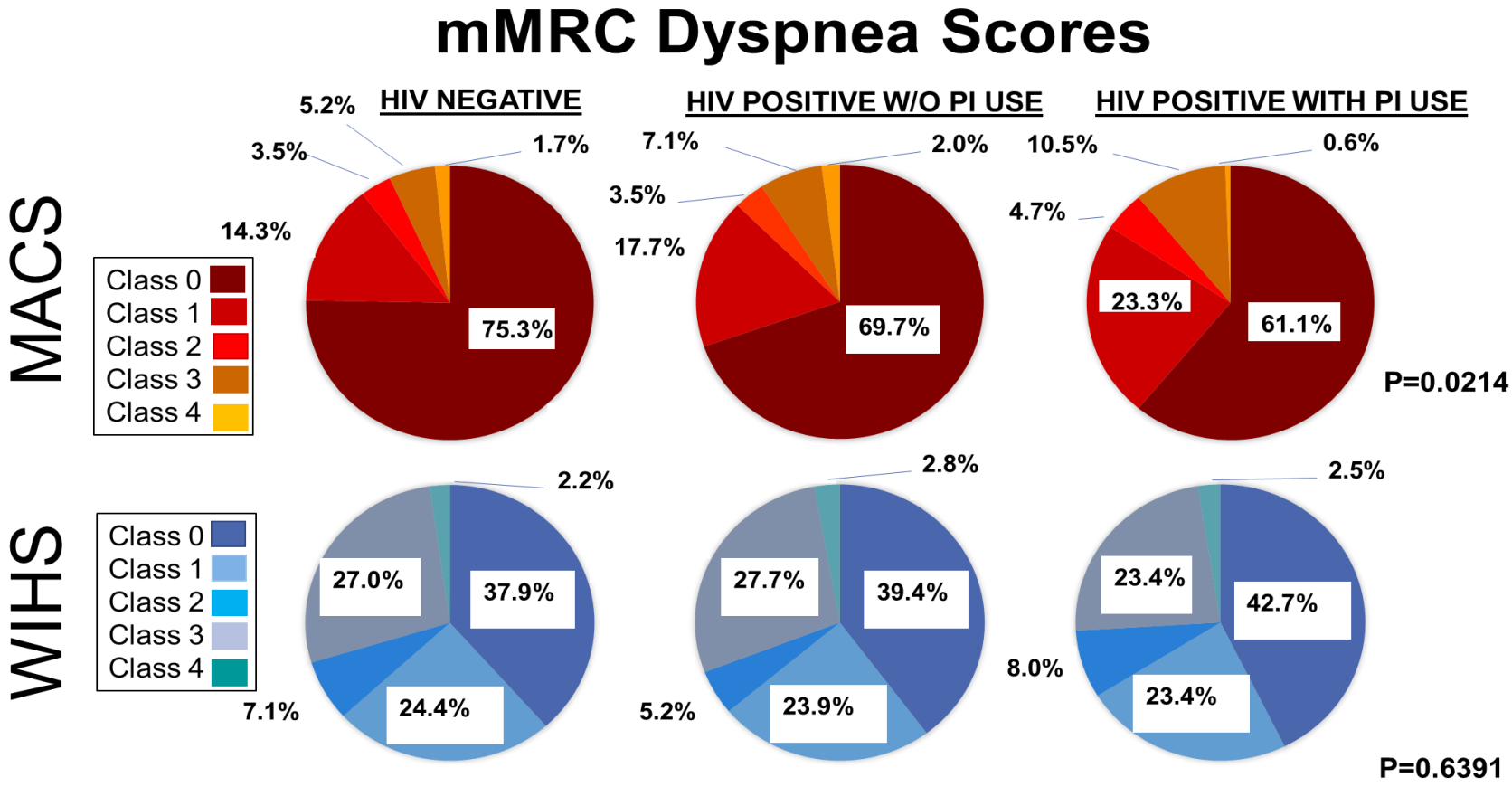


Figure 7. mMRC Dyspnea Scale Scores in the MACS and WIHS Cohorts. A higher proportion of participants in the MACS cohort in the HIV-seropositive PI-user group report an elevated mMRC dyspnea score. Among the WIHS cohorts there are no significant differences in dyspnea scores but they are all significantly elevated.

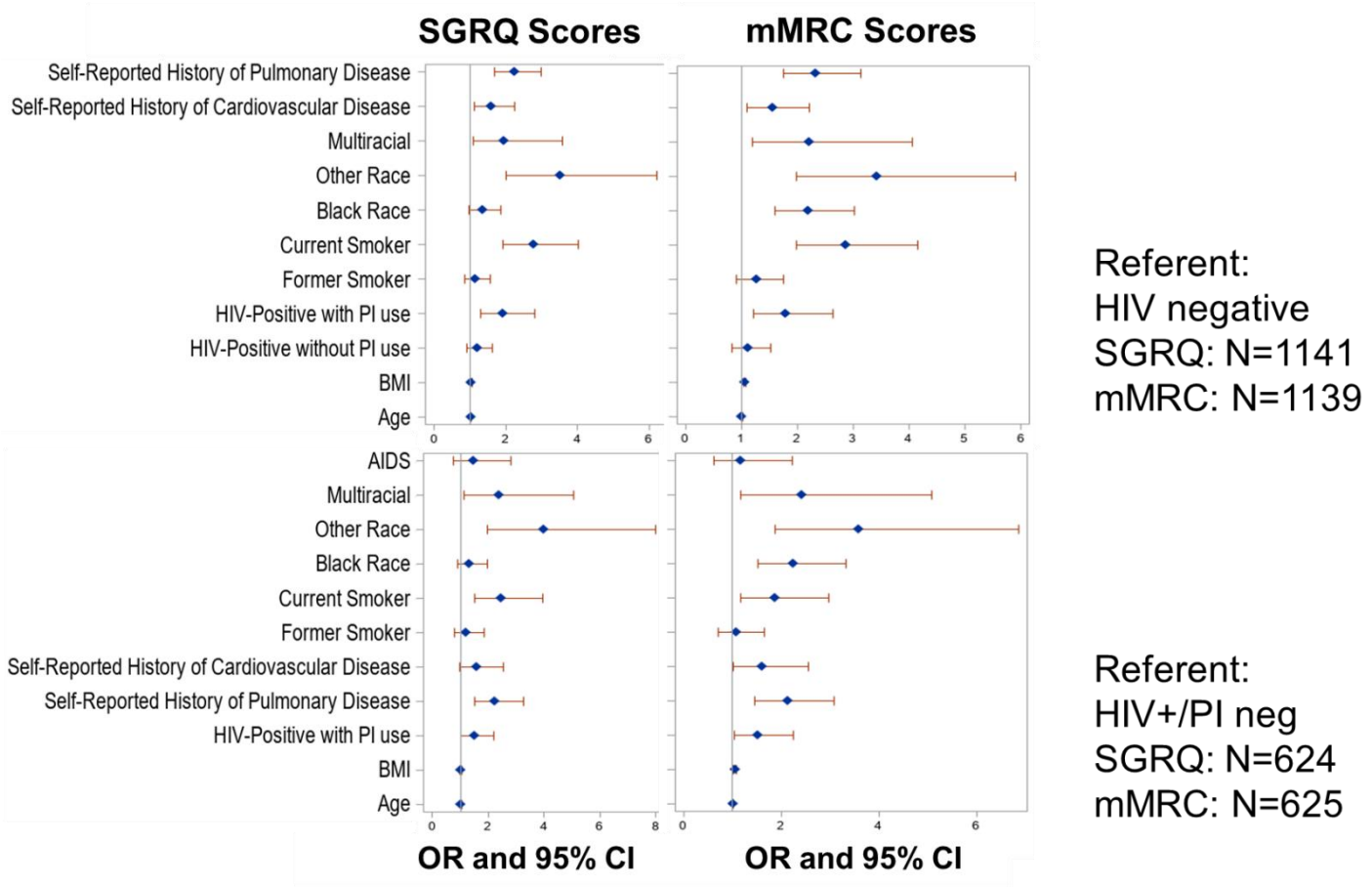


Figure 8.MACS Multivariable Ordinal and Binary mMRC and SGRQ Models. Forest plots for SGRQ and mMRC logistic models and covariables are listed for each model with the respective referent group for each model displayed on the right. Each model found significant associations with PI use and higher mMRC scores and SGRQ scores.

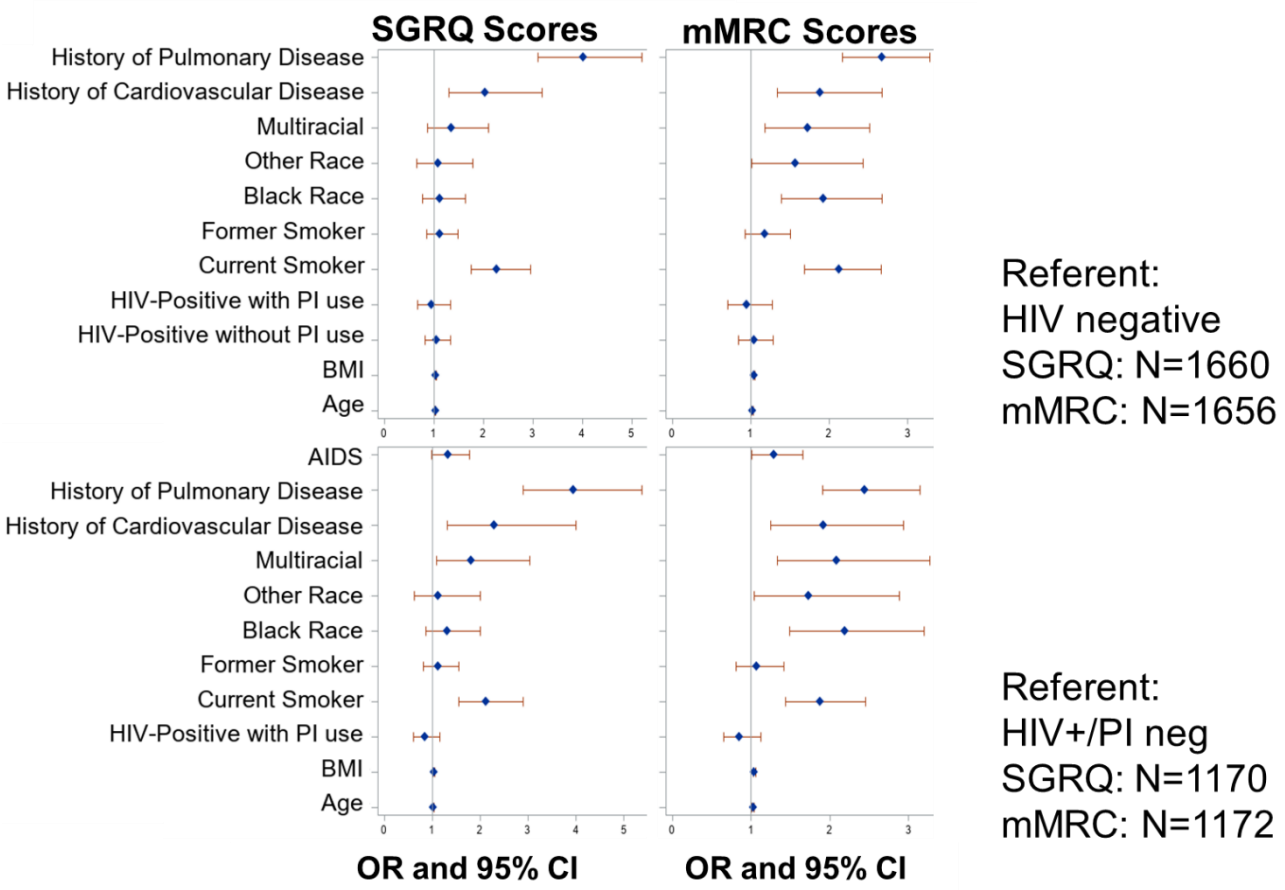


Figure 9. WIHS Multivariable Ordinal and Binary mMRC and SGRQ Models. Forest plots for SGRQ and mMRC logistic models and covariables are listed for each model with the respective referent group for each model displayed on the right. Each model found significant associations with PI use and higher mMRC scores and SGRQ scores.