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Pulmonary function in an international sample of HIV-positive, treatment-naïve adults with CD4 counts >500 cells/μL: a substudy of the INSIGHT Strategic Timing of AntiRetroviral Treatment trial

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Abstract

Objectives—To describe the prevalence and correlates of chronic obstructive pulmonary disease (COPD) in a multicentre international cohort of persons living with HIV (PLWH).

Methods—We performed a cross-sectional analysis of adult PLWH, naïve to HIV treatment, with baseline CD4 cell count >500 cells/μL enrolled in the Pulmonary Substudy of the Strategic Timing of AntiRetroviral Treatment trial. We collected standardised, quality-controlled spirometry. COPD was defined as forced expiratory volume in one second/forced vital capacity (FEV_1/FVC) ratio less than the lower limit of normal.

Results—Among 1026 participants from 80 sites and 20 countries, median (IQR) age was 36 (30, 44) years, 29% were female, and time since HIV diagnosis was 1.2 (0.4, 3.5) years. Baseline

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Author contributions:

KMK, DENiewoehner, and JEC were responsible for study conceptualisation.
KMK wrote the manuscript.
GC and JEC performed the primary statistical analysis.
KMK, DENiewoehner, JEC, DENixon, and ET designed the study.
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CD4 cell count was 648 (583, 767) cells/μL, viral load was 4.2 (3.5, 4.7) $\log_{10}$ copies/mL, and 10% had viral load ≤400 copies/mL despite lack of HIV treatment. Current/former/never smokers comprised 28%/11%/61% of the cohort, respectively. COPD was present in 6.8% of participants, and varied by age, smoking status, and region. 48% of those with COPD reported lifelong nonsmoking. In multivariable regression, age and pack-years of smoking had the strongest associations with FEV_1/FVC ratio ($p<0.0001$). There were significant differences between the effect of region on FEV_1/FVC ratio ($p=0.010$).

Conclusions—Our data suggest that among PLWH, naïve to HIV treatment and with CD4 cell count >500 cells/μL, smoking and age are important factors related to COPD. Smoking cessation should remain a high global priority for clinical care and research in PLWH.

Keywords

HIV; pulmonary disease; spirometry; smoking; START trial

INTRODUCTION

Emerging data in the era of effective antiretroviral treatment (ART) suggest that pulmonary complications of HIV are common, especially chronic obstructive pulmonary disease (COPD) (1). COPD is a major global health problem, being the third leading cause of death and fifth leading cause of disability in 2010 (2, 3). Although the most common cause of COPD is cigarette smoking, and smoking rates are often high in populations of persons living with HIV (PLWH), studies have consistently identified HIV infection as an independent risk factor for COPD, even when adjusted for smoking (4–7). The mechanism explaining how HIV infection increases COPD risk is not clear, but hypotheses include frequent respiratory infections, alterations in the lung microbiota, pulmonary inflammation (including alveolar CD8 T-cell recruitment and local upregulation of matrix metalloproteinase expression from HIV infection of alveolar macrophages) and oxidative stress (1, 8–10).

The role of ART as a factor in HIV-associated COPD is unclear, as existing studies disagree. Two studies implicated ART as associated with an increased risk of COPD (11,12), another study showed a lower incidence of COPD among ART users versus non-users (5), and others showed no association (6,13,14). In these studies, ART use might be confounded by other factors such as socioeconomic status and adherence to therapy (e.g., PLWH of low socioeconomic status may have difficulty accessing ART, and prescribers may be less willing to offer ART to those who are not likely to adhere).

To address this important knowledge gap, we are conducting a nested pulmonary substudy in the Strategic Timing of AntiRetroviral Treatment (START) trial to determine whether ART initiated at CD4 cell counts >500 cells/μL, compared with deferred ART to 350 cells/μL, slows decline in lung function among HIV-positive persons. The substudy also provides novel information about lung function in HIV patients from low-income countries. Current lung function data in HIV have exclusively come from North American or European cohorts, with no published data from other regions of the world where HIV infection is

highly prevalent, such as Africa and Asia. Here, we report on baseline spirometry data collected from around the world in the START Pulmonary Substudy.

METHODS

The design and methods of the START trial have been previously published (15). All substudy participants provided additional informed consent specific to their substudy participation and all site institutional review boards/ethics committees approved the substudy. We selected substudy sites on the basis of their interest and ability to participate. We set no specific criteria for regional distribution of sites. Initial recruitment began at 36 sites during the pilot phase of the main START trial, and we added 44 sites during the definitive expansion phase of START.

Pulmonary Substudy Inclusion and Exclusion Criteria

In addition to the entry criteria for the START trial, additional pulmonary substudy criteria included the requirement that participants be ≥25 years old, the age at which lung function, the primary outcome, begins to decline in most normal adults. Additional exclusion criteria were directed towards spirometry accuracy and safety and included: 1) an episode of respiratory illness with two or more symptoms of cough, wheezing, breathlessness, or increase in sputum production within the six weeks before baseline spirometry; 2) use of asthma medications (bronchodilator, inhaled corticosteroid, leukotriene inhibitor, or theophylline) for two or more consecutive weeks within the six months before baseline spirometry; 3) relative contraindications to spirometry, such as chest, abdominal, or eye surgery within the three months before baseline spirometry, or known retinal detachment at the time of baseline spirometry; 4) known allergy to albuterol/salbutamol, relative contraindications to albuterol/salbutamol, such as resting heart rate of >110 beats per minute, and 5) a known serious or recurrent or uncontrolled cardiac condition (such as unstable coronary artery disease, decompensated heart failure, or recurrent tachyarrhythmias).

Spirometry methods

Sites performed spirometry using the EasyOne ultrasonic flow device (ndd Medical, Zurich, Switzerland). Sites calibrated the device on the day of spirometry, using a standardised 3L calibration syringe (Hans Rudolph, Inc., Shawnee, Kansas, United States) to confirm device volume measurement to within ±3% accuracy. Participants inhaled 180 mcg of albuterol/salbutamol via a metered dose inhaler, then performed spirometry at least 15 minutes later.

Participants performed spirometry while seated, using a noseclip, with ndd brand spirettes™. Per American Thoracic Society (ATS)/European Respiratory Society (ERS) standards, participants performed at least three and no more than eight maneuvers. The EasyOne device automatically generates a suggested quality grade, with a grade of “A” and “B” both meeting the most updated ATS/ERS 2005 spirometry standards, which include the requirement that the two best measurements of both forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) be reproducible to within 150 mL of each other (16). A grade of “C” meets the older ATS 1994 standards, where FEV_1 and FVC

reproducibility had to be within 200 mL of each other (17). A grade of “D” or “F” did not meet accepted quality standards. The substudy goal was to achieve a grade of “A” or “B,” although we considered a grade of “C” acceptable.

Site staff training included formal didactic education and hands-on spirometry training. Due to the large numbers and global distribution of sites, we employed a train-the-trainer model. A core group of expert trainers was centrally trained in the United States by the study chair (author Ken Kunisaki), and these trainers returned to their home regions and trained technicians. When possible, the study chair also participated in regional training sessions. Once training was completed, technicians submitted spirometry tracings for study chair review for certification. Following certification, technicians also participated in a spirometry skill maintenance program and were asked to submit monthly spirometry tracings performed on spirometry-naïve volunteers.

Printed spirometry tracings were submitted to the INSIGHT Statistical and Data Management Center, where the study chair performed quality control review. If a device-assigned value for FEV_1, FVC, reproducibility, or quality grade was determined to be incorrect, corrected final values were assigned in the study database. The study chair provided written feedback to the study technician on every tracing and requested repeat spirometry in cases of unacceptable quality. In this analysis, we report baseline spirometry data only for tests with final grades of “A,” “B,” and “C,” as determined after study chair quality control review.

We used Global Lung Function Initiative (GLI) 2012 normative equations to determine predicted FEV_1, predicted FVC, and lower limit of normal (LLN) (i.e., fifth percentile) of FEV_1/FVC ratio (18). The GLI group pooled spirometry data collected from over 74,000 healthy individuals around the world to derive predictive equations that account for an individual’s age, height, gender, and ethnicity. GLI ethnic categories include Caucasian, African-American, South East Asian, North East Asian, and other. Of the countries and participants in the START Pulmonary Substudy, none were from the North East Asian region. GLI notably lacked data from Sub-Saharan Africa and India. We therefore analysed African blacks and non-African blacks in the African-American category; Indians were analysed in the “other” category. GLI also had no data from Peru and Argentina, but other Latin-American data (Brazil, Chile, Uruguay, Venezuela) led to Latin-Americans being classified as Caucasians, so we chose to include participants from Peru and Argentina as Caucasians for purposes of GLI predictive equations. There were no GLI data from Morocco, but data from Algeria and Tunisia led to North Africans being classified as Caucasians, so we chose to include participants from Morocco as Caucasians for purposes of GLI predictive equations.

Other data collection

Site staff also asked participants specific questions related to tobacco use to assess current and former cigarette use. We defined current smokers as having smoked more than 10 cigarettes in the past 30 days. We defined lifelong nonsmokers as having reported smoking less than 120 cigarettes in their lifetime. We calculated smoking pack-years as: (average number of cigarettes per day/20) x (number of years smoked). We also collected data about

noncigarette tobacco use, but only six participants reported exclusive use of cigarillos (n=2), cigars (n=2) or pipes (n=2).

Statistical analysis

Descriptive statistics of the cohort are means ± standard deviation or median (interquartile range) as appropriate. Statistical significance tests included t-tests, nonparametric tests, or chi-square tests as appropriate.

COPD is commonly defined using one of two definitions: 1) FEV_1/FVC ratio <0.70 or 2) FEV_1/FVC ratio <lower limit of normal (LLN), defined as being <5th percentile of a normal adult population, adjusted for age, height, gender, and ethnicity. There is disagreement about which definition is preferable, but the fixed ratio (i.e., ratio <0.70) definition tends to underdiagnose COPD at young ages and overdiagnose COPD at older ages. Given the young age of the START cohort, we used the LLN definition as our primary COPD definition, but we present data using both definitions. We classified COPD severity according to Global Initiative for Chronic Obstructive Lung Disease criteria of mild (FEV_1 ≥80% of predicted normal), moderate (FEV_1 between 50% to <80% of predicted), severe (FEV_1 between 30% and <50% of predicted), and very severe (FEV_1 <30% of predicted) (19).

We additionally performed multivariable linear regression analysis, using FEV_1/FVC ratio as the dependent variable and region, age, height, gender, ethnicity, and pack-years of smoking as independent variables.

The sample size of the substudy was determined based on the planned prospective randomised comparison of rate of FEV_1 decline between the immediate and deferred ART arms of START. Due to the strong effects of smoking on FEV_1 decline, we preplanned separate analyses for smokers and nonsmokers. Assumptions of the sample size determination included a standard deviation for rate of FEV_1 decline of 60 mL/year, a minimal clinically important difference of 15.5 mL/year in nonsmokers and 19.0 mL/year in smokers, a two-tailed alpha error rate of 0.05, and a desired power of 0.85. This resulted in a target sample size of 580 non-smokers and 332 smokers (total sample size was increased to 1,000 to allow for 10% study withdrawals and losses to follow-up).

RESULTS

The substudy enrolled 1026 participants from 80 sites in 20 countries between March 2010 and September 2013. Substudy participants were similar to the main START trial participants with respect to age, gender, CD4, HIV RNA, BMI, and comorbidities. Compared to the main START trial, the substudy had a higher percentage of participants from African sites. Substudy participants were also more likely to be female, have acquired HIV via heterosexual contact, and less likely to be current smokers.

The region with highest enrolment was Africa (n=328), followed by Europe/Israel/Australia (n=313), Mexico/South America (n=191), Asia (n=103), and the United States (n=91) (Table 1). Overall, pulmonary substudy participants had a median age of 36 years, and 29.1% were female. Most reported HIV acquisition via sexual contact (49.2% men who

have sex with men, 43.9% heterosexual contact), and median time since HIV diagnosis of 1.2 years. Median baseline CD4 cell count was 648 cells/μL, median viral load was 4.2 $\log_{10}$ copies/mL, and 9.5% had suppressed viral load (≤400 copies/mL) despite lack of ART use. Current/former/never smokers comprised 28.3%/10.8%/60.9% of the cohort, respectively, and the most common comorbidity was hypertension (18.7%).

There were significant regional differences in many baseline demographic characteristics (Table 1). For example, of the 299 women in the study, 211 came from sites in Africa; of the 290 current smokers, only 66 came from sites in Africa and Asia. The proportion of men who reported having sex with men was over 70% in Europe/Israel/Australia, Mexico/South America, and the Unites States, was 57.3% in Asia, but only 1.5% in Africa.

Spirometry was obtained in 1025 participants (99.9%) and overall quality was very good: 775 (75.6%) spirometry tests met ATS/ERS 2005 criteria (grade “A” or “B”) and 214 (20.9%) met ATS 1994 criteria (grade “C”). Thirty-six (3.5%) failed to meet quality standards.

Of the 989 high-quality spirometry tests, evidence of COPD, as defined by the LLN for the FEV_1/FVC ratio, was present in 6.8% of this cohort, with regional variation ranging from 2.0% in Asia to 9.1% in Europe/Israel/Australia (p=0.033) (Table 2). Participants with COPD generally had mild or moderate airflow obstruction, with 52.2% having an FEV_1 >80% of predicted, 43.3% having an FEV_1 between 50%–80% of predicted, 4.5% demonstrating an FEV_1<50% of predicted and none with an FEV_1 <30% of predicted. The prevalence of COPD varied by smoking status with COPD demonstrated in 11.7% of current smokers, 2.8% of former smokers, and 5.3% of never smokers (p<0.001) (Table 3). The prevalence of COPD also increased with age quartiles, from 3.9% (≤30 years) to 6.7% (31–36 years) to 7.6% (37–44 years) to 9.1% (>44 years), but was not statistically significant (p=0.14) (Table 3). COPD prevalence did not differ between women (6.2%) and men (7.0%) (p=0.63).

Comparing those with and without COPD, participants with COPD were a median of three years older (p=0.07) and had a higher proportion of current smokers (47.8% vs. 26.1%; p<0.001). Among those with COPD, while 47.8% were current smokers, the exact same proportion (47.8%) reported lifelong nonsmoking, and the median pack-year burden of smoking in those with COPD was 0.8 pack-years. There was no difference in HIV factors such as current/nadir CD4, CD4/CD8 ratio, CD8, viral load, or years since HIV diagnosis between those with and without COPD (all p-values >0.30).

Data regarding varying COPD prevalence by region, smoking status, and age were similar when using a fixed-ratio definition of COPD, although the fixed ratio definition showed a statistically stronger difference in COPD prevalence by age quartiles (p <0.001).

In multivariable linear regression analysis, increasing age and increasing pack-years of smoking were strong independent correlates of lower FEV_1/FVC ratio (Table 4). Height, white race, and region were also independently associated with FEV_1/FVC ratio. Black race and gender had no significant association with FEV_1/FVC ratio. There were significant differences between the effect of region on FEV_1/FVC ratio (p=0.011).

DISCUSSION

In our large, multisite, international cohort of mostly recently diagnosed PLWH, naïve to ART with CD4 cell count >500 cells/μL, we found an overall spirometry-confirmed prevalence of COPD of 6.8%. Importantly, smoking status had a substantial association with COPD prevalence, with current smokers demonstrating a COPD prevalence of nearly 12%. Regression analysis also identified increasing cumulative pack-years of smoking as an independent predictor of lower FEV_1/FVC ratio. These data continue to support strongly the need for continued focus on smoking cessation in PLWH.

Our finding that 6.8% of our overall cohort has COPD is within the range reported by other studies. Published data regarding spirometry in PLWH in the current ART era come from nine studies from six countries (Table 5). The four studies from the United States demonstrated COPD prevalence ranging from 7% to 21% in studies with samples ranging from n=98 to n=316. COPD prevalence in PLWH in other countries has been reported as 23% in Italy (n=106), 19% in Denmark (n=63), 17% in Spain (n=275), 10% in Japan (n= 49), and 3% in Canada (n=119). This wide heterogeneity in regional COPD prevalence may be partially due to differing characteristics of each cohort. All previously reported studies have been single-centre studies and may therefore not fully reflect clinical characteristics of PLWH globally. Even within a single city or country, PLWH seeking care at one hospital or clinic may be very different from PLWH in the wider city or country. For example, although the COPD prevalence reported in the cohort study from Baltimore, Maryland, United States was 17% (13), this cohort was selected on the basis of a history of injecting drug use, perhaps explaining the very high prevalence (94%) of current or former smoking. Therefore, while that cohort has provided important data regarding COPD in PLWH, extrapolating these single-centre data to the larger population of PLWH globally, in the United States, or even within Baltimore, should be done cautiously.

Compared to the existing studies, our cohort was not only the largest and included the most study sites and countries, but also had the youngest age and were ART naïve and therefore not subject to potential pulmonary effects of ART. Therefore, while our COPD prevalence estimate was on the lower end of those reported by other studies, we enrolled a young cohort of PLWH with relatively recent diagnosis of HIV infection. Our regression analysis showed a significant independent relationship between increasing age and lower FEV_1/FVC ratio, reinforcing the notion that as more PLWH age, COPD is likely to begin to emerge as a major comorbidity.

A major strength of our study was the inclusion of many sites across many regions of the world. We found significant regional differences in COPD prevalence. Some of this may be explained by differences in smoking rates (e.g., 19% current smokers in Asia compared to 45% in Europe/Israel/Australia). However, Africa had the lowest prevalence of current smokers (14%), yet had higher COPD prevalence than regions with more smokers, such as Asia and Mexico/South America. Regional differences persisted after adjustment for smoking status and other COPD risk factors in regression analysis. Among those with COPD, a high proportion (48%) also reported being lifelong nonsmokers. These data

suggest that other nontobacco exposures may be playing a role in COPD pathogenesis in this population.

Indoor air pollution is a common cause of COPD (20), and use of biomass fuels to heat the home and cook inside the home may contribute to a significant proportion of COPD in our participants, particularly those from Africa. Our study was not designed to address the topic of indoor air pollution or air quality, so we did not collect baseline information on these factors. Among the participants enrolled from Africa, 64% were women. Women traditionally have more biomass smoke exposure, due to women often performing more indoor labor than men, and some data also suggest that women are more susceptible to COPD than men (21). We found no difference in COPD prevalence by gender, but because 71% of our female sample was recruited from African sites, analyses of gender in our cohort are also significantly influenced by region.

Our primary definition of COPD has limitations. We used the common LLN definition of COPD, which assigns a COPD diagnosis when airflow obstruction (FEV_1/FVC ratio) is lower than the fifth percentile of predicted FEV_1/FVC ratio. Predicted FEV_1/FVC ratio is typically related to factors such as age, height, gender, and ethnicity. International studies have faced challenges due to predictive equations coming from samples with limited ethnic representation. However, we used newly available GLI equations to determine the fifth percentile (18). The GLI project pooled international data to derive unifying prediction equations for spirometry interpretation. Therefore, our lung function measures are based on the best available data for international studies. GLI did not have adequate data from Africa and India, so we can't determine how applicable our definitions are to those regions. The GLI project noted little ethnic variation in FEV_1/FVC ratio, suggesting that ethnicity does not affect our COPD prevalence estimates, but without further data from African and Indian samples, the true LLN in persons from these countries remains unclear.

One advantage of the LLN definition relates to our analysis of COPD by age quartile. The fixed-ratio definition would naturally be expected to show more COPD in older groups, due to normal age-related decline in FEV_1/FVC ratio. Our data in Table 3 exemplify this, where a fixed-ratio definition shows a stronger age-related increase in COPD compared to a LLN definition that adjusts for the effect of normal aging. The LLN definition showed a statistically insignificant difference in COPD prevalence by age (p=0.14), although there did appear to be a trend for higher COPD prevalence with each increase in age quartile.

Although our point estimate of COPD prevalence varied by which COPD definition we used, COPD was generally quite mild, with most FEV_1 values being generally only mildly impaired (FEV_1 ≥80% of predicted). This was also not surprising, given the young age of our study sample. Some data do suggest that PLWH lose lung function faster than predicted by aging alone (13, 22) and one small cohort study (n=63) in Denmark showed that an initial prevalence of COPD of 10% had increased to 19% at a median of 4.4 years of follow-up (23). Such data raise concerns that as PLWH continue to age, COPD may begin to emerge as a major comorbidity, with its attendant impact on quality of life and mortality (2,3). Our longitudinal follow-up, with each person serving as his or her own control, will provide a better study design to understand the effect of aging on COPD prevalence in PLWH.

CONCLUSION

In our novel international spirometry study of relatively young PLWH with CD4 cell count >500 cells/μL and naïve to ART, overall COPD prevalence was 6.8%. COPD prevalence varied substantially across global regions, as did demographics such as gender and smoking behaviour. Our data suggest that smoking and age are important factors related to COPD in PLWH. Smoking cessation should remain a high priority for clinical care and research in PLWH.

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TABLE 1

Baseline characteristics of START Pulmonary Substudy participants by region

	Total	Africa	Asia	Europe/Israel/Australia	Mexico/South America	United States
	1026 (100.0%)	328 (32.0%)	103 (10.0%)	313 (30.5%)	191 (18.6%)	91 (8.9%)
Demographics						
Age (years)	36 (30, 44)	37 (32, 44)	36 (30, 41)	38 (31, 45)	34 (29, 40)	36 (29, 47)
Female	299 (29.1%)	211 (64.3%)	27 (26.2%)	26 (8.3%)	26 (13.6%)	9 (9.9%)
Race						
Black	387 (37.7%)	321 (97.9%)	0 (0.0%)	22 (7.0%)	0 (0.0%)	44 (48.4%)
Latino/Hispanic	179 (17.4%)	0 (0.0%)	0 (0.0%)	14 (4.5%)	153 (80.1%)	12 (13.2%)
Asian	105 (10.2%)	0 (0.0%)	101 (98.1%)	1 (0.3%)	0 (0.0%)	3 (3.3%)
White	344 (33.5%)	6 (1.8%)	1 (1.0%)	268 (85.6%)	38 (19.9%)	31 (34.1%)
Other	11 (1.1%)	1 (0.3%)	1 (1.0%)	8 (2.6%)	0 (0.0%)	1 (1.1%)
HIV Factors						
Likely mode of HIV infection						
Injecting drug use	14 (1.4%)	0 (0.0%)	1 (1.0%)	5 (1.6%)	2 (1.0%)	6 (6.6%)
Male sexual contact with person of same sex	505 (49.2%)	5 (1.5%)	59 (57.3%)	238 (76.0%)	138 (72.3%)	65 (71.4%)
Sexual contact with person of opposite sex	450 (43.9%)	306 (93.3%)	34 (33.0%)	46 (14.7%)	46 (24.1%)	18 (19.8%)
Other/unknown	57 (5.6%)	17 (5.2%)	9 (8.7%)	24 (7.7%)	5 (2.6%)	2 (2.2%)
Time since first HIV diagnosis, years	1.2 (0.4, 3.5)	1.5 (0.5, 4.8)	0.8 (0.2, 3.4)	1.2 (0.5, 3.5)	0.6 (0.3, 2.2)	1.5 (0.4, 4.6)
CD4 cell count (cells/μL)	648 (583, 767)	695 (603, 814)	618 (561, 728)	634 (581, 738)	632 (574, 718)	674 (582, 773)
CD8 cell count (cells/μL)	1019 (758, 1394)	922 (692, 1275)	1079 (805, 1452)	1069 (800, 1547)	1023 (770, 1383)	959 (765, 1400)
CD4/CD8 ratio	0.66 (0.48, 0.94)	0.79 (0.56, 1.06)	0.58 (0.44, 0.81)	0.62 (0.44, 0.81)	0.63 (0.45, 0.91)	0.66 (0.51, 0.99)
Nadir CD4 (cells/μL)	552 (486, 661)	605 (519, 740)	542 (477, 618)	524 (452, 608)	545 (492, 630)	564 (479, 688)
Log_{10} HIV RNA (copies/mL)	4.2 (3.5, 4.7)	3.8 (3.0, 4.6)	4.5 (3.9, 4.9)	4.3 (3.8, 4.7)	4.4 (3.9, 4.8)	3.9 (3.3, 4.5)
HIV RNA ≤ 400 copies/mL	97 (9.5%)	62 (19.0%)	6 (5.9%)	9 (2.9%)	9 (4.7%)	11 (12.1%)
Medical History						
Body mass index, kg/m^2	24.8 (22.2, 28.4)	25.7 (22.2, 31.8)	22.8 (20.7, 25.7)	23.8 (22.2, 26.6)	25.5 (23.2, 28.2)	26.5 (23.1, 30.7)
Prior cardiovascular disease	7 (0.7%)	0 (0.0%)	1 (1.0%)	3 (1.0%)	1 (0.5%)	2 (2.2%)

	Total	Africa	Asia	Europe/Israel/Australia	Mexico/South America	United States
Hypertension	192 (18.7%)	65 (19.8%)	9 (8.7%)	73 (23.3%)	17 (8.9%)	28 (30.8%)
Diabetes	37 (3.6%)	20 (6.1%)	2 (1.9%)	5 (1.6%)	6 (3.1%)	4 (4.4%)
Hepatitis B or C	72 (7.1%)	22 (6.7%)	10 (9.7%)	23 (7.5%)	12 (6.3%)	5 (5.6%)
Osteoporosis	2 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (1.1%)
Smoking status						
Current smoker	290 (28.3%)	46 (14.0%)	20 (19.4%)	140 (44.7%)	54 (28.3%)	30 (33.0%)
Former smoker	111 (10.8%)	19 (5.8%)	11 (10.7%)	42 (13.4%)	27 (14.1%)	12 (13.2%)
Never smoker	625 (60.9%)	263 (80.2%)	72 (69.9%)	131 (41.9%)	110 (57.6%)	49 (53.8%)
Pack years smoking (current and former smokers only)	6.0 (2.0, 15.0)	2.5 (1.2, 5.0)	4.3 (1.2, 9.5)	10.0 (5.0, 20.0)	4.3 (1.0, 10.5)	4.6 (1.5, 12.0)

Data shown as n(%) or median (interquartile range).

Prior cardiovascular disease = history of stroke, myocardial infarction, or coronary revascularisation.

Hypertension= use of blood pressure-lowering medications, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg

Diabetes= prior diagnosis of diabetes, use of diabetes medication, or fasting baseline glucose ≥126 mg/dL.

Hepatitis B = positive Hepatitis B surface antigen test in the year prior to randomisation

Hepatitis C = positive Hepatitis C core antibody test any time prior to randomisation

Osteoporosis= prior diagnosis of osteoporosis or use of osteoporosis medication

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TABLE 2

Spirometry results and comparison of chronic obstructive pulmonary disease (COPD) prevalence/severity by region.

	Total (n=989)	Africa (n=322)	Asia (n=102)	Europe/Israel/Australia (n=298)	Mexico/South America (n=182)	USA (n=85)	p-values
FEV_1 %predicted	96.2 (85.4, 103.8)	96.1 (84.2, 104.9)	91.2 (81.4, 100.0)	96.0 (87.0, 103.9)	100.1 (91.8, 105.3)	90.0 (82.1, 101.7)	-
FEV_1/FVC ratio	0.83 (0.78, 0.86)	0.83 (0.78, 0.86)	0.87 (0.84, 0.89)	0.80 (0.76, 0.85)	0.84 (0.81, 0.86)	0.83 (0.79, 0.86)	-
FEV_1/FVC <LLN	67 (6.8%)	25 (7.8%)	2 (2.0%)	27 (9.1%)	6 (3.3%)	7 (8.2%)	p=0.033
FEV_1 ≥80% predicted	35 (52.2%)	10 (40.0%)	2 (100.0%)	18 (66.7%)	4 (66.7%)	1 (14.3%)	-
FEV_1 50%–79% predicted	29 (43.3%)	15 (60.0%)	0 (0.0%)	7 (25.9%)	2 (33.3%)	5 (71.4%)	-
FEV_1 30%–49% predicted	3 (4.5%)	0 (0.0%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	1 (14.3%)	-
FEV_1 <30% predicted	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-
FEV_1/FVC <0.70	54 (5.5%)	16 (5.0%)	0 (0.0%)	27 (9.1%)	5 (2.7%)	6 (7.1%)	p=0.002
FEV_1 ≥80% predicted	26 (48.1%)	4 (25.0%)	0 (0.0%)	18 (66.7%)	3 (60.0%)	1 (16.7%)	-
FEV_1 50%–79% predicted	25 (46.3%)	12 (75.0%)	0 (0.0%)	7 (25.9%)	2 (40.0%)	4 (66.7%)	-
FEV_1 30–49% predicted	3 (5.6%)	0 (0.0%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	1 (16.7%)	-
FEV_1 <30% predicted	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-

Data shown as n(%) or median (interquartile range). The primary COPD definition was FEV_1/FVC <lower limit of normal (LLN) by Global Lung Function Initiative prediction equations; the secondary COPD definition was FEV_1/FVC <0.70. FEV_1 % predicted was calculated using Global Lung Function Initiative prediction equations. p-values were calculated by chi-square test.

TABLE 3

Prevalence of chronic obstructive pulmonary disease (COPD) overall, by smoking status and by age quartiles.

	Total	**FEV_1/FVC <LLN**	**FEV_1/FVC <0.70**
Overall cohort	989 (100%)	67 (6.8%)	54 (5.5%)
Smoking status			
Current	273 (27.6%)	32 (11.7%)	28 (10.3%)
Former	109 (11.0%)	3 (2.8%)	4 (3.7%)
Never	607 (61.4%)	32 (5.3%)	22 (3.6%)
p-value	-	<0.001	<0.001
Age (years) quartile			
25 – 30	254 (25.7%)	10 (3.9%)	4 (1.6%)
31 – 36	255 (25.8%)	17 (6.7%)	13 (5.1%)
37 – 44	250 (25.3%)	19 (7.6%)	11 (4.4%)
>44	230 (23.3%)	21 (9.1%)	26 (11.3%)
p-value	-	0.14	<0.001

Data shown as n(%). The primary COPD definition was FEV_1/FVC <lower limit of normal (LLN) by Global Lung Function Initiative prediction equations; the secondary COPD definition was FEV_1/FVC <0.70. p-values were calculated by chi-square test.

TABLE 4

Multivariable linear regression analysis, with FEV_1/FVC ratio as dependent variable.

Variable	Coefficient	Standard Error	p-value
Age, per 10 years	−0.021	0.002	<0.001
Pack-years of smoking, per 10 pack-years	−0.007	0.002	<0.001
Height, per 6 inches	−0.009	0.004	0.03
Female gender	0.008	0.006	0.18
Region*			0.01
North America	−0.018	0.011	0.11
South America	−0.024	0.007	0.001
Europe/Israel/Australia	−0.023	0.010	0.02
Africa	−0.030	0.012	0.01
Race**			
White	−0.024	0.008	0.002
Black	−0.015	0.010	0.16

*Referent region: Asia

**Referent race: Other (Asian, Latino/Hispanic, and Other)

TABLE 5

Summary of regional chronic obstructive pulmonary disease (COPD) prevalence estimates among persons living with HIV in the highly active antiretroviral therapy era.

Study	Country	Sample size (n)	Sites (n)	Age, yrs	Female, %	ART use, %	Years of known HIV	Current smoker, %	Former smoker, %	COPD prevalence, %
Drummond 2013(13)	USA	316	1	48.0 ± 6.5	34.2%	55.0%	nr	84.2%	9.5%	16.5% (fixed ratio)
George 2009(11)	USA	234	1	44.1 ± 9.4	17.5%	83.3%	8–10 (IQR nr)	37.1%	22.6%	6.8% (fixed ratio) 8.6% (LLN)
Gingo 2010(12)	USA	167	1	46 (IQR nr)	26.4%	80.7%	13.0 (IQR nr)	52.7%	23.4%	21.0% (fixed ratio) 19% (LLN)
Hirani 2011(24)	USA	98	1	44.8 ± 11.2	16.3%	87.7%	8.3 ± 6.5	21.0%	34.0%	16.3% (fixed ratio)*
Samperiz 2013(25)	Spain	275	1	48.6 ± 6.6	21.8%	95.6%	11.9 ± 5.4	61.5%	25.1%	17.2% (fixed ratio)
Cui 2010(26)	Canada	119	1	43.4 ± 8.4	21.0%	84.0%	9.0 ± 6.6	43.7%	19.3%	3.4% (fixed ratio)
Madeddu 2013(14)	Italy	111	1	42.3 ± 8.1	30.6%	78.4%	nr	56.8%	nr	23.4% (fixed ratio)
Kristoffersen 2012(23)	Denmark	63	1	43.3 ± 9.0	11.1%	88.9%	9.3 ± 5.1	47.6%	nr	9.5% (fixed ratio) at baseline; 19.0% at 4.4 year follow-up
Nakamura 2014(7)	Japan	49	1	40 (IQR nr)	0.0%	97.9%	nr	44.9%	16.3%	10.2% (fixed ratio)
START Pulmonary Substudy	Multiple	989	80	36 (30, 44)	29.4%	None	1.2 (0.4, 3.5)	27.5%	11.0%	5.5% (fixed ratio) 6.8% (LLN)
	Africa	322	7	37 (32, 44)	64.0%	“	1.5 (0.5, 4.8)	14.0%	5.9%	5.0% (fixed ratio) 7.8% (LLN)
	Asia	102	8	36 (30, 41)	26.5%	“	0.8 (0.2, 3.4)	19.6%	9.8%	0.0% (fixed ratio) 2.0% (LLN)
	Europe/Israel/Australia	298	35	38 (31, 45)	8.7%	“	1.2 (0.5, 3.5)	44.0%	14.1%	9.1% (fixed ratio) 9.1% (LLN)
	Mexico/S. America	182	10	34 (29, 40)	12.6%	“	0.6 (0.3, 2.0)	26.9%	14.8%	2.7% (fixed ratio) 3.3% (LLN)
	USA	85	20	36 (29, 45)	10.6%	“	1.5 (0.4, 4.6)	32.9%	12.9%	7.1% (fixed ratio) 8.2% (LLN)

*FEV_1/FVC <0.7 and FEV_1 <80% of predicted

ART=antiretroviral therapy, COPD=chronic obstructive pulmonary disease, LLN=lower limit of normal, nr = not reported.

Studies are ordered in decreasing sample sizes of country-level data. Estimates from this current study are shown at the bottom. COPD prevalence reported as both FEV_1/FVC <0.70 (fixed ratio) and FEV_1/FVC <lower limit of normal (LLN). Continuous variables reported as mean ± standard deviation or median (interquartile range).