ORIGINAL RESEARCH

# Prevalence and predictors of airflow obstruction in an HIV tertiary care clinic in Montreal, Canada: a cross-sectional study

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### Objectives

The reported prevalence of chronic obstructive pulmonary disease (COPD) in people living with HIV (PLWHIV) varies widely. Our objective was to estimate the prevalence of airflow obstruction and COPD in unselected PLWHIV and identify characteristics that increase the risk of nonreversible airflow obstruction in order to guide case finding strategies for COPD.

### Methods

All adults attending the Chronic Viral Illness Service were invited to participate in the study, regardless of smoking status or history of known COPD/asthma. Individuals underwent spirometric testing both before and after use of a salbutamol bronchodilator. Airflow obstruction was defined as forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity (FVC) < 0.7 post-bronchodilation, whereas COPD was defined as $FEV_1$/FVC < 0.7 post-bronchodilation and Medical Research Council (MRC) score > 2. Multivariate logistic regression was used to evaluate risk factors associated with airflow obstruction, reported as adjusted odds ratios (aORs).

### Results

Five hundred and three participants successfully completed spirometry testing. The median (Q1; Q3) age was 52 (44; 58) years. The median (Q1; Q3) CD4 count was 598 (438; 784) cells/μL and the median (Q1; Q3) nadir CD4 count was 224 (121; 351) cells/μL. There were 119 (24%) current smokers and 145 (29%) former smokers. Among those screened, 54 (11%) had airflow obstruction whereas three (1%) of the participants had COPD. Factors that were associated with airflow obstruction included a history of smoking [aOR 2.2; 95% confidence interval (CI) 1.1; 4.7], older age (aOR 1.6; 95% CI 1.2; 2.2), and lower CD4 count (aOR 0.8; 95% CI 0.7; 1.0).

### Conclusions

Airflow obstruction was relatively uncommon. Our findings suggest that PLWHIV who are ≥50 years old, smokers and those with nadir CD4 counts ≤ 200 cells/μL could be targeted to undergo spirometry to diagnose chronic airflow obstruction.

**Keywords:** chronic obstructive pulmonary disease, HIV, obstructive lung disease, spirometry, tobacco smoking

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## Introduction

For people living with HIV (PLWHIV) on suppressive combination antiretroviral therapy (cART), prevention of chronic disease is a paramount concern. In the general population, chronic obstructive pulmonary disease (COPD) is a leading cause of death in developed nations and is estimated to be the third leading cause of death world-wide following cardiovascular and cerebrovascular diseases [1,2]. This disorder, comprised of both emphysema and chronic bronchitis, is associated with increased chronic inflammatory responses in the airways and lungs caused by chronic exposure to toxic stimuli [3]. There is progressive airflow obstruction, which results in flow limitation, with exhalation not being completed prior to the next inhalation, leading to hyperinflation and dyspnoea [4].

The prevalence of COPD in PLWHIV varies significantly between studies, depending on the methods used, settings and characteristics of the participants. It has been reported that between 7 and 60% of HIV-infected adults display physiological measures of COPD versus 7% of HIV-uninfected individuals in North America [1,5–9]. When spirometry – the gold standard method for measuring airflow obstruction – is used, the prevalence of COPD in PLWHIV in out-patient settings is lower and ranges from 6 to 21% [7,10–13]. The prevalence of COPD tends to be lower in health administrative data-based studies using International Classification of Diseases (ICD) definitions and in studies using patient-reported criteria [14], highlighting the issue that COPD may go unrecognized by physicians and patients. Although the most significant predictor of COPD in the general population is smoking exposure [3], approximately 25% of individuals with COPD do not have a tobacco smoking history [15]. HIV infection itself has also been suggested to be a risk factor for COPD, independent of tobacco smoking status [10,16].

In contrast with cardiovascular, renal, bone and liver diseases, there are no HIV-specific recommendations for testing for chronic lung disease. This may have important clinical implications as HIV-infected patients with undiagnosed COPD will remain untreated, while recommended therapy could alleviate their symptoms and unrecognized COPD exacerbation events have been shown to contribute much more than previously thought to the overall burden of COPD [17]. The objectives of our study were to estimate the prevalence of airflow obstruction (based on spirometric criteria alone) and COPD (based on both spirometric criteria and symptoms) in unselected PLWHIV and identify risk factors associated with chronic airflow obstruction using spirometry – the gold standard – in order to guide case finding strategies for pulmonary disease in PLWHIV.

## Methods

The Chronic Viral Illness Service (CVIS) is a multidisciplinary clinic focused on the care of individuals living with chronic viral infections, and is located at the McGill University Health Centre (MUHC) in Montreal, Canada. In 2017, there were 1614 patients in active follow-up at the CVIS for either HIV infection alone or HIV infection in addition to another viral coinfection. Between 1 November 2015 and 20 December 2017, consecutive eligible patients were invited to participate in the study. This study was approved by the Research Institute of the McGill University Health Centre (MUHC) Research Ethics Board (MUHC 2016-2356).

### Patient selection

All adult patients under care for HIV infection at the CVIS were offered participation in the study; however, patients who met any of the following criteria were excluded: (1) contraindications to spirometry testing (i.e. recent myocardial infarction or unstable cardiac condition); (2) active pulmonary infection or other acute pulmonary process; (3) neuromuscular disorders; (4) severe scoliosis; (5) thoracotomy, sternotomy or major cardiopulmonary intervention (e.g. open heart surgery) within the previous year; or (6) pregnancy. Patients who did not successfully undergo the spirometry test (i.e. those participants whose spirometry reports were not interpretable) were also excluded from all analyses. There was no age limit to participation.

Charts of all patients eligible to participate in the study were flagged before clinic visits and physicians were asked to mention the study to patients to assess interest. If individuals were not interested in participating, physicians were asked to indicate the reason for not wanting to participate. Participation was entirely voluntary and written informed consent was provided by each patient. Willing participants underwent a spirometry test, conducted by a certified technician or trained research staff, and completed standardized questionnaires at a single study visit. Participants already known to have COPD or asthma were asked not to use their puffers 24 h prior to spirometry testing.

### Spirometry

Spirometry is the gold standard used to quantify airflow obstruction and a requirement to make a diagnosis of COPD. It measures the forced expiratory volume in 1 s ($FEV_1$) and the forced vital capacity (FVC) [3]. We defined airflow obstruction as $FEV_1/FVC < 0.7$ post-bronchodilation

and set airflow obstruction as our primary outcome. We considered participants to have COPD if they met the spirometry criteria and had a Medical Research Council (MRC) score > 2 [18]. Furthermore, participants were classified on the severity of the airflow obstruction, which was assessed based on the $FEV_1$ relative to the predicted value. Specifically, patients with $FEV_1$ < 30% of the predicted value were classified as having very severe obstruction [Global Initiative for Obstructive Lung Disease (GOLD) 4], those with $FEV_1$ < 50% were classified as having severe obstruction (GOLD 3), those with $FEV_1$ < 80% were classified as having moderate obstruction (GOLD 2), and those with $FEV_1$ > 80% were classified as having mild obstruction (GOLD 1) [18]. The reversibility of the airflow obstruction – in patients found to have $FEV_1/FVC$ < 70% both pre- and post-bronchodilation – was assessed based on the change in $FEV_1$ pre- to post-bronchodilation. In order for the airflow obstruction to be considered reversible, an increase in $FEV_1$ of > 200 mL and an increase in $FEV_1$ by 12% were required.

## Clinical, laboratory and questionnaire data

Medical history and HIV-specific characteristics were collected by chart review from the clinic's internal electronic records. Collected data included information on sociodemographics, respiratory health and medication use. Data on tobacco smoking history were collected by questionnaire at the time of spirometry. Data on respiratory symptoms were collected using the Medical Research Council (MRC) dyspnoea scale, with possible scores ranging from 1 (asymptomatic) to 5 (very symptomatic) [19,20], and the St George's Respiratory Questionnaire (SGRQ), with possible scores ranging from 0 (asymptomatic) to 100 (very symptomatic) [19–22]. The SGRQ was used to produce four summary scores: a symptoms score measuring the frequency and severity of respiratory symptoms, an activity score measuring the extent to which day-to-day activities were limited by breathlessness, an impacts score measuring the psychosocial impact of respiratory disease, and a total score combining the three domain scores [21,22]. These scores were computed using the Excel-based scoring calculator distributed by St George's, University of London.

Occupational factors assessed included exposure to flour, feed or grain milling, cotton or jute processing, farming, forestry, saw-milling, coal mining, sandblasting, asbestos exposure, foundry or steel milling, chemical or plastic manufacturing, welding, firefighting, oil drilling, gas well or dust exposure. Environmental factors included using coal or coke on an indoor fire for cooking or heating the home, and using wood, crop residues or dung on an indoor fire for cooking or heating the home. Questions concerning these factors were taken directly from other previously published studies in respiratory journals [23–26].

## Statistical analysis

Unadjusted and adjusted logistic regression models were used to assess the association between HIV-specific characterics and the presence of airflow obstruction. As a consequence of the relatively limited number of study participants and the low prevalence of airflow obstruction, we selected *a priori* only a few covariates felt likely to be associated with airflow obstruction based on prior literature for evaluation in the multivariate analysis. The following variables were included in adjusted models: smoking status (past or current versus never), age, sex, and nadir CD4 count. As not all approached patients consented to participate, adjusted analyses were also weighted to better reflect the patient characteristics of the entire clinic population. As patients not taking part in the study can be thought of as censored, patient observations were weighted using inverse probability of censoring weights [27]. The probability of being selected for the study (i.e. not being censored) was estimated using a logistic regression model with the following patient-level covariates: age, sex, country of origin (Canada versus other), HIV infection duration, HIV viral suppression, CD4 count, history of opportunistic infections (i.e. *Pneumocystis* pneumonia, *Mycobacterium avium* intracellular/complex pneumonia, or cytomegalovirus pneumonitis), and use of asthma treatments (i.e. puffers, leukotriene antagonists, mast cell stabilizers or beta 2 agonists). Weights were truncated (rather than stabilized) to reduce the variance in model estimates [28]. Unadjusted and adjusted odds ratios are reported with their 95% confidence intervals. Both unweighted and weighted estimates are reported. All analyses were conducted using R statistical software [29].

## Results

Overall, 514 participants receiving regular care at the CVIS underwent spirometry testing. In six cases, participants could not undergo the spirometry test, while in five cases spirometry results were of poor quality and noninterpretable, leaving 503 participants with interpretable spirometries (Fig. 1). Patient characteristics are summarized in Table 1. Participants who underwent spirometry were similar to our entire clinic population in most respects. However, study participants were more likely to
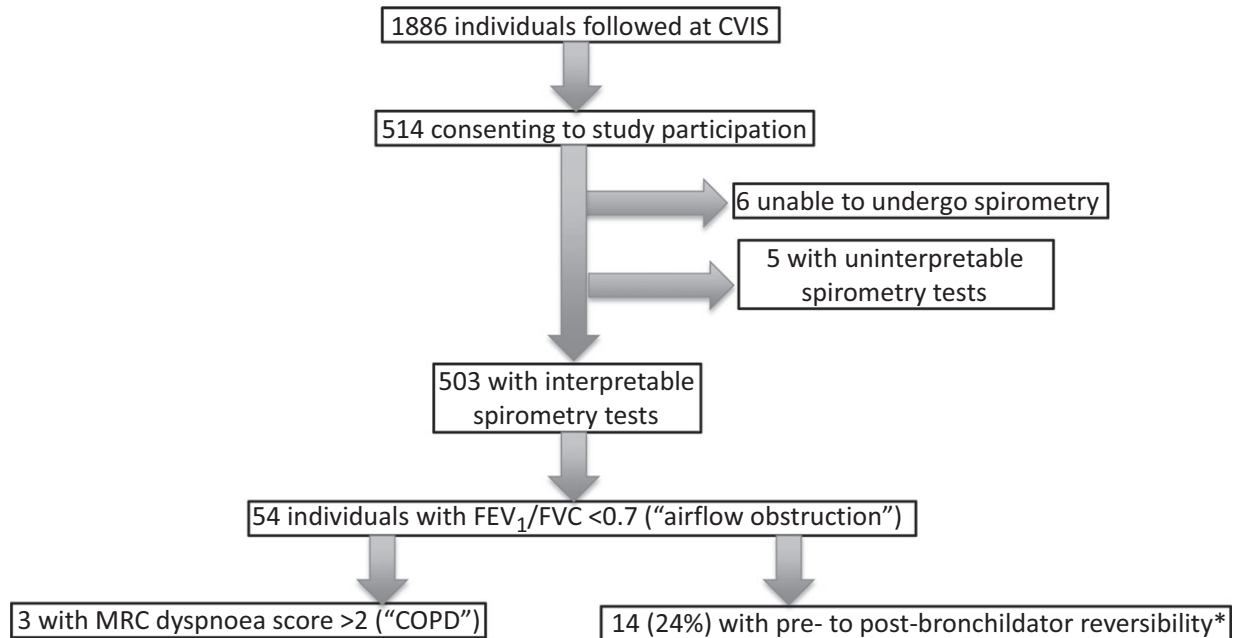
**Fig. 1** Flow diagram for spirometry screening study at the Chronic Viral Illness Service.

have an undetectable HIV viral load (92% versus 80% of the entire clinic population).

Based on spirometry testing, as shown in Table 2, we found airflow obstruction ($FEV_1$/FVC < 0.7 post-bronchodilation) to be present in 54 individuals (11%). The severity of airflow obstruction was moderate in 61% (GOLD 2) and mild in 26% (GOLD 1) of these patients. Furthermore, 14 (24%) participants with airflow obstruction had an increase in $FEV_1$ > 12% and > 200 mL from pre- to post-bronchodilation. Only eight patients reported a prior history of COPD (as diagnosed by a physician). Among these, three were confirmed to have airflow obstruction on spirometry at the study visit, suggesting that five out of eight persons were overdiagnosed and did not currently have airflow obstruction (or COPD). Thus, 51 of the 54 persons diagnosed with airflow obstruction represented new diagnoses. There were 49 individuals who had puffers listed as part of their routine medications and seven were identified as having COPD/asthma according to our clinical database. When symptoms were taken into account (according to the 2017 revised GOLD criteria for COPD), only three (1%) patients had *both* an $FEV_1$/FVC ratio < 70% post-bronchodilation *and* an MRC score > 2. Interestingly, in total, there were 38 patients out of 503 eligible patients who had an MRC score > 2 regardless of their spirometry results. Furthermore, 16 patients out of 503 eligible patients had MRC scores of 4 or 5. Out of the 54 individuals with airflow obstruction, two had MRC scores of 4 or 5 and 14 of the remaining patients (without airflow obstruction) had MRC scores of 4 or 5.

Participant characteristics at enrolment according to the presence of airflow obstruction, based on spirometry screening criteria, are shown in Table S1. Individuals with airflow obstruction were older, had a longer duration of HIV infection, were more likely to be current tobacco smokers and had smoked for a greater median number of years. There was no difference with regard to antiretroviral classes when comparing patients with and without airflow obstruction. Although there was no observed difference in the median MRC dyspnoea scale between the patients with and without airflow obstruction, patients with airflow obstruction exhibited more symptoms according to the St George's respiratory questionnaire (Table 3). According to multivariate analyses (Table 4), being a current or former smoker, older age, and lower nadir CD4 count were independent predictors of airflow obstruction. Unweighted estimates did not differ from weighted ones. Occupational and environmental exposures based on airflow obstruction status are presented in Table 5. Composite occupational exposures (≥ 3 months) and environmental exposures (≥ 6 months) were experienced by 23% and 34% of participants, respectively, and did not differ according to the presence of airflow obstruction. In multivariable analyses (Table S2), composite occupational and composite environmental exposures were not associated with airflow obstruction.

**Table 1** Characteristics of study participants at enrolment versus the entire clinic cohort

| Characteristic | Study participants [*n* (%) or median (IQR)] | Clinic cohort* [*n* (%) or median (IQR)] |
|---|---|---|
| Number of participants | 503 | 1886 |
| Age (years) | 52 (44, 58) | 51 (42–58) |
| Female | 147 (29) | 582 (31) |
| Ethnicity | | |
| Caucasian | 284 (56) | 734 (39) |
| Black African | 108 (21) | 410 (22) |
| Black Caribbean | 64 (13) | 205 (11) |
| Middle Eastern | 13 (3) | 32 (2) |
| Asian | 4 (1) | 23 (1) |
| South East Asian | 8 (2) | 23 (1) |
| Aboriginal/native | 7 (1) | 25 (1) |
| Missing | 15 (3) | 434 (23) |
| Yearly income | | |
| < 15 000 CAD | 144 (29) | Not available |
| 15 000–34 999 CAD | 111 (22) | |
| 35 000–49 999 CAD | 60 (12) | |
| > 50 000 CAD | 84 (17) | |
| Prefer not to answer | 56 (11) | |
| Missing | 48 (10) | |
| County of origin is Canada | 206 (41) | 824 (44) |
| Body mass index (kg/m$^2$) | 25 (22–28) | 26 (23–29) |
| Duration of HIV infection (years) | 15 (9–22) | 14 (8–22) |
| Currently on ART | 482 (96) | 1742 (92) |
| ART regimen | | |
| NRTI | 456 (91) | 1614 (86) |
| Integrase inhibitor | 309 (61) | 1002 (53) |
| NNRTI | 139 (28) | 545 (29) |
| Protease inhibitor | 131 (26) | 545 (29) |
| Fusion inhibitor or entry inhibitor | 12 (2) | 38 (2) |
| HIV RNA ≤ 50 copies/mL | 464 (92) | 1518 (80) |
| Enrolment CD4 cell count (cells/μL) | 598 (438–784) | 573 (390–783) |
| Enrolment CD4% | 32 (25–38) | 31 (24–38) |
| Enrolment CD4:CD8 ratio | 0.8 (0.5–1.1) | 0.8 (0.5–1.1) |
| Nadir CD4 cell count (cells/μL) | 224 (121–351) | 223 (98–378) |
| Peak CD8 cell count (cells/μL) | 1241 (886–1686) | 1249 (899–1729) |
| Nadir CD4:CD8 ratio | 0.3 (0.1–0.6) | 0.3 (0.1–0.6) |
| Log$_{10}$ peak viral load (log$_{10}$ copies/mL) | 4.63 (3.87–5.24) | 2.87 (1.65–4.46) |
| Comorbidities | | |
| HCV antibody positive | 50 (10) | 181 (10) |
| History of any opportunistic infections | 41 (8) | 300 (16) |
| History of any pulmonary opportunistic infection[†] | 39 (8) | 133 (7) |
| History of *Pneumocystis* pneumonia | 36 (7) | 115 (6) |
| History of pulmonary tuberculosis | 23 (5) | 44 (2) |
| Purified protein derivative skin test status | | |
| Positive | 32 (6) | 104 (6) |
| Negative | 183 (36) | 576 (31) |
| Missing | 288 (57) | 1206 (64) |
| Cytomegalovirus IgG status | | |
| Positive | 220 (44) | 742 (39) |
| Negative | 17 (3) | 57 (3) |
| Missing | 266 (53) | 1087 (58) |
| Use of inhaled puffers, leukotriene antagonists, mast cell stabilizers, or beta 2 agonists | 49 (10) | 150 (8) |

**Table 1** (*Continued*)

| Characteristic | Study participants [*n* (%) or median (IQR)] | Clinic cohort* [*n* (%) or median (IQR)] |
|---|---|---|
| Tobacco smoking status | | |
| Current | 119 (24) | 212 (11) |
| Former | 145 (29) | 247 (13) |
| Never | 239 (48) | 443 (23) |
| Missing | 0 (0) | 984 (52) |
| Among current and former smokers | | |
| Years smoked | 26 (13–37) | Not available |
| Smoking rate (packs[‡] per day) | 0.48 (0.2–1.0) | |
| Pack-years (years smoked × packs per day) | 11 (3–26) | |

ART, antiretroviral therapy; HCV, hepatitis C virus; IgG, immunoglobulin G; IQR, interquartile range; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; CAD, Canadian dollars.
[‡]25 cigarettes per pack of cigarettes.
*Data for HIV-positive adults extracted from the clinic database. Patients were seen at the clinic between November 2015 and December 2017, coinciding with the recruitment period for this study.
[†]Restricted to *Pneumocystis* pneumonia, Mycobacterium avium intracellulaire/Mycobacterium avium complex (MAI/MAC) pneumonia, or Cytomegalovirus (CMV) pneumonitis.

**Table 2** Results of spirometry testing

| Parameter (for *n* = 503 participants) | *n* (%) or median (IQR) |
|---|---|
| FEV$_1$ pre-bronchodilation (L) | 2.77 (2.20–3.35) |
| FEV$_1$ pre-bronchodilation (% predicted) | 89 (76–100) |
| FEV$_1$/FVC ratio | |
| Pre-bronchodilation | 79 (74–83) |
| Post-bronchodilation | 82 (76–85) |
| FEV$_1$/FVC < 70% post-bronchodilation | |
| Degree of airflow obstruction (based on 54 patients) | 54 (11) |
| Mild (FEV$_1$ ≥ 80% predicted) | 14 (26) |
| Moderate (FEV$_1$ 50–79% predicted) | 33 (61) |
| Severe (FEV$_1$ 30–49% predicted) | 6 (11) |
| Very severe (FEV$_1$ < 30% predicted) | 1 (2) |
| Airflow obstruction reversibility post-bronchodilation (based on 54 patients) | |
| > 12% increase in FEV$_1$ (%) and > 200 mL increase in FEV$_1$ (mL) | 14 (24) |

FEV$_1$, forced expiratory volume in 1 s; IQR, interquartile range.

## Discussion

In this spirometry study assessing airflow obstruction in PLWHIV, we demonstrated that relatively few PLWHIV met spirometry criteria for significant airflow obstruction (11%) and these obstructions were of mild to moderate severity (GOLD 1 or GOLD 2). Of the 503 eligible patients, most were mildly symptomatic, with only 38 (8%) having a dyspnoea MRC score of 3–5, 16 (3%) having a dyspnoea MRC score of 4 or 5 and 79 (16%) having an SGRQ score of > 25. Age > 50 years, a past history of smoking and a nadir CD4 count ≤ 200 cells/μL were associated with the presence of COPD. Given that the patients of the

**Table 3** Comparison of symptoms at enrolment, based on airflow obstruction versus no airflow obstruction as determined by spirometry

| Characteristic | Airflow obstruction [median (IQR)] (n = 54) | No airflow obstruction [median (IQR)] (n = 449) | P-value |
|---|---|---|---|
| MRC breathlessness scale | 1.0 (1.0; 2.0) | 1.0 (1.0; 2.0) | 0.379 |
| St George's Respiratory Questionnaire | – | – | – |
| Symptoms score | 24 (6–46) | 10 (0–28) | < 0.001 |
| Activity score | 13 (0–41) | 12 (0–30) | 0.264 |
| Impacts score | 4 (0–14) | 0 (0–8) | 0.029 |
| Total score | 13 (4–26) | 7 (2–18) | 0.038 |

IQR, interquartile range; MRC, Medical Research Council.

**Table 4** Logistic regression model for risk of airflow obstruction in people living with HIV

| Variable | Unadjusted OR (95% CI); unweighted | Adjusted OR (95% CI); unweighted | Adjusted OR (95% CI); weighted* |
|---|---|---|---|
| Smoking status (ever or current) | 2.9 (1.6–5.6) | 2.5 (1.3–5.0) | 2.2 (1.1–4.7) |
| Years smoked (per 10 years) | 1.6 (1.4–1.9) | – | – |
| Smoking rate (packs per day)† | 2.2 (1.3–3.5) | – | – |
| Pack-years (per 10 units) (years smoked × packs per day)† | 1.3 (1.2–1.5) | – | – |
| Age (per 10 years) | 1.7 (1.3–2.2) | 1.6 (1.2–2.2) | 1.6 (1.2–2.2) |
| Sex (female) | 0.6 (0.3–1.1) | 1.1 (0.5–2.2) | 0.9 (0.4–1.9) |
| Nadir CD4 count (per 100 cells/μL higher) | 0.9 (0.7–1.0) | 0.9 (0.7–1.0) | 0.8 (0.7–1.0) |
| Nadir CD4:CD8 ratio | 0.4 (0.1–1.1) | – | – |
| Duration of HIV infection (per 5 years) | 1.3 (1.1–1.5) | – | – |

CI, confidence interval; OR, odds ratio.
*Estimates were weighted using inverse probability of censoring weights computed from a logistic regression model which adjusted for the following patient-level covariates: age, sex, country of origin (Canada versus other), HIV infection duration, HIV viral suppression, CD4 count, history of opportunistic infections (i.e. *Pneumocystis* pneumonia, *Mycobacterium avium* intracellular/complex pneumonia or cytomegalovirus pneumonitis), and use of asthma treatments (i.e. puffers, leukotriene antagonists, mast cell stabilizers or beta 2 agonists). Weights were truncated at the 5th and 95th percentiles to stabilize variance.
†25 cigarettes per pack of cigarettes.

**Table 5** Occupational and environmental exposures by airflow obstruction status

| Characteristics | Airflow obstruction [n (%) or median (IQR)] | No airflow obstruction [n (%) or median (IQR)] |
|---|---|---|
| Total number of patients with interpretable spirometry | 54 | 449 |
| Born in a rural area | 9 (17) | 97 (22) |
| Continent on which childhood was spent | | |
| North America | 26 (48) | 210 (47) |
| Europe | 1 (2) | 18 (4) |
| Asia | 3 (6) | 13 (3) |
| South America | 9 (17) | 80 (18) |
| Africa | 5 (9) | 95 (21) |
| Missing | 10 (19) | 33 (7) |
| Immigrated to a developed country | 18 (33) | 198 (44) |
| Years since immigration | 25 (17–36) | 14 (8–26) |
| Passive smoking exposure 2 weeks prior to spirometry | 9 (17) | 72 (16) |
| Tobacco smoking status | | |
| Current | 23 (43) | 96 (21) |
| Former | 17 (31) | 128 (29) |
| Never | 14 (26) | 225 (50) |
| Occupational exposures (≥ 3 months) | | |
| Flour, feed or grain milling | 1 (2) | 8 (2) |
| Cotton or jute processing | 2 (4) | 4 (1) |
| Farming | 4 (7) | 18 (4) |
| Forestry | 2 (4) | 5 (1) |
| Saw-milling | 2 (4) | 7 (2) |
| Hard rock mining | 0 (0) | 4 (1) |
| Coal mining | 1 (2) | 1 (0) |
| Sandblasting | 0 (0) | 12 (3) |
| Work with asbestos | 1 (2) | 4 (1) |
| Foundry or steel milling | 1 (2) | 4 (1) |
| Chemical or plastic manufacturing | 1 (2) | 20 (4) |
| Welding | 1 (2) | 13 (3) |
| Firefighting | 0 (0) | 1 (0) |
| Oil drilling | 0 (0) | 2 (0) |
| Gas welling | 0 (0) | 1 (0) |
| At least one of the above | 13 (24) | 103 (23) |
| History of working in a dusty job (≥ 1 year) | 10 (19) | 61 (14) |
| Environmental exposures (≥ 6 months) | | |
| Indoor fire burning coal or coke for cooking | 12 (22) | 101 (22) |
| Indoor fire burning wood, crop residues or dung for cooking | 9 (17) | 96 (21) |
| Indoor fire burning coal or coke for heating home | 0 (0) | 33 (7) |
| Indoor fire burning wood, crop residues or dung for heating home | 5 (9) | 46 (10) |
| At least one of the above | 17 (31) | 152 (34) |

IQR, interquartile range.

CVIS clinic are ethnically diverse, with a large immigrant population, we believed that environmental and occupational exposures as possible risk factors for COPD merited exploration.

In the general population, major contributors to COPD are environmental and occupational exposures and approximately 15% of COPD cases are linked to occupational sources. Studies have shown associations between COPD and vapour gas, dust and fume (VGDF) exposure [30–32]. However, the majority of individuals included in these studies were Caucasians without HIV infection [33], so the effect of environmental and occupational exposures on risk of COPD among other ethnic groups with HIV infection may not have been captured [33].

Our finding of 1% for the prevalence of COPD in PLWHIV is at the lower range of previous estimates in

the literature [1,5–9]. However, our prevalence is consistent with that found in a recently published systematic review and meta-analysis by Bigna *et al.* [14] based on 30 studies, which found an overall, global prevalence of COPD in PLWHIV of 10.5% (95% CI 6.2–15.7). They included studies that used a variety of methods for diagnosing COPD. The global prevalence of COPD in PLWHIV varied from 5.6 to 10.6% depending on the diagnostic criteria used [14]. Adeloye *et al.* [34] estimated the overall, world-wide prevalence of COPD to be 11.7% (8.4–15.5%), although this varied by region and most prevalence studies were conducted in high-income countries, with fewer data available for African countries. The variation in ways of measuring COPD (ICD codes, patient self-report, spirometry criteria without symptoms or spirometry criteria with symptoms) probably contributes to the heterogeneity in the reported prevalences. However, overall, our prevalence of COPD, as measured by spirometric criteria, appears to be very consistent with those prevalences reported in the general population. In the Canadian Cohort of Obstructive Lung Disease (CanCOLD), the prevalence of spirometric airflow obstruction has been established at 17% [35]. As mentioned, the finding of a COPD prevalence similar to that in the general population may be attributable to the fact that our participants had high CD4 counts and a low proportion had a history of opportunistic infection.

Like Bigna *et al.* [36], we also found that tobacco smoking and older age were predictive of airflow obstruction and COPD. These findings make intuitive sense given that tobacco smoking is accepted as the strongest risk factor in the development of COPD. Smoking is very common in the HIV-infected population, with studies reporting 21–84% of individuals being current smokers (versus 19% of the general population [37]) and 9–30% being former smokers [5–8,12,38]. PLWHIV who are current smokers have increased rates of respiratory symptoms, COPD and bacterial pneumonia, and mortality is significantly increased in current versus never smokers [39]. Similarly, as in the meta-analysis by Bigna *et al* [14.], we also found that older age was associated with increased odds of airflow obstruction. This finding is not surprising as there is a reduction in $FEV_1$ during the normal aging process, with an annual decline of 25–30 mL/year, and this decline is more rapid in susceptible smokers [40]. Furthermore, we did not find sex to be a risk factor for COPD in PLWHIV [7,10–14]. While we observed that being female was slightly protective in unadjusted logistic regression, this protection disappeared after adjustment for smoking status. In our study, 74% of persons with airflow obstruction were either current or former smokers.

There is interest in determining whether any HIV-specific factors are associated with airflow obstruction or COPD in order to guide spirometric testing strategies for PLWHIV. While we found that participants with airflow obstruction had had HIV infection for a longer period of time than those without airflow obstruction, we did not observe any relationship with current CD4 count. However, although a higher nadir CD4 count appeared protective, the effect was relatively modest in our population which has been on long-term ART with good CD4 recovery (median CD4 count > 500 cells/μL). Using longitudinal data, other studies have also demonstrated accelerated decline of respiratory function ($FEV_1$) and FVC in PLWHIV with lower CD4 cell counts [12,13]. It has been reported that approximately one-third of individuals with suppressed viral load on ART are unable to mount a CD4 count > 350 cells/μL [41]. CD4 T-cell depletion as well as persistent immune activation have been suggested as possible drivers of inadequate CD4 T-cell recovery [42]. Furthermore, risk factors for poor CD4 T-cell recovery include chronically enhanced T-cell activation [defined by co-expression of CD38 and human leucoctye antigen (HLA)-DR on CD8 T cells] and increased plasma levels of inflammatory markers [42,43]. Persistent immune activation and chronic inflammatory are associated with increased risk of nonopportunistic complications including cardiovascular disease [42].

We found that individuals in our study had a low burden of respiratory symptoms, as measured by the MRC dyspnoea scale. Furthermore, individuals with and without airflow obstruction had similar median scores. In a Vancouver-based study by Leung *et al.* [44] in 199 men living with HIV, the median SGRQ score was 32 points (of a maximum of 100 points), which indicated more respiratory symptomatology than found in the Philadelphia-based study involving 98 PLWHIV by Hirani *et al.* [6], whose participants had a median SGRQ score of 7 points. Hirani *et al.* [6] also demonstrated that worse scores were correlated with increasing airflow obstruction in their sample of PLWHIV. This difference between studies could reflect differences in age and duration of infection or selection bias.

Our study has several strengths. Firstly, we used systematic spirometry testing of unselected individuals – the gold standard – to determine the presence of airflow obstruction. We also used weighting to ensure that the tested population closely reflected the base population from which it was drawn. We also assessed reversibility of airflow obstruction by measuring spirometry pre- and post-bronchodilation. The purpose of using post-bronchodilation spirometry is to minimize misclassification of people who have completely reversible airflow limitation

as having persistent airflow limitation. For example, some people with a pre-bronchodilation ratio < 0.7 normalize their ratio post-bronchodilation and therefore do not have persistent airflow limitation – a necessary feature of COPD. In addition to the observed prevalence of COPD, 24% of the sample had airflow limitation that warranted further investigation. Our sample size was one of the largest patient populations of PLWHIV reported in the literature to undergo spirometry testing and included a large number of nonsmoking participants, including black women – a population underrepresented in most other screening studies on airflow obstruction. Our study in PLWHIV was unique in that we examined a broad range of occupational and environmental exposures among PLWHIV attending our clinic, in addition to immigration history.

Several limitations of this study must also be acknowledged. The greater number of individuals in our study with suppressed viral load may reflect a greater tendency by the study population to attend clinic appointments and adhere to ART compared with the clinic base population. As our sample was relatively young, we may have underestimated the prevalence of airflow obstruction/COPD by using a fixed ratio (0.7) to define airflow obstruction/COPD. When using the fixed ratio criteria, there is a concern that one might underdiagnose COPD in the young and overdiagnose COPD in the old. This risk occurs as a consequence of the fact that $FEV_1/FVC$ decreases with age. For this reason, some people support using a lower limit of normal (LLN) rather than a fixed ratio, although the updated guidelines still recommend using a fixed ratio. In addition, the symptoms criteria we used to define COPD (MRC > 2) may have been too strict, underestimating the prevalence of COPD. Although the updated definition of COPD requires post-bronchodilation $FEV_1/FVC < 0.7$ and *persistent symptoms*, the guidelines do not explicitly recommend a symptom criterion. In clinical practice, this is usually not a problem as presumably the patient is being evaluated for symptoms. In prevalence research, the lack of symptoms criteria is challenging. In fact, in the ABCD classification of COPD, MRC > 2 is required to be classified as B or D [45]. Therefore, people with COPD classified as A or B, by definition, have an MRC score of 1–2 and therefore the symptom threshold of MRC score > 2 used in the study may be too high. For future prevalence studies, a broader assessment of symptoms (such as 'any breathlessness') may be preferable to using the MRC score. Furthermore, while spirometry is the gold standard used to quantify airflow obstruction, it is insensitive in detecting small airway (< 2 mm diameter) disease. Small airways are frequently involved

early in the course of COPD before symptom onset, although the predictive value is still a matter of debate. Asthma was not assessed in this study and it is well known to be a risk factor for COPD [46]. Long-standing asthma and the risk of COPD as defined by the presence of non-fully reversible chronic airway obstruction have been well documented in smokers and never-smokers. History of asthma was reported as the factor most consistently showing an independent association with COPD regardless of smoking status in CanCOLD. To date, four studies have been performed using computed tomography (CT) scans to examine the prevalence of emphysema among HIV-infected patients, all of which revealed a prevalence of 25–30% [11,47–50]. One study used plethysmography to examine maximal inspiratory and expiratory pressures in HIV-infected individuals, and found abnormally low values in 43% of HIV-infected individuals [51]. Individuals with HIV infection have also shown high rates of gas trapping and hyperinflation [49], which would not have been captured in our study. However, this is unlikely to be of importance in pulmonary function measured at rest in mild COPD, unless patients have diffuse bronchiolitis. Another limitation of our study was its retrospective nature and missing data for many patients with regard to nadir CD4 counts, history of latent tuberculosis infection (as assessed by the tuberculin skin test) and cytomegalovirus seropositivity. Similarly, because of missing information on cannabis use, we cannot comment on the number of patients in our clinic (or in this study) who routinely smoked cannabis. Furthermore, the small number of outcomes precluded us from examining interactions between variables, such as whether markers of immunity (CD4 count, CD4:CD8 ratio and CD4 count nadir) modified the association between pack-years of cigarette smoking and airflow obstruction. Finally, as our study was cross-sectional, we also did not have longitudinal data.

In conclusion, both smoking status and older age independently predicted the presence of airflow obstruction in our unselected cohort of PLWHIV, as demonstrated in the general population. Symptomatic airflow obstruction defined by the dyspnoea MRC scale and the SGRQ score were relatively uncommon. Furthermore, very few participants had COPD. In PLWHIV, pulmonary complications (including airflow obstruction) are common and contribute to the elevated risk for morbidity and mortality. Although prevalence was low, spirometry is inexpensive, noninvasive and without harm to the patient. Therefore, spirometry screening can be a useful tool to screen for airflow obstruction. Spirometry testing should especially focus on those at higher risk, such as smokers and those ≥ 40 years old and presenting with

respiratory symptoms, as is recommended in the general population. The possibility of considering spirometry screening for those with lower nadir CD4 counts merits further validation.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Comparison of characteristics at enrolment, based on airflow obstruction versus no airflow obstruction as determined by spirometry

**Table S2.** Logistic regression model for risk of airflow obstruction in people living with HIV: occupational and environmental exposures