Respiratory health status is impaired in UK HIV-positive adults with virologically suppressed HIV infection

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ORIGINAL RESEARCH

Respiratory health status is impaired in UK HIV-positive adults with virologically suppressed HIV infection

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Objectives

We sought to evaluate whether people living with HIV (PLWH) using effective antiretroviral therapy (ART) have worse respiratory health status than similar HIV-negative individuals.

Methods

We recruited 197 HIV-positive and 93 HIV-negative adults from HIV and sexual health clinics. They completed a questionnaire regarding risk factors for respiratory illness. Respiratory health status was assessed using the St George's Respiratory Questionnaire (SGRQ) and the Medical Research Council (MRC) breathlessness scale. Subjects underwent spirometry without bronchodilation.

Results

PLWH had worse respiratory health status: the median SGRQ Total score was 12 [interquartile range (IQR) 6–25] in HIV-positive subjects *vs.* 6 (IQR 2–14) in HIV-negative subjects ($P < 0.001$); breathlessness was common in the HIV-positive group, where 47% compared with 24% had an MRC breathlessness score ≥ 2 ($P = 0.001$). Eighteen (11%) HIV-positive and seven (9%) HIV-negative participants had airflow obstruction. In multivariable analyses (adjusted for age, gender, smoking, body mass index and depression), HIV infection remained associated with higher SGRQ and MRC scores, with an adjusted fold-change in SGRQ Total score of 1.54 [95% confidence interval (CI) 1.14–2.09; $P = 0.005$] and adjusted odds ratio of having an MRC score of ≥ 2 of 2.45 (95% CI 1.15–5.20; $P = 0.02$). Similar findings were obtained when analyses were repeated including only HIV-positive participants with a viral load < 40 HIV-1 RNA copies/mL.

Conclusions

Despite effective ART, impaired respiratory health appears more common in HIV-positive adults, and has a significant impact on health-related quality of life.

Keywords: lung, patient reported outcome, quality of life, respiratory, smoking

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Introduction

Antiretroviral therapy (ART) has transformed HIV infection into a manageable chronic condition [1]. Despite this, people living with HIV (PLWH) continue to have higher rates of comorbidities such as cardiovascular [2] and renal disease [3], as well as some malignancies [4]. There is also evidence that, despite ART, PLWH may have a higher prevalence of chronic respiratory illness [5]. For instance, in the large US Veterans Aging Cohort Study, after adjustment for smoking status and other characteristics, chronic obstructive pulmonary disease (COPD) was 50–60% more common in PLWH than in HIV-negative participants [6]. The development of persistent, noncommunicable respiratory disease such as COPD in HIV-positive individuals may impact significantly on their quality of life [7].

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There are, however, limitations to the currently available data concerning chronic respiratory disease in HIV-positive people on ART. In particular, most reported studies have included significant proportions of participants without virological suppression. Also, results may be influenced by residual confounding factors such as tobacco smoking and recreational drug use. Furthermore, most studies assessing respiratory health in HIV-positive populations have focused on objective measurements of lung function (such as spirometry) rather than the subjective impact of respiratory impairment on health-related quality of life [5, 8]. This is an important issue, as respiratory symptoms can correlate poorly with objectively measured lung function [9], yet may have a significant effect on quality of life. There is a need, therefore, to better understand the degree to which PLWH with access to effective ART have worse respiratory health than HIV-negative individuals (with similar risk factors), and the impact of this on their quality of life [10].

The use of validated patient-reported outcome measures allows the systematic evaluation of the impact of pathologies on health-related quality of life, and enables direct comparisons to be made between different groups and populations. These instruments can attempt to quantify general health status (such as the EuroQoL 5D 5L (EQ5D)) or may be disease or organ specific [e.g. the St George's Respiratory Questionnaire (SGRQ)]. In this study, we used these measures to provide an assessment of overall respiratory health (rather than an assessment specific to one condition such as COPD) – which we refer to as "respiratory health status".

We sought to evaluate whether respiratory health status was impaired in a contemporary (on ART) HIV-infected population and to test the hypothesis that HIV-positive adults have worse respiratory health than HIV-negative people with similar risk factors; to assess whether impaired respiratory health correlated with spirometric impairment in this population, and to explore the effect of potential confounding factors such as smoking, recreational drug use, and physical and mental comorbidities. In addition, for those with HIV infection, we describe the relationship between HIV-related factors such as blood CD4 count, HIV load and duration of HIV infection and respiratory health status.

Methods

Study population

We conducted a cross-sectional observational study in the HIV ambulatory care service and sexual health clinics (at Royal Free and Barnet Hospital sites) of the Royal Free London NHS Trust, London, UK from February to July 2015. Consecutive clinic patients were invited to take part in the study when they attended routine care appointments. Subjects provided written informed consent. London sexual health clinics were chosen as the site for recruitment of HIV-negative participants as this population was anticipated to have similar lifestyle characteristics, including smoking behaviours, to the HIV clinic population. As service users in the sexual health clinics were significantly younger than those attending clinics for HIV care, recruitment in sexual health clinics was restricted to those over the age of 35 years to achieve a sample that approximated the age of the HIV-positive participants. There were no exclusion criteria for the HIV-positive group. Ethical approval was granted by the London – Camden and Islington Research Ethics Committee (14/LO/1646).

Procedures

Participants completed a questionnaire including items on risk factors for respiratory illness, smoking and recreational drug use and health-related quality of life (using the EQ5D) [11,12,13]. As depression might affect the experience and expression of respiratory symptoms (and therefore act as an important confounding factor), symptoms of depression were evaluated using the Patient Health Questionnaire – 9 (PHQ-9) (a scale providing scores of 0–27, where scores of ≥ 10 suggest the presence of moderate or severe depressive symptoms [14]). Respiratory health status was measured using (a) the SGRQ and (b) the Medical Research Council dyspnoea (breathlessness) scale, a scale with scores from 1 to 5 recording the severity of breathlessness on exertion [15, 16].

The SGRQ is a patient-reported outcome measure which quantifies respiratory health using a 50-item self-completed questionnaire [15]. Responses are translated onto a scale from 0 to 100 in which higher scores indicate worse respiratory health status, with domains assessing symptoms, activities and impacts as well as a total score. Although initially developed for use in asthma and COPD, it is not disease-specific and has been widely used in other respiratory conditions.

Subjects underwent spirometry without bronchodilation (Carevision Micro I spirometer, Beckton Dickinson, New Jersey, USA) and had their height and weight measured. Normal values for spirometry were calculated using the Global Lung Function Initiative equations [17]; airflow obstruction was defined as an Forced Expiratory Volume in one second (FEV1)/ Forced Vital Capacity (FVC) of < 0.7. For current and past blood test results, data were obtained from hospital databases with participant consent. Self-

reported HIV status was noted and not independently confirmed in the sexual health clinic population.

Statistical analysis

Data were recorded and analysed in EXCEL (Microsoft) and SPSS version 22 (IBM, New York, USA). Univariable comparisons between HIV-positive and -negative participants were undertaken using χ^2 and Fisher's exact tests for categorical variables and unpaired *t*-tests or Mann–Whitney *U*-tests for continuous variables, as appropriate. To adjust for participant characteristics and to assess the independent associations of factors with respiratory measures, multivariable regression analyses were performed. SGRQ Total scores were log-transformed to normalize their distribution for these analyses. Multivariable linear regression analyses were used to assess factors independently associated with log-transformed SGRQ Total scores and estimates were then back-transformed to derive adjusted fold-changes in SGRQ score for covariates of interest. Multivariable logistic regression models were used to assess factors independently associated with having an MRC dyspnoea score of ≥ 2. For the multivariable analyses, a core set of variables of importance were selected *a priori* (age, tobacco smoking, gender and HIV status) and, following univariable analysis, additional variables found to be significantly associated at the 5% level with respiratory health status were added to the multivariable model.

Table 1 Comparison of demographic characteristics between HIV-positive and HIV-negative participants

	HIV-positive (*n* = 197)	HIV-negative (*n* = 93)	*P*-value
Gender			
Male [*n* (%)]	158 (80)	64 (71)	0.09*
Age (years) [median (IQR)]	50 (42–55)	43 (38–52)	0.025#
BMI (kg/m^2) [mean (SD)]	25.84 (5.04)	25.36 (4.23)	0.434×
Race/ethnicity [*n* (%)]			
White	143 (72)	54 (60)	0.003□
Black	37 (20)	15 (17)	
Other	15 (8)	24 (26)	
Born in UK [*n* (%)]	121 (62)	49 (54)	0.24*
Gender/sexuality [*n* (%)]			
MSM	131 (66)	25 (27)	< 0.001□
MSW	27 (14)	37 (40)	
Female	37 (20)	24 (28)	
Not stated	0	5 (5)	
Highest educational attainment [*n* (%)]			
None	24 (12)	10 (12)	0.64□
GCSE or equivalent	28 (14)	7 (8)	
A level or equivalent	31 (16)	14 (16)	
University degree or higher	106 (54)	50 (59)	
Other	6 (3)	4 (5)	
Employment [*n* (%)]			
Full-time	92 (47)	59 (67)	0.015□
Part-time	22 (11)	11 (12)	
Unemployed	25 (13)	5 (6)	
Retired	18 (9)	4 (4)	
Student	5 (3)	1 (1)	
Not working because of ill health	28 (14)	4 (5)	
Other	6 (3)	5 (5)	

BMI, body mass index; GCSE, General Certificate of Secondary Education; IQR, interquartile range; MSM, men who have sex with men; MSW, men who have sex with women; SD, standard deviation.
*χ^2 test.
#Mann–Whitney *U*-test.
□Fisher's exact test.
×Independent samples *t*-test.

Results

Study participants

Of 402 individuals invited to participate, 290 (72%) agreed: 197 HIV positive and 93 HIV negative. Recruitment of HIV-negative individuals was lower as fewer eligible individuals attended these clinics over the study period – however, the response rate was similar, being 75% among HIV-positive individuals and 73% among HIV-negative individuals. Demographics and details of comorbid conditions are listed in Tables 1 and 2.

The median blood CD4 count of HIV-positive participants was 627 cells/μL [interquartile range (IQR) 456–838 cells/μL]; 171 (94%) of PLWH reported using ART, with a median duration of treatment of 7 years. Eighty-nine per cent of all PLWH and 93% of those using ART had an undetectable plasma HIV load (< 40 HIV-1 RNA copies/mL) at their last clinic visit. The median nadir CD4 count of this cohort was 250 cells/μL (IQR 122–365 cells/μL). No significant differences were found in gender, educational attainment or being non-UK born between HIV-positive and -negative participants, but PLWH were more often ethnically white (72% *vs*. 60%, respectively; $P = 0.001$). HIV-negative participants had a lower median age than those recruited from the HIV ambulatory care clinic (43 *vs*. 50 years, respectively; $P = 0.05$) and were more likely to be heterosexual (71% *vs*. 32%, respectively; $P < 0.01$).

The HIV-positive and -negative groups had similar reported prevalences of a range of physical comorbidities (asthma, COPD, diabetes, heart disease and stroke). However, symptoms of depression were more common in the HIV-positive group: 39 (20%) of the HIV-positive group and 13 (14%) of the HIV-negative group had PHQ-9 scores of ≥ 10, indicating moderate/severe depression ($P = 0.64$).

Smoking and recreational drug use

Sixty (30%) HIV-positive and 31 (33%) HIV-negative participants were current smokers; 54 (28%) and 22 (25%), respectively, were ex-smokers (Table 3). In smokers, PLWH reported more intensive smoking than HIV-negative individuals, with

Table 2 Comparison of comorbidities and their management between HIV-positive and HIV-negative participants

	HIV-positive (n = 197)	HIV-negative (n = 93)	P-value
Diagnosis of comorbid conditions (self-report), ever [n (%)]			
Asthma	36 (18)	21 (23)	0.34□
COPD/emphysema	9 (5)	1 (1)	0.18□
Cancer (any)	9 (5)	3 (3)	0.76□
Heart disease	11 (6)	4 (4)	0.78□
Stroke	3 (1)	1 (1)	1□
Diabetes	10 (5)	6 (7)	0.59□
Currently receiving treatment for depression [n (%)]	40 (20)	8 (9)	0.02*
Patient Health Questionnaire – 9 score [median (IQR)]	4 (1–8)	2 (0–6)	0.002#
Patient Health Questionnaire – 9 score ≥ 10 [n (%)]	39 (20)	13 (14)	0.254□
Self-reported history of immunization against [n (%)]			
Influenza in past 12 months	138 (70)	27 (30)	< 0.01□
Streptococcus pneumonia (ever)	50 (26)	6 (7)	< 0.01□
Use of inhaled medications (any) [n (%)]	24 (12)	15 (17)	0.30*
Undertakes physical activity at least once per week [n (%)]	115 (59)	63 (71)	0.05*
History of acute respiratory illness in past year [n (%)]			
Sinusitis	23 (12)	7 (8)	0.41□
Bronchitis	6 (3)	3 (3)	1.0□
Chest infection	39 (20)	11 (12)	0.132□
Cold or flu serious enough to miss work or stop normal activities	54 (28)	19 (21)	0.307□
Pneumonia	3 (1.5)	0	0.55□
Any acute respiratory illness	93 (47)	30 (32)	0.02*

COPD, chronic obstructive pulmonary disease; IQR, interquartile range.
□Fisher's exact test.
*χ^2 test.
#Mann–Whitney U-test.

Table 3 Smoking and recreational drug use

	HIV-positive (n = 197)	HIV-negative (n = 93)	P-value
Smoking [n (%)]			
Current smoker	60 (30)	31 (33)	0.81□
Ex-smoker	54 (27)	22 (24)	
Never smoker	80 (41)	37 (40)	
Not stated	3 (1.5)	3 (3)	
Cigarettes smoked per day (current smokers only) [median (IQR)]	15 (8–20)	10 (5–13)	< 0.01#
Most cigarettes smoked per day in the past [median (IQR)]	20 (15–30)	12.5 (7.5–20)	0.04#
Currently using electronic cigarettes [n (%)]	20 (18)	8 (16)	0.83*
History of recreational drugs use, ever [n (%)]			
Any	118 (61)	41 (48)	0.07□
Cannabis	98 (51)	35 (41)	0.15□
Cocaine (smoked)	23 (12)	3 (3)	0.03□
Cocaine (sniffed or rubbed in gums)	71 (37)	21 (25)	0.05□
Ecstasy/Gamma-hydroxybutyrate/ ketamine/ crystal meth	72 (36)	13 (14)	< 0.001□
Heroin (smoked)	13 (7)	1 (1)	0.07□
Heroin (injected)	7 (4)	1 (1)	0.44□
History of recreational drug use in last 3 months [n (%)]			
Any	58 (30)	18 (20.7)	0.15□
Cannabis	39 (20)	14 (16.1)	0.51□
Cocaine (smoked)	3 (1)	0	0.55□
Cocaine (sniffed or rubbed in gums)	13 (7)	8 (9)	0.47□
Ecstasy/Gamma-hydroxybutyrate/ ketamine/crystal meth	22 (11)	3 (3)	0.025□
Heroin (smoked)	3 (1)	0	0.55□
Heroin (injected)	0	0	–

IQR, interquartile range.
□Fisher's exact test.
#Mann–Whitney U-test.
*χ^2 test.

a median of 15 (IQR 8–20) *vs.* 10 (5–13) cigarettes per day for current smokers, respectively ($P < 0.001$).

Past recreational drug use was more often reported in those with HIV infection, with 60% indicating drug use ever compared with 48% of HIV-negative participants ($P = 0.05$). No significant differences were found in the proportion of participants indicating any recreational drug use in the past 3 months.

Spirometry, respiratory symptoms and health-related quality of life

Spirometry was within normal limits in most people: 18 (11%) HIV-positive and seven (9%) HIV-negative participants had evidence of airflow obstruction (FEV_1/FVC < 0.7) ($P = 0.55$).

The MRC dyspnoea and SGRQ scores suggested a higher prevalence of breathlessness and respiratory health status impairment in PLWH (Table 4). SGRQ scores were higher in the HIV-positive group for all domains, with median SGRQ Total scores of 12 in the PLWH and 6 in HIV-negative participants ($P < 0.01$). Breathlessness was more common in the HIV-positive group, with 47% having an MRC dyspnoea score ≥ 2 (on a scale of 1–5), suggesting at least moderate breathlessness, compared with 25% of the HIV-negative participants ($P = 0.001$); 13% of HIV-positive *vs.* 1% of HIV-negative participants had MRC dyspnoea scores of ≥ 3 ($P = 0.001$).

There was no significant difference in general health-related quality of life scores between the HIV-positive and HIV-negative groups, with median EQ5D (UK) index values of 0.88 and 0.85 ($P = 0.06$) and median Visual Analogue Scale scores of 78 and 72, respectively ($P = 0.46$).

Factors associated with respiratory health status impairment in univariable analyses

In addition to HIV status, we explored other possible contributors to impaired respiratory health in the whole

Table 4 Respiratory symptoms and health status

	HIV-positive (n = 197)	HIV-negative (n = 93)	P-value
FEV_1			
Mean (SD) (L)	3.49 (0.87)*	3.25 (0.76)*	0.56[Δ]
% predicted	93	91	
FVC			
Mean (SD) (L)	4.29 (1.05)*	3.95 (0.91)*	0.23[α]
% predicted	91	89	
FEV_1/FVC < 0.7 [n (%)]	18 (11)*	7 (9)*	0.50[□]
MRC dyspnoea scale [n (%)]			
1. Not troubled by breathlessness except on strenuous exercise	99 (53)	61 (75)	0.02[□]
2. Short of breath when hurrying or walking up a slight hill	62 (33)	1 (24)	
3. Walk slower than contemporaries on level ground or have to stop for breath when walking at your own pace	8 (4)	1 (1)	
4. Stop for breath after walking about 100 m or after a few minutes on level ground	13 (7)	1 (0)	
5. Too breathless to leave the house, or breathless when dressing/undressing	4 (2)	0 (0)	
St George's Respiratory Questionnaire [median (IQR)]			
Symptoms	25 (7–48)	18 (0–29)	< 0.01[#]
Activity	17 (6–36)	12 (0–19)	< 0.01[#]
Impacts	5 (0–15)	0 (0–6)	< 0.01[#]
Total	12 (6–25)	6 (2–14)	< 0.01[#]

IQR, interquartile range; SD, standard deviation.
*157 (80%) HIV-positive and 74 (80%) HIV-negative participants had acceptable spirometry results.
[Δ]*t*-test; comparison of FEV % predicted.
[α]*t*-test; comparison of FVC % predicted.
[□]Fisher's exact test.
[#]Mann–Whitney *U*-test.

study sample (Table S1). Higher SGRQ scores were associated with impaired lung function, with a median total SGRQ score of 28.5 (IQR 7.2–41.9) in people with an FEV_1 < 80% predicted compared with 9.1 (IQR 4.4–17.4) in those with an FEV_1 in the normal range (P < 0.01). Symptoms of depression were associated with impaired self-reported respiratory health status: median SGRQ Total scores were 26.5 in the 52 participants with PHQ-9 scores of ≥ 10, and 7.7 in the 238 participants with PHQ-9 scores < 10.

Combining HIV-positive and HIV-negative groups, no significant associations were found between gender, ethnicity, smoking status or recreational drug use and impaired respiratory health status in univariable analyses. An association between body mass index (BMI) and SGRQ Total score was seen (with higher scores in those with BMI < 20 or > 25), which approached statistical significance (P = 0.07).

Associations between HIV-related parameters and respiratory health

In analyses restricted to HIV-positive participants, neither current nor nadir CD4 count was significantly associated with higher SGRQ Total score (although trends were seen for higher scores being related to lower current or nadir blood CD4 counts). No significant difference in median SGRQ Total score was identified in those with and without an HIV load < 40 copies/mL (Table 5). After adjustment for age in a log-scale linear regression model, there was a trend towards higher SGRQ Total scores in people with a longstanding HIV diagnosis. A significant association was present between higher SGRQ Total score and longer interval from HIV diagnosis to starting ART.

Multivariable analysis of factors associated with respiratory health status including all participants

To allow adjustment for potential confounding factors, we constructed multivariable (log scale) linear regression models including all participants, with log SGRQ as the dependent variable. In addition to those factors chosen *a priori* (smoking status, age and gender), PHQ-9 scores and BMI were also included as they reached statistical significance at the 5% level in univariable analysis.

After adjustment for these other factors, HIV infection remained independently associated with an increased SGRQ Total score, with a 54% higher SGRQ Total score compared with HIV-negative individuals [adjusted fold-change 1.54; 95% confidence interval (CI) 1.14–2.09; P = 0.005] (Table 6). Depression (PHQ-9 score ≥ 10) was also independently associated with a higher SGRQ Total score (adjusted fold-change 1.90; 95% CI 1.42–2.53; P < 0.001).

We found similar factors to be independently associated with an MRC dyspnoea score ≥ 2 in a multivariable logistic regression model (Table S2). Here, the adjusted odds ratio (aOR) for an MRC dyspnoea score of ≥ 2 was 2.84 (95% CI 1.35–6.00; P = 0.006) in HIV-positive compared with HIV-negative participants. Independent associations were found with female gender (aOR 4.69; 95% CI 1.85–11.45; P = 0.001) and depression (aOR 6.30; 95% CI 2.75–14.46; P < 0.001).

Comparing HIV-positive participants with an undetectable HIV viral load with HIV-negative participants

As other studies have suggested that untreated HIV infection is associated with chronic respiratory impairment [18, 19], a greater prevalence of respiratory symptoms

Table 5 Associations between HIV-related factors and St George's Respiratory Questionnaire (SGRQ) Total score

	HIV-positive participants [*n* (%)]	SGRQ Total [median (IQR)]	Unadjusted fold-change in SGRQ* (95% CI)	Age-adjusted fold-change in SGRQ (95% CI)*	*P*-value*
Current CD4 count (cells/μL)					
0–350	19 (11)	20 (6–35)	1.53 (0.88–2.18)	1.57 (0.94–2.62)	0.109
350–500	30 (18)	16 (9–34)	1.39 (0.91–2.54)	1.40 (0.90–2.19)	
≥ 500	119 (71)	11 (6–20)	Reference		
Viral load < 40 copies/mL at last clinic review					
No	19 (11)	15 (5–67)	1.31 (0.78–2.19)	1.52 (0.89–2.57)	0.12
Yes	149 (89)	13 (6–25)	Reference		
Nadir CD4 count (cells/μL)					
0–100	35 (21)	17 (7–43)	1.80 (0.98–3.32)	1.65 (0.88–1.74)	0.112
100–250	47 (28)	16 (8–33)	1.52 (0.85–2.73)	1.40 (0.76–2.55)	
250–500	67 (40)	12 (6–17)	1.04 (0.60–1.81)	1.0 (0.57–3.09)	
≥ 500	17 (10)	10.5 (4–14)	Reference		
Time since HIV diagnosis (years)					
> 20	47 (27)	16 (8–37)	1.72 (1.14–2.61)	1.56 (1.01–2.43)	0.067
10–20	62 (36)	11 (6–25)	1.24 (0.85–1.83)	1.19 (0.80–1.76)	
< 10	62 (36)	10 (4–20)	Reference		
Time between HIV diagnosis and ART (years)					
> 10	33 (20)	21 (11–48)	1.90 (1.23–2.91)	1.79 (1.17–2.75)	0.004
5–10	43 (25)	9 (5–26)	1.00 (0.68–1.45)	0.95 (0.64–1.39)	
< 5	93 (55)	12 (5–21)	Reference		
Duration of ART exposure					
> 10	68 (49)	17 (7–37)	1.73 (1.13–2.64)	1.58 (1.0–2.49)	0.148
5–10	26 (19)	13 (7–24)	1.54 (0.87–2.70)	1.41 (0.78–2.52)	
< 5	46 (33)	9 (4–21)	Reference		

ART, antiretroviral therapy; CI, confidence interval; IQR, interquartile range.
*Log-scale linear regression model.

Table 6 Associations with St George's Respiratory Questionnaire (SGRQ) Total score in multivariable log-scale linear regression analysis

	Adjusted fold-change in SGRQ* (95% CI)	*P*-value
HIV status		
HIV positive	1.58 (1.18–2.12)	0.002
HIV negative	Reference	
Age (per 1 year older)	1.01 (1.01–1.02)	0.335
Gender		
Female	1.37 (0.96–1.09)	0.083
Male	Reference	
Depression (PHQ-9)		
≥ 10	2.77 (1.98–3.88)	<0.001
< 10	Reference	
Body mass index (kg/m^2)		
< 20	1.18 (0.68–1.74)	0.681
≥ 20 < 25	Reference	
≥ 25 < 30	1.18 (0.85–1.37)	
≥ 30	1.23 (0.8–1.42)	
Smoking		
Current smoker	1.23 (0.89–1.24)	0.408
Ex-smoker	1.01 (0.72–2.57)	
Never smoker	Reference	

CI, confidence interval.
*Log-scale linear regression model.

within the PLWH population as a whole might result from increased symptoms only among HIV-positive individuals not yet taking ART, or on ART without virological suppression. We therefore undertook a subgroup analysis comparing HIV-negative participants with HIV-positive participants whose HIV viral load was measured as being undetectable (< 40 copies/mL) within 6 months of the study visit. Participants who declined consent to access clinical records were excluded from this analysis, leaving 157 HIV-positive participants with documented virological suppression, compared with the 93 HIV-negative participants. Those with virological suppression had similar demographic characteristics to the PLWH study population as a whole (Table S3) and had a median CD4 count of 684 (IQR 473–839) cells/μL. The differences in respiratory health scores between HIV-positive (HIV suppressed) and HIV-negative groups were similar to those present in the complete data set: median SGRQ Total scores were 12 (IQR 6–25) and 6 (IQR 2–14), respectively ($P < 0.001$); and seventy (47.3%) of the HIV-positive group had MRC dyspnoea scores of ≥ 2 compared with 20 (24.7%) of the HIV-negative group ($P = 0.001$). In a log-scale linear regression model (including the same predictive factors as the whole-group analysis), HIV status remained independently associated with a higher SGRQ Total score, with a similar effect size to that in the whole group (fold-change in SGRQ 1.53; 1.13–2.06; $P = 0.007$).

Sensitivity analysis

To further explore the possible effect of the difference in age distribution between the HIV-positive and HIV-negative groups, we undertook a sensitivity analysis where we examined only those aged ≤ 52 years (the 75th centile of the HIV-negative participants). Using this restricted analysis (including 127 HIV-positive and 69 HIV-negative participants), the age distributions were similar, with a median age of 42 years in both groups. The previously demonstrated differences remained, with median SGRQ Total scores of 11.2 (IQR 6–20) in the PLWH and 6.2 (IQR 3–15) in the HIV-negative group ($P = 0.01$). MRC dyspnoea scores were also higher, with 55 (46%) of the HIV-positive and 16 (27%) of the HIV-negative participants having a MRC dyspnoea score ≥ 2 ($P = 0.01$).

Discussion

We compared HIV-positive individuals to an HIV-negative group with similar exposures to risk factors such as tobacco smoking. Our results suggest that HIV infection remains associated with impaired respiratory health despite virological suppression on ART. Although some differences were present in the age and ethnicity compositions of our two groups, these could not explain the differences in respiratory health status seen after adjustment in multivariable analyses.

Breathlessness was common in HIV-positive participants, with 47% of PLWH reporting this to be present and of at least moderate severity, compared with 25% of the HIV-negative participants. Using the SGRQ respiratory health questionnaire (which assesses not only respiratory symptoms but also the impacts on activity and quality of life), we found a 6-point difference in the median total score between HIV-positive and HIV-negative groups (a minimum clinically important difference in SGRQ being around 4 points [20]), suggesting that there is a meaningful impairment of the respiratory health of PLWH. This difference was present despite the prevalence of airflow obstruction in our HIV-positive subjects (11%) being lower than that reported in other HIV-positive populations (for instance 23% in Italy and 27% in the USA [8, 21]). Of note, there was also no difference in the prevalence of airflow obstruction in our study between the HIV-positive and HIV-negative groups.

To our knowledge, no other study has used patient-reported outcomes to compare respiratory health status in HIV-positive and HIV-negative populations. Two previous reports used the SGRQ to evaluate respiratory health in HIV-positive adults: Hirani *et al.* evaluated 98 consecutive HIV-positive individuals (84% male) attending HIV care services in Philadelphia, USA, and found a mean SGRQ Total score of 7 [22]; in contrast, Leung *et al.* reported a mean SGRQ Total score of 32 in 199 HIV-positive men attending care services in Vancouver, Canada [9]. Our data therefore provide the first estimate of the difference in respiratory health (as experienced by individuals) between HIV-positive adults with optimized access to ART and HIV-negative adults.

What might be contributing to these findings? Impairment of lung function not measured by spirometry may be present, which could result from a higher frequency of respiratory infection prior to effective ART and lead to long-term lung damage [23]: this could also result from the direct effect of HIV in the lung [24]. Other possibilities include cardiovascular disease or other non-respiratory comorbidities which can lead to respiratory symptoms. Depression was strongly associated with impaired respiratory health in our population and this may contribute to the burden of physical symptoms (although it should be noted that the difference in respiratory health status persisted after adjustment for depression in our population). Persistent HIV-associated immune dysregulation despite ART may also contribute – an effect documented in the development of atherosclerosis [25]. This hypothesis is supported by Attia *et al.*'s finding that levels of circulating CD14 are associated with radiographic emphysema in HIV-positive individuals [26]. Prospective studies are needed to determine the relative importance of these possible causes.

The strengths of our study include the presence of an HIV-negative control group with similar exposures to tobacco smoking and recreational drugs and the use of well-validated measures of respiratory health status. Our high response rate (72%) suggests that participants were representative of the wider clinic population, who in turn are similar to the UK HIV-infected population as a whole [27].

Limitations include recruitment at a single study site and the cross-sectional nature of the data collected, meaning that temporality cannot be established. As people were not randomly selected to participate, recruitment bias is possible. Spirometry was our only objective measure of lung function, whereas several studies have suggested that impairment of gas transfer is more common than airflow obstruction in PLWH [28, 29]. The differences in age and ethnicity between groups could have influenced our results; however, our findings persisted after adjustment in multivariable analyses; and our sensitivity analysis is reassuring in that the difference in age distribution between HIV-positive and HIV-negative participants appeared to have little impact on the results.

Finally, we relied on self-reported HIV status in the HIV-negative participants, so we cannot exclude the possibility that HIV-positive or undiagnosed individuals were included in this group. However, we believe that this is unlikely to be a major issue as the prevalence of undiagnosed HIV infection in our sexual health clinics is low (data not shown). If this did occur, it would have acted to weaken the association between HIV infection and respiratory health status impairment.

Interventions that can preserve the respiratory health of people with chronic HIV infection are needed. The earlier use of ART may reduce non-AIDS-related comorbidities, including respiratory illness – although, notwithstanding a median duration of follow-up of only 2.8 years, this was not associated with differences in lung function decline in the recent Strategic Timing of Antiretroviral Treatment (START) trial [30]. However, the impaired respiratory health of PLWH despite effective virological suppression found in our study suggests that more than ART alone is required to maintain the health of this population. Reducing the effect of known risk factors such as tobacco is important, as many HIV-positive populations have high rates of smoking [31, 32]. Thus, the provision of appropriate smoking cessation services should be a priority. However, why HIV infection is associated with apparent worse respiratory health even in never-smokers remains uncertain and requires further investigation.

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Author contributions

J.B., S.C. and M.L. planned the study and obtained permissions; J.B., J.McG., H.C., D.I., M.J., L.S. and R.S. recruited participants for the study; J.B., J.McG., C.L., F.L., A.R. and M.L. analysed the data; J.B. created the first draft of the manuscript; all authors reviewed and approved the final manuscript.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Univariable associations between participant characteristics and respiratory health status impairment.
Table S2. Multivariable logistic regression of associations between MRC score ≥2 and participant characteristics.
Table S3. Comparison of HIV positive participants with an undetectable HIV viral load and HIV negative participants.