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ORIGINAL RESEARCH

Respiratory symptoms and chronic bronchitis in people with and without HIV infection

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Objectives

High rates of respiratory symptoms and chronic bronchitis (CB) are reported in people with HIV infection (PWH). We investigated the prevalence of respiratory symptoms and CB in PWH and HIV-negative people in the Pharmacokinetic and clinical Observations in PeoPle over fifty (POPPY) study.

Methods

Assessment of respiratory symptoms and CB was undertaken using the modified form of the St. George's Respiratory Questionnaire for chronic obstructive pulmonary disease (COPD). Univariate (χ^2 tests, Mann–Whitney *U* tests and Spearman's rank correlation) and multivariable (linear and logistic regression) analyses were performed to consider associations of respiratory symptoms with demographic, lifestyle and HIV-related parameters, and with depressive symptoms and quality of life.

Results

Among the 619 participants, respiratory Symptom scores were higher in older and younger PWH compared to older HIV-negative people, with median (interquartile range) scores of 17.7 (6.2, 39.5), 17.5 (0.9, 30.0) and 9.0 (0.9, 17.5), respectively ($P = 0.0001$); these differences remained significant after confounder adjustment. Sixty-three participants (10.2%) met the criteria for CB [44 (14.0%) older PWH, 14 (9.2%) younger PWH, and five (3.3%) older HIV-negative people; $P = 0.002$], with these differences also remaining after adjustment for confounding variables, particularly smoking status [older vs. younger PWH: odds ratio (OR) 4.48 (95% confidence interval (CI) 1.64, 12.30); $P = 0.004$; older PWH vs. HIV-negative people: OR 4.53 (95% CI 1.12, 18.28); $P = 0.03$].

Respiratory symptoms and CB were both associated with greater depressive symptom scores and poorer quality of life. No strong associations were reported between CB and immune function, HIV RNA or previous diagnosis of any AIDS event.

Conclusions

Respiratory symptoms and CB are more common in PWH than in demographically and lifestyle-similar HIV-negative people and are associated with poorer mental health and quality of life.

Keywords: chronic bronchitis, HIV infection, immunosuppression, patient-reported outcome measures, respiratory symptoms

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Introduction

With the increasing use of antiretroviral treatment (ART), and resulting near-normal life expectancy in people with HIV infection (PWH) in many parts of the world [1,2], clinical focus in this group has shifted towards other non-AIDS-related morbidities [3]. Chronic pulmonary disease and respiratory symptoms are reported to occur more frequently among PWH than in the general population [4,5], with rates of chronic obstructive pulmonary disease (COPD) in the Strategic Timing of AntiRetroviral Treatment (START) trial of 5.5–6.8% [6], although the reasons for these higher rates remain unclear.

Chronic bronchitis (CB) affects approximately 10 million people in the USA [7] and is associated with more rapid lung function decline, increased risk of COPD exacerbations, reduced health-related quality of life [8], and muscle weakness [9]. The primary risk factor for many respiratory conditions, including CB, in the general population is smoking [8], a behaviour that is prevalent in PWH [10]. However, other factors known to cause or exacerbate respiratory symptoms, including recreational drug use, are also common in PWH [11], and, even among those with controlled HIV viraemia on ART, previously diagnosed respiratory infections [including *Pneumocystis jirovecii* pneumonia (PJP), bacterial pneumonia, tuberculosis (TB) and cytomegalovirus (CMV) infection] in those with prior immunosuppression may continue to have a legacy effect. The identification of risk factors for respiratory symptoms and CB in PWH is therefore crucial if we are to effectively prevent and manage these conditions.

Here we describe the prevalence of respiratory symptoms and CB among PWH and HIV-negative people in the Pharmacokinetic and clinical Observations in PeOPle over fiftY (POPPY) study, describe their associations with patient-reported outcome measures, and investigate associations with markers of HIV infection and immunosuppression.

Materials and methods

POPPY is a prospective cohort study, conducted at seven clinical sites in the UK and one in Ireland, that aims to investigate the impact of HIV on the development and outcomes of comorbidities and pharmacotherapy among older PWH [12]. Three subgroups are studied: older PWH (≥ 50 years old), younger PWH (< 50 years old) and older HIV-negative people (≥ 50 years old). Eligible PWH acquired HIV through sexual transmission (either sex between men or sex between men and women; those acquiring HIV through other routes were excluded), were

cis-gender, and were of either white or black African ethnicity. The younger group of PWH were frequency-matched to the older PWH on gender, ethnicity, sexual orientation and participating clinic. HIV-negative participants were required to have a documented negative HIV test; this group was frequency-matched to the older PWH group on age, gender, ethnicity, sexual orientation and geographical location (in/out of London). All participants provided written informed consent and the protocol was approved by the UK National Health Service Health Research Authority and local ethics committees and/or institutional review boards.

POPPY participants are seen for approximately annual visits. At each visit, information is collected on socio-demographics, pharmacotherapy, family history, medical history, health care utilization and quality of life, with additional information on specific clinical conditions collected at some visits. Depressive symptoms are collected through the Center for Epidemiological Studies Depression (CES-D) and the Patient Health Questionnaire-9 (PHQ-9) scales, with health-related quality of life being assessed through the Short Form (36) Health Survey (SF-36). The resulting POPPY data set is linked to the UK Collaborative HIV Cohort (UK sites [13]) and to the UCD ID Cohort (Dublin [14]) for historic data on ART, prior AIDS events, and longitudinal data on CD4+ and CD8+ T-cell counts and HIV RNA.

Respiratory symptom assessment was introduced in September 2016, mid-way through the cycle of the third POPPY visit, using the short (40-question) version of the St. George's Respiratory Questionnaire for COPD (SGRQ-C) [15]. To minimize the visit length, and as the SGRQ-C was developed primarily for the assessment of respiratory symptoms in COPD, we modified the use of the questionnaire. Whilst all participants completed the first part of the SGRQ-C relating to the Symptoms component of the scale, only those who reported symptoms that affected them on several or most days of the week, who reported one or more episodes of sudden shortness of breath or who had only a few or no good days with few chest or breathing problems were asked to complete the full SGRQ-C for the Activity and Impacts components. We also used the SGRQ-C symptom questions to determine the presence of CB. Although CB is traditionally defined as cough and sputum for at least 3 months per year for 2 consecutive years, the use of SGRQ symptom questions has been shown to have good sensitivity (87%) and specificity (77%) for the traditional CB definition [16]. Participants were classified as having CB if they responded "almost every day" or "most days a week" to the following questions: "Over the last 4 weeks, I have coughed"

and “Over the last 4 weeks, I have brought up phlegm (sputum)”.

Statistical analysis

The scores for the Symptoms, Activity and Impacts components of the SGRQ-C as well as the total score were calculated as described in the study manual [15]. Missing responses to items relating to the Symptoms component were assumed to be negative, and individuals with missing data on more than one item for the Symptoms component, more than three items for the Activity component or more than five items for the Impacts component were excluded from the calculation of these scores. Scores were then adjusted to be comparable with the scores from the full SGRQ, with a total possible score ranging from 0 (perfect respiratory health) to 100 (worst respiratory health) and an established minimal clinically important difference (MCID) of four points for the total score [17]; component scores do not have an established MCID.

The distribution of the Symptoms component score (completed in all participants) was compared across groups defined by lifestyle and demographic factors using Mann–Whitney *U* tests. Factors considered were the POPPY study group (older PWH, younger PWH or older HIV-negative), gender, age (stratified as < 40 or ≥ 40; < 50 or ≥ 50; < 60 or ≥ 60; and < 70 or ≥ 70 years), ethnicity (white or black African), sexuality/mode of HIV infection (sex between men or sex between men and women), body mass index (BMI; five groups, defined by the quintiles of the distribution), smoking status (current/social smoker, ex-smoker or never smoker), recreational drug use in the past 6 months and educational attainment [low (none/lower school only/not known) or high (higher school/university/other higher education)]. Multiple linear regression was then used to investigate the association between POPPY study group and the Symptoms component score after log₁₀ transformation. Spearman's correlation was used to determine associations between the Symptoms component score and depressive symptom scores (CES-D and PHQ-9) and each subscale of the SF-36 questionnaire.

The proportions meeting the criteria for CB were compared between subgroups, as defined above, using χ^2 tests and univariable/multivariable logistic regression models to determine independent associations between POPPY study group and the prevalence of CB after adjusting for potential confounders. Depressive symptom scores and scores on each of the SF-36 subscales were summarized separately for those who did and did not meet the criteria for CB using medians and interquartile ranges (IQRs), and

were compared in the two groups using the Mann–Whitney *U* test. Associations with HIV-related parameters [current and nadir CD4 T-cell counts, duration of exposure to immunosuppression (years with a CD4 count < 200 cells/ μ L), current CD8 T-cell count, the current CD4:CD8 T-cell ratio, current HIV RNA, and prior diagnosis of any AIDS-related events] were tested for significance using χ^2 tests. All analyses were performed using SAS v9.3 (SAS Institute Inc., Cary, NC).

Results

Of the 1377 POPPY participants, 619 completed a SGRQ-C (315 older PWH, 152 younger PWH and 152 older HIV-negative people). There were no major differences in the characteristics of those attending for a visit who did and did not complete an SGRQ-C, other than the clinical site attended by participants, reflecting the staggered visit timing across sites. Table 1 shows the characteristics of participants with a completed SGRQ-C, stratified by study group.

Respiratory symptoms

Respiratory symptoms were more frequently reported in older and younger PWH compared to older HIV-negative people (Table S1a). The median (IQR) Symptoms component score was 17.7 (6.2, 39.5) in older PWH, 17.5 (0.9, 30.0) in younger PWH but only 9.0 (0.9, 17.5) in older HIV-negative people ($P = 0.0001$). In total, 149 (47.3%) older PWH, 56 (36.8%) younger PWH and 36 (23.7%) older HIV-negative people reported symptoms and were asked to complete the remainder of the SGRQ-C (Table S1b). Median (IQR) Activity scores were 33.1 (13.6, 59.5), 20.4 (7.0, 39.7) and 13.7 (7.0, 26.8), respectively, in the three groups ($P = 0.003$), whereas median (IQR) Impacts scores were 10.5 (4.0, 24.8), 6.9 (2.2, 19.3) and 4.0 (2.2, 9.2), respectively ($P = 0.009$). Overall, in this subgroup of participants reporting substantial symptoms, the median (IQR) total SGRQ-C score was 23.3 (12.2, 38.5; $n = 122$), 18.2 (9.6, 28.0; $n = 47$) and 13.3 (7.6, 18.4; $n = 34$) in the three groups, respectively ($P = 0.002$).

In addition to differences between PWH and HIV-negative people, unadjusted analyses showed that Symptoms scores were higher in men ($P = 0.0002$), those of white ethnicity ($P = 0.09$), those reporting sex between men ($P = 0.0009$), current/social and ex-smokers ($P = 0.0001$), those reporting recreational drug use in the past 6 months ($P = 0.001$) and those with lower educational attainment ($P = 0.001$) (Table 2). In unadjusted analyses, the mean log(Symptoms score) (LSS) was 0.13 [standard

Table 1 Characteristics of participants who provided respiratory data, stratified by Pharmacokinetic and clinical Observations in PeoPle over fifty (POPPY) study group

		Study group			
		Total	PWH ≥ 50 years	PWH < 50 years	HIV-negative ≥ 50 years
Number		619	315	152	152
Gender [n (%)]	Male	493 (79.6)	276 (87.6)	125 (82.2)	92 (60.5)
	Female	126 (20.4)	39 (12.4)	27 (17.8)	60 (39.5)
Ethnicity [n (%)]	White	536 (86.6)	275 (87.3)	124 (81.6)	137 (90.1)
	Black African	83 (13.4)	40 (12.7)	28 (18.4)	15 (9.9)
Sexuality/mode of infection [n (%)]	MSM	435 (70.3)	252 (80.0)	112 (73.7)	71 (46.7)
	Heterosexual	184 (29.7)	63 (20.0)	40 (26.3)	81 (53.3)
Age (years) [median (IQR)]		54 (50, 60)	56 (53, 62)	42 (36, 47)	57 (53, 62)
Body mass index (kg/m ²) [median (IQR)]‡		25.7 (23.2, 28.6)	25.7 (23.5, 28.7)	24.7 (22.4, 27.7)	26.5 (23.8, 29.3)
Smoking status [n (%)]‡	Current	127 (20.5)	65 (20.6)	46 (30.3)	16 (10.5)
	Ex-smoker	236 (38.1)	127 (40.3)	42 (27.6)	67 (44.1)
	Never/unknown	256 (41.4)	123 (3.0)	64 (42.1)	69 (45.4)
Recreational drug use in past 6 months [n (%)]	No	463 (74.8)	244 (77.5)	92 (60.5)	127 (83.6)
	Yes	156 (25.2)	71 (22.5)	60 (39.5)	25 (16.5)
Education† [n (%)]‡	Low/unknown	165 (26.7)	92 (29.2)	35 (23.0)	38 (25.0)
	High	454 (73.3)	223 (70.8)	117 (77.0)	114 (75.0)

IQR, interquartile range; PWH, people with HIV infection; MSM, men who have sex with men.

†Low: none/lower school only; high: higher school/university/other higher education.

‡Information was missing for the following numbers of participants: body mass index, $n = 8$; smoking status, $n = 2$; educational level, $n = 22$.

error (SE) 0.06] higher in older PWH (corresponding to a 34% higher value) when compared to younger PWH ($P = 0.05$), and was 0.40 (SE 0.06) higher (151%) in older PWH when compared to older HIV-negative people ($P = 0.0001$). Of the lifestyle/demographic factors, only gender, smoking status and educational attainment remained significant in adjusted analyses. After adjustment for these factors, the mean LSS in older PWH was 0.11 (SE 0.06) higher (29%) than in younger PWH ($P = 0.08$) but was 0.34 (SE 0.06) higher (119%) than in HIV-negative people ($P = 0.0001$).

There were strong correlations between the Symptoms component score and both the CES-D and PHQ-9, as well as each subscale of the SF-36 (Table 3) in the full cohort, with similar associations seen in the subgroup of PWH (data not shown). The median Symptoms component score was higher in the 202 participants with a previously reported chest problem than in the 417 without [27.2 (IQR 11.1, 47.3) and 11.1 (0.9, 21.7) in the two groups, respectively; $P = 0.0001$].

The 467 PWH in the study had a median CD4 count of 667 (IQR 522, 883) cells/ μ L, a median nadir CD4 count of 202 (IQR 98, 310) cells/ μ L ($n = 465$), a median CD8 count of 882 (IQR 652, 1160) cells/ μ L ($n = 450$) and a median current CD4:CD8 T-cell ratio of 0.75 (IQR 0.56, 1.05) ($n = 450$). Participants had been exposed to immunosuppression for a median of 0 (IQR 0, 0.5) years, all were currently receiving combination antiretroviral therapy (cART) and 424/465 (91.2%) had an HIV RNA level ≤ 50 HIV-1 RNA copies/mL. Associations with HIV-

related factors (Table 4) were generally weak and/or inconsistent.

Chronic bronchitis

Overall, 63 participants (10.2%) met the criteria for CB: 44 (14.0%) older PWH, 14 (9.2%) younger PWH and five (3.3%) older HIV-negative people ($P = 0.002$; χ^2 test). The prevalence of CB was higher in current and ex-smokers than in social or never smokers ($P = 0.0001$) but did not appear to differ by any other demographic or lifestyle factor (Table 2). In unadjusted logistic regression, the odds of having CB were 4.77 times as high in older PWH [95% confidence interval (CI) 1.85, 12.30; $P = 0.001$] and 2.98 times as high in younger PWH (95% CI 1.05, 8.50; $P = 0.04$) compared to older HIV-negative people (Fig. 1). These increased risks were not reduced after adjustment for smoking status alone [4.98 (95% CI 1.83, 13.57; $P = 0.002$) and 4.82 (95% CI 1.23, 18.92; $P = 0.02$), respectively] nor after adjustment for all factors shown in Table 2 [4.48 (95% CI 1.64, 12.30; $P = 0.004$) and 4.53 (95% CI 1.12, 18.28; $P = 0.03$), respectively], although CIs were wide (Fig. 1).

Those meeting the criteria for CB had more depressive symptoms and lower scores on each of the SF-36 subscales (Table 3). Thirty-seven (16.4%) of those with a previously reported chest problem met the criteria for CB compared to only 26 (6.6%) of those without ($P = 0.0001$; χ^2 test). As with the respiratory symptoms, associations of CB with HIV-related factors (Table 4) were generally weak and/or inconsistent.

Table 2 Median Symptoms scores and prevalence of chronic bronchitis in groups defined by demographic and lifestyle factors, and *P*-values from unadjusted analyses

		Median (IQR) Symptoms score	<i>P</i> -value	Chronic bronchitis [<i>n</i> (%)]	<i>P</i> -value
Total		15.0 (0.9, 31.2)		63 (10.2)	
POPPY study group	PWH ≥ 50 years	17.7 (6.2, 39.5)	0.0001	44 (14.0)	0.002
	PWH < 50 years	17.5 (0.9, 30.0)		14 (9.2)	
	HIV-negative ≥ 50 years	9.0 (0.9, 17.5)		5 (3.3)	
Gender	Male	17.5 (5.9, 33.4)	0.0002	55 (11.2)	0.15
	Female	11.1 (0.9, 17.9)		8 (6.4)	
Age	< 40 years	14.0 (11.1, 33.4)	0.96	6 (12.0)	0.40
	≥ 40, < 50 years	17.5 (0.9, 27.4)		8 (7.8)	
	≥ 50, < 60 years	14.3 (0.9, 33.1)		27 (9.2)	
	≥ 60, < 70 years	14.4 (5.9, 28.5)		17 (11.6)	
	≥ 70 years	14.1 (0.9, 47.1)		5 (20.0)	
Ethnicity	White	17.5 (5.9, 31.9)	0.09	57 (10.6)	0.45
	Black African	11.1 (0.9, 24.2)		6 (7.2)	
Sexuality/mode of infection	MSM	17.5 (5.9, 33.8)	0.0009	49 (11.3)	0.22
	Heterosexual	11.1 (0.9, 24.2)		14 (7.6)	
BMI	< 22.8 kg/m ²	17.5 (0.9, 38.2)	0.62	14 (11.6)	0.13
	≥ 22.8, < 24.8 kg/m ²	12.7 (0.9, 24.2)		7 (5.7)	
	≥ 24.8, < 26.9 kg/m ²	12.4 (0.9, 33.1)		19 (15.5)	
	≥ 26.9, < 29.5 kg/m ²	17.3 (6.2, 30.0)		13 (10.7)	
	≥ 29.5 kg/m ²	17.5 (5.9, 32.8)		10 (8.1)	
Smoking status	Current/social	23.8 (11.1, 45.0)	0.0001	27 (21.3)	0.0001
	Ex-smoker	17.5 (6.0, 33.3)		27 (11.4)	
	Never/unknown	11.1 (0.9, 21.7)		9 (3.5)	
Recreational drug use in past 6 months	No	11.1 (0.9, 27.8)	0.001	42 (9.1)	0.16
	Yes	18.6 (11.1, 37.4)		21 (13.5)	
Educational level†	Low/unknown	17.9 (6.0, 45.4)	0.001	20 (12.1)	0.42
	High	11.1 (0.9, 27.0)		43 (9.5)	

BMI, body mass index; IQR, interquartile range; MSM, men who have sex with men; POPPY, Pharmacokinetic and Clinical Observations in People over Fifty; PWH, people with HIV infection.

† Low: none/lower school only; high: higher school/university/other higher education.

Table 3 Associations of the Symptoms score and the prevalence of chronic bronchitis and patient-reported outcomes [Center for Epidemiological Studies Depression (CES-D), Patient Health Questionnaire-9 (PHQ-9) and Short Form (36) Health Survey (SF-36) scales], and *P*-values from unadjusted analyses

Measure	Symptoms score: Spearman's <i>r</i>	<i>P</i> -value	No chronic bronchitis Median (IQR)	Chronic bronchitis Median (IQR)	<i>P</i> -value
Depressive symptom score					
CES-D	0.41	0.0001	7 (3, 15)	16 (7, 28)	0.0001
PHQ-9	0.41	0.0001	2 (0, 6)	9 (2, 13)	0.0001
SF-36 subscale					
Physical functioning	-0.39	0.0001	95 (80, 100)	80 (40, 95)	0.0001
Physical limitations	-0.35	0.0001	100 (75, 100)	50 (0, 100)	0.0001
Emotional limitations	-0.31	0.0001	100 (67, 100)	67 (0, 100)	0.0005
Energy/fatigue	-0.42	0.0001	65 (50, 80)	50 (30, 65)	0.0001
Emotional wellbeing	-0.34	0.0001	80 (64, 92)	68 (48, 80)	0.0001
Social functioning	-0.38	0.0001	90 (68, 100)	68 (43, 90)	0.0001
Pain	-0.35	0.0001	80 (58, 100)	68 (32, 90)	0.0001
General health	-0.45	0.0001	70 (55, 85)	55 (30, 75)	0.0003

Discussion

In this large multicentre cohort of PWH, using a well-established and validated respiratory symptom questionnaire, we found that respiratory symptoms and CB were more common and had greater reported impact in PWH

than in demographically and lifestyle-similar HIV-negative people. These symptoms, which were associated with greater depressive symptoms and poorer quality of life, continued to be more common in PWH even after adjustment for known confounders. Importantly, and in contrast to our expectations, respiratory symptoms and CB

Table 4 Median Symptoms score and prevalence of chronic bronchitis in groups defined by HIV-related factors, and *P*-values from unadjusted analyses

		<i>n</i> (% of total group of PWH)	Median (IQR) Symptoms score	<i>P</i> -value	Chronic bronchitis <i>n</i> (% of those in each group)	<i>P</i> -value
Number		467 (100.0)			58 (12.4)	
Current CD4 count	< 200 cells/ μ L	8 (1.7)	33.8 (8.0, 56.1)	0.50	0 (-)	0.07
	\geq 200, < 350 cells/ μ L	30 (6.4)	24.2 (11.1, 50.8)		5 (16.7)	
	\geq 350, < 500 cells/ μ L	73 (15.6)	17.9 (6.2, 33.4)		7 (9.6)	
	\geq 500, < 750 cells/ μ L	184 (39.4)	17.5 (6.2, 30.5)		16 (8.7)	
	\geq 750 cells/ μ L	172 (36.8)	17.5 (5.9, 42.2)		30 (17.4)	
Nadir CD4 count	< 200 cells/ μ L	227 (48.6)	17.5 (9.2, 42.2)	0.35	29 (12.8)	0.01
	\geq 200, < 350 cells/ μ L	144 (31.1)	17.5 (0.9, 31.0)		13 (9.0)	
	\geq 350, < 500 cells/ μ L	61 (13.3)	19.3 (6.2, 36.2)		6 (9.8)	
	\geq 500, < 750 cells/ μ L	26 (5.4)	17.5 (0.9, 33.1)		7 (26.9)	
	\geq 750 cells/ μ L	7 (1.3)	17.5 (11.1, 57.0)		3 (42.9)	
Exposure to immunosuppression [†]	None	245 (52.5)	17.5 (0.9, 33.1)	0.07	29 (11.8)	0.87
	> 0–2 years	158 (33.8)	17.5 (7.7, 36.6)		20 (12.7)	
	> 2–4 years	26 (5.6)	15.0 (7.3, 45.4)		3 (11.5)	
	> 4 years	36 (7.7)	24.2 (14.7, 52.6)		6 (16.7)	
Current CD8 count	\leq 600 cells/ μ L	90 (20.0)	17.5 (6.2, 36.6)	0.81	12 (13.3)	0.82
	> 600, \leq 800 cells/ μ L	93 (20.7)	17.5 (0.9, 37.0)		10 (10.8)	
	> 800, \leq 1000 cells/ μ L	91 (20.2)	11.1 (5.9, 36.6)		13 (14.3)	
	> 1000, \leq 1200 cells/ μ L	70 (15.6)	17.5 (11.1, 28.1)		7 (10.0)	
	> 1200 cells/ μ L	106 (23.6)	17.5 (5.9, 42.5)		16 (15.1)	
Current CD4:CD8 ratio	\leq 0.4	53 (11.8)	17.3 (0.9, 24.2)	0.18	6 (11.3)	0.20
	> 0.4, \leq 0.6	91 (20.2)	17.5 (5.9, 34.8)		11 (12.1)	
	> 0.6, \leq 0.8	110 (24.4)	14.4 (6.2, 27.0)		8 (7.3)	
	> 0.8, \leq 1.0	69 (15.3)	11.1 (0.9, 33.4)		12 (17.4)	
	> 1.0	127 (28.2)	23.5 (7.7, 50.7)		21 (16.5)	
HIV RNA < 50 copies/mL	No	41 (8.8)	18.2 (11.1, 27.4)	0.92	4 (9.8)	0.76
	Yes	424 (91.2)	17.5 (6.2, 36.3)		54 (12.7)	
Ever had:						
Any AIDS event	No	339 (72.6)	17.5 (6.2, 33.1)	0.19	41 (12.1)	0.73
	Yes	128 (27.4)	23.6 (5.9, 46.0)		17 (13.3)	
Cytomegalovirus disease	No	457 (97.9)	17.5 (6.2, 35.2)	0.48	57 (12.5)	1.00
	Yes	10 (2.1)	24.2 (5.9, 50.6)		1 (10.0)	
<i>Pneumocystis jiroveci</i> pneumonia	No	425 (91.0)	17.5 (6.2, 35.0)	0.74	54 (12.7)	0.73
	Yes	42 (9.0)	24.2 (5.9, 50.6)		4 (9.5)	
Tuberculosis	No	433 (92.7)	17.5 (6.2, 35.0)	0.70	52 (12.0)	0.49
	Yes	34 (7.3)	17.5 (5.9, 45.4)		6 (17.7)	
Kaposi's sarcoma	No	439 (94.0)	17.5 (5.9, 33.4)	0.05	54 (12.3)	0.99
	Yes	28 (6.0)	25.7 (11.1, 53.3)		4 (14.3)	
Other AIDS event	No	424 (90.8)	17.5 (5.9, 33.4)	0.09	51 (12.0)	0.57
	Yes	43 (9.2)	24.2 (11.1, 47.0)		7 (16.3)	

IQR, interquartile range; PWH, people with HIV infection.

[†]Duration of time spent with a CD4 count < 200 cells/ μ L.

were not strongly associated with measures of immune dysfunction, suggesting that the higher rate seen in PWH may reflect unmeasured lifestyle, demographic or laboratory factors rather than specific disease effects or legacy effects of HIV disease *per se*.

PWH have been reported to have poorer respiratory health than the general population, although the reasons for this remain unclear. In a large systematic review and meta-analysis, Brown *et al.* [4] reported that, compared to HIV-negative people, PWH were more likely to have a cough in populations without access to ART. However, no strong association between HIV infection and the presence of a cough was seen among populations in

resource-rich settings with access to ART, suggesting that HIV may play a direct role in the development of respiratory symptoms. Using the SGRQ, Leung *et al.* [18] reported associations of respiratory health status with low CD4 count, systemic inflammation and forced expiratory volume among men with HIV infection in Canada; however, no assessment was made of associations with respiratory symptoms themselves, or with CB. Similarly, Kunisaki *et al.* reported worse SGRQ Symptoms scores in men with HIV infection compared to men without HIV infection. However, they did not investigate risk factors for having worse symptoms, the impact of symptoms on quality of life, or the presence of CB [19]. A higher

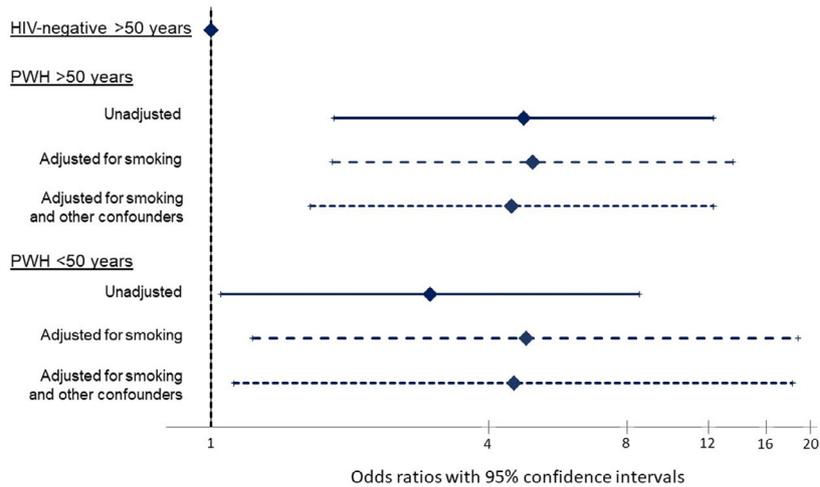


Fig. 1 Results from logistic regression analyses (odds ratios with 95% confidence intervals) for the association between Pharmacokinetic and clinical Observations in PeoPle over fifty (POPPY) study group and chronic bronchitis, before and after adjustment for (a) smoking and (b) smoking and all factors listed in Table 2.

prevalence of COPD has also been reported among PWH than among HIV-negative controls, particularly among those with a detectable HIV viral load [20] or low CD4 count [21,22]. Whilst we did not find associations between respiratory symptoms and measures of HIV status, we should note that very few PWH (8.1% of our cohort) had CD4 counts < 350 cells/ μ L, prior exposure to immunosuppression was uncommon and all PWH were on ART, restricting our ability to assess the effects of these factors.

As noted above, adjustment for socio-demographic and lifestyle factors, including smoking, did not substantially attenuate the associations with HIV infection in our study. It is possible that other confounders may be present which we have been unable to control for in analyses, including factors such as indoor air quality, second-hand smoke, occupational exposures, and exercise. Alternatively, HIV may exert an effect through novel, as yet undetermined, HIV-specific mechanistic pathways that are distinct from traditional measures of HIV control (CD4 count and HIV RNA). For example, recently published studies have suggested that lung disease in PWH could be related to factors such as a potential latent lung HIV reservoir, persistent viral protein production (e.g. Nef and Tat), oxidative stress, and alterations in the respiratory microbiome [23–27].

Although respiratory symptoms in the general population are associated with negative outcomes, including cardiovascular comorbidity, hospitalization and mortality [28,29], similar studies among PWH are lacking. Some studies have considered associations between lung function and outcomes in PWH, reporting associations of

airflow obstruction, impaired diffusing capacity and emphysema with mortality [30,31] and slower gait speed [32], the latter suggesting an association with frailty as also reported in the general population [9]. Whilst lung function is only moderately correlated with respiratory symptoms, these findings do suggest the potential for respiratory symptoms to impact on clinical outcomes, in addition to the strong associations with depressive symptoms and quality of life seen in our study. Although respiratory symptoms have been reported to have an impact on quality of life in the general population [33,34], there are few published data on their associations with mental health outcomes in PWH. Although a negative impact of respiratory symptoms on mental health would be hypothesized, we cannot rule out the possibility that poor mental health may result in behaviours (e.g. increased frequency of smoking or recreational drug use, decreased physical activity and increased use of polypharmacy with associated side effects) that themselves may increase the risk of respiratory symptoms and/or CB.

We confirmed a strong association between smoking and CB as in the general population [8,35], with no evidence that this association differed between PWH and HIV-negative people. Whilst it is known that smoking is associated with both higher COPD risk [20–22] and accelerated lung function decline [36] among PWH, the contribution of smoking to CB among PWH remains unclear. Whilst the importance of cigarette smoking cessation for the wider health of PWH has been widely documented [11,37–39], reports of CB in nonsmokers in the general population suggest the presence of other environmental, occupational and genetic risk factors [8].

Previous analyses of the original version of the SGRQ have demonstrated mean symptom scores of 7.63 (male)/6.49 (female) in healthy individuals compared to 22.55 (male)/12.43 (female) in patients with COPD and 32.82 (male)/26.34 (female) in patients with asthma [40], providing some indication of the expected values in different populations. The magnitude of the difference in Symptoms score between PWH and HIV-negative people in our study (10 points) suggests that a targeted assessment of respiratory symptoms in PWH might have high yield, particularly in older PWH who commonly reported respiratory symptoms. Although our study did not include a formal clinical assessment of respiratory symptoms, and we did not formally assess respiratory function using lung function tests (e.g. spirometry and tests measuring the diffusing capacity of carbon monoxide), which would have facilitated the diagnosis of underlying clinical conditions, our Symptoms score is associated with established risk factors for respiratory symptoms (e.g. smoking and male gender) and with a self-reported history of chest problems, suggesting that it is a valid marker of respiratory symptoms in this group.

The adaptation of the SGRQ for the diagnosis of CB [16] has been reported to have good diagnostic performance when assessed against the classic CB definition (chronic cough and sputum production for 3 months a year for 2 consecutive years). However, this SGRQ-based definition may identify a higher number of people with CB than the classic definition. Kim *et al.* assessed the presence of CB using both definitions in a cohort of 4513 current and former smokers and found that 26.1% met the traditional CB definition, while 39.9% met the SGRQ-based definition [16]. Thus, our findings may not be directly comparable to studies using the traditional CB definition. We are not aware of any previous data comparing CB prevalence in those with and without HIV infection. Our data suggest that smoking does not explain the higher CB prevalence in PWH, so other HIV-related factors may play a role. Despite this, our prevalence of CB was low, particularly in the HIV-negative group (possibly because of the low rate of cigarette smoking in the cohort overall compared to some other studies), and thus the power of our study to detect associations, particularly with HIV-related parameters, may be reduced.

Our study benefits from a large sample of PWH which is broadly representative of older PWH in Western European settings, a population with high levels of viral suppression. As such, our sample is predominantly made up of white MSM, limiting our ability to accurately report the prevalence of CB and respiratory symptoms in women or those of black and minority ethnic groups. In contrast to earlier studies, our study also benefits from the

inclusion of appropriately selected HIV-negative people with similar characteristics to the older PWH in the study, allowing us to investigate the role of HIV infection in the development of respiratory symptoms. However, associations that we can draw regarding causality are limited and we cannot rule out the possibility of unmeasured confounding. Furthermore, as items related to Activity and Impacts were only collected in the subgroup of participants who reported substantial symptoms, our findings relating to these components (and the total score) are not directly comparable to findings from other studies. Whilst the POPPY study captures information on current and past smoking, more detailed information on tobacco exposure (e.g. pack-years) or on smoking alternatives (e.g. vaping) may have provided additional ability to adjust for this confounding factor. Finally, it is possible that additional measures (e.g. the diffusing capacity of carbon monoxide, exhaled nitric oxide, or chest/cardiac computed tomography imaging) may provide additional information about the aetiology of respiratory conditions in this population.

Conclusions

In conclusion, respiratory symptoms and CB were more commonly reported in PWH than in demographically and lifestyle-similar HIV-negative people and were associated strongly with mental health and quality of life. The identification and management of risk factors for these conditions are essential if we are to ensure that PWH experience optimal health-related outcomes.

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Author contributions

CAS, KMK, PWGM and AW designed and obtained funding for the study. CAS performed all data analyses, undertook a literature search and prepared the first draft of the manuscript. DB provided study co-ordination and, together with EB, supported essential data collection and preparation of the data sets. KMK provided expert input to the interpretation of respiratory symptom data. FAP and MB provided clinical interpretation of study findings and are members of the POPPY study management team (with CAS, PWGM, MS and AW). JA, IW, JHV and MJ provided intellectual input to the POPPY study design, and supported study recruitment, data collection and clinical management. MS provided liaison with the HIV-infected patient community for all aspects of the study design and management. All authors provided critical review of the draft manuscript and have seen and approved the final version.

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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. (a) Respiratory questionnaire (SGRQ-C), part 1: Symptoms component. (b) Respiratory questionnaire (SGRQ-C), part 2: Activity and Impacts components