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ORIGINAL RESEARCH

Significant chronic airway abnormalities in never-smoking HIV-infected patients

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Objectives

The aim of the study was to describe chronic lung disease in HIV-infected never-smokers by looking at clinical, structural and functional abnormalities.

Methods

This comparative cross-sectional study included 159 HIV-infected never-smoking patients [mean (± standard deviation) age 54.6 ± 9.1 years; 13.2% female; 98.1% with undetectable viral load] and 75 nonmatched never-smoking controls [mean (± standard deviation) age 52.6 ± 6.9 years; 46.7% female]. We examined calcium scoring computer tomography (CT) scans or chest CT scans, all with a lung-dedicated algorithm reconstruction, to assess emphysema and airway disease (respiratory bronchiolitis and/or bronchial wall thickening), tested pulmonary function using spirometry, lung volumes and the diffusion lung capacity of carbon monoxide (DLCO), and assessed respiratory symptoms using the Chronic Obstructive Pulmonary Disease (COPD) Assessment Test (CAT).

Results

Twenty-five (17.2%) of the HIV-infected patients versus two (2.7%) of the controls had a CAT score > 10. Only 5% of the HIV-infected patients showed FEV1% < 80%, and 25% had DLCO < 75% of the predicted value. Based on the CT scans, they had increased prevalences, compared with the controls, of airway disease (37% versus 7.9%, respectively) and emphysema (18% versus 4%, respectively), with more severe and more frequent centrilobular disease. After correction for age, sex and clinical factors, HIV infection was significantly associated with CAT > 10 [odds ratio (OR) 7.7], emphysema (OR 4), airway disease (OR 4.5) and DLCO < 75% of predicted (OR 4).

Conclusions

Although comparisons were limited by the different enrolment methods used for HIV-infected patients and controls, the results suggest that never-smoking HIV-infected patients may present with chronic lung damage characterized by CT evidence of airway disease. A minority of them showed respiratory symptoms, without significant functional abnormalities.

Keywords: chronic obstructive pulmonary disease, HIV-1, multidetector computed tomography, respiratory function tests, respiratory signs and symptoms

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Introduction

HIV disease is characterized by low-grade inflammation and immune activation, which persist in people who experience effective antiretroviral therapy (ART)-induced immune reconstitution. This may account for the complex

contemporary disease spectrum characterized by cardiovascular disease, osteoporosis, anaemia, chronic kidney disease, cancer, physical function impairments and frailty, in all of which HIV infection acts as an independent risk factor [1].

It is a matter of debate whether chronic lung disease, including chronic obstructive pulmonary disease (COPD), should be considered in the context of HIV-associated non-AIDS (HANA) conditions. A high prevalence of respiratory symptoms, airflow limitation, and diffusion lung capacity of carbon monoxide (DLCO) impairment has been reported in HIV-infected patients [2–8]. It has also been suggested that HIV-infected patients may present with an accelerated form of COPD, with premature onset and rapid progression [9].

In most studies, smoking prevalence estimates in people living with HIV (PLWH) range from 40% to 84% [10,11]. Nearly 70% of patients attending our HIV clinic are current or former smokers, and often they present with respiratory symptoms resembling those of COPD. Moreover, COPD is now considered a chronic inflammatory disease [12]. This suggests that any chronic inflammatory condition may contribute to its pathogenesis. For example, it is estimated that one of the major worldwide causes of nonreversible airflow limitation may be tuberculosis [13,14].

As HIV disease is a chronic systemic inflammatory condition, we hypothesized that HIV may cause chronic lung disease even in the absence of a smoking history. To exclude the role of smoking, we investigated the prevalence of respiratory disease in lifelong never-smoking HIV-infected patients compared with HIV-negative never-smoking controls. The aim of this study was to describe the phenotype of chronic lung disease in HIV-infected never-smokers by looking at clinical, structural and functional pulmonary abnormalities.

Methods

Cohort description

This comparative cross-sectional study was approved by the institutional ethics review committee (AVEN - Area Vasta Emilia Nord comprehending Modena and others) (approval number 3788_90/13). Both HIV-infected patients and controls provided written consent to participate in this study.

The study design is briefly summarized in Figure S1. Never-smoking HIV-infected patients were recruited among subjects evaluated for cardiometabolic risk at the Modena HIV Metabolic Clinic (MHMC), a tertiary care hospital in northern Italy, between February 2012 and May 2017. The prevalence of noncommunicable comorbidities in MHMC patients is similar to that reported in other Italian and European cohorts [15–17]. Inclusion criteria were as follows: documented HIV-1 infection, age > 18 years, ART exposure > 18 months, no history of smoking (cumulative pack-years = 0), no history of major respiratory opportunistic infections, including tuberculosis and cryptococcal and *Pneumocystis jiroveci* pneumonias, and availability of at least one chest computed tomography (CT) scan and at least one spirometry measurement, with an interval of < 2 years between these diagnostic procedures. Chest CT scans were performed to assess coronary artery calcium (CAC) score in people attending the MHMC, when a dedicated radiologist was available. The clinical indication for CT scan was never related to respiratory symptoms or suspected respiratory diseases. Both CT scans and pulmonary function tests (PFTs) are routinely offered at the MHMC as part of the comorbidity assessment of asymptomatic patients.

Non-HIV-infected control group enrolment was conducted between November 2016 and April 2017. Participants were recruited from people who had undergone a chest CT scan in the same institution, within 2 years before the enrolment. Exclusion criteria were as follows: HIV infection, previous history of smoking, tuberculosis, systemic inflammatory diseases such as rheumatological or dermatological autoimmune conditions or inflammatory bowel diseases, and invasive malignant neoplasm requiring chemotherapy.

For both cases and controls, compliance with the exclusion criterion of being a current or former smoker was established through a detailed standardized questionnaire excluding the use of cigarettes, pipes, marijuana, cigarillos or electronic cigarettes [18]. No urinary cotinine test was performed.

Demographic and clinical data

Demographic data and lifestyle information collected at the time of study entry were as follows: age, sex, alcohol consumption [defined as absent, mild to moderate (1–2 alcohol units per day) or severe (> 2 alcohol units per day)] and level of physical activity [defined as absent, mild to moderate (1–3 h per week) or intense (> 3 h per week)].

On the same day as the CT scan for the HIV-infected patients and during the visit that followed enrolment for the controls, anthropometric measurements [waist circumference and body mass index (BMI)] were taken.

The comorbidity evaluation included: cardiovascular disease, hypertension, diabetes mellitus, osteoporosis, liver cirrhosis, kidney failure and previous neoplasm. Diagnostic criteria for comorbidities in the HIV-infected patients are reported in Appendix S1. During the visit that followed the enrolment of controls, data on comorbidities were collected by means of an interview about past illnesses and the evaluation of current medications. For both patient groups, multimorbidity was defined as the presence of at least two of the pathological conditions listed, excluding HIV infection.

Respiratory symptoms

Patients completed the COPD Assessment Test (CAT), a validated, short (eight-item) and simple questionnaire [19]. Respiratory symptoms were considered significant with a score of ≥ 10, which was previously used to define mild COPD in smokers [20].

Structural changes on thoracic CT scan

Chest scans were performed with a volume CT 64-slice scanner (GE Medical Systems, Milwaukee, WI). CAC scoring CT scans of the HIV-infected patients were acquired from lung apices to bases, and image reconstruction with a dedicated algorithm was always obtained for the evaluation of the whole lung parenchyma. As thoracic CT scans previously undergone by controls were performed as a result of different referrals, technical parameters of image acquisition were slightly heterogeneous. However, all scans included a reconstruction with a dedicated algorithm for lung parenchyma. Technical details are reported in Appendix S1. CT images of both HIV-infected patients and controls were evaluated for findings of pulmonary emphysema by three radiologists blinded to HIV serostatus, by consensus image reading. Emphysema types were classified as paraseptal, centrilobular or mixed. Emphysema severity was graded using a previously described semiquantitative score [21]. A total score of 0, 1–4 and > 4 indicated absence of emphysema, mild to moderate emphysema and severe emphysema, respectively. Airway disease was defined as the presence of at least one of the typical findings of COPD with airway involvement: respiratory bronchiolitis as the expression of small airway disease, and bronchial wall thickening as a sign of chronic bronchitis [22]. Other structural lung abnormalities included bronchiectasis and parenchymal noncalcified nodules > 4 mm in diameter. Further details on CT parameters and image evaluation are reported in Appendix S1. Figure S2 shows CT images from the HIV-infected never-smoking patients depicting signs of emphysema and airway disease.

Functional assessment

Pulmonary function testing (PFT) is part of the routine screening for lung disease performed in the MHMC, including pre- and post-bronchodilator spirometry and measurement of residual volume (assessed using the helium dilution technique), total lung capacity, and DLCO following European Respiratory Society and American Thoracic Society guidelines [23]. DLCO measurement has been included in HIV lung function screening since 2014. PFT results were expressed as a percentage of predicted values based on age, sex, race, weight and height. HIV-uninfected controls underwent identical PFT on the same day as the clinical assessment following enrolment. A post-bronchodilator ratio between forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) ratio < 0.70 was used to diagnose COPD, as per guidelines [24]. Further information on the PFT methodology is reported in Appendix S1.

Statistical analyses

Results are expressed as mean ± standard deviation (SD) or median and interquartile range for continuous variables based on the normality of distribution, and as frequencies and percentages for categorical variables. The significance of differences in continuous data between HIV-infected patients and controls was determined with a *t*-test for normally distributed variables and a Mann–Whitney *U*-test for nonnormally distributed variables, while the significance of differences in categorical data was determined with a χ^2 test and Fisher's exact test.

Univariable analyses, conducted with parametric and nonparametric tests as appropriate, were used to identify demographic and clinical factors associated with the presence of symptoms and structural (presence of emphysema and presence of airway disease) and functional (DLCO < 75% of predicted and FEV1 < 80% of predicted) abnormalities. Logistic regression analyses were conducted to identify independent predictors for symptoms and structural and functional abnormalities, by using as covariates age, sex and clinically significant predictors identified in univariable analyses.

All statistical analyses were performed with the R software, version 3.4.1.

Results

Population characteristics

Of 2553 HIV-infected patients who attended the MHMC between February 2012 and May 2017, 750 (29.4%) were

never-smokers. We recruited 159 never-smoking patients [mean (± SD) age 54.59 ± 9.12 years; 13.2% female] with at least one CT scan and one PFT available, performed during the same medical assessment in 80% of cases. An exploratory analysis confirmed that the age and sex of never-smokers attending the MHMC who did not undergo CT and PFT within 2 years were similar to those of the enrolled patients.

The individuals included had been HIV-infected for a median of 18.1 [interquartile range (IQR) 12.7–22.17] years; the HIV risk factor was men who have sex with men (MSM) in 80 patients (50.31%) and an HIV-infected partner in 60 patients (37.74%), while three (1.89%) of them were former injecting drug users (IDUs). The mean (± SD) nadir CD4 count was 215.52 (±145.35) cells/μL, the mean (± SD) current CD4 count was 680.74 (± 263.35) cells/μL, and 156 patients (98.11%) had an undetectable HIV RNA viral load. The median cumulative exposure to highly active antiretroviral therapy (HAART) was 7 (IQR 3.33–9) years for early HAART (until 2005; mainly unboosted protease inhibitors and more toxic nucleoside reverse transcriptase inhibitors) and 11.4 (IQR 11.4–11.4) years for late HAART (from 2006 onwards; mainly boosted protease inhibitors and integrase inhibitors). A total of 145 patients from this group completed the CAT questionnaire on the same day as the PFT.

Ninety-eight HIV-uninfected subjects met the control group inclusion criteria, of whom 23 were unavailable for study participation. Overall, 75 HIV-negative never-smoking patients were enrolled [mean (± SD) age 52.6 ± 6.9 years; 46.7% female]. Clinical referrals for CT scan in controls were principally for staging for noninvasive nonpulmonary neoplasm, follow-up of known pulmonary nodules, and exclusion of pulmonary embolism; more details are reported in Appendix S1. Figure S3 displays the patient enrolment flow chart for cases and controls.

Demographic and clinical characteristics of the studied population are reported in Table 1. Cases and controls did not differ in age or lifestyle. However, the sex distribution was significantly different, with a predominance of men in the HIV-infected group. The HIV-infected patients had significantly lower BMI and waist circumference. Most comorbidities and multimorbidity were significantly more prevalent in the HIV-infected patients, while the controls had a higher prevalence of neoplasm history, cancer staging being the main reason for CT scans.

Lung abnormalities

Respiratory symptoms

Compared to our controls, the HIV-infected patients had a significantly higher mean CAT score and a higher prevalence of respiratory symptoms, including cough ($P = 0.02$), phlegm ($P < 0.01$), chest tightness ($P = 0.08$), breathlessness walking up a hill or one flight of stairs ($P < 0.01$), and limitations leaving home because of respiratory disease ($P < 0.01$; Fig. 1). The percentage of patients with CAT ≥ 10 was significantly higher in the patient group compared to controls. However, only 17% had significant respiratory symptoms (Table 2).

Structural changes

CT signs of lung emphysema were found in 29 (18.4%) HIV-infected patients (versus 4% of controls; significant difference, $P < 0.01$), and nearly half of them had an emphysema score > 1. Controls had only paraseptal emphysema, while 57% of the HIV-infected patients with emphysema had centrilobular changes, alone or in association with paraseptal changes. CT signs of airway disease were found in 59 (37.1%) HIV-infected patients, while 31 (27.4%) had bronchiectasis, both bronchiectasis and airways disease (two different entities) have a prevalence of 6 (7.9%) in the controls (significant differences, $P < 0.01$ and $P = 0.02$). Finally, the prevalence of noncalcified nodules was higher in controls, probably because nearly 20% of them had undergone chest CT for pulmonary nodule follow-up (Table 2).

Functional abnormalities

The FEV1/FVC ratio was not significantly different between the two populations. Only two HIV-infected patients (versus none of the controls) had a post-bronchodilator FEV1/FVC ratio < 0.70 and were diagnosed as having COPD. FEV1% predicted was significantly lower in HIV-infected patients. However, only 5% of them showed FEV1% predicted < 80%. The HIV-infected patients had slightly increased pulmonary volumes, particularly residual volume (RV), and an initial DLCO decrease, with a diffusion capacity < 75% of the predicted value in 32 (25.4%) of them (Table 2).

Factors associated with lung abnormalities

Table 3 summarizes the results of the univariable analyses for demographic and clinical factors associated with the presence of symptoms and structural and functional abnormalities, while Figure 2 shows the results of different multivariable models.

HIV infection was the only factor independently associated with a CAT score ≥ 10, with an odds ratio (OR) of 7.74 [95% confidence interval (CI) 1.94–52.85; $P = 0.01$], after correction for age, sex and multimorbidity.

HIV infection was significantly associated with the presence of emphysema (OR 4.03; 95% CI 1.31–17.68; $P = 0.01$) after correction for age and sex, and airway

Table 1 Demographic and clinical characteristics of the studied population

Demographic and clinical characteristics	All (n = 234)	HIV-positive (n = 159)	HIV-negative (n = 75)	Point estimate of the difference (95% CI)
Age (years)	53.97 ± 8.52	54.59 ± 9.12	52.64 ± 6.95	−1.97 (−4.35; 0.41)
Female sex	54 (23.1)	21 (13.2)	33 (44)	**−0.30 (−0.43; −0.18)**
Ethnicity				
Caucasian	227 (97.0)	153 (96.2)	74 (98.7)	−0.025 (−0.06; 0.01)
African	5 (2.1)	5 (3.1)	0 (0)	**0.031 (0.00; 0.06)**
Hispanic	2 (0.9)	1 (0.7)	1 (1.3)	−0.01 (−0.03; 0.02)
Alcohol consumption				
Absent	156 (68.1)	109 (68.6)	52 (69.3)	0.03 (−0.1; 0.16)
Mild/moderate	72 (31.4)	49 (30.8)	23 (30.7)	−0.01 (−0.02; 0.01)
Severe	1 (0.44)	1 (0.6)	0 (0)	−0.02 (−0.15; 0.11)
Physical activity				
Absent	113 (49.3)	81 (51)	37 (49.3)	−0.02 (−0.16; 0.12)
Mild/moderate	98 (42.8)	63 (39.6)	35 (46.7)	−0.05 (−0.11; 0.01)
Intense	18 (7.9)	15 (9.4)	3 (4)	0.07 (−0.07; 0.20)
Weight (kg)	75.64 ± 13.6	74.54 ± 12.89	77.89 ± 14.77	3.33 (−0.4; 7.09)
Height (cm)	170.81 ± 8.94	171.18 ± 8.17	170.04 ± 10.35	−1.11 (−3.62; 1.41)
BMI (kg/m^2)	25.89 ± 4.07	25.41 ± 3.81	26.88 ± 4.41	**1.44 (0.31; 2.58)**
Waist circumference (cm)	93.66 ± 11.64	92.66 ± 10.78	96.53 ± 13.53	**3.63 (0.00; 7.27)**
Hypertension	135 (57.7)	109 (68.6)	26 (34.7)	**−0.34 (−0.47; −0.20)**
Previous cardiovascular events	11 (4.7)	9 (5.7)	2 (2.7)	−0.03 (−0.08; 0.02)
Osteoporosis	46 (19.7)	42 (26.4)	4 (5.3)	**−0.21 (−0.30; −0.12)**
Diabetes	39 (16.7)	37 (23.3)	2 (2.7)	**−0.18 (−0.26; −0.10)**
Kidney failure	24 (10.3)	24 (15.1)	0 (0)	**−0.14 (−0.20; −0.09)**
Liver cirrhosis	14 (6)	14 (8.8)	0 (0)	**−0.10 (−0.14; −0.05)**
Previous neoplasm	60 (25.6)	18 (11.3)	42 (56)	**0.44 (0.32; 0.57)**
Multimorbidity	120 (51.3)	100 (62.9)	20 (26.7)	**−0.36 (−0.49; −0.23)**

Significant differences between the two groups are reported in bold. Continuous variables are expressed as mean ± standard deviation, and categorical variables as n (%). CI, confidence interval; BMI, body mass index.

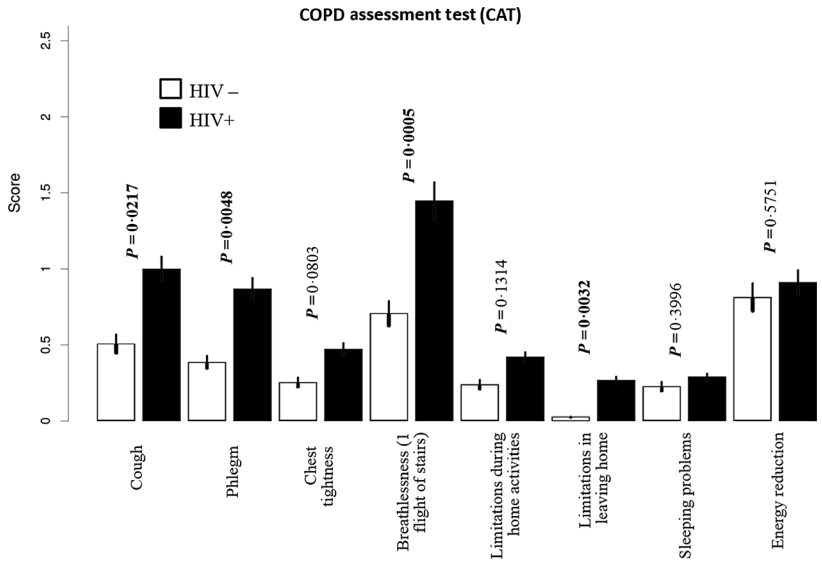

Fig. 1 Bar plot representing mean scores in cases and controls for each Chronic Obstructive Pulmonary Disease Assessment Test (CAT) question, with relative P values.

disease (OR 4.48; 95% CI 1.65–14.64; P = 0.01) after correction for age, sex, multimorbidity and waist circumference.

HIV infection persisted as a predictor of DLCO reduction after correction for age and sex, with an OR of 4.04 (95% CI 1.67–10.95; P = 0.003; Fig. 2).

Table 2 Respiratory symptoms, chest computed tomography (CT) findings, and pulmonary function test results of the studied population, with respective point estimate of the difference and 95% confidence interval (CI)

Respiratory symptoms				
	All (n = 220)	HIV-positive (n = 145)	HIV-negative (n = 75)	Point estimate of the difference (95% CI)
CAT score	4.82 ± 5.29	5.68 ± 5.9	3.16 ± 3.32	**−2.52 (−3.96; −1.07)**
Patients with CAT score ≥ 10	27 (12.3)	25 (17.2)	2 (2.7)	**−0.15 (−0.23; −0.07)**
	All (n = 234)	**HIV-positive (n = 159)**	**HIV-negative (n = 75)**	**Point estimate of the difference (95% CI)**
Structural changes on chest CT scan				
Emphysema score	0.26 ± 0.83	0.36 ± 0.98	0.04 ± 0.2	**−0.33 (−0.56; −0.09)**
Emphysema score				
0	201 (86.3)	129 (81.6)	72 (96)	**0.14 (0.06; 0.22)**
1	18 (7.7)	15 (9.5)	3 (4)	−0.05 (−0.11; 0.01)
> 1	14 (6)	14 (8.9)	0 (0)	**−0.09 (−0.14; −0.04)**
Emphysema type				
Paraseptal	37 (66.1)	12 (42.9)	3 (100)	**−0.44 (−0.63; −0.24)**
Centrilobular	14 (25)	12 (42.9)	0 (0)	**−0.16 (−0.30; −0.02)**
Mixed	5 (8.9)	4 (14.2)	0 (0)	**0.60 (0.41; 0.79)**
Respiratory bronchiolitis	39 (16.7)	38 (23.9)	1 (1.3)	**−0.21 (−0.28; −0.13)**
Bronchial wall thickening	45 (19.2)	40 (25.2)	5 (6.7)	**−0.17 (−0.26; −0.08)**
Bronchiectasis	37 (15.8)	31 (27.4)	6 (7.9)	**−0.12 (−0.20; −0.03)**
Noncalcified nodules > 4 mm	33 (14.1)	16 (10.1)	17 (22.7)	**0.12 (0.01; 0.22)**
Pulmonary function testing results				
RV (% predicted)	124.55 (108.3–142)	133 (117–152.1)	115 (102–126.5)	**−21.3 (−31.9; −10.7)**
FVC (% predicted)	109.8 (99.5–118)	105.3 (95–112)	117 (109.5–123)	**13.4 (8.6; 18.2)**
TLC (% predicted)	111 (102.6–119)	110.4 (101–117)	112 (106.5–119)	**1.36 (3.44; 6.16)**
FEV1 (% predicted)	107 (98–117.2)	105 (95.8–113.2)	112 (106–121.5)	**10.07 (5.42; 14.73)**
FEV1 < 80% predicted	8 (3.41)	8 (5.03)	0 (0)	**0.05 (0.01; 0.08)**
RV/TLC	38.1 (33.8–42.9)	41.0 (35.8–45.1)	35.31 (30.8–39.1)	**−5.86 (−8.09; −3.62)**
FEV1/FVC	80.2 (76.9–83.7)	80.4 (76.6–84.2)	80.1 (77.7–82.7)	−0.30 (−2.04; −1.44)
DLCO (% predicted) (n = 201)	83.1 (77–90.7)	81 (73–89.5)	85 (81–93.5)	**6.12 (2.40; 9.83)**
DLCO < 75% predicted	42 (20.9)	32 (25.4)	10 (13.3)	**0.13 (0.01; 0.24)**

Significant differences between the two groups are reported in bold. As DLCO measurement has been included in PFT screening since 2014, this variable was available for 126 of 159 HIV-infected patients. Continuous variables are expressed as mean ± standard deviation or median (interquartile range), and categorical variables as n (%). CAT, Chronic Obstructive Pulmonary Disease Assessment Test; DLCO, diffusion lung capacity of carbon monoxide; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second; RV, residual volume; TLC, total lung capacity.

FEV1% predicted < 80% was not significantly associated with demographic and clinical factors. However, a trend was found for HIV infection (Table 1).

Discussion

In never-smoking PLWH, we identified significant signs of airway disease even in the absence of a high burden of respiratory symptoms or functional abnormalities.

Previous studies reported a high prevalence of chronic lung disease in HIV-infected patients [2–7,25–,27]. The novelty of this study in never-smokers lay in the description of HIV-related chronic lung disease through a multidimensional approach including functional impairment, symptoms and structural changes. Moreover, this study investigated a particularly difficult-to-recruit population in both HIV-infected patients and the general population.

A recent study showed the high population attributable fractions of traditional risk factors, including smoking, for different HANA conditions [28]. In our study, we had the unique possibility of evaluating the effect of HIV itself, which probably accounts for a smaller proportion of the risk than smoking.

A minority of our HIV-infected never-smokers (17%) showed significant respiratory symptoms resembling COPD. This rate was higher than in controls, but similar to what has been reported in other studies conducted in the general population, including the cohort described by Woodruff *et al.* [20]. Although the population of this cohort was substantially different from our HIV-infected cohort, it is worth noting that the prevalence of CAT ≥ 10 in never-smoking subjects was 16%, similar to our finding. Moreover, analysing CAT answers in detail, HIV-infected and uninfected patients mainly differed in cough, phlegm, breathlessness, chest tightness, and limitations in leaving home. These symptoms are not specific

Table 3 Demographic and clinical factors in the studied population grouped according to structural computed tomography (CT) findings (emphysema and airway disease), respiratory symptoms (defined as CAT score ≥ 10) and functional abnormalities (DLCO <75% of predicted value)

Factors associated with structural changes on CT scan

	All (n = 234)	Emphysema = 0 (n = 202)	Emphysema > 0 (n = 32)	P	No airway disease (n = 169)	Airway disease (n = 65)	P
Age (years)	53.97 ± 8.52	53.58 ± 8.3	56.38 ± 9.56	0.19	53.37 ± 8.19	55.51 ± 9.21	**0.05**
Male sex	180 (76.9)	151 (74.8)	29 (90.6)	0.08	124 (73.4)	56 (86.2)	0.06
HIV-positive	159 (67.9)	130 (64.4)	29 (90.6)	**<0.01**	100 (59.2)	59 (90.8)	**<0.01**
Alcohol consumption							
Absent	156 (68.1)	139 (70.2)	17 (54.8)	0.20	112 (67.1)	44 (71)	0.20
Mild/moderate	72 (31.4)	58 (29.3)	14 (45.2)		55 (32.9)	17 (27.4)	
Severe	1 (0.44)	1 (0.5)	0 (0)		0 (0)	1 (1.6)	
Physical activity							
Absent	113 (49.3)	98 (49.5)	15 (48.4)	0.52	83 (49.7)	30 (48.4)	0.98
Mild/moderate	98 (42.8)	86 (43.4)	12 (38.7)		71 (42.5)	27 (43.5)	
Intense	18 (7.9)	14 (7.1)	4 (12.9)		13 (7.8)	5 (8.1)	
BMI (kg/m^2)	25.89 ± 4.07	26.03 ± 4.12	25.05 ± 3.7	0.34	26.24 ± 4.1	24.98 ± 3.88	**0.01**
Waist circumference (cm)	93.66 ± 11.64	93.9 ± 11.8	92.1 ± 10.6	0.66	94.76 ± 12.25	90.97 ± 9.55	**0.04**
Multimorbidity	120 (51.3)	103 (51)	17 (53.1)	0.97	80 (47.3)	40 (61.5)	0.07

Factors associated with respiratory symptoms (CAT ≥ 10) and functional abnormalities on PFT (DLCO ≥ 75%)

	All (n = 220)	CAT < 10 (n = 193)	CAT ≥ 10 (n = 27)	P	DLCO ≥ 75% (n = 159/201)	DLCO < 75% (n = 42/201)	P
Age (years)	53.94 ± 8.53	53.91 ± 8.49	54.15 ± 8.93	0.64	53.38 ± 8.08	54.52 ± 9.44	0.43
Male sex	167 (75.9)	147 (76.2)	20 (74.1)	1	126 (79.2)	26 (62)	**0.03**
HIV-positive	145 (65.9)	120 (62.2)	25 (92.6)	**<0.01**	94 (59.1)	32 (76.2)	0.06
Alcohol consumption							
Absent	145 (66.8)	129 (67.5)	16 (61.5)	0.76	108 (68.8)	31 (75.6)	0.64
Mild/moderate	71 (32.7)	61(31.9)	10 (38.5)		48 (30.6)	10 (24.4)	
Severe	1 (0.46)	1 (0.5)	0 (0)		1 (0.6)	0 (0)	
Physical activity							
Absent	108 (49.8)	95 (49.7)	13 (50)	0.66	77 (49)	21 (51.2)	0.49
Mild/moderate	93 (42.9)	83 (43.5)	10 (38.5)		68 (43.3)	19 (46.3)	
Intense	16 (7.4)	13 (6.8)	3 (11.5)		12 (7.6)	1 (2.5)	
BMI (kg/m^2)	25.94 ± 4.07	25.98 ± 4.06	25.68 ± 4.18	0.66	25.93 ± 4.3	25.6 ± 3.9	0.97
Waist circumference (cm)	93.89 ± 11.52	93.87 ± 11.63	94 ± 10.98	0.93	94.29 ± 11.99	92.26 ± 11.62	0.45
Multimorbidity	111 (50.5)	91 (47.2)	20 (74.1)	**0.02**	76 (47.8)	24 (57.1)	0.37

Significant differences between the two groups are reported in bold. Continuous variables are expressed as mean ± standard deviation, and categorical variables as n (%). BMI, body mass index; CAT, Chronic Obstructive Pulmonary Disease Assessment Test; DLCO, diffusion lung capacity of carbon monoxide; FEV1, forced expiratory volume in the first second; PFT, pulmonary function test.

to chronic lung disease and could reflect other conditions common in HIV infection, such as congestive heart failure or pulmonary hypertension.

Only two of 159 patients presented with airflow limitation as defined by a post-bronchodilator FEV1/FVC ratio < 0.70, while only 5% showed a clinically significant FEV1 reduction. Even the reduction in DLCO compared to controls was slight. In the HIV-infected patients, a slight RV increase was found. In an exploratory analysis, this was significantly associated with emphysema (P = 0.05; data not shown).

This paucity of symptoms and functional abnormalities, however, did not correspond to a lack of morphological changes, observed regardless of any suspicion of lung disease. In fact, in the HIV-infected patients, the CT scans showed a significant burden of abnormalities, especially located in the airways. HIV-infected patients had a moderate prevalence of emphysema (18%) and a high prevalence of airway disease in terms of bronchial wall thickening and respiratory bronchiolitis (37%) as well as bronchiectasis (27%). These rates are higher compared to both our HIV-negative controls and large never-smoking cohorts from the general population (3–11% for emphysema and 10% for airway disease) [29–31]. An important finding was the morphological type of emphysema. In our controls, all emphysematous changes were paraseptal. In our cases, conversely, 50% of them were centrilobular, which are usually described in smokers only. As

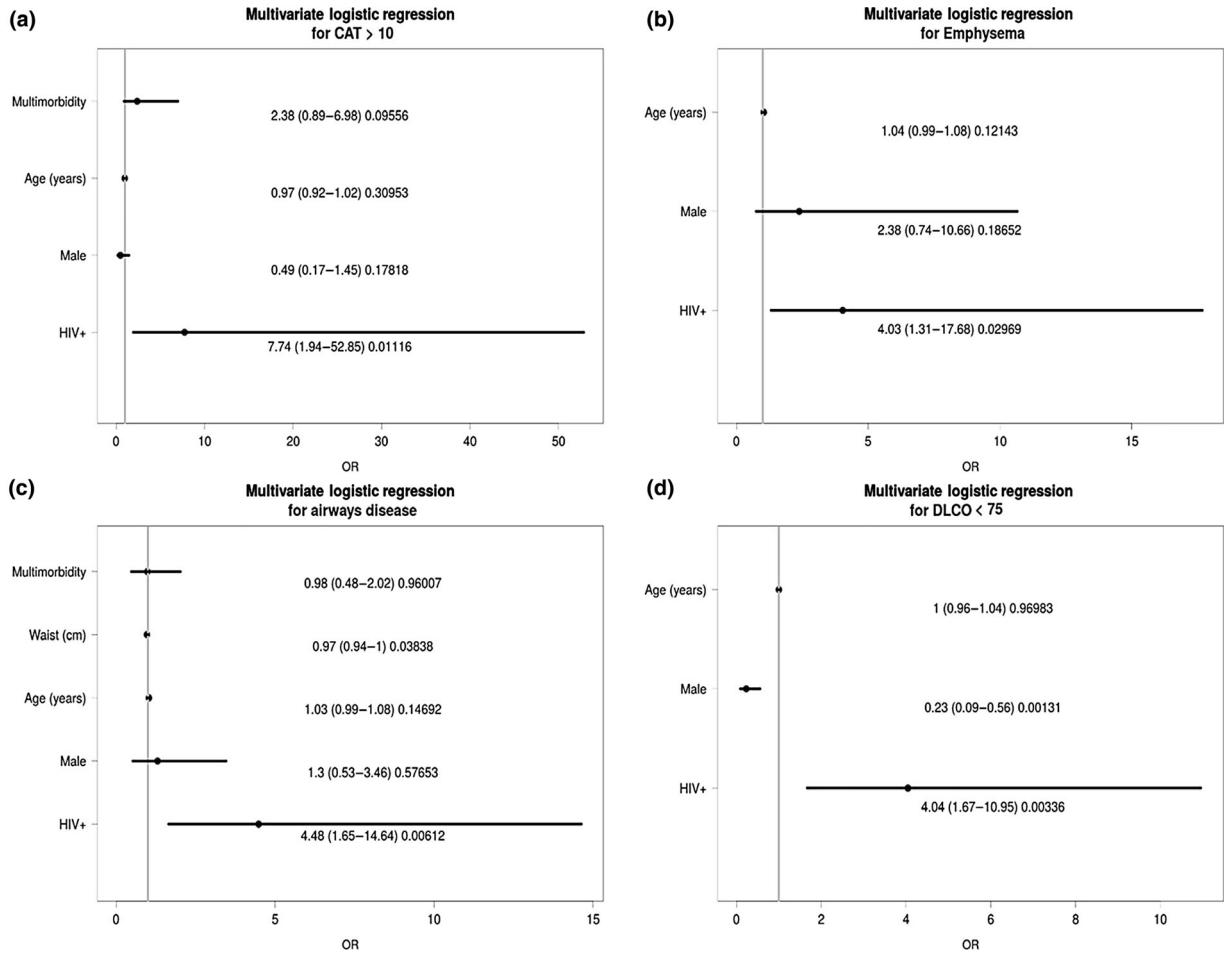

Fig. 2 Forest plot diagrams depicting factors associated with respiratory symptoms [Chronic Obstructive Pulmonary Disease Assessment Test (CAT)>10] (a), structural computed tomography (CT) findings of emphysema (b) and airways disease (c), and diffusion lung capacity of carbon monoxide (DLCO) reduction < 75% of the predicted value (d), in multivariable models. Covariates included age, sex and significant predictors in univariable analyses. Body mass index (BMI) was not included in model C because of its collinearity with waist circumference. OR, odds ratio.

centrilobular emphysema is considered to be subsequent to obstructive and inflammatory bronchiolitis [22,32], and considering the large burden of airway abnormalities in our population, we hypothesize that the origin of HIV-related pulmonary disease (CHPD) could be located in the small airways rather than in the lung parenchyma. HIV infection may induce chronic respiratory damage, which is probably mainly located in the airways, even in the absence of a smoking history.

This finding is consistent with the results of one of the few studies that addressed chronic lung disease in never-smoking HIV-infected patients: this reported an increased lung clearance index, a measure of lung physiology derived from multiple nitrogen breath washout, which identifies preclinical small airway dysfunction [33]. In another study by the same group including uninfected controls, HIV infection was not independently associated with emphysema, although PLWH with emphysema had more respiratory symptoms [34]. Although the HIV-related clinical characteristics of the cohort included in this last study appear to be similar to those of the MHMC cohort, the radiological findings suggest that the two cohorts are different. In the study by Ronit *et al.*, visually assessed emphysema was reported in a very small percentage of never-smoking patients (0.4%). Airway disease was not assessed.

Multivariable analyses showed that HIV *per se* may be the driver of all chronic lung abnormalities. Smoke risk was excluded as per protocol. Age, sex and multimorbidity were excluded in multivariable logistic regressions.

HIV-infected patients had a 7-fold increased risk of symptoms and a 4-fold increased risk of lung CT structural changes and DLCO impairment compared with controls.

We can hypothesize a pathogenic mechanism similar to that suggested for cardiovascular disease in never-smoking HIV-infected individuals [35,36]. The underlying mechanisms of CHPD might include persistent immunological activation and systemic inflammation, protease–antiprotease imbalance, oxidative stress, an altered lung microbiome, and ART toxicity. This multifactorial environment may lead to CHPD being considered as a component of the complex panorama of HANA conditions.

Our results suggest the need for larger prospective studies to evaluate whether HIV-infected patients may benefit from tailored screening for chronic lung disease during their routine assessment, as they represent a particular population with an additional risk compared to the general population. Different diagnostic algorithms to identify at-risk patients have been suggested. Lambert *et al.* recently proposed a structured questionnaire to identify HIV-infected patients who need spirometry [4], while Shirley *et al.* suggested using peak flow reduction in addition to a clinical questionnaire [37]. In our study, HIV infection was not associated with a significant obstructive pattern. In view of the small sample size, further studies are needed to confirm our results. However, it may be the case that obstruction comes as a late sign of CHPD, preceded by structural changes, and spirometry alone might be nonsensitive to identify at-risk patients. Our results suggest that future studies should focus on potential additional tests to assess small airways, although it has been pointed out that only a combination of different physiological tests, and possibly imaging analyses, may capture small airway disease [38].

The rationale of screening also depends on the possible interventions that could be envisaged for high-risk individuals. In a previous study in both smokers and never-smokers attending the MHMC, we were able to demonstrate a progression of CT findings potentially associated with adverse health outcomes [39]. Closer disease monitoring could be applied in high-risk patients to identify lung disease progression. Moreover, HIV-infected patients are at increased risk for lung cancer [40], and conditions such as emphysema and chronic bronchitis have been associated with lung cancer risk independently of smoking [41]. HIV-infected patients with lung abnormalities could be those at higher risk of developing lung cancer. It may be premature to consider treatment interventions for CHPD in PLWH. However, it is worth noting that a study in the setting of a cardiovascular screening programme, although not conclusive because it was a pilot with a small sample size, has suggested benefits of using rosuvastatin for 24 weeks to slow the worsening of airflow obstruction and improve DLCO in HIV-infected individuals [42]. A recent study conducted in patients with atherosclerosis from the general population also suggested that anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway could reduce lung cancer incidence and mortality [43], suggesting that therapeutic interventions will be available for high-risk patients in the near future.

Findings from our study require cautious interpretation: this was not a matched case–control study, and in the HIV-infected patients the prevalence of male sex, a known risk factor for chronic lung disease, was higher. Moreover, the two populations were also inevitably different with respect to comorbidities. For these reasons, we included sex in all multivariable analyses, along with multimorbidity. We also lacked data on other risk factors for chronic lung disease, such as second-hand smoking, alpha1-antitripsin deficiency, occupational dust or biomass fuel exposure, and respiratory infections during childhood. Multimorbidity assessment was different in the two groups: in fact, it was mostly based on self-reporting in the control group, leading to a possible underestimation. CT assessment of emphysema and airway disease was conducted only by means of visual scoring and not through quantitative evaluation. However, recent data have shown that visual scoring is more sensitive in early-stage emphysema [29]. Finally, it should be noted that our cohort was comprised of highly treatment-experienced HIV-infected patients, so that our results on lung disease may not apply to newly diagnosed and promptly treated HIV-infected patients with higher CD4 count nadir.

In conclusion, we provided significant CT scan evidence of airway disease in never-smoking HIV-infected patients. A minority of them showed respiratory symptoms resembling COPD, but without significant functional abnormalities. HIV infection was an independent risk factor for the presence of respiratory symptoms, CT signs of emphysema and airway disease, and DLCO reduction. Never-smoking HIV-infected individuals should not be excluded from lung disease screening. Further prospective studies are necessary to investigate the pathogenesis and natural history of CHPD. Furthermore, it will be crucial to build the correct diagnostic algorithm to identify high-risk individuals requiring close disease monitoring and, possibly, therapeutic interventions.

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Author contributions

GB, GG, LMF and PT contributed to the study design; AS, SZ, GO and GG evaluated HIV-infected patients, including CAT assessment; GB, SN, GP and MM recruited and evaluated controls, including CAT assessment; BB and LMF evaluated all PFTs; GL, GB and RS reviewed the CT scans; AM and SZ performed the statistical analyses; all authors contributed to drafting the paper.

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Supporting Information

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

Figure S1 Graphical representation of the study design.

Figure S2 CT images from HIV-infected never-smoking patients, depicting paraseptal emphysema (A); centrilobular emphysema (B, arrowhead); ill-defined centrilobular nodules – respiratory bronchiolitis (B, arrows); bronchial wall thickening (C); bronchiectasis (D).

Figure S3 Diagram illustrating patient enrolment flow chart for cases and controls.

Appendix S1 Methods.