HIV is associated with airway obstruction: a matched controlled study

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HIV is associated with airway obstruction: a matched controlled study

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Objective: To explore whether airway obstruction is associated with HIV in a cohort of HIV-infected and uninfected smokers.

Methods: People living with HIV (PLWHIV) participated in the ANRS EP48 HIV CHEST study, an early lung cancer diagnosis study with low-dose chest tomography. HIV-uninfected study participants were from the CONSTANCES cohort. Inclusion criteria were an age greater than 40 years, a smoking history of at least 20 pack-years, and for PLWHIV, a $CD4^+$ T-lymphocyte nadir less than 350/μl and last $CD4^+$ cell count more than 100 cells/μl. Two randomly selected HIV-uninfected study participants were matched by age and sex with one PLWHIV. Prebronchodilatator forced expiratory volume in 1 s (FEV1) to forced vital capacity (FVC) ratio was the primary outcome, and association of FEV1/FVC ratio less than 0.70 and FEV1 less than 80% of the theoretical value, as a proxy of chronic obstructive pulmonary disease, the secondary outcome.

Results: In total, 351 PLWHIV and 702 HIV-uninfected study participants were included. Median age was 50 years, and 17% of study participants were women. Plasma HIV RNA was less than 50 copies/ml in 89% of PLWHIV, with a median $CD4^+$ cell count of 573 cells/μl. HIV (β −2.19), age (per 10 years increase; β −2.81), tobacco

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use (per 5 pack-years increase; β −0.34), and hepatitis C virus serology (β−2.50) were negatively associated with FEV1/FVC. HIV [odds ratio (OR: 1.72)], age (per 10 years increase; OR 1.77), and tobacco use (per 5 pack-years increase; OR 1.11) were significantly associated with the secondary outcome.

Conclusion: Our study found a significant association of airway obstruction with HIV status in smokers aged more than 40 years with previous immunodeficiency.

Keywords: airway obstruction, comorbidity, chronic obstructive pulmonary disease, HIV, smoking, tobacco use

Introduction

The conjunction of small airway disease with parenchymal destruction (emphysema) results in airway obstruction and possibly chronic obstructive pulmonary disease (COPD). Prevalence of this condition in the HIV-infected population is high, partly related to a high prevalence of predisposing conditions, such as smoking [1–3] and history of lung infections [4–7]. Some studies have also found an association between HIV-related factors and COPD, including plasma HIV RNA more than 200 000 copies/ml [8], use of antiretroviral therapy [5], and lower lymphocyte $CD4^+$ cell counts [7].

Studies have shown higher prevalence of COPD in comparison to HIV-unexposed study participants [9–11]. However, in these studies, COPD diagnosis was based on ICD codes or self-report [9,10], smoking data were sometimes incomplete [10], and HIV was not always associated with COPD after adjusting for confounders [11]. Thus, we [1] compared the prevalence of airway obstruction in an all smoking HIV-infected cohort (exposed group) with an all smoking age and sex-matched HIV-uninfected population, and [2] explored whether HIV was independently associated with airway obstruction after adjusting for multiple confounders using spirometry to measure airway obstruction.

Methods

Study participants

HIV-infected study participants participating in the ANRS EP48 HIV CHEST study, a pilot study of early lung cancer diagnosis with low-dose chest tomography in a HIV-infected population with a heavy smoking history [12] (N° ID-RCB: 2010-A00781–38, clinical trials number NCT01207986). Inclusion criteria were an age of 40 years or more, having a smoking history of at least 20 pack-years, a $CD4^+$ T-lymphocyte nadir cell count less than 350/μl, and a last $CD4^+$ T-cell count more than 100 cells/μl. Study participants were included if they were active smokers, or had quitted in the 3 years prior to inclusion. Study participants were excluded if they had active cancer or an AIDS classifying disease, a history of lung infection in the last 2 months, were pregnant, breastfeeding, or had a contraindication to thoracic surgery.

HIV-unexposed study participants participated in the CONSTANCES cohort, a randomly selected population-based epidemiological cohort of 200 000 adults aged between 18 and 69 (http://www.constances.fr/index_EN.php). Study participants from the CONSTANCES cohort were aged 40 years or older and smoked more than 20 pack-years, possibly stopped in the 3 years prior to inclusion. Age (5 years categories) and sex-matched study participants were randomly selected to reach a matching ratio of 2 : 1 with the HIV cohort.

Procedures, variables, and outcomes

Spirometry was systematically offered to all volunteers in both cohorts. In the CONSTANCES cohort, only prebronchodilator measures of forced expiratory volume in 1 s (FEV1) and forced vital capacity (FVC) were performed. Predicted FEV1 was calculated using the Official Statement of the European Respiratory Society (ERS) Standardization of Lung Function Tests equations. [13], as predicted for the nonsmoking Caucasian population.

The GOLD criteria (http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/) or the ERS Society Standardization of Lung Function Tests equation of normal FEV1/FVC ratio [14] could not be used as an outcome because of lack of postbronchodilator measurements of FEV1 and FVC in the CONSTANCES cohort. We used the FEV1 to the FVC ratio as the primary outcome, and the FEV1/FVC ratio less than 0.70 and FEV1 value less than 80% of the theoretical value [13] as a proxy measure of moderate to severe COPD for a secondary outcome, as previously published [15,16]. Linear regression models explored the association of the FEV1/FVC ratio with HIV status, age, sex, BMI, smoking (in pack-years), active or past smoking status, cannabis inhalation, and hepatitis C virus (HCV)

status. Logistic regression models were used to evaluate the association of the secondary outcome with the same factors.

Results

In total, 352 people living with HIV (PLWH) had undertaken spirometry satisfying quality criteria. As all study participants were aged less than 70 years in the CONSTANCES cohort, the one study participants over 70 years of age in the ANRS EP48 study was excluded from analysis. In the CONSTANCES cohort, 1666 study participants satisfied our inclusion criteria and had valid spirometric measures, and we randomly matched 702 study participants to 351 PLWH (Table 1).

The FEV1/FVC ratio mean value was 0.77 in the CONSTANCES cohort (SD 0.08), versus 0.72 (SD 0.10) in the HIV-infected cohort ($P < 0.0001$). Airway obstruction, our secondary outcome (prebronchodilator FEV1/FVC ratio <0.70 and FEV1 value <80% of the theoretical value [13]), was diagnosed in 60 (9%) of the HIV-uninfected study participants, versus 68 (19%) of PLWH ($P < 0.0001$). In linear regression models with FEV1/FVC as outcome (Table 2), we found that HIV was strongly associated with lower FEV1/FVC values in univariate analysis [β −4.65; 95% CI (−5.77; −3.53)]. In multivariate analysis, we found that HIV [β−2.19; 95% CI (−3.52; −0.87)], age [per 10 years increase; β −2.81; 95% CI (−3.72; −1.90)], tobacco use [per 5 pack-years increase; β −0.34; 95% CI (−0.58; −0.09)], and HCV [β −2.50; 95% CI (−4.33; −0.67)] were negatively associated with FEV1/FVC, whereas being a woman [β 1.57; 95% CI (0.17; 2.98)] and increasing BMI [per one point increase; β 0.29; 95% CI (0.16; 0.43)] were significantly associated with an increase in FEV1/FVC. Use of inhaled cannabis and quitting smoking within 3 years prior to inclusion were not associated with FEV1/FVC.

In a first post-hoc analysis, HIV remained significantly associated with FEV1/FVC after excluding study participants with a history of tuberculosis or pneumocystosis ($P = 0.006$; data not shown). In a second analysis, we analysed the association of FEV1/FVC with the same variables in PLWH with a nadir $CD4^+$ level between 200 and 350 cells/μl only, 148 HIV-infected study participants were matched to 296 study participants from the CONSTANCES cohort. In multivariate analysis, HIV was not associated with FEV1/FVC, though the association was close to statistical significance [β−1.90; 95% CI (−3.83; 0.04)] (data not shown).

HIV [odds ratio (OR) 2.57; 95% confidence interval (CI; 1.76; 3.74)] was also significantly associated with airway obstruction, as measured by FEV1/FVC ratio less than 0.70 and FEV1 value less than 80% of the theoretical value [13]. In the multivariate analysis, factors independently associated with airway obstruction were HIV infection [OR 1.72; 95% CI (1.08; 2.73)], age (per 10 years increase; OR 1.77; 95% CI (1.28; 2.43)], and tobacco use [per 5 pack-years increase; OR 1.11; 95% CI (1.03; 1.20)]. Sex, BMI, smoking cessation within 3 years prior to inclusion, history of cannabis inhalation, and HCV status were not associated with airway obstruction (data not shown).

Discussion

In this age and sex-matched study of HIV-infected and uninfected study participants, we found that HIV infection was independently associated with lower FEV1/FVC ratios. HIV was also associated with an increased prevalence of airway obstruction as measured

Table 1. Primary characteristics of the HIV-infected and uninfected study participants.

	HIV-negative individuals ($n = 702$)	HIV-positive individuals ($n = 351$)	P value
Age (years; IQR)	50 (46–54)	50 (46–54)	0.90
Woman (%)	122 (17%)	61 (17%)	0.89
BMI (IQR)	26 (23–28)	23 (20–25)	0.0001
Smoking (pack-years; IQR)	28 (23–35)	30 (25–39)	0.0001
Smoking cessation (<3 years; %)	234 (33%)	30 (9%)	<0.0001
History of cannabis inhalation (%)	67 (10%)	125 (36%)	<0.0001
HCV (%)	13 (2%)[a]	106 (30%)	<0.0001
History of pulmonary tuberculosis	0	14 (4%)	<0.0001
History of pneumocystis	0	31 (9%)	<0.0001
FEV1 (l)	3.3 (2.7–3.7)	3.2 (2.6–3.7)	0.023
FEV1 (% of theoretical value)	95 (85–106)	94 (80–104)	0.021
FEV1/FVC ratio	0.78 (0.73–0.82)	0.74 (0.67–0.80)	0.0001
$CD4^+$ T-lymphocyte level (cells/μl)	NA	573 (395–767)	NA
$CD4^+$ nadir level (cells/μl)	NA	174 (75–259)	NA
History of AIDS	NA	104 (30%)	NA
Viral load <50 copies/ml	NA	311 (89%)	NA
History of intravenous drug use	NA	94 (27%)	NA

Data are *n* (%) or median (Q1–Q3). FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCV, hepatitis C virus; IQR, interquartile range.
[a]HCV data available for 686 study participants in the CONSTANCES cohort (16 missing).

Table 2. Univariate and multivariate analysis of the forced expiratory volume in 1 s/forced vital capacity ratio and factors of interest.

	Univariate analysis			Multivariate ($n = 1037$)		
Variable	β	95% CI	*P* value	β	95% CI	*P* value
HIV	−4.65	(−5.77; −3.53)	<0.0001	−2.19	(−3.51; −0.87)	0.001
Age (per 10 years increase)	−2.85	(−3.74; −1.95)	<0.0001	−2.81	(−3.72; −1.90)	<0.0001
Sex (woman)	1.39	(−0.05; 2.82)	0.058	1.57	(0.17; 2.98)	0.028
BMI	0.40	(0.27; 0.53)	<0.0001	0.29	(0.16; 0.43)	<0.0001
Smoking (per 5 pack-years)	−0.56	(−0.81; −0.32)	<0.0001	−0.34	(−0.58; −0.09)	0.007
Ceased smoking	2.19	(0.94; 3.44)	0.0006	0.85	(−0.41; 2.11)	0.186
Cannabis consumption (inhaled)	−3.08	(−4.48; −1.69)	<0.0001	−1.33	(−2.81; 0.15)	0.077
HCV-positive status[a]	−5.13	(−6.84; −3.44)	<0.0001	−2.50	(−4.33; −0.67)	0.008

CI, confidence interval; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCV, hepatitis C virus.
[a]Data available for 1037 study participants.

by prebronchodilator FEV1/FVC ratio less than 0.70 and FEV1 value less than 80% of the theoretical value [13]. To our knowledge, this is the first matched-control study undertaken in an all-smoking population over 40 years of age, a population in which screening for COPD is suggested by the GOLD recommendations (http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/).

Our study provides insights to what may be the differential results in both populations in terms of FEV1/FVC and prevalence of airway obstruction when screening at risk study participants with spirometry, and how much HIV infection itself can be considered as a risk factor of lower FEV1/FVC and of airway obstruction. PLWHIV are at increased risk of lung bacterial infection, pneumocystosis, tuberculosis, conditions which have all been associated with airway obstruction or emphysema [4,17,18]. However, other mechanisms may be implicated, as suggested by the persisting association between HIV and lower FEV1/FVC ratio after excluding study participants with a history of tuberculosis or pneumocystis infection. An interaction between HIV, increased lung immune activation despite antiretroviral therapy and smoking could increase levels of oxidative stress, local inflammation, and parenchyma destruction in comparison with the general population, though this hypothesis needs to be assessed.

Other factors associated with the presence of airway obstruction in our study are known risk factors in the general population. Smoking is the primary health hazard causing airway obstruction. Smoking cessation within 3 years prior to inclusion, however, was not firmly associated to outcomes, but a short duration of smoking cessation was probably insufficient to significantly modify FEV1 decline. Smoking and airway obstruction are also linked through recurrent and increased risk of pneumonia episodes in the general population [19]. Age is a well known factor of airway obstruction in the general population, as FEV1 declines with time faster than FVC [14]. The increase in FEV1/FVC ratio with female sex in our study remains to be explained, and data recently showed that COPD prevalence was similar in men and women [14]. BMI was associated with lower FEV1/FVC ratio. Cachexia and limb atrophy are common features in COPD, because of induced muscle atrophy inactivity, chronic inflammation, increased oxidative stress, muscular metabolic alterations, nutritional imbalance, and hypoxia [20,21]. Finally, inhaled cannabis consumption and HCV were both associated with a decline of FEV1/FVC only. Significant cannabis consumption was based on subjective clinical evaluation, suggesting that interpretation of our results must be cautious. Cannabis has been associated with a dose-related impairment of large airways function resulting in airway obstruction [22–24] and pulmonary hyperinflation [23–25]. The association between HCV and FEV1/FVC may well result from confounding factors in the HCV coinfected, such as intravenous drug use [26] and socioeconomic conditions.

Our study has limitations. The cross-sectional design can only reveal associations between factors and COPD, and not causality. Second, our study did not use the GOLD outcome (http://goldcopd.org/gold-2017-global-strategy-diagnosis-management-prevention-copd/) or the ERS Society Standardization of Lung Function Tests equation of normal FEV1/FVC ratio [14]; thus, our results may not be generalized to these outcomes. Third, ORs that reached significance are relatively small, and significance may be because of unmeasured confounders. In particular, we could not adjust on exposing particles other than tobacco smoking and cannabis inhalation. Fourth, differences in methods of inclusion in both cohorts may partly explain the association between HIV and airway obstruction, as healthier study participants from the general population may be more willing to volunteer for the CONSTANCES cohort. Finally, PLWH had a history of $CD4^+$ T lymphocyte value less than 350 cells/μl. Low nadir has been associated with a $CD4^+/CD8^-$ ratio less than 1 [27], a marker of persisting immune suppression correlated with emphysema [28] or severe bacterial infections, independently of last $CD4^+$ value [29]. Thus, the association between HIV and airway obstruction may not been as important in other PLWHIV at risk with higher nadir T $CD4^+$ cell levels.

In conclusion, our study found a higher prevalence of measured airway obstruction in PLWHIV with a history of important immunodeficiency than in an age and sex-matched control group of smokers aged 40 years of age or more.

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A.M. was the lead investigator, designed the trial, developed the protocol, interpreted the statistical analysis and wrote the manuscript. S.E-D. did the statistical analysis. V.L.M. and M.H. thoroughly reviewed the study protocol and results. All other authors participated in study accrual, and reviewed, revised, and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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