High prevalence of undiagnosed COPD in a cohort of HIV-infected smokers

To the Editor:

Studies in HIV-infected populations in developed countries have shown an increased prevalence of chronic obstructive pulmonary disease (COPD) in comparison with their HIV-uninfected counterparts [1, 2]. This is due in part to higher prevalence of smoking in these populations. Studies have included subjects with or without a history of smoking [3, 4], specific populations (*e.g.* history of intravenous drug use (IDU) [5]), and African-American or Hispanic minorities in the USA [4, 5]. Few studies have been performed in Europe [3]. When looking at HIV-related factors, history of *Pneumocystis* infection or colonisation [6], HIV viral load >200 000 copies·mL^{-1} [5] and antiretroviral therapy (ART) [4] were associated with COPD. However, further studies are needed.

The objective of our study was to evaluate the burden of COPD and associated factors in a French multicentric cohort of smoking, HIV-infected subjects aged ⩾40 years.

This was a cross-sectional prevalence study of COPD nested in the ANRS EP48 HIV-CHEST cohort, a French, multicentric, prospective study evaluating the relevance of low-dose chest tomography for early lung cancer diagnosis in HIV-infected subjects from 14 clinical centres (registered at www.clinicaltrials.gov with identifier NCT01207986). Inclusion criteria were age ⩾40 years, smoking history of ⩾20 pack-years within the last 3 years, a nadir CD4$^+$ T-cell count <350 μL^{-1} and last CD4$^+$ T-cell count >100 μL^{-1}. Exclusion criteria were active cancer, an AIDS-defining disease, a lung infection in the previous 2 months, pregnancy, breastfeeding or contraindication to thoracic surgery. All subjects gave their informed consent. The study was approved by the institutional review board (Comité de Protection des Personnes Sud Méditerranée IV, Montpellier, France).

Lung function was evaluated by spirometry, plethysmography and diffusing capacity of the lung for carbon monoxide (*D*LCO). Laboratories followed the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommendations [7, 8]. The primary outcome was the prevalence of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations: forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio <0.70 after administration of salbutamol [9]. Subjects were classified as GOLD 1 (mild), GOLD 2 (moderate), GOLD 3 (severe) or GOLD 4 (very severe) if their measured FEV1 was ⩾80%, ⩾50% to <80%, ⩾30% to <50% or <30% of that predicted using the ERS standardisation of lung function test equations [10] for the nonsmoking Caucasian population, respectively. Percentage of normal total lung capacity (TLC), residual volume (RV) and RV/TLC ratio were calculated according to the ERS standardisation of lung function test equations [8] and *D*LCO using the ATS criteria [7].

A generalised linear mixed model with centre as a random effect was used to evaluate the association between COPD and age (years), sex, low body mass index (BMI) (<18.5 kg·m^{-2}), smoking history (per 5-pack-year increase), cannabis inhalation (yes *versus* no), hepatitis C virus (HCV) infection, history of *Pneumocystis* pneumonia, last viral load <50 copies·mL^{-1}, last level of CD4$^+$ T-cells (per 100-μL^{-1} increase), nadir level of CD4$^+$ T-cells <200 μL^{-1} and duration of ART. Data on ethnic origin were unavailable. To account for COPD overdiagnosis [11], we performed a sensitivity analysis with GOLD ⩾2 as the outcome and calculated COPD prevalence according to the FEV1/FVC below the lower limit of normal (LLN) definition [10].

Between March 2011 and June 2012, spirometry, plethysmography and *D*LCO measurements were performed in 338, 301 and 199 of the 442 subjects from the ANRS EP48 study, respectively (table 1). COPD was present in 88 (26%) subjects: 31 (35%), 50 (57%) and seven (8%) had mild, moderate and severe COPD, respectively. In 64 (∼74%) subjects, COPD was previously unknown. Using the FEV1/FVC<LLN definition, COPD prevalence was 22% (75 subjects): 23 (31%) of whom had mild, 45 (60%) had moderate and seven (9%) severe COPD.

In univariate analyses, factors associated with COPD with a p-value <0.20 were age (OR 2.1, 95% CI 1.4–3.2; p<0.001), low BMI (OR 2.4, 95% CI 1.1–5.0; p=0.02), CD4$^+$ cell count (OR 0.9, 95% CI 0.8–1.0;

TABLE 1 Clinical, spirometric and plethysmographic characteristics

Characteristics	Total population	COPD	Absence of COPD
Subjects	338 (100)	88 (26)	250 (74)
Age years	50 (46–53)	52 (48–56)	49 (46–53)
Females	58 (17)	13 (15)	45 (18)
Low BMI[#]	36 (11)	15 (17)	21 (8)
Smoking duration years	30 (27–35)	34 (29–39)	30 (27–34)
Smoking pack-years	30 (25–38)	34 (27–40)	30 (25–37)
History of cannabis consumption	117 (35)	36 (41)	81 (32)
History of IDU	88 (26)	32 (36)	56 (22)
CD4$^+$ cell count μL^{-1}	571 (395–763)	498 (345–707)	594 (427–780)
Nadir CD4$^+$ cell count μL^{-1}	177 (76–260)	158 (71–232)	182 (83–267)
Nadir CD4$^+$ cell count <200 μL^{-1}	195 (58)	54 (61)	141 (56)
History of AIDS-defining complication	97 (29)	31 (35)	66 (26)
Known duration of HIV infection years	17 (10–22)	19 (11–24)	17 (10–21)
Duration of HIV treatment years	14 (7–16)	13 (7–16)	14 (7–16)
Last viral load <50 copies·mL^{-1}	298 (88)	78 (89)	220 (88)
HCV infection	100 (30)	35 (40)	65 (26)
History of *Pneumocystis* pneumonia	28 (8)	11 (13)	17 (7)
FEV_1 L	3.2 (2.6–3.7)	2.5 (2.0–2.9)	3.4 (2.9–3.8)
FEV_1 % predicted	89 (76–98)	71 (59–79)	93 (86–101)
FEV_1/FVC	0.74 (0.68–0.80)	0.61 (0.54–0.66)	0.77 (0.74–0.81)
TLC[¶] L	7.1 (6.2–7.9)	7.5 (6.7–8.4)	6.9 (6.1–7.7)
TLC[¶] % predicted	107 (97–116)	114 (104–126)	104 (96–112)
RV[§] L	2.5 (2.1–3.0)	3.1 (2.3–3.9)	2.4 (2.0–2.8)
RV[§] % predicted	119 (100–147)	152 (108–175)	114 (99–133)
RV/TLC[§]	37 (32–42)	41 (36–49)	35 (31–40)
RV/TLC[§] % predicted	108 (93–121)	120 (101–139)	104 (92–117)
***D*LCO[f,##] % predicted**	68 (59–83)	62 (52–76)	71 (62–86)

Data are presented as n (%) or median (interquartile range). COPD: chronic obstructive pulmonary disease; BMI: body mass index; IDU: intravenous drug use; HCV: hepatitis C virus; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; RV: residual volume; *D*LCO: diffusing capacity of the lung for carbon monoxide. [#]: <18.5 kg·m^{-2}; [¶]: n = 305; [§]: n = 302; [f]: corrected for haemoglobin; [##]: n = 199.

p=0.03), HCV infection (OR 1.8, 95% CI 1.1–3.1; p=0.02), history of *Pneumocystis* pneumonia (OR 2.0, 95% CI 0.9–4.5; p=0.11) and smoking (OR 1.1, 95% CI 1.0–1.2; p=0.10). In multivariate analysis, age (OR 2.3, 95% CI 1.4–3.6; p<0.001), low BMI (OR 2.2, 95% CI 1.0–4.9; p=0.04) and HCV infection (OR 1.9, 95% CI 1.1–3.4; p=0.02) were independently associated with COPD at a 5% threshold, but CD4$^+$ cells (OR 0.9, 95% CI 0.8–1.0; p=0.08), history of *Pneumocystis* pneumonia (OR 2.1, 95% CI 0.9–5.0; p=0.10) and smoking (OR 1.0, 95% CI 0.9–1.2; p=0.55) were not.

In the sensitivity analysis, factors associated with GOLD ⩾2 were age (OR 2.0, 95% CI 1.2–3.2; p<0.01) and low BMI (OR 3.1, 95% CI 1.4–6.8; p<0.01). CD4$^+$ cell count (OR 0.9, 95% CI 0.8–1.0; p=0.05), history of *Pneumocystis* pneumonia (OR 2.2, 95% CI 0.9–5.5; p=0.09) and intensity of smoking (OR 1.0, 95% CI 0.9–1.2; p=0.54) were not.

The rate of COPD in our selected HIV-infected population is in the range of that reported in the general population, such as in Salzburg, Austria, in the Burden of Obstructive Lung Disease study [12]. Prevalence of COPD in our selected population was still high using the FEV1/FVC<LLN definition for COPD diagnosis. COPD was also underdiagnosed, as described in the general population [13], due to insufficient COPD early diagnosis/screening of high-risk subjects.

Age and low BMI were associated with COPD, as previously described [11]. Smoking was not significantly associated with COPD in the multivariate analysis. This might be due to the limited range of accumulated doses and confounding by age. The role of cannabis in obstructive lung disease is conflicting in the literature [14] and we could not conclude on its relevance to COPD prevalence in our cohort as we lacked precise quantitative estimation of cannabis consumption. HCV infection was associated with COPD only in the primary analysis. This result may be due to confounders, as most intravenous drug users are infected by HCV, or to a true lack of association, as was reported in a recent study [15]. Concerning nadir

$CD4^+$ cell count, duration of ART and viral load, conclusions should be drawn cautiously, as all subjects had a nadir count <350 μL^{-1} and nearly all had an undetectable viral load due to high ART coverage. Finally, last $CD4^+$ cell count and *Pneumocystis* pneumonia history were not associated with COPD, which could be explained by lack of statistical power.

We found an increase in RV, TLV and the RV/TLC ratio in most subjects with COPD, consistent with emphysema or gas trapping. Values of the corrected D_{LCO} were low, underscoring impairment of the blood–air barrier in COPD and non-COPD subjects. D_{LCO} reduction in the HIV-infected has been associated with smoking, but also with low $CD4^+$ cell counts [16, 17], possibly through enhanced local inflammation and subacute infections.

Our study has limitations. The cross-sectional design can only reveal associations between factors and COPD. In addition, symptoms and quality of life assessed using validated questionnaires were not recorded. Finally, we did not correct FEV_1 and FVC values for ethnic origin [10]. However, these corrective factors would have only modified the numbers of subjects in the different GOLD stages, as FEV_1/FVC remains the same, and have not been validated in sub-Saharan Africans, the major ethnic minority in the French HIV-infected population [10].

In conclusion, prevalence of COPD in our selected population was high and COPD was mostly undiagnosed. Our study advocates early, active diagnosis of COPD by spirometry in similar HIV-infected smokers, and smoking cessation in all HIV-infected subjects.

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COPD prevalence is 26% in an HIV-infected cohort of smokers aged ⩾40 years and was largely underdiagnosed http://ow.ly/CkVzo

Alain Makinson[1–3], Maurice Hayot[4], Sabrina Eymard-Duvernay[2], Mylène Quesnoy[2], François Raffi[5], Laurence Thirard[6], Fabrice Bonnet[7], Pierre Tattevin[8], Sophie Abgrall[9], Xavier Quantin[10], Hervé Léna[11], Sébastien Bommart[12], Jacques Reynes[1,2], Vincent Le Moing[1,2] and the ANRS EP48 HIV CHEST Study Team[13]
[1]Infectious and Tropical Diseases Dept, University Hospital Montpellier 1, Montpellier, France. [2]UMI 233, IRD, University Montpellier 1, Montpellier, France. [3]Dept of Internal Medicine, Clinique Beau-Soleil, Montpellier, France. [4]INSERM U-1046, University Hospital Montpellier 1, Dept of Clinical Physiology, University of Montpellier I and II, Montpellier, France. [5]ANRS, Paris, France. [6]Pneumology Dept, Tourcoing University Hospital, Tourcoing, France. [7]Internal Medicine and Infectious Diseases Dept, University Hospital Bordeaux, INSERM U897, Bordeaux, France. [8]Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France. [9]Infectious and Tropical Diseases Dept, Groupement Hospitalier Nord, Bobigny, France. [10]Thoracic Oncology Unit, University Hospital Montpellier, Montpellier, France. [11]Respiratory Medicine Dept, Pontchaillou University Hospital, Rennes, France. [12]Dept of Radiology and INSERM U 1046, University Hospital Montpellier, Montpellier, France. [13]For a list of the ANRS EP48 HIV CHEST Study Team members and their affiliations, see the Acknowledgements section.

Correspondence: Alain Makinson, Infectious and Tropical Diseases Dept, University Hospital Montpellier 1, UMI 233, 80 Avenue Augustin Fliche, 34090, Montpellier, France. E-mail: a-makinson@chu-montpellier.fr

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Cladribine improves lung cysts and pulmonary function in a child with histiocytosis

To the Editor:

Langerhans' cell histiocytosis (LCH) is a rare disease of unknown aetiology involving accumulation of Langerhans' cells organised in granuloma, in various organs [1]. Pulmonary LCH (PLCH) is characterised by focal Langerhans' cell granulomas infiltrating and destroying distal bronchioles, which results in cysts, major destruction of the pulmonary tissue and pneumothorax [2, 3]. PLCH is rare in children <18 years old.

When cysts are present, in children or adults, the disease is usually considered no longer active, and no treatment is effective for chronic cysts. The long-term outcome is marked by a slow progression to