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COPD in HIV-Infected Patients: CD4 Cell Count Highly Correlated

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Abstract

Background

COPD is a frequent and significant cause of respiratory morbidity in HIV-infected patients despite the control of HIV. We aimed to analyze the factors correlated with COPD in this population to evaluate the existence of specific indicators of vulnerability in this population.

Methods and Findings

623 HIV-infected outpatients were enrolled during one year. This population was characterised by a dedicated questionnaire and electronic patient records. COPD screening was performed according to recommended spirometric criteria. The prevalence of COPD was 9.0%. Age and smoking were independently correlated with COPD (OR, 1.61 per 10 years increase, $P = 0.007$; OR, 1.28 per 10 pack-year increase, $P = 0.003$, respectively). Body mass index (BMI) and CD4 cell-count were independently and negatively correlated with COPD (OR, 0.78, $P < 0.001$; 0R, 0.77 per 100 cell/mm^3 increase, $P < 0.001$, respectively). Among COPD patients, 77% did not know their diagnosis. Five COPD-patients never smoked and 44.2% did not have any respiratory symptoms and so were not eligible to perform a spirometry according to the guidelines.

Conclusions

In addition to known risk factors, immune defect through CD4 cell count was independently and strongly correlated with COPD. COPD is largely underdiagnosed and thus unmanaged. However, early management and urgent smoking cessation are essential to improve prognosis. Clinicians' awareness on the particular vulnerability for COPD in HIV-infected patients is crucial. Moreover, indications to perform conventional spirometry to diagnose COPD may include more parameters than tobacco-smoking and respiratory complaints with a particular concern toward patients with a profound CD4 cell count defect.

Competing Interests: The authors have declared that no competing interests exist.

Introduction

COPD will become the third most common cause of death in 2030 in the general population [1]. Early detection and appropriate management is a priority in order to improve patients' prognosis and quality of life [2].

Human immunodeficiency virus (HIV) infects 150 000 people in France. Eighty-one percent of the patients receive antiretroviral therapy (ART) and HIV viral load is undetectable in 88.5% of cases [3]. In industrialized countries, HIV infection is now considered as a chronic disease in a population with a higher prevalence of various comorbidities [3–5]. International guidelines detailed specific recommendations for cardiovascular, hepatic, metabolic and psychiatric disorders in this population, but did not universally contain specific recommendations on chronic respiratory diseases [3–5].

Yet HIV-infected patients smoke two to three times more than the general population, and have a worrying prevalence of respiratory complaints and lower respiratory tract infections (LRTI) despite effective ART and immune restoration [6–10]. Epidemiological studies in the ART era showed more COPD among HIV-infected people [11–15]. In addition to known risk factors for COPD (tobacco smoking, age and body mass index), involvement of HIV-specific risk factors remains suspected. To date, studies assessing specific associations between HIV markers and HIV related parameters with COPD have yield contradictory results [12,13,16–20]. In order to explore this association, we studied, in a large cohort of HIV-infected outpatients, the prevalence of COPD and the related factors including all the factors previously tested in the literature between HIV and COPD.

Materials and Methods

Design and study population

This prospective monocentric cross sectional study took place in the Infectious Diseases Department of the Nice University Hospital where a cohort of 2453 HIV-infected patients is followed up with 93% of patients under ARV therapy and 80% of patients with a undetectable viral load. All the adult patients consulting at the outpatient clinic during 3 randomly selected days per week, from January 1st, to December 31st 2012 were eligible. Patients with recent LRTI ($\leq$ 2 months), or with mental or physical incapacity to perform pulmonary function test (PFT) were excluded.

Screening and data collection

Patients first completed a dedicated questionnaire (S1 Appendix) with the assistance of a medical student or a nurse and performed a rapid PFT with a hand-held COPD-6 spirometer. The questionnaire searched for respiratory symptoms (chronic bronchitis, recurrent acute bronchitis, dyspnea), history of hospitalization for respiratory-related conditions, known COPD or chronic bronchopathy, smoking history, use of illicit drugs (cannabis, intra-venous drug use), occupational respiratory exposure and socio-economical status. To characterize COPD, according to recent definitions, COPD frequent exacerbator phenotype was defined as a patient with 2 or more acute bronchitis per year [1,21]. Patient-orientated definitions of chronic bronchitis, recurrent acute bronchitis and dyspnea used in our questionnaire had previously been tested for their understandability and validated as conform by pneumologists [1,2,21].

All patients with respiratory symptoms, a previous mentioned COPD or chronic bronchopathy diagnosis, a history of hospitalization for a respiratory-related condition, or an abnormal

COPD-6 test, underwent a conventional spirometry performed by a pneumologist (FGdS and KR).

Data concerning HIV infection (date of HIV infection, AIDS-defining diagnosis according to Centers for Disease Control and Prevention staging, nadir CD4, CD4 and CD8 cell count within the last 6 months with CD4/CD8 ratio and HIV RNA load, treatment history, previous respiratory opportunistic infections) and comorbidities were collected from the Nadis® electronic patient medical record [22].

Definition of COPD

PFT tests were performed following the American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines [23,24]. According to the GOLD guidelines, diagnosis of COPD was defined as a Forced Expiratory Volume in one second (FEV1) / Forced Vital Capacity (FVC) $< 70\%$ after bronchodilators test [1].

Ethics

The Nice University Hospital Ethics Committee Board review approved the study. All patients provided with their written informed consent.

Statistical analysis

Based on an obstructive lung disease (OLD) prevalence rate of 7.5% in the French general population, a precision of 2% and a level of significance of 5%, the sample size required to estimate the prevalence of COPD in our population was 666 patients. Continuous variables are presented as mean ± standard deviation (SD). Student's t-test was used to compare continuous variables and Chi-squared and Fisher's exact tests were used for discrete variables. Statistical significance was considered at $P < 0.05$. We first estimated the prevalence of COPD and its 95% confidence interval (CI). Then, to identify factors independently correlated with COPD, we compared COPD patients to non-COPD patients using a logistic regression (LR) model introducing the usual risk factors for COPD (age per ten years increase, smoking per 10 pack years increase, body mass index), drug exposure (ever cannabis user and ever intravenous drug user), and several parameters of HIV infection (HIV infection duration, CD4 cell count, Nadir CD4 cell count, HIV RNA viral load, duration of HAART exposure for nucleoside reverse transcriptase inhibitor, non-nucleoside reverse-transcriptase inhibitors and protease inhibitor, HBV or HCV co-infection, mycobacterial lung infection). The statistical analysis was performed using SPSS© 14.0 software.

Results

Study population characteristics

The study's flowchart is presented in Fig 1. We enrolled 623 HIV-infected patients. These patients did not differ from our entire cohort (n = 2453) for age, gender distribution (data not shown), percentage of patients under-ARV therapy (93.5%), with undetectable viral load (80%) or CD4> 500 (64%). Forty-two patients screened by questionnaire or COPD-6 with an indication to perform a conventional spirometry refused to undergo the exam and were therefore excluded. Characteristics of patients included and excluded in our study are detailed in Table 1. Briefly, 73.8% of patients were men, mean age was 48 years with a mean duration of HIV infection of 15.5 years. At the time of the study, 93.5% of patients were receiving ART, with an undetectable HIV viral load for 85.2% and a mean CD4 cell-count of 622 cells/mm^3. Twenty percent of patients were past smokers, 51% were current smokers. In our institution,

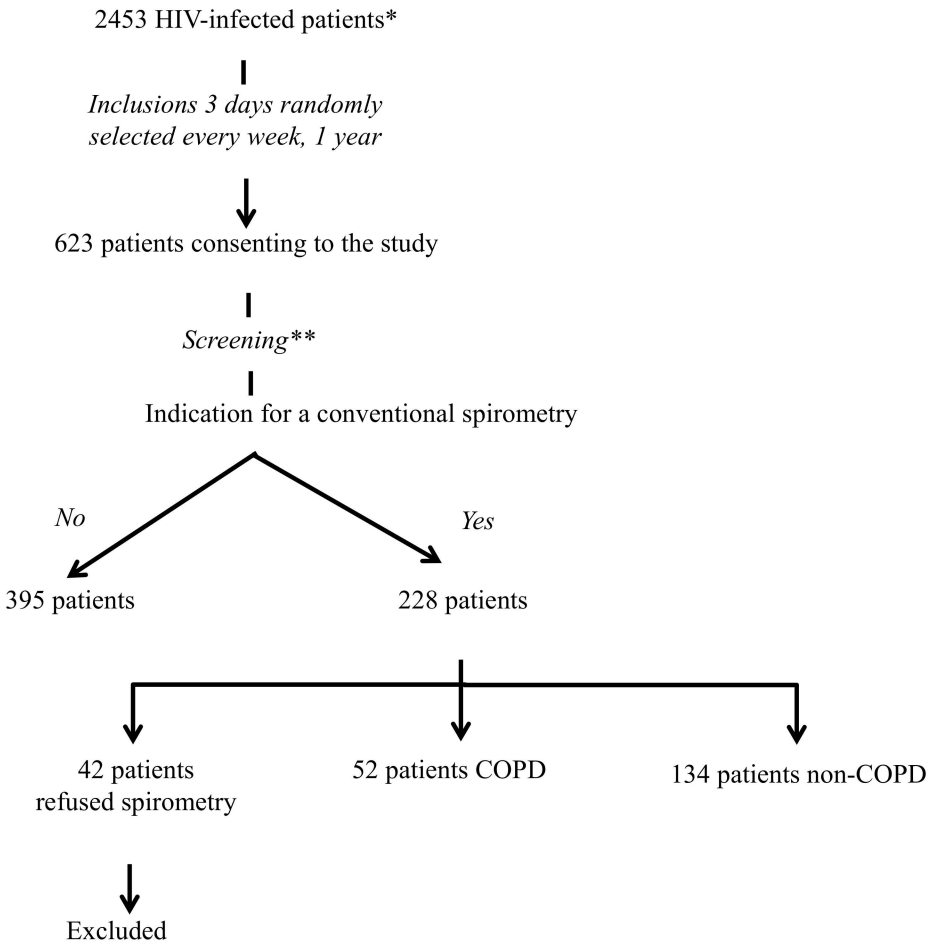

Fig 1. Study's flowchart. * Cohort of HIV-infected patients consulting in infectious department during 1 year. ** Dedicated questionnaire + Hand-Held spirometer.

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all the patients with CD4 cell count < 200/mm3 or < 15% were receiving pneumocystis pneumonia prophylaxis. Details concerning previous respiratory opportunistic infections, comorbidities, socio-economic status and educational level of patients are to be found in supporting information (S1 Table).

COPD among HIV-infected patients

The prevalence of COPD was 9% (52/581) (95% CI, 6.6%—11.3%). One hundred eighty-four conventional spirometries were performed after screening, enabling the diagnosis of 64 OLD (35%) and 52 COPD (28%). Previous hospitalization for a respiratory-related condition was more frequent among COPD-patients compared to non-COPD patients (63.5% vs. 32.5%, $P < 0.001$) Table 2. Previous community-acquired bacterial pneumonia (CABP) was also more frequent among COPD-patients (23.1% vs. 8.5%, $P = 0.001$).

COPD diagnosis and management

Screening tests results are summarized in Supporting Information (S2 Table). Among the 52 COPD-patients, 40 (77%) did not know they had a bronchopathy and 47 (90%) had never performed a spirometry. Only five patients (9.6%) were treated for COPD.

Table 1. Baseline characteristics of study cohort: comparison included/excluded.

Parameters	Patients included n = 581	Patients excluded n = 42	*P* value
Demographic characteristic			
Age (years)	48.3 ± 9.9	44.4 ± 10.2	**0.013**
Male Gender	429 (73.8%)	26 (61.9%)	0.092
Clinical characteristics			
Respiratory symptoms	136 (23.6%)	19 (45.2%)	**0.005**
Chronic bronchitis symptoms	45 (7.7%)	5(11.9%)	0.563
Recurrent acute bronchitis	50 (8.6%)	8 (19%)	**0.045**
Dyspnea	100 (17.2%)	13 (31%)	0.068
Hosp. for respiratory condition	32 (5.5%)	7 (16.7%)	**0.012**
Previous LRTI	205 (35.3%)	19 (45.2%)	0.194
Previous CABP	45 (9.8%)	6 (14.3%)	0.42
Known as chronic bronchitis	27 (4.7%)	5 (11.9%)	0.057
BMI (Kg/m^2)	23.5 ± 3.6	23.2 ± 4.3	0.69
Toxic exposure			
Current smoker	295 (50.8%)	25 (59.5%)	0.273
Current or past smoker	417 (71.8%)	34 (81.0%)	0.199
Pack-years history	16.1 ± 17.9	21. 4± 25.6	0.26
Current/past cannabis user	226 (40.4%)	18 (45.0%)	0.564
IDU	103 (18.3%)	6 (15.0%)	0.601
Professional resp. exposure	141 (24.7%)	13 (31.7%)	0.317
HIV disease			
HIV infection duration (years)	15.5 ± 8.6	14.9 ± 9.3	0.681
CDC stage			0.605
A	350 (60.2%)	22 (52.4%)	
B	93 (16.0%)	8 (19.0%)	
C	138 (23.8%)	12 (28.6%)	
CD4 T-cell count ($cells/mm^3$)	622 (291)	584 (412)	0.562
<200 $cells/mm^3$	32 (5.5%)	8 (19.0%)	**0.003**
200–349 $cells/mm^3$	59 (10.2%)	5 (11.9%)	
350–499 $cells/mm^3$	111 (19.1%)	10 (23.8%)	
>500 $cells/mm^3$	379 (65.2%)	19 (45.2%)	
CD4/CD8 cell ratio	0.79 ± 0.51	0.64 ± 0.42	0.069
HIV RNA (log_{10} cp/ml)	1.85 ± 0.77	2.22 ± 1.28	0.075
Undetectable HIV RNA	494 (85.2%)	30 (71.4%)	**0.018**
Nadir CD4 cell count ($cells/mm^3$)	255 ± 189	194 ± 162	**0.043**
HBV and/or HCV infection	193 (33.2%)	11 (26.2%)	0.349
HAART exposure			
Current HAART	543 (93.5%)	38 (90.5%)	0.517
HAART naïve	24 (4.1%)	2 (4.8%)	0.692
NRTI duration (month)	117.4 ± 81.2	107.1 ± 70.5	0.395
NNRTI duration (month)	37.0 ± 49.5	32.3 ± 48.2	0.54
PI duration (month)	63.5 ± 63.9	55.5 ± 54.5	0.415

Data are expressed as % (No./total No.) or mean ± standard deviation.

Abbreviations: Hosp. hospitalization, LRTI lower respiratory tract infection, CABP community-acquired bacterial pneumonia, BMI body mass index, IDU intravenous drug use, resp. respiratory, CDC Centers for Disease Control and Prevention, Undetectable HIV RNA < 40 cp/ml, HAART highly active antiretroviral therapy, NRTI nucleoside reverse transcriptase inhibitor, NNRTI non-nucleoside reverse-transcriptase inhibitors, PI protease inhibitor.

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Table 2. Comparison COPD-patients and non-COPD patients.

Parameters	Univariate analysis			Multivariate analysis	
	Non-COPD (529)	COPD (52)	*P* Value	OR[d] (95% CI)	*P* Value
Demographic characteristics					
Age (years) #	47.9 ± 9.8	52.5 ± 9.7	**0.001**	**1.61[a] (1.14–2.28)**	**0.007**
Male Gender	389 (73.5%)	40 (76.9%)	0.596		
BMI (Kg/m^2) #	23.7 ±3.6	21.5 ± 3.4	**<0.001**	**0.78 (0.70–0.89)**	**<0.001**
Toxic exposure					
Current smoker	261 (49.3%)	34 (65.4%)	**0.027**		
Current or past Smoker	370 (69.9%)	47 (90.4%)	**0.002**		
Pack-year history#	15.4 ± 17.5	23.6 ± 19.4	**0.001**	**1.28[b] (1.09–1.50)**	**0.003**
Current/past Cannabis use#	199 (38.9%)	27 (55.1%)	**0.028**		
IDU#	85 (16.6%)	18 (35.3%)	**0.001**		
Professional resp. exposure	128 (24.7%)	13 (25.0%)	0.957		
Clinical characteristics					
Respiratory symptoms	107 (20.3%)	29 (55.8%)	**<0.001**		
Chronic bronchitis symptoms	31 (6%)	14 (27%)	**<0.001**		
Recurrent acute bronchitis	37 (7%)	12 (23.1%)	**<0.001**		
Dyspnea	78 (14.7%)	23 (44.2%)	**<0.001**		
Hosp. for respiratory condition	19 (3.6%)	13 (25.0%)	**<0.001**		
Previous LRTI	172 (32.5%)	33 (63.5%)	**<0.001**		
Previous CABP	45 (8.5%)	12 (23.1%)	**0.001**		
HBV and/or HCV infection#	167 (31.6%)	26 (50.0%)	**0.007**		
Depression	103 (19.5%)	19 (36.5%)	**0.004**		
HIV story					
HIV infection duration (years) #	15.2 ± 8.5	18.7 ± 8.5	**0.005**		
CDC stage			0.376		
A	320 (60.5%)	30 (57.7%)			
B	87 (16.4%)	6 (11.5%)			
C	122 (23.1%)	16 (30.8%)			
CD4 cell count (cells/mm^3) #	634 ± 294	497 ± 232	**0.001**	**0.77[c] (0.68–0.88)**	**<0.001**
<200 cells/mm^3	28 (5.3%)	4 (7.7%)	**0.008**		
CD4/CD8 cell ratio	0.79 ± 0.51	0.71 ± 0.44	0.271		
CD8 cell count (cells/mm^3)	939 ± 467	830 ± 548	0.10		
HIV RNA (log_{10} cp/ml) #	1.87 ± 0.79	1.71 ± 0.54	**0.054**	0.59 (0.32–1.08)	0.088
Undetectable HIV RNA	446 (84.5%)	48 (92.3%)	0.129		
Nadir CD4 cell count (cells/mm^3) #	262 ± 191	188 ± 155	**0.007**		
HAART exposure					
HAART naïve	24 (4.5%)	0 (0.0%)	0.154		
NRTI (months) #	116.3 ± 81.5	128.5±77.9	0.465		
NNRTI (months) #	35.7 ± 48.1	50.7 ± 60.8	0.114		
PI (months)#	63.2 ± 63.8	66.9 ± 65.1	0.863		

Data are expressed as % (No./total No.) or mean ± standard deviation,

parameters included in the multivariate regression analysis,

[a] per 10 year-increase in age,

[b] per 10 pack-year-increase,

[c] per 100 cells/ mm^3 increase,

[d] only significant results are shown.

Abbreviations: COPD chronic obstructive pulmonary disease, OR odds ratio, CI confidence interval, BMI body mass index, IDU intravenous drug use, Hosp. hospitalization, LRTI lower respiratory tract infection, CABP community-acquired bacterial pneumonia, CDC centers for disease control and prevention, undetectable HIV RNA < 40 cp/ml, HAART highly active antiretroviral therapy, NRTI nucleoside reverse transcriptase inhibitor, NNRTI non-nucleoside reverse-transcriptase inhibitors, PI protease inhibitor.

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Factors associated with COPD in HIV-infected patients

In the univariate analysis (Table 2), COPD-patients were significantly older (52.5 years vs. 47.9 years; $P = 0.001$), more inactive, presenting long-term illness or disability ($P = 0.003$) (S1 Table). They had a significantly lower BMI (20.7 kg/m^2 vs. 23.4 Kg/m^2, $P < 0.001$). COPD-patients were more frequently current or past smokers (90.4% vs. 69.9%) with higher smoking exposure in pack-year (23.6 vs. 15.4). Exposure to cannabis and IDU was significantly more common among COPD-patients (55.1% vs. 38.9%, $P = 0.028$ and 35.3% vs. 16.6%, $P = 0.001$, respectively). Regarding HIV parameters, COPD-patients had a significantly lower CD4 cell-count (497 vs. 634 cells/mm^3, $P = 0.001$) and lower mean nadir CD4 cell-count (188 cells/mm^3 vs. 262 cells/mm^3; $P = 0.007$). Among associated comorbidities, we found in COPD-patients higher frequencies of co-infection (active or previous) with hepatitis B or C viruses (50.0% vs. 31.6%, $P = 0.007$) and depression (36.5% vs. 19, 5%, $P = 0.004$) (Table 2).

According to multivariate analysis, age (OR, 1.61 per 10 years increase, $P = 0.007$), BMI (OR, 0.78, $P < 0.001$), smoking (OR, 1.28 per 10 pack-years increase, $P = 0.003$) and CD4 cell-count (OR, 0.77 per 100 CD4 cell/mm^3 increase, $P < 0.001$) remained significantly and independently associated with COPD (Table 2).

Discussion

Our 623 patients randomly included were representative for age, sex ratio and HIV infection control of our entire cohort of 2453 patients. They were also representative of the HIV-infected patients population currently followed up in most industrialized countries for age and sex ratio [3,25]. This study showed a prevalence of 9.0% (95% CI, 6.6%—11.3%) for COPD and identified a CD4 cell count to be strongly and independently correlated with COPD.

The prevalence of COPD worldwide varies significantly across countries [1,2,26]. In France, the prevalence of obstructive lung disease in the general population (including asthma and COPD) was estimated at 7.5% [27]. This prevalence, lower than the one found in our study, was evaluated in a much older population (60±10 years) than ours [27].

A 2006 study by Crothers *et al.* alerted clinicians to an increased prevalence of COPD in HIV-infected patients on the basis of self-reported diagnosis (15% vs. 12%, $P = 0.04$) [11]. Since the publication of this result, 5 high quality studies using spirometric criteria have found COPD rates between 6% and 21% in groups of 65 to 400 HIV outpatients representative of patients commonly treated in consultation units in the United-States, Spain, Italy and Nigeria [12,13,16,19,20]. Differences in prevalence were expected due to dissimilarities of methodology, age, smoking, histories and country-related respiratory exposure usually observed between the countries, but all of these studies confirmed similar high frequency of COPD. COPD induced a worrying respiratory morbidity as attested by more frequent hospitalization for a respiratory condition (25% *vs*. 3.6%, $P < 0.001$) and previous lower respiratory tract infection (63.5% *vs*. 32.5% $P < 0.001$) (Table 2).

Aging and smoking were independently correlated with COPD (Table 2). These are the two most frequent risk factors for COPD in the general population, with cigarette smoking accounting for 95% of toxic respiratory exposure responsible for COPD in industrialized countries [1]. We confirmed this known high exposure to tobacco smoking in HIV-infected patients (50.8% of current smokers in our study, compared to 33% in the general French general population) [6,7,28]. These results are alarming, especially because the attributable risk of death associated with smoking among HIV-infected patients is doubled compared to uninfected population [29].

Regarding other factors correlated with COPD (Table 2), low BMI, which is known to be correlated with a poor COPD prognosis, was also correlated with COPD as in the general

population [30]. We did not find any independent correlation with the use of cannabis, IDU, depression, inactive status or long-term illness, probably because these factors were associated with smoking [31]. We did not find any correlation between ART exposure and COPD, nor between hepatitis and COPD, contrary to some previous studies using smaller populations [10,12,14,32]. Some previous studies also discussed an association between pneumocystis pneumonia or tuberculosis pneumonia with COPD [10, 19]. Our study did not find any association with these pathologies, but their low frequency in our population did not allow for any meaningful conclusions on this point (S1 Table).

More age-associated diseases characterize HIV-infected patients. Immune defects including nadir CD4, CD4 cell count, and low CD4/CD8 ratio are involved in a chronic inflammatory state. This contributes to accelerated aging and the development of cardiovascular, rheumatological, renal, neurological comorbidities [33,34,35]. We identified 2 markers of HIV infection negatively correlated with COPD (Table 2): nadir CD4 cell-count (188 CD4 cells/mm^3 in COPD-patients *vs* 262 CD4 cells/mm^3 in non COPD-patients, $P = 0.007$) in the univariate analysis only, and most recent CD4 cell-count in both the univariate and multivariate analyses (OR, 0.77 for each 100 cells/mm^3 increase; 95% CI, 0.68–0.88). *Madeddu et al*. concluded that HIV was probably a risk factor of COPD independently of smoking and age [12]. Ours results suggest that HIV could increase the risk of COPD through CD4 cell count depletion. The implication of CD4 T-cell count in the pathogenesis of OLD as been suggested in the literature [10,11,36,37]. In two recent studies, Drummond and Shirley have shown an accelerated decline of respiratory function (forced expiratory volume in one second (FEV1) and forced vital capacity (FVC)) in HIV-infected people with lower CD4 cell counts [18,20]. In his cohort of 303 HIV-infected patients, Drummond observed, contrary to our results, that this association with CD4 cell count disappeared after adjustment for HIV viral load suggesting that HIV viral load was more determinant in respiratory decline than CD4 cell level [18]. These results again confirm a plausible role played by poor control of HIV disease in COPD pathogenesis. However, the study was probably underpowered for testing the specific role of CD4 cell count because the population was limited to intravenous drug users, heavy tobacco smoker and various drug users with very poor control of their HIV-disease, including a global low level of CD4 cells (323/mm3 *vs*. 622 CD4 cells/mm^3 in our population) and a frequent high HIV viral load [17,18]. Studying CD4 cells in another body fluid compartment, *L. Popescu et al*. recently observed a significant correlation between CD4 cell count defect in bronchiolo-alveolar lavage liquid and COPD in HIV-infected patients [38]. Our study confirmed literature suspicion and found for the first time in a large cohort of patient a significant and independent correlation between COPD and CD4 cell count defect. This link between CD4 cell count and COPD is also supported by various pathogenetic explanations in the literature. A CD4 cell defect could favor COPD through bronchial colonization especially by *pneumocystis jiroveci* and secondary bronchial inflammation, dysimmune processes and accelerated aging [39–42]. Our study did not explore associated functional modifications in CD4 cells, but other interesting studies have suggested that tobacco smoking could impair T-cells function in HIV-infected patients [43,44].

Moreover, COPD is frequently not screened, and is under-diagnosed and ill-managed as a consequence. Seventy-seven percent of our COPD-patients were unaware of having a bronchopathy and 90% had never been previously tested or treated. Diagnosis of COPD reinforces the recommendation to quit smoking and enables clinicians to prescribe an appropriate inhaled treatment. Interactions between inhaled corticosteroid and protease inhibitors (PI) is no longer a problem because their indication is now limited to a small subset of COPD patients (COPD GOLD 3 or 4 with frequent exacerbations) and several alternative treatments to PI are

available if inhaled corticosteroids are required [1, 45]. Diagnosis of COPD also implicates a specific survey of respiratory function and lung cancer screening [1, 46].

International guidelines advocate COPD-screening for any patient older than 35 years with respiratory complaints (exertional breathlessness, chronic cough, regular sputum production, frequent winter 'bronchitis' or wheezing) and a history of exposure to disease risk factors (e.g., current or former smoker) [1,47]. Under-diagnosis of COPD in the general population is a well-known problem and has also been identified in HIV-infected patient populations [1,13,16]. As patients are frequently asymptomatic (44.2% of our COPD patients), the guidelines and criteria for COPD screening appear to be insufficient. The existence of an independent correlation between CD4 cell count and COPD should suggest to clinicians to be aware of COPD risk for patients with less than 200 CD4 cells/mm^3 and particularly if these patients are smokers. Further studies are required to identify more appropriate strategies to screen for COPD in this population.

Our study has some limitations: we may have underestimated the prevalence of COPD since the 42 patients screened by questionnaire or COPD-6 who refused to undergo conventional spirometry present a high risk of COPD according to subsequent results (see Tables 1 and 2). Moreover, exclusion of all patients with a recent history of LRTI (which might interfere with spirometric results) might have led to underestimating the prevalence of COPD. Therefore, for organizational and budget reasons, we were not able to perform a conventional spirometry for all patients and we applied a preliminary screening using a questionnaire and a hand-held spirometer. These tests were successful in detecting high-risk populations (S2 Table) but are known to have an insufficient sensibility and have probably under-estimate the real prevalence of COPD in our population [48]. We also did not collect the reasons why some patients refused to participate in our study, and we have no data on smoking exposure for our entire cohort, which could have provided a useful comparison.

In conclusion, this study shows that in HIV-infected people, smoking exposure, aging and CD4 cell count is associated with COPD. Moreover, we suggest that diagnosis of this disease, which is frequently asymptomatic at its beginning, could be improved by integrating vulnerability to COPD in connection to CD4 cell count defect into strategies for COPD-screening.

Supporting Information

S1 Appendix. COPD study's questionnaire (translated from French language).
(DOCX)

S1 Table. Comparison COPD / non-COPD patients for all parameters analyzed during study. Data are expressed as % (No./total No.) or mean ± standard deviation, # parameters included in the multivariate regression analysis, a per 10 year-increase in age, b per 10 pack-year-increase, c per 100 cells/ mm3 increase.
Abbreviations: COPD chronic obstructive pulmonary disease, OR odds ratio, CI confidence interval, BMI body mass index, IDU intravenous drug use, Hosp. hospitalization, LRTI lower respiratory tract infection, CABP community-acquired bacterial pneumonia, CDC centers for disease control and prevention, undetectable HIV RNA $<$ 40 cp/ml, HAART highly active antiretroviral therapy, NRTI nucleoside reverse transcriptase inhibitor, NNRTI non-nucleoside reverse-transcriptase inhibitors, PI protease inhibitor, pn. Pneumonia, mycobac mycobacteria.
(DOCX)

S2 Table. Results of screening test for the 184 conventional pulmonary function testing performed.
(DOCX)

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Data curation: LV PP.

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Investigation: KR FG LV PP AN JD ED IP EC PMR.

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Supervision: KR FG CHM PMR.

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References

1. Global strategy for the diagnosis, management, and prevention of COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://www.goldcopd.org/. 1.
2. WHO-Chronic obstructive pulmonary disease (COPD). http://www.who.int/respiratory/copd/en/.
3. Morlat P. Prise en charge médicale des personnes vivant avec le VIH. Rapport 2013. http://www.sante.gouv.fr/.
4. Aberg JA, Gallant JE, Ghanem KG, Emmanuel P, Zingman BS, Horberg MA. Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2013 Jan; 58(1):e1–e34. doi: 10.1093/cid/cit665 PMID: 24235263
5. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet 2013 Nov 2; 382(9903):1525–1533. doi: 10.1016/S0140-6736(13)61809-7 PMID: 24152939
6. Bénard A, Tessier JF, Rambeloarisoa J, Bonnet F, Fossoux H, Neau D et al. HIV infection and tobacco smoking behaviour: prospects for prevention. ANRS CO3 Aquitaine Cohort, 2002. Int J Tuberc Lung Dis Off J Int Union Tuberc Lung Dis 2006 Apr; 10(4):378–383.
7. Shirley DK, Kesari RK, Glesby MJ. Factors associated with smoking in HIV-infected patients and potential barriers to cessation. AIDS Patient Care STDs 2013 Nov; 27(11):604–12. doi: 10.1089/apc.2013.0128 PMID: 24138488
8. Diaz PT, Wewers MD, Pacht E, Drake J, Nagaraja HN, Clanton TL. Respiratory symptoms among HIV-seropositive individuals. Chest 2003 Jun; 123(6):1977–82. PMID: 12796177

9. Segal LN, Methe BA, Nolan A, Hoshino Y, Rom WN, Dawson R et al. HIV-1 and Bacterial Pneumonia in the Era of Antiretroviral Therapy. Proc Am Thorac Soc 2011 Jun; 8(3):282–7. doi: 10.1513/pats.201006-044WR PMID: 21653529
10. Gingo MR, Balasubramani GK, Kingsley L, Rinaldo CR Jr, Alden CB, Detels R et al. The Impact of HAART on the Respiratory Complications of HIV Infection: Longitudinal Trends in the MACS and WIHS Cohorts. PloS One 2013; 8(3):e58812. doi: 10.1371/journal.pone.0058812 PMID: 23554932
11. Crothers K, Butt AA, Gibert CL, Rodriguez-Barradas MC, Crystal S, Justice AC et al. Increased COPD among HIV-positive compared to HIV-negative veterans. Chest 2006 Nov; 130(5):1326–33. doi: 10.1378/chest.130.5.1326 PMID: 17099007
12. Madeddu G, Fois AG, Calia GM, Babudieri S, Soddu V, Becciu F et al. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the HAART era? Infection 2013 Apr; 41 (2):347–353. doi: 10.1007/s15010-012-0330-x PMID: 22971938
13. Gingo MR, George MP, Kessinger CJ, Lucht L, Rissler B, Weinman R et al. Pulmonary Function Abnormalities in HIV-Infected Patients during the Current Antiretroviral Therapy Era. Am J Respir Crit Care Med 2010 Sep 15; 182(6):790–6. doi: 10.1164/rccm.200912-1858OC PMID: 20522793
14. George MP, Kannass M, Huang L, Sciurba FC, Morris A. Respiratory symptoms and airway obstruction in HIV-infected subjects in the HAART era. PloS One 2009 Jul 21; 4(7):e6328. doi: 10.1371/journal.pone.0006328 PMID: 19621086
15. Hirani A, Cavallazzi R, Vasu T, Pachinburavan M, Kraft WK, Leiby B et al. Prevalence of obstructive lung disease in HIV population: a cross sectional study. Respir Med 2011 Nov; 105(11):1655–61. doi: 10.1016/j.rmed.2011.05.009 PMID: 21703841
16. Sampériz G, Guerrero D, López M, Valera JL, Iglesias A, Rios A et al. Prevalence of and risk factors for pulmonary abnormalities in HIV-infected patients treated with antiretroviral therapy. HIV Med 2014 Jul; 15(6):321–9. doi: 10.1111/hiv.12117 PMID: 24314004
17. Drummond MB, Kirk GD, Astemborski J, Marshall MM, Mehta SH, McDyer JF et al. Association between obstructive lung disease and markers of HIV infection in a high-risk cohort. Thorax 2012 Apr; 67(4):309–14. doi: 10.1136/thoraxjnl-2011-200702 PMID: 22090038
18. Drummond MB, Merlo CA, Astemborski J, Marshall MM, Kisalu A, McDyer JF et al. The Effect of HIV Infection on Longitudinal Lung Function Decline Among Injection Drug Users: A Prospective Cohort. AIDS Lond Engl 2013 May; 27(8):1303–11.
19. Akanbi MO, Taiwo BO, Achenbach CJ, Ozoh OB, Obaseki DO, Sule H et al. HIV Associated Chronic Obstructive Pulmonary Disease in Nigeria. J AIDS Clin Res. 2015 May; 6(5).
20. Shirley DK, Kaner RJ, Glesby MJ. Screening for Chronic Obstructive Pulmonary Disease (COPD) in an Urban HIV Clinic: A Pilot Study. AIDS Patient Care STDS. 2015 May; 29(5):232–9. doi: 10.1089/apc.2014.0265 PMID: 25723842
21. Burgel P-R. Chronic cough and sputum production: a clinical COPD phenotype? Eur Respir J 2012 Jul; 40(1):4–6. doi: 10.1183/09031936.00022412 PMID: 22753831
22. Pugliese P, Cuzin L, Cabié A, Poizot-Martin I, Allavena C, Duvivier C et al. A large French prospective cohort of HIV-infected patients: the Nadis Cohort. HIV Med 2009 Sep; 10(8):504–11. doi: 10.1111/j.1468-1293.2009.00719.x PMID: 19486189
23. Qaseem A, Wilt TJ, Weinberger SE, Weinberger SE, Hanania NA, Criner G et al. Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med 2011 Aug 2; 155(3):179–91. doi: 10.7326/0003-4819-155-3-201108020-00008 PMID: 21810710
24. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates R et al. Standardisation of spirometry. Eur Respir J 2005 Aug; 26(2):319–38. doi: 10.1183/09031936.05.00034805 PMID: 16055882
25. Centers for Disease Control and Prevention (CDC). Diagnoses of HIV Infection in the United States and Dependent Areas, 2011. HIV Surveillance Report. http://www.cdc.gov/hiv/topics/surveillance/reports.
26. Zielinski J, Bednarek M, Górecka D, Viegi G, Hurd SS, Fukuchi Y et al. Increasing COPD awareness. Eur Respir J 2006 Apr; 27(4):833–852. doi: 10.1183/09031936.06.00025905 PMID: 16585092
27. Roche N, Dalmay F, Perez T, Kuntz C, Vergnenègre A, Neukirch F, Giodanella JP et al. Impact of chronic airflow obstruction in a working population. Eur Respir J Off J Eur Soc Clin Respir Physiol 2008 Jun; 31(6):1227-33.
28. Beck F, Guignard R, Richard JB, Wilquin JL, Peretti-Watel P. Premiers résultats du baromètre santé 2010 Evolutions récentes du tabagisme en France. http://www.inpes.fr/Barometres/barometre-sante-2010/.

29. Helleberg M, Afzal S, Kronborg G, Larsen CS, Pedersen G, Pedersen C et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. Clin Infect Dis Off Publ Infect Dis Soc Am 2013 Mar; 56(5):727–734.

30. Marin JM, Alfageme I, Almagro P, Casanova C, Esteban C, Soler-Cataluña JJ et al. Multicomponent indices to predict survival in COPD: the COCOMICS study. Eur Respir J 2013; 42:323–32. doi: 10.1183/09031936.00121012 PMID: 23222874

31. Duval X, Baron G, Garelik D, Villes V, Dupré T, Leport C, et al. Living with HIV, antiretroviral treatment experience and tobacco smoking: results from a multisite cross-sectional study. Antivir Ther 2008; 13-(3):389–97. PMID: 18572752

32. Fischer WA 2nd, Drummond MB, Merlo CA, Thomas DL, Brown R, Mehta SH et al. Hepatitis C Virus Infection Is Not An Independent Risk Factor For Obstructive Lung Disease. COPD 2014 Feb; 11(1):10–6. doi: 10.3109/15412555.2013.800854 PMID: 23862666

33. Alcaide ML, Parmigiani A, Pallikkuth S, Roach M, Freguja R, Della Negra M et al. Immune activation in HIV-infected aging women on antiretrovirals—implications for age-associated comorbidities: a cross-sectional pilot study. PLoS One. 2013 May 28; 8(5):e63804.

34. Duffau P, Wittkop L, Lazaro E, le Marec F, Cognet C, Blanco P et al. ANRS CO3 Aquitaine Cohort Study Group. Association of immune-activation and senescence markers with non-AIDS-defining comorbidities in HIV-suppressed patients. AIDS. 2015 Oct 23; 29(16):2099–108. doi: 10.1097/QAD.0000000000000807 PMID: 26544576

35. Lanadula G, Chatenoud L, Gori A, Castelli F, Di Giambenedetto S, Fabbiani M et al. Risk of Severe Non AIDS Events Is Increased among Patients Unable to Increase their CD4+ T-Cell Counts >200+/μl Despite Effective HAART. PLoS One. 2015 May 28; 10(5):e0124741. doi: 10.1371/journal.pone.0124741 PMID: 26020949

36. Makinson A, Hayot M, Eymard-Duvernay S, Quesnoy M, Raffi F, Thirard L et al. High prevalence of undiagnosed COPD in a cohort of HIV-infected smokers. Eur Respir J. 2015 Mar; 45(3):828–31. doi: 10.1183/09031936.00154914 PMID: 25323226

37. Drummond MB, Kirk GD. HIV-associated obstructive lung diseases: insights and implications for the clinician. Lancet Respir Med. 2014 Jul; 2(7):583–92. doi: 10.1016/S2213-2600(14)70017-7 PMID: 24831854

38. Popescu I, Drummond MB, Gama L, Coon T, Merlo CA, Wise RA et al. Activation-induced cell death drives profound lung CD4(+) T-cell depletion in HIV-associated chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2014 Oct 1; 190(7):744–55. doi: 10.1164/rccm.201407-1226OC PMID: 25137293

39. Hogg JC. Lung structure and function in COPD. Int J Tuberc Lung Dis. 2008 May; 12(5):467–79. PMID: 18419881

40. Shipley TW, Kling HM, Morris A, Patil S, Kristoff J, Guyach SE, et al. Persistent pneumocystis colonization leads to the development of chronic obstructive pulmonary disease in a nonhuman primate model of AIDS. J Infect Dis. 2010 Jul 15; 202(2):302–12. doi: 10.1086/653485 PMID: 20533880

41. Morris A, Norris KA. Colonization by Pneumocystis jirovecii and Its Role in Disease. Clin Microbiol Rev 2012 Apr; 25(2):297–317. doi: 10.1128/CMR.00013-12 PMID: 22491773

42. Aberg JA. Aging, inflammation, and HIV infection. Top Antivir Med 2012 Aug-Sep; 20(3):101–5. PMID: 22954610

43. Marshall MM, McCormack MC, Kirk GD. Effect of cigarette smoking on HIV acquisition, progression, and mortality. AIDS Educ Prev. 2009 Jun; 21(3 Suppl):28–39. doi: 10.1521/aeap.2009.21.3_supp.28 PMID: 19537952

44. Valiathan R, Miguez MJ, Patel B, Arheart KL, Asthana D. Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study. PLoS One. 2014 May 19; 9(5):e97698. doi: 10.1371/journal.pone.0097698 PMID: 24842313

45. Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. HIV Med. 2013 Oct; 14(9):519–29. doi: 10.1111/hiv.12039 PMID: 23590676

46. Makinson A, Le Moing V, Reynes J, Ferry T, Lavole A, Poizot-Martin I et al. Lung Cancer Screening with Chest Computed Tomography in People Living with HIV. A Review by the Multidisciplinary CANCERVIH Working Group. J Thorac Oncol. 2016 Oct; 11(10):1644–52. doi: 10.1016/j.jtho.2016.06.026 PMID: 27449803

47. European AIDS Clinical Society Guidelines. October 2015. http://www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html/.

48. US Preventive Services Task Force Recommendation Statement. Screening for Chronic Obstructive Pulmonary Disease. JAMA. 2016 Apr; 315(13):1372–7.