Évolution du trouble ventilatoire obstructif chez les patients infectes par le VIH : un impact inquiétant du maintien du tabagisme

Céline Michelangeli

UNIVERSITE DE NICE SOPHIA-ANTIPOLIS

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THESE DE MEDECINE

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Le Lundi 7 novembre 2016

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A Monsieur le président du Jury

Monsieur le Professeur Pierre-Marie Roger

C'est un grand honneur de vous avoir pour président de ma thèse.

Je vous remercie également de m'avoir acceptée en DESC de pathologies Infectieuses, de m'avoir donné l'opportunité d'apprendre autant de si belles choses qui me passionnent depuis mon externat. Merci pour votre enseignement et votre soutien durant mon internat. Et je ne vous remercierai jamais assez pour votre implication dans mon avenir en tant qu'infectiologue. J'espère être à la hauteur de vos attentes.

Aux membres du Jury

Monsieur le Professeur Christian Pradier

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Monsieur le Professeur Charles-Hugo Marquette

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Madame le Docteur Francine De Salvador-Guillouet

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A ma directrice de thèse

Madame le Docteur Karine Risso

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Au service d'infectiologie

Merci à toute l'équipe de m'avoir accueillie lors de mon externat initialement, puis lors de mes 2 semestres d'internat. Je pense que vous vous souviendrez tous de cette externe aux cheveux roses, puis de cette interne en short en jean en plein hiver puis et qui a ensuite adopté des leggings aux motifs divers et variés, plus étranges les uns que les autres.

Ce que je me souviendrai, c'est surtout d'une atmosphère très agréable, où tous ceux qui y travaillent sont plus fous les uns que les autres. De cette petite ruche où le travail d'équipe arrive malgré tout à être impeccablement bien organisé, sous l'œil bienveillant de Marinette et Danièle, les meilleurs cadres du monde, il faut le dire, du savoir-faire et de la patience de toute l'équipe d'infirmiers et d'aides-soignants qui réalisent au quotidien un travail formidable dans l'intérêt des patients, et avec l'aide précieuse de nos et secrétaires préférées. Plein souvenirs positifs évidemment, mais comme toujours dans la vie, parfois des peines et des pleurs également. Une chose est sûre c'est que je ne vous oublierai jamais.

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A mes amis de la promo que j'ai quittée, depuis le tutorat (que de souvenirs!!) jusqu'au début – catastrophique – de mon externat et mon exile en Australie, vous êtes tous formidables, je suis chanceuse de vous avoir comme amis.

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A mes co-internes

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Aux co-internes de mes 2 semestres en infectio, et tout particulièrement :

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Evolution of the Obstructive Lung Disease in HIV-infected patients: a worrying impact of smoking maintenance

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Abstract:

Aims: HIV infected patients are more frequently impacted by COPD. We analyzed the evolution of the respiratory function and its determinants in our cohort of HIV-infected patients diagnosed with an obstructive lung disease (OLD) 4 years ago.

Methods: This monocentric study conducted during 1 year included the 64 HIV-infected patients diagnosed with an OLD in the Infectious Disease department of Nice University Hospital in 2012. A questionnaire, plus our electronic medical record NADIS® and a new spirometry permitted to analyze the evolution of respiratory function and factors correlated (smoking, body mass index, age, markers of HIV infection).

Results: 31 patients with 74% of men and a median age of 58 years were included. Viral load was undetectable for 93% and median CD4 cell count was 656 cells/mm3. The mortality rate was 7.8% in 4 years. Current smokers have a decline of their forced expiratory volume in 1 second (FEV1) of 300mL over 4 years, whereas former smokers had a gain of 40mL (P = 0.0008). Smoking maintenance was the only parameter correlated with an unexpected worsening of FEV1 and an aggravation of obstruction, in multivariate analysis, respective values: OR 18.5 CI [1.95 – 166.6], P = 0.01; OR 13.5 CI [2.19 – 83.3], P = 0.005, respectively. Smoking maintenance was correlated with cannabis use (P = 0.03).

Conclusion: Smoking maintenance appears to be the main risk factor of OLD aggravation in HIV-infected patients who show an immune and virologic control of their infection. Clinicians must be more aware of the benefit of smoking cessation which probably requires a specific care.

Introduction

Nowadays, with the use of antiretroviral therapies (ART), the life expectancy of HIV-infected patients has improved greatly (1). However, this ageing population is faced with an increase of non-AIDS comorbities, compared to the general population, with more cardiovascular, metabolic, osteoarticular, nephrological and neurological concerns (2, 3). Immunodeficiency and continuous immune activation seem implicated in these comorbidities via an accelerated ageing along with other factors such as environmental exposure (4-11).

Chronic obstructive pulmonary disease (COPD) is a largely underdiagnosed disease in the general population and is directly responsible of an increased mortality (12, 13). This disease is projected as the third cause of mortality in the general population by 2030 (14). COPD is also a comorbid condition more prevalent in HIV-infected people than in the general population (2, 15-18). This condition is in relation with cigarette and marijuana smoking, which are more frequent in the HIV-infected population (19, 20). In a study conducted 4 years ago in the Infectious Disease Department of Nice University Hospital, we identified that a low CD4 cell count was also independently correlated with COPD (article submitted to publication). This finding confirmed previous suspicions described in the literature (21-24).

We aimed to analyze the evolution of the respiratory function in this cohort of patients with obstructive lung disease (OLD) diagnosed in 2012. Our objective was to characterize factors correlated with evolution of respiratory function and more specifically to analyze the influence of CD4 cell count and other markers of HIV disease.

Patients and Methods

1. Population and study design

This prospective monocentric study took place in the Infectious Disease outpatient clinic department of the Nice University Hospital in France. We included the 64 patients diagnosed in 2012 with an OLD during a study performed in a randomly selected section of 623 HIV-infected patients from our entire cohort of 2453 HIV-infected patients (article submitted to publication). We used spirometric definition of OLD and COPD recommended by American Thoracic Society (ATS) / European Respiratory Society (ERS) guidelines (25, 26). Obstructive lung disease was defined as a Forced Expiratory Volume in one second (FEV1) / Forced Vital Capacity (FVC) < 70% prior bronchodilator test and COPD was defined as a FEV1/FVC < 70% after bronchodilator test [27]. In 2016 as in 2012, patients with a recent lower respiratory tract infection (LRTI) < 2 months or with mental or physical incapacity to perform a spirometry were excluded.

Guidelines recommend annual control of spirometry for COPD HIV-infected patients (27, 28). During a follow-up consultation, we performed a conventional spirometry, and the patients filled a questionnaire with the help of one of the two investigators (K.R, C.M). This questionnaire re-evaluated the same parameters than 4 years ago, with the same questions (respiratory symptoms, smoking history, marijuana use, previous LRTI or hospitalizations for a respiratory related conditions, occupational respiratory exposure), (Appendix).

Data concerning HIV-infection (date of contamination, CD4 nadir, CDC staging, HIV Viral Load, CD4 count within the last 4 years, and history of opportunistic infections) and comorbidities were collected from our electronic medical record (NADIS®) (29).

2. Ethics

All subjects provided their written informed consent to participate to this study. This study was realized in accordance with the ethical committee of our institution

3. Statistical analysis

In our study, we defined as an unexpected worsening of the FEV1, an annual loss of FEV1 over 50mL. This value corresponds in the literature to the mean annual loss of FEV1 in patients diagnosed with COPD still currently smoking. It is therefore a stringent value to define an unexpected aggravation of FEV1 (30-33). An aggravation of the airway obstruction was defined by a loss in the variation rate of the FEV1/FVC ratio.

We defined as former smokers, patients who have been abstinent for at least one year.

First, we compared epidemiological, respiratory exposure, respiratory symptoms, spirometric parameters and HIV markers between 2012 and 2016. Then, we searched for parameters correlated with the evolution of respiratory function. Our population including only patients with OLD, we compared patients who showed an annual loss of their FEV1 over 50mL, defined as an unexpected aggravation, with the other patients. Because FVC significantly decreased during 4 years, in order to target more specifically the obstructive disease, we compared patients who had an aggravation of their airway obstruction, based on a decreased of FEV1/FVC ratio, with the other patients.

Tobacco smoking remaining highly correlated with respiratory lung function degradation, in order to distinguish a correlation between markers of HIV-infection and respiratory function evolution, we separately compared the evolution of FEV1 and airway obstruction with marker of HIV-infection, in the population of former smokers and current smokers. These groups were compared in univariate analysis using Fisher's exact test and Mann-Whitney U test. Then, we performed two multivariate analyses, using a logistic regression model testing including all factors identified with a tendency ($p < 0.1$) in previous univariates analyses, firstly to search for a correlation with an unexpected aggravation of FEV1 and secondly to search for a correlation with an aggravation of airway obstruction.

Continuous variables are presented as median [minimum, maximum]. Wilcoxon signed rank 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 $P < 0.05$. Statview version 5.0 software was used for statistical analysis.

Results

The study's flowchart is presented in Figure 1. Over the 64 patients at baseline, 31 patients (48.4%) agreed to participate to the study, 16 patients (25%) were lost to follow-up, 12 patients (18.8%) refused to participate to the study and 5 patients (7.8%) had died.

Evolution of our population from baseline to 2016

Patients' characteristics at baseline and in 2016 are detailed in **Table 1.** Seventy-four percent were men and median age at baseline was 54 years [43, 73]. At baseline, the median HIV-infection duration was 23 years [4, 29], with a median CD4 nadir cell of 171 cells/mm^3 [4, 711]. All of the patients had an undetectable viral load (VL) at baseline, with 100% of patients under ART versus an undetectable HIV VL for 29 patients (93.5%) 4 years later ($P = 0.1$). Median CD4 cell count increased from 574 cells/mm^3 [144 – 2632] at baseline to 656 [106, 2300] in 2016 ($P = 0.04$).

The proportion of current smokers decreased from 25 patients (77.4%) to 20 patients (64.5%) ($P = 0.0013$) with a median pack-year history at baseline of 68 [1, 135]. Respiratory symptoms were present in the same proportion of patients in 2012 and 2016 (19 patients (61.3%) *vs*. 21 patients (67.7%), respectively), ($P = 0.6$). Dyspnea was the most reported pulmonary condition, followed by chronic bronchitis and recurrent acute exacerbation (Table 1).

The mortality during 4 years in our OLD cohort and in our entire population followed-up from 2012 in our Infectious Disease consultation department was 7.8 % (5/64 patients) and 3.9% (90/2516 patients) respectively. In our OLD cohort, two patients died of a cardiac arrest, 1 patient of a pulmonary embolism, 1 patient of an acute respiratory failure due to a community acquired bacteria pneumonia, and 1 patient committed suicide.

Evolution of respiratory function

In 4 years, all the functional respiratory parameters tested decreased with a median of 2320mL [970, 3340] to 2190mL [670, 3210] and 3880mL [2020, 5190] to 3620mL [1910, 4840] for FEV1 and FVC respectively ($P = 0.0006$ and $P < 0.0001$). Airway obstruction, expressed by FEV1/FVC ratio, did not differ in 2012 and in 2016. The median value of the decrease

of FEV1 over 4 years was of 130mL [-1060, 220], 260 mL [-1060, 120] and 300mL [-1060, 220] for the entire OLD cohort (31 patients), COPD patient and current smokers, respectively. The median value of FEV1 increased by 40 mL [-260, 180] in former smokers (*P* = 0.0008). Fourteen patients (45%) showed an unexpected worsening of their FEV1 and 17 patients (54.8%) an aggravation of their FEV1/FVC ratio.

Factors correlated with respiratory function degradation

The results are summarized in **table 2.** The unexpected worsening of the FEV1 was only correlated with the maintenance of tobacco smoking (92.8% current smokers in unexpected worsening *vs.* 41.2%, *P* = 0.008). This result remained significant even when smoking cessation was of 1 year (data not shown). The aggravation of the FEV1/FVC ratio was correlated with the smoking status in 2016 (88.2% current smokers *vs*. 35.7%, p = 0.007) and with the variation rate of CD8 cell count between 2012 and 2016 (delta CD8) (+21.9 % [-8.6, 185.7] *P* = 0.03). Smoking exposure being intensely correlated with worsening of respiratory function, we compared current smokers with former smokers to analyse the benefit of smoking cessation (**table 3**). Tobacco smoking cessation was not significantly correlated with a modification of respiratory symptoms but was correlated with a gain of 40 ml of FEV1 in 4 years [-260, 180] *vs.* a loss of 300mL [-1060, 220], (*P* = 0.0008) in patients who had continued smoking. Tobacco smoking maintenance was also correlated with cannabis use (*P* = 0.03).

Then, we analyzed separately our population of current and former smokers. We did not find any correlation between the variation of FEV1, obstruction or an unexpected worsening of FEV1 with CD4 cell count, variation rate of CD4 cell count, or CD8 cell count, variation rate of CD8 cell count, CD4/CD8 or its variation rate, or with HIV viral load (data not shown).

In multivariate analysis, only tobacco smoking remained correlated with an unexpected worsening of FEV1 (OR 18.5 CI [1.95 – 166.6], *P* = 0,01). The maintenance of tobacco smoking was also correlated with an aggravation of the FEV1/FVC ratio (OR 13.5 CI [2.19 – 83.3], *P* = 0.005), in multivariate analysis.

Analysis of the care and treatment of OLD

Results are summarized in **table 4.** At baseline, only 4 patients (12.9%) were diagnosed with COPD prior to the previous study. Twenty-five patients (80.6%) were current smokers, 24 (96%) received advice related to smoking cessation, with specialized help to smoking cessation proposed in 52% of cases. Three patients (11.5%) were receiving a pharmacologic treatment for their COPD. In 2016, 5 patients (20%) had quit smoking. Among the 20 patients who were still currently smoking in 2016, 11 patients (55%) stated having tried to quit smoking with nicotine substitutes, mainly electronic cigarette and nicotine patches, while 9 patients (45%) had reduced their consumption. Eleven patients (55%) were also cannabis users. Sixteen patients (51.6%) were informed in 2016 of the diagnosis of bronchopathy. Six patients (24%) received a pharmacologic therapy for COPD, 6 patients (24 %) had the recommended by guidelines follow-up, 7 patients (28 %) performed the recommended annual spirometry.

Discussion

The worsening of respiratory function was particularly important four years later for current smokers in our population of 31 HIV-infected patients with an OLD. This worsening seemed higher than what is observed in HIV-uninfected COPD individuals, even if we did not find any independent correlation between HIV parameters and respiratory function decline to explain these findings. On the other hand, we highlighted that smoking cessation was highly profitable. Our study also showed a concerning mortality rate in our OLD HIV-infected patients, and we pointed out a lack of COPD management from the clinicians despite a diagnosis established in a previous study.

The annual FEV1 decline is known in the general population of COPD individuals. It presents a high inter-individual variation and is markedly influenced by the maintenance of tobacco smoking and the severity of COPD (34-42). The FEV1 decline in our total cohort did not differ from what is expected in the general population (33mL/yr in general population *vs* 32.5mL/yr [-265, 55] in our population) but it seemed globally worse when we focused on our patients diagnosed with COPD and still currently smoking. Indeed, in HIV-uninfected individuals with COPD who maintain tobacco smoking, we expect an annual FEV1 loss of 50mL/yr, whereas in our study we observed a loss of 75mL/yr [-265, 55].

Then, given than data from previous studies seem to indicate an independent role-played by HIV-infection in the development and aggravation of COPD (2**,**17,21, 23, 24, 43, 44), we assessed the implication on the respiratory function evolution of diverse factors including HIV markers. With this goal and the suspicion that HIV could be a cofactor of COPD progression along with smoking maintenance, we arbitrarily chose to analyze patients with an unexpected decline of their FEV1 with the others patients. We did the same analysis with patients who presented an aggravation of their obstruction (decrease of FEV1/FVC ratio) with those who did not, to find correlated factors. The maintenance of tobacco smoking was the only factor correlated with an unexpected worsening of the FEV1, in univariate analysis (P = 0.008), and in multivariate analysis (OR 18.5 CI [1.95 – 166.6], P = 0,01).

Likewise, the maintenance of tobacco smoking was also the only factor correlated with an aggravation of the FEV1/FVC ratio, in univariate analysis (P = 0.007), and in multivariate analysis (OR 13.5 CI [2.19 – 83.3], P = 0.005), (**table 2**).

Our findings on the consequences of the maintenance of tobacco smoking are in accordance with previous studies (34-42, 45).

While smoking maintenance is correlated with a higher worsening of lung function, smoking cessation appeared clearly beneficial for the evolution of FEV1 and airway obstruction. Actually, among the former smokers, we noted that 6 patients (54.5 %) showed a gain of their FEV1. (**table 3**). Seeing the impact of smoking, we chose separately to analyze in the sub-group of former smokers and of current smokers, the variation rate of FEV1, an unexpected worsening of FEV1 and an aggravation of FEV1/FVC ratio with markers of HIV-infection (such as HIV duration, the nadir CD4 cell count, the Viral Load, the CD4 cell count, the CD8 cell count and the CD4/CD8 ratio and their variation rates). We did not find any independent correlation between the unexpected worsening of FEV1 and markers of HIV-infection, nor with the aggravation of FEV1/FVC ratio and markers of HIV-infection, either in the sub-group of former smokers or the sub-group of continuing smokers (data not shown).

Considering our entire OLD population, we observed a high level of CD8 cells (928 cells/mm^3 [357 – 2693]), *P* = 0.1) or an increase of CD8 cells count (21,9% [- 8.6 – 185.7], *P* = 0.03) in patients who showed an aggravation of airway obstruction, in univariate analysis but not in multivariate analysis. Increased CD8 cells had already been described as correlated with more inflammatory comorbidities especially when associated with a CD4/CD8 decrease (46). This association disappeared in multivariate analysis and was not correlated with the decrease of FEV1.

In recent studies, the results on the role played by HIV markers in the development and the decline of COPD are scarce and discordant. One study, performed in Italy, including 111 HIV-infected patients compared to HIV-uninfected age and sex-matched controls, found that HIV-infection was an independent risk factor of COPD (*P* = 0.008) but did not identify the parameters of HIV-infection implicated in this observation (17). The most suspected markers are mainly a low CD4 cell count (article submitted to publication, 2) or a high HIV viral load (43, 45). These appear only for extreme values, when HIV-infection is poorly controlled, with very low CD4 cell count and high viral load, which was not the case in our study. In our population, HIV-infection is highly controlled, as 93.5% have an undetectable VL, and the median CD4 cell count at baseline was 574 cells/mm^3 (144, 2632) increasing in 2016 to 656 cells/mm^3 (106, 2300), which did not allow us to test our hypothesis of an effect of these markers, especially CD4 cell count, in the progression of lung function and airway obstruction.

We observed the already known high mortality found in COPD patients, with a mortality rate of 7.8% in our study *vs.* 3.9% for our entire HIV-infected cohort [47, 48]. Furthermore, COPD as a cause of mortality in our out-patient active file may be under-estimated given the fact that we only considered the patients diagnosed with a COPD in our previous study in 2012 and we did not take into account the other outpatients who could have been diagnosed with COPD.

Early diagnosis and management have an impact on both the evolution and the prognostic of COPD (49, 50). Four years ago, patients and clinicians were informed of the diagnosis of OLD. We assessed their management (**table 4**). From this analysis, we noted that patients, in 2016, were under-informed about the diagnosis of OLD which was given to their clinician (51.6%) but smoking cessation was proposed to the major part of them (96%). A specific help including nicotine substitutes and consultations with the tabaccologist working in our department, were insufficiently offered (52%), when smoking cessation seems difficult in our population where 38.7% of our patients are current cannabis users. Actually, we noted that over half of the current smokers were also cannabis users (55%) *vs* 6 (54.5%) who managed to quit both tobacco smoking and cannabis use. Pharmacologic treatment was too largely under prescribed, with only 6 patients (24%) receiving a pharmacotherapy for their COPD. An annual spirometry was performed for 7 patients (28 %). We did not know the reasons for this lack of interest in COPD management by the clinicians in this population meticulously followed-up, with frequent consultations. Some studies show pharmacologic interactions between inhaled corticosteroids (ICS) and protease inhibitors (PI), which could be a reason why clinicians are reluctant to treat this population (51). Of course, while this pharmacologic interaction between ICS and PI must be taken into account, perhaps

it is important to inform clinicians that the indications of ICS in COPD management concern only GOLD 3 or 4 COPD patients with frequent exacerbations. In our study, only 1 patient required the use of ICS and did not have PI for the treatment of their HIV-infection. Nowadays, possibilities of switch PI to INI, which are particularly safe in this population, are numerous.

Our study has several limits. Considering our population, only 31 (48.4%) of OLD patients diagnosed in 2012 remained evaluable in 2016. Comparison with a HIV-negative controlled group with OLD would not have permitted to determine the effects of HIV-infection but would have been interesting in order to appreciate more precisely the evolution of respiratory function and airway obstruction in the absence of HIV-infection. With regard to the analysis of markers of HIV-infection, our population shows a very well-controlled infection. Consequently, we could not establish a suspected role of immune or viral markers on the evolution of respiratory function and airway obstruction. Finally, the size of our cohort also represents a limit to this study with only 48.4% of participation.

In conclusion, COPD in HIV-infected patients is frequent and presents a particularly serious evolution when with smoking maintenance. Smoking cessation, which is probably more difficult owing to the frequent association with cannabis use, seems to be particularly profitable and requires a particular concern including the use of specific tools. Our study did not allow us to conclude about the effects of markers of HIV-infection on the respiratory function evolution as all of our patients, as well as those usually followed-up in developed countries, present an excellent immune and virologic control of their HIV-infection.

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Figure 1. Study's Flowchart

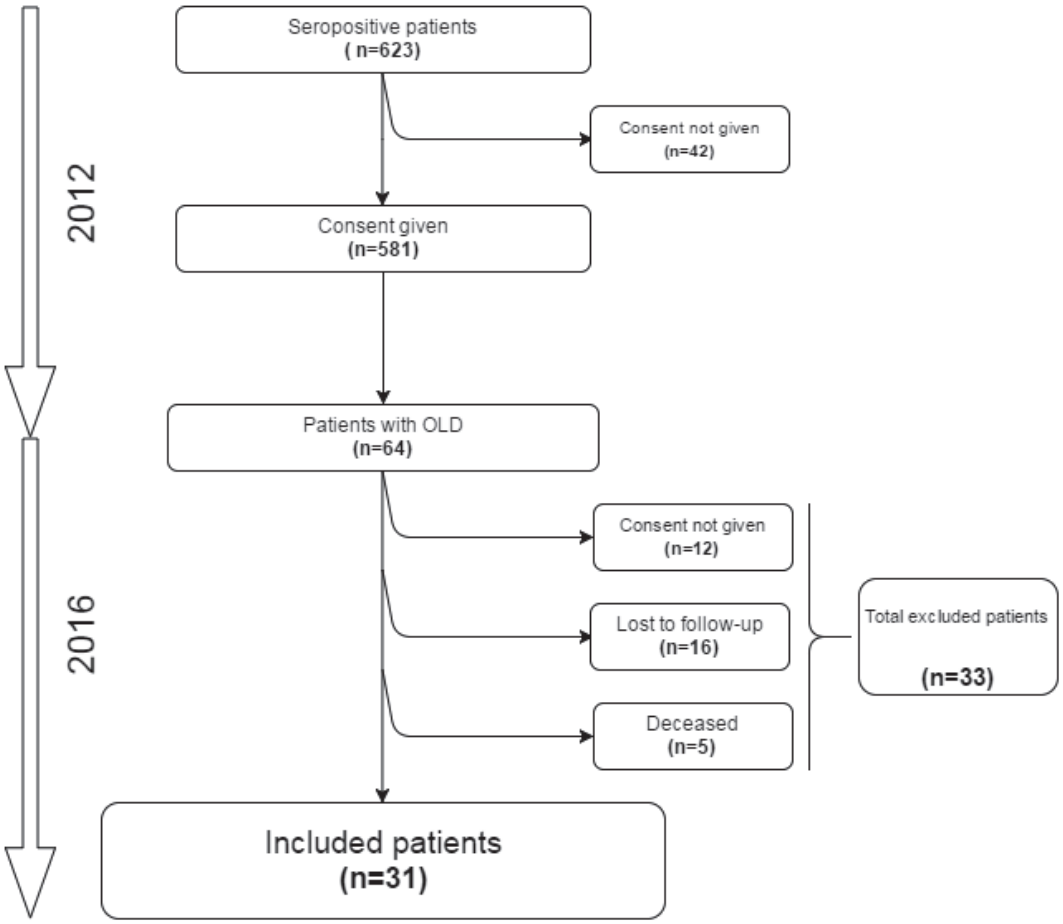

Table 1. Characteristics of the population at baseline and in 2016

	Population at Baseline, 31 (100%)	Population in 2016, 31 (100%)	
Demographic characteristics			
Age, yrs	54 [43, 73]	58 [47, 77]	
Male Gender	23 (74%)	23 (74%)	
BMI, kg/m²	21,2 [10,8, 25,9]	22,2 [16,7, 28,4]	p = 0,0007
Toxic exposure			
Smoking status			p = 0,0013
Current	25 (80,6%)	20 (64,5%)	
Former	6 (19,4%)	11 (35,5%)	
Pack-year history, yrs	68 [1, 135]	70 [1, 139]	p < 0,0001
Cannabis exposure			
Current cannabis use	14 (45,2%)	12 (38,7%)	p < 0,0001
Ever use	23 (74,2%)	23 (74,2%)	
IDU history	14 (45,2%)	14 (45,2%)	
Professional respiratory exposure history	10 (32,3%)	10 (32,3%)	
Clinical characteristics			
Respiratory symptoms	19 (61,3%)	21 (67,7)	p = 0,6
Dyspnea	15 (48,4%)	19 (61,3%)	p = 0,3
Chronic bronchitis	6 (19,4%)	12 (38,7%)	p = 0,2
Recurrent acute exacerbation	5 (16,1%)	7 (22,6)	p = 0,1
History of hosp. for respiratory condition	9 (29%)	9 (29%)	
LRTI history	23 (74,2%)	24 (77,5%)	
OLD characteristics			
Volumes Characteristics			
FEV1, mL	2320 [970, 3340]	2190 [670, 3210]	p = 0,0006
FEV1 loss, mL		-130 [-1060, 220]	
FVC, mL	3880 [2020, 5190]	3620 [1910, 4840]	p < 0,0001
FVC loss, mL		-350 [-970, 390]	
FEV1/FVC, %	64% (± 8,6)	61% (± 13,4)	p = 0,6
OLD severity			
Reversible OLD without COPD	5 (16,1%)	5 (16,6%)	
GOLD 1	12 (38,7%)	9 (30%)	
GOLD 2	11 (35,5%)	11 (36,7%)	
GOLD 3	1 (3,2%)	3 (10%)	
GOLD 4	2 (6,5%)	2 (6,7%)	
Knowledge of diagnosis by patients	4 (12,9%)	16 (51,6%)	
HIV characteristics			
HIV infection duration, yrs	23 [4, 29]	27 [8, 33]	
HIV RNA, log10 cp/mL*	40	55,6 [40, 490]	p = 0,1
HIV RNA undetectable	31 (100%)	29 (93,5%)	
Nadir CD4, cells/mm3	171 [4, 711]	171 [4, 711]	
CD4 cell count, cells/mm^3	574 [144, 2632]	656 [106, 2300]	p = 0,04
CD4 cell count 350 cells/mm^3	14 (45,2%)	6 (19,4%)	p = 0,09
CD8 cells count, cells/mm^3	780 [168, 2112]	874 [208, 2693]	p = 0,05
CD4/CD8 ratio	0,72 [0,16, 2,3]	0,77 [0,15, 2,7]	p = 0,04

Data are expressed as percentage (No/total No) or as median [minimum, maximum]

* Data expressed as mean (standard deviation)

yrs = years ; BMI = Body Mass Index ; IDU = Intraveinous Drug Use ; LRTI = Lower Respiratoiry Tract Infection ; OLD = Obstructive Lung Disease

COPD = Chronic Obstructive Pulmonary Disease ; FEV1 = Forced Expiratory Volume in 1 second ; FVC = Forced Vital Capacity

Table 2. Univariates comparisons of the patients with an unexpected worsening of FEV1 *vs* an expected evolution of FEV1 and with an aggravation of FEV1/FVC ratio *vs* no aggravation of the FEV1/FVC ratio

	Expected evolution or gain of FEV1	Unexpected worsening of FEV1		No aggravation of FEV1/FVC ratio	Aggravation of FEV1/FVC ratio	
	n = 17	n = 14		n = 14	n = 17	
Demographic characteristics						
Age, yrs	58 [47, 66]	57 [49, 77]	p = 0,8	57 [47, 66]	58 [49, 77]	p = 0,9
BMI, kg/m²	22,8 [19,4, 28,4]	21,5 [16,7, 25,9]	p = 0,1	22,48 [19,4, 25,9]	22,1 [16,7, 28,4]	p = 0,5
Toxic exposure						
Tobacco exposure						
Active smokers	7 (41,2 %)	13 (92,8 %)	**p = 0,008**	5 (35,7 %)	15 (88,2 %)	**p = 0,007**
Pack-year	68 [1, 115]	78 [30, 139]	p = 0,3	68 [1, 130]	74 [30, 139]	p = 0,6
Clinical characteristics						
Presence of symptoms	10 (58,8 %)	11 (78,6 %)	p = 0,4	8 (57,1 %)	13 (76,5 %)	p = 0,4
Presence of chronic bronchitis	4 (23,5 %)	8 (57,1 %)	p = 0,1	4 (28,6 %)	8 (47 %)	p = 0,4
Dyspnea	10 (58,8 %)	9 (64,3 %)	p = 0,7	8 (57,1 %)	11 (64,7 %)	p = 0,6
Frequent exacerbators	4 (23,5 %)	3 (21,4 %)	p > 0,9	4 (28,6 %)	3 (17,6 %)	p = 0,7
LRTI	12 (70,6 %)	12 (85,7 %)	p = 0,3	11 (78,6 %)	13 (76,5 %)	p > 0,9
HIV characteristics						
HIV duration, yrs	28 [13, 32]	26,5 [8, 33]	p = 0,7	27 [19, 32]	27 [8, 33]	p = 0,3
Nadir CD4, cells/mm^3	92 [4, 461]	186 [44, 711]	p = 0,1	81,5 [4, 521]	180 [44, 711]	p = 0,1
Viral load, log10 cp/mL	40 [40, 490]	40 [40, 40]	p = 0,19	40 [40, 490]	40 [40, 40]	p = 0,1
CD4 cell count, cells/mm^3	496 [106, 2300]	719 [256, 1254]	p = 0,4	404 [106, 2300]	860 [256, 1173]	p = 0,1
CD4 cell count < 350, cells/mm^3	5 (29,4 %)	1 (7,1 %)	p = 0,2	5 (35,7 %)	1 (5,9 %)	p = 0,09
CD8 cell count, cells/mm^3	874 [208, 2015]	854 [357, 2693]	p = 0,6	784 [208, 2015]	928 [357, 2693]	p = 0,1
CD4/CD8 ratio	0,76 [0,15, 1,6]	0,77 [0,17, 2,7]	p = 0,6	0,73 [0,15, 2,7]	0,77 [0,17, 2,2]	p = 0,5
Delta CD4, %	33,33 [-69,5, 150]	20,07 [-20,3, 146,5]	p = 0,7	0,023 [-69,6, 150]	36,2 [-17, 146,5]	p = 0,06
Delta CD8, %	10,8 [-51,6, 68,7)	14,02 [-34, 185,7]	p = 0,5	-8,4 [-51,9, 47,3]	21,9 [-8,6, 185,7]	**p = 0,03**
Delta CD4/CD8, %	2,35 [-66,7, 100]	3,12 [-38,6, 208]	p = 0,9	9,2 [-66,7, 100]	2,7 [-38,6, 208]	p = 0,8

Data are expressed as percentage (No/total No) or as median [minimum, maximum]

FEV1 = Forced Expiratory Volume in one second ; FVC = Forced Vitality Capacity ; yrs = years ; BMI = Body Mass Index ; LRTI = Low Respiratory Tract Infection

Table 3. Effects of smoking exposure on clinical characteristics, on the evolution of respiratory function and on the airway obstruction.

	Former smokers	Current smokers	
	n = 11	n = 20	
Clinical characteristics			
Presence of symptoms	6 (54,5 %)	15 (75 %)	p = 0,4
Chronic bronchitis	3 (27,2 %)	9 (45 %)	p = 0,5
Dyspnea	6 (54,5 %)	13 (65 %)	p = 0,8
History of LRTI	7 (63,6 %)	17 (85 %)	p = 0,3
Current cannabis use	1 (9,1 %)	11 (55 %)	**p = 0,03**
Spirometric parameters			
FEV1, mL	2340 [940, 3210]	2120 [670, 3040]	p =0,6
Difference of FEV1 between 2012 and 2016, mL	+ 40 [-260, 180)	- 300 [-1060, 220]	**p = 0,0008**
Annual loss of FEV1 > 50mL	1 (9,1 %)	13 (65 %)	**p = 0,008**
FEV1 gain	6 (54,5 %)	3 (15 %)	p = 0,8
FEV1/FVC ratio	0,67 [0,38, 0,72]	0,61 [0,33, 0,73]	p = 0,1
Aggravation of FEV1/FVC ratio	2 (18,2 %)	15 (75 %)	**p = 0,007**

Data are expressed as percentage (n/n total) and median [minimum, maximum]

LRTI = Low Respiratory Tract Infection ; FEV1 = Forced Expiratory Volume in one second ; FVC = Forced Vital Capacity

Table 4. Analysis of the care of OLD at baseline and in 2016

Care of OLD at baseline		Care of OLD in 2016	
Knowledge of the diagnosis by patient	4 (12,9 %)	Knowledge of the diagnosis by patient	16 (51,6 %)
Number of smokers	25 (80,6 %)	Number of smokers	20 (64,5 %)
Advice of quitting smoking from clinician	24 (96 %)	Use of help to quit smoking	11 (55 %)
Specific help to quit smoking proposed by clinician	13 (52 %)	Reduction of tobacco consumption	9 (45 %)
Cannabis users among current smokers	13 (52 %)	Cannabis users among current smokers	11 (55 %)
Pharmacologic treatment of COPD	3 (11,5 %)	Pharmacologic treatment of COPD	6 (24 %)
		Annual spirometry	7 (28 %)

OLD = Obstructive Lung Disease ; COPD = Chronic Obstructive Lung Disease

Appendix : Questionnaire (translated in English)

QUESTIONNAIRE COPD STUDY

READ WITH PRECAUTION QUESTIONS WITCH CONCERN YOUR RESPIRATORY SYMPTOMS AND YOUR RISK FACTOR OF RESPIRATORY DISEASE AND TRY TO PRECISELY ANSWER.

Weight, size: You weight _ _ _ kilograms You are _ _ _meter

Symptoms

1- If we ask you "do you spit?" you will respond (ONLY ONE RESPONSE)

YES ☐ I spit at last one time a day from 2 years
No ☐ I don't spit, or very occasionally

2- If we ask you if you are breathless, you will say (ONLY ONE RESPONSE)

YES ☐ I'm sometimes breathless if I climb the stairs, from 2 floors
YES ☐ I'm regularly breathless if I walk fast or if I walk a climb
YES ☐ I'm regularly breathless if I walk on the flat with the same speed than somebody as old than me
YES ☐ When I walk, I usually have to stop to catch my breath after several minutes or 100 meters
YES ☐ I'm breathless for a lesser effort
NO ☐ None of previous response, breathlessness is not a problem.

3- Have you do to take antibiotics or corticoids (solupred®, cortancyl®, prednisolone®, celestene®) **for a bronchitis, and that at least 2 times during previous year?** YES ☐ NO ☐

4- Have you already been hospitalized for respiratory problem? YES ☐ NO ☐

Care of the OLD

5- Some doctor has already say you that you have a chronic bronchitis (or chronic bronchitis of smoker)? YES ☐ NO ☐

If yes, which year? _____

6- Have you been taken in charge for your CPDO / Bronchopathy due to tobacco smoking since the diagnosis? YES ☐ NO ☐

Date of the last spirometry? _____
Do you take a treatment for your Breath/ for your respiration*? YES ☐ NO ☐

* exemple of treatment for respiratory disease: Sérétide®, Symbicort®, Ventoline®, Bécotide®, Béclojet®, Prolair®, Qvar®, Béclométasone®, Béclone®, Pulmicort®, Flixotide®, Miflonil®, Bronchodual®, Combivent®, Atrovent, , Spiriva, Asmabec®, Bemedrex®, Miflasone®, Onbrez®, A Spir®, Nexxair®, Ecobec®, Timos®, Formoair®, Breezhaler®, Atimos®, Formoair®, Tersigat®, Dilatrane®, Euphylline®, Theophylline®, Tédralan®, Xanthium®, Trentadil®, Singulair®

Toxic exposure

7- Tobacco smoking:

- Has a doctor ever explained to you the link between tobacco smoking and COPD? YES ☐ NO ☐
- Have you ever received the advice to quit smoking? YES ☐ NO ☐
- Have you ever received a help to quit smoking / a consultation with a tobaccologist? YES ☐ NO ☐
- Have you reduced your consumption since the diagnosis of COPD? YES ☐ NO ☐
  If yes, from how many? _____
- Have you quit smoking since the diagnosis of COPD? YES ☐ NO ☐

8- Do you currently smoke? YES ☐ NO ☐
If yes, have you tried to quit? YES ☐ NO ☐
If yes, have you had recourse to a pharmacologic of professional help? YES ☐ NO ☐
Please, precise: _____
Why did you start again? _____

9- If you smoke, or have ever smoked:

- When did you start: _____ years old
- On average, how much pack of cigarettes do you smoke (smoked) a day?
  (only one answer)
  ☐ less than a half packet a day ☐ between an half and one packet a day
  ☐ between one and two packet a day ☐ more than 2 packet a day
- Pack-year number: _____ pack-year

10- If you stopped smoking: when did you stop? _____ years old

11- Cannabis

- Do you currently smoke cannabis (at least one joint a week) YES ☐ NO ☐
  If yes, on average: ☐ between a joint a week and 1 joint a day
  ☐ between 1 and 5 joints a day
  ☐ more than 5 joints a day

In the past, have you regularly (at least one joint a week) during a period, smoked cannabis? YES ☐ NO ☐

12- Professional exposure

Have you in the past or are you currently been exposed during your job to dust, fumes (agriculture, mine, textile industry…) YES ☐ NO ☐

SERMENT D'HIPPOCRATE

Au moment d'être admis(e) à exercer la médecine, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité. Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.
Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l'intimité des personnes, je tairai les secrets qui me seront confiés. Reçu(e) à l'intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.
Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission. Je n'entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j'y manque.