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ORIGINAL RESEARCH

Spirometric profile of people living with HIV on antiretroviral drugs in Abidjan

Profil spirométrique des personnes vivant avec le VIH sous médicaments antirétroviraux à Abidjan

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ABSTRACT

Introduction. People living with HIV (PLHIV) are susceptible to developing non-communicable chronic respiratory diseases. Our objective was to study the spirometric profile of this population.

Material and methods. This was a descriptive and analytical cross-sectional retro-prospective study conducted from March 15 to June 15, 2022 and relating to the analysis of the medical files of asymptomatic and eligible for spirometry PLHIV, aged 18 years and above. They were received in the voluntary counselling and testing (VCT) centres of one of the two pulmonology departments in Abidjan.

Results. The study involved 54 subjects including 22 men (40.7%) and 32 women (59.3%) with an average age of 48.9 years. The majority of patients were non-smokers (81.4%) and the main history was pulmonary tuberculosis (35.2%). Only 29.6% had chronic respiratory symptoms and 42.6% had a normal BMI. The frequency of spirometric abnormalities was 57.4%. These spirometric abnormalities included 40.7% peripheral obstructive pattern; 9.3% restrictive pattern; 3.7% asthma and 3.7% COPD. A more than 10 years duration of HIV infection ($p=0.001$ OR= 0.2 (0.1 – 0.7)) and a duration of ART of at least 10 years ($p=0.001$ OR= 0, 2 (0.1 – 0.7)) were significantly associated with the existence of ventilatory abnormalities.

Conclusion. The high frequency of ventilatory anomalies in PLHIV independently of the existence of chronic respiratory signs leads us to propose spirometry in the follow-up assessment of PLHIV while paying particular attention to those on ARVs for more than 10 years.

KEYWORDS: Profile; Spirometry; PLHIV; Antiretroviral; Abidjan

RÉSUMÉ

Introduction. Les personnes vivant avec le VIH (PVVIH) sont susceptibles de développer des maladies respiratoires chroniques non transmissibles. Notre objectif était d'étudier le profil spirométrique de cette population.

Matériel et méthode. Il s'agissait d'une étude retro-prospective transversale descriptive et analytique conduite du 15 Mars au 15 Juin 2022 et portant sur l'analyse des dossiers médicaux des patients PVVIH âgés d'au moins 18 ans reçus dans le CDV de l'un des deux services de pneumologie d'Abidjan, asymptomatique et éligible à la réalisation de la spirométrie.

Résultats. L'étude a porté 54 sujets dont 22 hommes (40,7%) et 32 femmes (59,3%) avec un âge moyen de 48,9 ans. La majorité des patients était non-fumeur (81,4%) et le principal antécédent était la tuberculose pulmonaire (35,2%). Seulement 29,6% présentaient des symptômes respiratoires chroniques et 42,6% avaient un IMC normal. La fréquence des anomalies spirométriques était de 57,4%. Ces anomalies spirométriques étaient constituées 40,7% de TVO périphérique ; 9,3% de TVR ; 3,7% d'asthme et 3,7% de BPCO. L'ancienneté du diagnostic de l'infection à supérieure à 10 ans $p=0,001$ OR= 0,2 (0,1 – 0,7) et l'ancienneté du TARV depuis 10 ans ou plus ($p=0,001$ OR= 0,2 (0,1 – 0,7) étaient significativement associées à l'existence d'anomalies ventilatoires.

Conclusion. La fréquence élevée des anomalies ventilatoires chez les PVVIH indépendamment de l'existence de signes respiratoires chroniques nous amène à proposer la spirométrie dans le bilan de suivi des PVVIH tout en accordant une attention particulière à ceux traités depuis plus de 10 ans par ARV.

MOTS CLÉS: Profil; Spirométrie; PVVIH; Antirétroviraux; Abidjan

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INTRODUCTION

The Human Immunodeficiency Virus (HIV) remains a major public health problem worldwide [1]. People living with HIV (PLHIV) are the prerogative of opportunistic infections, the frequency of which is decreasing with the advent of triple antiretroviral therapy and cotrimoxazole prophylaxis. Currently, there is an increase in chronic non-communicable diseases in this population. The prevalence of non-communicable chronic respiratory diseases increased from 11.9 in 2007 to 14.1% in 2013[2]. Among the non-communicable chronic respiratory diseases described in PLHIV, asthma and chronic obstructive pulmonary disease (COPD) are cited as significant factors of morbidity and mortality [3,4,5]. Several Western studies have pointed out that HIV infection and antiretroviral treatment (ART) can contribute to the development of these diseases in PLHIV [6,7,8]. Also, HIV is a risk factor for developing chronic obstructive pulmonary disease (COPD), pulmonary arterial hypertension (PAH) and chronic respiratory failure (CRF) [2]. Studies conducted in developed countries have shown that the prevalence of obstructive ventilatory defect (OVD) in PLHIV ranged from 7 to 21% [9]. This high prevalence of OVD was observed in both children and adults infected with HIV. [5,7,10]. A history of pulmonary tuberculosis, low CD4 count, prolonged duration of HIV infection and smoking have been identified as factors associated with these ventilatory defects, although the mechanisms are not clearly established [11]. In sub-Saharan Africa, the region of the world with the highest proportion of PLHIV, very few studies have focused on spirometric abnormalities within this population. The frequency of spirometric abnormalities was 13% in South Africa and a prevalence of 5.2% of COPD and 5.2% of asthma in Cameroon [12,13]. Due to the additional morbidity that a non-communicable chronic respiratory disease would cause in this population, and given the lack of data on the subject in sub-Saharan Africa, specifically in Côte d'Ivoire, this works' objective has been set to study the spirometric profile of PLHIV followed in pneumology.

METHODS

This was a descriptive and analytical retro-prospective cross-sectional study, conducted in the voluntary counselling and testing (VCT) centres, specialized in monitoring PLHIV and supplying them with ART in the pulmonology units of the Cocody and Treichville University Hospital Centres in the district of Abidjan, from March 15 to June 15, 2022. This study concerned PLHIV aged at least 18 years, received in the VCT centres of one of the centres mentioned for the medical follow-up of HIV infection, presenting no acute respiratory or general symptoms (dyspnoea, cough, fever \leq 3 weeks), no contraindication to performing spirometry

according to the ATS/ERS 2019 criteria [14], and having agreed to participate in the study after obtaining informed consent. Were excluded from the study, those with known asthma or COPD (Figure 1). Spirometry was performed in every person included in the study. We used as equipment a 7-inch touch screen portable turbine spirometer with an integrated printer (Spirolab New®) with the accessories (turbine, disposable mouthpiece, an antibacterial filter, nose clip and an inhalation chamber), salbutamol spray dosed at 100 μ g and a pulse oximeter. When performing the test, acceptability and repeatability criteria of the parameters were applied according to the ATS/ERS recommendations [14]. The reference values were those of the African-American population, taken from the Global Lung Initiative (GLI) [15]. The instructions were well explained before any manoeuvre and at least three tests were carried out by the subject with a maximum of eight tests. For hygiene purpose, the material used, in particular the mouthpiece, turbine and antibacterial filter, was single-use and disposable. The spirometric data were interpreted using operational definitions. The diagnosis of COPD was made on the basis of a Tiffeneau index (FEV1/FVC) post bronchodilator less than 0.7 or below the lower limit of normal (LLN) [9,16]. The severity of COPD was assessed by the value of the FEV1; that of asthma was retained on the basis of at least 12% and 200 ml increase in the FEV1 after the inhalation of 400 micrograms of salbutamol through an inhalation chamber [17]; the obstruction of the small calibre bronchi was retained before a forced expiratory flow (FEF25-75%) below 65% of the predicted value. A proportional decrease in airflow and lung volume below the LLN with a stable or high Tiffeneau index was suggestive of a restrictive ventilatory defect (RVD) [16]. On the other hand, a disproportionate decrease in ventilatory flow and lung volumes below the LLN with a decreased Tiffeneau index was suggestive of a mixed ventilatory defect (OVD with restrictive pattern) [16]. Spirometry was considered normal when FVC and FEV1 values were greater than or equal to 80% of the predicted value, a Tiffeneau greater than 0.7 and peripheral flows above 65% of the predicted value [14]. Data was collected from the medical records of PLHIV using a standardized and anonymous survey form. These were socio-demographic data (age, sex, profession, level of education), clinical data including history (HIV status, lung infection, smoking), respiratory symptoms and physical examination (height, weight, BMI), biological (CD4 count, viral load) and spirometric parameters (lung flow rates and volumes). Data collected on individualized questionnaires were recorded in CSPRO 7.3 software and then exported to SPSS version 26 for statistical analysis. We performed bivariate analysis using the Chi² test or Fisher's exact test for predicted counts less than 5 to

determine factors potentially related to spirometric abnormalities, and logistic regression analysis to identify factors independently associated with spirometric abnormalities. Statistical significance threshold was set at 5% for all analyses.

RESULTS

During the study period, 145 HIV-positive subjects met the inclusion criteria, 54 subjects were definitively included as shown in *Figure 1*.

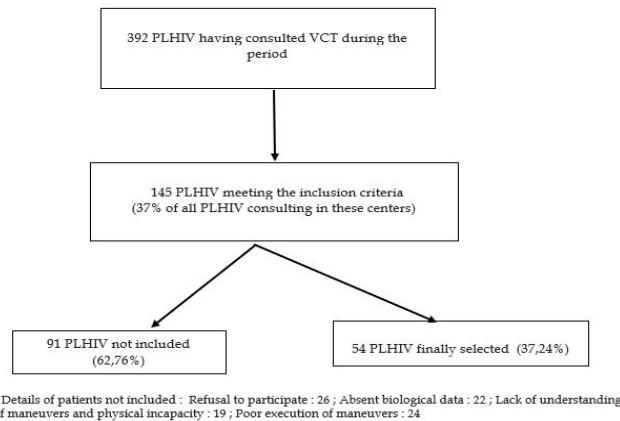


FIGURE 1. Patient Recruitment Flowchart.

Socio-demographic characteristics

The study population was composed of 32 women (59.3%) and 22 men (40.7%), with an average age of 48.9 ± 10.8 years with ages ranging from 24 to 79 years. The age group 40 to 50 years represented 42.6% (*Table 1*).

TABLE 1 Socio-demographic characteristics of PLHIV			
Socio demographic characteristics	Effective (n=54)	%	
Age	[20-30]	03	5.6
	[30- 40]	05	9.3
	[40 -50]	23	42.6
	[50 -60]	16	29.6
	[60 -70]	05	9.3
	≥ 70 years	02	3.76
Sex	Male	22	40.7
	Female	32	59.36
Age of HIV diagnosis	<5 years	11	20.4
	[5 - 10]	09	16.7
Duration of ARV treatment	≥ 10 years	32	59.3
	<5 years	12	22.2
	[5 - 10]	10	18.5
ARV treatment	≥ 10 years	32	0.9
	TDF/3TC/DTG	42	77.8
	TDF/3TC/EFV	07	13
Adherence to ARV treatment	Others*	05	9.4
	Yes	51	94.4
	No	03	5.6

* AZT/3TC/ATV-R (01) AZT/3TC/DTG (03) AZT/3TC/LPV-r (01)

PLHIV mostly worked in the informal sector (46.3%), the majority had attended the secondary level of education (37%) followed by the primary level (29.6%).

Characteristics of HIV infection

The majority (63%) of patients had been known to be PLHIV for at least 10 years with an average seniority of 11.3 ± 5.6 years and a standard deviation of 5.6 years (extremes: 1 – 21 years). All patients were on ART at the time of the study (100%). Among them 59.3% had been on ART for at least 10 years. The average duration of ART was 10.4 ± 5.3 years (extremes: 1 – 21 years). The majority of patients (77.8%) were on the Tenofovir/Lamivudine/Dolutegravir (TLD) triple therapy with good adherence to the ART in 94.4% of cases. (*Table 1*).

The CD4 count at diagnosis of HIV infection had a median of 240.5 (82.3 – 419) cells/mm³ (range: 1 – 709 cells/mm³). Majority of the patients had moderate immunosuppression (48.1%). The median viral load was 20 (1-50) copies/ml (range: 0 – 306.000 copies/ml) and was detectable in 51.9% of patients. Patients who received cotrimoxazole chemoprophylaxis is represented 25.9% compared to 3.7% who received isoniazid.

Clinical features

A history of lung infection was the most common (48.1%). Of these, pulmonary tuberculosis was the most frequent (35.2%). The larger number of our patients were non-smokers (81.4%). Biomass smoke (25.9%) and pesticides (7.4%) were the airborne contaminants to which PLHIV were most exposed. The average duration of exposure to biomass smoke was 24.3 ± 11.1 years and that of exposure to pesticides was 13.9 ± 5.9 years. Chronic respiratory symptoms found in 16 patients (29.6%) were mainly dyspnoea (16.7%) and dry cough (13%). The Body Mass Index (BMI) was normal in 42.6% of patients with an average BMI of $25.5 \text{ kg/m}^2 \pm 4.5 \text{ kg/m}^2$ (extremes: 17.1 – 35 kg/m²).

Spirometric characteristics

The majority of patients (72.2%) had a normal FEV1 with an average FEV1 of $90.1 \pm 16.0\%$ of theoretical (extremes: 64 – 128%). The average FVC was $97.7 \pm 15.8\%$ of the theoretical (extremes: 63 – 133%) and 87% of the patients had a normal FVC. The mean Tiffeneau ratio was $77.8 \pm 6.5\%$ (range: 56.7 – 91.2%). This ratio was normal in 94.4% of patients. The average FEF25 – 75 was $63.1 \pm 22.6\%$ (extremes: 26 – 135%).

More than half of the patients (59.3%) had a FEF25 – 75 higher than the norm. The frequency of spirometric abnormalities was 57.4%. Peripheral obstructive ventilatory defect (40.7%) was the most frequent ventilatory anomaly (*Figure 2*).

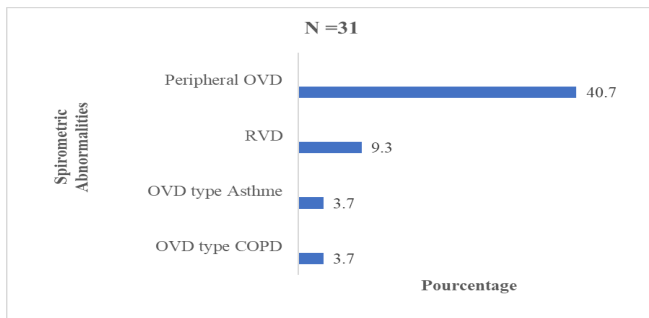


FIGURE 2. Spirometric abnormalities identified in patients.

Factors associated with spirometric abnormalities

The factors associated with spirometric abnormalities were a more than 10 years duration since the diagnosis of HIV infection ($p=0.001$ OR= 0.2 (0.1 - 0.7) and an ART of at least 10 years ($p=0.001$ OR= 0.2 (0.1 - 0.7)). However, there was no significant link between socio-demographic characteristics (gender, age, level of education), history of lung infection and smoking, respiratory symptoms, BMI and the presence of spirometric abnormalities (Table 2).

TABLE 2		Factors associated with spirometric disorders in PLHIV			
Variable	Spirometric abnormalities		OR (95% CI)	p - value	
	Yes, n (%)	No n (%)			
Age (years)					
<50 years	14 (45.2)	16 (69.5)	1.1 (0.4- 3.4)	0.13	
≥50 years	17 (54.9)	6 (26.1)			
Sex					
Male	12 (38.7)	10 (43.5) 13 (56.5)	0.8 (0.3- 2.5)	0.78	
Female	19 (61.3)				
Level of education					
< Secondary	15 (48.4)	12 (52.2)	1.1 (0.4- 3.4)	0.78	
≥ Secondary	16 (51.6)	11 (47.8)			
Length of HIV infection					
< 10 years	7 (22.6)	13 (56.5)	0.2 (0.1- 0.7)	0.01	
≥ 10 years	24 (77.4)	10 (43.5)			
ART duration					
< 10 years	8 (25.8)	14 (60.9)	0.2 (0.1 - 0.7)	0.01	
≥ 10 years	23 (74.2)	9 (39.1)			
ART combination					
TDF/3TC/DTG	25 (80.6)	17 (73.9)	1.5 (0.4 - 5.3)	0.56	
TDF/3TC/EFV	3 (9.7)	4 (17.4)	0.5 (0.1 - 2.5)	0.44	
Other	3 (9.7)	2 (8.7)	1.1 (0.2 - 7.3)	1.00	
Viral load					
Undetectable	15 (48.4)	11 (47.8)	1.1 (0.3 - 3.1)	0.97	
Detectable	16 (51.6)	12 (52.2)			
Initial CD4 count					
≤200	13 (41.9)	11 (47.8)	0.8 (0.3 - 2.3)	0.67	
>200	18 (58.1)	12 (52.2)			
Smoking					
Yes	6(19.4) 25(80.6)	4(17.4) 19(82.6)	1.1 (0.3- 4.6)	1.00	
No					
History of tuberculosis					
Yes	13(76.5)	6(66.7)	1.6 (0.3- 9.6)	0.66	
No	4(23.5)	8(33.3)			
History of pneumonia					
Yes	2(11.8)	3(33.3)	0.3(0.1 - 2.1)	0.30	
No	15(88.2)	6(66.7)			
BMI					
< 25 kg/m ²	16(51.6) 15(48.4)	10(43.5) 13(56.5)	1.4(0.5 - 4.1)	0.55	
≥ 25 kg /m ²					
Respiratory symptoms					
Yes	11(35.5) 20(64.5)	5(21.7) 18(78.3)	1.9(0.6 - 6.8)	0.27	
No					

DISCUSSION

Limits of the study

One of the weaknesses of our study lies in the non-inclusion of 29.65% of cases due to the inability to perform spirometric manoeuvres, responsible for our small sample size. The retrospective component of our study limited the data collected to the sole information available in the patients' files such as biological data (viral load, CD4 count), some of which were absent. However, the CD4 count and viral load are no longer mandatory for ART initiation. Finally, our analysis of ventilatory function was limited to spirometry. The presence of a RVD in spirometry requires plethysmography for confirmation of this disorder. Despite these limitations, to the best of our knowledge, this study is one of the first in Côte d'Ivoire to assess the ventilatory function of PLHIV. It analysis the profile of spirometric abnormalities observed in PLHIV treated with ARVs.

Socio-demographic characteristics

The mean age of the patients was 48.9 years with a standard deviation of 10.8 years. The age group of 40 to 50 years was the most represented (42.6%). Our results are close to the average age reported in many studies, particularly in the USA [18], South Africa [19] and Cameroon [13] which found an average age of 50, 43.5 and 42.6 years old respectively.

Our study population was mainly composed of women (59.3%) with a sex ratio M/F of 0.68. In the world population and particularly in Côte d'Ivoire, the prevalence of HIV is higher in women than in men [1,12].

Prevalence of spirometric abnormalities in PLHIV

The frequency of ventilatory anomalies in our study was 57.4%. This is higher than what is found in the literature mainly because of the peripheral OVDs which were not sought in these various studies [13,19,5,18,20]. The prevalence of peripheral OVD was 40.7% in our work. We did not find in the literature a study focusing on this peripheral damage, which would reflect damage to the small bronchi without abnormality of the large bronchi. Particularly in the early forms of COPD, inflammation and structural changes begin and predominate in the distal airways [21]. Unlike peripheral OVD, that of asthma was 3.7% in our study population. This frequency is lower than the hospital frequency of 5.2% for asthma found by Pefura-Yone et al. in Cameroon in 2015 [13] and at 7% by Van Riel et al in South Africa [19]. The frequency of asthma in our study is higher than the 2.99% found by Koffi N et al in Abidjan, Côte d'Ivoire in 2001 [22] and the 2.7% found by Hirani et al in their study [20]. The prevalence of COPD in our study population was 3.7%. This proportion was

higher than the Ivorian hospital prevalence of COPD found by Anon et al in 2020, which was 2.5% [23]. On the other hand, our frequency of COPD was significantly lower than those reported by several African and Western studies where it varied from 5.2 to 27%. [5,13,18,19,20] This difference could be explained by the higher percentage of smoking patients/former smokers in these different studies than that of our series where the majority of our patients (81.4%) were non-smokers. This high proportion of non-smoking patients is consistent with most studies conducted in sub-Saharan Africa [13,6,19], but remains lower than that of Western studies [2,5,18,20,11]. It is already established that smoking is a risk factor or even aetiology of COPD and several studies have demonstrated in their cohort of PLHIV, smoking as a risk factor for the development of non-reversible OVD [13,5,18]. However, in sub-Saharan Africa, another risk factor to consider in the occurrence of COPD is environmental exposure, particularly to biomass (25.9% in our study). The frequency of RVD in our series (9.3%) is close to that reported by Drummond et al (10%), although slightly higher than that of the general American population of 7% [18]. The prevalence of RVD was 38% in Cameroon among PLHIV naïve to ART [24]. Given the history of pleuropulmonary infection (48.1%), one would have expected a higher frequency of RVD among the PLHIV in our series. This low frequency of RVD could be related to the almost complete recovery of the lung parenchyma and pleura following these infections, with very few sequelae.

Factors associated with spirometric abnormalities

Previous studies have clearly demonstrated age as a factor associated with spirometric abnormalities in PLHIV [19], particularly in the 40 to 50 years age group [18]. This age group was independently associated with the presence of RVD [12]. In our series, this link was not significant. Similarly, male sex has been identified as a risk factor for developing spirometric disorders in PLHIV [19,25], but this association was not significant in our study. Other elements, particularly the low level of education (below secondary) have been described as a factor associated with RVD [26]. However, this was not the case in our study. The duration since HIV diagnosis was on average 11.3 years. A less than 13 years average duration of HIV diagnosis was obtained by Gingo et al in the United States [5], but was significantly higher than the 6.25 years obtained by van Riel et al in South Africa [19]. Patients with a more than 10 years diagnosis of HIV had significantly more ventilatory abnormalities ($p=0.001$). Similar observations have been made both in Europe and in Africa. Indeed, Kristoffersen et al in Denmark found an average duration of infection of 9.25 years and a duration of infection greater than 10 years significantly associated with the presence of

OVD [27]. Drummond et al [11] also found the prolonged duration of HIV infection as a risk factor for developing a ventilatory defect. This increased risk of ventilatory abnormalities with duration of HIV exposure could be explained by direct virus-related pulmonary toxicity, persistent systemic inflammation, altered antioxidant/oxidant balance resulting in oxidative stress, and accelerated immune deterioration. However, ART and duration would also play a role in the occurrence of ventilatory abnormalities. The average duration of ART instituted according to the WHO regimen was 10.4 years. Patients on ART for at least 10 years in our series had significantly more ventilatory abnormalities ($p=0.001$). TDF+3TC+DTG triple therapy was the most widely used treatment (77.8%) and the majority of our patients (94.4%) were adherent to treatment. Several studies also found an association between the duration of ART and the existence of a ventilatory abnormality. Indeed, Gingo et al in the United States found ART as a risk factor for developing non-reversible OVD. However, the triple therapy used was not specified in this study [5]. George et al reported that ART use was independently associated with the development of OVD [10]. The link between ART and ventilatory disorders is not known, but potential explanations include the direct effects of ART in the lungs, the restoration of the immune system resulting in a renewed response to subclinical infections and/or the development of auto-immunity. ART-associated cardiovascular diseases, metabolic syndrome, and osteoporosis may be directly linked to antiretroviral agents, particularly protease inhibitors [28], but there are no published reports of antiretroviral drugs and ventilatory disorders. On the other hand, literature notes a link between the degree of immunosuppression and the occurrence of ventilatory anomalies in this population. Several series [5,7,10,11,29] have found an association between low CD4 count, the high viral load and the development of ventilatory disorders. However, these data may not be applicable to patients with less severe immunodeficiency, as is the case in our study where 48.1% had moderate immunosuppression and an undetectable viral load. Whatever the case, ventilatory anomalies will lead to respiratory manifestations which may vary according to the patient's smoking profile. In our series, the high proportion of non-smokers (81.4%) observed is consistent with most studies conducted in sub-Saharan Africa [13,6,19,26] but remains lower than those of Western studies [2,5,18,20,11,29].

CONFLICT OF INTEREST

Non.

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Indeed, the prevalence of smoking in sub-Saharan Africa in the general population remains lower than that observed in the Western world. It has already been established that smoking is a risk factor or even an aetiology of COPD, but also described as a factor in the development of non-reversible OVD in PLHIV [5,13,18]. However, in sub-Saharan Africa, another risk factor to consider in the occurrence of COPD is environmental exposure, particularly to biomass (25.9% in our study). A history of pleuropulmonary infection was found in 48.1% of our patients and consisted mainly of pulmonary tuberculosis (35.2%). It has been demonstrated that PLHIV with a history of pulmonary tuberculosis are more at risk of developing RVD [5,12,26] and sometimes OVD [13,19,29], but the association was not statistically significant, possibly because of our small sample. Indeed, tuberculosis through its sequelae can lead to ventilatory restriction in these patients who are sometimes undernourished or even emaciated. Underweight (defined by a BMI<18.5 kg/m²) was found by certain series to be a risk factor for developing a ventilatory anomaly [6]. In our study, we did not find an association between BMI and the presence of ventilatory abnormality. This could be explained by the fact that the majority of our patients had a normal BMI (42.6%). Similarly, only 29.6% complained of chronic respiratory symptoms despite the high prevalence of ventilatory abnormalities. Gingo et al as well as Drummond et al had also found a discrepancy between patient complaints and the presence of ventilatory abnormalities [18,30]. This would mean that one should not always wait for the complaint of dyspnoea or chronic cough to consider spirometry for a PLHIV. Spirometry should therefore be part of the respiratory assessment of PLHIV whether they have chronic respiratory symptoms or not. However, the profile of these patients should be well defined.

CONCLUSION

The high frequency of ventilatory abnormalities in PLHIV independently of the existence of chronic respiratory symptoms leads us to propose spirometry in the assessment of PLHIV. Particular attention should be paid to PLHIV treated for more than 10 years with ARTs in view of the risk of developing these ventilatory disorders. A larger-scale study would better define the profile of PLHIV who should benefit from this routine spirometry.

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