Journal of AIDS and HIV Infections
Volume 5 | Issue 2
ISSN: 2454-499X

Research Article Open Access

Development of Chronic Obstructive Pulmonary Disease (COPD) in Patients Infected with Human Immunodeficiency Virus (HIV)

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Citation: da Silva IM, de Almeida VP, Medeiros DM (2020) Development of Chronic Obstructive Pulmonary Disease (COPD) in Patients Infected with Human Immunodeficiency Virus (HIV). J Aids Hiv Inf 5(2): 201

Received Date: May 15, 2020 **Accepted Date:** July 06, 2020 **Published Date:** July 08, 2020

Abstract

Introduction: Chronic Obstructive Pulmonary Disease (COPD) is considered a public health problem and its prevalence increases over the years, in Brazil. Currently, 37 million people are living with HIV and 4 million of these patients infected with the virus may have COPD. However, many of these cases may be underreported. In Brazil, these two clinical situations (HIV infection and COPD) have a high incidence, which causes a great expense for the public health, increased morbidity and mortality of these patients. We observed that, in the national literature, there is a gap on the association between these two scenarios.

Objectives: To identify the profile, frequency and prevalence of HIV-infected patients with COPD and to correlate with risk factors.

Methodology: 75 patients were recruited from hospitals treating HIV infection; they underwent spirometry examination. Other information was obtained through access to the patients' medical records.

Results: 38.7% of patients living with HIV presented obstructive ventilatory pattern after bronchodilator test. The model that explains 20% of the COPD outcome was composed of the following variables: smoking load (TC) with ($p = 0.002$), tuberculosis ($p = 0.019$) and education ($p = 0.05$).

Conclusion: Risk factors for the development of COPD in HIV-infected patients are associated with smoking load (TC), tuberculosis and low education in this population studied in Rio de Janeiro.

Abbreviations: AIDS: Acquired Immunodeficiency Syndrome; ART: Antiretroviral Therapy; BCT: Bronchiectasis; BMI: Body Mass Index; CAT: COPD Assessment Test; CI: Confidence Interval; COPD: Chronic Obstructive Pulmonary Disease; FEV1: Forced Expiratory Volume in the 1st Second; FVC: Forced Vital Capacity; HIV - Human Immunodeficiency Virus; mm3: Cubic Millimeters; MMRC: Modified Medical Research Council; PCP: Pneumocystis Carinii; PNM: Pneumonia; PT: Pulmonary Tuberculosis; SD: Standard Deviation; SL: Smoking Load; VL: Viral Load

Keywords: HIV; Chronic Obstructive Pulmonary Disease; Risk Factors; Pulmonary Tuberculosis

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is considered a major public health problem. It is currently the fourth leading cause of death in the world and may by 2020 be the third [1].

Despite the prevalence of COPD increasing over the years, in Brazil, the early diagnosis of this disease is still late. Frequently, many individuals have initial symptoms of the disease, and are often ignored and, therefore, there is no confirmation of their diagnosis through spirometry, the current gold standard [2].

According to Bigna (2018), the overall prevalence of COPD in patients with HIV is between 5.6-10.6%. Currently, there are 37 million people living with HIV and 4 million of these virus-infected patients may have COPD, however many of these cases may be underreported [3].

There is evidence in the literature that patients with HIV have a higher risk of developing COPD when compared to individuals not infected with the virus [4]. In addition to factors already known for the development of COPD (smoking, drugs, etc.), it is possible that seropositive patients have other causes for the evolution of this disease, such as the use of antiretroviral therapy (ART), lung infections, low CD4 lymphocytes and increased viral load itself [5]. COPD in people with HIV is more prevalent, evolves more quickly and has an early onset when compared to non-HIV individuals (HIV) [6].

Epidemiological studies have shown that HIV infection is an independent risk factor for COPD, due to the pulmonary macrophages infected by the virus, which promote alveolar inflammation, destruction of the epithelial barrier, increased cellular apoptosis and microbial alteration of the respiratory tract. All these events are associated with the development of COPD. Despite viral suppression, immune activation and systemic inflammation biomarkers persist in the body [4].

Another factor that seems to be associated with the onset of COPD in HIV-infected individuals is the increase in systemic biomarkers. It has been observed that HIV positive patients have an increase in these biomarkers such as interleukin 6, which may be associated with pulmonary emphysema [7]. Other factors associated with COPD are increased oxidative stress, cell senescence [4] and immune activation [7].

In Brazil, these two clinical situations (HIV infection and COPD) have a high incidence separately [3,6], which results in a great expense for public health, with increased morbidity and mortality of these patients. However, in the national literature, there is a gap about the association between these two scenarios.

The objective of this study is to identify the obstructive ventilatory pattern in patients with the HIV virus in Rio de Janeiro, to evaluate which variables are associated with this outcome, to answer some questions about this issue and about the possible associations, which so far, are not fully clarified.

Methods

This is a descriptive cross-sectional study, developed with people living with the HIV virus and who presented previous pulmonary infection, from March 2018 to January 2019, in two reference hospitals in Rio de Janeiro.

The patients were recruited in person through outpatient consultations. Inclusion criteria were having the HIV virus, older than 18 years, having cognitive ability to perform spirometry; and have a previous infectious pulmonary condition greater than three months. The following were excluded from the study: seropositive patients with heart disease not associated with previous respiratory diseases; individuals who at the time of recruitment had pulmonary decompensation or who were carriers of the HIV virus and were dependent on supplemental oxygen with rapid and severe fall oxygen saturation (below 85%) in ambient air; patients with neuromuscular dysfunction who may present alterations in spirometry due to muscle weakness. The following variables were collected from patient records: number of medical records, date of last medical appointment, age, height, weight, viral load, CD4 (last collected and date of both), use of ART and smoking load (pack-years).

A history of previous diseases such as systemic arterial hypertension, Diabetes Mellitus, pneumonia, tuberculosis (PT), *Pneumocystis jirovecii pneumonia* (PCP), asthma and bronchiectasis were investigated in the patients' medical records. The patients answered if they had been hospitalized in the last year due to pulmonary issues and the amount of exacerbations in the last year.

The patients underwent spirometry examination with bronchodilator test in order to identify the obstructive ventilatory disorder. The patient was considered to have obstructive ventilatory disorder when the relationship between forced expiratory volume and forced vital capacity (FEV_1 / FVC) was below 70% of predicted and FEV_1 < 80% after bronchodilator testing [7].

The individuals who composed the convenience sample answered two instruments: COPD Assessment-Test (CAT) questionnaire [8] and Modified Medical Research Council (mMRC) scale [9] in order to classify COPD patients [8].

Continuous data were analyzed by the Kolmogorov-Smirnov test to determine sample normality. Normally distributed data were expressed as mean ± standard deviation (SD), and non-normal data through medians and interquartile ranges. Anthropometric and clinical measurements were compared between COPD and non-COPD groups using the Mann Whitney test.

Univariate regression analysis was determined by potential anthropometric and clinical measures associated with obstruction level (FEV_1 / FVC <0.7 with FEV <0.8). For that, we used Pearson correlation (Table 2). To obtain the association strength of the variables collected in a predictive model of COPD, a logistic regression analysis was performed, assuming p <0.1 as the model variable.

Analysis with collinearity diagnosis was defined to determine the most appropriate logistic regression model, since we have many variables with mutual relationships. We adopted forward model for the insertion of the exploratory variable due to the persistence of collinearity in some variables and gradual inclusion of all selected variables in order of significance. Anthropometric parameters derived from BMI were removed from the model due to high collinearity (weight and height), as well as mutually correlated pathologies (bronchiectasis, pneumonia and tuberculosis) (Appendix A).

All statistical analyzes were performed using JASP software version 9.0.1. The significance level of 0.05 was considered in the two-tailed test.

The study is in accordance with resolution 466/12 and all patients signed an informed consent form. The project was approved by the Research Ethics Committee of the proposing institution. CAAE: 69817417.9.0000.5258. Opinion Number: 2.366.313.

Results

For this study, 90 patients were analyzed; however, due to exclusion criteria such as: ventilatory disorders altered by neuromuscular disorders, absent patients, patients with active respiratory infections and decompensated respiratory and / or cardiac patients at the time of the examination, fifteen patients were excluded. Totaling 75 patients for the study, who were recruited from the pulmonology, immunology and infectiology outpatient clinics of two reference centers for treating HIV infection, during outpatient consultations in person.

Table 1 also shows demographic and clinical data for all patients studied (75 patients), divided between COPD patients diagnosed in the study using spirometry [n = 29 (38.7%)] or not COPD [n = 46 (61.3%)].

Variable	Total (n=75)	COPD n=29 (38.7%)	No COPD n= 46 (61.3%)	*p* value
Gender (M/F)	36/39 (48/ 52%)	11/18 (37.9/ 62.1%)	25/21 (54.3/ 45.7%)	-
AGE (Yrs)	49.97±12.15	52.00 ± 11.62	48.70 ± 12.58	0.16
20-40	17 (22.7%)	5 (17.2%)	12 (26.1%)	-
41-60	40 (53.3%)	15 (51.7%)	25 (54.3%)	-
> 60	18 (24.0%)	9 (31.0%)	9 (19.6%)	-
BMI (Kg/M²)	25.88 ± 5.97	25.70 ± 6.75	26.00 ± 5.50	0.55
Scholarity				
≤9 Yrs	42 (56%)	20 (69%)	22 (47.8%)	-
>9 Yrs	33 (44%)	9 (31%)	24 (52.2%)	-
Skin Color				
White	25 (33.3%)	9 (31.0%)	16 (34.8%)	-
Brown	32 (42.7%)	11 (37.9%)	21 (45.7%)	-
Black	18 (24.0%)	9 (31.0%)	9 (19.6%)	-
Diagnosis				
≤10 Yrs	32 (42.7%)	10 (34.5%)	22 (47.8%)	-
>10 Yrs	43 (57.3%)	19 (65.5%)	24 (52.2%)	-
Taking Art				
≤10 Yrs	49 (65.3%)	17 (58.6%)	32 (69.6%)	-
>10 Yrs	26 (34.7%)	12 (41.4%)	14 (30.4%)	-
Nadir Cd4+	186.6 ± 169.5	156.7 ± 145.4	205.4 ±182.2	0.260
≤ 100	31 (41.3%)	13 (44.8%)	18 (39.1%)	
101-350	31 (41.3%)	13 (44.8%)	18 (39.1%)	
>350	13 (17.3%)	3 (10.3%)	10 (21.7%)	
CD4+ (Copies/Mm³)	678.6 ± 388.5	628.4 ± 357.0	710.3 ± 407.8	0.459
<100	2 (2.7%)	0	2 (4.3%)	-
101-350	16 (21.3%)	6 (20.7%)	10 (21.7%)	-
VL (Copies/Mm³)	8.77 ± 50.14	22.47 ± 79.54	0.125 ± 0.851	0.018
SL (Packs-Yr)	51 (68%)	25 (86.2%)	26 (56.5%)	-
0	24 (32%)	4 (13.8%)	20 (43.5%)	-
<20	16 (21.3%)	8 (27.6%)	8 (17.4%)	-
>20	34 (45.3 %)	16 (55.2%)	18 (39.1%)	-
Drugs				
Nonuser	63 (84.0%)	20 (69%)	42 (91.3%)	-
User	12 (17.3%)	9 (31%)	4 (8.7%)	-
Pnm	26 (34.7%)	13 (44.8%)	13 (28.3%)	-
Pt	38 (50.7%)	19 (65.5%)	19 (41.3%)	-
Pcp	14 (18.7%)	4 (13.8%)	10 (21.7%)	-
Bct	24 (32%)	13 (44.8%)	11 (23.9%)	-
Exacerbation				
≤ 1 Per Yr	53 (70.7%)	21 (72.4%)	32 (69.6%)	-
≥ 2 Per Yr	22 (29.3%)	8 (27.6%)	14 (30.4%)	-

YR = year; **BMI** = Body Mass Index; **ART** = Antiretroviral Therapy; **CD4+** = CD4 lymphocytes; **BMI** = Body Mass Index; **CD4+** = CD4 lymphocytes; **VL** = Viral Load; **SL** = Smoking Load; **PNM** = Pneumonia; **PT** = Pulmonary Tuberculosis; **PCP** = *Pneumocystis Jiroveci Pneumonia*; **BCT** = bronchiectasis. Continuous data described as mean and standard deviation; categorical variables described in frequencies and percentages

Table 1: Demographic and clinical data of all patients studied (n = 75)

Smoking was higher in the COPD patient group. It was also observed that the number of drug users was higher in the group of patients with obstructive ventilatory pattern. Regarding lung disease, the incidence of pulmonary tuberculosis (65.5%), pneumonia (44.8%), and bronchiectasis (44.8%) was higher in the group of COPD patients. The highest incidence of PCP was observed in the group of nonobstructive patients (21.7%).

Regarding education and race, respectively, most patients completed only elementary school (up to 9 years of study) (56%) and were of brown race (42.7%); when evaluating race, we accepted patients' self-declaration when asked. Regarding race, we found no statistical correlation with the COPD outcome in HIV patients.

No difference was observed regarding spirometric variables during the examination before and after bronchodilator testing, thus confirming the absence of bronchial hyperresponsiveness, absent in COPD patients. However, when comparing the two groups (COPD and non-COPD), we observed that there is a statistical difference between them in relation to spirometric variables after bronchodilator testing (P <0.001).

Table 2 shows the pearson correlations of the obstructive pattern (FEV1) with the demographic and clinical data of all patients studied.

Table 3 shows the logistic regression analysis with the best regression model (Mc Fadden R2 = 0.204), considering the following variables: smoking load (SL), tuberculosis and scholarity. Among all regression analyzes, these were the variables that maintained correlation strength. (APPENDIX A)

R Pearson	
Age (Years)	0.13
Cd4 Nadir (Copies/Mm3)	-0.14
Cd4 (Copies/Mm3)	-0.10
Viral Load	-0.01
Bmi (Kg/M2)	-0.03
Smoking Load (Packs-Year)	0.35*
Gender (Men)	-1.84
Drugs	0.29*
Pneumonia	-1.83
Tuberculosis	0.24*
Pneumocystosis	-0.10
Asthma	-0.08
Bronchiectasis	0.22*
Hospitalization/Year	0.17*
Scholarity	-0.21*

CD4 + = CD4 lymphocytes; **BMI** = Body Mass Index. * p <0.1
Table 2: Correlations of the obstructive pattern (FEV1) with the demographic and clinical data of all patients studied

Multivariate Logistic Regression Analysis. Mc Fadden R^2 =0.204								
	Pearson r	**Estimative**	**Default error**	**Odds ratio**	**z**	**p**	**CI 95%**	
Intercept		-1.017	0.818	0.362	-1.243	0.214	-2.622	0.587
SL (packs-yr)	0.35	0.039	0.013	1.04	3.106	0.002	0.014	0.064
Tuberculosis	0.24	1.385	0.592	3.996	2.341	0.019	0.226	2.545
Scholarity (years)	-0.21	-0.143	0.078	0.866	-1.848	0.05	-0.296	0.009

CI = confidence interval; **SL** = smoking load; **Schol** = scholarity; **Mc Fadden R^2** =0.204
Table 3: Multivariate Logistic Regression Analysis

Discussion

According to our analysis, the variables that were associated with the obstructive pattern in HIV-infected patients were smoking, pulmonary tuberculosis, bronchiectasis, drugs, hospitalization / year, and scholarity. However, in the regression analysis, only smoking, pulmonary tuberculosis, and scholarity in years remained associated, explaining 20% of the COPD outcome in the population studied.

The overall prevalence of COPD in HIV patients is between 5.6-10.6%", however our sample of COPD patients has a much higher percentage. We believe that finding this percentage of HIV-infected patients with COPD, is the result of a study carried out in two reference centers for the treatment of patients infected with the Human Immunodeficiency Virus in the state of Rio de Janeiro, Brazil.

Patients infected with the HIV virus have several factors that predispose the development of COPD, namely: smoking, recurrent respiratory infections, drug use and socioeconomic status [5,10].

It is already well established in the literature that tobacco is the main risk factor for the development of COPD [3]. Tobacco makes people with HIV more susceptible to the deleterious effects of smoking because nicotine has modulating effects on the immune system [11], leading them to develop abnormal lung function [12]. In this paper we find the same correlation. Smoking load (greater than 20 packs / year) maintained a positive correlation with COPD in HIV-positive patients.

PT is the most common respiratory infection in the HIV population. In most cases, the patient has had PT more than once during his or her clinical history [13]. This disease is considered a risk factor for COPD [6,10], as it is responsible for causing a mechanism of parenchymal healing, chronic airway inflammation and increased number of macrophages [6]. In this study, we observed that the most common pulmonary infection in the study group was pulmonary tuberculosis. In our analysis, we noted that PT had a major impact on the association with the COPD outcome, increasing the risk by up to three-fold of the HIV-infected population from developing COPD.

PT, HIV infection and smoking form a connection and pose a major challenge for Brazilian public health. Smoking increases the risk of PT infection, progression of active disease, not to mention that intra-household smoking smoke increases the risk of PT for those residing in the same household [11].

There are other factors that may be linked to the presence of obstructive pattern in individuals with HIV [14], including: drug use and socioeconomic issues [10]. In the present study, we did not evaluate wage income, however, observing the issue of education, we can infer that the individual who has less financial status may have a lower level of education. We observed in the correlations between COPD x drugs and COPD x low level of education a $p < 0.1$. When these variables were included in the logistic regression analysis model, we observed that low education reached a p value = 0.05, which shows that there is a correlation between low educational level (up to 9 years of schooling) and COPD. However, drug use did not fit the best regression model; we believe this fact may be related to the sample size and the collinearity between the variables. Thus, we can infer a tendency to associate COPD with drug use. ($r=0.29$; $p=0.07$)

Some studies [15-17] cite among the possible causes of the onset of COPD in HIV, Pneumocystis Jirovecii pneumonia. A study, in 2010, claims that even lower levels of carriage in Pneumocystis organisms may be associated with lung destruction and patients colonized by the same fungus worsen their airway obstruction; this colonization leads to a maintenance of inflammation, airway thickening and an accelerated form of COPD, in addition to being associated with high levels of elastase [15]. However, in our study no correlation was found between COPD and Pneumocystis.

We expected to find a greater number of PCP cases in patients with COPD, given the statistics already reported in the literature [4,10]. However, as we are dealing with outpatients from referral hospitals, it is possible that the worst prognosis of pneumocystis Carinii was the cause of the low prevalence of cases in our sample. Besides that, the notification of this pathology is not yet compulsory, as occurs in cases of PT. However, this correlation deserves to be better studied further in other studies in the Brazilian population.

We can cite as limitations in our study the sample number. The study sample is a convenience sample, as we were unable to access the total number of patients from the two referral centers for treating patients with HIV, it was not possible to perform the sample calculation. Another limitation was the lack of attendance (often due to economic reasons) of patients to outpatient consultations and the difficulty of closing the diagnosis of Pneumocystis in both institutions.

We chose to select patients with a previous pulmonary condition because the literature indicates that pulmonary sequelae and destruction of the lung parenchyma is one of the causes that have a major impact on the development of COPD, due to the production of elastase, resulting in the destruction of the pulmonary elastic component [4,8-12].

With this study we were able to identify individual factors that coexist with the HIV virus who were diagnosed with COPD, in the state of Rio de Janeiro. We found some variables that are associated with this outcome in this population, such as: smoking (with smoking load greater than 20 packs / year), pulmonary tuberculosis and low education (below nine years of study). However, we understand that other studies need to be carried out with the Brazilian HIV-infected population, with a larger sample and analyzing other factors for the development of COPD.

Acknowledgment

I would like to thank my supervisors Prof. Vívian Pinto, Monica Cruz and Denise Medeiros for their consistent support and guidance during the running of this project.

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