Respiratory symptoms and ventilatory function tests in Nigerians with HIV infection

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Abstract

Background: The impact of the human immunodeficiency virus (HIV) infection on the respiratory system of Africans has been little studied. This study aimed to determine the pattern of respiratory symptoms and ventilatory functions in HIV infected Nigerians.

Methods: In this cross sectional study, Respiratory symptoms frequency, Forced vital capacity (FVC), Forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, Forced expiratory flow between 25% and 75% of FVC, were determined in 100 HIV positive subjects and compared with values in 100 HIV negative controls.

Results: HIV positive patients had significantly more respiratory symptoms and lower ventilatory function tests values compared to the matched controls ($p<0.05$). HIV patients with at least one respiratory symptom and those with CD4 count less than 200cells/μl had lower ventilatory function values than their counterparts. 32% of the HIV patients had restrictive ventilatory functional impairment. ($p<0.05$). Using regression analysis, factors like HIV status, CD4 count and presence of respiratory symptoms were found to be associated with impairment in ventilatory functions.

Conclusions: HIV infected patients had more frequent respiratory symptoms and lower ventilatory function values. Further lung function studies and CT scanning in HIV positive patients especially in those with respiratory symptoms are indicated.

Key words: HIV, Respiratory symptom, ventilatory function, CD4, Nigeria.

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Introduction

HIV infection is known to affect all the systems including the respiratory system. Despite the high burden of HIV infection in Nigeria and sub-Saharan Africa, and the impact of HIV on the respiratory system, not many studies have looked at the frequency of respiratory symptoms and the pattern of ventilatory functions in HIV infected patients in Africa.

Previous reports from this region have looked at the spectrum of respiratory diseases among HIV infected individuals[1,2]. Earlier studies show that respiratory symptoms like cough, sputum production, chest pain are common in HIV patients and that ventilatory functions are also impaired in HIV infected patients[1-4]. Lung function studies done previously in HIV infected patients showed that most ventilatory parameters were altered significantly[5-8].Several reasons have been given for the alteration in ventilatory functions and increased frequency of respiratory symptoms among HIV infected individuals including viral compartmentalization and specific lymphocytic alveolitis of the lungs of HIV infected subjects.[9-14] Equally, repeated infections of the respiratory tract notably by PCP, bacteria pneumonia [7] and TB infection have been implicated as possible reasons too. This may even be more important in our environment with high burden of Pulmonary Tuberculosis and other respiratory infections.

Measurement of ventilatory function variables generally is important because impaired lung function is not only a predictor of increased respiratory mortality but is also associated with adverse cardiovascular events including myocardial infarction, stroke and cardiovascular death in general[15,16]. As at the time of this study, no previous work to our knowledge has looked at the prevalence of respiratory symptoms and ventilatory function impairment in Nigeria HIV infected individuals.

This study therefore aims to determine the pattern of respiratory symptoms and ventilatory functions among a cohort of HIV infected Nigerians. It also aimed to look at the factors that are associated with impaired spirometric lung volumes in HIV infected adult Nigerians.

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Methods

Ethical considerations

Ethical approval was obtained from the ethics committee of the University of Nigeria Teaching Hospital Enugu

Study design

This work was a cross sectional study. HIV positive patients attending the antiretroviral treatment clinic for the first time at the University of Nigeria teaching hospital Enugu, South East Nigeria, were recruited over a six month period between May and December 2006. Every third patient attending the clinic was recruited if he or she gave written informed consent and did not have any exclusion criterion. Majority of the patients attending are of same tribe (Igbo). The clinic runs once weekly and adult patients 18years and above are usually in attendance.

Sample size

The sample size was determined using the prevalence rate of HIV in the country by the National sentinel survey of 2003 which was 5.0%.[17] Thus using the formula for sample size determination for a definite population[18] ; considering 0.05 as the average proportion of HIV infected persons and 0.05 as the absolute sampling error that can be tolerated, 73 subjects were estimated but 100 patients were recruited and studied during this period to improve the accuracy of the study results and analysis..

Study population

An equal number of HIV negative individuals (100) who were comparable to the HIV positive patients in age, sex, height were recruited randomly and studied along side the study population if they gave written informed consent and did not have any of the exclusion criteria. On the average about four HIV positive patients and four HIV negative subjects were recruited and studied weekly.

The matching of the controls was a rigorous procedure carried out by simple observation first and then actual measurements of the parameters to be matched.

The same exclusion criteria were used for the HIV positive patients and HIV negative control subjects. Ethical approval was sought and obtained from the ethics committee of the University of Nigeria Teaching Hospital Enugu before the study was commenced.

In general, patients and subjects with the following conditions were excluded:

i) Pre existing and past history of cardio-respiratory diseases like bronchial asthma, chronic obstructive airway disease (COPD), pulmonary tuberculosis (PTB), Bronchiectasis, congestive cardiac failure (CCF) and spinal deformities.

ii) People who had worked in dusty environments like coal miners, quarry workers and wood workers.

iii) Patients that were already on highly active antiretroviral therapy.[3,4.]

iv) Patients with conditions where sub-optimal lung function results are likely as in those with acute onset chest or abdominal pain, those with oral or facial pain exacerbated by mouth piece, stress incontinence and those with dementia or confusional states.[19]

v) Patients with a history of smoking to remove the confounding effect of cigarette smoking on the respiratory system.[20, 21.] Patients who had worked indoors and outdoors with firewood or stoves were equally excluded. [22]

All patients and controls recruited were assessed using a structured pre tested respiratory questionnaire to obtain their clinical and anthropometric data. They all had normal chest examination findings. All the HIV positive patients recruited had chest X-ray and sputum examination for acid fast bacilli using *Ziehl-Nielsen (ZN) stain* method if they were coughing. All Chest films were reported by the same radiologist. All the patients had normal chest X ray results and those that had sputum examination had negative ZN stains.

Spirometry testing was performed using a portable spirometer (*Spirovit SP-1, SCHILLER-AG, AH gasse 68, post fach, 6340 Barr, Switzerland*) after the procedure was thoroughly explained to the patients and controls according to the ATS/ERS guidelines.[23]

Measurements were performed with the patients in sitting position without nose clip. Forced expiratory manoeuvres were repeated until three accepted and reproducible tests were obtained.[24]

The spirometer was calibrated every day of the study using the calibration syringe following the calibration procedures already set by the equipment manufacturer. The FVC, FEV1, FEV1/FVC and FEF25-75% were determined for each subject and control.

All the ventilatory function tests for the subjects and controls were conducted between 9.00am and 12.00noon and were all carried during the same season of the year (rainy season).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS Inc, Chicago 11.5version) was used for data entry, validation and analysis. For continuous variables, mean values and standard deviation were calculated and the mean compared using independent t-test. Qualitative variables were compared using the Pearson c^2 test. In all, critical P value of < 0.05 was regarded as significant and conclusions were drawn based on this level of significance. Confidence Interval was at 95%.

The frequencies of respiratory symptoms were compared between HIV positive patients and the negative controls.

The mean ventilatory indices of the HIV patients were compared with the values found in the matched HIV negative controls and were equally compared with the mean calculated values using reference equations generated for this sub region from previous studies [25, 26]

In the previous studies, the reference equation for comparison for the males goes thus;

FVC =4.62× Height (m)-0.023× Age (years)-3.42 [25]

FEV_1=3.847 × Height (m)-0.028 × Age (years)-2.49 [25]

While the reference equations for females are as follows;

FVC= 3.167 × Height (m) - 0.0199 × Age (years)-1.683.[26]

FEV_1= 1.488 × Height (m) - 0.0141 × Age (years) +0.275.[26]

The reference equations will be used to calculate ventilatory function values in HIV patients and HIV negative control subjects. Those with FVC less than 80% predicted with FEV_1/FVC % normal or increased will be classified as having restrictive lung impairment while those with FEV_1 /FVC less than 70% and those with FEV_1 less than 80% predicted will be classified as having obstructive functional lung impairment. Patients with ventilatory function values above 80% predicted will be classified as normal.

Multiple regression analysis was done to determine factors that are associated significantly with ventilatory function variables in both the HIV positive and negative individuals.

Results

One hundred eligible HIV positive subjects were recruited during this period and were studied with a hundred HIV negative controls. There were 49 HIV positive males representing 50.5% of the total males and 51 HIV positive females representing 49.5% of the total females. Out of the 100 control subjects, 48 were males while 52 were females.

The mean anthropometric values and age of the patients and control groups were comparable as their group means show no statistical significant difference as shown in Table 1.

Table 1: Mean anthropometric and ventilatory function variables in HIV positive subjects compared with HIV negative controls

Measured Variable	HIVpositive male subjects =49 Mean ± SD	HIV negative male controls n=48 Mean ± SD	T score	p valve	HIVpositive female subjects n=51 Mean ± SD	HIV Negative female controls n=52 Mean ± SD	T Score	Pvalue
Age (years)	38.2 ± 9.5	38.2 ± 9.4	-0.034	0.973	30.1 ± 5.7	31.3 ± 7.1	-0.874	0.384
Height (cm)	170.1 ± 8.5	172.6 ± 7.4	-1.503	0.136	160.6 ± 6.8	162.1 ± 6.4	-1.175	0.243
Weight (kg)	62.2 ± 9.2	65.3 ± 6.4	-1.945	0.054	55.4 ± 9.6	58.3 ±5.1	-1.922	0.060
BMI (kg/m^2)	21.4 ± 2.5	21.8 ± 1.3	-0.964	0.337	21.6 ± 3.9	22.2 ± 1.3	-1.061	0.291
FVC (L)	3.31± 0.71	3.71 ± 0.54	-3.094	0.003*	2.47 ± 0.45	2.98 ± 0.32	-6.665	<0.001*
FEV_1 (L)	2.91 ± 0.68	3.30 ± 0.50	-3.229	0.002*	2.22 ± 0.39	2.71 ± 0.31	-6.879	<0.001*
FEV_1/FVC (%)	87.6 ± 7.0	89.1 ± 5.0	-1.237	0.219	90.5 ± 5.2	90.8 ± 3.8	-.283	0.778
$FEF_{25\%-75\%}(L.S^{-1})$	3.56 ± 1.10	4.23 ± 1.41	-2.606	0.011*	2.89±0.77	3.55 ± 0.67	-4.603	<0.001*

* Statistically significant.

Common respiratory symptoms in HIV positive patients were cough, cough with sputum production, breathlessness and chest pains giving frequencies of 48%, 35%, 32% and 29% respectively. These frequencies were significantly more than the frequencies of the symptoms in HIV negative control subjects (P<0.05). This is further illustrated in Table2.

Table 2: Frequency of specific respiratory symptoms in HIV positive subjects compared with frequency in HIV negative controls

Respiratory symptom	HIV positive patients N=100	HIV negative controls N=100	χ^2 (df=1)	P value
Cough	48	8	39.683	<0.001*
Cough withSputum production	35	2	36.113	<0.001*
Chest pain	29	4	22.682	<0.001*
Breathlessness	32	0	38.095	<0.001*
Wheezing	7	0	7.254	0.007*
Nasal stuffiness	22	18	0.500	0.480
Sneezing	10	8	0.244	0.621

* Statistically significant.

The mean FVC, FEV_1, and FEF 25%-75% were significantly lower in the male HIV positive patients compared to mean in the male HIV negative controls. The mean FVC, FEV_1 and $FEF_{25\%-75\%}$ were significantly lower in the female HIV positive patients when compared with the female HIV negative controls ($p<0.001$).

The mean ventilatory function measurements in HIV positive males with at least one respiratory symptom were generally lower than the values measured in those without any symptoms except for FVC. (Table 3) Female HIV patients with respiratory symptoms have lower mean FVC, FEV_1, and $FEF_{25\%-75\%}$ than their asymptomatic counterparts also. These however did attain statistical significance except for FEV_1/FVC in the males.

Table 3: Comparative assessment of mean ventilatory function indices of symptomatic[a] and asymptomatic[b] HIV positive subjects

Ventilatory function parameter	Symptomatic HIVpositive male subjects N=28 mean± SD	Asymptomatic HIV positive male subjects N=21 mean± SD	T Score	Pvalue	Symptomatic HIV positive females N=38 mean ± SD	Asymptomatic HIV positive females N=13 Mean ± SD	T Score	Pvalue
FVC(l)	3.34 ± 0.71	3.27 ± 0.75	0.389	0.714	2.40 ± 0.46	2.66 ± 0.38	-1.825	0.074
FEV_1(l)	2.87 ± 0.66	2.97± 0.72	-0.506	0.615	2.19 ± 0.41	2.34 ± 0.33	-1.224	0.227
FEV_1/FVC	85.6 ± 7.4	90.2 ± 5.6	-2.401	0.020*	91.3 ± 5.2	88.3 ± 4.5	1.833	0.073
$FEF_{25\%-75\%}$ ($l.s^{-1}$)	3.32 ± 1.12	3.87 ± 1.03	-1.729	0.090	2.87± 0.78	2.96 ± 0.75	-0.357	0.722

*statistically significant a At least one respiratory symptom present b No respiratory symptom present

HIV patients of both sexes with CD4 count levels above 200cells/ul have higher mean FVC, FEV_1, and $FEF_{25\%-75\%}$ than their counterparts who have CD4 count levels below 200cells/ul. The difference in values for FVC and FEV1 attained statistical significance as indicated in Table 4.

Table 4: Comparative assessment of mean ventilatory function indices of all HIV positive subjects based on whether the CD4 count is above or below 200cells/ µ/1

Ventilatory Function	Males N=49		T score	P value	Females N=51		T score	P value
	CD4 <200 N=35	CD4>200 N=14			CD4 <200 N=31	CD4>200 N=20		
FVC(L) Mean± SD	3.19 ± 0.71 0.71	3.61± 0.67	-1.874	0.067	2.35 ± 0.42	2.65±0.44 0.44	-2.484	0.016*
FEV_1 (L) Mean± SD	2.81 ± 0.66 0.66	3.16± 0.71	-1.595	0.117	2.11 ± 0.37	2.40±0.38 0.38	-2.743	0.008*
FEV_1/FVC (%) mean± SD	88.2 ± 6.7	86.2 ± 7.8	0.870	0.389	90.3 ± 5.5	90.9±4.7	-0.353	0.726
$FEF_{25\%-75\%}$($l.s^{-1}$) mean± SD	3.46 ± 1.03 1.03	3.83± 1.28	-1.075	0.288	2.73 ± 0.63	3.14±0.90 0.90	-1.903	0.063

*Statistically significant

Calculation of ventilatory function values using published reference equations for normal Nigerian males and females showed that 32 HIV positive patients (14 males and 18 females) showed restrictive pattern of ventilatory function impairment while only three males have obstructive pattern.($p<0.05$) Sixty five HIV positive patients had normal ventilatory function as their values were above 80% of the predicted values as shown in Table 5.

Table 5: Classification of HIV positive patients into those with restrictive*, obstructive or normal*** ventilatory function pattern**

Functional classification	HIV positive number (male, female)	HIV Negative number (male, female)	Total
Normal	65 (32,33)	97(46,51)	162
Restrictive	32 (14,18)	3(2,1)	35
Obstructive	3 (3,0)	-	3
Total	100	100	200

$_c^2$ (df=2) =33.350, p value=0.000

Height, Age, gender, weight, HIV status, CD4 count, Presence of cough were shown to significantly affect ventilatory function variables in the study group using multiple regression analysis as illustrated further in Table 6 ($P<0.05$). Height and weight were shown to particularly to associated with increasing ventilatory function values as expected but HIV status remains an independent risk factor. The regression analyses show that males are found to have higher ventilatory function values than females.

Table 6: **Multiple regression analysis showing factors that affect ventilatory function variables**

Ventilatory Function	Age	Height	Gender	Weight	HIV Status	CD4 count	Cough
FVC	-0.012	0.028	-0.515	0.009	0.379	0.001	0.191
	**(0.002)	**(0.000)	**(0.000)	**(0.014)	**(0.000)	**(0.007)	**(0.012)
FEV_1	-0.017	0.023	-0.457	0.009	0.383	0.001	0.157
	**(0.000)	**(0.000)	**(0.000)	**(0.006)	**(0.000)	**(0.003)	**(0.023)
FEF25%-75%	-0.043	0.009	-0.741	0.020	0.602	0.001	0.206
	**(0.000)	(0.358)	**(0.000)	**(0.010)	**(0.009)	(0.059)	(0.210)

** Statistically significant

Discussion

This study to the best of our knowledge is the first study of ventilatory functions in Nigerians with HIV infection. The study shows that patients with HIV infection have a higher prevalence of respiratory symptoms and impairment in ventilatory function parameters compared with HIV negative counterparts. This has been established by some earlier studies[3-5,27-29].

All the patients studied in this study had normal chest x-ray and clinical examination findings. The prevalence of specific respiratory symptoms showed that cough, cough with sputum production, dyspnoea and chest pain were more common in HIV positive males and females when compared with their HIV negative controls and the differences attained statistical significance. This agrees with earlier observations by researchers working in Lagos[1], Zimbabwe[2] and the USA[3] who showed that cough, cough with sputum production and dyspnoea are the most prevalent respiratory symptoms in the HIV positive patients they studied.

The high prevalence rate of respiratory symptoms in HIV positive patients when compared to controls in this and earlier studies clearly showed that HIV positivity is associated with increased respiratory symptomatology. This may be due to the following factors acting either individually or collectively; repeated infections of the respiratory tract due to immunosupression notably PCP,[7] or the selective viral compartmentalisation and the lymphocytic alveolitis caused by CD8 cells which have been reported severally.[9-14]

It has equally been suggested by earlier studies that the impairment and or permanent decreases in ventilatory functions seen in HIV

infected patients could be due to low grade inflammation of the respiratory tract caused by repeated opportunistic infections notably *Pneumocystis carinii pneumonia* and repeated bacteria pneumonia.[7-8, 28-29] This is likely in the patients we studied as those with impairment showed restrictive pattern of ventilatory impairment in up to 32% cases. An earlier study also posited that ventilatory impairment in HIV positive patients could be as a result of CD8 T-lymphocytic alveolitis.[12]

It is not easy to ascertain how many of our patients had previous chest infections before the study as they gave negative history of previous chest infections, and had normal clinical and radiological examinations. It may well be that the decreased ventilatory functions established in this study could be due to unrecognised low grade opportunistic infections in our setting which is not surprising in a cohort of immunosuppressed patients from a developing country like Nigeria. We suggest that further studies like computerised tomography scan of the lungs and possibly fibre optic bronchoscopy with bronchoalveolar lavage should be done in future studies to elucidate the actual cause of the ventilatory impairment as has been suggested earlier.[8]

Patients with respiratory symptoms were generally found to have lower ventilatory parameters than those without respiratory symptoms though this did not attain statistical significance. This finding is not unexpected and could suggest that patients with respiratory symptoms have more affectation of the respiratory tract by the human immunodeficiency virus which has been shown to predispose them to both repeated infections and lymphocytic alveolitis. Further formal lung function laboratory studies with transfer factor tests preferably in a larger population of HIV infected individuals will be necessary to establish the significance of this finding.

In this study, patients with CD4 T lymphocyte count < 200cells/μl showed lower ventilatory function values than those with higher counts for both sexes. This finding is in keeping with the result of an earlier study that showed that advancing HIV infection characterised by lower CD4 count is associated with diminishing pulmonary functions.[29] It may be implied therefore that advancing HIV infection signified by low CD4 count with consequent high viraemia and possibly lymphocytic alveolitis as described earlier is associated with diminishing ventilatory functions as reported by previous studies.[11-13] It may not surprising therefore that up to 32% of the HIV positive patients studied had restrictive ventilatory impairment which may be the likely expected ventilatory functional impairment in cases of lymphocytic alveolitis and repeated lung infections.

Factors already known to affect ventilatory functions like height, gender, and weight were shown to significantly affect ventilation function variables in this study as well. In addition positive HIV status, reduced CD4 count and presence of respiratory symptoms appear to be significantly associated independently with ventilatory function impairment showing that the impairment in lung functions in the HIV positive patients may be related factors like decreasing immunity, repeated infections and lymphocytic alveolitis as have been described earlier.

Study limitations

The limitations of this study include the fact that the study was a cross sectional study so it could not look at the effect of the disease progression on lung function parameters, and the sample size of a hundred HIV patients was small and may have affected some of the conclusions made.

We suggest that HIV patients with low CD4 count and respiratory symptoms should be evaluated with lung function testing and patients found to have impairment in lung function tests should be evaluated further with imaging studies like CT scanning.

Studies to elucidate the effect of HIV disease progression and or the use of highly active antiretroviral therapy on ventilatory function parameters in HIV positive patients on treatment are called for as the present study was a cross sectional study on drug naïve patients.

There is paucity of data regarding current predicted ventilatory function value equations for native Nigerians in this sub region that will be used in comparing this kind of study and such studies are highly needed. Lung function testing in Africans in general has long been neglected unfortunately.

Conclusion

It is hoped that this preliminary study of ventilatory functions in HIV infected Nigerians will stimulate further research in this regard more especially in the area of identifying the actual cause of the ventilatory impairment among this patient population.

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Erratum

***Brown BJ**, Ajayi SO, Ogun OA, Oladokun RE

"Factors influencing time to diagnosis of childhood cancer in Ibadan, Nigeria"

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We regret the wrong abbreviation of one of the authors which appeared as James BO instead of Brown BJ.

Editor