

Association between CD4+ Lymphocyte Count and Left Ventricular Diastolic Function and Geometry in Newly Diagnosed Highly Active Antiretroviral Therapy (HAART) Naive HIV/AIDS Patients Seen at University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

Abaram Chesa Mankwe^{1*} and Osaretan James Odia²

¹Federal Medical Centre, Yenagoa, Bayelsa, Nigeria

²University of Port Harcourt Teaching Hospital, Port Harcourt, Nigeria

Abstract

Background: Human Immunodeficiency Virus (HIV) infection is one of the leading causes of acquired heart diseases and specifically of symptomatic heart failure and pulmonary arterial hypertension. In the clinical course of HIV infection, CD₄⁺ count decreases with disease progression and it has been considered to be correlated with LV dysfunction in the disease process.

Method: This was a cross-sectional case-control study. One hundred newly diagnosed HAART naive HIV/AIDS individuals seen in the retroviral clinic were evaluated clinically. One hundred age and sex matched HIV negative controls were recruited. Those with other cardiovascular risk factors were excluded. Blood samples were screened and confirmed for HIV1 and 2 infections using double ELISA. CD₄⁺ count was estimated using the flow cytometry method. Left ventricular diastolic function and geometry were assessed using transthoracic echocardiography.

Results: The mean age of cases with HIV/AIDS was 35.7 ± 10.13 years. Females were more than males in a ratio of 2.3:1. Diastolic dysfunction assessed by E/A ratio, deceleration time and isovolumic relaxation time (IVRT) occurred more in the cases compared to the controls (40% versus 6%) and this was statistically significant ($\chi^2=38.15$, $p=0.001$). Abnormal geometry assessed using LVMI and RWT was commoner in the cases than in the control group and this was statistically significant ($\chi^2=25.49$, $p=0.01$). There was an insignificant negative correlation between CD₄⁺ count and IVRT ($R=-0.0086$, $P=0.393$). Subjects with CD₄⁺ count <200 cells/ μ L were more likely to have diastolic dysfunction (OR=1.680, $P=0.2112$). Lastly, there was an insignificant negative correlation between CD₄⁺ count and LVMI ($R=-0.303$, $P=0.816$). Subjects with CD₄⁺ count <200 cells/ μ L were more likely to have abnormal geometry (OR=1.182, $P=0.6312$).

Conclusion: Left ventricular diastolic dysfunction and abnormal geometry were shown in this study to be more common in people with HIV/AIDS than in the control group and there was association between degree of immunosuppression and diastolic dysfunction as well as abnormal geometry, although these were statistically not significant.

Keywords: CD₄⁺ count; HIV; Left ventricle; Geometry; Diastolic function; Echocardiography

Introduction

Nigeria has the second largest HIV epidemic in the world [1] with 3.5 million people living with HIV in 2015 [2]. An estimated 60% of new HIV infections in western and central Africa occurred in Nigeria in 2015 [2]. HIV prevalence is highest in Nigeria's southern states (known as the South Zone), and stands at 5.5%.

The association of HIV infection with cardiovascular disease was recognized in the early stages of the HIV epidemic [3] cardiovascular complications in the course of Human Immunodeficiency Virus (HIV) infections are multifactorial and may be caused by the virus itself or by opportunistic infections and neoplasms. Highly active antiretroviral therapy (HAART) has increased survival of many patients, but the cardiac sequelae may progress despite HAART [4].

Cardiovascular complications of HIV infection may result in increased risk of myocardial Infarction (MI) [5] and cardiomyopathy [6] which in turn are associated with increased left ventricular mass [7,8] Increased LV mass is associated with increased risk of fatal and non-fatal MI, sudden cardiac death, severe heart failure, and

cerebrovascular events including stroke and transient ischemic attacks [7-9].

Left Ventricular Hypertrophy (LVH) is a well-recognized independent predictor of major cardiovascular events and since HIV infection has been shown to be linked to a wide range of abnormal ventricular geometric patterns, there is need to embark on echocardiographic evaluation of these patients with a view to identifying different patterns of ventricular geometry that could be found in them.

*Corresponding author: Abaram Chesa Mankwe, Federal Medical Centre, Yenagoa, Bayelsa, Nigeria, Tel: +234 706 933 7998; E-mail: chesamankwe@yahoo.com

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Though a lot more work has been done in the developed world describing the cardiac abnormalities in HIV and AIDS, little has been done in Africa, resulting in paucity of data on the prevalence of cardiac abnormalities in HIV/AIDS patient in this part of the world.

While there are few reports from the Eastern and Southern Africa as well as some parts of Nigeria, no work to the knowledge of the investigator has been done in South- South zone of Nigeria associating CD4+ lymphocyte count and left ventricular function and geometry in patients with HIV/AIDS.

Cardiac complications of HIV/AIDS are often clinically in apparent or subtle in the initial stages of the disease and so periodic screening of HIV-positive patients by electrocardiogram and echocardiogram is important [10].

CD4+ lymphocyte count and opportunistic infection are the major indicators for the clinical staging of HIV infection [11] and both have been considered to be correlated with LV dysfunction in the disease process with variable results. The purpose of this study is to investigate the association between CD4+ count and left ventricular diastolic function and geometry in newly diagnosed HAART naïve HIV/AIDS individuals seen in a tertiary health institution. This will facilitate early intervention to prevent or reduce development and progression of complications and adverse outcomes.

Materials and Methods

Study population

The study was a descriptive crosssectional case-control study. The study population consists of 100 newly diagnosed HIV/AIDS patients aged 18 years and above who had never received HAART seen at the clinics and medical wards of University of Port Harcourt Teaching Hospital (UPTH). 100 HIV negative, apparently healthy age and sex matched controls were randomly selected from hospital staff and patient relatives. Recruitment was also from those undergoing HIV screening for marriage, blood donation, insurance purposes and those who desired to know their HIV status.

Ethical considerations

Ethical approval was obtained from the Hospital's Ethical Committee before commencement of the study. Informed written consent was obtained from all patients and controls before enrollment into the study. The cost of the investigations was borne by the investigator. Subjects found to have abnormalities were advised and referred appropriately for further management. Taking part in this study was voluntary. Participants had the liberty to refuse to participate in this study without any consequence.

Sample size

The minimum sample size of patients required for this study was 61 patients. This was calculated using the method of Kish [12] for sample size determination in a population greater than 10,000.

$$n = \frac{z^2 pq}{d^2} \text{ and } nf = \frac{n}{1 + \frac{(n)}{N}}$$

Where:

Nf=the desired sample size when population is less than 10,000

n=the desired sample size when population is greater than 10,000.

Z=Standard deviation, usually set at 1.96, which corresponds to 95% confidence level

P=the proportion in the target population estimated to have HIV infection=4.1% (i.e.; 0.041) [13]

$$q=1 - P=1 - 0.041=0.959$$

d=degree of desired accuracy, set at 0.05.

N=estimation of population size, that is new patients with HIV/AIDS infection who are HAART naïve attending UPTH Port Harcourt annually is about 638.

$$n = \frac{z^2 pq}{d^2} = \frac{(1.96)^2(0.041)(0.959)}{(0.05)^2} = 60.41$$

$$nf = \frac{n}{1 + \frac{(n)}{N}} = \frac{60.41}{1 + \frac{60.41}{638}} = 55.17$$

Hence final sample size=60.686~61 (Accounting for 5% to 10% attrition). However, the sample size of 100 was used for better statistical power.

Study procedure

Individuals who met the study criteria were asked for informed consent and when granted were recruited into the study. Participants were asked to return on the day of the study for further evaluation after an overnight fast.

Participants received clinical assessments by the investigator using a structured questionnaire to assess demographic information and disease related variables including age, gender, and previous history of cardiovascular events. Physical examination was conducted by the investigator to determine weight, height, and blood pressure. Weight was measured with a mechanical weighing scale in kilograms with the subject wearing only light clothing (jackets and coats were removed) and with the subject's shoes off.

Height was measured in meters using a stadiometer with the subject standing feet together without shoes or head gear, back and heel together against a vertical ruled bar to which a movable attached horizontal bar was brought to the vertex of the head and reading taken to the nearest 0.5 cm.

Body mass index was calculated as body weight in kilograms divided by the square of the height in metres. Body mass index status was classified according to the WHO criteria as normal weight (18.5 kg/m² to 24.9 kg/m²), overweight (25 kg/m² to 29.9 kg/m²), class I obesity (30.0 kg/m² to 34.9 kg/m²), class II obesity (BMI 35.0 kg/m² to 39.9 kg/m²), and morbid obesity (BMI 40 kg/m²) [14]. Those that were obese were excluded from the study.

Body surface area was calculated using the formula of Dubois [15] which is body surface area in

$$m^2=0.0001 \times (71.84) \times (\text{weight in kg}^{0.4250}) \times (\text{height in m}^{0.725}).$$

Blood pressure was measured with a standard (Accosson) Mercury Sphygmomanometer (cuff size 12.5 cm × 40 cm) on the patients' right arm in the seated position with feet on the floor after at least a five-minute rest. Those found to be hypertensive were excluded from the study.

Venepuncture was carried out using a peripheral vein and 7 mL

of blood was collected from each subject, 5 mL of which was put into lithium heparin bottles for assessment of fasting lipid profile, and serum creatinine. 2 ml was put into fluoride oxalate bottles for fasting plasma glucose. Serum creatinine was used to calculate the estimated glomerular filtration rate (GFR) using the Cockcroft-Gault formula [16,17]. Patients with estimated GFR levels 60 mL/min or below 18 and those with fasting plasma glucose levels of 7.0 mmol/L and above were excluded from the study.

Fasting cholesterol and triglyceride levels were measured using the enzymatic method with a reagent from Atlas Medical Laboratories. Patients with abnormal lipid profile were excluded from the study. Whole blood samples were collected by venepuncture using a 10-mL hypodermic syringe and needle into EDTA anticoagulated tubes (5 mL) and non-anticoagulated tubes (5 mL). Sera derived from the non-anticoagulated tubes were screened and confirmed for HIV 1 and 2 infections using a double ELISA confirmatory method. CD4 T-helper lymphocyte count was estimated using the flow cytometry method. Both biochemical and hematological parameters were analyzed in the medical laboratory department of UPTH.

Echocardiography (Transthoracic): M-Mode, 2 dimensional and doppler echocardiographic examinations of the left ventricle were performed with the subjects in the left lateral decubitus position, using ALOKA 2 dimensional/doppler and color flow ultrasound machine, equipped with a 3.2 MHz transducer. A single sonographer who was blinded to each participant's HIV status and clinical characteristics performed all of the echocardiographic studies. All recordings and measurements were made using standard parasternal long axis and short axis views and apical 4-chamber views. Where necessary, an apical 2-chamber view was evaluated. Echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE) [18]. M-mode, interventricular septal thickness at end diastole (IVSd), the posterior wall thickness at end diastole (PWTd), the LV internal dimensions at end diastole (LVIDd) and at systole, and left atrial size at end systole were measured by use of a leading-edge technique according to the guidelines of the ASE. End-diastolic LV wall thickness (LVWT) was calculated as (IVSd+PWTd), whereas relative wall thickness (RWT) was calculated as (IVSd + PWTd/LVIDd). Increased RWT was taken as $RWT \geq 0.45$. Presence of diastolic dysfunction was determined according to guidelines from the American Society of Echocardiography [19-21]. Left ventricular diastolic filling pattern was assessed by echocardiographic pulsed Doppler analysis. The diastolic mitral flow assessed by early diastolic peak flow velocity (E), the ratio of E to A (E/A) and the deceleration time of the early mitral velocity was recorded with the sample volume at the mitral leaflet tips. Deceleration time was measured as the time from peak E velocity to the time when the E wave descent intercepts the zero line. Isovolumic Relaxation Time (IVRT) was measured with a continuous wave doppler beam intersecting left ventricular outflow and inflow tract [22]. Pulse doppler recordings of trans mitral flow velocities were obtained between the tips of the mitral leaflets for measuring peak early left ventricular filling velocity/peak atrial filling velocity (E/A) and deceleration time(EDT). Valsalva maneuver was performed when applicable. Three consecutive cardiac cycles were assessed and averaged for Doppler measurements [23].

Filling Patterns in evaluated patients were classified as:

A. Normal filling pattern: Normal myocardial relaxation [24]

B. Diastolic dysfunction [25]

i. Stage I (mild dysfunction): Defined as impaired relaxation with normal filling pressure.

ii. Stage II (moderate dysfunction): Defined as pseudo normal filling pattern

iii. Stage III (severe reversible dysfunction): Defined as a restrictive filling pattern and evidence of reversibility with valsalva maneuver; and finally

iv. Stage IV (severe irreversible dysfunction): Defined as a restrictive filling pattern without reversibility with Valsalva [26]

The left ventricular mass index (LVMI) and left ventricular geometry were determined by m- mode and 2-dimensional echocardiography. Left ventricular mass was indexed to body surface area [27]. The LV mass was calculated using the American Society of Echocardiography formula modified by Devereux [26] as follows:

$LVM(g) = 0.8 \times [1.04 (LVIDd + LVPWd + IVSd)^3 - LVIDd^3] + 0.6$. LVH was considered to be present when LVMI exceeds 110 g/m² for female and 134 g/m² for male [28]. The LV geometry were classified based on the evaluations of LVMI and RWT as follows:

A. Normal Geometry-Normal LVMI and RWT

B. Concentric Remodeling-Normal LVMI and Increased RWT.

C. Eccentric Hypertrophy-Increased LVMI and $RWT < 0.45$

D. Concentric Hypertrophy-Increased LVMI and $RWT \geq 0.45$

Statistical analysis

All data were analyzed using the commercially available Statistical Package for Social Sciences (SPSS) version 20.0 analytic software. Data were expressed as mean \pm standard deviations and percentages. Continuous variables were compared with the Students t-test, or one-way analysis of Variance as considered appropriate. Proportions or categorical parameters were compared with the chi-square test. Relations among continuous variables were assessed using Pearson correlation test and multiple linear regression analysis. All tests were considered to be statistically significant at the p-value<0.05.

Results

Sociodemographic characteristics of the entire study population

A total of 200 subjects were included in this study of which 100 constituted the cases (participants with HIV/AIDS) and 100 formed the control group (healthy HIV negative subjects).

The mean age of the cases with HIV/AIDS was 35.7 ± 10.13 years (range of 20 to 62 years) while the mean age of the control population was 38 ± 9.63 years (range of 21 to 65 years). The most common age group was the 30 to 39 years both among the cases and control group. The mean difference in age between the cases and the control was not statistically significant (student's t-test=1.646, p=0.10) and therefore the cases and controls were matched for age (Table 1).

The frequency of females was higher than the males among the cases (70% versus 30%) giving male to female ratio of 1:2.3. Among the controls also, there was a female preponderance with 64 (64.0%) being females and 36 (36.0%) being males giving a male to female ratio of 1:1.8. There was no statistically significant difference between the two groups and therefore the cases and controls were also matched for sex (student's t-test=0.902, p=0.37) (Table 1).

CDC CD4+ classification of the sociodemographic characteristics of the cases with HIV/AIDS

All the AIDS patients used in this study had one or more AIDS

Variables	Cases	Controls	χ ²	p-value
Sex				
Male	30 (30.0%)	36 (36.0%)	0.81	0.37
Female	70 (70.0%)	64 (64.0%)		
Age				
20-29 years	30 (30.0%)	21 (21.0%)	7.22	0.13
30-39 years	42 (42.0%)	36 (36.0%)		
40-49 years	16 (16.0%)	31 (31.0%)		
50-59 years	10 (10.0%)	11 (11.0%)		
60-69 years	2 (2.0%)	1 (1.0%)		
Diastolic Function				
Normal Diastolic Function	60 (60.0%)	94 (94.0%)	38.15	0.001
Mild Dysfunction	2 (2.0%)	3 (3.0%)		
Moderate Dysfunction	22 (22.0%)	3 (3.0%)		
Severe Dysfunction	16 (16.0%)	0		
IVRT				
<100 m/s (normal)	76 (76.0%)	100 (100.0%)	27.27	0.001
>100 m/s (prolonged)	24 (24.0%)	0		
Geometry				
Normal geometry	50 (50.0%)	83 (83.0%)	25.49	0.001
Concentric remodeling	34 (34.0%)	12 (12.0%)		
Eccentric hypertrophy	8 (8.0%)	4 (4.0%)		
Concentric hypertrophy	8 (8.0%)	1 (1.0%)		
LAD				
<4.1 cm (normal)	93 (93.0%)	99 (99.0%)	4.69	0.03
4.1 cm to 4.6 cm (mildly dilated)	7 (7.0%)	1 (1.0%)		

Table 1: Baseline characteristics of the entire study population.

CD4+ CLASSIFICATION					
Variables	<200 cells/ul	200 to 499 cells/ul	>500 cells/ul	χ ²	p-value
Normal diastolic function	21 (52.5%)	25 (58.1%)	14 (82.4%)	14.29	0.03
Mild dysfunction	2 (5.0%)	0	0		
Moderate dysfunction	6 (15.0%)	14 (32.6%)	2 (11.8%)		
Severe dysfunction	11 (27.5%)	4 (9.3%)	1 (5.9%)		
IVRT					
<100 m/s (normal)	29 (72.5%)	33 (76.7%)	14 (82.4%)	0.66	0.72
>100 m/s (prolonged)	11 (27.5%)	10 (23.3%)	3 (17.6%)		
Geometry					
Normal geometry	19 (47.5%)	19 (44.2%)	12 (70.6%)	6.66	0.35
Concentric remodeling	12 (30.0%)	18 (41.9%)	4 (23.5%)		
Eccentric hypertrophy	4 (10.0%)	4 (9.3%)	0		
Concentric hypertrophy	5 (12.5%)	2 (4.7%)	1 (5.9%)		
LAD					
<4.1 cm (normal)	39 (97.5%)	37 (86.0%)	17 (100.0%)	5.72	0.06
4.1 cm to 4.6 cm (mildly dilated)	1 (2.5%)	6 (14.0%)	0		

Table 2: CDC classification of the echocardiographic characteristics of the HIV/AIDS patients.

indicator conditions with CD4+ count <200 cells/μl and therefore belong to either category A3, B3 or C1-C3. The HIV positive subjects with CD4+ count >200 cells/μl (subdivided into two groups: 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl) were either asymptomatic or symptomatic and therefore belong to either categories A1, A2, B1 or B2. Therefore, the cases with HIV/AIDS were divided into three groups according to the level of their CD4+ count: <200 cells/μl (AIDS patients), 200 cells/μl to 499 cells/μl and >500 cells/μl.

Forty (40%) of the cases had CD4+ count <200 cells/μl, 43 (43%) had CD4+ count ranging between 200 cells/μl to 499 cells/μl and 17 (17%) had CD4+ count ≥ 500 cells/μl.

The mean age was 36.17 ± 1.55 years among the cases with CD4+ count <200 cells/μl, 36.67 ± 1.37 years among the cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl and 32.53 ± 1.96 years for cases with CD4+ count ≥ 500 cells/μl. The mean difference in age was not statistically significant in the three (3) groups (p=0.28). Among the forty (40%) cases with CD4+ count <200 cells/μl, 25 (62.5%) were females and 15 (37.5%) were males. And of the 43 (43%) cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, 31 (72.1%) were females and 12 (27.9%) were males. Also, among the seventeen (17%) cases with CD4+ count ≥ 500 cells/μl, 14 (82.4%) were females and 3 (17.6%) were males.

Echocardiographic parameters

Diastolic function: Diastolic dysfunction assessed by E/A ratio, deceleration time and Isovolumic relaxation time was more in the cases compared to the control group (40% versus 10%) The difference in the diastolic function was statistically significant (x²=38.15, p=0.001). Among the cases, 60 (60.0%), 2 (2.0%), 22 (22.0%) and 16 (16.0%) had normal diastolic function, mild, moderate and severe diastolic dysfunction respectively while in the control group, 94 (94.0%), 3 (3.0%) and 3 (3.0%) had normal diastolic function, mild and moderate diastolic dysfunction respectively (Table 1).

Among the forty (40%) AIDS patients with CD4+ count <200 cells/μl, 21 (52.5%), 2 (5.0%), 6 (15.0%) and 11 (27.5%) had normal diastolic function, mild, moderate and severe diastolic dysfunction respectively while in the 43 cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, 25 (52.1%), 14 (32.6%) and 4 (9.3%) had normal diastolic function, moderate and severe diastolic dysfunction respectively. Also in the seventeen (17%) cases with CD4+ count ≥ 500 cells/μl, 14 (82.4%), 2 (11.8%) and 1 (5.9%) had normal diastolic function, moderate and severe diastolic dysfunction respectively. The difference in diastolic function among these 3 groups was statistically significant (x²=14.29, p=0.03) (Table 2).

Isovolumic relaxation time (IVRT): There was prolongation of the IVRT in the cases compared to control. 76 (76%) and 24 (24%) of the cases had normal and prolonged IVRT respectively while all (100.0%) in the control group had normal IVRT. The difference in IVRT between the cases and control was statistically significant (x²=27.27, p=0.001) (Table 1).

Among the cases with CD4+ count <200 cells /μl, 29 (72.5%) and 11 (27.5%) had normal and prolonged IVRT respectively while in the cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, 33 (76.7%) and 10 (23.3%) had normal and prolonged IVRT respectively. Also 14 (82.4%) and 3 (17.6%) had normal and prolonged IVRT in the cases with CD4+ count ≥ 500 cells/μl. The difference in IVRT was not statistically significant (x²=66, p=0.72) (Table 2).

The mean IVRT in the cases with CD4+ count <200 cells/μl, ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl were 88.78 ms ± 3.74 ms, 86.63 ms ± 2.99 ms and 83.24 ms ± 5.06 ms respectively. The mean difference in IVRT among the three groups was not statistically significant (f=0.40, p=0.67) (Table 3).

Deceleration time (DT): The mean deceleration time of the cases was 169.16 ms ± 39.85 ms (range=78 ms to 252 ms) while the mean deceleration time of the control group was 171.87 ms ± 26.990 ms (range=136 ms to 258 ms). The mean difference in deceleration time

between the cases and control was not statistically significant (student's t-test=0.563, p=0.574). The mean DT in the cases with CD4+ count <200 cells/μl, ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl were 150.85 ms ± 6.94 ms, 183.30 ms ± 5.21 ms and 176.47 ms ± 6.13 ms respectively. The mean difference in the DT among the three groups was statistically significant (f=8.28, p=0.001) (Table 3).

E:A ratio: Grade 1 diastolic dysfunction assessed using E/A ratio was more in the cases than the control group 11 (11.0%) versus 3 (3.0%). This was statistically significant (student's t-test=2.217, p=0.03). However, the mean E/A ratio of the cases and control group were 1.55 ± 0.66 and 1.53 ± 0.45 respectively and the mean difference in E/A ratio was statistically insignificant (student's t-test=0.168, p=0.87). Also, among the AIDS patients with CD4+ count <200 cells/μl, the mean E/A ratio was 1.55 ± 0.09 while amongst the cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, the E/A ratio mean was 1.56 ± 0.13. Lastly, the cases with CD4+ count ≥ 500 cells/μl had mean E/A ratio of 1.49 ± 0.08. The mean difference in E/A ratio between the three groups was not statistically significant (f=0.07, p=0.93) (Table 3).

Left atrial dimension (LAD): The left atrial enlargement was more in the cases than in the control group and this difference was statistically significant (x²= 4.69, p=0.030) (Table 1). 7 (7.0%) of the cases had mildly dilated left atrium (4.1 cm to 4.6 cm) as against 1 (1.0%) in the control group.

The mean LAD in the AIDS patients with CD4+ count <200 cells/μl was 3.12 cm ± 0.08 cm while in the cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl were 3.27 cm ± 0.08 cm and 3.27 cm ± 0.10 cm respectively. The difference in mean LAD between these three groups was not statistically significant (f=1.09, p=0.34) (Table 3). Among the 40 cases with CD4+ count <200 cells/μl, 39 (97.5%) had normal LAD while 1 (2.5%) had mildly dilated left atrium. Among the 43 cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, 37 (86.0%) had normal LAD while 6 (14.0%) had mildly dilated left atrium. More so, all the 17 cases with CD4+ count ≥ 500 cells/μl had normal LAD. There was no statistically significant difference amongst these three groups (x²=5.72, p=0.06) (Table 2).

Geometry

Abnormal geometry was higher in the cases than in the control

Variables	CDC Classification			Values	
	CD4+ <200 cells/ul	CD4+ 200-499 cells/ul	CD4+ >500 cells/ul		
	N=40	N=43	N=17	F	p-value
	Mean (sem)	Mean (sem)	Mean (sem)		
Left ventricular mass (G)	152.90 (8.90)	155.77 (7.57)	151.35 (9.81)	0.06	0.94
Left ventricular mass index (G/M)	95.13 (5.38)	92.56 (4.05)	86.94 (4.73)	0.48	0.62
Relative wall thickness	0.50 (0.04)	0.47 (0.02)	0.51 (0.07)	0.22	0.81
Geometry	1.88 (0.17)	1.74 (0.13)	1.41 (0.19)	1.54	0.22
E:A Ratio	1.55 (0.09)	1.56 (0.13)	1.49 (0.08)	0.07	0.93
Deceleration time (Ms)	150.85 (6.94)	183.30 (5.21)	176.47 (6.13)	8.28	0.001
Isovolumic relaxation time (Ms)	88.78 (3.74)	86.63 (2.99)	83.24 (5.06)	0.4	0.67
Left atrial diameter (Cm)	3.12 (0.08)	3.28 (0.08)	3.27 (0.10)	1.09	0.34

Table 3: CDC classification of the mean values of the echocardiographic parameters of the cases with HIV/AIDS.

group (50% versus 17%). Among the 50 (50.0%) cases with abnormal geometry, 34 (34.0%), 8 (8.0%) and 8 (8.0%) had concentric remodeling, eccentric hypertrophy and concentric hypertrophy respectively. This is in comparison to the control group where 12 (12.0%), 4 (4.0%) and 1 (1.0%) had concentric remodeling, eccentric hypertrophy and concentric hypertrophy. The difference in the geometric patterns in both groups was statistically significant (x²=25.49, p=0.001) (Table 1). Left ventricular hypertrophy was commoner in the cases compared to the control group (16.0% versus 5.0%) and this was statistically significant (student's t-test=2.537, p=0.01).

Among the 40 (40.0%) AIDS cases with CD4+count <200 cells/μl, 19 (47.5%), 12 (30.0%), 4 (10.0%) and 5 (12.5%) had normal geometry, concentric remodeling, eccentric hypertrophy and concentric hypertrophy respectively. Also, among the 43 (43.0%) of cases with CD4+ count ranging between 200 cells/μl to 499 cells/μl, 19 (44.2%), 18 (41.9%), 4 (9.3%) and 2 (4.7%) had normal geometry, concentric remodeling, eccentric hypertrophy and concentric hypertrophy respectively. In the 17 (17%) cases with CD4+ count ≥ 500 cells/μl, normal geometry, concentric remodeling and concentric hypertrophy was observed in 12 (70.6%), 4 (23.5%) and 1 (5.9%) respectively. There was no statistically significant difference in the geometric patterns of these three groups (x²=6.66, p=0.35) (Table 2).

Left ventricular mass (LVM)

The mean LVM was higher in the cases than in the control group (153.87 ± 50.613 g versus 149.34 g ± 38.867 g). The range of LVM in the cases and control group was 72 g to 380 g and 58 g to 287 g respectively. However, the mean difference in LVM was not statistically significant (students t-test=0.710, p=0.4786). The mean LVM of the AIDS patients with CD4+ count <200 cells/μl, ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl were 152.90 g ± 8.90 g, 155.77 g ± 7.57 g and 151.35 g ± 9.81 g respectively. The mean difference in LVM of these three groups was not statistically significant (f= 0.06, p=0.94) (Table 3).

Left ventricular mass index (LVMI)

The mean LVMI was higher in the cases than in the control group (92.63 g/m² ± 28.719 g/m² versus 80.25 g/m² ± 17.793 g/m²). The mean difference in LVMI between the cases and control group was statistically significant (student's t-test=3.664, p< 0.03). The mean LVM of the AIDS patients with CD4+ count <200 cells/μl, ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl were 95.13 g/m² ± 5.38 g/m², 92.56 g/m² ± 4.05 g/m² and 86.94 g/m² ± 4.73 g/m² respectively. The mean difference in LVMI among these three groups was not statistically different (f=0.48, p=0.62) (Table 3).

Relative wall thickness (RWT)

The mean RWT was higher in the cases compared to the control group (0.4892 ± 0.22537 versus 0.3952 ± 0.06870). The mean difference in RWT between the cases and control group was statistically significant (student's t-test= 3.990, p< 0.01). The AIDS patients with CD4+ count <200 cells/μl, had a mean RWT of 0.50 ± 0.04 while the cases with CD4+count ranging between 200 cells/μl to 499 cells/μl and ≥ 500 cells/μl had mean RWT of 0.47 ± 0.02 and 0.51 ± 0.07 respectively. There was no statistically significant difference in the mean RWT of the three groups (f=0.22, p=0.81) (Table 3).

Impact of gender on the clinical and echocardiographic parameters of HIV/AIDS subjects

In this present study, there was no statistical difference between the ages of the male and female subjects (t- test=1.67, p=0.09). Also, there

was no statistically significant difference in the body mass index of the male and female subjects (t-test=1.43, p=0.16). Males had higher body surface area than the female subjects which was statistically significant (t-test=5.39, p=0.001) (Table 4). Furthermore, males had higher left ventricular mass (LVM) and left ventricular mass index (LVMI) than the female subjects. The LVM of the male and female subjects were 184.63 g ± 11.10 g and 140.69 g ± 4.68 g respectively and this was statistically significant (t-test=4.32, p=0.001) (Table 4). Also, the LVMI of the male and female subjects were 104.33 g/m² ± 6.41 g/m² and 87.61 g/m² ± 2.88 g/m² respectively and this was statistically significant (t-test=2.76, p=0.007). Lastly, left atrial diameter (LAD) was greater in the male than in the female subjects and this was statistically significant (t-test=2.86, p=0.005) (Table 4).

Correlation of CD4+lymphocyte count with clinical and echocardiographic parameters

A correlation study of CD4+ lymphocyte count with some clinical and echocardiographic parameters was carried out and the outcome is shown in Table 5.

Association between AIDS (CD4 count < 200 cells/μl) and left ventricular diastolic dysfunction

The measure of association between AIDS (CD4 count <200 cells/μl) and left ventricular diastolic dysfunction was assessed using the odds ratio. The cases with AIDS (CD4 count <200 cells/μl) were 1.68 times more likely to develop diastolic dysfunction than cases

without AIDS (CD4 count >200 cells/μl) and this was statistically not significant. (At 95% confidence level, the confidence interval is 0.74 to 3.8 and p=0.2112).

Association between AIDS (CD4 count < 200 cells/μl) and abnormal left ventricular geometry

The measure of association between AIDS (CD4 count <200 cells/μl) and abnormal left ventricular geometry was assessed using the odds ratio. The cases with AIDS (CD4 count <200 cells/μl) were 1.18 times more likely to develop abnormal left ventricular geometry than cases without AIDS (CD4 count >200 cells/μl) and this was statistically not significant. (At 95% confidence level, the confidence interval is 0.53 to 2.63 and p=0.63)

Discussion

The study set out to determine the prevalence of left ventricular diastolic dysfunction and abnormal geometric patterns among newly diagnosed HAART naïve HIV/AIDS patients and to determine the relationship between left ventricular diastolic dysfunction and abnormal geometry and CD4 lymphocyte count.

The study cohort consisted of mostly female patients. The female preponderance in this study corroborates with the UNAIDS [29] finding that of the 33.3 million adults living with HIV/AIDS, more than half are women.

Most of the patients were in the age group 30-39 years with a mean age of 35.7 ± 10.13 years. This is similar to a mean age of 35 ± 10.4 years observed by Danbauchi et al. [30] in Zaria in their study on cardiac manifestations of stage III and IV HIV/AIDS compared to subjects on ARV.

HIV is a CD4+ T lymphocyte depletor and the concentration of CD4+ T lymphocyte in the blood has been used to classify the disease condition [31]. The range of CD4+ count in the cases was from 20 cells/μl to 1847 cells/μl with a mean of 318.51 cells/μl ± 261.66 cells/μl. AIDS is also defined as CD4+ count of <200 cells/μl. Forty patients fell into this category accounting for 40% of the studied cases. Forty-three (43%) cases had CD4+ count between the range of 200 cells/μl to 499 cells/μl. while only seventeen (17%) had CD4+ count of 500 cells/μl and above.

This explains the high prevalence of cardiac abnormalities seen in this study, as HIV/AIDS associated cardiovascular disease is said to be a late complication of HIV infection [32,33].

The prevalence of diastolic dysfunction assessed by reversed E/A ratio, deceleration time and isovolumic relaxation time in patients with HIV/AIDS in this study was 40.0%. Mild diastolic dysfunction was observed in 2.0% of the cases while moderate and severe diastolic dysfunction was seen in 22.0% and 16.0% of the cases respectively. This corroborates with the work done by Danbauchiet al. [28] in Zaria in which 30.0% of patients with stage III/IV HIV infection were found to have diastolic dysfunction. However, the higher prevalence in this study could be as a result of the higher number of cases recruited. Similarly, Hunt et al. in their work on impact of HIV infection on diastolic function and left ventricular mass found that HIV-infected patients had a higher prevalence of diastolic dysfunction and higher LVMI compared to controls [34]. These differences were not readily explained by differences in traditional risk factors and were independently associated with HIV infection.

In this study, the cases had lower E/A ratio compared to the control which was statistically significant (11.0% versus 3.0%). This agrees with

Variables	Male	Female	T value	p-value
	N=30	N=70		
	Mean (SD)	Mean (SD)		
Age (Years)	38.10 (1.39)	34.77 (1.16)	1.67	0.09
Body mass index (Kg/M ²)	23.08 (0.54)	21.99 (0.44)	1.43	0.16
Body surface area	1.78 (0.03)	1.59 (0.02)	5.39	0.001**
Pulse rate (Bpm)	86.90 (2.98)	85.99 (1.95)	0.26	0.79
Left ventricular mass (G)	184.63 (11.10)	140.69 (4.68)	4.32	0.001**
Left ventricular mass index (G/M ²)	104.33 (6.41)	87.61 (2.88)	2.76	0.007**
Relative wall thickness	0.55 (0.06)	0.46 (0.02)	1.79	0.08
Geometry	1.90 (0.18)	1.67 (0.11)	1.14	0.26
E:A ratio	1.65 (0.11)	1.50 (0.08)	1.03	0.31
Deceleration time (Ms)	161.20 (8.70)	172.57 (4.28)	1.31	0.19
Isovolumic relaxation time (Ms)	91.97 (4.07)	84.74 (2.49)	1.56	0.12
Left atrial diameter (Cm)	3.43 (0.09)	3.12 (0.06)	2.86	0.005**

Key: Data expressed as mean ± standard deviation, N=number of cases, **Statistically significant at p<0.01

Table 4: Clinical and echocardiographic parameters of male and female subjects.

Variables	Correlation co efficient (r)	P value
Left ventricular mass (g)	-0.303	0.816
LVMI (g/m ²)	-0.092	0.365
RWT	0.018	0.861
Geometry	-0.01	0.918
Deceleration time (ms)	0.197	0.049
IVRT (ms)	-0.0086	0.393
Diastolic function	-0.202	0.044
Left atrial diameter (cm)	0.006	0.956

Key: LVMI=Left Ventricular Mass Index, RWT=Relative Wall Thickness, IVRT=Isovolumic Relaxation Time.

Table 5: Correlation between CD4 count and variables in the cases with HIV/AIDS.

the work done by Martinez et al. [35] in which the ratios of the mitral E and A velocity of HIV patients were compared with healthy controls and those with HIV showed a significant reduction in their E/A ratio when compared with the normal controls.

Another significant finding in this study is prolongation of isovolumic relaxation time (IVRT) which was found in 24.0% of the cases studied. This corroborates with one large multicenter echocardiographic study in which asymptomatic HIV-infected patients had 34.6% lower E/A ratio and 19.7% longer isovolumic relaxation time than healthy adults [36]. Martinez et al. also found that the IVRT was prolonged in the patients with HIV infection. In a research carried out by Coudray et al. [37] LV diastolic function estimated by doppler echocardiography in HIV patients showed an increase in the IVRT and a decrease in the E-wave velocity when compared with healthy control. The African study by Longo Mbenza et al. [38] noted diastolic dysfunction in 80.0% of its study population and attributed it to systemic amyloidosis and concentric LVH developed by the HIV patients in the course of the study. Endocardial fibrosis is a noted finding in hearts of patients infected with the HIV and can account for the diastolic dysfunction in this group [39].

The prevalence of abnormal geometry in cases with HIV/AIDS was 50.0%. Concentric remodeling was found in 34.0% of the cases while LVH constituted 16.0% of the prevalence of which 8.0% had concentric hypertrophy and 8.0% had eccentric hypertrophy. Left ventricular geometry was assessed using the left ventricular mass index (LVMI) and relative wall thickness (RWT). The mean LVMI and RWT were higher in the cases than in the healthy control group. This study shows a negative correlation between LVMI and CD4+ count. Prior studies have evaluated LV mass among HIV-infected patients and the results have been conflicting [39,40] None has determined the prevalence of LVH in this population group. Barbaro reported increased LV mass in asymptomatic HIV patients compared to healthy controls. Lipshultz described a higher LV mass among children with HIV infection [40] Ather et al. [41] in their study found that HIV infection is associated with greater LV mass but not with a higher prevalence of LVH. In that study, RWT but not LV mass was associated with the degree of immunosuppression among HIV infected women.

Multiple factors may be involved in increasing LV mass in the setting of HIV infection. Several autopsy and animal studies have shown that HIV virions directly affect myocardial cells and are associated with the local release of cytokines and other factors leading to inflammation, myocarditis and dilated cardiomyopathy [6,39]. Alternatively, increases or decreases in LV mass have been suggested to be associated with opportunistic infections [42] and malnutrition.

Conclusion

Diastolic dysfunction and abnormal geometry were shown to be present even in asymptomatic sero positive carriers at the early stage of the HIV infection.

HIV-infected patients had a higher prevalence of diastolic dysfunction and higher left ventricular mass index (LVMI) compared to controls. And there was association between degree of immunosuppression and diastolic dysfunction as well as abnormal geometry, although these were statistically not significant. There was a higher prevalence of concentric remodeling amongst the HIV positive patients with abnormal geometry.

Limitations of this study

Limitations of this study include its cross-sectional design as a longitudinal

follow up would have provided further data on incidence and progression of abnormal left ventricular diastolic function and geometry.

Because of stigmatization, the cohorts of patients who present to the University of Port Harcourt Teaching Hospital for the treatment of this condition are mostly traders and artisans who are unlikely to afford treatment in private hospitals. The results, therefore, may not represent the affluent population that is of higher risk for cardiovascular events.

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