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Original Article

Impact of CD_4^+ lymphocyte count on left ventricular systolic function in newly diagnosed HAART naïve HIV/AIDS patients seen at University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State

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ABSTRACT

Background: *HIV-related cardiomyopathy is a notable complication of HIV infection attributed to various aetiologic factors including myocardial infection with HIV itself, opportunistic infections, nutritional deficiencies and cardiotoxicity from therapeutic or illicit drugs. These factors become more manifest as CD_4^+ count decreases in the clinical course of HIV infection.*

Method: *This was a cross-sectional case-control study. One hundred newly diagnosed HAART naïve HIV/AIDS subjects and one hundred age and sex matched HIV negative controls were recruited and evaluated clinically. CD_4^+count of the cases were estimated. Left ventricular function was assessed using transthoracic echocardiography.*

Results: *Systolic dysfunction assessed using ejection fraction was more common in the cases than in the control group (26% versus 5%). There was statistically significant difference in the systolic function of the two groups (p=0.001) and a significant positive correlation between the ejection fraction and CD_4^+ count (r=0.310, p=0.002). Subjects with CD_4^+ count <200 cells/µL were more likely to have systolic dysfunction (OR=3.33, P=0.01).*

Conclusion: *Left ventricular systolic dysfunction was shown in this study to be more common in people with HIV/AIDS than in the control group and there was a significant positive correlation between $CD4^+$ lymphocyte count and left ventricular systolic function.*

Recommendation: *The heart may be a marker of the HIV infected patient's overall health, and a decline in cardiac function may suggest low CD_4^+ count and should trigger more comprehensive evaluation and possibly early intervention of the patient.*

Keywords: *Systolic function, $CD4^+$ count, HIV, ejection fraction, echocardiograghy.*

INTRODUCTION

Infection with the Human Immunodeficiency Virus (HIV) and its sequelae, Acquired Immunodeficiency Syndrome (AIDS) has today assumed global importance as it continues to ravage many nations especially in the Sub Saharan Africa including Nigeria.[1]

There is growing recognition of increased cardiovascular risk among human immunodeficiency virus infected patients.[2]

Cardiovascular disease in HIV infection may be seen as a direct consequence of the virus, or as a consequence of anti-retroviral therapy (like lipodystrophy syndrome) or both.[3] Cardiovascular complications of HIV infection may result in increased risk of myocardial Infarction (MI)[4], Stroke[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 (LV) dysfunction has also been described in patients with human immunodeficiency virus infection.[10-11] For instance; both diastolic and systolic dysfunctions have been shown to be present even in asymptomatic seropositive carriers at the early stage of HIV infection.[12-13]

Danbauchi et al found that 10% of the studied subjects had diastolic dysfunction and 3.6% had depressed ejection fraction on echocardiography after 1 to 2 years of ARV treatment.[14]Okeahialam and Anjorin[15] in a local study described cardiac symptoms in 58% of AIDS patients studied.

In the clinical course of HIV infection, CD4 Lymphocyte count decreases with disease progression. When CD4 Lymphocyte count falls below 200 cells/µl, the incidence of opportunistic infection increases.[16-18]Since CD4 Lymphocyte count and opportunistic infection constitute the major components for clinical staging of HIV infections, [19] both have been considered to be correlated with LV dysfunction in the disease process.

However, literature reviews have yielded variable results. Currie et al[20], Herskowitz et al,[12,21,] Barbaro et al,[6] and Barbaro and Di Lorenzo[22] demonstrated that LV dysfunction was associated with lower CD4 Lymphocyte counts, while Blanchard et al,[23] showed no significant correlation between CD4 Lymphocyte count and abnormal LV function. The purpose of our study was to determine the impact of CD4 lymphocyte count on left ventricular systolic function in newly diagnosed HAART naïve HIV/AIDS patients attending a tertiary health institution.

MATERIALS AND METHODS

The study was a descriptive cross sectional case-control study. 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.

Clinical and Sociodemographic Characteristics: Recruited subjects 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 0.5cm.

Body mass index was calculated as body weight in kilograms divided by the square of the height in meters. Body mass index status was classified according to the WHO criteria as normal weight (18.5 – 24.9kg/m2), overweight (25 – 29.9kg/m2), class I obesity (30.0 – 34.9kg/m2), class II obesity

(BMI 35.0 – 39.9kg/m2), and morbid obesity (BMI ≥ 40 kg/m2).[24] Those that are obese were excluded from the study.

Body surface area was calculated using the formula of Dubois[25] which is body surface area in m^2 = 0.0001 x (71.84) x (weight in $kg^{.4250}$) x (height in $m^{0.725}$)

Blood pressure was measured with a standard (Accosson) Mercury Sphygmomanometer (cuff size 12.5cm x 40cm) on the patients' right arm in the seated position with feet on the floor after at least a five minute rest. Tight clothing was removed from the arm and the arm was supported at the level of the heart. The cuff was placed over the brachial artery, inflated to about 30mmHg above the occlusion of the radial pulse, and subsequently deflated slowly (~2mm/sec). The systolic and diastolic blood pressures were taken at Korotkoff phases 1 and 5 respectively to the nearest 2mmHg. The average of two blood pressure measurements taken 5 minutes apart was used. Those found to be hypertensive were excluded from the study.

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. Subjects found to have abnormalities were advised and referred appropriately for further management.

Laboratory Assays: Venepuncture was carried out using a peripheral vein and 7mls of blood was collected from each subject, 5mls of which was put into lithium heparin bottles for assessment of fasting lipid profile, and serum creatinine. Two mls was put into fluoride oxalate bottles for fasting plasma glucose. Fasting plasma glucose and serum creatinine were analyzed to exclude patients with diabetes mellitus or chronic kidney disease respectively. Serum creatinine was used to calculate the estimated glomerular filtration rate (GFR) using the Cockcroft-Gault formula.[26] Patients with estimated GFR levels 60ml/min or below[27] and those with fasting plasma glucose levels of 7.0mmol/1 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. Fasting HDL was measured with the precipitation method. LDL cholesterol values were calculated using the Friedewald equation when the triglyceride level was less than 4.0mmol/L: LDL = TC – (HDL + TG/2.2).[28] Abnormal lipid profile was defined as elevated triglyceride with TG >1.7mmol/L, hypercholesterolemia with TC > 5.2mmol/L, low high density lipoprotein cholesterol with HDL-c <1.03mmol/L and elevated low density lipoprotein cholesterol LDL-c > 3.0mmol/L1.[29] Patients with abnormal lipid profile were excluded from the study. Biochemical parameters were analyzed in the chemical pathology laboratory of UPTH.

Whole blood samples were collected by venepuncture using a 10 milliliters hypodermic syringe and needle into EDTA anticoagulated tubes (5 milliliters) and non-anticoagulatedtubes (5milliliters). Sera derived from the non-anticoagulated tubes were screened and confirmed for HIV 1 and 2 infection using a double ELISA confirmatory method involving the World Health Organization (WHO) approved immunocomb HIV 1 and 2 kits (Orgenics, Israel) an immunochromatographic test for the qualitative and differential detection of antibodies in HIV 1 and 2 and Genscreen HIV 1 and 2 ELISA kits (Bio Rad, France) – an in vitro qualitative enzyme immunoassay (EIA) test for the detection of antibodies to HIV 1 and 2 in human serum. CD4 T-helper lymphocyte count was estimated using the flow cytometry technique. Hematological parameters were analyzed in the Hematology laboratory of UPTH.

ECHOCARDIOGRAPHY (TRANSTHORACIC)

Echocardiography was performed by a single sonographer who was blinded to each participant's HIV status and clinical characteristics 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. All recordings and measurements were made using standard parasternal long axis and short axis views and apical 4-chamber views. Echocardiography was performed according to the recommendations of the American Society of Echocardiography (ASE).[30] LV ejection fraction was calculated by Teicholz's[31] formula.

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 ± 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

Participant Characteristics: One hundred subjects with HIV/AIDS in the medical wards and retroviral clinics of the university of Port Harcourt teaching hospital were included in this study. One hundred age and sex matched HIV negative individuals were included as controls. The mean age of cases with HIV/AIDS was 35.7±10.13 years and females were more than males in a ratio of 2.3:1 (Table 1)

Table 1.shows that age and sex distribution of the study group and the control group.

	CASE n (%)	CONTROL n (%)
SEX		
MALE	70 (70.0)	64 (64.0)
FEMALE	30 (30.0)	36 (36.0)
TOTAL	100 (100.0)	100 (100.0)
AGE GROUP		
20-29 YEARS	30 (30.0)	21 (21.0)
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)
TOTAL	100 (100.0)	100 (100.0)

Key:n= number of cases/controls, %= percentage

CLINICAL PRESENTATION OF THE CASES

Sixty (60%) of the cases presented with fever, forty seven (47%) presented with cough either from pulmonary tuberculosis or other opportunistic infections. Sixty seven (67%) presented with weight loss, forty five (45%) presented with easy fatigability and thirty (30%) presented with breathlessness (shortness of breath 21(21%), orthopnea 5(5%) and PND 4(4%)). Only five (5%) of the cases had bilateral leg swelling (Table 2).

Table 2 Shows symptoms and signs of HIV/AIDS patients in the study group.

SYMPTOMS	FREQUENCY	PERCENTAGES (%)
FEVER	60	60%
WEIGHT LOSS	67	67%
COUGH	47	47%
EASY FATIGUABILITY	45	45%
SHORTNESS OF BREATH	21	21%
ORTHOPNOEA	5	5%
PAROXYSYMALNOCTURNALDYSPNOEA	4	4%
LEG SWELLING	5	5%
ABDOMINAL SWELLING	2	2%
DIARRHOEA	25	25%
PLEURITIC PAPULAR ERUPTIONS(PPE)	30	30%
HERPETIC RASH	6	6%
ORAL THRUSH	13	13%
SIGNIFICANT LYMPHADENOPATHY	19	19%

Key: % = percentage

Echocardiographic Findings

Systolic dysfunction assessed using ejection fraction was higher in the cases than in the control group (26% versus 5%). Among the 26 cases with systolic dysfunction, 17(17.0%), 8(8.0%) and 1(1.0%) had mild, moderate and severe systolic dysfunction respectively. All the 5 individuals in the control group had mild systolic dysfunction. There was statistically significant difference in the systolic function of the two groups (p=0.001) (Table 3).

Among the forty (40.0%) cases with CD4 count < 200 cells/µl, 24(60.0%), 8(20.0%), 7(17.5%) and 1(2.5%) had normal ejection fraction, mild systolic dysfunction, moderate systolic dysfunction and severe systolic dysfunction respectively. And of the forty three (43%) cases with CD4 count ranging between 200-499 cells/µl, 35(81.4%), 7(16.3%) and 1(2.3%) had normal systolic function, mild systolic dysfunction and moderate systolic dysfunction respectively. While seventeen (17%) of the cases with CD_4 count ≥ 500 cells/µl had normal systolic function and mild systolic dysfunction in 15(88.2%) and 2(11.8%) persons respectively. There was no statistically significant difference in the systolic function among these three groups (x^2=11.45, p=0.08) (Table 4). However, there was statistically significant difference among the subjects that had systolic dysfunction in the three groups (x^2=15.047, p=0.0046) (Table 4).

Table 3. Shows the Systolic Function of the Entire Study Population

SYSTOLIC FUNCTION	CASES n (%)	CONTROLS n (%)	χ^2	p-value
NORMALSYSTOLIC FUNCTION	74(74.0%)	95(95.0%)	18.16	0.001**
MILD SYSTOLIC DYSFUNCTION	17(17.0%)	5(5.0%)		
MODERATE SYSTOLIC DYSFUNCTION	8(8.0%)	0		
SEVERE SYSTOLIC DYSFUNCTION	1(1.0%)	0		

Key: n = number of cases/control, % = percentage, ** = Significantly different from control at p < 0.01

Table 4.CDC CD4 Count Classification of the Systolic Function of the HIV/AIDS Patients

	CDC CLASSIFICATION OF CD4 COUNT				
SYSTOLIC FUNCTION	<200 cells/µl	200 - 499 cells/µl	>500 cells/µl	χ^2	p-value
NORMAL SYSTOLIC FUNCTION	24(60.0%)	35(81.4%)	15(88.2%)	11.45	0.08
MILD SYSTOLIC DYSFUNCTION	8(20.0%)	7(16.3%)	2(11.8%)		
MODERATE SYSTOLIC DYSFUNCTION	7(17.5%)	1(2.3%)	0		
SEVERE SYSTOLIC DYSFUNCTION	1(2.5%)	0	0		

Key: % = percentage, CDC = Center for Disease Control

CORRELATION OF CD4 COUNT WITH CLINICAL AND ECHOCARDIOGRAPHIC PARAMETERS

AGE: There was negative correlation between the CD4 count and age which was statistically insignificant (r = - 0.173, p = 0.085)

BODY MASS INDEX: There was a positive correlation between the CD4 count and BMI which was statistically insignificant (r = 0.161, p = 0.109)

PULSE RATE: There was a negative correlation between CD4 count and pulse rate which was statistically significant (r = - 0.289, p = 0.004).

EJECTION FRACTION: There was a positive correlation between the CD4 count and the ejection fraction which was statistically significant (r = 0.310, p = 0.002).

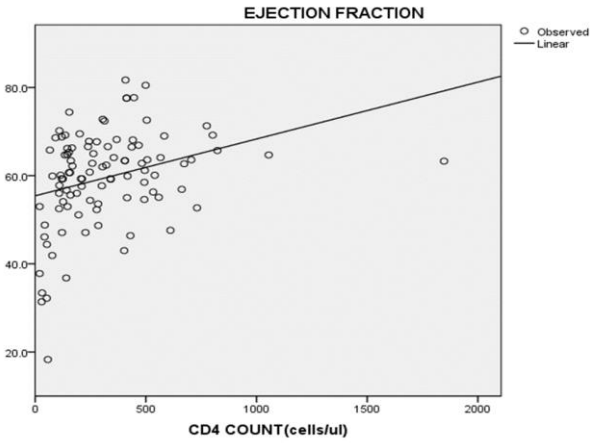

Figure 1 Correlation graph showing relationship between CD4 count and ejection fraction.

MULTIPLE REGRESSION ANALYSIS

Multiple linear regression analysis was used to assess how much of the variance in ejection fraction could be explained by the subjects age, pulse rate, body mass index (BMI) and CD4 count.

EJECTION FRACTION: The variables combined explained 18.8% of the variance observed (F = 12.567, P<0.01).

CD4 count was the strongest contributor to the ejection fraction, accounting for 57.4% (p = 0.001) of the variation in ejection fraction. The BMI accounted for 12.1% (p = 0.42), the subjects age accounted for 11.3% (p = 0.43) and the pulse rate accounted for 3% (p = 0.85) of the total variation in ejection fraction.

ASSOCIATION BETWEEN AIDS (CD4 COUNT < 200 cells/µl) AND LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

The measure of association between AIDS (CD4 count < 200 cells/µl) and left ventricular systolic dysfunction was assessed using the odds ratio (Table 5).

Table 5 Association Between AIDS (CD4 Count < 200 cells/µl) and LEFT Ventricular Systolic Dysfunction

	SYSTOLIC DYSFUNCTION **YES**	SYSTOLIC DYSFUNCTION **NO**	TOTAL
AIDS (CD4 COUNT <200 CELLS/µL) **YES**	16	24	40
AIDS (CD4 COUNT <200 CELLS/µL) **NO**	10	50	60
TOTAL	26	74	100

Odds ratio = (a/b) ÷ (c/d)

= (16/24) ÷ (10/50) = 3.33

Thus, cases with AIDS (CD4 count < 200 cells/µl) were 3.33 times more likely to develop systolic dysfunction than cases without AIDS (CD4 count > 200 cells/µl and this was statistically significant. (At 95% confidence level, the confidence interval is 1.32 to 8.4 and p = 0.01).

DISCUSSION

SOCIO-DEMOGRAPHIC CHARACTERISTICS OF THE CASES WITH HIV/AIDS

This was a cross-sectional comparative study of 100 HIV/AIDS subjects who have never received HAART seen in a tertiary health institution and 100 healthy controls matched for age and sex. The study set out to determine the prevalence of left ventricular systolic dysfunction among newly diagnosed HAART naïve HIV/AIDS patients and to determine the relationship between left ventricular systolic dysfunction and CD4 lymphocyte count.

The study cohort consisted of mostly female patients. The female preponderance in this study corroborates with the UNAIDS[32]finding that of the 33.3 million adults living with HIV/AIDS, more than half are women. Women are more vulnerable to HIV infection than men as a result of the following factors: Biologically women have large mucosal surface and micro lesions which can occur during intercourse which may be entry points for the virus. Very young women are even more vulnerable in this respect. There are more viruses in sperm than in vaginal secretions. As with sexually transmitted infections (STIs), women are at least four times more vulnerable to infection and the presence of untreated STIs is a risk factor for HIV infection. Lastly coerced sex which is commoner in women increases the risk of micro lesions.

Economically financial or material dependence on men means that women cannot control men, with whom and in what circumstances they have sex. Many women have to exchange sex for material favors, for daily survival. There is formal sex work, but there is also this exchange which in many poor settings, is many women's only way of providing for themselves and their children.[33]

Socially and culturally, women are not expected to discuss or make decisions about sexuality and they cannot request, let alone insist on using condoms or any form of protection. If they request condom use or refuse sex, they often risk abuse, as there is a suspicion of infidelity. The many forms of violence against women mean that sex is coerced which is itself a risk factor for HIV infection. Lastly for married and unmarried men, multiple partners (including sex workers) are culturally accepted.[33]

Most of the patients were in the age group 30-39 years with a mean age of 35.7±10.13 years. This is consistent with the study of Danbauchi et al[14] in Zaria on cardiac manifestations of stage III and IV HIV/AIDS compared to subjects on ARV which recruited subjects with a mean age of 35±10.4 years.

CLINICAL CHARACTERISTICS OF THE CASES WITH HIV/AIDS

Chronic weight loss is a common finding in HIV/AIDS and this condition has been described by some authors as wasting disease. In the present study, 9% of the cases were underweight probably from chronic debilitating disease of HIV infection; associated opportunistic infections like tuberculosis and HIV associated malignancies.

There was statistically significant difference in the pulse rate of the cases compared to controls (p=0.001). Sinus tachycardia was present in 15.0% of the cases. Saniet al,[34]reported a high prevalence of sinus tachycardia in their work on electrocardiographic abnormalities in Nigeria AIDS patients. The heart rate is known to increase as body temperature increases. Unexplained fever is a feature of myocarditis and myocarditis can be caused by HIV disease. The impact of anemia can also explain the sinus tachycardia seen in these patients.

However, some workers view tachycardia as being due to excessive sympathetic stimulation which could be from autonomic imbalance or stimulation of beta-receptors by the gp120 protein of HIV virus[35]but emotion maybe another contributory factor.

DISTRIBUTION OF CD4 LYMPHOCYTE COUNT AMONG CASES WITH HIV/AIDS

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.[19] The range of CD4+ count in the cases was from 20cells/µl to 1847cells/µl with a mean of 318.51 ± 261.66cells/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 to 499cells/µl. while only seventeen (17%) had CD4 count of 500cells/ 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.[3, 36]

ECHOCARDIOGRAPHIC FINDINGS

SYSTOLIC DYSFUNCTION IN CASES WITH HIV/AIDS

Left ventricular systolic dysfunction accessed by ejection fraction was a notable finding in this study. Systolic dysfunction was found in twenty six (26.0%) of the cases. Among the cases with systolic dysfunction 17(17.0%), 8(8.0%), and 1(1.0%) had mild, moderate and severe systolic dysfunction respectively. The cases had lower ejection fraction compared to the control. Depressed ejection fraction has been attributed to elaboration of inflammatory cytokines that depresses the myocardium notably nitric oxide[37]. Studies have shown that the myocardium of these patients stain more intensely for nitric oxide.[37]Autoimmunity has also been implicated and auto-antibodies have been seen in greater concentration[37]. This may go a long way to explain the globular nature of the hyperkinesia seen in some of these patients implicating a systemic rather than a local elaboration of cytokines.

In another study, HIV- infected individuals with dilated cardiomyopathy were much more likely to have myocarditis and had a broader spectrum of viral infections than HIV- negative patients with

idiopathic dilated cardiomyopathy.[5] Also levels of TNF-α and induced nitric oxide synthase were higher in myocytes from the HIV-infected patients with dilated cardiomyopathy, particularly those with viral co-infections and levels varied inversely with the CD4 count[37].Dilated cardiomyopathy has been noted to occur late in the course of HIV infection and is usually associated with significantly reduced CD4 count. There is no clear correlation between the CD4 count and the occurrence of dilated cardiomyopathy in HIV positive patients but it has been shown to occur at a CD4 count less than 400cells/µl and dilated cardiomyopathy was strongly associated with a CD4 count of less than 100cells/µl.[6]

CONCLUSION AND RECOMMENDATION

Left ventricular systolic dysfunction was shown in this study to be more common in people with HIV/AIDS than in the control group and there was a significant positive correlation between $CD4^+$ lymphocyte count and left ventricular systolic function.

The heart may be a marker of the HIV infected patient's overall health, and a decline in cardiac function may suggest low CD_4^+ count and should trigger more comprehensive evaluation and possibly early intervention of the patient.

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SOURCE OF SUPPORT

Department of Internal Medicine, University of Port Harcourt Teaching Hospital permitted us to use the departmental echocardiographic machine

CONFLICT OF INTERESTS: No Conflicts of Interest

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