

The Relationship Between Cd4 Count And Echocardiographic Abnormalities In Hiv Patients.

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ABSTRACT:

Background: Human Immunodeficiency Virus (HIV) is CD4 T lymphocyte depletory and the concentration of CD4 T lymphocyte in the blood has been used to classify the HIV disease condition. Cardiac complications in HIV disease are believed to reflect advanced and late presentation of the disease. HIV cardiac manifestation is however of varying types. Dilated cardiomyopathy also known as HIV cardiomyopathy is known to manifest at CD4 count < 200cells/l and pericardial effusion has been associated with opportunistic co infection which is present in advanced disease with low CD4 receptor cells. This study seeks to corroborate these findings and ascertain the relationship between other cardiac abnormalities with CD4 T lymphocyte count.

METHODS: Study cases were randomly selected amongst adult patients aged 18 years and above, who fulfilled the inclusion criteria, presenting at the University of Port Harcourt Teaching Hospital with a diagnosis of HIV disease. The study period was from July 2010 to July 2014. CD4count and other parameters were assessed for all HIV positive patient. Pattern of disease in relation to CD4 count was assessed and simple linear correlation performed with echocardiographic parameters.

RESULTS: The study subjects were 200 HIV positive patients:76 (38%) males and 124 (62%) females with a male to female ratio of 1:1.6. They were aged between 18 yrs. and 56 years, with a mean \pm SD age of 33.13 ± 8.4 years. The controls were made up of 100 individuals who met the inclusion criteria:64 females (64%) and 36 males (36%) with age range between 19 and 54 years with a mean \pm SD age of 31.82 ± 8.72 years. The mean \pm SD of CD4 count of the study population was $246.51 + 176$ cells/l. Fifty percent (50%) of Cardiac abnormalities occurred commonly in patients with CD4 count lower than 200cells/l. Some cardiac abnormalities continued to occur despite appreciation in CD4 lymphocyte count level.

CONCLUSION: HIV heart disease occurs commonly with CD4 count less than 200cells/l. Some conditions like asymptomatic depressed ejection fraction, diastolic dysfunction and pulmonary hypertension do not follow a particular pattern relative to CD4 count. HIV cardiomyopathy, (DCM) and pericardial effusion occurred almost exclusively with CD4 count less than 200cells/l and should be considered surrogate markers of advanced HIV disease and AIDS. Correlation by simple linear correlation showed correlation between CD4 count and left atrial size(.058,.001) and Left ventricular end systolic area(.037,.020).

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I. Introduction

HIV effect on the heart is via either any or a combination of three mechanism. Direct viral replication in cardiac mitochondrial, indirect via opportunistic infections and from cardiotoxicity from treatment with highly acting antiretroviral therapy HAART^[1]. HIV is well known to penetrate cells that bear CD4 receptors, notably the cardiac interstitial cells^[2,3]. The myocytes because they do not bear CD4 receptors were thought to evade invasion by the HIV. However, studies^[4] have isolated viral sequences in cardiac myocytes obtained from endocardial biopsies. HIV accesses the cardiac cells through other pathways independent of CD4 receptors. HIV has been shown to access the cardiac myocytes by inducing gp 120, tat and cytokine apoptotic signalling^[5]

HIV is CD4 T lymphocyte depletory and the concentration of CD4 T lymphocyte in the blood has been used to classify the disease condition^[6]. With CD4 count depletion the heart becomes prone to opportunistic infections, viral, bacterial and fungal infections are heightened and these have all shown to play a role in development of cardiac disease in HIV positive patient. In addition, the presence of HIV cells in the Interstitials and the myocytes initiates fibrotic process which has been largely implicated as a cause of cardiac dysfunctions and heart failure^[7,8].

In addition, Endothelial dysfunction and injury have been described in HIV infection^[9]. The elaboration of circulating endothelial markers in HIV positive individuals has suggested heightened endothelin injury in this group of patients. Coronary endothelium CXCR4, CCR3 and CCR2A co-receptors and chemokine activation has been proposed as an entry route for HIV cells into the vascular endothelium^[9]. 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 but it has been shown to occur at a CD4 count less than 400 CD4 cells/ml and dilated cardiomyopathy was strongly associated with a CD4 count of less than 100 cells/ml^[10].

Pericardial Effusion is an important pointer to possible AIDs or late manifestation of HIV as it is usually evidence of opportunistic infection^[11]. HIV-infected patients with pericardial effusions generally have a lower CD4 count, marking more advanced disease, than those without effusions. Opportunistic organisms differ depending on geographically prevalent diseases. A study^[12] of 22 AIDS patient who underwent a pericardial window procedure identified causative organism in 7. The causes were Staphylococcus aureus (1), mycobacterium tuberculosis (1) adenocarcinoma (2) and lymphoma (3). Lymphomas are also evidence of AIDs or late-stage disease^[13,14]

In a study of 82 patients^[15] with HIV and pulmonary arterial hypertension, the CD4 count was independently associated with survival. This study would expect a higher percentage of HIV heart complication amongst subjects with CD4 count less than 200 cells/l.

II. Method

STUDY DESIGN:

This was a prospective, descriptive, cross-sectional study.

STUDY SITE:

This study was conducted at the University of Port Harcourt Teaching Hospital. This hospital serves as a major referral centre for Rivers state, Bayelsa state and its subregions. It is situated in Choba. Port Harcourt is a cosmopolitan city with residents from all over the country.

ETHICAL CONSIDERATION:

Clearance for this study was obtained from the Ethical Committee of the University of Port Harcourt Teaching Hospital. At all stages the researcher adhered to the guidelines of the ethical committee and standard research protocol. All case and control subjects gave informed consent.

STUDY POPULATION: The minimum number of patient required for this study was calculated from the method of kish:^[16]

$$NF = \frac{n}{1 + (n) / N} \quad \text{And} \quad n = p g z \frac{2}{d} 2$$

$$n = \frac{0.5 * 0.5 * 1.96 \frac{2}{0.05} 2}{2} = 384$$

$$NF = \frac{384}{1 + (384) / 380} = \frac{384}{2.01} = 190$$

NF= 190

NF= final sample size

n= the desired sample size

z= the standard normal deviation usually set at 1.96 which corresponds to the 95% confidence level .

p= proportion of likely patient with cardiovascular disease estimated at 50%

q= 1.0 - p =50%

d= degree of accuracy desired 0.05

N = estimation of population size i.e new patients with HIV disease managed in UPTH port Harcourt annually = 500.

PATIENTS: The study sample was made up of 200 HIV positive patients, who were antiretroviral naive. They were randomly selected without fore knowledge of their CD4+ count. The random numbers were generated using the table of random numbers`

INCLUSION CRITERIA FOR PATIENTS

Newly diagnosed HIV positive, antiretroviral naïve individuals, irrespective of CD4 count and who have consented to be a part of the study.

EXCLUSION CRITERIA FOR PATIENTS

1. Hypertensives.
2. Diabetics.
3. Patients with no significant history of alcohol ingestion. (Patients that consume less than 30g/day)
4. History of cigarette smoking.
5. Poor Echocardiography window.

CONTROLS:

Normal values for echocardiographic variables were generated by analysing echocardiograms of 100 healthy adults with age range 18-80yrs of age, with no history of cardiovascular disease or any other medical condition. They were of comparable ages and sex with the HIV positive patients.

CLINICAL EVALUATION:

Baseline demographics,clinical history and detailed physical examination of all subjects were carried out including their age, .gender, height, weight and baseline blood pressure.Packed cell volume and fasting blood sugar was assessed.

HIV CONFIRMATION: Double Elisa using a rapid screening kit was used to confirm a diagnosis of HIV infection. This is the method used in University of Port Harcourt Teaching Hospital ^[17]. This was also used in the Enugu study by Ikechebelu et al. The World Health Organization(WHO) endorses alternative algorithm for use in recourse-limited setting where a double Elisa confirms HIV positivity.^[18]

CD4 COUNT:CD4 count was assayed using the Apogee A50 micro flow cytometer.

ECHOCARDIOGRAPHY

All subjects had Echocardiography done, using the Aloka prosonic SSD 4000 after due explanation to the patients and controls alike. Subjects were asked to lie in a steep lateral decubitus position with the patients left arm extending over their heads.

Standard M-Mode, 2D, Doppler(pulsed, continuous and colour wave) was performed on all subjects.The area of the chambers was used as opposed to the internal diameter following the guidelines of the American Society of Echocardiography.^[18]

A predefined imaging protocol was used. For each variable, two representative beats were analysed and the mean results calculated. Echocardiography was carried out before checking the result for the CD4 count to eliminate bias. Supervisor cross checked random samples of echocardiography findings, for quality control. The bills of the investigations were not borne by the patients.A waiver and project grant was obtained from the authorities of the University of Port Harcourt Teaching Hospital.

III. Results

TABLE 1

Comparison of demographic data of cases and controls

CHARACTERISTICS	CASES N=200	CONTROLS N=100	t-test	p-value
<i>Gender</i>				
<i>Male</i>	76	36		
<i>Female</i>	124	64		
<i>Mean Age ± SD</i>	33.13 ± 8.4	32.83 ± 8.72	0.11	0.91
<i>Age Range</i>				
<i>BMI(kg/m²)</i>	18-53	19-50		
	21.09 ± 4.0	25.06 ± 6.2	-6.40	<0.001*
<i>Systolic BP(mmHg)</i>	113.09 ± 16.1	114.9 ±22.3	-1.69	0.094
<i>Diastolic BP(mmHg)</i>	71.87 ± 11.3	72.72 ± 15.11	0.52	0.60

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Pulse Rate(beats/min)	90.24 ± 18.3	67.92 ± 15.71	7.04	<0.001*
CD4 Count(cells/l)	246.51 ± 176			

P values < 0.05 are significant

TABLE 2: CLINICAL AND BIOCHEMICAL PARAMETERS AMONG HIV CASES ACCORDING TO SEX.

PARAMETER	FEMALES	MALES	t-test	P-Value
PCV(%)	33.14 ± 8.66	28.67 ± 7.40	-3.86	0.000*
DIASTOLIC BP(mmHg)	71.6 ± 14.0	71.31 ± 12.04	0.791	0.430
SYSTOLIC BP (mmHg)	114.45 ± 20.58	111.13 ± 17.27	1.886	0.064
PULSE RATE (Beats/min)	85.31 ± 18.8	92.17 ± 19.9	. 2.21	0.029*
CD4 COUNT (Cells/l)	251.34 ± 188.6	237.91 ± 171.0	-0.050	0.618
BMI Kg/m ²	20.71 ± 4.2	21.05 ± 4.41	0.313	0.744

P values < 0.05 are significant

TABLE 3: CD4 COUNT

RANGE OF CD4 COUNT(cells/l)	NO OF CASES	PERCENTAGE(%)
0-100	43	21.5
101- 200	57	28.5
201- 300	37	18.5
301- 400	26	13
401- 500	21	10.5
>500	16	8

Table 4: COMPARISON OF HEART ABNORMALITY ECG :ECHO

TEST MODALITY	TOTAL	NORMAL	ABNORMAL	% PATIENT WITH CARDIAC ABNORMALITIES
ECHOCARDIOGRAPHY	200	63	137	68.5%
ELECTROCARDIOGRAPHY	156	55	101	64.74%

TABLE 5 : THE SPECTRUM OF ECHOCARDIOGRAPHIC CARDIAC ABNORMALITIES IN HIV POSITIVE PATIENTS IN RELATION WITH CD4 COUNT.

CARDIAC ABNORMALITIES	1- 100	101 - 200	201- 300	301 - 400	401- 500	> 500
DCM	4	3				
PERICARDIAL EFFUSION	26	34				
RWMA	3	4		1	2	
DEPRESSED LV EF(LVsystolic dysfunction)	4	4	6	3	2	
DEPRESSED RV EF(RV systolic dysfunction)	4	1	1		1	
BOTH DEPRESSED LY AND RV EF (Biventricular Dysfunction)	7	3	1	6	1	
PULMONARY HYPERTENSION	1	9	1	1	1	2
ISOLATED LV DIASTOLIC DYSFUNCTION	19	24	3	3	6	
ISOLATED RV DIASTOLIC DYSFUNCTION	6	3	1	1		1
ISOLATED LV AND RV DIASTOLIC DYSFUNCTION	17	14	4			1
AORTIC ROOT DILATATION			1	1	1	

DCM : dilated cardiomyopathy, RWMA: regional wall motion abnormality, EF :ejection fraction, MR: mitral regurgitation, TR: tricuspid regurgitation. PR: pulmonary regurgitation.AR: Aortic regurgitation

TABLE 5. SIMPLE LINEAR CORRELATION BETWEEN CD4 COUNT AS PREDICTOR AND VARIOUS ECHO PARAMETERS.

PARAMETERS	B	SE β	R	R ²	P-value
LVM/BSA(kg/m ²)	-0.003	0.020	0.132	0.000	0.88
LAA(cm ²)	0.014	0.005	0.241	0.058	0.005*
LAA/M(cm ² /m)	.0006	0.001	0.006	0.000	0.94
RAA(cm ²)	0.003	0.002	0.138	0.019	0.11
RAA/M(cm ² /m)	0.002	0.001	0.141	0.20	0.10
LVEDA(cm ²)	0.002	0.003	0.056	0.003	0.51
LVESA(cm ²)	0.005	0.002	0.193	0.037	0.02*
LVEDA/M(cm ² /m)	0.0011	0.002	0.052	0.003	0.55
LVEF(%)	0.0071	0.059	0.102	0.010	0.23
RVEDA(cm ²)	0.003	0.002	0.098	0.001	0.26
RVEDA/M(cm ² /m)	0.001	0.001	0.099	0.010	0.26
RV EF(%)	0.002	0.007	0.002	0.000	0.98
LV E/A	0.003	0.000	0.119	0.014	0.17
LVCO(l/min)	0.003	0.001	0.168	0.028	0.53
RVCO(l/min)	0.001	0.002	0.54	0.003	0.54
PASP(mmHg)	0.002	0.005	0.04	0.001	0.689
PADP(mmHg)	0.004	0.071	0.01	0.815	0.416

P values <0.05 are significantLVDT: Left ventricular deceleration time; RVDT right ventricular deceleration time; LVEF: left ventricular ejection fraction; RVEF: Right ventricular ejection fraction; LVCO: left ventricular cardiac output RVCO: Right ventricular cardiac output; PASP: pulmonary artery systolic pressure, PADP; pulmonary artery diastolic pressure;LAA/m:left atrial area indexed for height RAA/m: right atrial area indexed for height,LVEDA/M: left ventricular end diastolic area indexed for height RVEDA/m : right ventricular end diastolic area indexed for height LVESA/m: left ventricular end systolic area indexed for height RVESA/m: right ventricular end systolic area indexed for height.LVM/BSA: left ventricular mass indexed for body surface area. LVE/A:ratio of Mitral inflow measurement of E-velocity to A velocity, RVE/A: :ratio of tricuspid inflow measurement of E-velocity to A velocity.* significant=p value<0.05. (SE β =standard error of slope, r- correlation co-efficient.

IV. Discussion

Some cardiovascular parameters were significantly different between the HIV and controls. The pulse rate was faster(t-7.04,p-0.001) with a range of 55 to 137 beats/min and mean± SD of 90.83 ± 16.6 beats/min for HIV populace and controls ranged from 65- 95beats/min with a mean ± SD of 69.62 ± 11.5beats/min. The HIV had significantly lower(t-6.40,p-0.001) BMI for HIV patients relative to controls with mean± SD of 21.22. ± 3.50 kg/m²(range 14.09 - 33.8kg/m²) and 25.71.± 4.7 kg/m²(range of 15.41-36.33kg/m²) There were no significant differences in blood pressure for HIV and Controls with systolic blood pressure (HIV) range from 70-140 mmHg with a mean ± SD of 114.02± 12.9mmHg and (controls) range of 100-140 mmHg with a mean± SD of 117.95 ± 11.9 mmHg.For diastolic blood pressure(HIV) ranged from 70 - 90mmHg with a mean± SD: 72.44.± 9.5 mmHg. Controls had a range of 50- 90 mmHg with a mean± SD of 74.63 ± 9.38 mmHg.

The mean CD4 count of the patients in this study was 246.51 + 176cells/l, there was no significant difference in CD4 count between sexes. The range was from 26-936cells/l. AIDS has been defined as CD4 count ≤ 200cells /l. One hundred (100) patients fell into this category accounting for 50 % of the study cases. Eight four (42%) patients had CD4 count between the range of 201 to 500 cells/l. While only 16(8%) had CD4 count of above 500. This explains the high prevalence of cardiac abnormalities seen in this study. The prevalence of cardiac abnormalities in this study was 68.5% with echocardiography and 64.5 % by electrocardiography as seen in table 4.

Table 5 reveals all cardiac abnormalities seen on Echocardiography relative to CD4 count. Most cardiac abnormalities occurred below CD4 count <200cell/l, however some heart manifestation continued to appear even with higher CD 4 count. This was particularly so for LV and RV depression without chamber dilatation. Asymptomatic LV depressed ejection fraction also termed LV systolic dysfunction^[19] is a common manifestation of HIV heart disease, and it is important to note that it can be present regardless of CD4 count. This also the case with diastolic dysfunction and pulmonary hypertension in this study.

However, dilated cardiomyopathy and pericardial effusion appears to be isolated markers of late disease or advanced disease and a possibility of AIDs should be entertained when they are encountered. This is most likely from opportunistic infection that are heightened in this stage of the HIV infection as well as the increased viral load in advanced disease state.

A simple linear correlation carried out between CD4 lymphocyte count and the echocardiographic parameters, showed a significant correlation with left atrial area (LAA)(0.58,.001) and left ventricular end systolic area (LVESA)(.037,.02) . An Indian study corroborated the findings of this study as HIV Heart disease commonly occurs in CD4 count less than 200cells/l^[20]

V. Conclusion:

HIV heart disease occurs commonly with CD4 count less than 200cells/l. Some conditions like asymptomatic depressed ejection fraction, diastolic dysfunction and pulmonary hypertension do not follow a particular pattern relative to CD4 count. HIV cardiomyopathy, (DCM) and pericardial effusion occurred almost exclusively with CD4 count less than 200cells/l and should be considered surrogate markers of advanced HIV disease and AIDS.

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