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Echocardiographic Assessment of Ventricular Function in Children with Human Immunodeficiency Virus on Highly Active Antiretroviral Therapy

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Authors' contributions

This work was carried out in collaboration among all authors. Authors COD and JMC contributed to conception writing and proof reading of this manuscript. Author BFC contributed in data management, statistical analysis and interpretation of results. All authors read and approved the final manuscript.

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ABSTRACT

Background: Children with Human Immunodeficiency Virus (HIV) infection could present with varying degrees of cardiac abnormalities, however the effect of Highly Active Antiretroviral Therapy (HAART) has not been extensively studied in them.
Objectives: To compare the ventricular functions of HIV positive children on HAART with that of HIV negative children using echocardiography.
Methods: This was a comparative cross sectional descriptive study involving 54 HIV positive children on HAART and 50 HIV negative controls. Using transthoracic echocardiography, trans annular plane systolic excursion (TAPSE), Left ventricular ejection fraction (LVEF), Left ventricular fractionating shortening (LVFS), Left ventricular (LV) mitral inflow velocities, left ventricular mass index (LVMI) and Left ventricular hypertrophy (LVH) were used to assess right ventricular (RV) and left ventricular (LV) function.
Results: The mean TAPSE for subjects and controls were 26.78±5.92mm and 25.82±3.59mm respectively (t = 1.0, p = 0.32). The prevalence of right ventricular systolic dysfunction using

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TAPSE was significantly higher among the subjects; 29.63% compared with 8.0% in controls ($\chi 2$ = 7.82, p=0.005). There was no significant correlation between TAPSE and CD4 counts (Spearman's correlation coefficient = 0.15, p = 0.31). The mean left ventricular mass index (LVMI) in subjects was 141.6±45.5g/M^2. Forty-one (75.9%) of the subjects had left ventricular hypertrophy (LVMI > 103G/M^2) compared with 26.0% (13/50) of the controls and the difference in proportion was significant (Chi-square = 30.49, p<0.001). Left ventricular systolic function was similar in subjects and controls. The prevalence of left ventricular diastolic dysfunction was significantly higher in subjects (15.5%) than in controls (4.0%); {$\chi 2$ = 37.89, p<00.1)

Conclusion: This study shows that children with HIV on HAART regimen have a very high prevalence of ventricular dysfunction compared with normal controls.

Keywords: Ventricular function; HIV infection; HAART regimen; TAPSE; children; LVH.

1. INTRODUCTION

Globally, about 38 million people were estimated to be living with Human Immunodeficiency Virus (HIV) by the year 2019, of which about 2.8 million of them were children aged 0-19 years [1]. The introduction of Highly Active Antiretroviral Therapy (HAART) has greatly modified the course of HIV due to the dramatic reduction in HIV associated morbidity and mortality [2]. The cardiovascular system is one of the systems affected in HIV positive children with reported rates of prevalence of cardiac dysfunction from 40 to 76.9% in different regions of the world. [2-4]. The pathogenesis of these cardiac manifestations in children with HIV infection, remain conjectural. Many theories have been propounded, ranging from secondary infections to concurrent disease states, side effects of therapy and nutritional deficiencies [5-8]. All components of the cardiovascular system could be affected in HIV positive children, of which the most commonly reported is ventricular dysfunction [5-8]. Though the role of HAART in the prevention of cardiac related HIV disease has not been fully elucidated, Barbaro et al. [9] noted that children on HAART regimen have a significantly modified course and prognosis of HIV related heart disease, prolonged survival, and improved quality of life.

Idris et al. [10] noted that children on ART-single therapy had compromised ventricular systolic function with chamber dilatation, while the HAART-exposed children had less functional impairment despite thicker LV posterior wall, larger internal diameter, and higher mass. They however concluded that HAART regimen, had some efficacy in abating viral replication [10,11].

Children with HIV who did not receive antiretroviral therapy (ART) often experience abnormal left ventricular (LV) mass and diastolic dysfunction, a harbinger of mortality [12]. It is noteworthy that the cardiovascular effects of HIV and ART are still in the primordial state. Children with HIV who are on HAART usually present with sub-clinical cardiac abnormalities which may develop into severe left ventricular dysfunction and eventual LV hypertrophy. For instance, studies have linked the use of nucleoside reverse-transcriptase inhibitor (NRTI) to adverse cardiac function, probably from mitochondrial toxicity [13-15]. Protease inhibitors (PIs) have also been implicated in adversely affecting cardiac function [10]. A study has also shown a significant increase in LV hypertrophy and diastolic dysfunction in children who had HIV on PIs [16].

Left ventricular hypertrophy (LVH) is an independent predictor of major cardiovascular events in children with HIV. Increased LV mass and LVH are associated with increased risk for myocardial infarction, hypertension, serious ventricular arrhythmias, cerebrovascular events including stroke and sudden cardiac death [17-22]. Emerging data has shown that left ventricular abnormalities may not be improved by HAART or immune reconstitution. For instance, a large cohort has shown a high prevalence (18%) of mild left ventricular (LV) dysfunction with a 12% progressive increase in LV mass [23]. Few studies have documented the prevalence of LV mass/hypertrophy among patients with HIV infection and its impact on gender, age and blood pressure. Furthermore, treatment-related drug effects pose a serious challenge to the cardiovascular system especially the use of protease inhibitors (PIs). Most studies on echocardiographic assessment of cardiac function in children with HIV did not actually ascertain the real proportion of children that actually present with left ventricular dysfunction. Again, TAPSE, was not used in so many studies on this topic to assess right ventricular function in

children with HIV infection. Moreover, very little work has been done on the assessment of left ventricular hypertrophy using left ventricular mass, indexed to surface area.

This study is thus aimed at determining:

1. The mean Trans annular plane systolic excursion (TAPSE) in millimeter in children with HIV infection on HAART regimen compared with age and sex matched controls.
2. The prevalence of right ventricular systolic dysfunction using TAPSE in subjects and controls.
3. The prevalence of left ventricular diastolic dysfunction using mitral inflow velocity (MV E/A) in children with HIV infection on HAART regimen compared with that obtained in age and sex matched controls.
4. The prevalence of left ventricular systolic dysfunction using LVEF and LVFS in children with HIV infection on HAART regimen compared with that obtained in age and sex matched controls.
5. The relationship between left ventricular systolic function and CD4, blood pressure and HIV staging in children with HIV infection on HAART regimen compared with that obtained in age and sex matched controls.
6. The relationship between right ventricular systolic function and CD4, blood pressure and HIV staging in children with HIV infection on HAART regimen compared with that obtained in age and sex matched controls.
7. The prevalence of left ventricular hypertrophy in children with HIV infection who are on HAART compared with that obtained in age and sex matched controls.

2. MATERIALS AND METHODS

2.1 Study Design

This was a comparative cross-sectional conducted over a period of 3 months (October to December 2019) at the Niger Delta University Teaching Hospital (NDUTH) Okolobiri Bayelsa State and the University of Nigeria Teaching Hospital, Enugu. Both hospitals are tertiary institutions located in the Southern part of Nigeria and provide specialized paediatric services for children. The hospitals also serve as a referral centres for children with HIV from other peripheral hospitals in the Southern region of Nigeria. The study population consisted of HIV positive children aged 1 to 18 years who attended the HIV clinic of the NDUTH and had been on HAART for at least 3 months and were recruited consecutively. Those in the study group had their HIV status confirmed by Western blot if aged 18 months or older, or by polymerase chain reaction if aged below 18 months. An equal number of age- and sex-matched apparently healthy HIV-negative controls without congenital or acquired heart diseases, or any other chronic medical illnesses were recruited from the Paediatric Outpatients Clinic of the University of Nigeria, Enugu.

On recruitment, anthropometry was conducted on each participant. Weight was measured in kilograms using a SECA weighing scale with weight measured to the nearest 0.5kg. Height or recumbent length (for those less than 2 years) was measured in centimetres with child placed on a fixed stadiometer or infantometer and measurement taken to the nearest 0.5cm. Each participant had a complete transthoracic echocardiography done using a portable echocardiography machine- My Lab Esaote Gamma (series 7410 model 2016) which had 2D and Doppler capabilities and was fitted with probes of 1-4MHz and 3-12MHz frequencies.

The right ventricular systolic function was assessed using the TAPSE which was obtained by using the M-mode in two dimensional echocardiography. The cursor was placed at the lateral portion of the tricuspid valve annulus in a conventional apical four-chamber view. The annular systolic excursion of the tricuspid valve was measured from the base of the heart to the apex at end systole [21]. Normal reference value of TAPSE was 0.9-30 mm [22].

Left ventricular diastolic function was ascertained using the mitral inflow velocity (MVE/A). The cursor was placed at the lateral aspect of the mitral valve annulus before the mitral inflow velocity was measured with a pulse wave [23].

The prevalence of left ventricular diastolic dysfunction was calculated by the number of those with abnormal mitral inflow velocities divided by the total population of subjects and controls. Left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS) were derived using the formula below:

$$LVFS\ (\%) = [(LVEDD - LVESD) / LVEDD]\ 100\%.$$
$$LVEF\ (\%) = (LVEDD^3 - LVESD^3)100\%/LVEDD.$$

Normal LV systolic dysfunction was defined as LVSF of 50% and above while FS of 25 % and above were considered as normal [24]. Left ventricular mass index (LVM index) was calculated by dividing the LV mass by the body surface area [25]. Left ventricular hypertrophy was defined as LV mass index that is above 95th percentile (>103 g/m2) [25-26].

Left ventricular diastolic function was done using the mitral inflow velocity (MVE/A). The cursor was placed at the lateral aspect of the mitral valve annulus before the mitral inflow velocity was measured with a pulse wave. Normal left ventricular diastolic dysfunction (MV E/A) was taken as 0.8 to less than 2.1. [27].

2.2 Inclusion and Exclusion Criteria

Children with HIV infection who are on HAART aged 1 year to 18 years and who gave consent or assent were included in the study while children with congenital heart disease, children with HIV but not on HAART and children with congenital heart disease or any chronic illness were excluded. Children whose parents refused to give consent or children who did not give assent were excluded from the study.

2.3 Data Analysis

Categorical variables were analysed in form of proportions and percentages and presented in form of tables while quantitative variables were analysed in form of means and standard deviations. Differences in proportions were compared using chi-square test and differences in mean were compared using Student t test. The association between discrete variables was analysed using Pearson correlation coefficient. Significant probability value was taken as $p<0.05$.

3. RESULTS

There were 54 children with HIV infection (subjects) and 50 children without HIV infection (controls) recruited for the study. The gender distribution of study participants is as in Table 1.

The mean trans annular plane systolic excursion (TAPSE) in millimetre for subjects and controls were 26.78±5.92 and 25.82±3.59 ($t = 0.9$, $p = 0.2$) respectively. The TAPSE values of each participant was compared with that of the standard population to derive the z-scores. When TAPSE was converted to z-scores, the difference in mean was still not significant; 4.03±3.98 and 3.84±2.06 respectively ($t = 0.29$, $p = 0.8$).

Mean z-score of TAPSE was comparable in both sexes among the subjects and controls as indicated in Table 2. However, the prevalence of right ventricular systolic dysfunction using TAPSE was higher among the subjects, 22.5% compared with 8.0% of the controls. This difference in proportion was observed to be statistically significant ($\chi2 = 22.0$, $p<0.001$).

There was positive correlation between TAPSE and age in subjects and controls, (Pearson correlation coefficient; 0.6, $p<0.002$). There was also positive correlation between TAPSE and body mass index (BMI). While the correlation between TAPSE and BMI was significant in the controls (Pearson correlation coefficient; 0.5, $p = 0.001$), it was not in subjects (Pearson correlation coefficient; 0.1, $p = 0.3$). There was no significant correlation between TAPSE and CD4 counts (Spearman's correlation coefficient = 0.15, $p = 0.31$). Fig. 1. There was negative correlation between TAPSE and WHO clinical stage of HIV, although the correlation was not significant (correlation coefficient = -0.21, $p = 0.13$).

As illustrated in Table 3, the mean left ventricular mass index was significantly higher in subjects' relative to the controls while the mean age, weight, height and systemic blood pressure were comparable. Both the systolic and diastolic pressure were within normal range in both subjects and controls, range of systolic blood pressure for subjects and controls was 80 to 120mmHg and diastolic, 50 to 80 mmHg.

The mean left ventricular mass index (LVMI) in subjects was 141.6±45.5g/M^2. Forty-one (75.9%) of the subjects had left ventricular hypertrophy (LVMI > 103G/M^2) compared with 26.0% (13/50) of the controls and the difference in proportion was significant (Chi-square = 30.49, $p<0.001$). There was no correlation between LV mass index and systolic blood pressure (coefficient = 0.2, $p = 0.12$) as well as diastolic blood pressure (coefficient = 0.14, $p = 0.27$). There was no difference in the mean LVMI between the males (150.3±43.1g/M^2) and females (135.6±46.7g/M^2), {$t = 1.3$, 0.2}. Among the people that have left ventricular hypertrophy (LVH), 43.1% were males and 58.9% females. The difference in number of individuals with LVH between the males and female was however not significant ($\chi2= 0.5$, $p = 0.5$). The prevalence of abnormal EF in the

subjects and controls was not significant ($\chi 2$ = 5.4, p = 0.1). The prevalence of abnormal FS in subjects and controls was also not statistically significant ($\chi 2$ = 1.9, p = 0.4).

There was no correlation between the left ventricular mass index and CD4 count (correlation coefficient = -0.02, p = 0.91). There was also no correlation between LV mass index and clinical stage of HIV (correlation coefficient = 0.08, p = 0.53). Figs 2 and 3.

Also there was no correlation between EF and CD4 count (correlation coefficient = -0.05, p = 0.74) nor between FS and CD4 count (coefficient = -0.54, p = 0.72). The FS had no significant correlation with clinical stage of HIV (coefficient = -0.05, p = 0.67). EF also did not have any significant correlation with clinical stage of HIV (coefficient = -0.06, p = 0.65).

The mean mitral inflow velocity (MV E/A) in subjects, 1.78±0.4 was comparable with that of controls, 1.69±0.2 (t = 1.26, p = 0.2). There was no significant difference in MV E/A among the sexes in both subjects and controls as shown in Table 2. The prevalence of left ventricular diastolic dysfunction was significantly higher in subjects (15.5%) than in controls (4.0%); {$\chi 2$ = 37.89, p<00.1), when normal MV E/A was taken as 0.8 to <2.1.

Table 1. Gender distribution of subjects and controls

		Frequency	Percent
Subject	Male	19	35.2
	Female	35	64.8
	Total	54	100.0
Controls	Male	26	52.0
	Female	24	48.0
	Total	50	100.0

Table 2. Gender comparison of TAPSE

Identity	Sex	N	Mean	Std. Deviation	P value
TAPSE	Male	19	27.47	5.84	
Subjects	Female	35	26.41	6.014	0.54
TAPSE	Male	26	25.98	3.71	
Controls	Female	24	25.64	3.518	0.74

Table 3. Comparison of mean age, weight, height, blood pressure and left ventricular mass index in subjects and controls

	Group	N	Mean	Std. Deviation	P value
Age in months	Subjects	54	119.81	49.46	0.15
	Controls	50	106.08	47.78	
Weight in kg	Subjects	54	32.12	14.14	0.98
	Controls	50	32.17	15.10	
Height in cm	Subjects	54	134.03	20.55	0.51
	Controls	50	136.76	21.60	
Systolic blood pressure	Subjects	49	95.51	11.24	0.86
	Controls	39	95.10	10.06	
Diastolic blood pressure	Subjects	49	61.02	8.72	0.83
	Controls	43	60.65	8.00	
LVM index	Subjects	52	140.82	43.20	<0.001
	Controls	50	71.68	56.06	
	Subjects		66.88	7.35	0.57
EF (%)	Controls		67.72	7.48	
	Subjects		36.67	5.73	0.26
FS (%)	Controls		38.20	7.82	

LVM index; left ventricular mass index, EF; ejection fraction

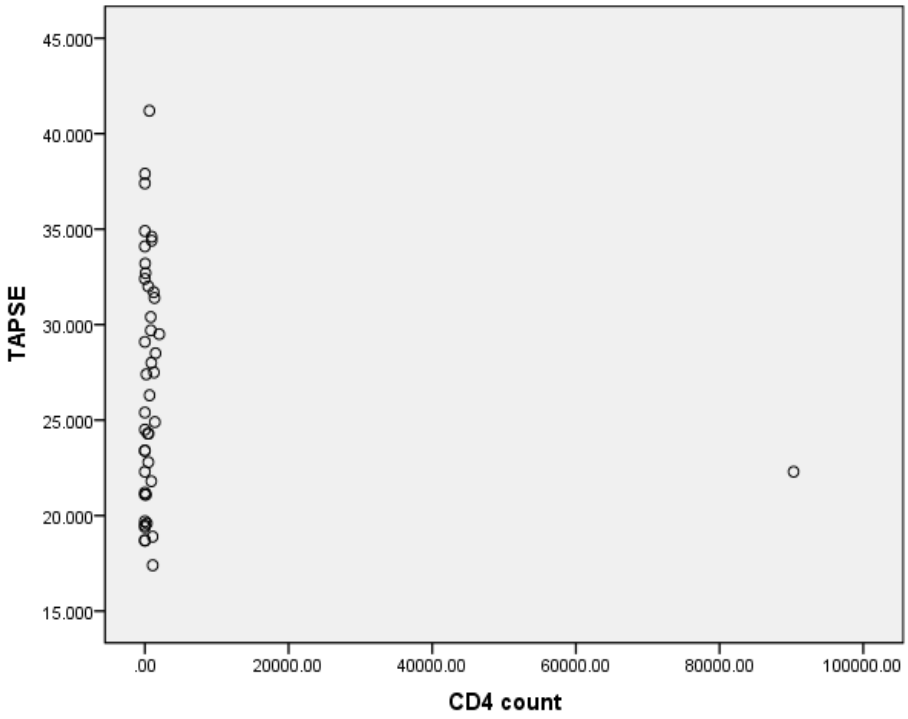

Fig. 1. Correlation between TAPSE and CD4 count among the subjects

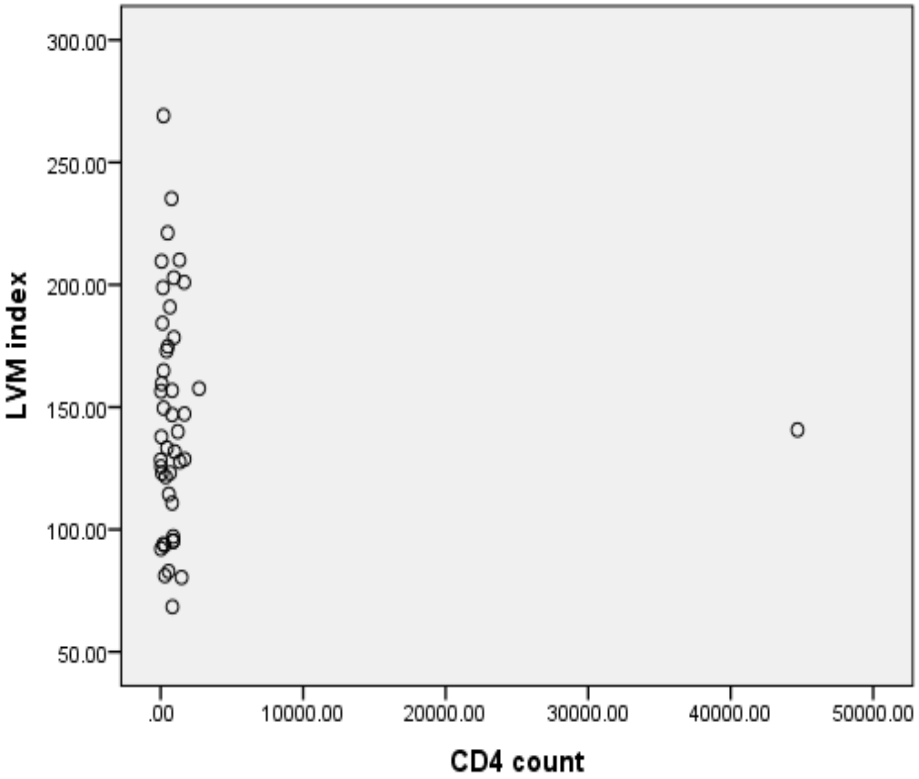

Fig. 2. Correlation between left ventricular mass index (LVM index) and CD4 count

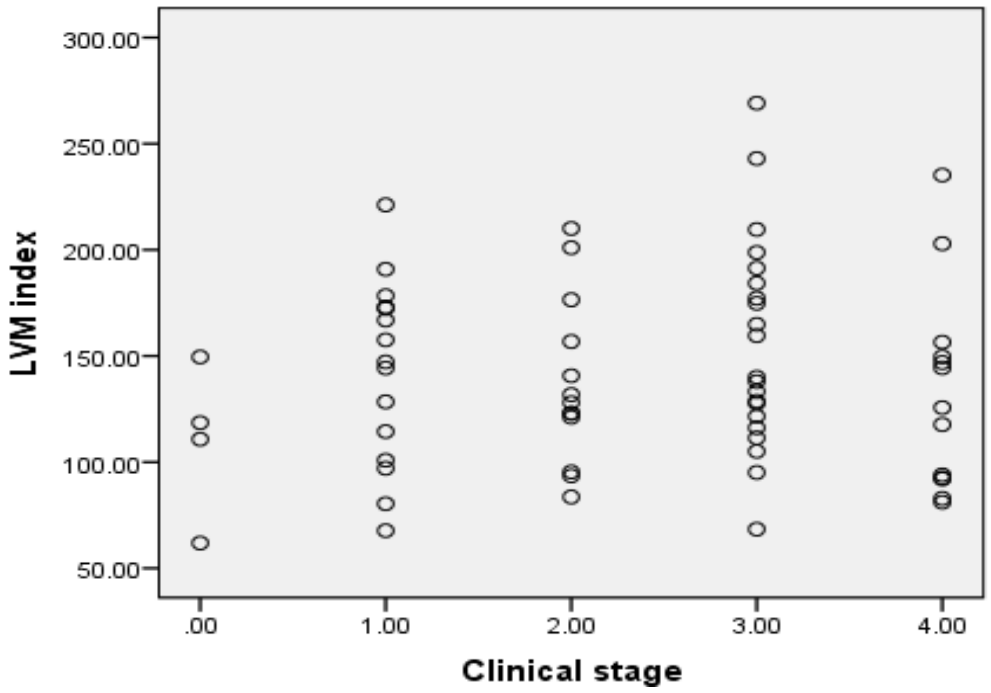

Fig. 3. Correlation between left ventricular mass index (LVMI) and clinical stage of HIV infection in subjects

4. DISCUSSION

The findings from this study have provided evidence of right ventricular dysfunction (abnormal TAPSE) in children with HIV who are on HAART. We noted no significant difference in TAPSE values among children with HIV infection on HAART and control which both were within normal reference range. However, when we further analyse the actual prevalence of right ventricular dysfunction (abnormal TAPSE) in both subjects and control, the prevalence of right ventricular systolic dysfunction among the subjects was 22.5% which is significantly higher than a prevalence of 8.0% obtained in controls.

Very few studies have reported the use of TAPSE to ascertain right ventricular (RV) systolic function in children with HIV infection. For instance, Nikmah et al. [28] noted that ART-naïve HIV-infected children had significantly reduced right ventricular systolic function (using TAPSE) compared with the uninfected reference group.

The authors previously used TR jet velocity to ascertain right ventricular function but noted an underestimation of the true effect of ART-naïve HIV infection on right ventricular function using tricuspid jet velocity. This is because not all children had sufficient tricuspid regurgitation to accurately estimate RV systolic function and pulmonary pressure [28].

Careful search in literature has shown that right ventricular pressure in children with HIV was usually assessed by tricuspid regurgitation velocity instead of TAPSE. This could account for variation of results in so many studies. Tricuspid annular plane systolic excursion (TAPSE) has shown to have a better sensitivity and specificity than tricuspid regurgitation velocity in assessing right ventricular pressure. It has a proven utility among children with right ventricular dysfunction and heart failure. [29] Further studies have also shown that TAPSE has a superior predictive value in assessing right ventricular function [30].

On further stratification of right ventricular function by age, TAPSE was found to increase with age in subjects and controls. Koestenberger et al. [27] noted a continuous increase in levels of TAPSE in healthy individuals from birth to adolescence, nevertheless, the increased stoke volume and heart rate in children with HIV further explains the findings among them [31].

This study showed no correlation between right ventricular function with CD4 count. The fact that elaboration of HIV-induced inflammatory

mediators (e.g. cytokines or proteolytic enzymes), and autoimmune response to infecting pathogens, posed no effect on TAPSE remain plausible. [32-35] This finding of no correlation of right ventricular function and CD4 patient was similar to that obtained by Scott et al [36] who noted no significant correlation between low CD4 count and RV function. The similar findings could be explained by the similar methodology.

We noted an increase of TAPSE values with age in children with HIV infection and controls. This can be explained by the fact that aging causes RV dysfunction in patient receiving ART with a high cardiovascular risk which is also worsened by increases in blood pressure, dyslipidaemia, and metabolic syndrome as one ages [37].

LV mass index is a marker for early HIV mortality. Left ventricular mass index, which assesses left hypertrophy (LVH), is an independent predictor of major cardiovascular events among children with HIV infection. [31-33] We noted the prevalence of Left ventricular hypertrophy (LVH) as 77.3% in this study. Few studies mainly among adult population, had estimated LV mass among patients with HIV and the results have been conflicting. None of those studies determined the prevalence of LVH in this population group. Barbaro et al. [33] reported increased LV mass in asymptomatic HIV patients compared to healthy controls while Lipshultz [19] described a higher LV mass among children with HIV infection. In contrast, Martinez-Garcia found decreased LV mass in asymptomatic HIV-infected patients. [19] These studies, however, are limited by their lack of LV mass indexation to body surface area (BSA). Mondy et al. [35] noted a prevalence of left ventricular hypertrophy among their subjects with HIV as 6.5%. It is important to note that they did not index their left ventricular mass to body surface area and the study was among adult population. This could account for this low prevalence.

This study is one of the few studies that examined the burden of left ventricular hypertrophy in children with HIV infection using left ventricular mass, indexed to body surface area. Whether these patients developed left ventricular hypertrophy from the HIV infection or if it is aggravated by HAART regimen remains uncertain. This could be an area for future deliberations.

It is documented that LVH and increased LV mass are usually associated with a high risk of myocardial ischemia, life threatening arrhythmias, and sudden death in children with HIV infection. It is pertinent to note that this high prevalence of Left ventricular hypertrophy in this study could be unravelled by the fact that in this HAART era, evidences abound to highlight the fact that echocardiographic abnormalities are neither improved by HAART regimen nor by immune reconstitution. [36-39] The high prevalence may also be explained by the fact that our subjects were placed on nucleoside reverse-transcriptase inhibitor (NRTI). This drug is cardio-toxic and has its attendant deleterious effects on the mitochondria [36-38]. Furthermore, they were also on Protease inhibitors (PIs). These drugs are notorious for adverse cardiac dysfunction [36-39].

We noted no correlation between LVMI and CD4 count. Ather et al. [40] also noted that increased LV mass among HIV-infected patients was not associated with severity of current or past immunosuppression nor with a nadir $CD4^+$ cell count <200 cells/μl nor with the use or duration of HAART.

This study showed no correlation between LV hypertrophy and blood pressure among children with HIV. Left ventricular hypertrophy is a maladaptive response to pressure overload systolic and diastolic heart failure and sudden death in children with hypertension. Though not all patients with hypertension develop left ventricular hypertrophy, a thorough history, clinical examination and early echocardiography is necessary to avert numerous complications that may follow these patient with hypertension with no LVH [41].

In the contrary, Seaberg et al. [42] documented a lower nadir CD4 count in patients with higher LV mass index. They noted that hypertension which is often associated with antiretroviral therapy [43-45] especially the protease inhibitors evokes left ventricular mass hypertrophy with impending diastolic dysfunction. Furthermore, lower CD4 count and longer duration of NRTI use were linked with diastolic dysfunction, increased LV mass and LV hypertrophy [40,46].

The above studies were mainly among adult population where hypertensive cases were documented. We noted no hypertension in our subjects and controls.

There was no statistical significance in diastolic function of both subjects and control seen in this study. On further analysis on left ventricular diastolic function, in subjects and control, we

noted a prevalence rate of 15.5 % among the subjects compared with 4% seen in control. Increase in sympathetic tone, with attendant increase in catecholamine surge and myocardial ischemic changes could explain the reason for diastolic dysfunction obtained in subpopulation of children with HIV infection on HAART [47]. Ige et al. [46] also noted prevalence of left ventricular diastolic dysfunction as 30.7% in subjects and 12.7% among the control. Augustini et al. [47] noted a prevalence of 39.6% in his study involving 53 subjects on HAART. The high prevalence rates obtained by Augustini and colleagues could be due to very small size used in their studies. The difference of prevalence report in Ige et al. [46] and this present study, is that, the former assessed HIV children who are not all on HAART regimen. Furthermore, mitral inflow velocities (a very prognostic marker and harbinger of left ventricular diastolic dysfunction) was not used in the former as assess left ventricular diastolic function. It is interesting to note that majority of studies on ventricular function in children with HIV focused more on systolic function such as ejection fraction and fractionating shortening. Only very few studies actually assessed left ventricular diastolic function of children with HIV infection using the standard inflow velocities' method.

We noted no significant increases in left ventricular function with age in both subjects and controls. Notwithstanding, it is important to note that in children with HIV infection, aging is associated with increased risk of myocardial ischemic changes and impairment of relaxation of the left ventricle which could further lead to worsening of diastolic function. Children with HIV infection normally present with inflammatory responses, coagulopathy and perturbation of the endothelial lining of the coronary arteries as they age, which can also worsen left ventricular diastolic function [47].

There was no statistical difference on left ventricular ejection fraction and fractionating shortening in subjects and controls. Though this is contrary to findings obtained in several studies where LVEF and FS were found to be impaired, majority of these studies are on children with HIV infection who were not all on HAART regimen [48-49].

5. CONCLUSION

This study shows that children with HIV on HAART regimen have a very high prevalence of ventricular dysfunction compared with normal controls.

What is already known

There are overwhelming evidence from studies on ventricular dysfunction in children with HIV infection using echocardiography, especially the assessment of basic ventricular function such as ejection fraction, fractionating shortening and chamber sizes.

What this study adds

Most studies on echocardiographic assessment of cardiac function in children with HIV did not actually ascertain the real proportion of children that actually present with left ventricular dysfunction. Again, TAPSE, was not used in so many studies on this topic to assess right ventricular function in children with HIV infection. Moreover, very little work has been done on the assessment of left ventricular hypertrophy using left ventricular mass, indexed to surface area.

CONSENT

Consent was sought from each parent/ caregiver of the subjects and controls and assent from any child older than 7 years.

ETHICAL APPROVAL

Ethical approval was obtained from the Research and Ethics Committee of the Niger Delta University Teaching Hospital Okolobiri Bayelsa State.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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