Original Article

Cardiac size and systolic function of HIV-infected Lagos children accessing routine care: a pilot study

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Background: Previous studies have reported high, though declining, prevalence of HIV-associated cardiac dysfunction globally. However, there is relative paucity of data on the prevalence and pattern of HIV-associated cardiac disorders in Nigerian children. The index study aimed to conduct a pilot evaluation of the frequency and pattern of cardiac dysfunctions in HIV-infected children in a tertiary health facility in Lagos, Nigeria.

Methods: Thirty-nine HIV-infected children, with 41 age- and sex-matched controls, were prospectively recruited in a cross-sectional study. Subjects had echocardiography to obtain measures of cardiac dimensions and function. Subjects' anthropometry, blood pressure and clinical profile were also obtained.

Results: HIV-infected children had significantly thicker interventricular septal diameter (IVSD) (P=0.0018) and larger left atrial diameter (P=0.003) and aortic root diameter (P=0.023); other parameters (right ventricular diameter, left ventricular diameter, left ventricular posterior wall diameter, left ventricular mass (LVM), ejection fraction, fractional shortening) were similar between both groups. There was no significant difference in the prevalence of LVH between those on zidovudine-based regimen compared to those on non-zidovudine-based regimen (P=0.703).

Conclusions: The prevalence of subclinical echocardiographic abnormalities was high and was more in those below five years of age. In a setting of limited resources, this age group may be prioritized for serial monitoring of cardiac abnormalities.

Keywords: Cardiac dysfunction; children; Nigeria; HIV/AIDS; echocardiography

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Introduction

Sub-Saharan Africa is home to over 65% of the global paediatric HIV burden (1). As the HIV pandemic matures, more HIV-infected children are surviving into and beyond adolescence because of increasing access to highly active antiretroviral therapy (HAART). With this increasing survival, there is increasing reports of chronic diseases involving cardiopulmonary, neurologic, musculoskeletal and metabolic systems (2-4). Cardiovascular complications of HIV are one of the most commonly reported chronic complications of HIV (5-8).

HIV-infected children are at increased risk of chronic cardiac conditions owing to cumulative lifelong exposure of the myocardium to both the HIV virus, opportunistic pathogens and ARVs particularly during early developmental stages (7-10). Several mechanisms have been proposed for the deleterious effect of the virus on the heart, including direct viral invasion of the myocardium, chronic inflammation, endothelial dysfunction, autoimmunity,

lung injury, malnutrition and drug-induced cardiotoxicity. Metabolic complications of prolonged ART such as dyslipidemias and insulin resistance have also been implicated (5,11).

A wide spectrum of echocardiographic abnormalities has been reported from studies in paediatric HIV-infected subjects, ranging from subclinical to florid pathology such as pericardial effusions (5,9,12-14). Other reported abnormal findings include left ventricular systolic and diastolic dysfunctions, and increased left ventricular mass (LVM)/left ventricular hypertrophy (LVH) (5,8,9,15,16). Echocardiographic abnormalities such as increased left ventricular dimensions, thickness and mass are associated with increased risk of fatal arrhythmias, sudden death, stroke, severe cardiac failure and myocardial infarction, independent of CD4 counts (14,17). Thus, routine baseline and serial cardiac evaluation of HIV-infected children with electrocardiographic and echocardiographic studies are advocated (5,7,17,18).

In Nigeria, studies on echocardiographic profile of HIV-infected children are relatively few (7,9,16,19,20). These studies reported prevalence rates of cardiovascular disorders ranging from 31–76%, based on clinical examination, electrocardiography and echocardiography. Specifically, no previous study has profiled the cardiovascular status of HIV-infected children in the current study center which attends to a high population of these subjects. Hence, the need for this study; this study aimed to document the prevalence and pattern of echocardiographic abnormalities of HIV-infected children assessing routine outpatient care at the paediatric HIV clinic of the Lagos State University Teaching Hospital in Lagos, South-West Nigeria. This pilot study will provide baseline data on the pattern of echocardiographic abnormalities in this population and establish the need for larger studies which will help guide local, and national, policy on routine cardiovascular screening and care.

Methods

The study was a prospective, cross-sectional study, carried out from 2011 to 2013 at the outpatient paediatric HIV clinic of LASUTH. The clinic has been running routine outpatient follow-up care of HIV-infected children since 2004 when it commenced as a pilot programme supported then by the US' President's Emergency Plan for AIDS Relief (PEPFAR). The clinic offers free comprehensive guidelines-based paediatric HIV care including HIV prevention, treatment, care and support services to enrolled HIV-infected children and their families. Baseline and follow-up haematological and biochemical investigations and ART are also provided free of charge.

Study population

This comprised of previously-diagnosed HIV-infected children aged 15 years and below accessing routine outpatient followed-up care in the unit and in whom, parents had given an informed consent. Patients with acute illnesses or those previously diagnosed with congenital or acquired heart diseases were excluded.

Data collection procedure

With the aid of a structured proforma, trained residents and interns obtained relevant socio-demographic and clinical information from participants whose parents or guardian consented in writing after explanation of the study. Eligible subjects were clinically evaluated for the presence of cyanosis, finger clubbing, tachypnea, tachycardia, cardiac murmur and tender hepatomegaly.

Subjects' anthropometry (weight, height or length) were obtained following standard guidelines (21). Transcutaneous oxygen saturation (SpO_2) was measured with a Nonin® finger pulse oximeter. The subjects also had their blood pressure measured in sitting position.

Clinical definitions

We defined *significant tachycardia* as heart rate greater than the upper limit of normal for age: greater than or equal to 160 beats/minute in infancy, 140 beats/minute at 2 years, 120 beats/min at 4 years, and 100 beats/minute at 6 years and above. *Tachypnoea* was defined as resting respiratory rate above or equal to 60 cycles per minute in the first two months of life, 50 cycles/minute or more from third to 12th month of life, 40 cycles and more beyond infancy. *Congestive heart failure* was defined as the presence of any two of tachycardia, tachypnoea or cardiomegaly WITH tender hepatomegaly (22). However, clinical presence of cardiomegaly determined by displaced apex beat was not assessed; LVH by echocardiography was thus employed as a criterion for cardiomegaly.

Echocardiography

Echocardiographic study was done for all subjects by a single well-experienced certified Paediatric Cardiologist

in two-dimensional, Doppler and M-mode based on the American Society of Echocardiography (ASE) guidelines (23). The machine was a *GE Vivid Q*® 2-D echocardiography machine (reference number 14502 WP SN 2084) with facility for colour Doppler and M-mode. Measured parameters included main pulmonary artery (MPA) diameter, aortic root dimension (AO), left atrial dimension (LAD), left ventricular end diastolic diameter (LVEDD), left ventricular end systolic diameter (LVESD), interventricular septum (IVS) and left ventricular posterior wall diameter (LVPW). These parameters were used to derive the left ventricular ejection fraction (LVEF), left ventricular fractional shortening (LVFS), LVM and relative wall thickness (RWT) (23,24):

$$LVM(g) = 0.8\left\{1.04\left[(LVEDD + LVPW + IVS)^3 - (LVEDD)^3\right]\right\} + 0.6 \quad [1]$$

$$LVFS(\%) = \left[(LVEDD - LVESD)/LVEDD\right]100\% \quad [2]$$

$$LVEF(\%) = \left(LVEDD^3 - LVESD^3\right)100\%/LVEDD^3 \quad [3]$$

$$RWT = 2(LVPW)/LVEDD \quad [4]$$

In order to correct for confounding effect of varying body size with age, the LVM was indexed to height raised to the power of 2.7 ($height^{2.7}$) and a cut-off value of 51 g/m$^{2.7}$ was used as indicative of *increased LVM* (25). LVEDD was expressed as z-scores based on available references and LVEDD z-score values >2 was defined as *LV dilatation* (26,27). LV systolic dysfunction was defined as LVSF <28% and *dilated cardiomyopathy* as LVSF <28% with LVD (28). Increased RWT was defined as RWT ≥0.42. RWT was used to classify subjects with increased LVM (LVH) as either *concentric LVH* (when both RWT and LVM are elevated) or *eccentric LVH* (when LVM is elevated with a normal RWT) (29).

Data of control subjects were extracted from an electronic database of the Paediatric Cardiology Unit. Control subjects were gender- and age-matched apparently normal (clinically stable HIV-uninfected subjects with structurally normal heart) who had their echocardiographic parameters documented as above by the same Paediatric Cardiologist.

Statistical analysis

Statistical analysis was performed using SPSS version 20 (IBM, Chicago, USA). Continuous variables were presented as mean (SD) or median (interquartile range) while categorical variables were presented as frequencies (%). Student *t*-test, or Mann-Whitney U-test, was used to compare continuous variables between HIV-infected subjects and controls. Chi square test, or Fisher exact test where appropriate, was used to compare proportions between the two groups. Level of statistical significance was set at P<0.05.

Results

The study cohort consisted of 41 HIV-infected children, with 41 age- and sex-matched controls. Two HIV-infected subjects were excluded from further analysis due to gross data entry errors; further analysis was thus based on 39 HIV-infected subjects with 41 control subjects.

Demographic characteristics of subjects and controls

Table 1 shows comparison of the demographic characteristics of the study and control groups; there was no significant difference in their baseline characteristics. The ages of the HIV-infected group ranged from 2.7 to 14 years while it ranged from 2.0 to 14 years among the controls. Fifty-four percent (54%) of the HIV-infected subjects were females. About half of the HIV-infected subjects were in the age group 5 to 10 years. The median ages (± interquartile range) of the study subjects and controls were 7.0±5.0 and 6.0±7.0 years respectively (P=0.585). All, but one, (97%) of the subjects were on HAART with 11(28%) of them on zidovudine-based regimen.

Clinical findings in HIV-infected subjects

Table 2 shows anthropometric and clinical date of the HIV-infected subjects while *Table 3* shows the frequency of clinical signs elicited during clinical examination. Of the 39 HIV-infected subjects, 8 (21%) had one or more clinical symptoms or signs. However, none met the criteria for congestive heart failure; tachypnoea, tachycardia or tender hepatomegaly occurred in isolation. The subject that had a cardiac murmur had no feature of heart failure and subsequent echocardiography did not reveal any cardiovascular abnormality.

Echocardiographic measurements of subjects and controls

Table 4 shows a comparison of the echocardiographic parameters of the HIV-infected subjects and matched

Table 1 Sex and age comparison of HIV-infected subjects and non-infected controls

Demographic parameter	Group, N [%]		Total (N=80) [%]	P value
	Cases (N=39)	Controls (N=41)		
Age (years)*	7.0 (5.0)	6.0 (7.0)		0.585
Age group				
≤5	12 [31]	19 [46]	31 [39]	
>5–10	19 [49]	10 [24]	29 [36]	
>10	8 [20]	12 [30]	20 [25]	
Total	39 [100]	41 [100]	80 [100]	
Gender				
Male	18 [46]	19 [46]	37 [46]	
Female	21 [54]	22 [54]	43 [54]	
Total	39 [100]	41 [100]	80 [100]	

*, median with interquartile range (IQR); Mann-Whitney U-test.

Table 2 Anthropometric and clinical variables of the subjects

Variable	N	Mean [SD]	Range
Weight (kg)	38	22.3 [8.2]	10.0–46.0
Height (cm)	37	117.3 [25.3]	72.0–150.0
Respiratory rate (c/min)	38	28 [6]	20–56
SBP (mmHg)	27	90 [11]	70–110
DBP (mmHg)	27	56 [8]	40–70
SpO_2 (%)	22	98.4 [1.9]	94–100

SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, transcutaneous oxygen saturation; c/min, cycles per minute.

Table 3 Frequency of clinical findings among HIV-infected subjects

Clinical signs	Frequency
Dyspnea	1
Cyanosis	0
Tachypnea	2
Tachycardia	5
Cardiac murmur	1
Gallop rhythm	0
Tender hepatomegaly	2
Total	11*

*, some subjects had more than one clinical features.

control group. Although all the echocardiographic data (except RVAW and LVPWD) were larger in the HIV-infected group, only IVSD, LA and AO were significantly larger; that is HIV-infected group had significantly larger interventricular septal diameter (IVSD), LA and aortic diameter. The functional parameters (LVFS and LVEF) were not significantly different between the groups.

Prevalence and pattern of cardiac abnormalities in HIV-infected subjects

Eighteen (44%) subjects had abnormal echocardiographic abnormalities thus: 2 (5%), 5 (13%), 6 (15%) and 11 (28%) subjects, respectively, had depressed LVEF, LV dilatation, systolic dysfunction (depressed LVFS) and LVH (*Figure 1*). Four of those with LVH had concentric LVH

Table 4 Comparison of echocardiographic dimensions and LV systolic functional parameters between HIV-infected subjects and non-infected controls

Echocardiographic measurements	Groups		t value	P value
	Cases	Control		
MPA (cm)	2.00±0.4	1.99±0.47	0.134	0.893
RVAW (cm)	0.39±0.10	0.39±0.12	–0.216	0.829
RVD (cm)	1.20±0.38	1.09±0.43	1.191	0.237
IVSD (cm)	0.70±0.17	0.59±0.22	2.419	0.018*
LVEDD (cm)	3.74±0.62	3.49±0.54	1.913	0.059
LVPWD (cm)	0.65±0.16	0.67±0.16	–0.471	0.639
LVEDS (cm)	2.38±0.40	2.32±0.41	0.697	0.488
AO (cm)	2.14±0.30	1.95±0.42	2.329	0.023*
LAD (cm)	2.56±0.41	2.25±0.50	3.034	0.003*
LAD/AO	1.21±0.20	1.16±0.17	1.049	0.297
LVFS (%)	36.70±10.33	34.03±7.09	1.344	0.183
LVEF (%)	71.82±11.08	70.30±10.09	0.637	0.526
LVM (g)	61.61±32.68	48.49±30.90	1.854	0.023**
RWT	0.36±0.09	0.39±0.09	–1.722	0.089

*, P<0.05; **, Mann-Whitney U test. LV, left ventricle; MPA, main pulmonary artery; RVAW, right ventricular anterior wall; RVD, right ventricular dilatation; IVSD, interventricular septal diameter; LVEDD, left ventricular end diastolic diameter; LVPWD, left ventricular posterior wall in diastole; LVEDS, left ventricular end systolic diameter; AO, aortic root dimension; LAD, left atrial dimension; LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction; LVM, left ventricular mass, RWT, relative wall thickness.

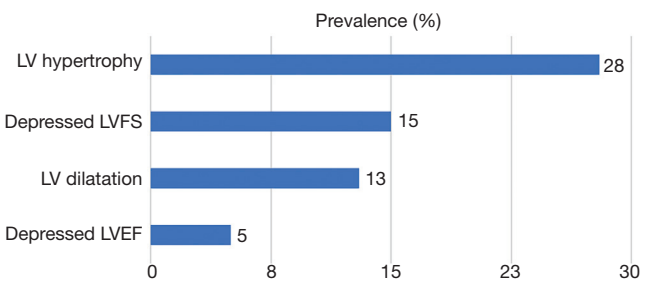

Figure 1 Prevalence and types of abnormal echocardiographic abnormalities in HIV-infected children. LV, left ventricular; LVMI, left ventricular mass index.

while seven had eccentric LVH. None of the subjects fulfilled criteria for pericardial effusion or dilated cardiomyopathy. Four subjects had both LV dilatation and LVH. Only one of the subjects with LVH had elevated blood pressure (stage 1 hypertension) and the LVH type was eccentric. Of the 18 subjects with echocardiographic abnormalities, only 1 (0.1%) was symptomatic: a 42-month old boy with fever, mild tachypnoea and tender hepatomegaly but no tachycardia who had both LV dilatation and LVH.

Clinical characteristics of HIV-infected subjects with cardiac abnormalities

Subjects with cardiac abnormalities were younger, lighter and shorter than those with normal cardiac measurements and they also had lower systolic and diastolic blood pressure; albeit these differences were not statistically significant (*Table 5*).

A comparison of the distribution of subjects by age group between those with abnormal echocardiographic abnormalities and those with normal parameters shows that majority (56%) of those with abnormalities were less than 5 years of age; thus 83% of children less than 5 years had abnormal cardiac abnormalities (P=0.001; *Table 6*).

Table 7 shows the distribution of each of LVFS and LVMI in the HIV-infected subjects based on age group. There was

Table 5 Comparison of clinical variables between HIV-infected subjects with cardiac abnormalities and those with normal cardiac parameters

Variable	Echocardiographic abnormalities		P value*
	Present, mean [SD]	Absent, mean [SD]	
Age (years)	6.4 [3.4]	8.3 [2.7]	0.052
Weight (kg)	20.1 [8.9]	24.1 [7.2]	0.131
Length (cm)	107.1 [19.4]	120.1 [28.4]	0.119
SBP (mmHg)	88 [11.9]	91 [11.3]	0.509
DBP (mmHg)	51 [12]	57 [9.2]	0.997
SpO_2 (%)	99 [1]	98 [2]	0.210

*, independent *t*-test. SBP, systolic blood pressure; DBP, diastolic blood pressure; SpO_2, transcutaneous oxygen saturation; SD, standard deviation.

Table 6 Distribution and frequency of echocardiographic abnormalities in HIV-infected subjects by age-group

Age group	Echocardiographic abnormalities, n [%]		Total, n [%]
	Present	Absent	
<5 years	10 [83]	2 [17]	12 [100]
5–10 years	5 [26]	14 [74]	19 [100]
>10 years	3 [38]	5 [62]	8 [100]
Total	18 [46]	21 [54]	39 [100]

Fisher Exact test, P=0.001.

Table 7 Distribution of frequency of left ventricular function and mass of HIV-infected subjects by age group

Age groups	LVFS* (n)			LVMI** (n)		
	Depressed	Normal	Total	Elevated	Normal	Total
<5 years	2	9	11	8	2	10
5–10 years	2	16	18	2	16	18
>10 years	2	6	8	1	7	8
Total	6	31	37	11	25	36

*, χ=0.831; **, Fisher Exact test, P=0.001. LVFS, left ventricular fractional shortening; LVEF, left ventricular ejection fraction.

no significant difference in the distribution of abnormal LVFS among the age groups. However, most (73%) of the subjects with elevated LVMI (LVH) were less than five years of age.

Relationship between zidovudine exposure and cardiac abnormalities

Of the 36 subjects with data on ARV regimen, 25 subjects were on zidovudine-based regimen (*Table 8*). There was no significant difference between the prevalence of LVH between those on zidovudine-based regimen compared to those unexposed to zidovudine (P=0.703).

Discussion

We present data on echocardiographic characteristics

Table 8 Comparison of LVMI of HIV-infected subjects based on exposure to zidovudine

LVMI	Zidovudine exposure		Total
	Yes	No	
Elevated	7	4	11
Normal	18	7	25
Total	25	11	36

Fisher Exact test; P=0.703; LVMI, left ventricular mass index.

of HIV-infected children on routine outpatient care at the paediatric HIV clinic of the Lagos State University Teaching Hospital, Lagos in South-West Nigeria. Majority of the study subjects were less than 10 years old, most presumed to have been infected via vertical transmission. Vertical transmission is still the predominant mode of transmission of HIV in paediatric population in the developing world due mainly to low coverage of PMTCT services (9,30).

The present study shows high prevalence of subclinical abnormal echocardiographic profile of HIV-infected children: almost half (46%) of the subjects had one or more abnormalities of cardiac size and/or function. This prevalence was higher than values of 7%, 27%, 37% in a Ugandan study and two separate Indian studies, respectively (30). A study conducted on Nigerian children in Lagos by Okoromah *et al.* (7) reported a higher prevalence of 76% based on abnormal clinical, electrographic and echocardiographic findings unlike the index study based only on abnormal echocardiographic parameters. Moreover, the subjects in the index study were stable HIV-infected children on outpatient care and were less ill compared to Okoromah study, which included acutely ill, hospitalized children. Another explanation for the widely disparate prevalence values from one study to another is the varying spectrum of echocardiographic abnormalities studied. For example, while the index study evaluated left ventricular systolic function, the Cameroonian study evaluated both diastolic and systolic functions of the right and left ventricles.

The subjects with cardiac abnormalities in the index study were largely asymptomatic as shown by the fact that one subject had clinical symptoms. This is similar to most reports in the post-HAART era as against the pre-HAART dominated by high prevalence of symptomatic cardiac disorders (7,30-34). In a study of Thai children by Pongprot *et al.* (35), almost all the 27 subjects studied presented with symptoms such as dyspnoea, oedema, finger clubbing, cyanosis and gallop rhythm. The index study was a prospective study of ambulatory outpatient subjects on ART in contrast to this Thai study, which was a retrospective study of ART-naïve children evaluated primarily for HIV-related cardiac disorders. More recent longitudinal studies have shown long-term ART to be cardio-protective at least in the first decade of life (6). The finding of low prevalence of cardiorespiratory symptoms in HIV-infected children with cardiac abnormalities may suggest that clinical symptoms and signs have low sensitivity in the early detection of HIV-associated cardiac dysfunctions. Hence, routine serial echocardiographic studies are mandatory in the early detection HIV-associated heart diseases.

Similar to findings by Okoromah *et al.* (7) most of the echocardiographic parameters were similar between HIV-infected children and controls.

Left ventricular dilatation (defined as LVEDD >2 z-score), a subclinical precursor to more life-threatening cardiac complications such as dilated cardiomyopathy and congestive heart failure, has been widely reported in HIV-infected subjects (7,8,13,32,34-37). The LVEDD of the study subjects were not significantly larger than those of controls. However, the P value was close to statistical significance. The index study observed a prevalence of LV dilatation of 12.8%; higher than prevalence of 1% and 7% in Cameroonian and Zimbabwean children respectively but lower than 37% reported in a European study (38). None of the subjects in the index study met criteria for dilated cardiomyopathy similar to a study of Cameroonian children (13). Anaemia has been reported to contribute to chamber dilatation in HIV-infected children (37). Recent reports suggest that the prevalence of dilated cardiomyopathy has remarkably declined since the advent and wide availability of HAART (7,13,19,28,34-37).

The right ventricular dimension of HIV-infected subjects was larger than that of controls, albeit non-

significantly, in the present study. However, the prevalence of right ventricular dilatation (RVD) was not specifically determined. In a study of 100 Cameroonian children, Chelo *et al.* (13) reported a very high prevalence 76% whereas the prevalence of LV dilatation was just 1%. Surprisingly only 8% of the subjects with RVD had pulmonary hypertension presumably secondary to chronic HIV-associated lung disease. The authors suggested that the use of Caucasian references may have resulted in overdiagnosis of RVD in the cohort. Lower prevalence rates 14-30% have been reported in other African studies of HIV-infected children (17,32).

The present study observed a significantly larger LVM among subjects compared to controls. This is similar to findings in reports from other centres (7,9,20). The prevalence of LVH in this cohort (28%) was similar to 21% and 29% reported in studies of Nigerian (9) and Indian (31) children, respectively. It was lower than 67% in Zimbabwean (17) children but higher than 14% reported in another cohort of Nigerian children in northern Nigeria (9). Differences in the diagnostic criteria for LVH may partly contribute to the variations in reported prevalence, in addition to true geographic variations in disease pattern and distribution. For example, while the index study used LVM indexed to height raised to the power of 2.7 ($ht^{2.7}$), a previous Nigerian study indexed LVM to body surface area (9) while another used unindexed LVM (7). The need to use indexed LVM, rather than LVM, arose because of the increasing cardiac size that normally occurs with increasing age and body composition in the paediatric age group (23). LVM indexed to $ht^{2.7}$ has been reported to account better for the confounding influence of body fat on LVM compared to LVM indexed to BSA (7-9). Due to absence of local reference values for LVMI indexed to $ht^{2.7}$, most studies, including the index study, have used the adult cut-off value of 51 $g/m^{2.7}$ which has been shown to be imprecise in children because of its significant variation with height particularly in preadolescents. Use of percentile curves or z-scores has thus been proposed as better alternatives in children (39). However, absence of local references precludes use of these methods in the index study.

LVH and LVM are important parameters useful in prediction of risk of mortality and adverse cardiovascular events in HIV-infected children (40). Concentric LVH has been associated with increased cardiovascular morbidity and mortality in adults while those with eccentric LVH have an intermediated risk (41). Majority of the subjects with LVH in the present study were below five years of age. Other studies have also suggested this age group may be at higher risk for HIV-associated cardiac abnormalities (9,38). The reasons for this observation is not immediately apparent but may not be unconnected with the effect of long-term HAART: the longer the duration on HAART the smaller the incidence of cardiovascular complications of HIV (28).

LVH in HIV-infected subjects has been attributed to a subclinical myocardial inflammation, which underlies a spectrum of heart disease ranging from asymptomatic LV dilatation to full-blown dilated cardiomyopathy in later years. Hence, such individuals require long-term monitoring and, when necessary, interventions such as selenium supplementation and use of immunoglobulins which have been shown to reverse these cardiac aberrations (28,42).

Despite larger left atrial and ventricular sizes, the HIV-infected group had better left ventricular systolic function in the index study. However, the differences were not significant. Other authors reported significantly lower LVFS and LVEF in HIV-infected children compared to normal population (7,20,37). LVFS is a product of several cardiovascular processes such as preload, afterload, heart rate and cardiac contractility; derangement of any of these processes may thus result in abnormal LVFS (23,40). Singly or in conjunction with LVH, LVFS is a long-term predictor of mortality in HIV-infected children (18,40).

The prevalence of systolic dysfunction (defined as LVFS <28%) in the present study was lower than 35% reported by Okoromah *et al.* (7) a study conducted about seven to nine years earlier than the index study. Whereas the present study defined LV dysfunction as LVFS <28% the Okoromah study used a cut-off value of ≤25%. However, another study of Nigerian children by Ige *et al.* (19) reported a prevalence rate of 50% despite use of cut-off value of <28%. Another explanation of this disparity could be the fact that 97% of the subjects in the present study were on ART compared to 56% in the latter study; HIV-infected children on HAART have lower prevalence of LV dysfunction (37). A very low prevalence of **LVFS** of about 2% was reported in a Ugandan study—the study population was characterised by 94% optimal ART adherence and 68% virologic suppression (8). It is interesting to note that an Ugandan study conducted 10 years earlier reported a much higher prevalence of LVFS dysfunction of 51% at a time when less than 1% of subjects were on ART (32). This observation supports the overall cardio-protective effect of ART compared to non-therapy.

The presence of thicker ventricular wall, ventricular dilatation and LVH in ARV-exposed HIV-infected

children, as observed in the index study, are postulated to be compensatory mechanisms that arise in response to HIV-associated anaemia and myocardial inflammation aimed at preserving cardiac output. However, as these responses progress a point is reached when they become detrimental resulting in reducing LVFS (37). Early detection of subclinical HIV-associated cardiovascular disorders is thus important to reduce the frequency of full-blown cardiovascular events. Treatment with drugs such as angiotensin converting enzyme inhibitors (ACEIs), intravenous immunoglobulins, selenium supplementation and beta-blockers like carvedilol may slow or reverse this disease progression (28-31).

Data on clinical and laboratory measures of disease severity were not available for the subjects in the index study. Hence, their association with cardiac abnormalities could not be assessed. Although cardiac abnormalities tend to be prevalent with declining immune status, CD4 count has been reported to be a poor marker of cardiovascular disorders (31,43).

Although drugs such as zidovudine and abacavir have been reported to have adverse cardiovascular effect when HIV-infected children are perinatally exposed to them, the LVMI of subjects on zidovudine-based therapy in the present study was not significantly different from those of subjects on other regimen (7,28). This is similar to other reports (17). Recent data from longitudinal studies strongly suggest that HAART is generally cardio-protective at least for the first decade of life after which this protective effect seem to decline gradually into adulthood (6,28,44).

The strengths of this study include use of a prospective design and exclusion of acutely ill patients. However, the small sample size limits generalization of the findings of the study to the larger population of HIV-infected children in our center or beyond. Nonetheless, the findings were not widely different from findings from other Nigerian studies with larger sample sizes (7,9,19,20). Use of control subjects obtained from our echocardiographic database is also a limitation as rigorous inclusion and exclusion criteria could not be applied to the control group. However, careful matching was done and the same cardiologist did the echocardiography for both groups, thus minimizing inter-rater bias. Also, this study did not evaluate the diastolic function of the subjects which may precede systolic dysfunctions in the spectrum of cardiac disease in HIV-infected children (45).

In conclusion, this study has highlighted the presence of asymptomatic borderline cardiac dysfunction in HIV-infected children and thus lends it voice to advocacy for the inclusion of baseline and follow-up echocardiography in the routine care of HIV-infected children (7,9,20,28). Scale-up of PMTCT services with wider access to early infant diagnosis will reduce the burden of vertically transmitted HIV infection and, by extension, its cardiac complications. There is also need for local reference values for paediatric echocardiographic parameters using current standards such as z-scores to enhance accurate diagnosis of childhood cardiac dysfunctions.

As HIV-infected children and adolescents with subclinical cardiac abnormalities grow into adulthood and get exposed to other cardiovascular risk factors such as hypertension, smoking, obesity or hyperlipidaemia there is concern that they may eventually become symptomatic (40). Large prospective longitudinal, preferably multi-center, studies, specifically in sub-Saharan African context, are thus needed to ascertain the current cardiac profile of HIV-infected children and elucidate it clinical determinants such as genetic factors and micronutrient deficiencies such as selenium deficiency. Lastly, where resources are scarce, perinatally-infected HIV-infected under-five children may be prioritized for detailed cardiovascular assessment.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jxym.2018.03.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Lagos State University Teaching Hospital (LREC.06/10/823). Informed consent was taken from all subjects.

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