Cardiovascular Dysfunction in HIV-infected Children in a Sub-Saharan African Country: Comparative Cross-sectional Observational Study

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Summary

Objective: Cardiac dysfunction is rarely diagnosed in HIV-infected children in our setting and standard care does not include baseline and follow-up echocardiography. We aimed to determine the prevalence, pattern and predictors of HIV-related cardiac dysfunction. Methods: Pre-diagnosed HIV-infected children aged 18 months to 12 years from a tertiary teaching hospital in Lagos, South-West Nigeria were enrolled in a comparative, observational cross-sectional study; matched with apparently healthy controls of the same age group, were recruited sequentially between May 2004 and 2007. Proportions of pre-defined cardiac abnormalities such as heart failure diagnosed by clinical examination and dilated cardiomyopathy and ventricular dysfunction by echocardiography were determined. Results: Prevalence of cardiac abnormalities in HIV-infected children was 75.9%. Abnormalities included heart failure, dilated cardiomyopathy (33.7%), decreased LVSF of $\leq 25\%$ in 33.7%, increased left ventricular mass (20.5%) and pericardial effusion (14.5%). Conclusion: Structural and functional abnormalities are prevalent in HIV-infected African children and therefore justify inclusion of routine echocardiography in their standard care.

Key words: HIV/AIDS, cardiac dysfunction, children, cross-sectional study, Lagos, Nigeria.

Introduction

The human immunodeficiency virus (HIV) infection and the resulting acquired immunodeficiency syndrome (AIDS) constitute one of the most frightening diseases to appear in modern times. HIV/AIDS constitutes a global health burden with overwhelming social, economic and political repercussions [1]. The HIV/AIDS epidemic has had its most profound impact to date in sub-Saharan Africa, which constitutes only 12% of the world's population. Nearly 70% of people living with HIV/AIDS, cases of new HIV infections, and AIDS-related deaths occur in this region [1–6]. Almost all countries in sub-Saharan Africa have generalized epidemics defined as prevalence rates >1% and HIV infection is the leading cause of death and a shortened life expectancy in this region.

HIV/AIDS affects multiple organ systems and the lungs, brain, skin, gastrointestinal tract, kidneys and heart are the major organs affected. Cardiac complications of HIV disease are multifactorial and may result from a complex interplay of events ranging from direct myocardial invasion with HIV, prolonged immunosuppression, opportunistic infections, viral infections, autoimmune response to viral infection, pulmonary hypertension from recurrent

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parenchymal lung disease, drug-related cardiotoxicity to nutritional deficiencies [7–15]. Although the endocardium, myocardium, pericardium and vasculature may be affected by HIV infection, the myocardium remains the most vulnerable and this may present as myocarditis, dilated cardiomyopathy or isolated left or right ventricular dysfunction. Both adults and children are affected with disease severity ranging from incidental microscopic inflammatory findings at autopsy to clinically significant cardiac disease with chronic cardiac dysfunction [14]. Cardiac dysfunction has been associated with poor prognosis and results in symptomatic heart failure in up to 5% of HIV patients [16].

Cardiac dysfunction in HIV infection have been widely reported in developed countries, and shown to contribute to morbidity and mortality in children [7–17], Lipshultz *et al*. [13] in a cohort, longitudinal, multicenter study found that among HIV-infected children, baseline echocardiographic abnormalities are prevalent, persistent and often progressive, and some are associated with cumulative all-cause mortality [16]. Depressed baseline left ventricular systolic performance and increased left ventricular wall thickness have been shown to contribute significantly to the prediction of mortality after adjusting for severity of immunodeficiency, HIV viral load, encephalopathy and clinical care setting [16]. Also, reports show that although HIV-related cardiac dysfunction may be severe, they are usually sub-clinical, subtle and non-specific to be easily identified [18–20]. Also, the symptoms and signs of cardiac dysfunction when present may mimic non-cardiac pathologies and may be attributed to lung parenchymal disease. Therefore, a high index of suspicion and objective evaluation using echocardiography are necessary for early detection of HIV-related cardiac abnormalities.

Although cardiac dysfunction in HIV-infected children has been well characterized among Caucasians using echocardiography and rigorous study designs, the contrast is the case for infected children in the sub-Saharan African region, which bears the greatest burden of HIV/AIDS. The few existing published reports in the developing regions of the world especially African region are mostly on adults and study designs lacked controls [18–21]. The advent of highly active anti-retroviral therapy (HAART) and improved medical care of HIV/AIDS patients imply increasing survival for HIV-infected children and long-term systemic complications of the disease and its treatment. Also, routine cardiovascular evaluation using echocardiography is not standard practice in the management protocol of HIV infected in most sub-Saharan African setting largely due to lack of changes in policy and practice to support its use. Low awareness about HIV-linked cardiac dysfunction and lack of reliable scientific evidence to support or refute the use of routine echocardiography in HIV-infected children has been reported [19, 20]. We hypothesized that HIV-related cardiovascular dysfunction-based on clinical assessment and echocardiography- is a prevalent but under-diagnosed and under-treated problem in HIV-infected children and that its predictors are modifiable. The present study aimed to determine functional and structural cardiac abnormalities by clinical evaluation and echocardiography in a cohort of HIV-infected children using a controlled observational cross-sectional study design.

Methods

This was a comparative, observational, cross-sectional study of 83 pre-diagnosed HIV-infected children with or without AIDS who were aged between 18 months and 12 years. They were recruited sequentially between May 2004 and May 2007 from the weekly specialized paediatrics outpatient clinic for perinatally exposed newborns and HIV-infected children receiving standard outpatient care at the Lagos University Teaching Hospital (LUTH). Positive HIV status is a prerequisite for all children attending the special clinic. Currently, the upper age limit of children registered at the specialized clinic is 12 years. Eighty-three age- and sex-matched apparently healthy controls free from HIV infection were randomly. Also, selected from the Well-Child Clinics (WCC) of the same hospital, and from a neighborhood primary school. Informed consent was obtained from parents and other legal caregivers before enrolment. Diagnosis of HIV infection is routinely based on positive HIV serology confirmed by the western blot technique.

Exclusion criteria

Children with known congenital or acquired cardiovascular disease documented in their medical records or detected at enrolment were excluded from the study. Also, children with additional comorbidities like recognizable or confirmed genetic/chromosomal anomalies, dysmorphic features, e.g. craniofacial disproportion, obvious extracardiac malformations, tuberculosis, malignancies, syndromic anomalies, chronic illnesses other than HIV infection, associated with visible/demonstrable wasting or oedema; any serious ongoing acute illness requiring hospitalization; or those receiving medications with cardiovascular effects such as digoxin, propranolol, salbutamol. Those whose caregiver refused to give consent for the study, were also excluded from the study.

Social classification

Socio–economic status of study participants was grouped into three classes—upper, middle and lower—based on the classification by Oyedeji [22].

Participants handling protocol
A standard pre-tested questionnaire was used to extract relevant medical data retrospectively from the medical records of enrolled HIV-infected children and other relevant information at the point of recruitment. Data extracted included biodata (age and sex), sociodemographic characteristics (parents' or caregivers' education, occupation and income), HIV-status, age at diagnosis of HIV infection, duration of HIV infection, HIV/AIDS category (based on the revised Centers for Disease Control and Prevention (CDC) classification system currently in use for the care of HIV-infected children at LUTH [3]), duration of HIV infection with or without AIDS, type and duration of anti-retroviral (ARV) therapy. Aspects of data extracted from medical records relating to past medical, family and social histories were corroborated on the day echocardiography was performed on the children. All subjects for the study underwent a thorough physical examination just prior to performing echocardiography on them.

A child was classified as infected with HIV if he/she showed a positive enzyme-linked immunoassay (EIA) screening and western blot electrophoresis tests. $CD4^+$ lymphocyte cell count and viral load were estimated in only 16 (19.3%) subjects due to cost constraints. All sera from potential controls were subjected to HIV testing using the Capillus© HIV testing kit (Trinity Biotech, California, USA) after a verbal consent was obtained from either the parent(s) or caregiver(s) and patients where applicable. Only those that tested negative were recruited into the study.

Anthropometry and blood pressure measurements
Anthropometry measurements were performed according to standard procedures of the World Health Organization [23]. Height and weight were obtained using an AVERY® stadiometer and weighing scale (Birmingham, UK). Weight measurements were recorded in kilogram while the height/length measurements were recorded in centimeters.

Systolic and diastolic blood pressure (BP) measurements were obtained using an aneroid sphygmomanometer with an appropriate cuff bladder size, covering at least two-third of the child's upper arm, after the child had rested for at least 5 minutes. The average of two readings was taken 10 minutes apart to represent the BP estimate.

Echocardiography
All study participants (HIV-infected children and controls) underwent a protocol-directed transthoracic echocardiography (2-Dimensional, M-mode and Doppler evaluation) using a Hewlett Packard Sonos 1000 model echocardiography machine (Soma Technology Inc, USA) and a transducer frequency of 3.5 or 5 MHz where applicable. All measurements were based on the criteria of the American Society of Echocardiography [24]. Two independent paediatricians trained and experienced in Paediatric echocardiography carried out the echocardiography and differences in their findings were resolved at a joint session. These operators were blinded to the HIV and clinical status of the children. Standard procedures and techniques were applied to the parasternal, apical and subcostal views for the echocardiography. The parasternal long axis view was applied for M-mode measurements of the heart chamber dimensions in systole and diastole. Left ventricular fractional shortening (LVFS) was generated by the machine and values were randomly cross checked manually using the LV dimensions measured in systole and diastole to assure accuracy of readings. All M-mode measurements were performed twice and an average was taken to optimize intra-rater reliability. Anthropometric measurements and physical examinations were done just prior to the echocardiography. Doppler and colour flow studies were done to study valve and orifice pressure gradient and directionality of blood flow. Continuous Doppler recordings were obtained, with the sample volume located between the tips of the heart valve. Regurgitation was considered mild if the back flow seen on colour Doppler did not reach the middle, moderate if the flow reached the middle and severe if it exceeded the middle of the receiving chamber. Young children >5 years were sedated if necessary with chloral hydrate if they were uncooperative for the echocardiography. M-mode measurements were made based on the Devereux *et al.* [25] and normative values for the echocardiographic measures according to age or body surface area (BSA) were based on measurements obtained from controls or reference values for children.

Baseline measures of cardiac function performed were left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD), left ventricular posterior wall and corresponding ventricular volumes: left ventricular end systolic volume (LVESV), left ventricular end diastolic volume (LVEDV) were measured. Left ventricular systolic function was determined by the LVFS computed from the basic measurements using appropriate formulae and corrected to the BSA: $\text{LVFS} = 100 \times (\text{LVEDD} - \text{LVESD})/\text{LVEDD}$.

Definition of terms:

1. Pre-AIDS subjects [3] were HIV-infected children with category A or B symptoms of the CDC revised classification system.
2. AIDS subjects [3] referred to HIV-infected children with category C symptoms of the CDC revised classification system.

3. Age at diagnosis: this is the age at which the diagnosis of HIV infection was confirmed using western blot or viral studies.
4. Duration of symptoms is the difference between age at onset of symptoms and age at enrollment into the study.
5. Cardiac failure was defined by four cardinal features, tachycardia (with or without gallop rhythm), tachypnoea, tender hepatomegaly and cardiomegaly [25]. Tenderness of the liver was an absolute consideration for diagnosing heart failure as it suggested acute congestion of the liver in congestive heart failure.
6. Left ventricular fractional shortening (LVSF) is a measurement of overall LV systolic performance that is affected by contractility, pre-load, after-load and heart rate. Left ventricular systolic dysfunction was defined as LVSF $\leq$25%.
7. Dilated cardiomyopathy (DCM) was diagnosed based on three criteria: diffuse hypokinesia on 2-D echocardiography, LV systolic dysfunction (LVSF $\leq$25%), and left ventricular dilatation (LVEDD/BSA) $\geq 3.2\,cm/m^2$ or greater than upper limit of normal for BSA.
8. Pericardial effusion was identified as effusions that measured $\geq 5.0\,mm$

Ethical consideration

Permission to conduct the study was obtained from the LUTH Ethics Committee and informed consent was obtained from children, their parents or caregivers of all children who participated in the study.

Analysis

The data were entered, validated and analysed using SPSS for Windows version 11 (SPSS Inc. Chicago, IL, USA) and Epi info version 6.04 computer statistical packages (CDC, Atlanta, Georgia, USA), to determine prevalence of cardiac abnormalities. Comparisons were made between two main study groups (HIV-infected children and controls). Where relevant, the HIV-infected children were categorized into two sub-groups (pre-AIDS and AIDS) and matched with equal number of controls for comparison. Continuous variables were expressed as means and standard deviations if they were normally distributed and as median and range if skewed. Two sample (unpaired) Students *t*-test, two-way ANOVA and multivariate logistic regression analysis were used to compare means and test the relationship between covariates. The χ^2-test, Mann–Whitney U-test and other appropriate non-parametric tests were used for categorical (discrete) variables. For variables that were highly skewed such as duration of symptoms and age at diagnosis of HIV infection, a logarithmic transformation was done before analysis. Where numbers or frequencies were small (less than five in one cell), Fishers exact test was used. Pearson's and Spearman's rho correlation coefficients were used for symmetric quantitative and ordered or asymmetric variables respectively. Analysis of variance was performed for comparison of means of more than two groups and Student's *t*-test for comparison of two different groups. Differences between groups were considered statistically significant if $p < 0.05$. All risk variables for cardiac dysfunction significant at $p < 0.001$ were included in a stepwise multivariate logistic regression analysis. Odds ratios were 95% confidence intervals were computed.

Results

Table 1 shows the summary of baseline, socio–demographic and other characteristics of the main study population. The main study groups (HIV-positive cases and HIV-negative controls) were similar and comparable in terms of age, sex distribution and social class. Children in the age group 36–144 months constituted 72.3% of HIV positive cases.

Clinical characteristics of the HIV-positive children

Of the 83 HIV-positive cases, 69 (83.9%) had AIDS. They presented with category C symptoms

TABLE 1
Baseline sociodemographic and other characteristics of the study population

Variable	HIV positive (cases) $n = 83$	HIV negative (controls) $n = 83$	*p*-value
Age (months)	42.20 (38.10)	42.40 (38.10)	0.99
Age range (months)	18–144	18–144	
Social class, *n* (%)			
Upper class (I and II)	24 (28.9)	26 (31.3)	0.42
Middle class (III)	28 (33.7)	27 (32.5)	
Lower class (IV and V)	31 (37.3)	30 (36.1)	
Mean age at onset of symptoms of HIV/AIDS (months)	29.20 (28.90)		
Mean duration of symptoms (months)	34.50 (25.90)		

Values for continuous variables represent mean (SD), unless otherwise specified.

TABLE 2
Clinical parameters of HIV/AIDS cases and controls

Variable	HIV/AIDS cases $n = 83$	Controls $n = 83$	p-value
Weight (kg)	16.75 (7.17)	22.44 (9.42	0.0002**
Height/Length (cm)	104.44 (19.82)	114.67 (21.77)	0.0002**
Body surface area (m^2)	0.68 (0.2)	0.84 (0.25)	0.0001**
Respiratory rate/min	30 (7)	26 (5)	0.0001**
Heart rate/min	107 (19)	97 (13)	0.0001**
Systolic BP (mmHg)	83 (12)	80 (9)	0.15
Diastolic BP (mmHg)	54 (8)	54 (7)	0.07

Figures shown are mean (SD).
**Highly significant difference.

TABLE 3
Clinical parameters of the pre-AIDS subgroup and controls

Variable	Pre-AIDS $n = 14$	Controls $n = 14$	p-value
Weight (kg)	15.43 (11.69)	15.12 (6.74)	0.92
Height/length (cm)	95.08 (26.28)	95.40 (20.27)	0.98
Body surface area (m^2)	0.63 (0.31)	0.63 (0.2)	0.98
Respiratory rate/min	32 (6)	29 (6)	0.27
Heart rate/min	121 (19)	107 (16)	0.07
Systolic BP (mmHg)	83 (4)	77 (7)	0.24
Diastolic BP (mmHg)	53 (9)	50 (9)	0.39

Figures shown are mean (SD). $p < 0.05$ not statistically significant.

(wasting syndrome) based on the CDC classification. The remaining 14 (16.1%) subjects were classified as being in the pre-AIDS phase. In the pre-AIDS category, 4 (4.8%) and 10 (12.0%) children had category A and category B symptoms, respectively.

Table 2 displays the clinical parameters of HIV positive with or without AIDS children compared with age- and sex-matched healthy controls. The differences in weight, height, BSA, respiratory rates and heart rates between the two groups were statistically significant.

A subgroup analysis of the clinical parameters of 14 HIV-positive children without AIDS and 14 matched controls showed that there was no statistically significant difference in their clinical parameters as illustrated in Table 3.

Echocardiography findings

Tables 5 and 6 display echocardiography findings in the two main study groups. Table 5 highlights structural and functional echocardiographic parameters in HIV/AIDS group compared with matched controls. Mean aortic root diameter (AO) and mean fractional shortening (FS) were significantly lower in the HIV/AIDS group compared with controls ($p = 0.0001$).

Prevalence of cardiovascular abnormalities

Based on physical examination and echocardiography, cardiovascular abnormalities were seen in 63 of 83 HIV-infected children giving a prevalence rate of 75.9%. None of the controls had abnormal echocardiography findings. The pattern of cardiac abnormalities are displayed in Table 6. Some patients had multiple cardiac abnormalities.

Cardiovascular changes were significantly more prevalent in HIV-infected patients on anti-retroviral drugs (ARV) drugs and these included heart failure, pericardial effusion and increased left ventricular mass (LVM). As noted above, depression of fractional shortening was most pronounced in children with full blown AIDs on ARV. There were no significant difference in the characteristics of children with and without cardiovascular dysfunction in relation to their age, gender, weight, height, BSA, mean age at diagnosis of HIV infection and the stage of the disease. There was no significant association between occurrence of cardiovascular abnormalities and some variables such as age, gender, mean age at diagnosis and even stage of disease except with ARV therapy, odds ratio 3.33 (95% confidence interval 2.30–4.56); $p = 0.001$.

Discussion

There is a dearth of data on cardiovascular dysfunction in HIV-infected children in the sub-Saharan

TABLE 4
Clinical parameters of children with AIDS and controls

Variable	AIDS $n=69$	Controls $n=69$	p-value
Weight (kg)	17.77 (6.28)	21.02 (9)	0.01*
Height/length (cm)	104.63 (18.69)	111.3 (20.81)	0.048*
Body surface area (m^2)	0.71 (0.18)	0.8 (0.24)	0.02*
Respiratory rate/min	29 (70)	26 (50)	0.002**
Heart rate/min	103 (18)	97 (12)	0.003**
Systolic BP (mmHg)	85 (12)	82 (90)	0.01*
Diastolic BP (mmHg)	54 (90)	53 (60)	0.38

Figures shown are mean (SD).
*Significant difference; **highly significant difference.

TABLE 5
Echocardiography parameters of the pre-AIDS/AIDS and control groups

Variable	Pre-AIDS/ AIDS $n=83$	Controls $n=83$	p-value
AO (cm)	1.75 (0.32)	1.87 (0.33)	0.02*
LA (cm)	2.35 (0.49)	2.46 (0.35)	0.1
LA/AO	1.35 (0.23)	1.34 (0.21)	0.76
EDD (cm)	3.51 (0.51)	3.55 (0.51)	0.61
ESD (cm)	2.38 (0.46)	2.48 (0.47)	0.17
FS (%)	32.09 (9.83)	39.97 (6.14)	0.0001**
EF (%)	67.43 (13.39)	63.57 (12.3)	0.06
LVPW (cm)	0.67 (0.14)	0.64 (0.16)	0.2
IVS (cm)	0.69 (0.17)	0.71 (0.13)	0.4
LVM (gm)	79.94 (30.12)	71.24 (22.49)	0.04*

Figures shown are mean (1SD); $p < 0.05$ statistically significant difference.
*Significant; **Highly significant.
AO, aortic diameter; LA, left atrial diameter; LA/AO, left atrial to aortic diameter ratio; EDD, end-diastolic diameter; ESD, end-systolic diameter; FS, fractional shortening; EF, ejection fraction; LVPW, left ventricular posterior wall diameter; IVS, inter-ventricular septal diameter; LVM, left ventricular mass.

TABLE 6
Pattern of cardiac abnormalities in HIV-infected children, $n=83$

Cardiac abnormality	n (%)
Congestive cardiac failure	10 (12.0)
Dilated cardiomyopathy	28 (33.7)
Depressed LVFS ($\leq$25%)	28 (33.7)
Increased LVM	17 (20.5)
Pericardial effusion ($\geq$5.0 mm)	12 (14.5)

region and none has been published among Nigerian children. Cardiac dysfunction is rarely diagnosed in HIV-infected children in our setting and standard care does not include baseline and follow-up echocardiography. The authors reasoned that although the spectrum of cardiac abnormalities may be similar to previous reports, local data will strengthen future recommendation to incorporate routine baseline and periodic cardiovascular evaluation including echocardiography in HIV management protocol in our practice setting. The second area of specific interest was to identify the link between certain variables and the presence of cardiovascular abnormalities in children with HIV/AIDS. The present study aimed to determine the prevalence, pattern and predictors of cardiovascular dysfunction in HIV-infected children using clinical assessment and echocardiography and to ascertain differences with matched controls.

Prevalence of cardiovascular dysfunction

A very high prevalence rate of 75.9% for cardiovascular abnormalities was observed in HIV-infected children. Although published reports show a wide variation in magnitude of cardiac dysfunction in different regions of the world, significantly lower prevalence rates of 40, 44, and 55% were reported in three sub-Saharan African countries [18–20]. Much higher prevalence rate of 93% has been reported when both electrocardiography (ECG) and echocardiography were used as the ascertainment methods, while significantly lower rates of 44 and 55% were reported by Blanchard *et al.* [26] and Longo-Mbenza *et al.* [27], respectively.

In contrast, very high proportions of cardiac dysfunctions similar to our findings have been previously reported in other developing and developed countries. Shah *et al.* [28] in India, Sherron *et al.* [29] in San Antonio and Fink *et al.* [30] in Washington, USA, published prevalence rates of 76.9, 74 and 73%, respectively. Methodological differences including patient selection, sample size, study design, definition of cardiac dysfunction, inclusion criteria, disease severity and disease ascertainment methods used may have contributed to the reported widely variable prevalence rates. For example, combining ECG and echocardiography

was reported to detect more cardiac abnormalities than either methods used singly or by clinical symptoms and physical examination alone [28]. A much higher prevalence rate of 93% was reported when both ECG and echocardiography were used as the ascertainment methods [28] in the same study. Echocardiography is the leading technology for evaluating cardiovascular structure and function in children and adults, and norms for echocardiographic measurements in children have been established [24].

The present study in addition to using age- and sex-matched controls, applied echocardiography and clinical evaluation to ascertain cardiovascular abnormalities, and the cardiac abnormalities were predefined. The controlled design of our study strengthens association between HIV infection and presence of cardiac abnormalities and their relationship to specified variables compared with uncontrolled studies.

It is important to state that the very high rates of cardiac abnormalities previously reported for developed countries like the USA may not represent the current trend because extensive and successful reduction in vertical transmission of HIV infection from mother to child and routine serial echocardiography of HIV-infected newborns to support early detection and appropriate intervention for any significant cardiac dysfunction.

The mean weight observed in the AIDS group was significantly lower than the controls. This is expected, especially in symptomatic HIV-infected subjects where the loss of lean body mass specifically muscle protein has been well documented [31, 32]. Even in the absence of HIV infection, malnutrition has been known to be associated with decrease in LVM, left ventricular volume and ventricular function [29, 30]. Similar to previous reports [31, 32], LVM was increased in HIV-infected children, thus suggesting that there may be factors that counteract the usual effects of malnutrition on heart muscle mass. Could inadequate nutrition in HIV/AIDs patients possibly cause subnormal hypertrophic responses relative to left ventricular dimension? These hypotheses need to be further explored. The role of nutrition and nutritional status may have contributed to the high prevalence of cardiac dysfunction in the present study, but determining the nature of such association was not the aim of the present study.

Pattern of cardiovascular abnormalities

The distribution of cardiac dysfunction in HIV-infected children in the present study were diverse and ranged from clinically innocuous abnormalities such as mild pericardial effusion to potentially life-threatening structural abnormalities such as dilated cardiomyopathy (DCM), decreased LVFS and increased LVM. Although, there is a wide variation in prevalence across specific cardiac abnormalities compared with some previous reports, findings in the present study were proportionately higher that findings elsewhere. For example, the prevalence of DCM in the present study (33.7%) was higher than 3.0, 14.8, and 16% reported by Lubega *et al.* [33] in Uganda, Nzuobontane *et al.* [34] in Cameroon and Lipshultz *et al.* [35] in USA, respectively, but lower than reports by Sherron *et al.* [36] (45%) compared with present study, noted high prevalence of decreased LVFS. Similar to findings in the present study, increased LVM has been reported in HIV/AIDS patients. It is noteworthy that some of the HIV-linked cardiac abnormalities found in the present study such as decreased LVFS and increased LVM have been reported in developed countries to predict mortality [35]. Also, the high prevalence of clinically apparent but unrecognized congestive heart failure deserves mention. Respiratory diseases were the primary diagnoses in all HIV-infected children diagnosed with heart failure during this study. The authors attribute this finding to the inherent tendency to miss heart failure when the manifestation of respiratory disease is overwhelming unless the clinician has a high index of suspicion. With the wide spectrum of cardiac dysfunction identified in the present study, it is hoped this will raise the awareness among care providers.

There was no significant difference in the mean heart rate, systolic and diastolic BP of HIV/AIDS and control groups in the present study. Similar findings were reported by Coudray *et al.* [36] in France. However, the mean heart rate was significantly higher in the AIDS group, a finding that has been attributed to autonomic to dysfunction in HIV-infected children [37]. This may also be a pathophysiological response in congestive heart failure, systemic infection or hyppoxaemia associated with pulmonary disease in HIV-infected children.

The prevalence rate of pericardial effusion in this study was 12% and these were predominantly mild effusion that measured values were <0.50 cm, which corresponds to an estimated volume of <100 ml of pericardial fluid. Our finding falls within the range of 8.8–15% reported for pericardial effusion in published literature. Higher prevalence rates ranging between 21% and 58% have also been documented in both adults and children [38, 39]. Estok and Wallace [38] in New York reported a rate of 21% in adults, while Mast *et al.* [39] in Brooklyn reported a rate of 58% in children, including autopsy findings, which may have swelled the number. Although the volume of effusion found in the present study was not significant enough to cause a tamponade, these children will need to be followed up closely.

In the present study, FS $\leq$25% was defined as depressed. Many of the children with cardiovascular abnormalities had a significantly depressed FS, which accounted for 28% of all cardiac impairments observed in this study. This is similar to the 29% rate reported by Lipshultz *et al.* [40] in Boston. As

mentioned earlier, the significance of a high proportion of decreased LVSF indicating impaired LV systolic function relates to its association with mortality in a multicenter, cohort prospective study conducted in the USA [35].

The spectrum of clinical cardiovascular abnormalities associated with HIV infections with or without AIDS in the present study included tachypnoea, tachycardia, cardiomegaly and tender hepatomegaly, which were associated with congestive cardiac failure found in 10 (12%) of HIV-infected children. Starc *et al*. [41] in New York reported a similar prevalence rate of 10% for heart failure in HIV-infected children.

The present study did not find any significant association between occurrence of cardiovascular abnormalities and some variables such as age, gender, mean age at diagnosis and even stage of disease.

Advanced stage of disease, which is a well recognized and reported risk factor for cardiac involvement in HIV infection, was not significantly associated with the presence of cardiac abnormality in the present study [13, 35]. The reason for this finding was not obvious considering that most of the subjects with cardiovascular abnormality had clinical category C symptoms. It is hoped that future studies will investigate this finding further. A striking observation in this study was the increased occurrence of cardiovascular abnormalities in subjects on ARV medications when compared to ARV-naive subjects. ARV medications consisted of combinations of zidovudine, nevirapine and lamivudine. The links between HIV infection, ARV treatment and cardiovascular abnormalities have been widely debated and reported especially in relation to treatment with AZT [40–42]. The design of the present study is fundamentally limited to attribute any cause and effect relationship between the use of ARV medications and occurrence of cardiovascular abnormalities. A longitudinal cohort study design or randomized controlled trial comparing various drugs will best suit that purpose. Some workers have expressed contrary views regarding reports on the relationships between HIV infection, ARV medications and cardiovascular abnormalities [31, 32], who reported that AZT had no effect on cardiac changes in HIV infection.

Some of the limitations of the present study include its cross-sectional design, which limited any definite statement on causality and precluded assessment of the natural and clinical course of the cardiovascular abnormalities detected. A longitudinal cohort study design should be used for similar studies in future. Our inability to perform Doppler studies during this study may have under-estimated the magnitude of cardiac dysfunction.

The present study showed that cardiac dysfunction is highly prevalent in HIV-infected children with or without full blown AIDs, and underscores the importance of integrating routine baseline and periodic cardiovascular function assessment including echocardiography in the management protocol of these children. Future research should explore the natural history and conduct risk analysis of cardiovascular dysfunction in HIV/AIDs using a longitudinal cohort study design.

What is already known

In developed countries, best available evidence support baseline and serial cardiac evaluation including echocardiography for early detection, treatment and follow-up monitoring of HIV-infected children due to HIV-linked cardiac dysfunction such as LV systolic dysfunction.

What this study adds

There is a dearth of controlled published studies on HIV-associated cardiovascular dysfunction in sub-Saharan African setting and baseline/serial echocardiography is not included as standard care for affected patients. This study provides epidemiological data based on a comparative cross-sectional study design and showed a high prevalence of cardiac abnormalities that have been reported in developed countries to predict mortality in HIV/AIDS. Our findings provide justification for changes in policy and practice in the care of HIV-infected children in the study setting.

References

1. Joint United Nations Programme on HIV/AIDS and World Health Organization (WHO). *Report on the Global HIV/AIDS Epidemic*. Geneva: World Health Organization, 1997.
2. UNAIDS/WHO. AIDS Epidemic updates 2006. Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization. December 2006.
3. Centers for Disease Control and Prevention (CDC). Revised classification system for Human Immunodeficiency Virus (HIV) infection in children under 13 years of age. Morb Mortal Wkly Rep 1994; 43:1–19.
4. Melvin DC. Cardiovascular complications of HIV/AIDS. In: Sande MA, and Volberding PA (eds). The Medical Management of AIDS. 6th edn. Philadelphia: WB Saunders, 2000; pp. 275–84.
5. National AIDS/STIs Surveillance and Control Program (NASCAP). HIV/SYPHILIS Sentinel seroprevalence survey in Nigeria. Technical Report Series. Nigeria: Federal Ministry of Health, 2006.
6. Rubbert A. Pathogenesis of HIV infection. In: Hoffman C, Rocktosh JK, Kamps BJ (eds). HIV Medicine 2007. 14th edn. Paris: Flying publishers, 2007; pp. 59–64.
7. Bestetti RB. Cardiac involvement in acquired immunodeficiency syndrome. Int J Cardiol 1989;22: 143–6.

8. Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. Am Coll Cardiol 1989;13:1144–54.
9. Yunis NA, Stone VE. Cardiac manifestation of HIV/AIDS: a review of disease spectrum and clinical management. Acquir Immune Defic Syndr Hum Retrovirol 1998;18:145–54.
10. Kaul S, Fishbein MC, Siegel RJ. Cardiac manifestations of acquired immunodeficiency syndrome: a 1991 update. Am Heart J 1991;122:535–44.
11. Arshad A, Bansal A, Patel RC. Cardiac complications of human immunodeficiency virus infection; diagnostic and therapeutic considerations. Heart Dis 2000;2: 133–45.
12. Kattan M, Beck G, Boyett J, *et al*. The paediatric pulmonary and cardiovascular complications of vertically transmitted human immunodeficiency virus ($P^2C^{2)}$ infection study: designs and methods. Clin Epidemiol 1996;49:1285–94.
13. Lipshultz S, Chanock S, Sanders SP, *et al*. Cardiac manifestations of human immunodeficiency virus infection in infants and children. Am J Cardiol 1989;63: 1489–97.
14. Reynolds M, Berger M, Hecht S, *et al*. Large pericardial effusions associated with the acquired immunodeficiency syndrome (AIDS). J Am Coll Cardiol 1991;17: 221A.
15. Hinelman RB, Chung WS, Chernoff DN, *et al*. Cardiac manifestation of human immunodeficiency virus infection: a two-dimensional echocardiographic study. J Am Coll Cardiol 1989;13:1030–6.
16. Lewis W. AIDS: cardiac findings from 115 autopsies. Prog Cardiovasc Dise 1989;32:207–15.
17. Herskowitz A. Cardiomyopathy and other symptomatic heart diseases associated with human immunodeficiency virus infection. Curr Opinion Cardiol 1996;11: 325–31.
18. Cetta F, Michels VV. The natural history and spectrum of idiopathic dilated cardiomyopathy, including HIV and peripartum cardiomyopathy. Curr Opin cardiol 1995;10:332–8.
19. Longo-Mbenza B, Segheri LV, Vita EK. Assessment of ventricular diastolic function in AIDS patients from Congo: a Doppler echocardiographic study. Heart 1998;8:184–9.
20. Longo-Mbenza B, Tonduangu K, Kintonki VE. The effect of HIV infection on high incidence of heart diseases in Kinshasa: echocardiographic study. Ann Cardiol Angeiol 1997;46:81–7.
21. Rerkpattanepipat P, Wonpraparut N, Jacobs LE. Cardiac manifestations of AIDS. Arch Intern Med 2000;160:602–8.
22. Oyedeji GA. The effect of socio–economic factors on the incidence and severity of gastroenteritis in Nigerian children. N Med J 1987;6:229–32.
23. WHO Multicentre Growth Reference Study Group. WHO child growth standards based on length/height, weight and age. Acta Paediatr Suppl 2006;450:76–85.
24. Cheitlin MD, Armstrong WF, Aurigemma GP, *et al*. American College of Cardiology; American Heart Association; and American Society of Echocardiography. ACC/AHA/ASE 2003 guideline update for the clinical application of echocardiography. Circulation 2003;108:1146–62.
25. Devereux RB, Wachtell K, Gerdts E, *et al*. Prognostic significance of left ventricular mass change during treatment of hypertension. JAMA 2004;292:1–7.
26. Blanchard DG, Hagenhoff C, Chow LC. Reversibility of cardiac abnormalities in HIV infected individuals: a serial echocardiographic study. J Am Coll Cardiol 1991; 17:1270–6.
27. Longo-Mbenza B, Seghers KV, Phuati M. Heart involvement and HIV infection in African patients: determinants of survival. Int J Cardiol 1998;64:63–73.
28. Shah I, Prabhu SS, Sumitra V, *et al*. Cardiac dysfunction in HIV infected children: A pilot study. Ind Paediatr 2005;42:146–9.
29. Sherron P, Pickoff AS, Ferrer PL, *et al*. Echocardiographic evaluation of myocardial function in paediatric AIDS patients [abstract]. Am Heart J 1985;110:710.
30. Fink L, Reicheck N, Sutton MG. Cardiac abnormalities in acquired immunodeficiency syndrome. Am J Cardiol 1984;54:1161–3.
31. Miller TL, Evans SJ, Orav EJ. Growth and body composition in children infected with the human immunodeficiency virus-1. Am J Clin Nutr 1993;57:588–92.
32. Cooley GO, Loveless MO, Merrill TM. The HIV wasting syndrome: a review. J AIDS 1994;7:681–94.
33. Lubega S, Zirembuzi GW, Lwabi P. Heart disease among children with HIV/AIDS attending the paediatric infectious disease clinic at Mulago hospital. African Health Sciences 2005;5:219–26.
34. Nzuobontane D, Blackett KN, Kuaban C. Cardiac involvement in HIV infected people in Yaounde. Postgrad Med J 2002;78:678–81.
35. Lipshultz SE, Easley KA, Orav EJ, *et al*. Cardiac dysfunction and mortality in HIV-infected children: the prospective P^2C^2 HIV multicenter study circulation. 2000;102:1542–8.
36. Coudray N, de Zuttere D, Force G, *et al*. Left ventricular diastolic function in asymptomatic and symptomatic HIV carriers: an echocardiographic study. Eur Heart J 1995;16:61–7.
37. Villa A, Foresti V, Confalonieri F. Autonomic neuropathy and prolongation of QT interval in HIV infection. Clin Auton Res 1995;5:48–52.
38. Estok L, Wallace F. Cardiac tamponade in a patient with AIDS: a review of pericardial disease in patients with HIV infection. Mt Sinai J Med 1998;65:33–9.
39. Mast HL, Haller JO, Schiller MS, *et al*. Pericardial effusion and its relationship to cardiac disease in children with AIDS. Paediatr Radiol 1912;22:548–51.
40. Lipshultz SE, Kirk AE, Orav EJ, *et al*. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P^2C^2 HIV multicentre study. Am J Cardiol 1998;97:1246–56.
41. Starc TJ, Lipshultz SE, Kirk AE. Cardiac complications in children with HIV infection. Paediatr 1999;2:14.
42. Levy WS, Simon GL, Rios JC, *et al*. Prevalence of cardiac abnormalities in human immunodeficiency virus infection. Am j Cardiol 1989;63:86–9.