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Cardiac Dysfunction Among Ugandan HIV-Infected Children on Antiretroviral Therapy

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Abstract

Background—Despite effective antiretroviral therapy (ART), HIV-infected children on treatment have been observed to have cardiac abnormalities. We sought to determine the prevalence, types and factors associated with cardiac abnormalities among HIV-infected Ugandan children on combination ART.

Methods—We carried out a cross-sectional study from July 2012 to January 2013, at Joint Clinical Research Centre among HIV infected children aged 1 to 18 years. Cardiac abnormalities were assessed using electrocardiography (EKG) and echocardiography. CD4 counts, viral load and complete blood count were performed at enrollment. The prevalence of cardiac abnormalities was determined using simple proportions with the associated factors ascertained using logistic regression.

Results—Among 285 children recruited, the median (IQR) age was 9 (6, 13) years, 54% were female; 72% were on first line cART. Their mean (±sd) CD4 count was 1092 (±868.7) cells/mm^3; median (IQR) viral load was 20 (20, 76) copies/ml. 94% had adherence to ART of more than 95%. Cardiac abnormalities were detected in 39 (13.7%) children. The most common abnormalities by EKG and echocardiography were non specific T-wave changes (4.6%) and pericardial disease (thickened pericardium with or without pericardial effusion) (2.8%), respectively. No factor assessed was found to be significantly associated occurrence of cardiac dysfunction.

Conclusions—The prevalence of cardiac dysfunction among the HIV-infected children on ART was 13.7 % which was high, with non specific T wave changes and pericardial disease being the most frequent abnormalities observed. No factor assessed was found to be associated with cardiac dysfunction.

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Disclosure statement

No competing financial interests exist.

Keywords

HIV; Africa; children; cardiac dysfunction; antiretroviral therapy

Introduction of antiretroviral therapy (ART) in the developing world has significantly reduced mortality due to HIV [1]. Survival of children starting on combination ART (cART) is high with a 94% survival rate at 12 months and 91% at 24 months [2].

However, despite effective ART, there is still significant morbidity and even mortality associated with HIV-infection. The observed co-morbidities are a result of side effects of antiretroviral therapy such as metabolic abnormalities, disorders of lipid metabolism, organ dysfunction including cardiac disease; co-infections especially following ART failure or the immune reconstitution inflammatory syndrome; and the virus itself in sanctuary sites [1, 3]. The cardiac muscle appears to be one of the sanctuary sites and could result in cardiac dysfunction, which may present with subclinical or overt functional or conduction abnormalities [4].

Some conduction abnormalities have also been associated with life threatening events among the sufferers [5]. The burden of cardiac dysfunction has been reportedly high among ART naïve children in Uganda and elsewhere [6–8]. There is paucity of data that elaborates on both conduction and functional cardiac abnormalities among ART experienced children in Uganda and other Sub Saharan African countries.

We therefore, set out to determine the magnitude, types and factors associated with cardiac dysfunction among HIV infected children on anti retroviral therapy.

METHODS

Study design

This was a cross-sectional study conducted from July 2012 to January 2013 among 285 HIV infected children aged 1 year to 18 years attending Joint Clinical Research Centre (JCRC), Kampala, Uganda. These were children stable on cARTfor at least 6 months, whose parents/guardians provided written informed consent and the children assent as appropriate. The study was approved by the Makerere University School of Medicine Research Ethical Committee, and permission to conduct the study was obtained from the Management of JCRC.

Study procedures

Each participant underwent physical examination including general appearance; any dysmorphic features were noted; and anthropometric measurements taken. A questionnaire was then completed including details of the drug history, previous and current ART regimens. The adherence to ART was determined by self report and a care taker interview inquiring about drug intake in the preceeding 30days.

Absolute CD4 cell counts and CD4 percentages were assessed on blood samples in the JCRC laboratories by fluorocytometry with a BD (Becton, Dickinson and Company) machine using Trucount kits with four color antibodies (FITC, PE, PerCP, and APC).

Blood viral load was also assessed in the JCRC laboratories by the standard protocol (limit of detection, 400 copies per ml) or the ultrasensitive protocol (limit of detection, 50 copies per ml) of the Cobas Amplicor HIV-1 monitor kit (Version 1.5, Roche Molecular Systems) respectively.

The children were then taken to the Uganda Heart Institute at Mulago National Referral Hospital, 14km away, along with their caretakers for echocardiography and electrocardiography (EKG). The participants who were not able to have echocardiography or EKG on the day of enrollment were booked for a later date.

A 12- lead resting EKG was performed by a well trained nurse using a Mortara Model EL1-350 machine (Milwaukee, WI 53224 USA) after the child rested for at least 5 minutes. The EKG tracing was interpreted by two personnel, including at least one Pediatric cardiologist. In the EKG tracing, the QT interval was determined and corrected (QTc) using the Bazzette's formula; dividing the measured QT interval by the square root of the preceding R-R interval ($QTc/\sqrt{r-r}$). The QT interval was taken from the onset of the QRS complex to the end of the T wave, while the corrected QT interval of more than 0.44 seconds was considered prolonged [5]. Left ventricular hypertrophy (LVH) was calculated by the amplitude measurements for RV_6 and SV_1 > 40mm and left posterior wall diameter with body surface area [9].

Echocardiography was performed using a Philips IE33 machine (Eindhoven, Netherlands); MMode, 2 Dimension and Doppler studies were conducted. The measurements obtained included: the parasternal long axis, short axis, sub costal, and four apical chamber view to assess cardiac structure and function; chamber sizes including the left atrial dimension and aortic root diameter; left ventricular diameter in both diastole and systole; fractional shortening (FS) and ejection fraction (EF) to determine systolic function. Each echocardiogram was performed by a pediatric cardiologist and reviewed by a second pediatric cardiologist and the 2 agreed on the findings reported.

LV dysfunction was indicated by FS<28% or EF<50%. Dilated cardiomyopathy (DCM) was defined as LV systolic dysfunction with a dilated left heart chamber (LAD or LVEDd z-score of > 3 SD with parameterz calculator) [10]. Rheumatic heart disease (RHD) was defined according to the 2012 World Heart Federation criteria [11].

Statistical analysis

Cardiac dysfunction was described as any abnormalities identified by EKG or echocardiography. However those known to be normal variants, such as LVH and Right bundle branch block (RBBB) on EKG alone without confirmation on echocardiography, Persistent Foramen Ovale (PFO), and sinus tachycardia were not taken as indicators of cardiac dysfunction. The prevalence of the abnormalities was determined using simple proportions. The factors associated with cardiac dysfunction were ascertained using logistic

regression models. Adherence to ART was one of the factors assessed, with optimal adherence taken as a level of >95%. Data analysis was conducted using STATA version 12 (Stata corporation, Houston, Texas, USA).

RESULTS

Of 285 childrem enrolled, 153 (54%) were female. The median age of the children was 9 years (IQR 6, 13); (range 1 to 18 years), (Table 1).

One hundred eighty three (66%) were in early WHO stages (I and II) and 34% were in late WHO stages (III and IV) before initiation of cART.

Ninety four percent of the children had optimal adherence to ART. Of the children, 68% (194/285) were viroligically suppressed, i.e. had viral load <400 copies/ml.

Other demographic characteristics are shown in Table 1.

Prevalence of cardiac dysfunction

Cardiac abnormalities were seen in 39/285 (13.7%) of the children. EKG abnormalities were observed in 19(6.7%) children and echocardiography abnormalities in 20 (7.0%) children. Eight (2.8 %) children had both EKG and echocardiogram abnormalities.

Types of cardiac dysfunction

EKG abnormalities—Of the 19 children with abnormal EKG tracings: 13(4.6%) had non specific T wave changes; 4 (1.4%) children had a prolonged QTc interval; 1(0.4%) had right atrial enlargement (confirmed by echocardiography); and 1 (0.4%) 16 year old girl on abacavir, lamivudine and lopinavir/ritonavir had first degree heart block (PR interval – 0.24 seconds). Of note although 14(4.9%) children had LVH by voltage, this was not confirmed on echocardiography.

Also 11 (3.9%) of the children had sinus tachycardia but this was taken as a normal variant and not an indicator of cardiac dysfunction.

Echocardiography findings—Twenty children had abnormalities by echocardiography. Among these, left ventricular dysfunction and dilated cardiomyopathy (DCM) were detected in 6(2.1%) children (mean FS - 25% and mean EF - 52%) and 1 child (LVDdd – 3.9cm, FS 24%, EF - 49%; CD4 – 2121 cells/mm^3 (24%), respectively.

Congenital heart disease was found in 3 children (1%); the abnormalities were: Patent Ductus Arteriosus (1 child), Secundum Atrial Septal Defect (1 child), and an isolated cleft mitral valve (1child). Ten (3.5%) children suffered from acquired heart disease; 8 (2.8%) had pericardial disease (5 with pericarditis, as shown by a thick pericardium and an acoustic shadow; and 3 with pericardial effusion) and 2 (0.7%) had Rheumatic Heart Disease (RHD). All the children who had pericardial effusion were above 5 years, had tachypnea, a high viral load and a low CD4 count (Table 2). Two were treated for tuberculosis (TB); one was on chemotherapy for Kaposi’s sarcoma. The children with RHD had definitive disease: one 11year old girl had a grade 3/6 holosystolic murmur, a thick mitral valve with moderate

mitral valve regurgitation; the other had subclinical disease [11]. No child was seen to have features of pulmonary hypertension.

Factors associated with cardiac dysfunction

No factor assessed including: age, gender, viral load, CD4 count, history of TB, ART regimen, duration from HIV diagnosis and duration of ART, was found to be associated with occurrence of cardiac dysfunction, as shown in Table 3.

DISCUSSION

Cardiac dysfunction could be life threatening among HIV infected individuals. Few studies have evaluated the magnitude of cardiac dysfunction among HIV-infected children on ART in Sub Saharan Africa. We found the prevalence of cardiac abnormalities to be 13.7% by EKG and echocardiography. This is quite high but lower than the 26.6% observed among children in India, 80% of whom were on ART [12].

This prevalence is also lower than the 51% observed in the same city 10 years earlier in a study where only 2 of 230 children were on ART [8]. In our study, most (66%) children were in WHO stages 1 and 2 before initiation of ART, 68% had good virological suppression and overall they had high CD4 counts/percentages. The lower prevalence of cardiac dysfunction among the children in the current study could suggest a protective effect of ART. Of note, none of the children was previously known to have documented cardiac disease.

In our study non specific T wave changes were the most frequent EKG abnormality observed, while the study done in the same city earlier reported sinus tachycardia as the most common EKG abnormality that was greatly associated with AIDS [8]. In our study, we took sinus tachycardia as a normal variant. Of note, the children in our study with sinus tachycardia were over 8years and particular care was taken to calm them down before the examination, for example no ECG examination was done within 5 minutes of arrival at the clinic. Sinus tachycardia was also reported among 64% of 81 children in the United States in a study of cardiac morbidity and mortality in 1993 (pre-ART). [13]. Our study reports a much lower prevalence (3.9%) which could be due to improved quality of life as a result of ART. Though less common, conduction abnormalities can cause life threatening events. Prolonged QTc− Interval is one of the serious EKG abnormalities among HIV infected children; others include Tosades de pointes, supraventricular tachycardia, atrial fibrillation and third degree heart block. Prolonged QTc is a predictor for Torsades de pointes which is a type of ventricular tachycardia [5]. In our study only 1.4% of the children had prolonged QTc interval which was lower than that reported among ART naïve HIV infected patients in Nigeria [14].

Protease inhibitors have been reported to cause arrhythmias including first degree heart block. [14, 15]. In our study, first degree heart block was found in a 16 year old female who had been on lopinavir/rotinavir based regimen for 4 years. This may be as a result of vagotonia [16]. The prevalence of pericardial effusion is much lower than that observed in the earlier Ugandan study which had most participants as ART naive [8]. In that study, 5%

of the 230 children had pericardial effusion. In our study, pericardial effusion was reported only in children with low CD4 counts and high viral load. Pericardial effusion is usually caused by TB, Cytomegalovirus and HIV associated malignancies like Kaposi's sarcoma [17].

Left ventricular systolic dysfunction was lower than what was reported in other studies among ART naïve children in Brazil (24.7% of 93 children) and earlier in Uganda (17% of 230 children) [7, 8]. ART reduces the viral load which in turn reduces myocardial invasion by cardiotropic viruses which would cause cardiac dysfunction [20].

DCM was rare in our study unlike in the pre-ART era 10 years earlier [8]. The single child in our study was an eight year old girl who was on zidovudine, lamuvidine and abacavir for 4 years. It is not clear what was responsible for the DCM in the child given that it has been previously associated with advanced disease [8] and that she had a high CD4 count/ percentage. It is possible, the zidovudine she was on caused the DCM as has been observed elsewhere [21].

Rheumatic heart disease was also rare in our study. A large Ugandan study among 4869 HIV uninfected school children, found higher prevalences of 1.4 % among those from a higher socioeconomic class and 2.7% among those from a low socioeconomic class [22]. The children in our study were probably from a similar socioeconomic status as the group taken be in a high socioeconomic status. Of note, the two children with RHD were asymptomatic and above 10 years of age.

The occurrence of congenital heart disease was lower than the 5% found among the 230 HIV infected children in the same city 10 years earlier [8].

No factor assessed was found to be associated with cardiac dysfunction, possibly because of the relatively small number of events.

This is one of the first studies to be conducted on cardiac dysfunction among children on ART in Africa. However, it had some limitations. Due to logistical constraints, we were not able to perform strain echocardiography or ascertain selenium levels and lipid profiles. Selenium deficiency has been associated with cardiomyopathy among the HIV infected adults and deranged lipids would increase cardiovascular risk. Similarly, the 24- Holter EKG which would give more information about arrhythmias was not done.

In conclusion, among HIV infected children taking cART, cardiac dysfunction was observed in 13.7% of the population which is quite high with non specific T wave changes and pericardial disease being the most common abnormalities. Dilated cardiomyopathy was rare and echocardiographic abnormalities were more common among those failing ART.

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Table 1

Descriptive data of the participants

Variable	Frequency (n=285)	Percent (%)
Gender		
Female	154	54.0
Male	131	46.0
Age		
<5yrs	44	15.4
≥5 yrs	241	84.6
cART		
First line	205	72.0
Second line	80	28.0
Duration of cART		
<5yrs	166	58
≥5yrs	119	42
Cotrimoxazole prophylaxis (n=223)	213	95.5
Viral load (copies/ml) (n=217)	20[a]	(20,76)*
CD4 count (cells/mm^3)	944[a]	(596,3462)*
Hb level		
<11g/dl	33	11.6
>11g/dl	252	88.4
History of TB treatment	83	29

[a] median

* interquatile range, Hb- hemoglobin, cART-combination anti retroviral therapy

Table 2

Features of children with pericardial effusion

Age (years)	CD4 count (cells/mm^3)	Viral load (copies/ml)	Viral load log	ART Regimen
7	14	100,000	5.0	ABC/3TC/LPV/r
15	161	256,125	5.4	CBV/EFV
17	95	Not done	-	TDF/3TC/LPV/r

ART – antiretroviral therapy; ABC – abacavir; 3TC – lamivudine; LPV/r – lopinavir/ritonavir; EFV – efavirenz; TDF - tenofovir

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Table 3

Factors associated with cardiac dysfunction among HIV infected children on combination antiretroviral therapy by univariate analysis

	Cardiac dysfunction		Total	Crude Odds Ratio (95% CI)	p-value
	Present (39)	Absent (246)			
Age(yrs)					
< 5	3	41	44	1.00	
≥ 5	36	205	241	2.1 (0.635,7.40)	0.22
Gender					
Female	22	132	154	1.00	
Male	17	114	131	0.71 (0.35,1.46)	0.36
Viral Load (copies/ml)					
<400	22	172	194	1.00	
400–5000	3	12	15	1.4(0.37,5.22)	0.61
>5000	11	8	19	0.96 (0.44,2.08)	0.9
CD4 Count (cells/mm^3)					
<350	7	22	29	1.00	
350–750	9	62	71	0.5(0.32,1.00)	0.16
>750–1000	5	36	41	0.08 (0.137,1.141)	0.19
>1000	12	88	100	0.05 (0.171,1.013)	0.11
History of TB					
Yes	10	73	83	1.00	
No	29	173	202	1.26(0.56,2.82)	0.56
ART					
First line	28	177	205		
second line	11	69	80	0.8(0.37,1.86)	0.66
Duration from HIV diagnosis					
<5yrs	19	109	128		
≥5yrs	20	137	157	0.89 (0.44,1.81)	0.77
Duration of ART					
<5yrs	22	144	166	1.00	
≥5yrs	17	102	119	0.99 (0.49,2.02)	0.99

CI – confidence interval; TB – Tuberculosis; ART – antiretroviral therapy