

**Incidence and progression of echocardiographic abnormalities in HIV-infected
older children and adolescents taking antiretroviral therapy: A prospective
cohort study**

Edith D Majonga ^{1,2}, Andrea M Rehman ¹, Grace Mchugh ², Hilda A Mujuru ³, Kusum Nathoo ³, Jon
O Odland ^{4,5}, Rashida A Ferrand ^{1,2}, Juan Pablo Kaski ^{6,7,*}

¹London School of Hygiene and Tropical Medicine, London, United Kingdom; ²Biomedical Research
and Training Institute, Harare, Zimbabwe; ³University of Zimbabwe, Harare, Zimbabwe; ⁴NTNU The
Norwegian University for Science and Technology, Trondheim, Norway; ⁵ Department of Public
Health, University of Pretoria, South Africa; ⁶ Centre for Inherited Cardiovascular Diseases, Great
Ormond Street Hospital, London, United Kingdom; ⁷ Institute of Cardiovascular Science, University
College London, United Kingdom; * Member of the European Reference Network on Heart Diseases
(ERN GUARD-HEART)

Key words: Cardiac abnormalities, HIV, children, ART, echocardiography, Africa

Running title: Incidence of cardiac abnormalities in children on ART

Corresponding Author:

Dr Edith Majonga, Biomedical Research and Training Institute, 10 Seagrave Rd, Avondale, Harare,
Zimbabwe

edithmajonga@gmail.com Tel: +263 776 296 357

Alternate Corresponding Author:

Dr Juan Pablo Kaski, Centre for Inherited Cardiovascular Diseases, Great Ormond Street Hospital
London WC1N 3JH, United Kingdom

j.kaski@ucl.ac.uk Tel: +44 (0)20 7829 8839

Main point

Older children and adolescents with HIV and receiving ART in Sub-Saharan Africa have a high incidence of echocardiographic abnormalities which are likely primary HIV-related heart muscle disease. The abnormalities have a potential for progression over time.

Abstract

Background

A high prevalence of cardiac abnormalities has been reported in children with HIV taking ART in sub-Saharan Africa. We investigated the incidence and progression of cardiac abnormalities among children taking ART in Zimbabwe.

Methods

A prospective cohort study was conducted at a paediatric HIV clinic from 2014 to 2017. Children with HIV aged between 6 and 16 years and taking ART ≥ 6 months were enrolled. Transthoracic echocardiography was performed at baseline and 18 months.

Results

Of 197 participants recruited at baseline, 175 [(89%), 48% female, median age 12 (IQR, 10-14) years] were followed up. The incidence of left and right heart abnormalities was 3.52 and 5.64 per 100 pys, respectively. Stunting was associated with the development of any cardiac abnormality [adjusted OR 2.59 (95% CI, 1.03-6.49); $p=0.043$]. Right ventricular (RV) dilatation persisted at follow up in 92% and left ventricular (LV) diastolic dysfunction in 88%. Cardiac abnormalities present at baseline reverted to normal over the follow up period in 11(6%). There was an overall increase in mean z-scores for LV, left atrium (LA), RV, interventricular septum and LV posterior wall diameters at 18 months ($p<0.001$).

Conclusions

Despite ART, children with HIV have a high incidence of cardiac abnormalities, with only a minority being transient. Mean z-scores for LV, LA, RV, interventricular septum and LV posterior wall diameters increased over a relatively short follow up period, suggesting the potential for progression of cardiac abnormalities. Longer follow up is required to understand the clinical implications of these abnormalities.

Introduction

The global scale-up of antiretroviral therapy (ART) programmes has been followed by a dramatic decline in mortality among individuals living with HIV infection [1]. While ART facilitates immune reconstitution and reduces the risk of infections, there is increased recognition that longstanding HIV infection is associated with an increased risk of chronic co-morbidities. This may be a result of the HIV infection itself, its treatment or sequelae of infections [2]. One of the most well-recognised co-morbidities is cardiac disease, with several studies showing an increased risk of developing cardiac disease in adults despite ART [3, 4]. An important limitation of studies in adults is confounding by well-established risk factors for cardiac disease such as age, smoking and hypertension [4].

In the pre-ART era, infants and younger children with HIV were also reported to be at increased risk of developing cardiac disease, with a five-year cumulative incidence of cardiac dysfunction of 18-39% [5]. The most commonly reported abnormalities were left ventricular (LV) systolic dysfunction and LV dilatation; these were often progressive and were a predictor of all-cause mortality [6, 7]. Most of these studies were conducted in high-income settings, mainly in younger children and with some cohorts including children taking monotherapy for treatment of HIV infection [5, 7]. In high-income countries most children start ART in infancy, which not only decreases mortality but may prevent organ damage; [8] in these settings, the incidence of cardiac disease in children on ART has declined [9]. These findings cannot be generalised to children growing up with HIV in Sub-Saharan Africa (SSA), where 90% of the world's children with HIV live, most of whom have had delayed diagnosis of HIV and/or started ART in older childhood [10, 11].

Nevertheless, increasing numbers of children in SSA, who would have died in early childhood, are now reaching adolescence and adulthood due to ART [12]. We and others have reported a high prevalence of cardiac abnormalities among African children despite treatment with ART and absence of the traditional risk factors for cardiac disease[13, 14]. However, little is known about the incidence and clinical course of cardiac abnormalities in African children in the ART era. We investigated the incidence and progression of cardiac abnormalities in children taking ART in Harare, Zimbabwe.

Methods

A prospective cohort study was conducted from August 2014 to December 2017 at the paediatric HIV clinic at Harare Central Hospital, Zimbabwe, a public-sector HIV clinic that provides care to over 4000 children. ART is provided free of charge according to national guidelines. This study was part of a larger study aiming to investigate cardiorespiratory disease in children with HIV infection taking ART [INHALE (Investigation of Heart and Lung Diseases in HIV among older children)]. Baseline cardiac findings in this cohort of HIV infected children have recently been reported [13]. Findings from this cohort pertaining to chronic lung disease have also been published [15, 16].

Participants

Children with HIV aged 6 to 16 years attending the outpatient HIV clinic, taking ART for at least six months and clinically stable (defined as not requiring hospital admission and not too ill to participate) were consecutively enrolled on week days, limited to the first five eligible participants per day for logistical ease, as previously described [13]. Participants were followed up at 18 months.

Study procedures

An interviewer-administered questionnaire was used to collect socio-demographic data and clinical history. Assessment of pubertal stage was based on Tanner staging [17]. Clinical assessment included measurement of height, weight, heart and respiratory rates and blood pressure, pulse oximetry, spirometry, HIV viral load and CD4 count tests and a transthoracic echocardiogram (full methods in supplementary data 1). The methods and definitions of this study have also been previously described [13].

Data management and statistical analysis

Data were extracted from paper forms using optical character recognition software (Cardiff TELEFORM Intelligent Character, Version 10.7) and analysed using STATA version 12 software (StataCorp, Texas, USA). Continuous data were presented as mean \pm standard deviation (SD) if they were normally distributed or median (interquartile range, IQR) if not normally distributed. A paired t-test, Mann-Whitney and McNemar tests were used to compare clinical characteristics of participants and mean values of cardiac measures and z-scores at baseline and follow up. There was temporal blinding during analysis of echocardiograms at follow-up. The mean change in z-scores for each cardiac measure was calculated as mean z-score (18 months) minus mean z-score (baseline) and adjusted for baseline z-scores using linear regression. The incidence rate and risk for right and left heart abnormalities respectively were calculated in those without abnormalities at baseline, and risk is reported as a proportion. Logistic regression was used to assess for risk factors for incident cardiac abnormalities at follow up. These included baseline HIV-related and clinical factors. As previously described, HIV-related factors were categorised as CD4 cell count (>200 cells/ μ l and ≤ 200 cells/ μ l), HIV viral load (≤ 400 copies/ μ l and >400 copies/ μ l), age at ART initiation (0–5, 6–10 and 11–16 years), duration on ART (≤ 2 years and >2 years) [13]. Age (categorised as 6–10 years and 11–

16 years) and sex were included as a priori variables. Antiretroviral drugs including nevirapine and zidovudine were also assessed. HIV-related variables with a p-value ≤ 0.1 were retained for inclusion in the multivariate model and clinical factors were added into the model one at a time and those which were significant at $p \leq 0.1$ was retained for inclusion in the final model. We explored the association between baseline factors as linear variables and mean change in z-scores for cardiac measures, adjusted for baseline z-scores using linear regression. A p-value ≤ 0.05 was considered statistically significant.

Ethical approval was obtained from the Medical Research Council of Zimbabwe, the London School of Hygiene and Tropical Medicine Ethics Committee, the Biomedical Research and Training Institute Institutional Review Board and the Harare Central Hospital Ethics Committee. Written informed consent from guardians and assent from participants was obtained prior to enrolment.

Results

Clinical characteristics

A total of 197 participants were recruited of whom 175 (89%) were followed up at 18 months, giving 283.9 person-years (pys) of follow up (Figure 1). The median age of participants at 18 months follow up was 12 (IQR, 10-14) years and 84 (48 %) were female. Forty percent of participants were virally suppressed (<400 copies/ml) at 18 months compared to 78% at baseline ($p < 0.001$; Table 1). Supplementary Figure 1 shows the flow diagram of viral suppression over time. Four participants died, all of whom had echocardiographic abnormalities at baseline. The causes of death were pulmonary tuberculosis; meningitis; cardiac failure due to dilated cardiomyopathy; and unknown. The 22 participants lost to follow up either relocated or were unreachable due to change of contact details. There were no significant differences in age, CD4 count, viral load, duration on ART, clinical characteristics, height-for-age and weight-for-age z-scores and cardiac dimensions z-scores at baseline

between participants who were followed up and those lost to follow up. Data on pubertal staging were available at follow up on all participants. Thirty (35%) participants had reached menarche. Of the female participants, 34 (40%) and 40 (48%) were in Tanner stage 1 of breast and pubic hair development, respectively, compared to 3 (3%) testicular volume and 66 (73%) pubic hair development of the male participants (data not shown).

Echocardiographic findings

Baseline echocardiographic findings have been previously reported.[13] Briefly, at baseline, 40 participants (23%) had LV diastolic dysfunction; 18 (10%) had LVH; 14 (8%) had LA dilatation; RV systolic dysfunction in 2 (1%) and 12 (7%) had RV dilatation. At 18 months, 23 (13%) participants had RV dilatation and 6 (3%) had RV systolic dysfunction. Apart from right heart abnormalities, there was no significant change in the proportions of left heart cardiac abnormalities at follow up (Table 1). We observed an overall increase in mean z-scores for LV, LA, RV, interventricular septum and LV posterior wall diameters and TAPSE for all participants at follow up ($p < 0.001$) (Table 1). Table 2 shows mean baseline and 18 months z-scores and adjusted mean (SD) change in z-scores for cardiac parameters and estimated risk for cardiac abnormalities. The risk of developing RV dilatation was highest 12/163 (7%) with mean (SD) z-score for RV diameter at baseline of +1.10 (0.7) and increased to +2.51 (0.5). Of those with RV dilatation at follow up, n=4 had mild tricuspid regurgitation and n=7 had mild pulmonary regurgitation, two of whom had both tricuspid and pulmonary regurgitation. There was a negative correlation between change in z-score and baseline z-scores, e.g. participants with high z-scores at baseline had a smaller change in z-score at follow up. Mean changes in z-scores adjusted for baseline z-score of the same parameter were 0.64 SD (95% CI: 0.52, 0.77) for RV diameter; 0.36 SD (95% CI: 0.25, 0.47) for LV diameter; 0.63 SD (95% CI: 0.52, 0.74) for IVS diameter; 0.74 SD (95% CI: 0.63, 0.85) for LVPW diameter; 0.42 SD (95% CI: 0.33, 0.51) for LA diameter and -0.06 SD (95% CI: -0.24, 0.13) for TAPSE. Overall, 10 participants

developed left heart abnormalities and 16 developed right heart abnormalities at 18 months, giving an estimated incidence of 3.52/100 pys and 5.64/100 pys, respectively.

Of the 23 (13%) participants who had RV dilatation at follow up, 10 (43%) had concurrent left heart abnormalities and 11 (48%) also had RV dilation at baseline. Of the 6 participants with RV systolic dysfunction at 18 months, two had systolic dysfunction at baseline. None of the participants met criteria for pulmonary hypertension by echocardiography. LVH was present in 15 (9%) participants at follow up, of whom 13/15 (87%) also had LVH at baseline and 3 (20%) and 5 (33%) had LA dilatation and LV diastolic dysfunction, respectively, at baseline. LV dilatation persisted from baseline in 7 (4%) participants, 2 of whom had concurrent LA dilatation at baseline and follow up. Regression of abnormalities was observed in 11(6%) participants; two had LV systolic dysfunction, five had LVH (one with concurrent LV systolic dysfunction), five had isolated LV diastolic dysfunction (one with concurrent LVH) and one had RV dilatation at baseline. Cardiorespiratory symptoms were reported by 48/175 (27%) at baseline and of these 85% were asymptomatic at 18 months.

On multivariate logistic regression, stunting was associated with development of any new cardiac abnormality (adjusted OR 2.59 (95% CI, 1.03- 6.49; p=0.043). No HIV-related factors, including CD4 count, viral load, duration on ART, age at ART initiation and type of ART, were associated with incidence of any cardiac abnormalities. Supplementary Table 1 shows the type of ART and proportion of participants receiving the different drugs. There was no association between incidence of right heart abnormalities and abnormal spirometry. Menarche or the different indices of pubertal growth were not associated with change in mean z-scores for cardiac dimensions (data not shown). On linear regression, no association was observed between baseline factors and mean change in z-scores for cardiac dimensions (supplementary Table 2).

Discussion

To our knowledge, this is the first cohort study from SSA reporting the incidence and progression of cardiac abnormalities in children taking ART. Despite ART, participants continue to develop cardiac abnormalities, with the highest risk being development of RV dilatation, which was not associated with abnormal lung function. Most of the children with RV dilatation had isolated dilatation without associated RV systolic dysfunction. Currie *et al*, reported that heart muscle disease among people with HIV manifests as global or borderline LV dysfunction and isolated RV dilatation, [18] and we hypothesise that the isolated RV dilatation observed in the present study may be part of the spectrum of HIV-related cardiomyopathy and that it is manifest before LV involvement becomes apparent. Isolated RV enlargement has been previously reported in adults with HIV who had preserved LV function [19]. Notably, none of the participants with RV dilatation met the criteria for pulmonary hypertension using Doppler echocardiography, although we acknowledge that right heart cardiac catheterisation is the gold standard in diagnosing pulmonary hypertension. Despite the limitations of Doppler echocardiography in assessment of right heart pressures in children, there was no association between right heart abnormalities and abnormal lung function, further suggesting that the abnormalities are more likely due to primary heart muscle disease.

Most cardiac abnormalities present at baseline persisted at follow up, and we observed an overall increase in mean z-scores for cardiac dimensions over this short period of follow up. However, the majority had no symptoms, suggesting that there may be a prolonged period of subclinical cardiac abnormalities before overt disease develops. The results of our study suggest the potential for progression of cardiac abnormalities and highlight the importance of routine screening for cardiac disease in children with HIV, even in the absence of symptoms.

A minority of participants had transient cardiac abnormalities. LV systolic dysfunction and LVH may have been a consequence of an acute infectious myocarditis [20]. Transient ventricular wall thickening has previously been observed in participants with acute myocarditis [21]. The participant with RV dilatation at baseline which resolved by follow up had a respiratory tract infection near time of the initial echocardiogram, which then resolved. Lung infection may result in transient pulmonary hypertension and RV enlargement, which resolve with effective treatment of the infection [22]. Reversible cardiac abnormalities have also been reported among HIV infected adults in the USA, more than two-thirds (71%) of whom had AIDS [23].

The aetiology of myocardial disease in HIV infection is complex. Several pathogenic mechanisms have been hypothesised, including chronic systemic immune activation of cardiac myocytes that occurs in HIV infection and is not completely reversed by ART [24]. Infection of the heart by opportunistic pathogens, including cytomegalovirus, Epstein Barr virus, coxsackievirus and adenovirus, may also result in cardiac damage [25]. Cardiotoxicity from ART has also been suggested, particularly nucleoside reverse transcriptase inhibitors (NRTIs), the backbone of ART including abacavir, and zidovudine [26, 27]. This may be related to mitochondrial dysfunction, which has been observed following use of stavudine, didanosine and zidovudine, while abacavir reportedly increases risk of myocardial infarction in adults [28]. Abacavir and zidovudine were being taken by 4% and 52% of the participants, respectively, but no association between antiretroviral drugs and cardiac abnormalities was identified in this study. This further supports the possibility of the abnormalities being due to primary heart muscle disease.

Stunted children had a higher likelihood of developing cardiac abnormalities. Miller *et al.* also reported that stunting was associated with LV diastolic dysfunction in their retrospective study

of HIV infected adolescents, 71% of whom were on ART [29]. Stunting is a marker of chronic inflammatory conditions in childhood and underlying systemic inflammation may also play a role in pathogenesis of cardiac disease [30, 31]. Notably, the proportion of participants who were virally non-suppressed had increased over the follow up period. Poor adherence and high rates of viral non-suppression among adolescents have been reported previously [32]. This would mean ongoing viral replication which is in turn associated with dysregulated systemic immune activation. In adults with HIV, systemic immune activation is a risk factor for development of cardiac disease [30]. HIV persists in reservoir cells even after effective treatment with ART and may continue to release cytotoxic cytokines which subsequently contribute to progressive and late tissue damage (cardiac myocytes) [33]. The median age of ART initiation in this cohort was 6 (IQR, 3-8) years and immunosuppression and opportunistic infections prior to ART initiation may cause cardiac damage. Poor adherence to ART may also explain the higher incidence of cardiac disease in our cohort compared to previous studies in high-income settings [9].

Strengths and limitations

This study is the first to report the incidence and progression of cardiac disease in a paediatric HIV population from SSA, where the vast majority of children with HIV live. The main strengths include the prospective, systematic evaluation for cardiac abnormalities and use of local reference ranges to define the abnormalities, rather than reference ranges derived from North American or European populations, which have been shown not to be appropriate for SSA [34, 35]. Furthermore, participants were consecutively enrolled and not selectively enrolled on the basis of symptoms. Limitations of the study include lack of viral load measures on all participants and as a result, we may have been underpowered to detect any associations between incident cardiac disease and viral load. Study of biomarkers was not within the scope

of this study but, we do have stored blood samples and investigation of systemic markers of inflammation is ongoing. The use of advanced echocardiographic techniques such as three-dimensional echocardiography may have provided more imaging by allowing direct calculation of chamber volumes as well as global or regional function through elimination of geometric assumptions used in M-mode and minimised the errors arising from foreshortened apical views. Notably, we only used optimum images to acquire the various measurements from in this study. Speckle tracking imaging would have been more sensitive to detecting subclinical ventricular function, which may not be identified by measurement of the LV ejection fraction. Tissue doppler imaging may have assessed LV diastolic dysfunction better because it is less dependent on loading conditions compared to transmitral inflow velocities. However, we also included pulmonary venous flow velocities which provided additive value to the evaluation of LV diastolic function. Importantly, this study was performed in a resource-limited setting and use of more contemporary imaging measures was not available. In most healthcare settings in this region, there is not widespread availability of advanced echocardiographic techniques and so our findings will be more readily applicable to a low-resource setting, which is where the majority of these patients are seen.

Conclusion

There is a high incidence of cardiac abnormalities in children with HIV and taking ART in SSA and the lack of association with lung and HIV factors suggests that these abnormalities are primary HIV-related heart muscle disease. There is some evidence of disease progression over a short follow up period. Longer follow up is needed to understand the clinical implications of these abnormalities, and the pathogenesis of these abnormalities needs further study.

Funding

This work was funded by the Wellcome Trust (095878/Z/11/Z), Nina-Ireland Program for Lung Health and Norwegian Research Council through GLOBVAC. Salary support for AMR was provided by the UK Medical Research Council through a grant to the LSHTM Tropical Epidemiology Group; grant code MR/K012126/1. JPK is supported by Max's Foundation, Great Ormond Street Hospital Children's Charity and the NIHR GOSH BRC. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Acknowledgments

We would like to thank Harare Children's Hospital, the clinic staff, participants and their families and the HIV Research Trust.

Conflict of Interest: none declared

References

1. Fetting J, Swaminathan M, Murrill CS, Kaplan JE. Global Epidemiology of HIV. *Infectious Disease Clinics of North America* **2014**; 28:323-37
2. Hunt PW. HIV and inflammation: mechanisms and consequences. *Current HIV/AIDS Reports* **2012**; 9:139-47
3. Hsue PY, Waters DD. Heart failure in persons living with HIV infection. *Current Opinion in HIV & AIDS* **2017**; 12:534-9
4. Mondy KE, Gottdiener J, Overton ET, et al. High Prevalence of Echocardiographic Abnormalities among HIV-infected Persons in the Era of Highly Active Antiretroviral Therapy. *Clin Infect Dis* **2011**; 52:378-86
5. Starc TJ, Lipshultz SE, Easley KA, et al. Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: The prospective P2C2 HIV study. *J Pediatr* **2002**; 141:327-34
6. Fisher SD, Easley KA, Orav EJ, et al. Mild dilated cardiomyopathy and increased left ventricular mass predict mortality: the prospective P2C2 HIV Multicenter Study. *American Heart Journal* **2005**; 150:439-47
7. Lipshultz SE, Easley KA, Orav EJ, et al. Left Ventricular Structure and Function in Children Infected With Human Immunodeficiency Virus : The Prospective P2C2 HIV Multicenter Study. *Circulation* **1998**; 97:1246-56
8. Violari A, Cotton MF, Gibb DM, et al. Early antiretroviral therapy and mortality among HIV-infected infants. *New England Journal of Medicine* **2008**; 359:2233-44
9. Fisher SD, Starc TJ, Guerra V, Williams PL, Wilkinson JD, Lipshultz SE. Declining Incidence of Systolic Left Ventricular Dysfunction in Human Immunodeficiency Virus-Infected Individuals Treated With Highly Active Antiretroviral Therapy. *Am J Cardiol* **2016**; 117:1194-5
10. Slogrove AL, Schomaker M, Davies MA, et al. The epidemiology of adolescents living with perinatally acquired HIV: A cross-region global cohort analysis. *PLoS Med* **2018**; 15:e1002514
11. Ferrand RA, Munaiwa L, Matsekete J, et al. Undiagnosed HIV infection among adolescents seeking primary health care in Zimbabwe. *Clin Infect Dis* **2010**; 51:844-51
12. Lowenthal ED, Bakeera-Kitaka S, Chapman J, Goldrath K, Ferrand RA. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *The Lancet Infectious Diseases* **2014**; 14:627-39
13. Majonga ED, Rehman AM, Simms V, et al. High prevalence of echocardiographic abnormalities in older HIV-infected children taking antiretroviral therapy. *AIDS (London, England)* **2018**; 32:2739
14. Chelo D, Wawo E, Siaha V, et al. Cardiac anomalies in a group of HIV-infected children in a pediatric hospital: an echocardiographic study in Yaounde, Cameroon. *Cardiovascular Diagnosis and Therapy* **2015**; 5:444-53
15. Desai SR, Nair A, Rylance J, et al. HIV-Associated Chronic Lung Disease in Children and Adolescents in Zimbabwe: Chest Radiographic and High-Resolution Computed Tomography Findings. *Clinical Infectious Diseases* **2017**; cix778-cix
16. Rylance J, McHugh G, Metcalfe J, et al. Chronic lung disease in HIV-infected children established on antiretroviral therapy. *AIDS* **2016**; 30:2795-803
17. Tanner JM, Whitehouse RH. Clinical longitudinal standards for height, weight, height velocity, weight velocity, and stages of puberty. *Archives of disease in childhood* **1976**; 51:170-9

18. Currie PF, Jacob AJ, Foreman AR, Elton RA, Brettle RP, Boon NA. Heart muscle disease related to HIV infection: prognostic implications. *BMJ : British Medical Journal* **1994**; 309:1605-7
19. Rangasetty UC, Rahman AM, Hussain N. Reversible right ventricular dysfunction in patients with HIV infection. *South Med J* **2006**; 99:274-8
20. Kuhl U, Schultheiss HP. Viral myocarditis. *Swiss Med Wkly* **2014**; 144:w14010
21. Hiramitsu S, Morimoto S-i, Kato S, et al. Transient ventricular wall thickening in acute myocarditis. *Japanese Circulation Journal* **2001**; 65:863-6
22. Kolb TM, Hassoun PM. Right Ventricular Dysfunction in Chronic Lung Disease. *Cardiology Clinics* **2012**; 30:243-56
23. Blanchard DG, Hagenhoff C, Chow LC, McCann HA, Dittrich HC. Reversibility of cardiac abnormalities in human immunodeficiency virus (HIV)-infected individuals: a serial echocardiographic study. *J Am Coll Cardiol* **1991**; 17:1270-6
24. Ntusi N, O'Dwyer E, Dorrell L, et al. HIV-1–Related Cardiovascular Disease Is Associated With Chronic Inflammation, Frequent Pericardial Effusions, and Probable Myocardial Edema- Clinical Perspective. *Circulation: Cardiovascular Imaging* **2016**; 9:e004430
25. Barbarini G, Barbaro G. Incidence of the involvement of the cardiovascular system in HIV infection. *AIDS* **2003**; 17:S46-S50
26. Patel K, VanDyke RB, Mittleman MA, Colan SD, Oleske JM, Seage GR. The impact of HAART on cardiomyopathy among children and adolescents perinatally infected with HIV-1. *AIDS* **2012**; 26:2027-37
27. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV- infected patients on highly active antiretroviral therapy: a population- based nationwide cohort study. *HIV Medicine* **2010**; 11:130-6
28. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. *Antiviral Research* **2010**; 85:201-9
29. Miller RF, Kaski JP, Hakim J, et al. Cardiac disease in adolescents with delayed diagnosis of vertically acquired HIV infection. *Clin Infect Dis* **2013**; 56:576-82
30. Longenecker CT, Sullivan C, Baker JV. Immune activation and cardiovascular disease in chronic HIV infection. *Curr Opin HIV AIDS* **2016**; 11:216-25
31. Prendergast AJ, Rukobo S, Chasekwa B, et al. Stunting Is Characterized by Chronic Inflammation in Zimbabwean Infants. *PLOS One* **2014**; 9:e86928
32. Bygrave H, Mtangirwa J, Ncube K, Ford N, Kranzer K, Munyaradzi D. Antiretroviral therapy outcomes among adolescents and youth in rural Zimbabwe. *PLoS One* **2012**; 7:e52856
33. Remick J, Georgiopoulou V, Marti C, et al. Heart Failure in Patients With Human Immunodeficiency Virus Infection. *Circulation* **2014**; 129:1781-9
34. Majonga ED, Norrish G, Rehman AM, et al. Racial Variation in Echocardiographic Reference Ranges for Left Chamber Dimensions in Children and Adolescents: A Systematic Review. *Pediatric Cardiology* **2018**:1-10
35. Majonga ED, Rehman AM, McHugh G, et al. Echocardiographic reference ranges in older children and adolescents in sub-Saharan Africa. *International Journal of Cardiology* **2017**; 248:409-13

Figure 1. Flow chart for participant recruitment and follow up

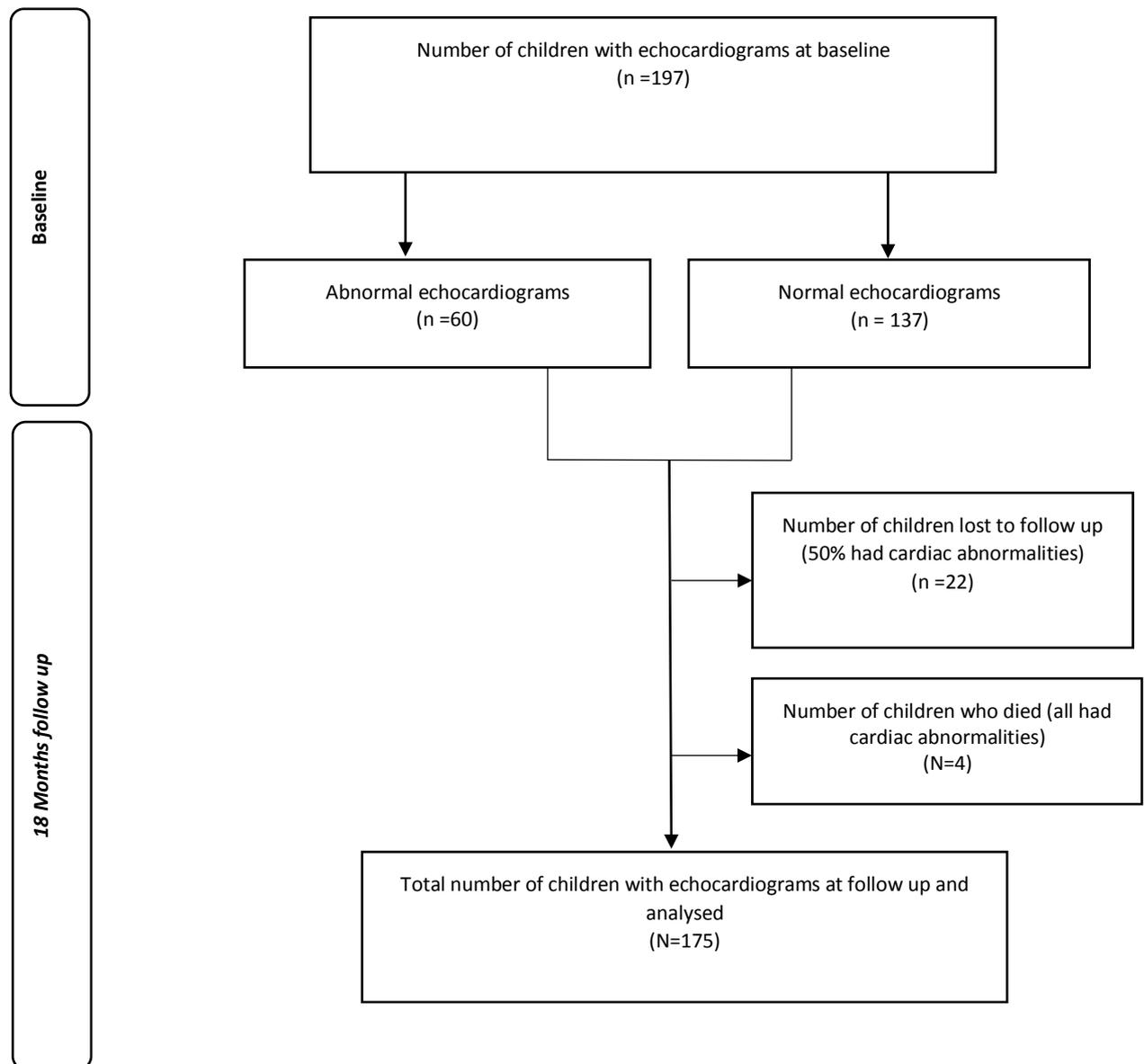


Table 1. Clinical characteristics of participants

Variable	N=175		P-value
	Baseline Mean (SD)	18 Months Mean (SD)	
Female, N (%)	84 (48)		
Age, y (median, IQR)	11 (9 – 13)	12 (10 – 14)	<0.001
CD4, cell/μl (median, IQR)	726 (473 - 935)	734 (462 - 989) *	0.455
Viral load, copies/ml, (median, IQR)	19 (19 - 208)	456 (165 - 4080) **	<0.001
Duration on ART, y (median, IQR)	4.8 (2.8 - 6.4)	6.5 (4.3 - 8.1)	<0.001
Systolic Blood Pressure, mmHg	110 (11)	109 (10)	0.247
Diastolic Blood Pressure, mmHg	73 (9)	72 (9)	0.392
Respiratory rate, breaths per min	21.8 (4.5)	21.9 (2.3)	0.697
Signs and Symptoms n (%)			
Chest pains on exertion	20 (11)	5 (3)	<0.001
Tachycardia	10 (6)	6 (3)	0.317
Tachypnoea	24 (14)	10 (6)	0.013
Hypoxia at rest	1 (1)	0	-
Abnormal spirometry***	37 (24)	23 (15)	0.144
Wasting	38 (22)	35 (20)	0.106
Stunting	40 (23)	39 (22)	0.117
Cardiac Measures			
RV diameter z-score	0.40 (1.3)	0.91 (1.1)	<0.001
LV diameter z-score	0.49 (1.1)	0.72 (1.1)	<0.001
IVS diameter z-score	0.06 (1.0)	0.65 (0.8)	<0.001
LVPW diameter z-score	0.29 (1.2)	0.88 (0.9)	<0.001
LA diameter z-score	0.36 (1.1)	0.66 (1.0)	<0.001
TAPSE	-0.63 (0.9)	-0.26 (1.0)	<0.001
Ejection fraction (%)	61.7 (6.2)	64.5 (6.6)	<0.001
E wave (m/s)	0.91 (0.1)	0.93 (0.2)	0.142
A wave (m/s)	0.53 (0.1)	0.55 (0.1)	0.105
E/A ratio	1.76 (0.4)	1.74 (0.4)	0.656
Deceleration Time (ms)	174 (27.7)	169 (15.6)	0.044

PV S wave (m/s)	0.49 (0.1)	0.51 (0.1)	0.069
PV D wave (m/s)	0.55 (0.5)	0.51 (0.1)	0.388
PV A wave (m/s)	0.19 (0.2)	0.22 (0.5)	0.352
PV S/D ratio	0.98 (0.3)	1.02 (0.2)	0.062
Cardiac abnormalities n (%)			
LV dilatation	7 (4)	8 (5)	0.317
LVH	18 (10)	15 (9)	0.257
LA dilatation	14 (8)	15 (9)	0.317
LV systolic dysfunction	2 (1)	1 (1)	0.563
LV diastolic dysfunction	40 (23)	40 (23)	1.000
RV dilatation	12 (7)	23 (13)	0.002
RV systolic dysfunction	2 (1)	6 (3)	0.046
Tricuspid regurgitation	31 (18)	34 (20)	0.564
Mitral regurgitation	5 (3)	3 (2)	0.317
Pulmonic regurgitation	37 (21)	28 (16)	<0.001
Aortic regurgitation	-	-	-

, n=159; **, n=91; *, n=150*

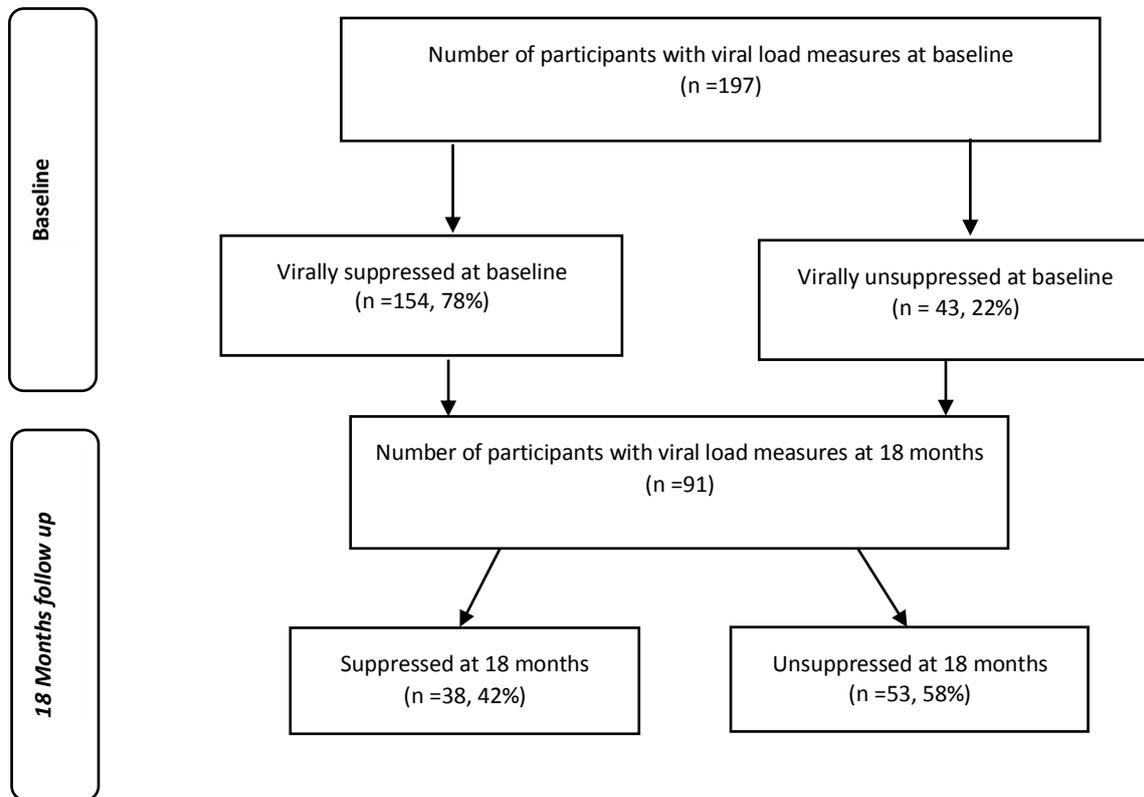
LV, left ventricle; IVS, interventricular septum, LA, left atrium; RV, right ventricle; E/A ratio, mitral valve peak early to late left ventricular filling velocity; PV, pulmonary venous; S, systolic; D, diastolic; TAPSE, tricuspid annular plane systolic excursion

Table 2. Z-scores at baseline and follow up for participants

Cardiac variable	Baseline	Follow up	N (%)	Z-score baseline mean (SD)	Z-score 18 months mean (SD)	Adjusted change in z- score after 18 months, SD (95% CI)	P-value	Risk
RV diameter diastole	Normal	Normal	151 (86)	0.15 (1.1)	0.64 (0.9)	0.55 (0.43- 0.67)	<0.001	
	Normal	RV dilatation	12 (7)	1.10 (0.7)	2.51 (0.5)	2.47 (1.90- 3.03)	<0.001	12/163 (7%)
	RV dilatation	Normal	1 (1)	2.23 (0.0)	1.81 (0.0)	-0.79 ^a		
	RV dilatation	RV dilatation	11 (6)	2.91 (0.7)	2.85 (0.8)	0.59 (-1.21- 2.39)	0.478	
LV diameter diastole	Normal	Normal	167 (95)	0.37 (1.0)	0.62 (1.0)	0.35 (0.24- 0.47)	<0.001	
	Normal	LV dilatation	1 (1)	1.04	2.10	1.06 ^a		1/168 (1%)
	LV dilatation	LV dilatation	7 (4)	3.27 (0.3)	2.94 (0.4)	-0.46 (-2.20- 1.27)	0.523	
IVS diameter diastole	Normal	Normal	172 (98)	0.02 (0.9)	0.62 (0.8)	0.61 (0.51- 0.71)	<0.001	
	Normal	IVS hypertrophy	2 (1)	1.82 (0.2)	3.13 (1.1)	1.31 (1.3)		2/174 (1%)
	IVS hypertrophy	Normal	1 (1)	2.50	1.63	-0.87 ^a		
LVPW diameter diastole	Normal	Normal	158 (90)	0.05 (1.0)	0.72 (0.8)	0.70 (0.59- 0.81)	<0.001	
	LVPW hypertrophy	Normal	4 (2)	2.43 (0.2)	1.63 (0.2)	-0.80 (0.4) ^a		
	LVPW hypertrophy	LVPW hypertrophy	13 (7)	2.61 (0.5)	2.61 (0.4)	1.00 (0.11- 1.89)	0.032	
LA diameter diastole	Normal	Normal	160 (91)	0.17 (1.0)	0.52 (0.9)	0.41 (0.31- 0.50)	<0.001	
	Normal	LA dilatation	1 (1)	1.99	2.07	0.08 ^a		1/161 (1%)
	LA dilatation	LA dilatation	14 (8)	2.44 (0.3)	2.44 (0.2)	2.74 (1.77-3.70)	<0.001	
TAPSE	Normal	Normal	154 (88)	-0.59 (0.9)	-0.16 (1.0)	-0.04 (0.22-0.14)	0.673	
	Normal	RV systolic dysfunction	4 (2)	-1.36 (0.6)	-2.32 (0.3)	-0.96 (0.8) ^a		4/158 (3%)
	RV systolic dysfunction	RV systolic dysfunction	2 (1)	-2.23 (0.1)	-2.20 (0.1)	-0.02 (0.1) ^a		

^a, unadjusted change (if $n=1$), or adjusted mean and (SD if $n>1$) has been reported; RV, right ventricle; LV, left ventricle; IVS, interventricular septum, LVPW, left ventricular posterior wall; LA, left atrium, TAPSE, tricuspid annular plane systolic excursion

Supplementary figure 1: Flow diagram of viral suppression of participants over time



Supplementary Table 1: Antiretroviral drugs received by participants

Antiretroviral drug	(N=175)	n (%)
<i>Zidovudine</i>		91 (52)
<i>Stavudine</i>		1 (1)
<i>Tenofovir</i>		75 (43)
<i>lamivudine</i>		173 (99)
<i>Didanosine</i>		2 (1)
<i>Abacavir</i>		7 (4)
<i>Atazanavir</i>		7 (4)
<i>Lopinavir/ritonavir (Aluvia)</i>		8 (5)
<i>Atazanavir/ritonavir</i>		28 (16)
<i>Nevirapine</i>		61 (35)
<i>Efavirenz</i>		39 (22)

Supplementary Table 2: Association between change in z-scores and baseline risk factors

Variables	RV diameter		LV diameter		IVS diameter		LVPW diameter		LA diameter		TAPSE diameter	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Age												
6 – 9 years	1	0.78	1	0.69	1	0.80	1	0.80	1	0.26	1	0.46
10 -12 years	-0.080		-0.071		-0.004		-0.089		-0.167		0.006	
13 – 16 years	-0.099		-0.117		-0.087		0.198		-0.081		-0.027	
Viral load												
≤ 400 copies/ml	1											
> 400 copies/ml	-0.119	0.41	0.034	0.79	0.170	0.20	0.080	0.55	0.002	0.99	-0.120	0.41
CD4 count												
≥ 350 cell/μl	1											
<350 cell/μl	0.202	0.32	0.154	0.39	0.110	0.55	0.060	0.75	0.041	0.78	-0.275	0.30
Duration on ART												
0 – 3 years	1	0.96	1	0.34	1	0.68	1	0.43	1	0.40	1	0.60
4 – 7 years	0.009		0.171		-0.093		0.155		-0.067		0.174	
8 – 12 years	0.054		0.126		0.019		0.098		0.201		0.126	
Age at ART initiation												
0 -5 years	1	0.07	1	0.65	1	0.80	1	0.92	1	0.75	1	0.06
6 – 10 years	0.320		-0.035		0.040		0.009		-0.056		0.196	
11 – 15 years	0.169		-0.184		0.133		0.265		0.050		-0.531	

Height-for-age z-scores	-0.085	0.13	-0.035	0.42	0.015	0.73	-0.092	0.06	-0.023	0.57	-0.048	0.56
Weight -for-age z-scores	-0.001	1.00	-0.008	0.86	0.044	0.33	-0.062	0.22	-0.049	0.23	-0.032	0.67

RV, right ventricle; LV, left ventricle; IVS, interventricular septum, LVPW, left ventricular posterior wall; LA, left atrium, TAPSE, tricuspid annular plane systolic excursion