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Original Article

Highly active antiretroviral therapy and left ventricular diastolic function in children with human immunodeficiency virus infection

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Abstract

Background In the past, cardiovascular involvement did not seem to be a common complication of HIV, but in recent years it has been described more frequently. With the advent of highly active antiretroviral therapy (HAART), the symptoms of cardiac disease has changed, as the number of HIV-infected patients with abnormal diastolic parameters has increased significantly, often presenting as symptomatic rather than asymptomatic.

Objective To analyze for a possible correlation between HAART duration and left ventricular diastolic function in HIV-infected children.

Methods This cross-sectional study was conducted from December 2016 to December 2017 at the Cardiology and Allergy-Immunology Division/Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital, Denpasar, Bali. Subjects with HAART were collected using a consecutive sampling method. The following data were recorded for each subject: age, sex, current stage of HIV, CD4+ level, as well as HAART regimen and duration of use. Transthoracic echocardiography was performed for tissue doppler imaging (TDI) of diastolic function. Spearman's test was used to analyze the strength of correlation based on normality test results.

Results This study involved 53 subjects, 21 of whom had impaired diastolic function. There was no correlation between HAART duration and diastolic function in children with HIV infection (r= -0.03; P=0.82).

Conclusion Diastolic dysfunction is found in children under HAART treatment, but there is no correlation between HAART treatment duration and diastolic dysfunction. **[Paediatr Indones. 2019;59:139-43; doi: http://dx.doi.org/10.14238/pi59.3.2019.139-43]**.

Keywords: *HIV; left ventricular diastolic function; HAART*

Human immunodeficiency virus (HIV) is an important cause of childhood morbidity and mortality, affecting more than 1.3 million children worldwide.[1] With the advent of highly active antiretroviral therapy (HAART), HIV infection has become a chronic disease with longer life expectancy.[2] Cardiac diseases are frequent complications in these patients.[2] The potential mechanisms of cardiac complications in HIV include, but are not limited to, direct cardiotoxicity by the virus itself, immune-mediation mainly by cytokines, nutritional deficiencies, and antiretroviral medications.[3]

Some of the medicines used to treat HIV infection may have a deleterious effect on the myocardium. Mitochondrial toxicity is an acknowledged side effect of HAART.2 Defects in mitochondrial DNA (mtDNA) replication and decreased energetics are caused by zidovudine, as well as other nucleoside reverse transcriptase inhibitors (NRTI). The spectrum of cardiac disease varies significantly between the

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pre-HAART and post-HAART eras.[4] In the pre-HAART era, HIV-associated cardiomyopathy was defined as symptomatic, systolic dysfunction with dilated left ventricle, and seen almost exclusively in patients with advanced clinical stage of HIV and low CD4 levels.[2,5] In the post-HAART era, the symptoms of the cardiac disease has changed into diastolic dysfunction, and the condition has changed from mostly symptomatic to asymptomatic. Chelo *et al.* showed that from 100 children with HIV, 32% had LV diastolic dysfunction.[6]

Prior studies have reported that HAART may contribute to impaired diastolic function in adults. However, this effect is unclear in children. A previous study reported only reduced diastolic function in HIV-negative children exposed to HAART in utero.[7] Hence, we aimed to assess for a correlation between left ventricular diastolic function in HIV-infected children and HAART duration of use.

Methods

This cross-sectional study was done from December 2016 to December 2017, at the Cardiology and Allergy-Immunology Division/Department of Child Health, Universitas Udayana Medical School/Sanglah Hospital Denpasar, Bali. Target populations were inpatient and outpatient children with HIV infection in Sanglah Hospital. Informed consent was obtained from the parents. The inclusion criteria were patients on HAART and aged under 18 years. Patients on medications with known cardiovascular effects (such as antiarrhythmic drugs, theophylline, and adriamycin), patients with pre-existing cardiac diseases, or poor adherence to HAART were excluded.

Subjects were consecutively enrolled until the required sample size was complete. Sample size was calculated using the formula based on consideration of analytic, single group, unpaired, two-tailed study, with alpha 0.05, power 80, and correlation score 0.4 based on clinical judgment. The minimum required sample size was calculated to be 48. The total number of subjects obtained was 53.

Subjects underwent uniform clinical evaluations and the following data were recorded: age, sex, current stage of HIV, CD4+ level, as well as HAART regimen and duration. Transthoracic echocardiography was performed and interpreted by a cardiologist. All studies were performed on a *General Electric Vivid 7* ultrasonograph with 3s-MHZ or 7s-MHZ transducers. Tissue doppler imaging (TDI) was obtained using pulsed-wave tissue Doppler. Pulsed wave TDI velocity measurements were obtained by placing the sample volume at the mitral annular level from the septal annulus. The TDI signal over a cardiac cycle has three peaks: a positive systolic peak and two negative diastolic peaks. The negative waves represent the early diastolic myocardial relaxation (é velocity) and active atrial contraction in late diastole (á velocity). The TDI é septal velocity was recorded. The variables were defined as follows:

- Left ventricular diastolic function was represented by TDI é medial, as measured from the septal annulus.[8] A medial é velocity < 12 cm/s indicated impaired LV diastolic function or cardiomyopathy.[9]
- HIV clinical stages were categorized as 1 through 4 based on *World Health Organizatio*n (WHO) 2014 guidelines.[10]
- Highly active antiretroviral therapy (HAART) was defined as any regimen that included three antiretroviral drugs from 2 or more antiretroviral drug classes [nucleoside reverse transcriptase inhibitors (NRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI)]. The first line therapy typically consists of 2 NRTI and 1 NNRTI.[10] The duration of HAART was the time from the start of HAART use to the time of the study (months).
- Adherence to HAART was defined as a patient's ability to follow a treatment plan, as well as take medications at prescribed times and frequencies.[11] Data were obtained by parents' or caregivers' reports.
- The CD4 data were obtained from within three months of subjects' echocardiography examination.

Characteristics of subjects are presented descriptively in table and narrative form. The data distribution was analyzed with Kolmogorov-Smirnov test because the sample size was more than 50, and considered to be normally distributed if P value > 0.05. Normality test of HAART duration and TDI é medial results revealed an abnormal data distribution. After data transformation by log10, HAART

duration data were still abnormally distributed and nonparametric, with P value < 0.05. Data were numeric and Spearman's test was used to analyze the strength of correlation based on normality test results. Statistical analysis was performed with *SPSS version 18* software. This study was approved by the Medical Ethics Committee of Universitas Udayana, Sanglah Hospital, Denpasar.

Results

Between December 2016 and December 2017, 66 children with HIV participate in the primary study. Twelve children did not consume HAART and 54 subjects fulfilled the inclusion criteria for this study. One subject was excluded because of improper adherence due to an allergic reaction. Fifty-three subjects underwent echocardiography and retained for analysis.

Table 1. Subjects' characteristics

Clinical characteristics	¯(N = 53)
Age, n (%)	
≤ 5 years	12 (22.6)
> 5 years	41 (77.3)
Male, n (%)	33 (62.2)
Current stage of HIV, n (%)	
Stage I	43 (81.1)
Stage II	4 (7.5)
Stage III	4 (7.5)
Stage IV	2 (3.7)
CD4+ level (age ≤ 5 years), n	12
≥15%	8
<15%	4
CD4+ level (age > 5 years), n	41
≥ 200 cell/mm^3	28
< 200 cell/mm^3	13
HAART regimen, n (%)	
First line	45 (84.9)
Second line	8 (15.0)
Median duration of HAART use (range), months	48 (2-120)
Median TDI é medial (range), cm/s	12 (8-16.6)

The characteristics of subjects are described in **Table 1**. The age range of the subject was 2 to 14 years, with median age of seven years. A total of 81.1% subjects were HIV stage one. The frequency of subjects using a second line HAART regimen was 15%. More than 50% of subjects had absolute CD4+ levels above 200 cell/mm^3 and percentages above 15%. There were 21 subjects with TDI é medial less than 12 cm/s.

Spearman's test was used to analyze for a possible correlation between duration of HAART and TDI é medial. The two variables had a negative association and very weak correlation, with r=-0.03, but were not statistically significant (P=0.82) (**Table 2**).

Discussion

The subjects in our study ranged from 2 to 14 years in age. Most were above five years and had stage 1 infection. More than 50% of subjects had CD4+ level ≥15% or ≥ 200 cells/mm^3. The overall data indicated that subjects had good control of the disease.

The longest duration of HAART usage was 120 months, and the shortest was two months. Longer HAART duration indirectly showed an increase in life expectancy among children with HIV. This result was in agreement with that of Ewings et al. who noted that the proportion of patients expected to survive 5, 10, and 15 years after seroconversion in the HAART era were 99%, 93%, and 89%, respectively.[12]

The risk of premature cardiovascular disease has been associated with specific antiretroviral therapies.[13] Nucleoside reverse transcriptase inhibitors (NRTIs) have been associated with mitochondrial toxicity.[7] Zidovudine may inhibit cardiac mitochondrial DNA polymerase and induce ultrastructural changes in cardiac myocytes.[14] Protease inhibitors (PIs) have also been implicated in adversely affecting cardiac function and atherogenic risk in both adults and children. The PI-containing regimens have specifically been

Table 2. Correlation between HAART duration and diastolic function

Variables	Median (range)	Correlation coefficient	P value
Duration of HAART use, months	48 (2-120)	-0.03	0.82
TDI é medial, cm/s	12 (8-16.6)		

associated with an increase in LV mass and diastolic dysfunction in adults.[7]

In our study, HAART regimens used in our setting were categorized as first line or second line. The first line regimen included two NRTIs (zidovudine and lamivudine) and one NNRTI (nevirapine), and was most commonly used by our subjects. Eight subjects with previous treatment failure had second line HAART regimen, which consisted of two NRTIs (tenofovir or abacavir and lamivudine) and one PI (lopinavir/ritonavir).

In the HAART era, the prevalence of systolic dysfunction has decreased and the number of patients with severely impaired ejection fraction is quite low. However, the number of HIV-infected patients with abnormal diastolic parameters has increased significantly.[2,5] Previous study evaluating the relationship between HAART and diastolic dysfunction in children with HIV has been limited. In 1992, Lipshultz *et al.* only evaluated the effect of zidovudine on systolic function and left ventricular dimension. Zidovudine was administered every 6 hours in that study, with conventional echocardiography used to evaluate the left ventricular dimension.[15] Kuswiyanto et al. (2011) also assessed left ventricular function disorder in children with HIV and its associations with CD4+ level and clinical stage, but not its association with HAART.[16]

Our study differs with others because we assessed for an association between HAART administration duration and diastolic function. Left ventricular diastolic function was assessed by TDI, which is more sensitive than conventional echocardiography for detecting early myocardial alterations. The TDI is useful for screening and detection of subclinical myocardial dysfunction.[8] We found 21 (39%) patients with diastolic dysfunction. Similiarly, Mondy et al. showed that 26% of HIV-infected subjects suffered from diastolic dysfunction.[17] However, the risk of left diastolic dysfunction in children with HIV was not significantly increased with longer HAART duration. An in vitro study by Lewis *et al.* demonstrated that zidovudine and HIV infection led to the independent development of cardiomyopathic changes in a transgenic mouse model. The dose of zidovudine used in that study was much higher than that used clinically in HIV-infected patients (~200 mg/kg *vs.* 8 mg/kg, respectively).[18] Studies in adults also revealed different results. Luo *et al.* showed that zidovudine exposure was associated with higher prevalence of diastolic dysfunction. A potentially important finding was that using zidovudine for more than 12 months showed a trend towards increased diastolic dysfunction.[19] Our study population, which were children, might explain the disparate results, as they are less likely to have risk factors for cardiovascular disorders than adults. Cardiac abnormalities in adults might result from the complex interactions among HIV infection itself, HAART medication, and other non-HIV related factors such as smoking, obesity, hypertension, and diabetes. Meng *et al.* also showed that HAART exposure was correlated with increased diastolic dysfunction in adults.[20] The different results may be related to the few patients who used PIs in our study (only eight subjects), compared to previous study.[7]

A limitation of this study was that adherence to the drug regimen was evaluated by parents' or family reports, without any validated methodology. Adherence affects the drug level in blood, thus potentially affecting study results. The diastolic dysfunction (cardiomyopathy) that occurred in HAART-treated children in this study was not correlated to HAART treatment duration. Our results suggest that HAART can be safely used in this population, even though regular monitoring of diastolic function should be considered. Further study is required to elucidate relationships between stratified variables and duration of HAART treatment, as well as comparison to a control group with no HAART history.

Conflict of interest

None declared.

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