

AIDS in Childhood: Cardiac Involvement with and without Triple Combination Antiretroviral Therapy

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Summary

Objective: To describe the prevalence of cardiac abnormalities in the echocardiogram of children with AIDS followed up in a reference service at 18±6 months of AIDS confirmed diagnosis.

Methods: A cross-section study with a cohort after 18±6 months of AIDS diagnosis. The study included a total of 93 children with a confirmed diagnosis of AIDS with vertical transmission, with no malignancies and who underwent echocardiogram (echo) during cardiologic evaluation. Cardiac abnormalities were assessed in patients who were not treated (G1) and patients who were treated (G2) with combination antiretroviral therapy.

Results: When diagnosed with AIDS, the children were on average 3.07 years old and 50.50% were female. The combination regimen with antiretroviral agents was used by 47 patients (G2). Cardiac involvement was present in 40 children (43.00%). The presence of left ventricular dysfunction (G1: 39.10%; G2: 10.60%) and the isolated enlargement of left ventricle (G1: 6.60%; G2: 14.90%) were the most frequent findings. We observed a significant association between the groups without and with combination antiretroviral therapy as regards the presence of left ventricular dysfunction (PR = 3.42; [1.41-8.26]; p = 0.02) and malnutrition (PR = 1.79; [1.00-3.20]; p = 0.04).

Conclusion: Cardiac involvement was frequent in children with AIDS and left ventricular dysfunction was the most common abnormality on echocardiogram. There was a statistically significant difference between the groups with and without triple combination treatment as regards the presence of left ventricular dysfunction and malnutrition. (Arq Bras Cardiol 2008;90(1):11-17)

Key words: AIDS; acquired immunodeficiency syndrome; antiretroviral, highly active; child.

Introduction

Infection by the human immunodeficiency virus (HIV) is one of the major public health problems in the world, with high mortality and morbidity rates, affecting young people in their productive and reproductive years. In Brazil, following worldwide trends, there is increased contamination among women at childbearing age, which leads to increased cases of mother-child transmission¹.

Cardiac abnormalities in children with AIDS have been described. Although frequently subclinical, they can be persistent and/or progressive and tend to occur in the late stages of the disease²⁻⁴. These findings are considered poor prognostic factors, with a higher mortality in children presenting reduced percentage of left ventricle shortening⁵.

Highly Active Antiretroviral Therapy (HAART) has significantly changed the course of the disease with increased survival and improved quality of life for AIDS patients. However, little is known about the clinical cardiac presentations in the post-HAART stage. There are reports of an increased incidence of peripheral artery diseases and coronary artery involvement in adults⁶ as well as of a reduced incidence of cardiomyopathy in children⁷⁻⁹.

The applicability of data previously published about the cardiac involvement in patients using protease inhibitors is unknown, and it is necessary to verify if this new therapy has modified the incidence of cardiac manifestations¹⁰. This current study aims to describe the cardiac clinical manifestations, results of laboratory tests that evaluate the immunological status and echocardiographic findings after 18±6 months of AIDS diagnosis, trying to relate them to the type of antiretroviral therapy available. On an exploratory basis, we also analyzed possible associations between the findings in patients without combination antiretroviral therapy – G1 Group – and patients on combination therapy – G2 group

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Manuscript received July 24, 2006; revised manuscript received April 10, 2007; accepted June 14, 2007.

– with nutritional status and the presence of left ventricular dysfunction on echocardiogram. Therefore, this study intends to contribute to the scientific knowledge about the cardiac involvement of pediatric AIDS patients taking or not triple combination antiretroviral therapy (HAART).

Methods

This is a descriptive study with retrospectively collected data, with a cohort at 18 ± 6 months of AIDS diagnosis, carried out in a pediatric reference center. The inclusion criteria were children aged under 13 years at hospital admission between 1990 and 2002, AIDS diagnosis (C and/or 3 category classification) by vertical transmission according to the criteria defined by the Ministry of Health (MS – acronym in Portuguese)¹¹ and absence of malignant disease evidence.

The study variables included sex, child age when diagnosed with HIV infection, clinical-immunological classification upon diagnosis, age at the time of definition of C and/or 3 category classification in years, and age upon reference echocardiogram. At 18 ± 6 months after AIDS diagnosis: weight, hematocrit, and the presence of the following cardiologic manifestations: cardiomegaly, congestive heart failure (tiredness, tachypnea not explained by infection, dyspnea, ictus cordis deviated to the left, third heart sound, hepatomegaly), pulmonary artery hypertension (palpable right ventricle, second heart sound with hyperphonic pulmonary component, hepatomegaly; persistent tachycardia)^{12,13}, hematocrit and CD4 lymphocyte count, in addition to echocardiogram evaluation.

Bidimensional echocardiogram was performed with the usual standard technique^{14,15}, with 2.5 and 5.0 mHz transducers. Sedation was necessary in some cases and children were assessed in supine position or left lateral decubitus. Sequence analysis was applied to evaluate possible congenital cardiopathies and longitudinal and cross sections were used for mode M measurements. The examination was performed with simultaneous registration of a reference ECG lead.

All measurements and calculations were performed based on M-mode tracings in three cardiac cycles, following the recommendations of the American Society of Echocardiography^{14,15}. The following measurements were directly obtained and analyzed: diameter of aortic root (Ao), diameter of left atrium (LA), diameter right ventricle (RV), diastolic dimension of left ventricle (LVd), systolic dimension of left ventricle (LVs), thickness of posterior wall (PW) during diastole and thickness of interventricular septum (IVS) during diastole. In assessing the reference echocardiogram measurements, the indicator used was weight/age, with the reference pattern published by the American Heart Association^{14,15}. The Z score was calculated with base on the mean of expected measurements in normal children with the same weight and age divided by a standard deviation. Therefore, a Z- score of zero represents the adjusted normal mean value and the upper and lower limits considered were +2 and -2.

To evaluate the ventricular function we calculated the percentage of systolic LV diameter shortening ($\Delta\%$ LV) calculated by the equation: $\Delta\% \text{ LV} = (\text{LVd} - \text{LVs}) / \text{LVd} \times$

100, with normal values considered being $\Delta\%$ LV between 28% and 40%¹⁶.

In this study, left ventricular dysfunction was the percentage of systolic LV diameter shortening lower than 28%, associated with increased left ventricle volume and/or presence of localized hypokinesia with no other explainable cause. The severity of dysfunction was quantified by $\Delta\%$ LV, that is, the lower the percentage, the more severe the left ventricular involvement. Values of 28% to 25% were considered mild dysfunction and, in most cases, patients were asymptomatic; values $<25\%$ and up to 19% were considered as moderate dysfunction, usually with clinical symptoms, and values lower than 19% were considered as severe dysfunction, almost always associated with a clinical picture of more severe heart failure¹⁰.

Antiretroviral therapy used – when the clinical status became severe, children could be on different treatments (depending on the time when this fact occurred): with no antiretroviral therapy, therapy with one antiretroviral agent, therapy with two antiretroviral agents or therapy with three antiretroviral agents¹¹.

On the exploratory approach, cardiac abnormality (left ventricular dysfunction) and presence of malnutrition were the dependent variables. The type of AIDS treatment, respectively without (G1) and with triple antiretroviral therapy combination (G2) for a period equal to or longer than six months before the baseline echocardiogram, as per MS¹¹ recommendations, was the independent variable considered.

The data were stored and analyzed using the software EPIINFO version 6.04¹⁸, by means of descriptive statistics (distribution of frequencies for categorical variables and measurements of central trend for continuous variables). For analysis of association, we used the prevalence ratio (PR) and, for statistical inference, the chi-square test and confidence interval (CI) with a significance limit of 0.05 were considered.

The project was approved by the Research Ethics Committee of the Health Unit.

Results

Out of 387 children with a confirmed diagnosis of HIV infection as per criteria of the Ministry of Health/CDC 1994, from January 1990 to December 2002, 288 children had a confirmed diagnosis of vertical transmission and 183 children had severe cases of the disease (C and/or 3 classification). The echocardiographic evaluation at 18 ± 6 months after clinical-immunological diagnosis of AIDS had been confirmed (C and/or 3) was carried out in 93 children. These children comprise the sample of this study.

In 93 patients analyzed, there was no prevalence of sex - 47 females and 46 males. Mean age of children was 3.07 ± 3.05 years upon confirmation of diagnosis.

As to body weight evaluation, most children were well nourished (64.50%), but 35.50% of them presented some degree of malnutrition and 14% had severe clinical malnutrition.-

The mean hematocrit value was $32.48 \pm 3.56\%$ in the total

population. The mean hematocrit in patients with a normal heart at echocardiogram was $33.18 \pm 3.34\%$; in patients with enlarged left ventricle at echocardiogram the mean hematocrit was $32.11 \pm 4.10\%$ and, in children with left ventricular dysfunction it was $31.08 \pm 3.27\%$. Therefore, these variations in hematocrit did not have statistical significance. As regards the clinical-immunological classification at the beginning of follow-up at the IPPMG, 70 (75.4%) children already presented severe cases of the disease. Thirteen children had moderate involvement (Class B and/or 2) (13.9%) and 10 (10.7%) had mild condition (A and/or 1). During the study, all the children presented severe cases of the disease (inclusion criterion).

The mean percentage count of CD4 lymphocytes in a date close to the echocardiogram was $17.65\% \pm 11.56$. The level of CD4 lymphocytes in children with no cardiac disease was 10.39 ± 8.30 and at 18 ± 6 months it was 20.15 ± 11.71 , as opposed to patients with left ventricular dysfunction, who presented values of 8.21 ± 6.80 upon AIDS diagnosis, and 14.30 ± 11.86 at 18 ± 6 months at the time of echocardiographic examination.

When echocardiography was performed, the prevalence of clinical cardiac abnormalities was 24.73% (n= 23 children): 12 children presented clinically diagnosed heart failure; 7 patients had enlarged cardiac area and four had a physical examination suggestive of pulmonary artery hypertension. All children with probable pulmonary artery hypertension presented repeat respiratory infections and/or lymphocytic interstitial pneumonia.

The type of therapy administered to each patient varied according to the year the follow-up started (recommendations and availability of drugs in Brazil have shown differences along the years) and the clinical presentation upon diagnosis.

Prophylaxis with AZT was carried out in only three children in the group studied; they had been classified as C3 since the age of three months, which was when they started combination therapy (triple therapy). Four children, although presenting severe cases of the disease, did not receive any antiretroviral therapy in the first 18 ± 6 months of follow-up.

Up to the time of echocardiogram (18 ± 6 months after confirmed AIDS diagnosis), nine children (9.70%) received only monotherapy and 25 children were first on monotherapy and later were switched to two antiretroviral agent regimen. In monotherapy, AZT (azithromycin) was always used as the first agent and in eight cases it was replaced by ddl (didanosin). The double-agent therapy was used in 51 children (54.80%) in this study (some children were switched to the triple combination regimen at least six months before echocardiogram), and the regimen containing AZT + ddl was initially used in 47 of those children (92.10%). AZT + 3TC (lamivudine) was the first regimen in four children. In 16 children, the initial double regimen was replaced due to intolerance or no response. The double regimens were as follows: AZT + 3TC in 13 cases; ddl + 3TC in two cases and ddl + D4T in one case. In 47 children (50.50%) combination therapy or triple therapy was used for at least six months before echocardiogram, according to the regimens recommended by the Ministry of Health, described in Table 1 (five of these patients had initially used the double therapy).

Table 1 - Distribution of children according to several (triple) combination therapy regimens. IPPMG/UFRJ 1990-2002

	1° Regimen
2 ITRN + 1 ITRNN (NVP ou EFZ)	21 (44, 70%)
3 ITRN (AZT + 3TC + ABC)	3 (6,40%)
2 ITRN + IP (NFV, TRV ou IDV)	23 (48,90%)
2 ITRN + LPV/r	0
Total	47 (100,00%)

NNRTI - nucleoside reverse transcriptase inhibitor (AZT - zidovudine; ddl - didanosin; d4T - stavudine; 3TC - lamivudine; ABC - abacavir); NRTI - non-nucleoside reverse transcriptase inhibitor; (NVP - nevirapine; EFV - efavirenz) PI - protease inhibitor (NFV - nelfinavir; RTV - ritonavir; IDV - indinavir; APV - amprenavir; LPV/r - lopinavir + ritonavir).

In the echocardiographic examination performed 18 ± 6 months after diagnosis of AIDS, the prevalence of cardiac abnormalities was 43.00%, and left ventricular dysfunction was the most frequent abnormality, observed in 24.70% of children (Table 2). Septal hypokinesia was found in four cases and inferior-posterior hypokinesia, in one children. Another patient presented an intracavitary thrombus. Isolated enlargement of left ventricle was confirmed in 10 children.

Table 2 - Distribution of children according to main cardiologic diagnoses on echocardiogram of children performed 18 month after Aids diagnosis. IPPMG/UFRJ. 1990-2002 (n=93)

Normal	n %
Left ventricular dysfunction	53 (57,0%)
Enlarged left ventricle	23 (24,7%)
Congenital cardiopathy	10 (10,7%)
Pulmonary arterial hypertension	4 (4,4%)
Isolated pericardial effusion	2 (2,1%)
Total	1 (1,1%)

The echocardiographic signs of pulmonary artery hypertension were detected in two children. In this selected population referred to the IPPMG, the isolated congenital cardiomyopathies observed were: interventricular communication, interatrial communication, mild mitral insufficiency and mitral valve prolapse (one case of each abnormality). In one patient, the echocardiogram showed only a small pericardial effusion, in a child who presented a clinical picture of pneumonia.

Left ventricular function, evaluated through the percentage of systolic left ventricle diameter shortening ($\Delta\%$ LV), was decreased in 21 children and, in two other children, although $\Delta\%$ LV was $> 28\%$, the diagnosis of left ventricular dysfunction was considered in light of the marked isolated reduction in interventricular septum contractility without another cause for this fact. When severity of myocardial dysfunction was assessed, it was noticed that most children presented moderate grade dysfunction (52.20%); mild dysfunction was present

in 39.10% of patients and, in only two patients (8.70%), dysfunction was considered severe upon examination.

The mean values of $\Delta\%LV$ were decreased in the group (23 children) of patients with left ventricular dysfunction ($24.52 \pm 4.65\%$). On the other hand, the group of patients with normal echocardiogram (53 children) presented mean values of $\Delta\%LV$ of $34.70 \pm 3.90\%$.

Table 3 shows the mean scores of cardiac cavities at echocardiogram in patients with normal LV function and in patients with left ventricular dysfunction; the abnormalities are evidenced with a marked shift of the left ventricular measurements in systole and diastole with scores $> +2$.

Table 3 - Mean scores of HIV+ child cavities on echocardiogram 18 months after diagnosis of Aids; children with normal diagnosis and with left ventricular dysfunction. IPPMG/UFRJ 1990-2002

	Normal (n=53) mean sc \pm SD	LV dysfunction (n=23) mean sc \pm SD
Aorta	+ 0,770 \pm 0,902	+ 1,020 \pm 1,222
Left atrium	- 0,396 \pm 0,96	+ 0,355 \pm 2,021
Diastole LV	+ 0,543 \pm 0,572	+ 2,173 \pm 1,952
Systolic LV	+ 0,644 \pm 0,693	+ 4,298 \pm 3,172
Interventricular septum	-1,101 \pm 1,098	- 0,581 \pm 1,791
Posterior wall	-1,037 \pm 0,914	- 0,309 \pm 1,268

LV - Left ventricle; SD - standard deviation.

For analysis of association, the 93 cases were separated into two groups, with base on the use or not of triple combination regimen for more than six months. Group 1, who did not use the triple combination regimen, was composed of 46 children, and G2, in which the triple therapy was used, comprised 47 children. No significant difference was noticed as to age at diagnosis between the two groups: the mean age was 2.67 ± 2.59 years in G1 and 3.46 ± 3.43 in G2 ($p=0.21$). There was also no significant difference ($p=0.45$) between the groups in terms of age when AIDS severity was established (C and/or 3): 3.76 ± 2.77 years old in G1 and 4.24 ± 3.36 years old in G2.

There was a positive association (PR = 3.42; CI = 1.41 – 8.26; $p= 0.002$) between the absence of combined antiretroviral treatment and the presence of left ventricular dysfunction in the echocardiogram (total of 23 cases – G1 = 18; G2 = 5). And no association in children with normal LV function (total of 53 cases – G1 = 21; G2 = 32). Also, there was a higher number of moderately or severely malnourished children in the group without triple treatment (21 out of 46) than in the treatment group in which, in a total of 47 children, only 12 were malnourished. This difference was statistically significant (CI = 1.00 – 3.20; $p = 0.004$).

Discussion

In spite of the development of policies and prevention and care programs for HIV patients in the last decades, in the current national statistics there is still a significant number of children contaminated by this virus transmitted by the mother¹⁹.

The interval of 18 months after diagnosis of AIDS, with a variation of ± 6 months, was considered the most appropriate to assess cardiac abnormalities in the echocardiogram for the following reasons:

1. It excludes patients with the rapidly progressive form, who evolve to death within the first two years of life^{20,21} and represent about 20% of pediatric patients that die before the first cardiologic evaluation and use of medication. They present a lower incidence of cardiac involvement which when present, manifests itself in a form distinct from the remaining 80%^{16,22,23}. Therefore, the priority was to study patients with slow progression seen in the older age group (pre-school and school age) with higher probability of cardiac involvement^{20,24} and therapeutic intervention¹⁰.

2. Since sick children come to the Infectious and Parasitic Diseases outpatient clinic, in average, at the age of 3 years, if the interval for echocardiographic evaluation were longer than 24 months after AIDS diagnosis, many children with cardiac involvement could already have evolved to death²⁵.

3. The 18-month interval allows the use of combined antiretroviral therapy for at least six months, which would not occur in a shorter interval.

As to nutritional status, the data in the literature are related to studies but do not specify the clinical-immunological classification of patients, thus hindering comparisons. In this study, the exploratory analysis showed that the proportion of malnourished children was lower in the group with triple combination therapy, as above mentioned^{2,26}.

As to the clinical presentation, heart failure was present in 12% of children and represented the most frequent cardiologic diagnosis. It was noticed that 11 out of 23 children diagnosed with left ventricular dysfunction on the echocardiogram had no clinical symptoms, and this fact is corroborated by the literature and not only in children with AIDS^{11,13}. The absence of congestive heart failure (CHF) symptoms in a great number of children with an echocardiographic diagnosis of left ventricular dysfunction emphasizes the need of an early performance of this examination in those at higher risk of developing heart disease, since the appropriate cardiac treatment could contribute to a better quality of life. However, CHF presentations are frequently confused with clinical presentations of the disease itself. Lipshultz et al²⁶ draw attention to the differential diagnosis of these clinical pictures and recommend routinely carrying out cardiologic evaluation in any stage of HIV infection.

Four children had a physical examination suggestive of pulmonary artery hypertension (PAH), presented an associated lymphocytic interstitial pneumonia (LIP) and were not receiving the combination therapy. Pulmonary

artery hypertension has been frequently described in adults and children with HIV as a consequence of left ventricular dysfunction and repeat respiratory infections but also, occasionally, as a primary process of unknown cause²⁷.

In this investigation it is possible to observe that the drug regimens were in accordance with the standards recommended for each period. This study did not aim to evaluate the quality of drug regimens.

The prevalence of cardiac abnormalities in the echocardiogram was 43%; left ventricular dysfunction was the most frequent abnormality found and affected 24.70% of children with severe disease at 18±6 month follow-up. The data published about this prevalence vary according to the methodology used, time of collection, profile of children studied and type of therapy used, ranging from 14%²⁸ of cardiac involvement in the neonatal period to incidences as high as 45% to 75% in naive severe patients²⁹.

In patients with left ventricular dysfunction, the mean percentage of left ventricular shortening was 24.50%. Some facts may have minimized these values, such as: a) examinations that might have been performed after initiating CHF treatment; b) when undergoing the examination, at 18±6 months of severe disease, patients with fulminant disease and with generally more severe forms of the disease who evolve to death in the first couple of months might have been excluded; c) due to the analysis of only one time interval, transient forms of dysfunction could have improved during the clinical course – this fact is confirmed when it is possible to notice children with normal echocardiographic examinations while using any positive inotropic agent (especially digitalis), in spite of having presented a previously documented myocardial disease; d) it is also possible that this study includes patients who have already had left ventricular dysfunction and attained normal echocardiographic results during the clinical course.

The isolated enlargement of the left ventricle was present in 10.70% of children. Some abnormalities were investigated in this group of children in an attempt to justify this datum, but were ruled out: a) presence of severe anemia; b) cardiac arrhythmias leading to decreased ventricular emptying; c) existence of structural cardiopathy or infectious endocarditis. As previously described^{29,30}, an enlarged left ventricular cavity was deemed the most probable factor, secondary to mild or transient damage of the myocardial structure and, in this case, we would have the regression phase of a transient involvement or the beginning of a cardiopathy, which had not yet met the criteria for left ventricular dysfunction.

Only two children had documented pulmonary hypertension, less than those with clinical suspicion of pulmonary artery hypertension (four cases). This is probably due to the fact that PAH can be transient or even reversible after treatment of pulmonary diseases; moreover, patients may have improved clinically after introduction of antiretroviral therapy. Blanchard et al³¹ pointed out the return to normality of certain cases of pulmonary hypertension with treatment, and the resulting improvement of pulmonary abnormalities. This reversibility

is probably responsible for the few cases observed in this study because, in addition to control of respiratory conditions, the use of combination therapy also led to a marked reduction of repeat infections and the presence of interstitial lymphocytic pneumonia.

Since the use of antiretroviral combination therapy has already resulted in clinical and laboratory evidence of improved quality of life and longer survival^{30,32}, it is not possible, from the ethical point of view, to propose any type of prospective clinical trial with a naive control group, in order to show the effects of antiretroviral agents in the clinical course of cardiologic involvement in these AIDS children.

The results described suggest an association between the non use of triple combination antiretroviral therapy and the presence of left ventricular dysfunction in the echocardiogram.

This study did not aim to evaluate the effect of antiretroviral therapy in cardiac involvement, an analysis that had already been carried out by Plebani et al⁸, in which 38 children with vertically transmitted AIDS were followed up for five years. The authors observed the resolution of previous left ventricular dysfunction (documented in five cases) upon initiating treatment and absence of new cardiovascular events or metabolic abnormalities during administration of therapy. Some hypotheses may be advanced in light of the results presented here, suggesting a lower incidence of left ventricular dysfunction in AIDS patients treated with triple combination antiretroviral therapy (HAART):

- a) triple combination antiretroviral therapy could be directly responsible for non aggression to the cardiac muscle;
- b) triple combination antiretroviral therapy could revert the previous picture of dilated cardiomyopathy and, since only one interval was evaluated here, an initial disease was not detected (according to description of Plebani et al⁸).
- c) triple combination antiretroviral therapy could delay the emergence of dilated cardiomyopathy.

The lower incidence of left ventricular dysfunction observed should not reduce caution in the case of HIV+ children being treated with antiretroviral therapy. On the contrary, they should receive more attention, since long-term evolutionary studies in adults have described cerebrovascular, cardiovascular and endothelial abnormalities, probably secondary to the use of the agents and/or to the disease itself after long periods of life^{33,34}.

A longer follow-up time of children is necessary to rule out the possibility that, with the advent of combination antiretroviral therapy, there is only a delay in the onset of cardiac manifestations.

In this study of children with AIDS, the results confirm the epidemiological findings of the international literature in poor populations, in which diagnosis of vertically transmitted disease in children is still late; in many cases, severe clinical and immunological involvement is already present.

Likewise, the results described, although coming from children with severe disease who were selected and referred for follow-up in a reference service, suggest lower

cardiologic involvement, improvement of immunological and nutritional status of children with AIDS when treated with triple combination antiretroviral therapy (HAART), similarly to the few studies recently published with specific groups of patients. With a future prospective analysis of this group, still being followed up, it will be possible to better study the clinical course of cardiologic involvement caused by AIDS in our midst.

Potential Conflict of Interest

No potential conflict of interest relevant to this article

was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Maria do Carmo Soares Alves Cunha, from Universidade Federal do Rio de Janeiro.

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