# Cardiac Longitudinal Study of Children Perinatally Exposed to Human Immunodeficiency Virus Type 1

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## Objective

To determine the frequency of cardiac abnormalities and its natural history in children perinatally exposed to HIV-1.

## Methods

Eighty-four children exposed to HIV-1 were evaluated by serial clinical, electrocardiographic (ECG), and Doppler-echocardiographic (ECHO) examinations.

## Results

Group I – (seroreversion) - 43 children (51.2%). Absence of clinical abnormalities. ECG: incomplete right bundle branch block (RBBB) – 5 cases. ECHO: atrial septal defect (ASD) and ventricular septal defect (VSD) – 1 case each. Group II – 41 HIV-infected children (48.8%), of whom 51.2% were found to have cardiac abnormalities. Asymptomatic or mildly symptomatic children without immunosuppression: no clinical and echocardiographic abnormalities; ECG: incomplete right bundle branch block (RBBB) – (2 cases). Children with moderate and severe symptoms and immunological impairment: the following abnormalities were found: 1) clinical (31.7%)-isolated tachycardia (1 case), congestive heart failure (12 cases). 2) electrocardiographic (43.9%)-sinus tachycardia associated with other abnormalities (10 cases), incomplete right bundle branch block (5 cases), left anterior hemiblock (1 case), right anterior hemiblock (1 case), changes in ventricular repolarization (11 cases), right ventricular overload (2 cases), left ventricular overload (1 case), right QRS axis deviation (1 case), and arrhythmias (3 cases). 3) echocardiographic (26.8%)-dilated cardiomyopathy (5 cases), pericardial effusion with tamponade (2 cases), pulmonary hypertension (2 cases), and mitral valve prolapse (1 case).

## Conclusion

Cardiac involvement was a characteristic of the HIV-infected group. Higher prevalence of abnormalities was found among children belonging to the most advanced clinical and immunological category. The most commonly observed clinical, electrocardiographic and echocardiographic findings were congestive heart failure (CHF), changes in ventricular repolarization, and dilated cardiomyopathy, respectively. The latter was reversible in one case. Electrocardiogram changes were significantly more frequent than clinical and echocardiographic changes.

## Keywords

HIV, heart disease, vertical transmission, electrocardiogram, echocardiogram

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*Received on 10/19/04 • Accepted on 04/29/05*

It has been twenty years since human immunodeficiency virus type I (HIV-1) was isolated, yet the cure for acquired immunodeficiency syndrome (AIDS) is still not a reality. Despite the improvement in survival and quality of life of HIV-1-infected patients, AIDS remains a serious public health problem. Since the outbreak of the pandemic, more than 42 million people have been infected worldwide, with sixteen thousand new cases daily. In Brazil, over 500,000 cases were reported, and half of the patients have already died. The incidence of infected women has greatly increased during the last twenty years due to the current predominance of heterosexual transmission, thus raising the prevalence of the disease in pregnant women from 1% to 5%. Accordingly, the number of perinatally infected children now accounts for 3.5% of all reports.[1]

AIDS is a systemic, infectious disease characterized by immunosuppression, which predisposes infected individuals to both opportunistic infections and neoplasias. It is progressive in nature and may impair the cardiovascular apparatus in multiple ways. The prevalence of cardiac abnormalities seems to be underestimated both in the adult and pediatric population. Most studies conducted to date suggest values between 40% and 70%, if electrocardiogram (ECG) and Doppler echocardiogram (ECHO) findings are included in addition to clinical findings. Autopsy studies show a high prevalence of cardiac abnormalities. In pathological studies, about 50% of HIV-1-infected individuals without cardiovascular symptoms are found to have interstitial lymphocytic myocarditis. This figure rises to 83% in individuals who develop congestive heart failure (CHF).[2-11] The mechanism by which the heart is injured in patients with AIDS remains unclear. Childhood mortality due to cardiac complications ranges from 1% to 9%.[2,4,8,10,12-23]

The ever-increasing number of children born to HIV-positive mothers, coupled with the complex etiopathogenesis of heart involvement and the need for further understanding of the natural history of clinical cardiac manifestations during childhood, led us to study children exposed perinatally to HIV-1. This is an eight-year clinical, electrocardiographic, and echocardiographic follow-up study.

## Methods

From July 1996 to July 2004, following approval by the Institutional Research Ethics Committee (filed under nº 089/96), eighty-four children perinatally exposed to HIV-1 were prospectively studied. Thirty-nine were girls (46.4%) and 45 were boys (53.6%), ages ranging for both from thirteen days to thirteen years old.

All children were Brazilian and resident in São Paulo. Inclusion criteria were the following: children born to HIV-positive mothers and, thus, perinatally exposed to HIV-1 (via transplacental, labor or breastfeeding routes); less than 13 years old at the time of the baseline cardiac evaluation; regular follow-up at the pediatric cardiology outpatient clinic with a minimum of two clinical and electrocardiographic evaluations and one echocardiographic study. Only children whose legal guardians agreed with their participation and provided a written "Informed Consent" were enrolled in the study.

Clinical and immunological status of the infected children was defined according to the Centers for Disease Control[24] "Revised classification system for human immunodeficiency virus infection in children less than 13 years of age", as shown in table I.

Diagnosis was made using Elisa and agglutination serological assays and confirmed by quantification of plasma RNA viral load, evaluated in number of copies by the NASBA method (Nucleic acid sequence-based amplification) (Organon Teknika). The lower detection limit of the assay was 80 copies/mL. CD4 T-lymphocyte counts were determined using flow cytometry Laboratory follow-up and included Elisa assay, plasma viral load, and CD4 T-lymphocyte count.

A complete cardiac evaluation was performed. Heart failure was diagnosed on the basis of standard clinical criteria for children.[25,26]

No sedation was used during ECG recordings. Electrocardiograms were performed using Hewlett Packard PageWriter 100, USA; ECAFIX ECG-6 – 023236, Brazil, and Dixtal DX-2500, Brazil, equipment. The guidelines set by the Committee on Electrocardiography of the American Heart Association were followed.[27] Standard 12-lead ECGs were used. The following variables were evaluated: heart rate (HR), rhythm, P wave (in lead II),

| Immunological Categories | Clinical Categories | | | |
|---|---|---|---|---|
| | N | A | B | C |
| | Signs/symptoms Absent | Signs/symptoms Mild | Signs/symptoms Moderate | Signs/symptoms Severe |
| 1 No suppression | N1 | A1 | B1 | C1 |
| 2 Moderate suppression | N2 | A2 | B2 | C2 |
| 3 Severe Suppression | N3 | A3 | B3 | C3 |

*Table I - Revised classification system for HIV-infection in children less than 13 years of age issued by the Centers for Disease Control (CDC) - 1994*

**Table II - Children from group II according to the initial and final clinical classification**

| | Initial | | Final | |
|---|---|---|---|---|
| Group | n | % | n | % |
| **II-A** | 18 | 43.9 | 11 | 26.8 |
| **II-B** | 12 | 29.3 | 11 | 26.8 |
| **II-C** | 11 | 26.8 | 19 | 46.3 |
| Total | 41 | 100.0 | 41 | 100.0 |

*Group II-A (N + A): N1+ N2 + A1+ A2 + A3; group II-B: B1+ B2 + B3 group II-C: C1+ C2 + C3*

PR interval (in lead II), QRS complex, ST segment, T wave, QT interval corrected for heart rate (in lead II). All ECGs were analyzed by two different observers. Electrocardiographic analysis was performed taking as reference the normal ECG standards for infants and children set by Davignon et al.[28]

Doppler echocardiogram was performed using different echocardiographs currently available equipped with 3,5 and 5 MHz transducers capable of producing B-mode and M-mode images. Spectral Doppler and color flow imaging were used for measurement of blood flow velocity. The use of sedatives was avoided. The guidelines set by the American Society of Echocardiography were followed.[29] Left ventricular function was estimated by ejection fraction (cube method) and fractional shortening [Dd – Ds/Dd) x 100]. Snider et al.'s[30] criteria for normality in children were employed, as well as reference values issued by Escola Paulista de Medicina, UNIFESP, resulting from the fifteen-year cumulative experience of its Echocardiographic Department (unpublished data). Dilated cardiomyopathy was defined as left ventricular dysfunction characterized by a diffuse decrease in myocardial contractility, with fractional shortening below normal limits (< 28%), followed by left ventricular enlargement, with diastolic diameter above normal values for the weight range.[10, 31,32]

The results were assessed by means of non-parametric tests, the nature of the studied variables considered. The following tests were performed: 1) Kappa test,33 to evaluate the agreement of clinical and immunological classification of HIV-infection noted in the first and second examination; 2) McNemar test, 34 to study the disagreement observed above and below the diagonal in Kappa test; 3) Cochran G-test,35 to compare simultaneous clinical, electrocardiographic, and echocardiographic changes; 4) chi-square test, 36 for 2 x N tables, to compare groups refarding the presence of cardiac abnormalities. Significance level for rejection of the null hypothesis was set at 0,05 or 5% in all tests.

## Results

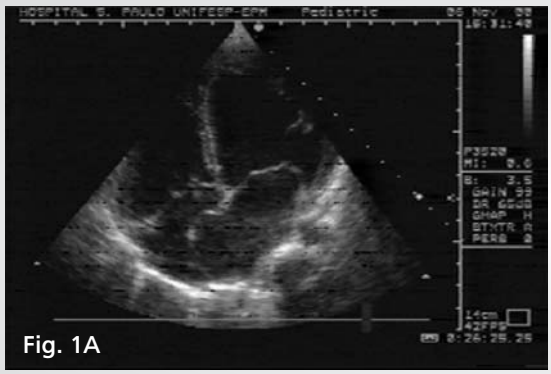
The 84 children exposed to HIV-1 were divided in two groups: Group I: 43 children (51.2%) who seroreverted (SR), i.e., they were exposed to HIV-1 but did not get infected. Mean age at the first and last visit was 6.8 months and 34.1 months, respectively. Group II: 41 infected children (48.8%). Mean age at the first and last visit was 40.8 months and 76.4 months, respectively.

Distribution of infected children according to initial and final clinical classification is shown in Table II.

Among the groups of children infected with HIV-1, 14 children (34.1%) changed clinical group and 6 children (17.6%) changed immunological group between the beginning and end of study, showing significant clinical and immunological worsening.

Group I (SR) – Absence of clinical abnormalities in all cases. ECG: incomplete right bundle branch block in 5 children (11.6%). ECHO: small *ostium secundum* atrial septal defect (1 case), and small perimembranous ventricular septal defect (1 case). These were the only congenital heart diseases found in the study (2/84 or 2.4%).

Group II – Of the 41 infected children, 51.2% developed some kind of cardiac abnormality. Fourteen children experienced clínical worsening in terms of the HIV-1 infection. Among these, 10 (71.4%) had cardiac abnormalities; electrocardiographic changes were



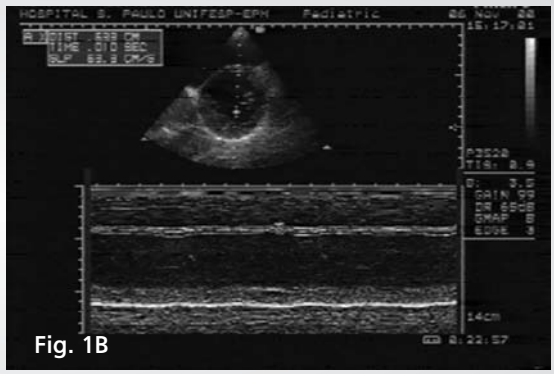




***Fig. 1*** *- Ten-year-old, AIDS C2. Dilated cardiomyopathy. a) Two-dimensional ECHO: heart in diastole - apical four-chamber view showing left chamber dilation; b) Two-dimensional ECHO, parasternal cross-sectional view (figure 1A) and M-mode ECHO (figure 1B): left ventricle dilation. LVDd = 62, LVDs = 51, ΔD% = 17*

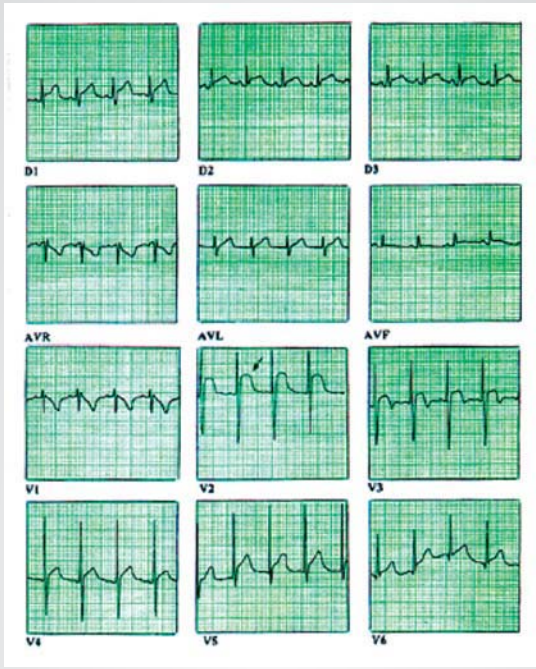



Fig. 2A

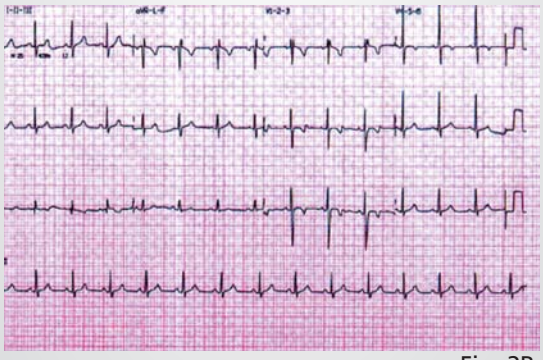


Fig. 2B

***Fig. 2*** *- Nine-year-old, AIDS B3. Bacterial pericarditis. A) ECG - acute phase: diffuse changes in ventricular repolarization with ST-segment elevation (arrow); b) ECG one year later; reversion of the changes in ventricular repolarization*

significantly more frequent (9 cases) than either clinical (4 cases) or echocardiographic changes (3 cases).

Of the 41 infected children, 13 (31.7%) developed clinical cardiac changes, one of whom had tachycardia as an isolated symptom. The other 12 patients developed CHF associated with the following etiologies: dilated cardiomyopathy (5/41 – 12.2%) (fig. 1); pericardial effusion with cardiac tamponade caused by bacterial pericarditis (2/41 – 4.9%) (figs. 2 e 3); pulmonary hypertension secondary to chronic lung disease (2/41 – 4.9%) (fig. 4); respiratory infection; sepsis; and anemia: 3/41 (7.3%). No changes in Group II-A were found; 2 cases occurred in Group II-B and 11 cases (84.6%) in Group II-C.

Of the 41 infected children, 20 (48.8%) developed electrocardiographic changes.

In group II-A only 2 cases of incomplete right bundle branch block occurred. In group II-B, the following five changes were observed: incomplete right bundle branch block, left anterior hemiblock (1 case), right QRS axis deviation, right ventricular overload, and junctional rhythm (one case each). Most changes (13 cases – 65%) occurred in group II-C, distributed as follows: 4 cases of sinus tachycardia with change in ventricular repolarization; 3 cases of incomplete right bundle branch block; 1 case each of isolated sinus tachycardia, isolated change in ventricular repolarization, alternating sinus and junctional bradycardia associated with change in ventricular repolarization, change in ventricular repolarization with prolonged QTc, right ventricular overload, and left ventricular overload. One child developed ventricular arrhythmia with frequent bigeminal extrasystoles and periods of ventricular tachycardia.

Of the 41 infected children, 11 (26.8%) developed echocardiographic changes: no changes in Group II-A; 3 changes in Group II-B and 8 changes in Group II-C. The following changes were found in Group II-B: pulmonary hypertension with RV dysfunction and tricuspid insufficiency; mild isolated mitral insufficiency; and pericardial effusion with cardiac tamponade, one case of each. Changes in Group II-C were: five cases of LV dysfunction and dilation, three cases of mild/moderate secondary mitral insufficiency; one case each of infectious pericardial effusion with tamponade, moderate pulmonary hypertension with mild tricuspid insufficiency and mitral valve prolapse with mild mitral insufficiency.

Children with dilated cardiomyopathy were clinically highly compromised. They suffered from severe protein-calorie malnutrition (PCM), recurrent respiratory infection, and chronic anemia. Three of them progressed to sepsis and death. Of the children who developed dilated cardiomyopathy, two are still alive. One manifested the disease early on, with increased severity and multiple organ damage associated with AIDS. Now, at 9 years old, however, this child is clinically stable and receiving antiretroviral therapy, with no CHF signs or symptoms and normal ECG and ECHO. The other is thirteen years old, and although cardiomyopathy have not been reverted, is stable and under treatment for CHF (fig. 1). This child underwent cardiac catheterization with myocardial biopsy, which was negative for myocarditis.

Both cases of bacterial pericarditis with effusion and cardiac tamponade were managed using pericardiocentesis and antibiotic therapy. Valvular insufficiencies were common and usually secondary to left and/or right ventricular dilation, with mitral insufficiency predominating.

Infected children who developed cardiac abnormalities belonged to moderate and, especially, severe immuno-suppressed groups. Eight children, 19.5% of those infected, died during the cardiac follow-up, and all of them belonged to group II-C, category C3. They were severely ill and infected with opportunistic microorganisms.

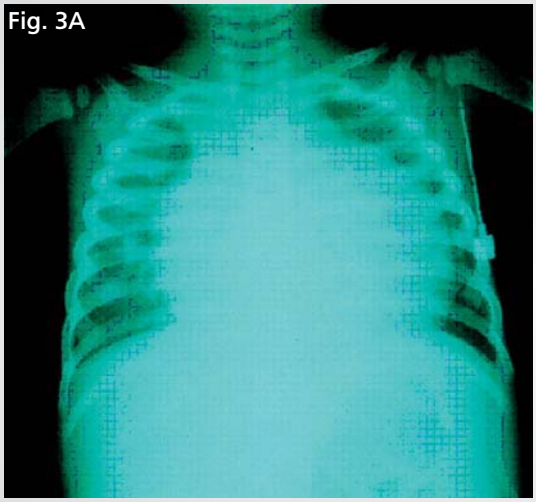




***Fig. 3*** *- Two-year-old, AIDS C2. Pyopericardium with cardiac tamponade. a) Pre-drainage chest x-ray (PA): severe global cardiomegaly with a globe-shaped cardiac contour; b) post-drainage chest x-ray (PA): cardiac area of normal dimension*

## Discussion

Congestive heart failure, dilated cardiomyopathy, pericardial effusion with or without tamponade, arrhythmias, marantic and infective endocarditis and, more rarely and still controversial, congenital heart diseases, are cardiac abnormalities that can result from the acquired immunodeficiency syndrome.[4,10,15,20-22,37-40] Cardiac studies performed on HIV-1 infected children provided greater understanding of the evolution and clinical management of the diseased heart. However, in the reviewed literature, we found no longitudinal study correlating cardiac changes and progression of the infection, either clinically or immunologically.

Analysis of the clinical evolution of the 41 infected children showed that cardiac changes occurred in the AIDS groups with moderate clinical and immunological signs and symptoms. Cardiac manifestations of HIV infection were significantly more frequent in the groups whose patients were in advanced stages of the disease. Heart failure was the most frequent clinical finding, most often caused by dilated cardiomyopathy, and a finding unique to category C, particularly C3. These results are similar to those found in the literature. Cardiac changes frequency increases as the disease progresses, and early detection of these changes usually depends on complementary examinations, such as electrocardiograms and echocardiograms.[4-42] Unlike the results obtained in this study, in the experience of Luginbuhl *et al*.,[20] Lipshultz *et al*.,[23] and Della Negra *et al*.,[43] tachycardia was the most frequent and early sign of clinical manifestations. According to our experience, in all but one case tachycardia occurred only at the time of cardiac decompensation.

The etiopathogenesis of myocardial dysfunction in AIDS, however, remains unclear. Even though HIV has already been isolated from myocardial cells derived from endomyocardial biopsies and autopsy specimens, in which non-specific lymphocytic myocarditis is a common finding, the direct cytolytic effect of HIV is debatable. Biopsy was performed only in one case, and was found to be negative. Cardiac damage is believed to be multifactorial, meaning that several elements work together to affect the heart adversely, leading to functional and anatomical changes with a strong autoimmune component. In addition to the immunological aspects, among the factors involved in the genesis of cardiac dysfunction are the co-infections with cardiotropic viruses, such as citomegalovirus, Epstein-Bar, and cocksackie B, anemia, PCM, autonomic dysfunction, and trace element deficiency, such as selenium and L-carnitine, vitamin A deficiency, toxic response to antiretroviral agents, pentamidine and sulfamethoxazole with trimethoprim, oxidative stress, and genetic susceptibility.[8,10,18,37,41,44-55]

Pyopericardium and cardiac tamponade occurred in 2 cases (4.9%) in this study, but these are serious cardiac complications and clinical emergencies that could have resulted in death. Prevalence of pericarditis with effusion in the literature is about 22%; however autopsy findings put this as higher.[56] Approximately 30% of adults infected with HIV but without cardiac symptoms have pericardial damage. This figure rises to 48% in symptomatic patients. Few cases of cardiac tamponade in children with infectious effusion have been reported in the literature.[22,37,57]

Similar to the clinical course of HIV-infected patients, electrocardiographic and echocardiographic changes were more common in categories with more advanced clinical and immunological involvement. In this study, ventricular repolarization change was the most significant electrocardiographic abnormality. Its onset was progressive and observed in the most severe clinical and immunological groups. According to the literature, changes

in ventricular repolarization are common findings in ECGs of children with AIDS in advanced clinical and immunological stage.[4,10,20,22]

The incidence of arrhythmia in this study was 7.3%, a low incidence compared to that reported in the literature, as only electrocardiogram was used.[58-61] Incomplete right bundle branch block was the most frequent manifestation in infected children (7 cases – 17%). This conduction disturbance was the earliest of all changes, since it was the only one observed in the group of asymptomatic children. However, the small size of the sample did not allow us to prove that this finding is clinically relevant in infected children, because normal children may also have this kind of change. Incomplete right bundle branch block was a common finding in other studies as well.[4,43]

Echocardiographic studies in HIV-infected children and adults show a high prevalence of cardiac changes even in the absence of clinical signs and symptoms.[3,8,10,16,20,21-22] Nevertheless, in this series, no echocardiographic changes were found in clinically asymptomatic or mildly symptomatic children, and thus similar to the course of the seroreverted children. Echocardiographic manifestations were detected in children with moderate signs and symptoms and moderate immunosuppression, and predominated in the highly compromised clinical and immunological groups. Dilated cardiomyopathy was the most common finding of the study, being reversible in one patient, a striking case due to its severe and premature nature.[62] This was the first reported case of reversibility of a severe case during childhood with long-term cardiac follow-up. The results of the multicentric study $P^2C^2$, involving 196 HIV-infected children[23], showed that LV dysfunction and dilation are common abnormalities that can be also subclinical. The authors found echocardiographic changes in all symptomatic children (88%).

As for pulmonary hypertension in children with AIDS, despite the high incidence of respiratory compromise, the literature is scant[63,64]. In this study, 2 patients developed severe pulmonary hypertension and *cor pulmonale* secondary to chronic pulmonary infection.

In summary, this longitudinal study showed a clear correlation between AIDS and progressive cardiac compromise, with mortality of 19.5% at the advanced stage. Also, in the eight-year follow-up, no cardiac changes were found in children exposed to but not infected with HIV. Similar result has not been reported in the literature.

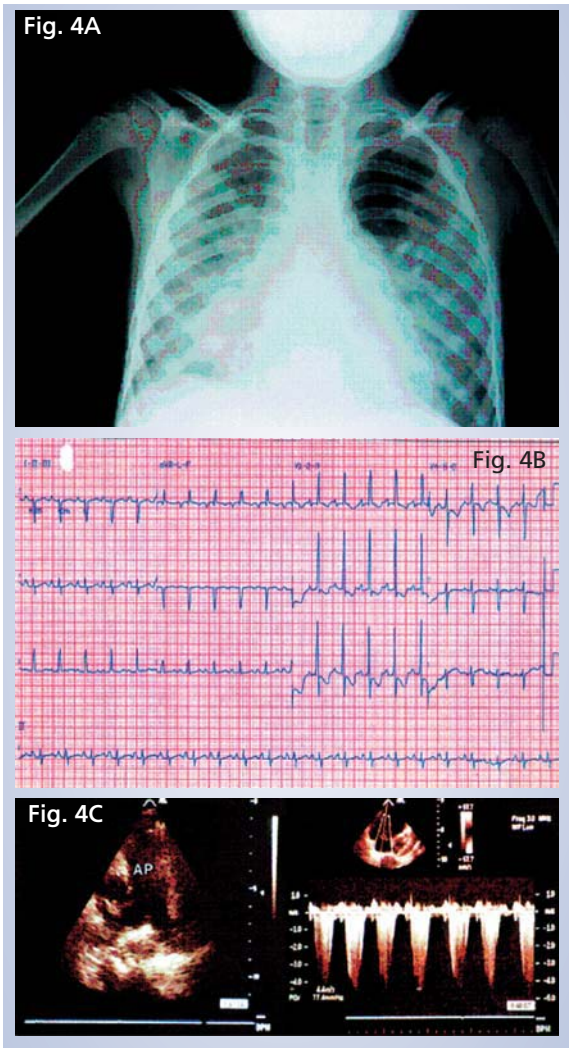



***Fig. 4*** *- Eight-year-old, AIDS B2. Pulmonary hypertension secondary to chronic lung disease. Chest x-ray (PA): enlargement of right chambers, bulging of the middle arch and heterogeneous hypolucent pulmonary images due to infection; b) ECG: severe right atrial and ventricular overload; c) Two-dimensional ECHO - parasternal cross-sectional axis view: enlargement of pulmonary artery trunk (AP); ECHO/ Doppler - Pulmonary artery pressure estimated at 87 mm Hg*

## Conclusions

Clinical, electrocardiographic, and echocardiographic changes in children exposed to HIV-1 were a characteristic of the infected group (AIDS), manifested in a progressive form and become prominent in the clinical and immunological advanced stages of the disease. They were more frequent in children who switched clinical and immunological grouping.

From a clinical perspective, CHF was the most common manifestation, as well as change in ventricular repolarization was the most frequent ECG finding. Dilated cardiomyopathy was the most frequent echocardiographic change, and was found to be characteristic of the severe clinical and immunological stages of the disease. One case of reversion occurred, clinically, electrocardiographically and echocardiographically. Pericardium with tamponade was a clinical emergency.

Children exposed to but not infected with HIV-1 did not develop any form of cardiovascular disease, a valuable and highly reassuring finding for the families of those involved.

## Acknowledgements

Our most sincere thanks to Drs. Ivan R. Rivera, Samira M. Leal, Solange Tatani, Enilda Meire Santos, Denise Araújo, Patrícia Kuga, Ednelson Cunha Navarro, Seila Auxiliadora de O. Silva, Ana Milena Sales, and Yara Machado. We are also grateful to the electrocardiograph technicians, Mrs. Neide Bueno, Neilda Pereira, and Neusa Bregalante; as well as all those who indirectly contributed to making this work possible.

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