Echocardiographic Follow-up of Perinatally HIV-infected Children and Adolescents

Results From a Single-center Retrospective Cohort Study in Brazil

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Background: The effects of HIV and antiretroviral therapy on cardiovascular system of perinatally infected children throughout their development are not fully understood.

Objectives: To determine the prevalence of cardiac abnormalities in a retrospective cohort of perinatally HIV-infected patients and to investigate associations between echocardiographic and clinical data during their follow-up.

Methods: Review of medical records and echocardiogram reports of 148 perinatally HIV-infected patients between January 1991 and December 2015.

Results: Four hundred and eighty echocardiograms were analyzed and 46 (31%) patients showed cardiac abnormalities, frequently subclinical and transient. Nadir CD4 count was higher in patients with consistently normal echocardiogram: 263 (4–1480) versus 202 (5–1746) cells/μL, $P = 0.021$. Right ventricular (RV) dilation was detected in 18.9%, left ventricular (LV) dilation in 21.6%, septal hypertrophy in 12.2%, LV posterior wall hypertrophy in 6%, LV systolic dysfunction in 8% and pulmonary hypertension in 8.7% of patients. Opportunistic infections were associated with RV dilation [odds ratio (OR = 4.34; 1.78–10.53; $P < 0.01$)], pulmonary hypertension (OR = 8.78; 2.80–27.51; $P < 0.01$) and LV systolic dysfunction (OR = 5.38; 1.55–18.71; $P < 0.01$). Longer duration of highly active antiretroviral therapy was associated with reduced risk of LV dilation (OR = 0.91; 0.85–0.97; $P < 0.01$) and systolic dysfunction (OR = 0.71; 0.59–0.85; $P < 0.01$). Protease inhibitors use was associated with reduced risk of RV dilation (OR = 0.54; 0.30–0.97; $P < 0.05$), LV dilation (OR = 0.35; 0.21–0.60; $P < 0.01$) and LV systolic dysfunction (OR = 0.07; 0.02–0.31; $P < 0.01$). Higher CD4 count was associated with lower risk of LV systolic dysfunction (OR = 0.82; 0.69–0.98; $P < 0.05$).

Conclusions: Echocardiograms identified cardiac abnormalities among children with perinatally acquired HIV infection, and data suggest that immunologic status and therapeutic strategies throughout development can influence cardiac disease burden in this population.

Key Words: HIV, children, antiretroviral therapy, echocardiogram

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According to the World Health Organization, about 1.7 million individuals under the age of 15 were living with HIV across the world in 2018. Despite drastic reduction of perinatal transmission because of the use of antiretroviral therapy (ART) in pregnancy and in infants of HIV-infected women, 160,000 new pediatric cases were recorded in the same year.[1–3]

The combination of highly active antiretroviral therapy (HAART) with early diagnosis has significantly reduced mortality and morbidity for children living with HIV.[4,5] However, cardiovascular compromise, probably attributable to both direct and indirect actions of HIV, remains a concern.[6–14]

To date, the largest study investigating the effects of HIV on the cardiovascular system of patients with perinatal HIV infection (Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study),[15,16] conducted in the pre-HAART era, identified increased mass and reduced left ventricular (LV) contractility as early predictors of mortality. The Adolescent Master Protocol (AMP),[17] conducted in the HAART era, documented a drastic reduction in the incidence of left ventricular cardiomyopathy among patients with perinatal HIV infection to 4% from 44% in Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection Study.

The role of screening echocardiography in perinatally HIV-infected patients is unclear, and the ideal frequency of examinations is still undetermined. Most echocardiographic studies in perinatally HIV-infected populations are based on a single evaluation of each patient, which precludes the precise analysis of what happens throughout their development.

The present retrospective longitudinal study aimed to determine the prevalence of cardiovascular compromise in a cohort of perinatally HIV-infected patients, submitted to serial clinical and echocardiographic assessment. Possible associations between echocardiographic and clinical data were interrogated, with special concern to immunological status and therapeutic strategies adopted at the time of each evaluation.

METHODS

Study Design and Population

This is a longitudinal retrospective study, based on the review of medical records and echocardiogram reports from children and adolescents (0–18 years) with perinatal HIV infection, who were seen at our Pediatric Infectious Disease Clinic between January 1991 and December 2015. All patients were diagnosed according to the Centers for Disease Control and Prevention (CDC) criteria.[18]

Exclusion criteria included lack of digitized medical records, congenital heart disease and absence of echocardiograms during the follow-up period. The ethics committee of our institution approved the study.

In the 1990s, echocardiograms were indicated for symptomatic patients. More recently, echocardiograms have been adopted as part of our routine screening, at least once a year.

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Patients with cardiovascular symptoms or echocardiographic abnormalities are seen more frequently and have individualized schedules of evaluation.

Echocardiogram

Echocardiograms were performed by experienced pediatric cardiologists, according to the guidelines of the American Society of Echocardiography.[19] Evaluations included M and 2-dimensional (2D) modes, besides standard Doppler examination with color flow mapping. Our first patients were evaluated in the nineties, when there was not a formal recommendation to use preferentially 2D derived measurements in pediatric echocardiograms. To maintain the same technic for the whole cohort, we have decided to compute M-mode measurements of right ventricle (RV) and LV and to evaluate LV ejection fraction using the Teichholz method, although 2D derived methods like Simpsons would be undoubtedly more accurate. Diastolic and systolic ventricular diameters were measured using M-mode in the parasternal short-axis view (at the level of papillary muscles), as also the thickness of interventricular septum and of the LV posterior wall. Values obtained were compared with the expected average for the body surface area, allowing calculation of the Z-score for each measure.[20] Z-score values between −2 and +2 were considered normal. LV ejection fraction values equal to or above 55% were considered normal for all ages. Pulmonary artery systolic pressure was estimated through tricuspid regurgitation; pulmonary hypertension (PH) was diagnosed whenever pulmonary artery systolic pressure > 35 mm Hg.[21] LV diastolic dysfunction could not be adequately investigated since tissue Doppler velocities were not routinely described in our early 90s echocardiogram reports.

Clinical, Laboratory and Therapeutic Parameters

Patients' digitized medical records were carefully reviewed for clinical, laboratory and therapeutic data within 3 months of the echocardiographic evaluation. Demographic information assessed included age, gender, age at diagnosis and disease duration. Clinical classification of HIV infection was determined according to the 1994 CDC criteria.[18]

Nutritional status was assessed through body mass index Z-score.[22] The presence of anemia, a potential contributor to ventricular dilation and high-output heart failure, was also interrogated. Anemia was defined as hemoglobin of 110 g/L between 6 and 59 months, 115 g/L between 5 and 11 years, 120 g/L between 12 and 14 years, 120 g/L for women ≥ 15 years and 130 g/L for men ≥ 15 years.[23] The presence of lymphocytic interstitial pneumonia (LIP) and/or opportunistic infections associated with HIV by the time of the echocardiogram were also documented.

Functional class was established according to the New York Heart Association (NYHA).[24] Classical cardiovascular risk factors, such as systemic arterial hypertension and dyslipidemia, were investigated, as well as the use of cardiovascular drugs. Hypertension was diagnosed whenever systolic and/or diastolic blood pressure were ≥ 95th percentile for gender, age and height on ≥ 3 occasions.[25] Dyslipidemia was diagnosed if total cholesterol was ≥ 170 mg/dL, low-density lipoprotein cholesterol ≥ 130 mg/dL, high-density lipoprotein cholesterol < 45 mg/dL and triglycerides ≥ 130 mg/dL.[26]

For the quantitative analysis of HIV viral load (copies/mL), the following techniques were used: nucleic acid sequence-based amplification,[27] chain polymerization reaction (COBAS AMPLICOR HIV-1 MONITOR version 1.5 and 2.0—Roche Diagnostics),[27] bDNA method (branched DNA—SIEMENS),[27] and more recently, real-time polymerase chain reaction.[27] CD4 cell count was obtained from flow cytometry.

Antiretroviral drug history was abstracted from the medical record.

Initially, patients were divided into 2 groups, according to the presence or absence of echocardiographic abnormalities:

Group 1: patients with consistently normal echocardiograms.

Group 2: patients with at least one abnormal echocardiogram during the follow-up.

The 2 groups were compared regarding demographic and therapeutic parameters, as well as nadir CD4 cell counts and age.

The pool of echocardiograms was then divided according to the presence or absence of each echocardiographic abnormality, as follows: RV dilation, LV dilation, interventricular septum hypertrophy, left posterior wall hypertrophy, LV systolic dysfunction and PH. The resulting groups were compared regarding patient's demographic, clinical, laboratorial and therapeutic variables at the time of the exams.

Finally, the frequency of patients that showed transient echocardiographic abnormalities throughout follow-up was obtained.

Statistical Analysis

To compare groups 1 and 2, categorical data were reported as percentages and continuous data as mean (SD) or median (range). Student *t* test was used to assess normally and Mann-Whitney *U* test to assess non-normally distributed continuous data. Fisher exact test was chosen to compare categorical data. To analyze the association between independent variables and different echocardiographic outcomes, we performed crude and adjusted regression (for those variables with a $P < 0.1$). Adjustments were done for the confounder effects of age, sex and decade in which the patient was examined. We fitted population-averaged panel-data models by using Generalized Estimating Equations, with logit as link function and assuming equal correlation (option exchangeable in software) as the within-group correlation structure. The software that was used was Stata 14.0.

RESULTS

Of the 424 children and adolescents seen during the study period, 44 were excluded due to non-perinatal HIV infection, 50 excluded due to lack of digitized medical records, 3 due to congenital heart defects and 179 due to the absence of echocardiograms. The resulting 148 enrolled patients generated 480 echocardiograms. One hundred two (68.9%) patients showed consistently normal echocardiograms (group 1), with a median of 2 (1–8) exams/individual, performed at a median interval of 2.2 (0.2–9.6) years. Forty-six (31.1%) patients had at least one abnormal echocardiogram (group 2), with a median of 4 (1–11) exams/individual, performed at a median interval of 1.4 (0.5–6.6) years (Fig. 1). The median follow-up duration was 14.8 (0.2–20) years in group 1 and 13.4 (3–19) years in group 2 (Table 1). Only 2 patients had echocardiograms from 1990 to 1999, generating 3 exams. From 2000 to 2009, 121 patients were examined and 290 echocardiograms were registered. Finally, from 2010 to 2015, 103 patients were examined and 187 echocardiograms were done.

Only 6 (1.2%) of 480 echocardiograms were accompanied by symptoms of heart failure (NYHA functional class > 1). Among the 148 patients, 15 (10.1%) received cardiovascular drugs, mainly due to LV dilation and/or systolic dysfunction detected by echocardiogram (13 patients), or systemic hypertension secondary to ART nephrotoxicity (2 patients). The most commonly used drugs were diuretics (9/15) followed by angiotensin-converting enzyme inhibitors (8/15), digoxin (6/15), carvedilol (5/15), amlodipine (2/15), losartan (1/15) and hydralazine (1/15).

All patients were considered normotensive by the time of the echocardiograms, even the 2 individuals under antihypertensive

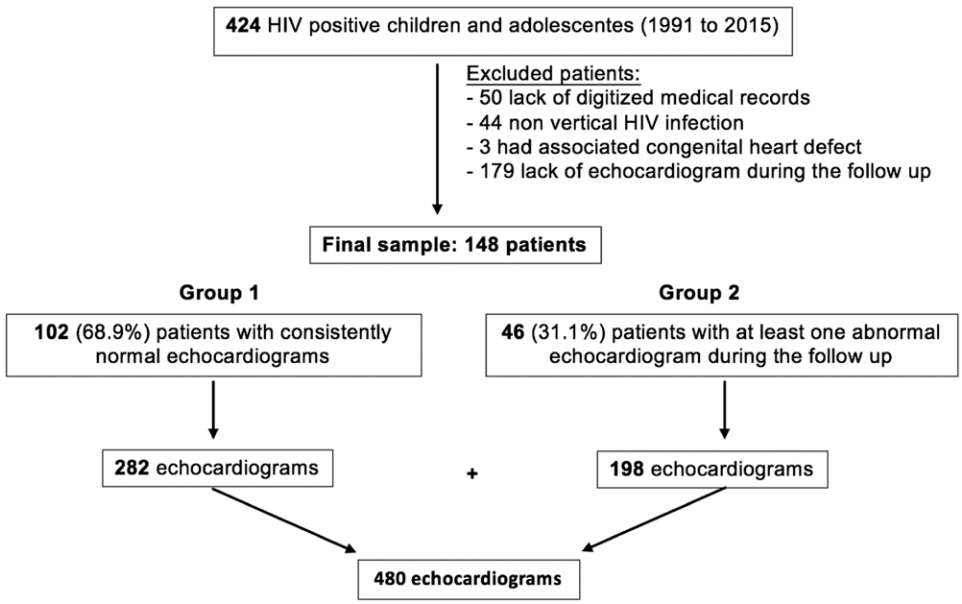

FIGURE 1. Study overview.

TABLE 1. Comparison Between Patients With Consistently Normal Echocardiograms (Group 1) and Patients With at Least One Abnormal Echocardiogram During Follow-up (Group 2)

Variables	Group 1 (n = 102)	Group 2 (n = 46)	*P**
Gender (male)	45/102 (44.1%)	23/46 (50%)	0.59
Age at initial follow-up (y)	1.3 (0.1–13.2)	2.9 (0.1–13.8)	0.067
Follow-up duration (y)	14.8 (0.1–20)	13.4 (3–19)	0.98
Age at ART introduction (y)	1.8 (0.1–18.3)	2.8 (0.1–17.2)	0.43
ART duration of therapy (y)	14.1 (0.2–18.9)	13.5 (1.5–18.5)	0.69
HAART use†	99/102 (97%)	45/46 (97.8%)	1.00
Age at HAART introduction (y)	4.9 (0.1–18.4)	6.6 (0.1–17.8)	0.17
HAART duration‡ (y)	10 (0.1–16.9)	8.5 (0.1–17.8)	0.8
CD4 nadir (cells/μL)	263 (4–1480)	202 (5–1746)	0.021
CD4 nadir (%)	17 (1–45)	15 (1–38)	0.55
CD4 nadir age (y)	12.8 (0.2–18.1)	13.8(2.1–18)	0.18

ART indicates antiretroviral therapy; HAART, highly active ART.
*$P < 0.05$ was considered statistically significant.
†HAART use: means that HAART was received at some point of the follow-up period.
‡HAART duration: total duration of HAART during the whole follow-up period.
§Categorical data: percentages; Fisher exact test was chosen to compare categorical data.
¶Continuous data: mean (SD) or median (range); Mann-Whitney *U* test to assess continuous data.

treatment. Dyslipidemia was detected in 133 (89.8%) and anemia in 62 (41.9%) patients.

Among the 480 echocardiograms, 27 (17.7%) were performed in the presence of opportunistic infections. In fact, 5 exams were accompanied by multiple infections. Herpesvirus infections were the most frequent (13/27), followed by pulmonary tuberculosis (6/27) [*Mycobacterium tuberculosis* (5/27) and *Mycobacterium gordonae* (1/27)], cytomegalovirus (7/27), atypical mycobacterial infection (2/27), cryptococcosis (2/27), *Pneumocytis jirovecii* pneumonia (1/27), esophageal candidiasis (1/27), bone tuberculosis (1/27) and diarrhea caused by *Cryptosporidium sp* (1/27).

Lymphocytic interstitial pneumonia was diagnosed in 5 patients during the study period and all of them had echocardiographic abnormalities; at the time of diagnosis, 3 of them had been receiving HAART for less than a year and one was still receiving monotherapy, reflecting limited access to effective therapy. Lymphoma was detected in 3 patients and 2 of them had echocardiographic abnormalities. A single patient died during the follow-up, due to lymphoma and septic shock.

Group 1 was similar to group 2, except for the nadir CD4 cell count, which was lower in group 2: 263 (4–1480) cells/μL vs. 202 (5–1746) cells/μL, $P = 0.021$ (Table 1).

RV dilation was diagnosed in 28 (18.9%) of 148 patients and in 61 (12.7%) of the 480 echocardiograms. RV dilation was transient in 15/28 (53.5%) patients. After adjusted analysis, RV dilation was associated with CDC category C, the use of non-nucleoside reverse transcriptase inhibitors, opportunistic infections and LIP. Increasing duration of ART and the use of protease inhibitor (PI) reduced the risk of RV dilation (Table 2).

The most frequent echocardiographic abnormality was LV dilation, detected in 32 (21.6%) of the 148 patients and in 82 (17.1%) of the 480 echocardiograms. LV dilation was transient in 14/32 (43.7%) patients and was associated with LIP, body mass index (BMI) Z-score < −2, NYHA > 1 and the use of cardiovascular drugs. Reduced risk of LV dilation was associated with HAART

TABLE 2. Crude and Adjusted Analysis of Parameters Associated With Echocardiographic Abnormalities

	RV Dilation				LV Dilation				Septal Hypertrophy			
	Crude Analysis		Adjusted Analysis		Crude Analysis		Adjusted Analysis		Crude Analysis		Adjusted Analysis	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CD4 (deciles of cells/μL)*	0.95	0.86–1.05			0.93	0.85–1.01	0.94	0.86–1.03	1.05	0.90–1.23		
CD4 (%)*	0.98	0.95–1.01			0.97	0.95–1.00	0.97†	0.95–0.99	1.02	0.98–1.07		
CDC category C	1.63	1.10–2.40	1.61†	1.08–2.40	1.03	0.77–1.37			1.29	0.73–2.28		
Viral load log*	0.98	0.86–1.13			1.06	0.94–1.20			1.50	1.14–1.98	1.28	0.99–1.67
Viral load log > 5	1.43	0.60–3.40			1.19	0.53–2.69			5.46	2.09–14.31	2.79	0.90–8.71
ART use	0.67	0.22–2.03			0.98	0.32–2.96			1.12	0.14–8.68		
ART duration (y)*	0.93	0.87–0.99	0.87‡	0.80–0.95	0.98	0.93–1.04			0.85	0.77–0.95	0.94	0.80–1.11
HAART use	0.90	0.48–1.68			0.33	0.20–0.55	0.38‡	0.22–0.64	0.53	0.22–1.29		
HAART duration (y)*	0.98	0.92–1.04			0.91	0.86–0.96	0.91‡	0.85–0.97	0.89	0.79–1.00	0.96	0.83–1.11
NRTI	0.74	0.24–2.23			1.54	0.45–5.29			1.23	0.16–9.48		
NNRTI	1.81	1.03–3.16	1.82†	1.03–3.20	1.37	0.83–2.27			1.09	0.44–2.72		
PI	0.57	0.33–0.99	0.54†	0.30–0.97	0.34	0.20–0.56	0.35‡	0.21–0.60	0.47	0.20–1.13	0.64	0.25–1.62
FI	1.00	(no outcome)			1.00	(no outcome)			1.00	(no outcome)		
INI	2.03	0.72–5.67			0.21	0.03–1.58			1.00	(no outcome)		
Anemia	1.59	0.86–2.95			1.52	0.87–2.64			2.79	1.14–6.82	2.03	0.78–5.23
Dyslipidemia	1.53	0.66–3.54			0.57	0.31–1.05	0.59	0.31–1.11	3.06	0.40–23.67		
SAH	1.00	(no outcome)			1.00	(no outcome)			1.00	(no outcome)		
Opportunistic infection	3.86	1.65–9.03	4.34‡	1.78–10.53	1.76	0.72–4.32			5.48	1.86–16.13	4.03†	1.22–13.34
LIP	11.32	3.10–41.37	15.56‡	3.66–66.14	5.10	1.44–18.06	11.74‡	2.64–52.26	25.06	6.65–94.37	14.07‡	3.04–65.19
BMI Z-score < –2	1.49	0.63–3.53			2.30	1.12–4.75	2.59†	1.22–5.50	1.67	0.47–5.88		
NYHA class > 1	1.74	0.36–8.40			5.10	1.44–18.06	4.39†	1.19–16.21	1.00	(no outcome)		
Cardiovascular drug use	2.79	0.96–8.12	2.69	0.90–8.00	5.33	2.05–13.88	5.27‡	1.95–14.22	4.74	1.26–17.82	4.04	0.99–16.53

	Posterior Wall Hypertrophy				Ejection Fraction < 55%				Pulmonary Hypertension			
	Crude Analysis		Adjusted Analysis		Crude Analysis		Adjusted Analysis		Crude Analysis		Adjusted Analysis	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
CD4 (deciles of cells/μL)*	1.08	0.87–1.35			0.80	0.67–0.94	0.82†	0.69–0.98	0.93	0.79–1.09		
CD4 (%)*	1.02	0.96–1.08			0.96	0.91–1.00	0.96	0.92–1.01	0.94	0.89–0.98	0.93‡	0.89–0.98
CDC category C	2.58	0.83–8.08			0.78	0.50–1.23			3.00	1.23–7.29	2.93†	1.19–7.18
Viral load log*	2.66	1.59–4.47	1.78†	1.05–3.02	0.94	0.76–1.16			0.99	0.79–1.24		
Viral load log > 5	9.42	2.74–32.39	3.76	0.81–17.52	1.00	(no outcome)			3.97	1.35–11.65	2.74	0.79–9.51
ART use	0.55	0.07–4.41			1.00	(no outcome)			0.24	0.07–0.90	0.32	0.08–1.29
ART duration (y)*	0.81	0.69–0.94	1.22	0.76–1.96	0.98	0.90–1.07			0.84	0.75–0.94	0.82‡	0.71–0.93
HAART use	0.40	0.12–1.29			0.09	0.04–0.22	0.10‡	0.04–0.25	0.83	0.29–2.35		
HAART duration (y)*	0.83	0.69–1.00	0.97	0.74–1.25	0.71	0.59–0.85	0.71‡	0.59–0.85	0.91	0.81–1.02		
NRTI	0.60	0.07–4.82			1.00	(no outcome)			0.45	0.10–2.05		
NNRTI	1.81	0.56–5.80			0.97	0.39–2.37			1.87	0.73–4.74		
PI	0.18	0.04–0.81	0.25	0.05–1.26	0.07	0.02–0.31	0.07‡	0.02–0.31	0.52	0.20–1.35		
FI	1.00	(no outcome)			1.00	(no outcome)			1.00	(no outcome)		
INI	1.00	(no outcome)			1.00	(no outcome)			1.00	(no outcome)		
Anemia	5.53	1.53–19.98	3.13	0.77–12.69	0.69	0.23–2.06			6.08	2.29–16.12	5.43‡	2.00–14.73
Dyslipidemia	1.07	0.12–9.25			1.85	0.42–8.19			3.06	0.40–23.67		
SAH	1.00	(no outcome)			1.00	(no outcome)			1.00	(no outcome)		
Opportunistic infection	9.65	2.71–34.41	5.82†	1.27–26.68	3.40	1.08–10.68	5.38‡	1.55–18.71	9.67	3.34–27.96	8.78‡	2.80–27.51
LIP	38.42	9.05–163.02	13.92‡	2.38–81.35	1.00	(no outcome)			32.57	8.45–125.50	31.60‡	6.24–159.87
BMI Z-score < - 2	1.00	(no outcome)			5.75	2.32–14.24	6.88‡	2.58–18.40	3.10	0.98–9.82	3.49†	1.05–11.64
NYHA class > 1	1.00	(no outcome)			13.55	3.56–51.50	9.42‡	2.30–38.54	2.79	0.34–23.22		
Cardiovascular drug use	2.56	0.31–21.07			6.15	1.85–20.42	6.77‡	1.88–24.45	3.27	0.70–15.38		

Adjusted models were controlled for gender, age and decade in which patients were examined; adjusted analysis was performed in all models that had a $P < 0.10$.

95% CI indicates 95% confidence interval; FI fusion inhibitors; INI, integrase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; NYHA: New York Heart Association; PI, protease inhibitors; and SAH, systemic arterial hypertension.

*Continuous variables: estimates correspond to 1 unit increase or category change in risk factor.

†$P < 0.05$.

‡$P < 0.01$.

and PI use, HAART duration, as well as increase in CD4 percentage (Table 2).

Septal hypertrophy was identified in 18 (12.2%) of the 148 patients and in 23 (4.8%) of the 480 echocardiograms. It was transient in 15/18 (83.3%) patients and was associated with opportunistic infections and LIP.

LV posterior wall hypertrophy was diagnosed in only 9 (6%) of the 148 patients and in 12 (2.5%) of the 480 exams. It was transient in all cases and associated with higher viral load, presence of opportunistic infections and LIP (Table 2).

LV systolic dysfunction was documented in 12 (8%) of the 148 patients and in 26 (5.4%) of the 480 echocardiograms. It was transient in 9/12 (75%) patients and associated with opportunistic infections, BMI Z-score < −2, NYHA > 1 and the use of cardiovascular drugs. Protective factors for LV systolic dysfunction included the use of HAART and PI, higher CD4 cell count and longer HAART duration (Table 2).

PH was detected in 13 (8.7%) of the 148 patients and in 19 (4%) of the 480 echocardiograms. PH was associated with CDC category C, anemia, opportunistic infections, LIP and BMI Z-score < −2. Protective factors for PH included the higher CD4 percentage and in ART duration (Table 2).

DISCUSSION

The present study stands out for the serial echocardiographic evaluation of a cohort of pediatric patients with perinatal HIV infection, enabling determination of the frequency and course of cardiac impairment throughout their development. Furthermore, it revealed significant associations between echocardiographic abnormalities and clinical, immunological and therapeutic parameters in this particular population.

Similarly to Patel et al,[28] an association between lower CD4 values at nadir and the occurrence of cardiac compromise was detected. In fact, this was the only parameter that differed significantly between those with consistently normal and ever abnormal echocardiograms.

RV impairment in perinatally HIV-infected patients has not been extensively investigated since most studies focused exclusively on LV abnormalities. Moreover, RV dilation or systolic dysfunction is frequently attributed to PH in this population. The frequency of RV dilatation (18.9%) among our patients was higher than the frequency of PH (8.7%). Consequently, RV enlargement could not be interpreted solely as a consequence of an increased afterload. In fact, Simon et al[29] proposed that RV compromise in HIV may represent an independent entity from PH and also from LV cardiomyopathy. In agreement with our results, those authors pointed out opportunistic infections and HAART toxicity as possible contributors to RV myocardial impairment. The use of non-nucleoside reverse transcriptase inhibitors, recently associated with LV dilation in HIV-infected patients,[30] was otherwise associated with RV dilation in our cohort. The absence of PI in the antiretroviral regimen, previously related only to the LV dilation in children with HIV,[30] was also associated with the presence of RV dilation in our patients. Similar to what was described for the LV in the AMP study,[17] more severe HIV infection (CDC clinical classification C) was associated with greater RV compromise.

In agreement with Patel et al,[28] the frequency of LV dilation (21.6%) in our study was much lower than that reported in the pre-HAART era studies. In accordance with the AMP study,[17] lower CD4 count was associated with LV dilation among our patients. The increased risk of LV dilation in the presence of LIP in our cohort may be explained by limited access to HAART, known to be implicated in both conditions.[31,32] Indeed, our data support that the use of HAART, as well as the longer HAART duration, can reduce the risk of LV dilation.

Like Idris et al,[33] we detected not only LV dilation but also septal and LV posterior wall hypertrophy in a small portion of our cohort. Those authors proposed that LV hypertrophy results from incomplete viral load suppression in pediatric patients. Consistent with the findings of Okeke *et al*[34] in an adult cohort, we identified elevated viral load as a risk factor for LV hypertrophy, highlighting potential direct HIV cardiotoxicity. The increased risk of septal and LV posterior wall hypertrophy in the presence of opportunistic infections reinforces the contribution of other cardiotropic agents to myocardial architecture damage in our perinatally HIV-infected patients.[34] The peculiar association between septal/LV posterior wall hypertrophy and LIP in our patients could be related to the frequent use of corticosteroids, especially in symptomatic patients.[35]

HAART duration was also shorter in our cases with systolic dysfunction, strengthening this therapeutic regimen as cardioprotective in perinatally HIV-infected patients.[36] PI usage, classically related with atherogenesis and a higher incidence of heart attack in adults with HIV,[37] was associated with smaller diameters and with better LV systolic function in our cohort. Similar results were described by Williams *et al*,[30] suggesting a protective role of PI in the pediatric population. Although dyslipidemia was frequent among our patients (89.8%), it was not associated with LV dysfunction, at least in infancy and adolescence.

BMI Z-score < −2 was associated with LV dilation and systolic dysfunction, in our cohort. This data can be interpreted in 2 different ways. First, LV myocardial impairment may be the result of micronutrient deficiency, malabsorption, diarrhea and consumptive syndrome, which also compromise children's development in HIV infection.[5] Second, the very existence of LV systolic dysfunction decreases delivery of nutrients and increases basal metabolic rate, harming those patients' growth.[38] Not surprisingly, LV dilation and dysfunction in the echocardiogram were both associated with heart failure symptoms (NYHA class > 1) and to the need of cardiovascular drugs.

PH prevalence in patients with perinatally HIV infection is controversial, ranging from 2.1% in a Brazilian cohort[39] to 41% in a study conducted in Thailand.[40] PH was diagnosed in 8.7% of our patients, which was associated with lymphocytic interstitial pneumonia, in accordance to the findings of Pongprot *et al*[40] We also documented association between PH and anemia, CDC clinical classification C and failure to thrive (BMI Z-score< −2), which characterizes the greater severity of HIV infection in those patients.[41] The association between PH and opportunistic infections is probably due to the predominance of respiratory infections in our cohort. The increase in ART duration and in CD4 percentage both reduced the risk of PH, favoring immunological recovery as relevant to PH management.[42,43]

One of the most relevant findings of our study was that echocardiographic abnormalities can be transient, raising the hypothesis that changes in the therapeutic regimen, improvement of immunological status, or even nutritional recovery may influence in the prevalence of cardiovascular impairment in children and adolescents with perinatal HIV infection. Moreover, the majority of patients had echocardiographic abnormalities detected before showing any heart failure symptoms. Our findings favor the inclusion of echocardiogram in the routine screening for perinatally HIV-infected children and adolescents, enabling early detection and therapeutic interventions.

Our study was limited by its retrospective character and the fact that it was conducted in a single academic center. In addition, information on prenatal care, such as exposure to ART during pregnancy, was not included. Many patients were not born at our

institution or were not in parental custody, which prevented reliable data acquisition. We have also excluded a great number of patients followed at the outpatient clinic due to absence of an echocardiogram in their medical records (n = 179). Sicker children may have also been more likely to have echocardiograms performed. It is important to emphasize that our analysis was made through the review of echocardiographic reports; since our institution does not routinely store echocardiographic images, revision by a blinded expert was not possible.

CONCLUSIONS

Echocardiograms identified subclinical cardiac abnormalities in perinatally HIV-infected patients, which were transient in a significant number of cases. Immunologic status and therapeutic strategies can influence cardiac outcomes in perinatally HIV-infected patients. Further prospective studies should be held to define which strategies adopted throughout childhood will reduce cardiovascular risk in adult life.

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