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Echocardiography and carotid initima-media thickness among asymptomatic HIV-infected adolescents in Thailand

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Introduction

Before the availability of highly active antiretroviral therapy (HAART), cardiovascular diseases (CVD) were commonly found in adult HIV-infected patients with advanced HIV disease.[1–3] However, the risk of CVD has remained despite the existence of HAART. Among HIV-infected children aged 18 months to 12 years with no prior cardiac problems in a tertiary teaching hospital in Nigeria, although 84% were receiving HAART, 33.7% were found to have dilated cardiomyopathy and 14.5% had pericardial effusion ≥ 5.0 mm.[4] The US National Institutes of Health (NIH) Multicenter Pediatric HIV/AIDS Cohort Study (PHACS) found that among children receiving long-term HAART, 10% had an extreme left ventricle (LV) dimension, increased aortic valve area or diameter, or a reduction of left ventricular ejection fraction (LVEF).[5] Children with HIV infection had increased carotid intima-media thickness (cIMT) compared to normal children.[6–8] Increased cIMT is a marker of CVD risk in the adult population.[9–10] These cardiovascular risks have not been studied in children and adolescents in Asia. Moreover, the long-term outcome of CVD in children and adolescents receiving HAART is unknown.

Some pro-inflammatory cytokines such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 have been found to be higher in HIV-infected children compared to normal children[11] and high-sensitivity C-reactive protein (hs-CRP) has been found to be associated with increased cIMT.[12] These findings suggest that chronic inflammation and vasculopathy were the likely causes of CVD in HIV infection and these cytokines may be

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K.L., K.C., and P.K. designed study, analysed data. K.L, K.C., S.Sr., and N.K. established the cohort including subject finding, invitation, and inform consent process. P.K. performed echocardiogram. All the authors performed study procedures and provide clinical care and contributed to manuscript writing.

Conflicts of interest

All authors declare no conflict of interest.

predictive of CVD. Recently, the N-terminal pro brain natriuretic peptide (NT-pro-BNP), a hormone released from the heart, has been widely used to assess the severity of left ventricular dysfunction, heart failure, and acute coronary syndromes.[13–15] However, NT-pro-BNP has not been studied in cardiovascular assessment in any HIV-infected patients.

Most of the cardiac abnormalities detected by studies using echocardiography in HIV-infected children were often asymptomatic.[16–17] Echocardiography has been the standard method to assess cardiovascular structure, but generally has been of limited accessibility in resource-limited settings. Therefore, CVD or abnormal cardiac conditions in asymptomatic patients have been largely unrecognized and underreported. Evaluating CVD by echocardiography and associated risks in HIV-infected children is, however, useful for early detection of cardiovascular abnormalities. In this study, we evaluated the cardiovascular conditions and cIMT by echocardiography in perinatally HIV-infected adolescents who had no apparent cardiovascular problems and were receiving HAART, and compared their results with those of age-matched healthy controls. We also evaluated risk factors and biomarkers associated with cardiovascular abnormalities.

Methods

A cross-sectional study was conducted at the Department of Pediatrics, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. The perinatally HIV-infected adolescents aged 12–20 were recruited from the pediatric HIV clinic and the healthy age-matched controls were recruited from HIV-uninfected siblings of the patients in the pediatric HIV clinic or from adolescents who came to the hospital for other minor illnesses or an annual medical checkup. The subjects in both groups had to be apparently healthy without any history or clinical sign or symptom of CVD and with a normal chest x-ray (CXR). The adolescents with perinatal HIV infection had to have been receiving HAART for at least 6 months. The exclusion criteria included presence or suspicion of CVD conditions, receipt of treatment for active opportunistic infection except for tuberculosis, taking of drugs that may affect cardiovascular function other than antiretroviral ones, and pregnancy.

Study procedures

The study procedures conducted after informed consent and assent included a physical examination of heart rate and blood pressure measurement, weight and height measurement, and a CXR. If any evidence of CVD was found in the physical examination or CXR, subjects were excluded from the study. If the CXR was normal, the subject would then have blood drawn for complete blood count, fasting lipid profiles, hs-CRP (hs-CRP, Roche Diagnostics GmbH, Mannheim, Germany), and NT-pro-BNP (Elecsys proBNP, Roche Diagnostics GmbH, Mannheim, Germany). For the HIV-infected subjects, CD4 and HIV-1 RNA were also included. The subjects then underwent an echocardiogram to assess cardiac anatomy and function. The cIMT measurement was performed right after the echocardiogram. The case record forms were filled in using data extracted from the medical records, which included demographic data, medical history including previous illnesses and hospitalizations, and HIV-related treatment.

Blood pressure and heart rate measurement—Blood pressure and heart rate were measured at the left arm by trained nurses after the subjects had been rest for 10 minutes in sitting position using automatic oscillometric recorder (Dinamap pro 100, Critikon, Tampa, FL) The standard small adult (limb circumference 17–25 cm) or adult cuff (limb circumference 23–33 cm) was used appropriately.

Echocardiography—The protocol-directed transthoracic echocardiography was performed using a Philips iE 33 model echocardiography machine and a transducer frequency of 5 or 8 MHz by one of three experienced pediatric cardiologists who were blind to the subjects' HIV status. All M mode measurements were performed twice and an average was taken to enhance intra-rater reliability. The presence of left ventricular systolic or diastolic dysfunction was determined according to the guidelines of the American Society of Echocardiography (ASE).[18] Systolic function was assessed by determining the ejection fraction and diastolic function by using spectral Doppler of mitral, pulmonary venous inflow velocity patterns and Doppler tissue imaging of the medial mitral annulus. Three consecutive cardiac cycles were assessed and Doppler measurements averaged. The modified Bernoulli equation was used to estimate the pressure gradient between the right ventricle and the right atrium. Systolic pulmonary artery pressure (PAP) was qualified by adding the calculated pressure gradient to the mean right atrial pressure, which can be 5, 10, 15, 20 and > 20 mmHg depending on the diameter of the inferior vena cava.

Impaired left ventricular systolic dysfunction was defined as LVEF < 55%: mildly decreased (LVEF 45–54%), moderately decreased (LVEF 35–44%) or severely decreased (LVEF < 35%). Diastolic dysfunction was classified as grades 1–4 according to ASE guidelines.[19] The left ventricular index of myocardial performance (LVIMP) was used to evaluate the integrative ventricular diastolic and systolic capabilities. LVIMP was calculated using the formula: LVIMP = [Mitral valve Closure to Opening Time (MCOT) – LV Ejection Time (LVET)]/LVET, and the normal cut-off was < 0.5. Pulmonary hypertension was determined by the right ventricular systolic pressure (RVSP). Pulmonary hypertension was defined as normal (15–30 mmHg), borderline (31–35 mmHg), mild (36–40 mmHg), moderate (41–50 mmHg), or severe (> 50 mmHg).[19] Pericardial effusion was diagnosed if the effusion was found to be ≥ 5.0 mm.[4]

cIMT measurement—The carotid ultra-sonogram was performed by only one cardiologist using a Philips iE 33 model echocardiography machine equipped with a L15-7io 15 mmHz linear probe. Images of the bilateral proximal, distal common carotid arteries (CCA) and internal carotid arteries (ICA) were separately obtained in longitudinal views. The means of two measurements of each side (right and left side), and of the far and near wall, were used for each site.[20]

Sample size—Thirty four percent of asymptomatic HIV-infected children in Nigeria were found to have dilated cardiomyopathy or depressed left ventricular shortening fraction (LVSF) (< 25%) detected by echocardiogram. Using this estimated prevalence, with a confidence level of 95% and a relative error around 27% of the prevalence, the calculated necessary sample size was 100. We arbitrarily enrolled 50 healthy HIV-uninfected controls to be the references in the absence of published normal references.

Statistical analysis—Continuous values were compared between perinatally HIV-infected adolescents and HIV-uninfected controls using Wilcoxon rank sum tests, as well as nominal variables using a chi-squared analysis or Fisher's exact test as appropriate. The relationships between the cIMT and variables of interest in normal controls were analyzed first by Spearman's rank correlation coefficients. The cIMT of each carotid vessel was compared between groups, and within the HIV-infected group between the adolescents with and without PI exposure. The relationships between the cIMT and variables of interest in HIV-infected adolescents and control were analyzed separately by Spearman's rank correlation coefficients. The backward stepwise regression model was used for multivariate analysis and the variables with correlation coefficients whose *P*-values were less than or equal to 0.10 or those with evidence of clinical significance were included.

All analyses were carried out using STATA 9.2 (StataCorp, Lakeway Drive, College Station, Texas, USA). The level of significance for all other analyses was set at 0.05.

Protection of human subjects—The study material as well as the informed consent materials used were reviewed and approved by the local Institutional Review Board before initiation of the study.

Results

Of the 150 adolescents enrolled, 100 were HIV-infected. Baseline demographic and clinical characteristics are shown in Table 1. The overall median (range) age was 15.8 (12.0–20.4) years, and the male to female ratio was 1.2:1. The known risk factors of CVD found at the baseline were smoking in 2 perinatally HIV-infected adolescents, obesity (body mass index [BMI] ≥ 30 kg/m^2) in 1 HIV-uninfected adolescent, dyslipidemia [21] in 40 perinatally HIV-infected and 13 HIV-uninfected adolescents, and high blood pressure in 2 perinatally HIV-infected and 1 HIV-uninfected adolescent. (Hypertension [22] is defined as an average systolic blood pressure and/or diastolic blood pressure that is greater than or equal to the 95th percentile for sex, age, and height on three or more occasions.) The HIV-infected and HIV-uninfected groups were not different in age and sex ratio. However, the HIV-infected group had lower weights (43.6 vs. 50.1 kg, $P < 0.001$), heights (155 vs. 163.2 cm, $P < 0.001$), and BMIs (18.1 vs. 19.6 kg/m^2, $P < 0.001$).

Among perinatally HIV-infected adolescents, 31% experienced Centers for Disease Control and Prevention (CDC) clinical stage C with the median (range) nadir CD4 count and percentage of 94 (2–3010) cells/mm^3 and 5.3 (0.1–30.2)%, respectively. At the time of the study, the median (range) CD4 count was 654 (54–1811) cells/mm^3, 76 (76.0%) had CD4 count > 500 cells/mm^3, 82 (82.0%) had HIV-1 RNA < 40 copies/mL, and 10 (10.0%) had HIV-1 RNA > 1,000 copies/mL. The median (range) duration of antiretroviral therapy (ART) was 129.3 (6–190) months. Of the 49 adolescents who were receiving PI, the median (range) duration of PI therapy was 64.9 (9.3–155.9) months, and 30 (30.0%) had been receiving PIs for more than 5 years. The total duration of PI exposure was 3639.7 person-months, 52 (100%) had exposure to lopinavir/ritonavir (LPV/r), 28 (53%) to boosted indinavir (IDV/r), 8 (15%) to boosted atazanavir (ATV/r), and 7 (13%) to boosted darunavir (DRV/r). The lipid profile and hs-CRP in perinatally HIV-infected adolescents and healthy

controls are shown in Table 2. In comparison with healthy controls, perinatally HIV-infected adolescents had higher triglycerides (117 vs. 62 mg/dl, $P < 0.001$) and lower high-density lipoprotein (HDL) (50 vs. 57 mg/dl, $P = 0.007$). The HIV-infected adolescents had a significantly higher frequency of hypertriglyceridemia (triglycerides ≥ 150 mg/dl) and lower HDL (HDL ≤ 35 mg/dl) than HIV-uninfected controls (37% vs. 2%, $P = 0.017$ for triglycerides, and 8% vs. 0%, $P < 0.001$ for HDL, respectively). Hypercholesterolemia (cholesterol ≥ 200 mg/dl) was found in a quarter of adolescents in both groups. Among perinatally HIV-infected adolescents, hypertriglyceridemia was found in 27 of 52 (51.9%) of those who had received PIs for more than 6 months, significantly higher than 21.3% (10/47) in those who had never received PIs (OR = 4.0, 95% CI 1.6 – 9.7, $P = 0.002$). Their current treatment consisted of LPV/r in 18, ATV/r in 4, DRV/r in 4, and EFV in 6 patients. No association between receiving PIs and hypercholesterolemia or hyper low-density lipoprotein (LDL) was found.

There was no difference in the median hs-CRP between the perinatally HIV-infected adolescents and HIV-uninfected controls (0.58 mg/dl vs. 0.57 mg/dl, $P = 0.49$); however, the number of adolescents with high hs-CRP level (>3.0 g/dl) was significantly greater in the HIV-infected group (22% vs. 8%, $P = 0.039$). The median (range) NT-pro-BNP level in perinatally HIV-infected adolescents was 29 (5–180) pg/ml, not different from the level of 33.5 (7–257) pg/ml in HIV-uninfected controls ($P = 0.3243$). There was no association between NT-pro-BNP and cIMT, LVIMP, PAP, CD4, viral load, lipid profile or PI treatment for more than 6 months.

The echocardiogram revealed overall normal LV systolic function with the median LVEF of 66% and normal LV diastolic function in both groups (Table 3). None of the adolescents in either group had LV dilatation or hypertrophy. The median LVIMPs were normal in both groups but perinatally HIV-infected adolescents had a higher index than healthy controls (0.3 vs. 0.24, $P = 0.004$). There were four (4%) perinatally HIV-infected adolescents, and no healthy control, found to have abnormal myocardial performance; three had LVIMP > 0.5 and one had LVEF < 55%. These adolescents had NT-pro-BNP of 6, 21, 25 and 85, which are not alarming values. All were female and had experienced CDC stage C3 for approximately 6.5 years before receiving HAART. The duration of HAART was 35–58 months and all had HIV-1 RNA < 40 copies/mL with the current CD4 of 547–940 cells/mm^3. There was no difference of PAP between the two groups and none of the subjects in either group had pericardial effusion. Three perinatally HIV-infected adolescents had intra-structural cardiac defects detected (1 small flap patent foramen ovale, 2 mitral valve prolapses with mild mitral regurgitation) and one healthy control had a small flap patent foramen ovale.

There was no difference of cIMT between perinatally HIV-infected adolescents and the HIV-uninfected controls. In univariate analysis of perinatally HIV-infected adolescents, systolic and diastolic blood pressure and PI therapy for more than 6 months were found to be correlated with overall cIMT. Receiving PI treatment for more than 6 months was associated with higher median cIMT of proximal (0.391 vs. 0.370 mm, $P = 0.009$) and distal CCA (0.394 vs. 0.376 mm, $P = 0.010$), as well as the overall cIMT (0.381 vs. 0.364 mm, $P = 0.009$). There was no association between cIMT and CD4 level, HIV-1 RNA, or CDC

clinical stage (data not shown). On the other hand, only weight and BMI were found to be correlated with overall cIMT in the HIV-uninfected controls.

In multivariate regression analysis, diastolic blood pressure and duration of receiving PIs were correlated with the overall cIMT in perinatally HIV-infected adolescents (Table 4).

Discussion

This is the first report of echocardiographic examinations and cIMT in perinatally HIV-infected adolescents in Asia. All of these adolescents were in stable health, had been receiving ART for a median of 10 years, and were asymptomatic for any cardiovascular condition. The majority had CD4 > 500 cells/mm^3 and complete viral suppression. The major finding was that these perinatally HIV-infected adolescents had comparable myocardial function and similar cIMT measurements to healthy adolescents. However, receiving PIs, mostly lopinavir, was found to be associated with hypertriglyceridemia and increased cIMT. We also found that hypercholesterolemia was common, found in about a quarter of adolescents both with and without HIV infection.

A prospective study among adolescents with perinatal HIV infection in Zimbabwe, 70% of whom had been receiving ART with a mean duration of 20 months, found that more than half had asymptomatic echocardiographic abnormalities.[23] Contrary to that report, we found a very low rate (4%) of abnormal echocardiography in the context of much longer times on ART. Our subjects had a longer duration of successful antiretroviral therapy than other reports. Our study suggests that the incidence of CVD was low in this group of adolescents who had been successfully managed on long-term ART. ART reduced the HIV-associated cardiovascular diseases in adult patients [24]; however, some antiretroviral drugs may induce adverse cardiovascular events or metabolic syndrome that could result in CVD in the long term.[25–27] PIs are the most important class of second-line regimens in adults and children in resource-limited settings. We found PI treatment to be associated with hypertriglyceridemia. All four adolescents with abnormal myocardial function were receiving PIs, 2 LPV/r, 1 ATV/r and 1 DRV/r. Unlike the reports from other studies, we did not find increased cholesterol with PI treatment.[28–29]

Increased cIMT has been found to be a marker of coronary artery disease risk in adults.[9–10] Chronic HIV infection also leads to vascular endothelial damage and an increase in vessel wall thickness from sustaining a low degree of inflammation.[30] A large case-control study in adults reported increased cIMT in chronic HIV-infected patients compared with age- and sex-matched controls.[31] Likewise, a few studies of HIV-infected children also reported increased cIMT and cardiovascular abnormalities compared to HIV-negative children.[5–7] One study reported an increase of cIMT in patients with a low CD4 nadir[32], whereas others found a higher CD4 count associated with a more rapid increase of cIMT.[33] A study from the UK demonstrated structural (by cIMT) and functional (by brachial artery flow-mediated dilatation) changes of the vasculature in HIV-infected children. These changes were found more in PI-treated children but were also observed in non-PI-treated and untreated children. This suggested the roles of both HIV infection and PI use in pathogenesis of early vascular disease.[8] However, there are also studies that did not find

an effect of PI treatment on cIMT.[34, 35] The contradictory results may stem from study design, type of PI drug, duration of PI exposure and follow-up, and the availability of HIV-uninfected controls.[27, 34–36] Darunavir and atazanavir have been found to cause fewer metabolic side effects than lopinavir, ritonavir, and indinavir.[37–38] Some studies have reported an association between increased cIMT and isolated systolic hypertension.[39–41]

Although we did not find a difference of cIMT in our perinatally HIV-infected adolescents and the HIV-uninfected controls, we found the increased cIMT correlated with diastolic blood pressure and duration of PI exposure. Elevated diastolic blood pressure often leads to elevated systolic blood pressure over time. The results from our study supported the need for longer-term follow-up on the risk of cardiovascular problems among those receiving PIs. We found no correlation between HIV disease severity markers, such as CD4, nadir CD4, viral load, or clinical stage, and cIMT, suggesting that the effect of HIV infection on cIMT may have been resolved by long-term successful ART.

The HIV-uninfected controls in our study had different factors demonstrating increased cIMT; only weight and BMI were independent factors. Several studies of HIV-uninfected populations described increased cIMT as being correlated with obesity and high fasting triglyceride levels.[42–43] Another study[44] also found that men had significantly greater cIMT compared to women. We found perinatally HIV-infected adolescents had lower weight, height, and BMI than HIV-uninfected controls, which was probably due to the delayed initiation of ART in many of them.[45] Moreover, many of these adolescents were exposed to stavudine, resulting in irreversible lipodystrophy, which also affects growth parameters. Because of long-term ART, including suboptimal regimens, in the early era of ART, drug resistance was common and finally required PI treatment. All these factors contributed to the increased cIMT more than the risk factors found in HIV-uninfected individuals.

Elevated hs-CRP has been shown in the general population to be consistently correlated with CVD, especially myocardial infarction.[46] Studies of HIV-infected adults found atherosclerosis progresses preferentially in the carotid bifurcation region and was associated with elevated hs-CRP levels.[32] Studies of healthy children also revealed the association of hs-CRP and cIMT, supporting a role for inflammation in CVD risk in HIV-infected children.[12] In contrast, we did not find a correlation between hs-CRP levels and cIMT, and the medians of these parameters were not different between the HIV-infected and HIV-uninfected groups in our study. However, we found that a higher proportion of adolescents with perinatal HIV infection had hs-CRP > 3.0 g/dl. These results suggest that hs-CRP is not useful to predict CVD risk in this long-term treated adolescent population. This is similar to what was found with NT-pro-BNP, i.e. no difference of NT-pro-BNP between the two groups. This biomarker was found to be of benefit for the patients at higher risk of LV dysfunction but not in apparently normal cardiovascular conditions.[47–49]

Limiting the causality, our study had some limitations including its cross-sectional design; therefore, further information is needed from long-term follow-up to corroborate the findings. However, this is the first study in the region to evaluate cIMT in HIV-infected adolescents. The strength of this study was the prospective design that comprised HIV-

uninfected healthy age-matched controls. With the control group, we were able to confidently conclude that the hypercholesterolemia and cIMT were not found more often than the norm.

Conclusion

In this cross-sectional study, perinatally HIV-infected adolescents had relatively normal myocardial function and similar cIMT compared to healthy HIV-uninfected adolescents. However, they were smaller and had a higher rate of hypertriglyceridemia. Receiving PIs was associated with hypertriglyceridemia and increased cIMT. In the era of HAART, HIV-infected children are surviving and have a long life expectancy. Prevention of cardiovascular disease in HIV-infected patients should be a standard of care. Our study supports the need to screen for dyslipidemia in HIV patients receiving PI therapy. Longer-term follow-up is needed to evaluate the CVD risk in this population.

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Table 1

Demographics and clinical characteristics of perinatally HIV-infected adolescents and healthy controls

Characteristics	Perinatally HIV-infected adolescents (n = 100)[a]	Healthy controls (n = 50)	p[b]
Age (year)	15.5 (12.0–20.4)	16.1 (12.1–19.4)	0.290
Sex; male (%)	56.0%	48.0%	0.360
Body weight (kg)	43.6 (27.7–75.8)	50.1 (33.6–116.9)	< 0.001
Height (cm)	155 (135–181)	163.2 (146.0.–176.5)	< 0.001
BMI (kg/m^2)	18.1 (13.8–26.1)	19.6 (14.0#x02013;38.2)	< 0.001
CDC staging (%)		N/A	
N	6(6.0)		
A	20(20.0)		
B	43(43.0)		
C	31(31.0)		
Nadir CD4 %	5.27% (0.1–30.1)	N/A	
Nadir CD4 count (cells/mm^3)	94 (2–3010)	N/A	
Current CD4%	26.5% (3.2–44.3)	N/A	
Current CD4 count (cells/mm^3)	654 (54–1811)	N/A	
Current HIV-1 RNA (copies/mL)	40 (40–429219)	N/A	
Current HIV-1 RNA < 40 copies/ml (%)	82 (82.0)	N/A	
Cumulative duration of ARV therapy (months)	129.3 (6.3–190.0)	N/A	
Age at start of ARV therapy (years)	4.9 (0.8–14.5)	N/A	
Experience of ARV drugs (%)		N/A	
- NRTI	100 (100.0)		
- Lamivudine (3TC)	100 (100.0)		
- Abacavir (ABC)	4 (4.0)		
- Stavudine (d4T)	55 (55.0)		
- Zidovudine (AZT)	96 (96.0)		
- PI	52 (52.0)		
- Lopinavir (LPV)	52 (52.0)		
- Atazanavir (ATV)	8 (8.0)		
- Darunavir (DRV)	7 (7.0)		
- Indinavir (IDV)	28 (28.0)		
- NNRTI	96 (96.0)		

Characteristics	Perinatally HIV-infected adolescents (n = 100)[a]	Healthy controls (n = 50)	p[b]
- Nevirapine (NVP)	41 (41.0)		
- Efavirenz (EFV)	70 (70.0)		
Current regimen at study entry (%)		N/A	
- NNRTI-based	52 (52.0)		
- PI-based	38 (38.0)		
- NNRTI + PI-based	10 (10.0)		

[a] The values are presented as medians (ranges) unless stated otherwise.

[b] *P*-values were calculated using the $\chi 2$ test, Fisher's exact test, or Mann-Whitney rank sum test as appropriate.

Abbreviations: BMI, body mass index; CDC, Centers for Disease Control and Prevention; ARV, antiretroviral; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; N/A, not applicable.

Table 2

Lipid profile and biomarkers in perinatally HIV-infected adolescents and healthy controls

	Perinatally HIV-infected adolescents (n = 100)[a]	Healthy controls (n = 50)	*p*[b]
Total cholesterol (mg/dl)	177 (106–379)	176 (109–285)	0.650
Triglycerides (mg/dl)	117 (35–441)	62 (27–230)	< 0.001
LDL (mg/dl)	100.4 (40.8–234.4)	104.6 (48.2–177.6)	0.640
HDL (mg/dl)	50 (18–99)	57 (37–129)	0.007
No. with hypercholesterolremia (total cholesterol > 200 mg/dl), n (%)	25 (25.0)	12 (24.0)	0.867
No. with hypertriglyceridemia (triglycerides > 150 mg/dl), n (%)	37 (37.0)	1 (2.0)	< 0.001
No. with hyperLDL (LDL > 130 mg/dl), n (%)	16 (16.0)	8 (16.0)	0.733
No. with hypoHDL (HDL < 35 mg/dl), n (%)	8 (8.0)	0 (0)	0.017
hs-CRP (g/dl)	0.58 (0.13–52.89)	0.57 (0.14–57.01)	0.490
No. with hs-CRP > 3.0 g/dl	22 (22.0)	4 (8.0)	0.039
NT-pro-BNP	29 (5–180)	33.5 (7–257)	0.324

[a] The values are presented in medians (ranges) unless stated otherwise.

[b] *P*-values were calculated using the $\chi 2$ test, Fisher's exact test, or Mann-Whitney rank sum test as appropriate.

Abbreviations: hs-CRP, C-reactive protein; NT-Pro BNP, N-terminal pro brain natriuretic peptide

The blood cholesterol levels refer to the National Cholesterol Education Program: report of the expert panel on blood cholesterol levels in children and adolescents.[50]

Table 3

The echocardiographic measurements of cardiac function and cIMT in perinatally HIV-infected adolescents and healthy controls

	Perinatally HIV-infected adolescents (n = 100)[a]	Healthy controls (n=50)	*P*[b]
LVEF (%)	66 (53.50–86)%	66 (55–78)%	0.825
Mean PAP (mmHg)	20 (13–33)	19 (12–29)	0.380
LVIMP	0.30 (0.05–0.53)	0.24 (0.06–0.47)	0.004
Proximal CCA IMT (mm)	0.380 (0.283–0.477)	0.375 (0.308–0.456)	0.398
Distal CCA IMT (mm)	0.388 (0.272–0.475)	0.380 (0.321–0.480)	0.541
ICA IMT(mm)	0.350 (0.260–0.513)	0.355 (0.302–0.452)	0.464
Overall cIMT (mm)	0.373 (0.284–0.451)	0.371 (0.324–0.446)	0.744

[a] The values were presented in medians (ranges) unless stated otherwise.

[b] *P*-values were calculated using χ^2 test, Fisher's exact test, or Mann-Whitney rank sum test as appropriate.

Abbreviations: cIMT, carotid intima-media thickness; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure; LVIMP, left ventricular index of myocardial performance; IMT, intima-media thickness; ICA, internal carotid artery.

Table 4

Multivariate regression analysis of factors correlated with overall cIMT in perinatally HIV-infected adolescents

	Perinatally HIV-infected adolescents (n = 100)			
	Univariate		Multivariate	
	Coefficient of overall cIMT	*P*-value	Coefficient of overall cIMT	*P*-value
Age at enrollment (years)	0.279	0.076	-	-
Male	0.107	0.869	-	-
BMI	0.194	0.102	0.170	0.138
Systolic blood pressure	0.083	0.004	-	-
Diastolic blood pressure	0.108	0.005	0.100	0.009
Cholesterol	0.008	0.289	-	-
Triglycerides	0.004	0.356	-	-
HDL	0.007	0.740	-	-
LDL	0.011	0.300	-	-
CRP	0.017	0.657	-	-
EF	−0.047	0.287	−0.066	0.131
LVIMP	1.448	0.661	-	-
PAP	−0.057	0.481		
Nadir CD4%	0.001	0.988	-	-
Nadir CD4 cell count	0.000	0.894	-	-
Current CD4 cell count	−0.002	0.133	-	-
Current viral load	0.000	0.282	-	-
Duration of PI treatment (months)	0.013	0.078	0.015	0.037