ARTICLE

Cardiac Status of Children Infected With Human Immunodeficiency Virus Who Are Receiving Long-term Combination Antiretroviral Therapy

Results From the Adolescent Master Protocol of the Multicenter Pediatric HIV/AIDS Cohort Study

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Importance: Prior to contemporary antiretroviral therapies (ARTs), children infected with human immunodeficiency virus (HIV) were more likely to have heart failure. This study suggests that highly active ART (HAART) does not appear to impair heart function.

Objective: To determine the cardiac effects of prolonged exposure to HAART on HIV-infected children.

Design: In the National Institutes of Health–funded Pediatric HIV/AIDS Cohort Study's Adolescent Master Protocol (AMP), we used linear regression models to compare echocardiographic measures.

Setting: A total of 14 US pediatric HIV clinics.

Participants: Perinatally HIV-infected children receiving HAART (n=325), HIV-exposed but uninfected children (n=189), and HIV-infected (mostly HAART-unexposed) historical pediatric controls from the National Institutes of Health–funded Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2-HIV) Study (n=70).

Exposure: Long-term HAART.

Main Outcomes and Measures: Echocardiographic measures of left ventricular (LV) function and structure.

Results: The 325 AMP HIV-infected children had lower viral loads, higher CD4 counts, and longer durations of ART than did the 70 HIV-infected children from the P^2C^2-HIV Study (all $P<.001$). The *z* scores for LV fractional shortening (a measure of cardiac function) were significantly lower among HIV-infected children from the P^2C^2-HIV Study than among the AMP HIV-infected group or the 189 AMP HIV-exposed but uninfected controls ($P<.05$). For HIV-infected children, a lower nadir CD4 percentage and a higher current viral load were associated with significantly lower cardiac function (LV contractility and LV fractional shortening *z* scores; all $P=.001$) and an increased LV end-systolic dimension *z* score (all $P<.03$). In an interaction analysis by HIV-infected cohort, the HIV-infected children from the P^2C^2-HIV Study with a longer ART exposure or a lower nadir CD4 percentage had lower mean LV fractional shortening *z* scores, whereas the mean *z* scores were relatively constant among AMP HIV-infected children ($P<.05$ for all interactions).

Conclusions and Relevance: Long-term HAART appears to be cardioprotective for HIV-infected children and adolescents.

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In the early 1990s, children infected with human immunodeficiency virus (HIV) usually did not receive antiretroviral therapy (ART), or they only received monotherapy with zidovudine. They often had abnormalities in left ventricular (LV) structure and function that were some of the strongest predictors of subsequent mortality.[1] These abnormalities occurred before the widespread use of highly active ART (HAART) and likely have multiple causes, such as HIV-infected myocardial cells, myocardial cells coinfected with cardiotropic viruses, and cardiotoxicity from pharmacologic agents and inflammatory cytokines.[2-4] Abnormalities included dilated cardiomyopathy with depressed LV contractility and LV dilation, heart failure, and aortic dilation.[1,3,5-11] Similar abnormalities associated with cardiomyopathic changes have

been observed in animal models and in individuals who became infected with HIV as adults.[12-21] In utero exposure to 2-drug nucleoside reverse transcriptase inhibitor therapy in HIV-exposed but uninfected (HEU) children was associated with mitochondrial dysfunction, which could have negative cardiac effects, although a study of in utero exposure to zidovudine monotherapy in HEU children found no deleterious cardiac effects.[22,23]

The effects of HIV and ART on the cardiovascular system of HIV-infected children are not completely understood. Children infected with HIV are routinely exposed to ART for many years, including in utero exposure to HAART while the cardiovascular system is still developing. The effects of ART and HIV on the cardiovascular system of children may be interactive; however, the direction and magnitude of such effects are unknown.

Children and adolescents offer a unique opportunity to study the physiologic mechanisms of HIV-associated cardiomyopathy because they are less likely than adults to be exposed long term to such confounding factors as hypertension, smoking, obesity, diabetes mellitus, and coronary atherosclerosis. The effect of HIV infection and ART on children suggests that subclinical abnormalities of cardiac structure and function may eventually result in symptomatic cardiomyopathy in adulthood as they become exposed to the other cardiovascular risk factors already mentioned.[1,3-11,24-26]

To date, the largest echocardiographic study of the effects of HIV infection and ART on the cardiac status of children was the Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2-HIV) Study, which was funded by the National Heart, Lung, and Blood Institute and conducted from 1990 to 1997.[3,27] Subclinical increased LV mass and decreased LV contractility were early predictors of mortality for HIV-infected children in the pre-HAART era.[1,7] The echocardiographic measurements were associated with postmortem diagnoses of cardiomegaly.[1,6,28] The P^2C^2-HIV Study also found that HIV-infected children older than 5 years of age were more likely to die of cardiac causes or wasting syndrome than of pulmonary disease.[28]

To identify the cardiovascular effect of ART (in addition to the cardiovascular effect of HIV infection) on children, we compared 3 groups of children who had echocardiograms: (1) perinatally HIV-infected children who were exposed to HAART; (2) HEU children; and (3) perinatally HIV-infected children from the P^2C^2-HIV Study who were relatively unexposed to ART. Data from the perinatally HIV-infected children and HEU children were obtained from the Adolescent Master Protocol (AMP) of the PHACS network.

METHODS

STUDY POPULATION

The AMP is a prospective cohort study, conducted at 14 US sites, designed to evaluate the effect of HIV infection and ART on the development of children and adolescents with perinatal HIV infection and to compare these children with a control group of HEU children. The study enrolled children 7 to 16 years of age between March 2007 and November 2009. The study protocol was approved by the institutional review board of each participating site and the Harvard School of Public Health (Boston, Massachusetts). Written informed consent was obtained from the parent or legal guardian, and written informed assent was obtained from older participants, per local institutional review board rules.

We also analyzed data from a cohort of HIV-infected participants, 7 years of age or older, from the P^2C^2-HIV Study, born before April 1, 1985, in a period when ART was much less intensive. The P^2C^2-HIV Study was approved by local institutional review boards. The detailed methods for the P^2C^2-HIV Study are published elsewhere.[27] The P^2C^2-HIV Study data set was obtained by the PHACS Data and Operations Center through a data use agreement approved by the National Institutes of Health. Data elements were similar to those in PHACS.

Our analysis included 3 study groups: (1) perinatally HIV-infected children from the AMP who were exposed to HAART (n=325); (2) HEU children from the AMP who typically were exposed to prenatal combination ART and short-term neonatal ART prophylaxis (n=189); and (3) perinatally HIV-infected children from the P^2C^2-HIV Study who were relatively unexposed to ART (n=70). Children were excluded from analysis if they had congenital cardiac abnormalities, such as a large atrial septal defect or a ventricular septal defect with pulmonary stenosis.

At each semiannual AMP study visit, information about participants and their families was gathered through clinical interviews and chart reviews. Current health status was ascertained through physical and laboratory evaluations. The ART regimens with start and stop dates were abstracted. Highly active ART was defined as any regimen that included 3 or more ART drugs from 2 or more ART drug classes. The Centers for Disease Control and Prevention (CDC) clinical disease classification was determined at study entry and at each study visit.[29]

ECHOCARDIOGRAPHIC ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION

The PHACS-trained site staff obtained a protocol-based single M-mode echocardiogram (recording the short axis of the LV from the parasternal short-axis view and the LV transverse view), with concurrent blood pressure and heart rate measurements. To improve reliability, all echocardiograms were centrally remeasured at the echocardiographic core laboratory at Boston Children's Hospital in Massachusetts.

Children in the P^2C^2-HIV Study had serial echocardiograms, clinical data collected from chart review, and laboratory evaluations collected in a manner similar to that in the AMP study. For this analysis, to make the age groups as similar as possible, we used the most recent echocardiogram (at least 6 months prior to death) and associated clinical data from the P^2C^2-HIV Study children who were 7 years of age or older at time of echocardiography. All echocardiograms for the P^2C^2-HIV Study children were obtained with criteria consistent with those of the AMP and were centrally remeasured at the same site by the same investigator as for the AMP study, at Boston Children's Hospital.

STATISTICAL METHODS

We compared demographic and anthropomorphic covariates among the 3 groups using χ^2 tests for categorical variables and Kruskal-Wallis tests for continuous measures. Measures of HIV disease severity and ART characteristics (latest available measures before or at the time of echocardiography) were compared between the HIV-infected children in the AMP and the HIV-infected children in the P^2C^2-HIV Study using Wilcoxon

Table 1. Characteristics and Echocardiographic Measurements of Participants in the P²C²-HIV Study and Participants in the PHACS AMP, by HIV Infection Status and Cohort

Characteristic	AMP-HEU Cohort (n = 189)	AMP-HIV Cohort (n = 325)	P²C²-HIV Cohort (n = 70)	*P* Value[a]
Age at assessment, mean (SD), y	11.0 (2.5)	13.0 (2.7)	9.7 (2.1)	<.001
Age group, No. (%)				
7-9 y	79 (42)	68 (21)	46 (66)	
10-12 y	63 (33)	66 (20)	18 (26)	
13-14 y	25 (13)	91 (28)	5 (7)	
≥15 y	22 (12)	100 (31)	1 (1)	
Sex, No. (%)				
Male	93 (49)	153 (47)	31 (44)	.77
Female	96 (51)	172 (53)	39 (56)	
Race/ethnicity, No. (%)				
Non-Hispanic white	11 (6)	22 (7)	7 (10)	<.001
Non-Hispanic black	103 (54)	215 (66)	27 (39)	
Hispanic	68 (36)	76 (23)	35 (50)	
Other/unknown	7 (4)	12 (4)	1 (1)	
z Scores for growth measures, mean (SD)				
Height	0.23 (1.11)	−0.43 (1.26)	−1.49 (1.58)	<.001
Height <3rd percentile	4 (2)	35 (11)	27 (39)	<.001
Weight	0.70 (1.36)	0.16 (1.32)	−0.89 (1.30)	<.001
Body mass index	0.70 (1.31)	0.39 (1.20)	−0.31 (1.32)	<.001
Body surface area	0.52 (1.67)	0.02 (1.29)	−0.37 (0.26)	<.001
z Scores for blood pressure, mean (SD)				
Systolic	−0.35 (1.00)	−0.34 (1.03)	0.23 (1.04)	<.001
Diastolic	0.34 (0.83)	0.33 (0.89)	0.09 (0.85)	.048

Abbreviations: AMP, Adolescent Master Protocol; HEU, human immunodeficiency virus–exposed but uninfected; HIV, human immunodeficiency virus; P²C²-HIV, Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection; PHACS, Pediatric HIV/AIDS Cohort Study.

[a] Determined by use of the χ^2 test for sex, race, ethnicity, and abnormal growth status and by use of the Kruskal-Wallis test for all other measures.

rank sum tests or χ^2 tests. We also compared the characteristics of children with echocardiograms with those of children without echocardiograms, to assess the representativeness of our study population.

To minimize the burden on participating children, their families, and site staff while maximizing efficiency, the study was designed to obtain echocardiograms from 500 children to provide 80% power for detecting differences in mean *z* scores of 0.26 or greater. Echocardiography was therefore discontinued in December 2010 when the target was achieved. Echocardiographic *z* scores were calculated using normative data from an established reference cohort of healthy children from Boston Children's Hospital not known to be infected with HIV or exposed to HAART, with adjustment for age and body-surface area, as appropriate.[30] The distributions of *z* scores were compared among the 3 groups (HIV-infected children from the AMP, HEU children from the AMP, and HIV-infected children from the P²C²-HIV Study) using analysis of variance ($df = 2$) from general linear regression models, both unadjusted and adjusted for age, sex, race, ethnicity, and other potential confounders, such as body mass index *z* score.[31] Within each group, overall 1-sample *t* tests were performed to determine whether echocardiographic *z* scores differed from those of the normal pediatric reference population.

General linear regression models were also fit to data from both groups of HIV-infected children to evaluate the association between characteristics of ART regimens (duration of ART and type of current ART regimen) and measures of HIV disease severity ($CD4^+$ T lymphocyte percentage [CD4 percentage]), HIV-1 viral load (VL), and CDC classification (N, not symptomatic; A, mildly symptomatic; B, moderately symptomatic; and C, severely symptomatic). Each measure of HIV disease severity and each characteristic of ART were evaluated for association with echocardiographic *z* scores, with adjustment for age, sex, race/ethnicity, and body mass index *z* score. Potential differences in the association between HIV disease severity measures and echocardiographic measures by cohort, representing pre-HAART era vs HAART era, were investigated via inclusion of interaction terms. Analyses were conducted using SAS version 9.2 (SAS Institute Inc) and were based on data submitted as of January 2012.

RESULTS

PARTICIPANT CHARACTERISTICS

Of the 678 children in the PHACS AMP study, 451 were HIV-infected children, and 227 were HEU children. Of these 678 children, 514 (76%) (325 of 451 HIV-infected children [72%] and 189 of 227 HEU children [83%]) had echocardiograms available for analysis, slightly exceeding the target of 500 children. The AMP children with echocardiograms were demographically similar to those without echocardiograms. Seventy HIV-infected children with echocardiograms obtained at 7 years of age or older were included from the P²C²-HIV Study (**Table 1**).

The children in the P²C²-HIV Study were younger than the HIV-infected children and HEU children in the AMP at the time of echocardiography (mean age, 9.7 years vs 13.0 years vs 11.0 years, respectively; $P < .001$). In the P²C²-HIV Study group, there was a significantly higher proportion of Hispanics and a lower proportion of blacks than in either of the AMP groups ($P < .001$). The HIV-infected children in both the AMP and the P²C²-HIV Study were significantly shorter and lighter than the AMP HEU children.

The AMP HIV-infected children had significantly less advanced HIV disease, in terms of VL, CD4 counts, and CD4 percentage, at the time of echocardiography than did the HIV-infected children in the P2C2-HIV Study (**Table 2**). The AMP HIV-infected children were more likely to have had a prior AIDS-defining condition (CDC classification C) than were the HIV-infected children in the P2C2-HIV Study ($P < .001$). At the time of echocardiography, 89% of AMP HIV-infected children and 17% of HIV-infected children in the P2C2-HIV Study were receiving HAART ($P < .001$), and 80% of AMP HIV-infected children had received HAART for more than 5 years, whereas none of the HIV-infected children in the P2C2-HIV Study had received HAART for more than 5 years. The AMP HIV-infected children were also significantly more likely to have received a protease inhibitor than were the HIV-infected children in the P2C2-HIV Study.

ECHOCARDIOGRAPHIC FINDINGS BY STUDY COHORT

Regarding LV function, the HIV-infected children in the P2C2-HIV Study had the lowest adjusted mean LV contractility *z* score (−1.56; **Table 3**). Both HIV-infected cohorts had lower mean LV fractional shortening *z* scores than that of the AMP HEU cohort, with the HIV-infected children in the P2C2-HIV Study having the lowest mean *z* score (−1.94). For LV mass, LV end-diastolic dimension, and LV end-systolic dimension mean *z* scores, the 3 cohorts had significantly different values, with the AMP-HEU cohort having the lowest and the P2C2-HIV cohort having the highest. The AMP-HEU and AMP-HIV cohorts had lower end-diastolic septal wall thickness and LV end-systolic wall stress *z* scores than did the P2C2-HIV cohort. Differences in mean *z* scores also had clinical significance: 31 of the 70 HIV-infected children (44%) in the P2C2-HIV Study met the definition for cardiomyopathy (either a *z* score of less than −2 for LV fractional shortening or greater than 2 for LV dimension), whereas 12 of the 325 HIV-infected children in the AMP and 3 of the 189 of the HEU children in the AMP met the definition for cardiomyopathy ($P < .001$).

ASSOCIATION OF HIV DISEASE SEVERITY MEASURES WITH ECHOCARDIOGRAPHIC PARAMETERS IN HIV-INFECTED CHILDREN (AMP-HIV AND P2C2-HIV COHORTS COMBINED)

Children with a nadir CD4 percentage of less than 15% and those with a VL of greater than 5000 copies had significantly lower LV contractility, LV fractional shortening, and higher LV end-systolic dimension and LV end-systolic wall stress *z* scores than did those with less severe disease (**Table 4**). In addition, children with current VLs greater than 5000 copies had significantly higher end-diastolic septal thickness. Children with a prior AIDS-defining condition (CDC classification C) had shifts in mean *z* scores similar to those already described (Table 4). In multivariable models including all 3 HIV disease measures from Table 4, a current VL of greater than 5000 copies/mL and a nadir CD4 percentage of less than 15% remained significant independent predictors for these echocardiographic measures, whereas CDC classification C was no longer associated with these echocardiographic parameters.

Table 2. HIV Disease Severity and Antiretroviral Characteristics for HIV-Infected Participants

Characteristic at Time of Echocardiogram	No. (%) of Participants: AMP-HIV Cohort (n = 325)	No. (%) of Participants: P2C2-HIV Cohort (n = 70)	*P* Value[a]
Viral load, copies/mL			
0-400	224 (69)	5 (8)	<.001
401-5000	56 (17)	10 (17)	
5001-50 000	35 (11)	30 (50)	
>50 001	11 (3)	15 (25)	
Missing values	0	10	
CD4 absolute count, median (IQR), cells/mm3	693 (512-924)	178 (11-564)	<.001
CD4 absolute count, cells/mm3			
0-250	20 (6)	38 (54)	<.001
251-500	59 (18)	11 (16)	
501-750	100 (31)	12 (17)	
>750	146 (45)	9 (13)	
Nadir CD4 percentage			
<15	100 (31)	43 (61)	<.001
15-25	131 (40)	15 (21)	
>25	94 (29)	12 (17)	
CDC classification C	82 (25)	48 (69)	<.001
ART regimen at assessment			
HAART with PI	227 (70)	10 (14)	<.001
HAART without PI	62 (19)	2 (3)	
ART	19 (6)	38 (54)	
No ART	17 (5)	20 (29)	
Receiving PIs	228 (70)	10 (14)	<.001
Receiving NRTIs	307 (94)	50 (71)	<.001
Receiving NNRTIs	90 (28)	2 (3)	<.001
Duration of treatment, median (IQR), y			
Any ART regimen	11.2 (9.0-13.1)	4.5 (2.6-6.2)	<.001
HAART regimen	9.0 (6.3-10.6)	0 (0-0)	<.001
PI-based regimen	8.3 (4.2-10.4)	0 (0-0)	<.001
Receiving HAART for ≥5 y	259 (80)	0 (0)	<.001

Abbreviations: AMP, Adolescent Master Protocol, from the Pediatric HIV/AIDS Cohort Study; ART, antiretroviral therapy; HEU, human immunodeficiency virus–exposed but uninfected; HAART, highly active ART (defined as at least 3 drugs from at least 2 drug classes: nucleoside reverse transcriptase inhibitors [NRTIs], nonnucleoside reverse transcriptase inhibitor [NNRTIs], and protease inhibitors [PIs]); HIV, human immunodeficiency virus; IQR, interquartile range (25th percentile to 75th percentile); P2C2-HIV, Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection.

[a] Determined by use of the χ^2 test for categorical measures and by use of the Wilcoxon rank sum test for continuous measures.

RELATIONSHIPS OF HIV DISEASE MEASURES WITH ECHOCARDIOGRAPHIC PARAMETERS: DIFFERENCES BY COHORT

Relationships between certain HIV disease severity measures and some echocardiographic parameters differed between the 2 HIV-infected cohorts. In the P2C2-HIV cohort, those with a longer duration of ART had lower mean LV fractional shortening *z* scores. However, in the AMP-HIV cohort, the mean *z* scores for LV fractional shortening were constant, regardless of duration of ART (inter-

Table 3. Adjusted Echocardiographic *z* Score Mean Values From Linear Regression Models, by Cohort

LV Echocardiographic Measure	AMP-HEU Cohort (n = 189) No.	AMP-HEU Cohort (n = 189) *z* Score Mean (SE)	AMP-HEU Cohort (n = 189) *z* Score Adjusted Mean (SE)[a]	AMP-HIV Cohort (n = 325) No.	AMP-HIV Cohort (n = 325) *z* Score Mean (SE)	AMP-HIV Cohort (n = 325) *z* Score Adjusted Mean (SE)[a]	P^2C^2-HIV Cohort (n = 70) No.	P^2C^2-HIV Cohort (n = 70) *z* Score Mean (SE)	P^2C^2-HIV Cohort (n = 70) *z* Score Adjusted Mean (SE)[a]	Significant Pairwise Differences[b]
Contractility	162	0.26 (0.08)	0.26 (0.09)	255	0.19 (0.06)	0.21 (0.08)	65	−1.53 (0.26)	−1.56 (0.16)	P^2C^2-HIV vs AMP-HIV, P^2C^2-HIV vs AMP-HEU
Fractional shortening	189	0.35 (0.07)	0.35 (0.08)	325	0.09 (0.05)	0.10 (0.07)	67	−1.95 (0.25)	−1.94 (0.15)	All pairwise
Mass	186	−0.60 (0.08)	−0.60 (0.08)	322	−0.28 (0.06)	−0.22 (0.06)	67	0.49 (0.16)	0.20 (0.13)	All pairwise
ED dimension	186	−0.50 (0.07)	−0.46 (0.08)	322	−0.16 (0.06)	−0.13 (0.06)	67	0.60 (0.22)	0.39 (0.14)	All pairwise
ES dimension	186	−0.51 (0.06)	−0.47 (0.08)	322	−0.12 (0.05)	−0.11 (0.06)	67	1.45 (0.27)	1.30 (0.14)	All pairwise
ED wall thickness	186	−0.24 (0.07)	−0.25 (0.07)	322	−0.11 (0.05)	−0.09 (0.05)	70	0.03 (0.12)	−0.04 (0.12)	None
ED septal thickness	186	−0.55 (0.06)	−0.56 (0.07)	322	−0.43 (0.05)	−0.41 (0.05)	64	0.17 (0.16)	0.09 (0.12)	P^2C^2-HIV vs AMP-HIV, P^2C^2-HIV vs AMP-HEU
ES wall stress	165	−1.16 (0.08)	−1.22 (0.09)	265	−1.13 (0.07)	−1.04 (0.07)	65	0.62 (1.65)	0.41 (0.15)	P^2C^2-HIV vs AMP-HIV, P^2C^2-HIV vs AMP-HEU

Abbreviations: AMP, Adolescent Master Protocol; ED, end-diastolic; ES, end-systolic; HEU, human immunodeficiency virus–exposed but uninfected; HIV, human immunodeficiency virus; LV, left ventricular; P^2C^2-HIV, Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection.

[a] Adjusted least squares mean values calculated from general linear regression models, adjusted for age, sex, race/ethnicity, and body mass index *z* score.

[b] Pairwise differences significant at $P < .05$.

Table 4. Adjusted Effects of HIV Disease Severity Measures on Echocardiographic *z* Scores for HIV-Infected Participants in the PHACS AMP and in the P^2C^2-HIV Study

LV Echocardiographic Measure	HIV Disease Severity Measures[a]: Nadir CD4 Percentage <15% Participants, No.	Difference in Estimated Mean (SE) *z* Score	*P* Value	Current VL >5000 Copies/mL Participants, No.	Difference in Estimated Mean (SE) *z* Score	*P* Value	CDC Classification C Participants, No.	Difference in Estimated Mean (SE) *z* Score	*P* Value
Contractility	320	−0.58 (0.17)	.001	312	−0.54 (0.16)	.001	320	−0.40 (0.17)	.02
Fractional shortening	392	−0.52 (0.15)	.001	384	−0.51 (0.15)	.001	392	−0.44 (0.15)	.003
Mass	389	0.10 (0.11)	.40	381	0.09 (0.12)	.48	389	−0.013 (0.11)	.91
ED dimension	389	0.08 (0.13)	.52	381	0.06 (0.13)	.65	389	0.02 (0.13)	.88
ES dimension	389	0.33 (0.14)	.02	381	0.30 (0.12)	.01	389	0.26 (0.14)	.07
ED wall thickness	392	0.12 (0.10)	.21	382	−0.07 (0.11)	.55	392	−0.06 (0.10)	.52
ED septal thickness	386	0.05 (0.10)	.66	376	0.25 (0.12)	.03	386	0.09 (0.10)	.39
ES wall stress	330	0.51 (0.15)	.001	322	0.47 (0.16)	.004	330	0.28 (0.15)	.06

Abbreviations: AMP, Adolescent Master Protocol; CDC, Centers for Disease Control and Prevention; ED, end-diastolic; ES, end-systolic; HIV, human immunodeficiency virus; LV, left ventricular; P^2C^2-HIV, Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection; PHACS, Pediatric HIV/AIDS Cohort Study; VL, HIV-1 RNA viral load.

[a] Estimates reflect change in *z* score for those with vs those without characteristic, adjusted for age, sex, race/ethnicity, and body mass index *z* score.

action, $P = .04$). In addition, the HIV-infected children in the P^2C^2-HIV Study with lower nadir CD4 percentages had worse cardiac function, on average, with lower mean *z* scores for LV fractional shortening and higher mean *z* scores for LV end-systolic dimension. However, for the HIV-infected children in the AMP, these *z* scores (**Figure**) appeared relatively constant over levels of nadir CD4 percentage (interaction, $P = .001$ and 0.001, respectively). Thus, the overall shifts in mean *z* scores associated with a nadir CD4 percentage of less than 15% shown in Table 4 are primarily attributable to associations within the P^2C^2-HIV cohort, for which a much higher percentage of children fell into this low immunological category. For other measures of HIV disease severity, such as CDC classification C and current VL, there was no evidence of interaction for any echocardiographic parameter. Thus, the overall measures of association with HIV disease severity shown in Table 4 apply to both HIV-infected cohorts.

DISCUSSION

We compared echocardiographic measures of LV structure and function between a cohort of HIV-infected children from an earlier treatment era who were relatively unexposed to ART (from the P^2C^2-HIV Study) and a con-

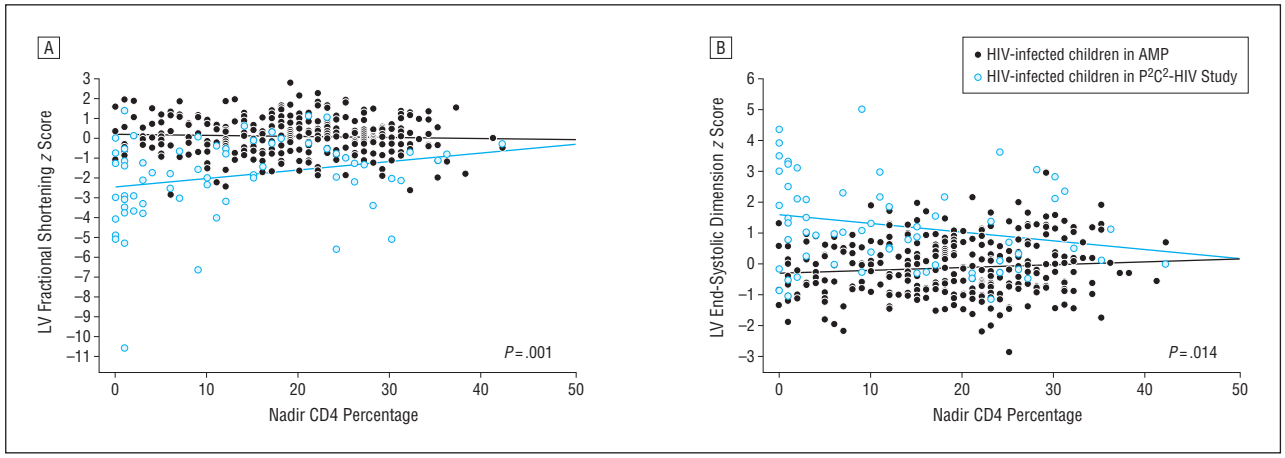

Figure. Association between certain echocardiographic parameters and nadir CD4 percentage. For children infected with human immunodeficiency virus (HIV), the level of exposure to antiretroviral therapy (ART) is an effect modifier on the association between the nadir CD4 percentage and the left ventricular (LV) fractional shortening *z* score ($P = .001$ for interaction) (A) and between the nadir CD4 percentage and the LV end-systolic dimension *z* score ($P = .014$ for interaction) (B). Perinatally HIV-infected children in the Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection (P^2C^2-HIV) Study were relatively unexposed to ART (1990-1997). Perinatally HIV-infected children in the Adolescent Master Protocol (AMP) were exposed to highly active ART. The solid lines represent separate regression lines for each cohort.

temporary cohort of HIV-infected children who were more exposed to ART (usually HAART; from the AMP). We also compared both of these cohorts with a contemporary cohort of HEU children and determined the associations of HIV disease severity with echocardiographic characteristics in the HIV-infected cohorts.

In the P^2C^2-HIV cohort, increased LV mass, dimension, wall thickness, and wall stress and decreased LV fractional shortening and contractility all predicted mortality.[1,7] After about 5 to 6 years of age, these children were more likely to die of chronic cardiac disease than pulmonary disease.[28] A subset of this cohort developed clinical heart disease.[4] These same echocardiographic parameters in the AMP-HIV cohort were closer to normal, and none of the children had symptomatic heart disease. This finding suggests an overall cardioprotective effect of long-term HAART. Whether this effect is the result of better immunological health, more normal somatic growth, direct killing of intramyocardial HIV, or other mechanisms is unclear.

The HIV-infected children in the P^2C^2 HIV Study who had a longer duration of ART tended to have lower LV fractional shortening. In this group, lower LV fractional shortening was associated with a lower nadir CD4 percentage. Increased LV end-systolic dimension *z* score, which is associated with myocardial contractility, was also associated with a lower nadir CD4 percentage. In contrast, LV fractional shortening *z* scores appeared relatively constant over all durations of ART and over all nadir CD4 percentages for the HIV-infected children in the AMP. We believe these differences suggest that some children in the P^2C^2-HIV cohort with evidence of substantial immunosuppression had already experienced substantial cardiac damage before they received effective ART regimens, if they received any ART at all. This conclusion is consistent with previous reports from the P^2C^2-HIV Study showing that many of the deleterious cardiac changes occurred in the first few years of life in children with marked immunosuppression without effective ART or multidrug therapy.[1,3,6]

The longitudinal National Heart, Lung, and Blood Institute Cardiac Highly Active Antiretroviral Therapy II (CHAART-II) Study compared echocardiographic measurements between a HAART-exposed, HIV-infected cohort (3-16 years of age), which was contemporary to the AMP cohort, and the much less ART-exposed P^2C^2-HIV cohort.[32] During the early years of follow-up, the CHAART-II HAART-exposed children had consistently higher LV fractional shortening and contractility, lower LV wall stress, and more normal LV mass and LV wall thickness than the children in the P^2C^2-HIV cohort.[32] At longer follow-up, the better LV function in terms of both fractional shortening and contractility was even more marked when compared with the P^2C^2-HIV cohort.[32] However, some of the structural differences between the cohorts, such as for LV mass or dimension, became attenuated with longer follow-up.[31]

Consistent with our findings, the results from the CHAART-II Study suggest that HAART-exposed, HIV-infected children maintain normal cardiac function for at least the first 10 years of follow-up, whereas HIV-infected children from the pre-HAART era had progressive deterioration in function.[32] However, differences in cardiac structure between the 2 groups appeared to lessen over time. Another group of children who were exposed to cardiotoxins are survivors of childhood cancer who were treated with anthracyclines.[33] These survivors have shown an initial maintenance of or improvement in cardiac health that was followed by a deterioration in cardiac status more than 10 years after exposure.[34] Therefore, HIV-infected children and adolescents currently receiving HAART may benefit from a follow-up echocardiogram to determine the trajectory of their cardiac status, although the cost-effectiveness and optimal timing of a follow-up echocardiogram are unknown.

This study was a cross-sectional analysis, so no causal inferences can be made. Also, analyzing only 1 echocardiogram per participant does not allow us to know whether their cardiac status was static, improving, or deteriorating. We also did not examine the effects of indi-

vidual ART or specific combinations of these drugs on cardiac structure or function. Finally, the Boston Children's Hospital reference cohort used to calculate the *z* scores was very different in terms of racial distribution and socioeconomic status from both of the HIV-infected cohorts.

Children with more severe HIV disease appear to experience more serious adverse effects on cardiac structure and function. Our results indicate that the current use of combination ART, usually HAART, appears to be cardioprotective in HIV-infected children and adolescents. This finding is even more relevant in the developing world where the prevalence of HIV disease in children is much higher. The long-term cardiac health of the HIV-infected children in the AMP in the HAART era is unknown.[35] A recent report[35] of HIV-infected adolescents and young adults receiving long-term HAART found that, while traditional echocardiographic measures of cardiac function were normal, measures of cardiac strain and strain rate were significantly impaired. Sims et al[35] suggest that these echocardiographic measures could be prognostic of long-term myocardial dysfunction in this population. Examining the associations between individual ART agents and combinations of ART might identify optimal ART regimens, both in terms of optimizing HIV outcomes and protecting long-term cardiac health and represents a future research opportunity using this data set. Finally, an analysis of renal function data from these 2 HIV-infected pediatric cohorts, relative to the cardiac findings from both the P^2C^2-HIV and AMP-HIV cohorts, could be a potentially interesting next research step in better characterizing the potential contributing factors to cardiac outcomes in pediatric HIV-infected populations.

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