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Cardiac Effects of *in utero* Exposure to Antiretroviral Therapy in HIV-Uninfected Children Born to HIV-Infected Mothers

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INTRODUCTION

Prevention of mother to child HIV transmission (MTCT) has been a resounding public health success story. In the past 20 years, the rate of MTCT in the US has been reduced from 26% to under 1% using potent combination antiretroviral (cARV) regimens [1-4]. As the use of cARV regimens in pregnancy has increased, concerns have been raised regarding the potential risk of *in utero* cARV exposure on long-term outcomes among HIV-exposed but uninfected (HEU) children, including mitochondrial toxicity which has also been associated with cardiomyopathy in HIV-unexposed children [5-12].

Among HIV-infected children, cardiomyopathy was common prior to widespread use of cARV and was associated with high mortality [13]. However, a study of both HEU and

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HIV-infected children in the National Heart, Lung, and Blood Institute (NHLBI) Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study (P^2C^2) born between 1990-1994 found no association between perinatal exposure to zidovudine (ZDV) monotherapy and abnormalities of left ventricular (LV) structure or function [14]. In another report, compared to the subset of ARV-unexposed HEU children in the P^2C^2 study, 136 children (96% exposed to cARV *in utero*) born between 2003-2006 in the NHLBI-funded Cardiovascular Status of Highly Active Antiretroviral Therapy (HAART) in HIV-Exposed Infants and Children cohort study (CHAART I) had significantly lower LV mass, septal wall thickness, and LV diameter, and higher LV contractility at age 2 years [15].

Since these prior studies were limited by their small sample size and/or they were conducted during an earlier era when there were fewer antiretroviral (ARV) options compared to the contemporary era which has more robust combination ARV combination therapy options, we evaluated the relationship between perinatal ARV drug exposure and echocardiographic measurements from the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring for ART Toxicities (SMARTT) study.

METHODS

Study Population

The PHACS SMARTT study is a prospective cohort study designed to identify adverse effects of in utero ARV exposures on HEU children at 22 US pediatric HIV clinical centers. A reference cohort of children born to HIV-uninfected mothers was enrolled from the same study sites. The SMARTT protocol was reviewed and approved by the institutional review boards (IRB) at all participating clinical sites and the PHACS Data and Operations Center at the Harvard School of Public Health. Written informed consent was obtained from the children's parent or legal guardian, and minor assent per site IRB requirements.

Maternal ARV regimen and substance use (illicit drugs, alcohol, and tobacco) by trimester were collected at study entry or from participation in previous studies including the PACTG 219C study and the Women and Infant Transmission Study [4]. After enrollment, annual SMARTT child study visits included physical exams and collection of new diagnoses and caregiver information.

Study Echocardiograms

To achieve appropriate statistical power in addressing our scientific question, we determined that we needed to perform a single echocardiogram on 400 HEU children in the SMARTT cohort at the first study visit between age 3 and 5 years. All site sonographers received specific protocol training. Using 2-dimensional and M-mode echocardiography, measures of cardiac function (LV ejection fraction, fractional shortening, and stress velocity index) and structural parameters (LV end diastolic (ED) short axis dimension, posterior wall thickness, septal thickness, LV mass, and thickness-to-dimension ratio, and end systolic (ES) wall stress) were measured. All digitized echocardiograms were assessed for image quality and were centrally measured at the PHACS echocardiographic core laboratory at Boston

Children's Hospital (S. Colan). The echocardiographic core laboratory was blinded to patient, prior therapy, and echocardiographic measurements performed at the study centers. The HIV-unexposed reference cohort underwent a single echocardiogram at ages 3-5 years. The only exclusion criterion for this analysis was presence of a significant congenital heart defect (2 [2%] children excluded from the HIV-unexposed reference cohort and 11 [2.7%] from the HEU cohort). All echocardiographic parameters were expressed as *Z*-scores to adjust for variation in age and body surface area in the cohorts. The *Z*-scores for both SMARTT cohorts were calculated using normative data from a healthy pediatric reference cohort from the echocardiography laboratory at Boston Children's Hospital (BCH). The designation of "healthy" was determined by a detailed clinical evaluation and medical record review 1 year after the echocardiographic evaluation. The BCH reference cohort was more likely to be non-Hispanic white and may not have been from the same socioeconomic strata as the SMARTT cohorts [16].

Child and Maternal Factors and Maternal Antiretroviral Use

Child demographic factors, body mass index, birth characteristics at the time of study echocardiogram as well as maternal characteristics including substance use during pregnancy, age at delivery, and HIV viral load and CD4 count prior to delivery were considered as potential confounders (Table 1). cARV was defined as use of at least 3 ARV drugs. We also evaluated the subset of cARV regimens defined as HAART (≥ 3 ARV drugs from ≥ 2 drug classes) but results were similar to those of cARV and are not presented here. Intrauterine exposures to individual ARV drugs, ARV drug class, and cARV were examined overall and by first trimester exposure as this is the most critical period of cardiac development. ARV drug classes included nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs).

The SMARTT HEU cohort echocardiographic parameters were descriptively compared to results from HEU children enrolled in the prior P^2C^2 HIV study (1990-1994) which serves as a cARV-unexposed historical comparison group, and the CHAART I study (2003-2006) which serves as a comparably cARV-exposed group to the SMARTT cohort from an earlier ARV treatment era. In the P^2C^2 cohort, 34% were exposed to ZDV and the rest were unexposed to ARV. In the CHAART I cohort, 96% were exposed to cARV. Detailed methods of these studies have been previously published [17,18]. All P^2C^2 and CHAART I echocardiograms were also centrally re-measured at the PHACS echocardiography core laboratory. Access to the P^2C^2 and CHAART I databases was provided via inter-institutional data use agreements between the University of Miami, Clinical Trials & Survey Corporation (Owings Mills, MD) and the Harvard School of Public Health.

Statistical Analysis

The *Z*-scores of the echocardiographic parameters were summarized by HIV exposure status and compared between HEU and HIV-unexposed groups using a two-sample *t* test. Among those in the HEU cohort with detailed information on maternal ARV exposure, unadjusted linear regression models were first used to assess associations between these *Z*-scores and *in utero* ARV exposures. For each echocardiographic parameter, a core model of potential

confounders (child demographic variables and maternal factors) was built using a backward selection procedure including variables with a *P* value < 0.20 in univariable models. Pregnancy outcomes (e.g., low birth weight, prematurity) were not considered for the selection procedure due to concerns that they may be on the causal pathway between *in utero* ARV exposure and echocardiographic outcomes. All covariates with *P* value < 0.15 were retained as part of the core model of potential confounders. Linear regression models were then fit to assess the association between *in utero* ARV exposures and echocardiographic *Z*-scores, adjusting for the core model covariates. In a sensitivity analysis, the models were restricted to children with cARV exposure as opposed to any ARV exposure. Finally, the *Z*-scores of selected echocardiographic parameters from the P^2C^2 and CHAART studies were summarized and displayed graphically, along with those from the SMARTT cohorts.

Since SMARTT is a drug safety study, we prioritized limiting Type II statistical errors (falsely missing a safety signal) rather than Type I errors (falsely rejecting the null hypothesis) and thus no adjustments for multiple testing were used [19-22]. Statistical analyses were conducted using SAS Version 9.2 (SAS Institute, Cary, NC) using data submitted as of April 2012, and two-sided *P* values ≤ 0.05 were considered statistically significant.

RESULTS

Between 2007 and 2012, 428 (74%) HEU and 100 (100%) HIV-unexposed had an echocardiogram performed, meeting the study's target sample sizes for echocardiograms. After excluding subjects with a congenital cardiac malformation, child and maternal characteristics are compared between the remaining 417 SMARTT HEU and 98 HIV-unexposed children in Table 1. The two groups were generally similar, although the mothers in the HIV-unexposed reference cohort were younger at parturition and had a trend for less often reported tobacco use during pregnancy compared to mothers in the HEU cohort, and the children were leaner and less likely Hispanic and had a trend for lower rate of preterm delivery.

A comparison of select echocardiographic *Z*-scores between the SMARTT HEU and HIV-unexposed reference cohorts and the CHAART I and P^2C^2 HEU children is shown in Figure 1. The P^2C^2 HEU cohort had markedly lower LV function (LV shortening fraction and stress velocity index *Z*-scores) and a much greater septal thickness compared to the other three groups. There were no significant differences in mean *Z*-scores between the SMARTT HEU and HIV-unexposed cohorts for any echocardiographic parameter (Table 2 and Figure 1), whether with or without adjustment for characteristics which differed between the two cohorts.

All further results are limited to the 411 SMARTT HEU participants with information on timing of maternal ARV exposure.

Left ventricular function measures

(Table 3) Among the SMARTT HEU participants, there were no statistically significant adjusted mean differences in *Z*-scores for three measures of LV function (fractional shortening, ejection fraction and stress-velocity index) when those exposed anytime during pregnancy to a specific ARV regimen or individual ARV drugs were compared to those unexposed to that ARV regimen or specific ARV drug. However, first trimester exposures to cARV, tenofovir, emtricitabine, or lopinavir/ritonavir were each associated with significantly lower mean LV stress velocity index *Z*-scores (a load-independent measure of LV contractility [23]) compared to those not exposed to these regimens or individual ARV drugs, with mean decreases of 0.22 to 0.40 standard deviations (SD).

Structural left ventricular measures

(Table 4) Exposure to cARV, both overall and during the first trimester, was associated with lower LV dimension *Z*-scores. First trimester, but not overall, exposures to cARV were also associated with higher mean LV posterior wall thickness and mean thickness-to-dimension ratio *Z*-scores. Exposure to abacavir at any time during pregnancy was significantly associated with a lower mean LV dimension and a higher mean LV thickness-to-dimension ratio compared to those not exposed to abacavir. Exposure to atazanavir, both overall and in the first trimester, was associated with a higher mean LV posterior wall thickness *Z*-score, while overall exposure to nelfinavir or lopinavir/ritonavir was associated with lower mean LV posterior wall thickness *Z*-scores. First trimester exposure to nevirapine was associated with higher mean LV posterior wall thickness and mass *Z*-scores compared to children not exposed *in utero* to nevirapine.

The results of a sensitivity analysis limited to children with *in utero* exposure to cARV (95% of the SMARTT HEU cohort) were generally similar to those of the original analysis with two exceptions: 1) overall ZDV exposure was associated with a significantly higher mean LV stress velocity index *Z*-score in the sensitivity analysis ($P = 0.022$) but not in the original analysis ($P=0.10$), and 2) overall exposure to abacavir was not significantly associated with the LV dimension *Z*-score in the sensitivity analysis ($P=0.09$) although it was in the original analysis ($P = 0.041$).

In addition to the associations of echocardiographic *Z*-scores with *in utero* ARV exposures, we also observed several maternal and fetal factors that were independently associated with echocardiographic measures among the HEU cohort. Tobacco and alcohol use during pregnancy were associated with significant decreases in the LV ejection fraction *Z*-score. Tobacco use during pregnancy was also associated with a 0.23 mean decrease in LV fractional shortening *Z*-score ($P = 0.034$). Both tobacco and alcohol use during pregnancy were associated with higher septal thickness *Z*-score ($P=0.032$ and $P=0.019$, respectively), and maternal alcohol use was associated with a 0.51 increase in mean LV mass *Z*-score ($P=0.004$). In contrast, there was no association observed between echocardiographic parameters and any pregnancy outcomes, maternal age at delivery, or maternal health status as reflected by CD4 and viral load measurements prior to delivery. Girls had significantly lower LV ejection fraction (adjusted mean difference vs. boys = -0.15, $P=0.040$) and significantly lower mean *Z*-scores for several structural parameters (LV dimension, posterior

wall thickness, septal thickness, and mass). White and Hispanic children had significantly higher mean *Z*-scores for LV dimension as compared to non-white and non-Hispanic children, respectively.

DISCUSSION

We found no evidence of clinically significant cardiac toxicity associated with perinatal ARV exposure among HEU children 3-5 years of age. There were no statistically significant differences between the HEU (95% exposed to cARV) and the HIV-unexposed SMARTT cohorts in mean *Z*-scores for any echocardiographic parameter. However, we did observe some associations between specific ARV exposures and certain echocardiographic parameters within the HEU cohort. While the overall cardiac function of the HEU children was similar to that of the SMARTT HIV-unexposed cohort, there was significant variability within the HEU cohort in echocardiographic *Z*-scores which could be at least partially explained by ARV exposures. Both the SMARTT HEU and HIV-unexposed cohorts differed from the BCH reference cohort's mean *Z*-scores of zero for some parameters. This observation may reflect the effects of differences between the SMARTT cohorts and the BCH reference cohort for factors such as race-ethnicity, income and education level, nutritional status, environmental exposures, and other demographic and lifestyle characteristics. However, these differences would be unlikely to affect our observed associations of echocardiographic parameter with certain early prenatal cARV exposures in the HEU group.

As noted above, certain ARV exposures were associated with differences in mean *Z*-scores for echocardiographic parameters within the HEU group. We found significantly lower LV stress velocity index (a load-independent measure of LV function) in HEU children exposed in the first trimester to cARV and specific NRTIs (tenofovir, emtricitabine) or lopinavir/ritonavir, compared to HEU children not exposed to cARV or these specific agents. Exposure to cARV and specific NRTI and PI agents anytime during pregnancy was generally associated with lower LV dimension than lack of exposure to these regimens or agents, although this does not necessarily reflect a lower LV dimension than expected in comparison to the BCH reference cohort. Because the number of cardiac myocytes is fixed at birth, a small LV is a potential concern regarding the ability of the LV to meet the increased cardiovascular demands as these children grow into adulthood. Only longitudinal cardiac reassessment of this population can address this concern. First trimester exposures to cARV and to specific agents from all 3 ARV drug classes were associated with higherLV posterior wall thickness. All of the differences in *Z*-scores were less than 1 SD, and most were less than 0.5 SDs. Differences in echocardiographic *Z*-scores greater than 2 SD are typically considered pathologic, but the potential clinical significance of the smaller changes we observed are unknown.

The current findings of slightly lower LV function, lower dimension, and higher posterior wall thickness associated with cARV and specific ARV exposures, compared to children unexposed to cARV or these specific ARVs, could be consistent with a subclinical inflammatory response characterized by injury or death of cardiac myocytes along with an inflammatory infiltrate in the LV posterior wall and interventricular septum. These findings

are found in other inflammatory heart conditions such as myocarditis [24-26]. These conclusions are further supported by a previous evaluation of cardiac and inflammatory biomarkers in the same SMARTT study population which could be consistent with a myocardial inflammatory process [27]. Since almost all mothers received ARVs during pregnancy, the relative contributions to a possible inflammatory response of prenatal exposure to ARVs vs. maternal HIV cannot be addressed in this analysis. Future studies of cardiac biomarkers may help identify HEU children who require further cardiac evaluation including echocardiography. Innate immune activation has been proposed as one of the reasons for the increased cardiovascular risk and mortality seen in HIV-infected adults receiving long-term ARV therapy [28-31].

We also found that maternal alcohol and tobacco use during pregnancy were associated with lower LV function as well as higher septal thickness and LV mass, independent of the observed ARV associations. Maternal alcohol use during pregnancy has been associated with structural cardiac defects, long QT syndrome (a potential risk for sudden cardiac death), and heart muscle disease in both human and animal studies [32-37]. Prenatal tobacco exposure has been associated with inhibition of cardiac DNA synthesis, impaired vascular smooth muscle structure and function, and structural cardiac defects [37].

A descriptive comparison of the SMARTT cohort with the earlier CHAART I and P^2C^2 HEU studies showed echocardiographic findings which were generally consistent for the SMARTT and previous CHAART I studies (both conducted in the cARV era) in terms of direction, although not always of the same magnitude. Echocardiographic findings were generally more extreme in the P^2C^2 HEU cohort and sometimes in the opposite direction, compared to the SMARTT and CHARRT-I cohorts but these differences were not consistent across all echocardiographic parameters. The P^2C^2 HEU cohort was either ARV-unexposed or only ZDV-exposed in the perinatal period and generally had more extreme changes in echocardiographic parameters. This suggests that the cARV regimens taken by mothers in the SMARTT and CHAART I cohorts and the resulting decrease in maternal viral load or inflammatory mediators led not only to a marked reduction in MTCT of HIV but also to a healthier echocardiographic profile at age 3 to 5 years. However, there could be differences in non-cARV exposures in the SMAART and CHAART-I mothers, such as maternal health, lifestyle, or environmental exposures, compared to the P^2C^2 HEU mothers, which could contribute to the healthier echocardiographic profile in their young HEU children.

In the SMARTT study we found lower *Z*-scores for several echocardiographic parameters in girls compared to boys. In the CHAART I study, differences in several echocardiographic measures were greater in girls, as opposed to boys, when compared to the P^2C^2 comparison group [15]. In healthy children, there are no gender differences in echocardiographic *Z*-scores. The reason for these gender differences in echocardiographic measures in HEU children in the SMARTT and CHAART I studies is not clear.

Study limitations include that a single echocardiographic assessment per child does not allow evaluation of the trajectory or persistence of any cardiac changes associated with ARV exposures. This study design cannot differentiate between potential cardiac effects of perinatal exposure to HIV and perinatal exposure to specific ARV agents. Our comparison

of the SMARTT and CHAART I ARV exposed cohorts to the P^2C^2 ARV-unexposed cohort suggests that potential cardiac effects of perinatal ARV exposure in the cARV era are less extreme than in the pre-cARV era. Alternatively, this may indicate that poorer HIV control in pre-cARV era mothers could explain the cardiac effect differences instead of, or in addition to, any ARV effects. Finally, the current analysis utilized an initial "predictive" screening analysis which is appropriate to identify potential safety signals, but cannot evaluate causal relationships. However, the large number of participants and inclusion of both internal (SMARTT HIV-unexposed) and external (Boston Children's Hospital) comparison groups are key strengths of this study, although the BCH reference cohort differed in terms of racial distribution and possibly socioeconomic status from both the HEU and HIV-unexposed cohorts. The analyses were adjusted for known potential confounders. However, there is still the possibility of residual confounding from unmeasured covariates. Finally, since the SMARTT study was primarily a safety study, we did not adjust for multiple comparisons to minimize Type II errors. Due to the large number of comparisons, some associations could be due to chance and findings should be confirmed in further studies.

We found no evidence of clinically significant cardiac toxicity associated with perinatal ARV (mostly cARV) exposure in HEU children at 3 to 5 years of age compared to a demographically similar reference cohort of HIV-unexposed and apparently healthy children. However, the associations of subclinical differences in LV structure and function with specific *in utero* ARV exposures, particularly in the first trimester, suggest that these children should be longitudinally studied to determine if long-term deleterious cardiac effects emerge as they age. Such follow-up studies could inform the selection of optimal ARV regimens in pregnancy that will simultaneously prevent perinatal transmission of HIV and optimize long-term cardiac health in infants born to HIV-infected mothers.

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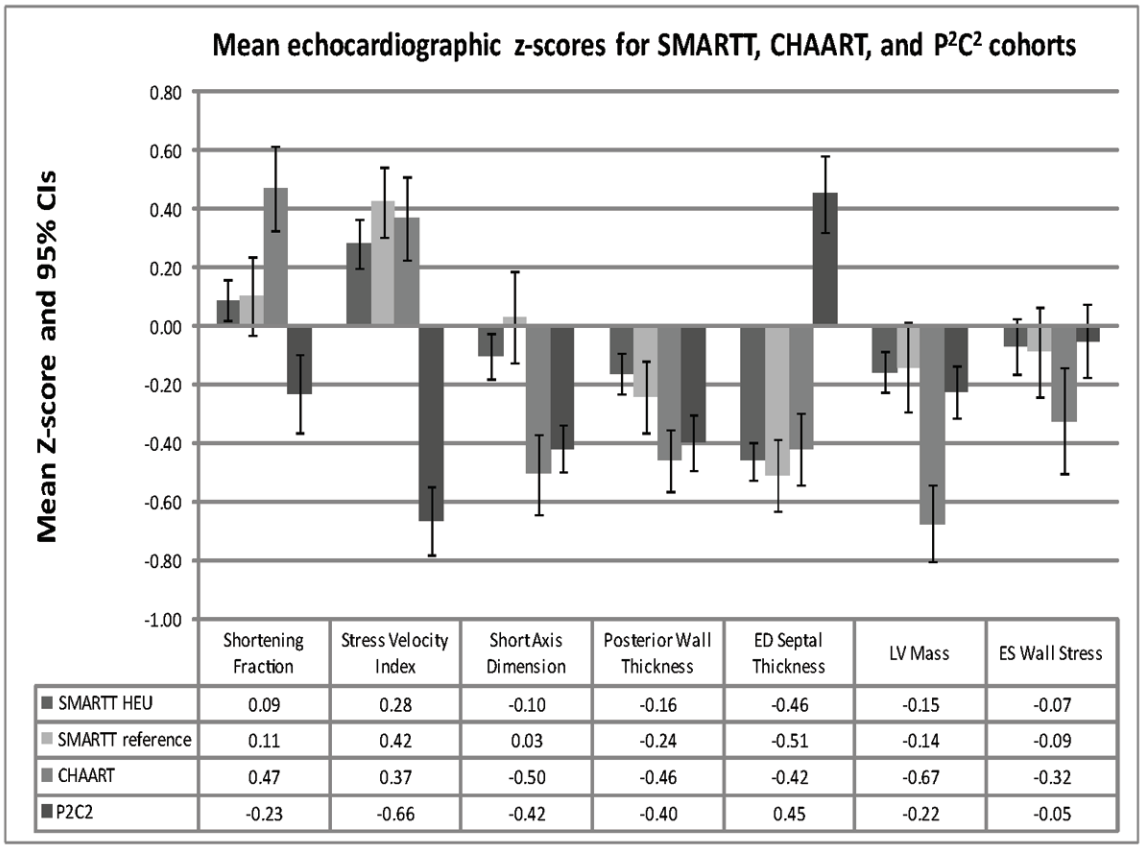

	Shortening Fraction	Stress Velocity Index	Short Axis Dimension	Posterior Wall Thickness	ED Septal Thickness	LV Mass	ES Wall Stress
SMARTT HEU	0.09	0.28	-0.10	-0.16	-0.46	-0.15	-0.07
SMARTT reference	0.11	0.42	0.03	-0.24	-0.51	-0.14	-0.09
CHAART	0.47	0.37	-0.50	-0.46	-0.42	-0.67	-0.32
P2C2	-0.23	-0.66	-0.42	-0.40	0.45	-0.22	-0.05

Figure 1.

Echocardiographic *Z*-score comparisons between the SMARTT HIV-exposed uninfected (SMARTT HEU) and HIV-unexposed (SMARTT HIV-unexposed) cohorts and results from the previous NHLBI-funded CHAART and P^2C^2 studies. CI = confidence interval; ED = end diastolic; LV = left ventricular; ES = end systolic.

Table 1

Child and maternal characteristics for 3 to 5 year old children with an echocardiogram (PHACS SMARTT Study, United States, 2006-2013)

	SMARTT Cohort		
Characteristic[a]	**HIV-exposed uninfected (HEU) cohort (*n* = 417)**	**HIV-unexposed reference cohort (*n* = 98)**	***P* Value** [b]
Age at echocardiogram (years), median (min, max)	4.0 (2.8, 7.4)	4.8 (2.8, 5.9)	0.53
Female	207 (50%)	52 (53%)	0.58
Race			0.16
Black/African-American	257 (62%)	69 (70%)	
White	123 (30%)	25 (26%)	
Other/not reported	37 (9%)	4 (4%)	
Hispanic ethnicity	161 (39%)	22 (22%)	0.002
Child's BMI at echocardiogram, mean (SD)	16.7 (2.3)	15.7 (2.4)	<0.001
Child's birth characteristics			
Birth weight <2.5kg	84 (20%)	15 (16%)	0.47
Gestational age <37 weeks	82 (20%)	11 (12%)	0.10
Small for gestational age (<10th percentile weight for gestational age)	44 (11%)	9 (10%)	1.00
Mother's age at delivery (years)			
Mean (SD)	28.2 (6.0)	26.2 (6.4)	0.002
<25 years at delivery	124 (30%)	50 (55%)	<0.001
Mother's VL >1000 cpm prior to delivery	55 (14%)	---	---
Mother's CD4 count <200 cells/mm^3 prior to delivery	32 (8%)	---	---
Maternal substance use during pregnancy			
Tobacco	76 (20%)	10 (11%)	0.067
Alcohol	26 (7%)	4 (4%)	0.63
Illicit drugs	37 (10%)	4 (4%)	0.15

BMI = body mass index, SD = standard deviation, VL = viral load, cpm = copies per milliliter

[a] Data on certain characteristics were unavailable for reference and HEU subjects, for ethnicity (n = 0 and 1), birth weight (n = 5 and 0), gestational age (n = 6 and 2), SGA (n = 12 and 17), maternal age (n = 7 and 0), substance use (n = 9 and 32), and for HEU, maternal VL (n = 22) and CD4 (n = 25).

[b] P value by Fisher's exact test for binary characteristics, Chi-Square test for categorical characteristics (race), and Wilcoxon rank-sum test for continuous characteristics

Table 2

Comparison of mean echocardiographic parameter *Z*-scores between the SMARTT HIV-exposed uninfected cohort and the HIV-unexposed reference cohort

	SMARTT Cohort		Unadjusted Comparison		Adjusted Comparison[a]	
Echocardiographic *Z*-score	**HIV-exposed uninfected (HEU) cohort (*n* = 417) Mean (SE), *N***	**HIV-unexposed reference cohort (*n* = 98) Mean (SE), *N***	**Mean Difference (95% CI)**	***P* Value**	**Adjusted Mean Difference (95% CI)**	***P* Value**
FUNCTIONAL MEASURES						
LV ejection fraction	0.20 (0.04), 398	0.29 (0.07), 92	0.09 (-0.07, 0.26)	0.26	0.04 (-0.14, 0.21)	0.70
LV M-mode shortening fraction	0.09 (0.04), 413	0.11 (0.08), 98	0.02 (-0.17, 0.20)	0.86	-0.06 (-0.26, 0.15)	0.57
LV stress velocity index	0.28 (0.05), 370	0.42 (0.10), 91	0.14 (-0.07, 0.35)	0.18	0.12 (-0.11, 0.35)	0.30
STRUCTURAL PARAMETERS						
LV M-mode ED short axis dimension	-0.10 (0.05), 412	0.03 (0.09), 98	0.13 (-0.07, 0.34)	0.20	0.07 (-0.15 0.29)	0.52
LV M-mode ED post wall thickness	-0.16 (0.04), 412	-0.24 (0.08), 98	-0.08 (-0.26, 0.10)	0.39	-0.05 (-0.25, 0.15)	0.65
M-mode ED septal thickness	-0.46 (0.04), 412	-0.51 (0.08), 98	-0.05 (-0.22, 0.13)	0.59	-0.06 (-0.25, 0.13)	0.51
LV M-mode mass	-0.15 (0.04), 412	-0.14 (0.09), 98	0.02 (-0.18, 0.21)	0.87	-0.02 (-0.23, 0.19)	0.83
LV M-mode ES wall stress	-0.07 (0,05), 376	-0.09 (0.11), 93	-0.02 (-0.26, 0.22)	0.89	-0.02 (-0.29, 0.25)	0.88
LV M-mode thickness-to-dimension ratio	-0.52 (0.04), 412	-0.64 (0.08), 98	-0.12 (-0.30, 0.05)	0.16	-0.07 (-0.26, 0.12)	0.46

LV = left ventricular; ED = end-diastolic; ES = end-systolic; SE=standard error; CI=confidence interval

[a]Adjusted linear regression models include Hispanic ethnicity, child body mass index, younger maternal age (<25yrs) at delivery, and maternal tobacco use during pregnancy.

Table 3

Adjusted differences in functional echocardiographic parameter mean *Z*-scores for 411 HIV-exposed uninfected children in SMARTT exposed vs. unexposed *in utero* to specific antiretroviral regimens or drugs

		Left Ventricular Functional Echocardiographic Parameter[a]								
		Ejection Fraction			Fractional Shortening			Stress Velocity Index		
ARV Exposure	**Percent exposed**	**Estimated mean difference**	**(95% CI)**	***P* Value**	**Estimated mean difference**	**(95% CI)**	***P* Value**	**Estimated mean difference**	**(95% CI)**	***P* Value**
Anytime during pregnancy										
cARV	95%	0.26	(-0.09, 0.61)	0.14	0.03	(-0.40, 0.46)	0.90	-0.11	(-0.60, 0.37)	0.64
NRTIs										
Zidovudine	82%	0.06	(-0.14, 0.26)	0.55	-0.00	(-0.24, 0.23)	0.98	0.23	(-0.04, 0.49)	0.10
Lamivudine	85%	0.07	(-0.14, 0.28)	0.50	0.04	(-0.21, 0.30)	0.74	0.04	(-0.25, 0.33)	0.79
Abacavir	28%	0.02	(-0.14, 0.18)	0.84	0.07	(-0.13, 0.27)	0.49	0.03	(-0.19, 0.25)	0.80
Didanosine	6%	0.11	(-0.22, 0.44)	0.51	0.23	(-0.17, 0.62)	0.26	-0.17	(-0.62, 0.28)	0.46
Stavudine	5%	0.12	(-0.20, 0.44)	0.45	-0.09	(-0.49, 0.32)	0.67	-0.25	(-0.70, 0.20)	0.27
Tenofovir	24%	-0.08	(-0.25, 0.10)	0.39	-0.01	(-0.22, 0.19)	0.89	-0.06	(-0.29, 0.18)	0.64
Emtricitabine	12%	-0.03	(-0.26, 0.20)	0.81	0.05	(-0.22, 0.33)	0.70	-0.01	(-0.32, 0.31)	0.97
NNRTIs										
Efavirenz	5%	0.09	(-0.26, 0.44)	0.62	-0.08	(-0.49, 0.33)	0.71	-0.11	(-0.56, 0.35)	0.64
Nevirapine	14%	0.08	(-0.12, 0.29)	0.43	-0.06	(-0.31, 0.20)	0.65	-0.12	(-0.41, 0.17)	0.41
PIs										
Atazanavir	8%	-0.02	(-0.30, 0.26)	0.89	0.19	(-0.15, 0.53)	0.27	-0.06	(-0.45, 0.33)	0.76
Nelfinavir	43%	0.02	(-0.13, 0.17)	0.76	-0.01	(-0.20, 0.18)	0.92	0.02	(-0.19, 0.22)	0.88
Lopinavir/Ritonavir	27%	-0.03	(-0.19, 0.14)	0.76	-0.12	(-0.32, 0.08)	0.25	-0.06	(-0.29, 0.18)	0.62
1st Trimester Exposure (only associations with *P* ≤ 0.10 for at least one parameter)										
cARV	49%	0.12	(-0.03, 0.27)	0.12	0.03	(-0.15, 0.22)	0.72	-0.22	(-0.42, -0.01)	0.036
NRTIs										
Lamivudine	42%	0.10	(-0.06, 0.25)	0.21	0.06	(-0.12, 0.25)	0.50	-0.17	(-0.38, 0.03)	0.10
Tenofovir	14%	-0.00	(-0.21, 0.21)	0.99	-0.01	(-0.26, 0.25)	0.96	-0.32	(-0.60, -0.03)	0.029
Emtricitabine	7%	0.06	(-0.24, 0.36)	0.70	-0.02	(-0.38, 0.33)	0.90	-0.40	(-0.80, -0.00)	0.049

		Left Ventricular Functional Echocardiographic Parameter[a]								
		Ejection Fraction			Fractional Shortening			Stress Velocity Index		
ARV Exposure	Percent exposed	Estimated mean difference	(95% CI)	*P* Value	Estimated mean difference	(95% CI)	*P* Value	Estimated mean difference	(95% CI)	*P* Value
PIs										
Lopinavir/Ritonavir	11%	-0.00	(-0.23, 0.22)	0.98	-0.11	(-0.39, 0.16)	0.42	-0.40	(-0.72, -0.09)	0.013

ARV = antiretroviral, BMI = body mass index, cARV = combination antiretroviral, CI = confidence interval, NRTI = nucleoside reverse transcriptase inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

[a]Each echocardiographic parameter was modeled separately in an adjusted linear regression model comparing those with the exposure of interest to unexposed (to that ARV regimen or drug), with adjustment for covariates as follows: mother's use of illicit drugs during pregnancy and child's sex (LV ejection fraction); child's race and mother's use of illicit drugs during pregnancy (LV fractional shortening); age at echo, mother's use of alcohol during pregnancy, and child's BMI (LV stress velocity index).

Table 4

Adjusted differences in structural echocardiographic parameter mean *Z*-scores with at least marginal significance for 411 HIV-exposed uninfected children in SMARTT exposed vs. unexposed *in utero* to specific ARV regimens or drugs

		Left Ventricular Structural Echocardiographic Parameter[a]					
		Short Axis Dimension	Posterior Wall Thickness	Septal Thickness	Mass	Wall Stress	Thickness-to-Dimension Ratio
ARV Exposure	Percent Exposed	Mean (95% CI), *P* value	Mean (95% CI), *P* value	Mean (95% CI), *P* value	Mean (95% CI), *P* value	Mean (95% CI), *P* value	Mean (95% CI), *P* value
ANYTIME DURING PREGNANCY							
cARV	95%	**-0.44 (-0.85,-0.02) 0.040**	0.05 (-0.34,0.44) 0.82	0.14 (-0.23,0.50) 0.46	-0.16 (-0.54,0.23) 0.43	-0.12 (-0.63,0.39) 0.65	0.14 (-0.25,0.54) 0.47
Nucleoside Reverse Transcriptase Inhibitor (NRTIs)							
Abacavir	28%	**-0.22 (-0.41,-0.02) 0.031**	0.18 (-0.01,0.36) 0.061	0.02 (-0.16,0.19) 0.84	-0.09 (-0.27,0.10) 0.36	-0.16 (-0.40,0.08) 0.19	**0.23 (0.06,0.41) 0.010**
Didanosine	6%	-0.11 (-0.49,0.27) 0.59	0.20 (-0.18,0.58) 0.30	0.05 (-0.30,0.40) 0.78	-0.03 (-0.41,0.35) 0.89	-0.48 (-0.96,0.00) 0.051	0.26 (-0.10,0.62) 0.15
Non-Nucleoside Reverse Transcriptase Inhibitor (NRTIs)							
Nevirapine	14%	-0.01 (-0.26,0.24) 0.93	0.21 (-0.03,0.45) 0.084	0.22 (-0.00,0.45) 0.052	0.24 (-0.00,0.47) 0.053	-0.16 (-0.47,0.16) 0.33	0.12 (-0.11,0.35) 0.31
Protease Inhibitors (PIs)							
Atazanavir	8%	**-0.38 (-0.71,-0.04) 0.030**	**0.47 (0.15,0.78) 0.004**	-0.14 (-0.44,0.15) 0.34	-0.15 (-0.46,0.17) 0.36	-0.11 (-0.52,0.31) 0.62	**0.61 (0.30,0.91) <0.001**
Nelfinavir	43%	-0.03 (-0.21,0.16) 0.76	**-0.21 (-0.38,-0.04) 0.017**	-0.10 (-0.26,0.06) 0.22	-0.12 (-0.29,0.05) 0.16	0.07 (-0.15,0.30) 0.51	**-0.21 (-0.38,-0.04) 0.017**
Lopinavir/RTV	27%	0.10 (-0.10,0.30) 0.33	-0.19 (-0.38,0.00) 0.055	-0.13 (-0.31,0.05) 0.16	-0.12 (-0.31,0.07) 0.21	0.02 (-0.23,0.27) 0.88	-0.16 (-0.34,0.02) 0.083
FIRST TRIMESTER EXPOSURES							
cARV	49%	**-0.19 (-0.37,-0.01) 0.040**	**0.20 (0.03,0.37) 0.023**	-0.02 (-0.18,0.14) 0.81	-0.02 (-0.19,0.15) 0.81	**-0.27 (-0.49,-0.05) 0.016**	**0.18 (0.02,0.35) 0.030**
Nucleoside Reverse Transcriptase Inhibitor (NRTIs)							
Zidovudine	39%	-0.15 (-0.33,0.04) 0.12	**0.19 (0.02,0.37) 0.031**	0.02 (-0.15,0.18) 0.85	0.01 (-0.16,0.19) 0.91	**-0.27 (-0.49,-0.05) 0.017**	0.14 (-0.04,0.31) 0.12
Lamivudine	42%	-0.10 (-0.29,0.08) 0.27	**0.18 (0.01,0.35) 0.039**	-0.01 (-0.17,0.15) 0.91	0.04 (-0.13,0.21) 0.63	-0.21 (-0.43,0.01) 0.068	0.11 (-0.06,0.28) 0.20
Abacavir	14%	-0.14 (-0.40,0.12) 0.28	0.22 (-0.02,0.46) 0.075	-0.01 (-0.23,0.22) 0.96	-0.03 (-0.27,0.21) 0.82	-0.25 (-0.57,0.07) 0.13	0.23 (-0.00,0.45) 0.052
Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTIs)							
Nevirapine	10%	-0.08 (-0.38,0.21) 0.58	**0.34 (0.06,0.62) 0.019**	0.24 (-0.02,0.50) 0.076	**0.28 (0.00,0.56) 0.049**	-0.15 (-0.52,0.21) 0.41	0.23 (-0.04,0.50) 0.094
Protease Inhibitors (PIs)							
Atazanavir	5%	-0.37 (-0.77,0.02) 0.064	**0.64 (0.27,1.01) 0.001**	-0.09 (-0.44,0.27) 0.63	-0.00 (-0.38,0.37) 0.99	-0.15 (-0.65,0.35) 0.55	**0.72 (0.37,1.07) <0.001**
Nelfinavir	19%	-0.11 (-0.35,0.12) 0.34	-0.05 (-0.28,0.17) 0.64	-0.18 (-0.39,0.03) 0.093	-0.13 (-0.35,0.09) 0.26	-0.02 (-0.30,0.25) 0.87	-0.12 (-0.34,0.11) 0.31
Lopinavir/RTV	11%	-0.02 (-0.29,0.26) 0.91	-0.05 (-0.32,0.21) 0.70	-0.12 (-0.36,0.13) 0.36	-0.13 (-0.39,0.13) 0.33	-0.30 (-0.65,0.05) 0.094	-0.02 (-0.27,0.23) 0.86

ARV = antiretroviral, BMI = body mass index, LV = left ventricular

[a] Each echocardiographic parameter was modeled separately in an adjusted linear regression model comparing those with the exposure of interest to unexposed (to that ARV regimen or drug), with adjustment for covariates as follows: child's race, child's sex, child's BMI, and mother's age at delivery (LV short axis dimension); mother's alcohol use during pregnancy (LV posterior wall thickness); mother's alcohol use during pregnancy and child's sex (septal thickness); maternal alcohol use during pregnancy, child's sex and child's BMI (LV mass);age at echo, child's sex, and mother's age at delivery (LV wall stress); child's race, mother's alcohol use during pregnancy and child's BMI (LV thickness-to-dimension ratio)