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Reduced Diastolic Function and Left Ventricular Mass in HIV-Negative Pre-Adolescent Children Exposed to Antiretroviral Therapy *in Utero*

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Keywords

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Introduction

Abnormalities in left ventricular (LV) function are well-described in vertically-infected HIV-positive children [1-4]. Although antiretroviral therapy (ART) is effective in preventing the vertical transmission of HIV during pregnancy and parturition, HIV-negative children exposed to ART *in utero* may have depressed LV contractility, lower LV mass and resting tachycardia [4-6]. Subclinical LV dysfunction in HIV-negative children born to HIV+ women and exposed to ART may be clinically relevant given the relationship in adults between subclinical LV dysfunction and the progression to overt heart failure [7, 8]. Earlier studies [4, 5, 9] have shown LV morphologic and systolic abnormalities are present in HIV-negative infants exposed to HIV and ART *in utero* which persist throughout pre-school age. However it is currently unclear if LV dysfunction in these children persists, worsens, or resolves in pre-adolescence. It is also unknown if diastolic function is altered in HIV-negative children exposed to ART but may be important due to the prognostic value of diastolic function in predicting clinical outcomes in children with known cardiac disease [10]. Therefore, the objective of this study was to characterize LV systolic and diastolic function in HIV-negative pre-adolescent children exposed to ART *in utero* and compare them to healthy unexposed children. We hypothesized that abnormalities in LV morphology and LV function would be present in HIV-negative pre-adolescent ART-exposed children compared to unexposed children.

Participants

Thirty pre-adolescent HIV-negative children (8-12 yrs) born to HIV-positive women and exposed to ART *in utero* (ART(+)) and 30 HIV-negative age, sex, and race matched HIV-negative children (8-12 yrs) born to HIV-negative women (ART(-)) were compared. ART-exposed children were recruited from a convenience sample of women attending the AIDS Clinical Trials Unit at Washington University School of Medicine (WUSM) and all were enrolled in routine pediatric care. Children born to HIV-negative women were recruited through WUSM Volunteers for Health. ART(+) children received prophylactic ART for 6 wks postpartum. None of the children had been diagnosed with growth restriction or cardiovascular/metabolic disease and were not taking medications that would affect LV function. HIV+ women received ART during pregnancy according to standard-of-care (10% mono-therapy with zidovudine and 90% combination ART) and all but one had intravenous zidovudine during parturition. None of the women had a diagnosis of pre-pregnancy or gestational diabetes. The study was approved by the WUSM Human Research Protection Office and all children/parents provided written assent/consent prior to participation.

Procedures

Echocardiography

A complete 2-D, Doppler and tissue-Doppler echocardiographic examination was conducted (General Electric, Milwaukee, WI). LV end-diastolic and end-systolic volumes and LV mass were determined according to recommendations of the American Society of Echocardiography [11]. Pulsed-wave Doppler mitral inflow velocities of early LV filling (E) and atrial filling (A) were obtained at the mitral leaflet tips in the apical 4-chamber view. Tissue-Doppler imaging (TDI) was performed in the apical 4-chamber view to determine the peak systolic shortening velocity (S') and early diastolic myocardial relaxation velocity (E') for regional assessment of systolic and diastolic function, respectively [12]. E' and S' were calculated by averaging the velocities of the lateral and septal base as recommended [13]. The ratio of mitral E-wave to E' velocity was derived as an estimate of LV filling pressure. Color TDI-derived longitudinal strain imaging was performed at the lateral and septal base to derive peak systolic strain. All echocardiograms were performed and analyzed by one of the authors, unaware of the maternal or child history.

Statistical Analysis

Sample size was based on anticipated differences in neonatal systolic function (fractional shortening, strain) between groups and was based on data from Lipshultz et al [4] and a previous study from our institution [14]. Comparisons of outcome parameters were performed by independent t-tests, Mann-Whitney U-test or linear regression, as appropriate. Regression models were then run with group as the primary predictor of interest, adjusting for sports participation and hours of daily television viewing since these variables tended to differ between groups. Within HIV+ women, backward elimination linear regression was used to examine the relationship between HIV-related and specific LV function variables, while also considering child and maternal demographics, maternal smoking/cocaine use, and maternal pregnancy characteristics. Variables remaining in the model were those with $p < .10$. Beta coefficients, standard errors, p values, and the overall R^2 of the final models are reported. Statistical significance was determined at $p < 0.05$.

Results

Demographics

Age, gender, race, anthropometric, and birth characteristics were similar between groups (Table 1). Seventy-three percent of HIV+ women used lamivudine/zidovudine (among others) and 43% of HIV-positive women took a protease inhibitor during pregnancy. A greater percentage of HIV+ women had lower 3rd trimester blood pressure than HIV-negative women (Table 1). Other maternal characteristics during pregnancy were similar between HIV+ and HIV-negative women (Table 1).

Left Ventricular Function

Results with and without statistically controlling for organized sport participation and TV viewing were similar therefore data is presented without statistical controlling for these variables. There was no difference in resting heart rate between groups. LV mass index was significantly lower in ART(+) than ART(−) children (Table 2). Other variables of LV structure and function including TDI-derived peak systolic strain did not differ between groups. The diastolic mitral early (E) to late (A) mitral inflow velocity ratio (E/A) tended to be lower in ART(+) children compared to ART(−) children. Early diastolic annular velocity (E') was significantly lower in ART(+) children compared to ART(−) children (Table 2).

Regression Analysis

Multivariate analysis revealed that older maternal age ($\beta = -1.2$, $p < 0.06$) and lower maternal 3rd trimester CD4 count ($\beta = 0.04$, $p < 0.01$) were independently associated with lower E' ($R^2 = 0.37$). Maternal cocaine use during pregnancy was associated with significantly lower LV mass index ($\beta = -12.95$, $p < 0.001$). Males ($\beta = 7.34$, $p < 0.001$) and older children ($\beta = 1.63$, $p < 0.001$) had higher LV mass index (model $R^2 = 0.66$) as expected. No HIV-related variables were significantly associated with LV mass index. Smoking during pregnancy ($\beta = -2.87$, $p < 0.03$), maternal prior hypertension ($\beta = -4.17$, $p < 0.04$) or preeclampsia ($\beta = -3.67$, $p < 0.02$), and increasing gestational age ($\beta = -0.57$, $p < 0.001$) were independently associated with lower peak systolic strain ($R^2 = 0.66$).

Discussion

The results of this study demonstrate the identification of reduced (but within normal limits) LV diastolic function in HIV-negative pre-adolescent children exposed to ART *in utero* and post-partum. To our knowledge, this is the first study to characterize LV diastolic function, in addition to systolic function and LV structure, in HIV-negative children exposed to ART *in utero* and suggest that exposure to ART has residual effects on LV diastolic function through pre-adolescence. These data also are consistent with the CHAART-1 and P2C2 HIV studies [1, 3, 5, 9] demonstrating that morphologic alterations persist but indicate that systolic function abnormalities in ART exposed infants and pre-school age children may resolve by pre-adolescence; however, this needs to be confirmed by large, longitudinal studies.

Our finding that myocardial relaxation based on tissue-Doppler imaging (TDI)-derived E' was lower in HIV-negative children exposed to ART is novel. Previous studies in ART-exposed children have demonstrated reduced end diastolic volumes [4, 5] however the authors did not report TDI-derived myocardial velocities or Doppler-derived inflow velocities during diastole as in the current study. TDI is an alternative method to measure diastolic function that complements traditional 2D and Doppler analyses to detect diastolic abnormalities [13] and may be more sensitive as it is relatively load independent [15]. Impaired diastolic function has been reported in adults with HIV [16-19] and has been

associated with HIV infection [18, 20, 21], depressed immune function [22], and advanced disease [23]. Altered diastolic function in those with HIV has also been associated with impaired whole-body and myocardial glucose metabolism [24]. These findings may be consistent with the fetal origins hypothesis where an abnormal metabolic environment *in utero* is reported to be associated with future cardiovascular disease [25]. Prior studies have reported that ART may contribute to impaired diastolic function in adults [26] however, this is unclear in children [27]. Animal studies suggest that nucleoside reverse transcriptase inhibitors may result in cardiomyopathic effects when administered in high doses [28]: including mitochondrial ultrastructural abnormalities [29] and mtDNA depletion and mutations [30] through the inhibition of DNA polymerase gamma [31]. It is possible that exposure to ART *in utero* may impair energy dependent myocardial relaxation secondary to altered mitochondrial function in children born to HIV+ women.

The clinical implications of lower diastolic function in children exposed to ART are unclear. Impaired myocardial relaxation in HIV-negative adults with heart disease has important clinical implications as diastolic dysfunction frequently precedes LV systolic dysfunction [7, 8, 32]. In children with dilated cardiomyopathy, lower E' is associated with increased rates of adverse clinical outcomes and hospitalizations [10]. It is possible that in ART-exposed children during adolescence and early adulthood, lower diastolic function coupled with accumulating cardiovascular risk factors (e.g. obesity, inactivity, insulin resistance) could lead to worsening diastolic function and future systolic dysfunction [7, 8]. This is speculative, but overall, our results are consistent with Lipshultz et al. [3] and agree that monitoring of LV function in ART exposed children should be considered through adolescence and likely into adulthood.

Our study extended the previous findings of lower LV mass in HIV-negative infants and pre-school age children exposed to ART [4, 5] showing that this LV structural difference persists into pre-adolescence. The mechanism for lower LV mass in ART exposed children is unknown but may be due to abnormal myocyte development as previously demonstrated in rodents who were exposed to ART *in utero* [33, 34]. Cardiac growth as assessed by LV mass is positively associated with higher myocardial relaxation velocities in healthy children [12] thus lower LV mass in ART-exposed children may have contributed to the differences in diastolic function between groups in the current study. Interestingly, whole-body growth was shown to be stunted in uninfected children exposed to ART [35] suggesting ART exposure may impede both ante- and post-natal growth.

Limitations

The study design was cross-sectional and measurements of LV function were not obtained in participants at birth, during infancy or pre-school age and as such longitudinal changes in LV function were not determined. Due to the small sample size, it is possible that the echo-Doppler variables may be different if conducted in a larger population. It was not possible to determine whether the differences in LV function were attributable to maternal illicit drug use, maternal blood pressure, or more sedentary lifestyles of HIV+ cohort and because all participants took prophylactic ART for 6 wks, we cannot discern whether the effect was due to exposure to ART *in utero*, during the postpartum period, or both.

Conclusion

HIV-negative pre-adolescent children exposed to ART *in utero* and post-partum have lower values of LV diastolic function and LV mass compared to their peers but the clinical implications remain unclear. Differences in LV systolic function previously reported in infancy were not present in pre-adolescence. Additional data is required to determine

whether echocardiographic evaluations are needed for children exposed to ART throughout adolescence and adulthood.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Left ventricular structure and function in children infected with human immunodeficiency virus: the prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. *Circulation*. 1998; 97:1246–1256. [PubMed: 9570194]
2. Al-Attar I, Orav EJ, Exil V, Vlach SA, Lipshultz SE. Predictors of cardiac morbidity and related mortality in children with acquired immunodeficiency syndrome. *J Am Coll Cardiol*. 2003; 41:1598–1605. [PubMed: 12742303]
3. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Cardiac dysfunction and mortality in HIV-infected children: The Prospective P2C2 HIV Multicenter Study. Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection (P2C2 HIV) Study Group. *Circulation*. 2000; 102:1542–1548. [PubMed: 11182983]
4. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Cardiovascular status of infants and children of women infected with HIV-1 (P(2)C(2) HIV): a cohort study. *Lancet*. 2002; 360:368–373. [PubMed: 12241776]
5. Lipshultz SE, Shearer WT, Thompson B, Rich KC, Cheng I, Orav EJ, et al. Cardiac effects of antiretroviral therapy in HIV-negative infants born to HIV-positive mothers: NHLBI CHAART-1 (National Heart, Lung, and Blood Institute Cardiovascular Status of HAART Therapy in HIV-Exposed Infants and Children cohort study). *J Am Coll Cardiol*. 2011; 57:76–85. [PubMed: 21185505]
6. Zareba KM, Lavigne JE, Lipshultz SE. Cardiovascular effects of HAART in infants and children of HIV-infected mothers. *Cardiovasc Toxicol*. 2004; 4:271–279. [PubMed: 15470274]
7. Stevens SM, Farzaneh-Far R, Na B, Whooley MA, Schiller NB. Development of an echocardiographic risk-stratification index to predict heart failure in patients with stable coronary artery disease: the Heart and Soul study. *JACC Cardiovasc Imaging*. 2009; 2:11–20. [PubMed: 19356527]
8. Das SR, Drazner MH, Yancy CW, Stevenson LW, Gersh BJ, Dries DL. Effects of diabetes mellitus and ischemic heart disease on the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure: a retrospective analysis from the Studies of Left Ventricular Dysfunction (SOLVD) Prevention trial. *Am Heart J*. 2004; 148:883–888. [PubMed: 15523322]
9. Starc TJ, Lipshultz SE, Easley KA, Kaplan S, Bricker JT, Colan SD, et al. Incidence of cardiac abnormalities in children with human immunodeficiency virus infection: The prospective P2C2 HIV study. *J Pediatr*. 2002; 141:327–334. [PubMed: 12219051]
10. McMahon CJ, Nagueh SF, Eapen RS, Dreyer WJ, Finkelstyn I, Cao X, et al. Echocardiographic predictors of adverse clinical events in children with dilated cardiomyopathy: a prospective clinical study. *Heart*. 2004; 90:908–915. [PubMed: 15253966]
11. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a

- branch of the European Society of Cardiology. *J Am Soc Echocardiogr.* 2005; 18:1440–1463. [PubMed: 16376782]
12. Eidem BW, McMahon CJ, Cohen RR, Wu J, Finkelshteyn I, Kovalchin JP, et al. Impact of cardiac growth on Doppler tissue imaging velocities: a study in healthy children. *J Am Soc Echocardiogr.* 2004; 17:212–221. [PubMed: 14981417]
 13. Nagueh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *J Am Soc Echocardiogr.* 2009; 22:107–133. [PubMed: 19187853]
 14. Cade W, Holland MR, Stephens AS, Reeds DN, Laciny DN, Cilbulka N, Overton ET, Singh GK. Decreased Myocardial Longitudinal Strain in HIV-Negative Neonates Exposed to HIV and HAART in Utero (abstract). *Antiviral Therapy.* 2009:14.
 15. Sohn DW, Chai IH, Lee DJ, Kim HC, Kim HS, Oh BH, et al. Assessment of mitral annulus velocity by Doppler tissue imaging in the evaluation of left ventricular diastolic function. *J Am Coll Cardiol.* 1997; 30:474–480. [PubMed: 9247521]
 16. Mondy KE, Gottdiener J, Overton ET, Henry K, Bush T, Conley L, et al. High Prevalence of Echocardiographic Abnormalities among HIV-infected Persons in the Era of Highly Active Antiretroviral Therapy. *Clin Infect Dis.* 2011; 52:378–386. [PubMed: 21217185]
 17. Reinsch N, Kahlert P, Esser S, Sundermeyer A, Neuhaus K, Brockmeyer N, et al. Echocardiographic findings and abnormalities in HIV-infected patients: results from a large, prospective, multicenter HIV-heart study. *Am J Cardiovasc Dis.* 2011; 1:176–184. [PubMed: 22254197]
 18. Hsue PY, Hunt PW, Ho JE, Farah HH, Schnell A, Hoh R, et al. Impact of HIV infection on diastolic function and left ventricular mass. *Circ Heart Fail.* 2010; 3:132–139. [PubMed: 19933410]
 19. Schuster I, Thoni GJ, Ederhy S, Walther G, Nottin S, Vinet A, et al. Subclinical cardiac abnormalities in human immunodeficiency virus-infected men receiving antiretroviral therapy. *Am J Cardiol.* 2008; 101:1213–1217. [PubMed: 18394461]
 20. Oliviero U, Bonadies G, Bosso G, Foggia M, Apuzzi V, Cotugno M, et al. Impaired diastolic function in naive untreated human immunodeficiency virus infected patients. *World J Cardiol.* 2010; 2:98–103. [PubMed: 21160704]
 21. Kelly K, Tarwater P, Karper J, Bedja D, Queen S, Tunin R, et al. Diastolic dysfunction is associated with myocardial viral load in simian immunodeficiency virus-infected macaques. *AIDS.* 2012
 22. Chang WT, Wu CC, Hung CC, Chen MY, Fang CT, Chen WJ, et al. Left ventricular dysfunction is associated with CD4 lymphocyte count rather than opportunistic infection in human immunodeficiency virus infection. *J Formos Med Assoc.* 2003; 102:158–163. [PubMed: 12783132]
 23. Longo-Mbenza B, Seghers LV, Vita EK, Tondouangu K, Bayekula M. Assessment of ventricular diastolic function in AIDS patients from Congo: a Doppler echocardiographic study. *Heart.* 1998; 80:184–189. [PubMed: 9813567]
 24. Cade WT, Reeds DN, Overton ET, Herrero P, Waggoner AD, Davila-Roman VG, et al. Effects of human immunodeficiency virus and metabolic complications on myocardial nutrient metabolism, blood flow, and oxygen consumption: a cross-sectional analysis. *Cardiovasc Diabetol.* 2011; 10:111. [PubMed: 22151886]
 25. Barker DJ. Fetal origins of coronary heart disease. *BMJ.* 1995; 311:171–174. [PubMed: 7613432]
 26. Meng Q, Lima JA, Lai H, Vlahov D, Celentano DD, Strathdee S, et al. Use of HIV protease inhibitors is associated with left ventricular morphologic changes and diastolic dysfunction. *J Acquir Immune Defic Syndr.* 2002; 30:306–310. [PubMed: 12131567]
 27. Lipshultz SE, Easley KA, Orav EJ, Kaplan S, Starc TJ, Bricker JT, et al. Absence of cardiac toxicity of zidovudine in infants. *Pediatric Pulmonary and Cardiac Complications of Vertically Transmitted HIV Infection Study Group.* *N Engl J Med.* 2000; 343:759–766. [PubMed: 10984563]
 28. Lewis W, Papoian T. Molecular mechanisms of heart muscle disease. *West J Med.* 1991; 154:91. [PubMed: 2024517]

29. Lewis W, Papoian T, Gonzalez B, Louie H, Kelly DP, Payne RM, et al. Mitochondrial ultrastructural and molecular changes induced by zidovudine in rat hearts. *Lab Invest.* 1991; 65:228–236. [PubMed: 1715447]
30. Gerschenson M, Poirier MC. Fetal patas monkeys sustain mitochondrial toxicity as a result of in utero zidovudine exposure. *Ann N Y Acad Sci.* 2000; 918:269–281. [PubMed: 11131713]
31. Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. *Lancet.* 1991; 337:508–510. [PubMed: 1671889]
32. Tan YT, Wenzelburger F, Lee E, Heatlie G, Leyva F, Patel K, et al. The pathophysiology of heart failure with normal ejection fraction: exercise echocardiography reveals complex abnormalities of both systolic and diastolic ventricular function involving torsion, untwist, and longitudinal motion. *J Am Coll Cardiol.* 2009; 54:36–46. [PubMed: 19555838]
33. Torres SM, March TH, Carter MM, McCash CL, Seilkop SK, Poirier MC, et al. In utero exposure of female CD-1 Mice to AZT and/or 3TC: I. Persistence of microscopic lesions in cardiac tissue. *Cardiovasc Toxicol.* 2010; 10:37–50. [PubMed: 20101476]
34. Bishop JB, Tani Y, Witt K, Johnson JA, Peddada S, Dunnick J, et al. Mitochondrial damage revealed by morphometric and semiquantitative analysis of mouse pup cardiomyocytes following in utero and postnatal exposure to zidovudine and lamivudine. *Toxicol Sci.* 2004; 81:512–517. [PubMed: 15229369]
35. McGrath CJNR, Richardson BA, Kristal AR, Mbori-Ngacha D, Farquhar C, John-Stewart GC. The Prevalence of Stunting Is High in HIV-1-Exposed Uninfected Infants in Kenya. *J Nutr.* 2012; 142:757–763. [PubMed: 22378334]

Table 1**Maternal and Child Demographics**

Variable	ART Unexposed (n=30)	ART Exposed (n=30)	p-value
Maternal			
Maternal age at birth (yrs)	30 ± 7	28 ± 7	0.38
Pre-pregnancy height (cm)	165.4 ± 7.4	167.3 ± 6.2	0.33
Pre-pregnancy weight (kg)	86.6 ± 19.1	79.3 ± 25.7	0.37
Pregnancy weight (kg)	93.8 ± 21.0	89.7 ± 27.0	0.58
Gestational weight gain (kg)	14.9 ± 7.2	12.1 ± 6.7	0.23
Smoking during pregnancy (%)	17	20	1.00
Known illegal drug use (%)	7	17	0.44
Prior HTN/Pre-eclampsia (%)	17	10	0.26
3rd trimester SBP (mmHg)	125.2 ± 17.5	113.3 ± 14.9	0.01
3rd trimester DBP (mmHg)	73.5 ± 12.4	66.8 ± 11.1	0.05
HIV duration (yrs)	N/A	5.9 ± 5.0	
Nadir CD4 (cells/mm ³)	N/A	261 ± 204	
3rd trimester CD4 (cells/mm ³)	N/A	469 ± 274	
3rd trimester viral load (copies/ml)			
<400 (%)	N/A	83	
400-1000 (%)	N/A	3	
>1000 (%)	N/A	14	
Child			
Age (yrs)	8 ± 2	8 ± 3	0.38
Sex (Male/Female, %)	(63/37)	(63/37)	
Race (African American/Caucasian/ Mixed, %)	(74/20/6)	(76/20/4)	
Gestational age at birth (wks)	38.4 ± 1.9	37.5 ± 2.9	0.15
Birth weight (kg)	3.2 ± 0.5	2.9 ± 0.7	0.21
Birth length (cm)	49.2 ± 1.9	49.0 ± 4.3	0.82
APGAR 1-min	8.0 ± 1.2	7.5 ± 1.6	0.26
Current height (cm)	131.9 ± 16.5	131.6 ± 19.2	0.95
Current weight (kg)	35.8 ± 15.0	35.0 ± 17.7	0.73
BMI (kg/m ²)	19.2 ± 5.0	19.0 ± 5.2	0.89
BMI percentile (%)	71 ± 27	65 ± 34	0.49
Body surface area (m ²)	1.1 ± 0.3	1.1 ± 0.3	0.84
Tanner stage	1.6 ± 0.9	1.7 ± 0.8	0.66
Organized sport participations (%)	57	30	0.07
Vigorous activity > 1 hr/day (%)	90	100	0.24
Estimated television viewing	2.4 ± 0.9	3.9 ± 1.9	0.01

Values are mean ± SD. ART: antiretroviral therapy, HTN: hypertension, OGTT: oral glucose tolerance test, BMI: body mass index.

Table 2**Echocardiographic Parameters of Children**

Variable	Born to HIV(–) Women (n=30)	Born to HIV(+) Women (n=30)	p-value
HR (bpm)	85 ± 13 (60-108)	89 ± 11 (71-110)	0.14
SBP (mm/Hg)	97 ± 11 (72-117)	96 ± 13 (70-119)	0.80
DBP (mm/Hg)	58 ± 7 (40-70)	57 ± 7 (46-70)	0.52
LV structure			
LVM (g)	76 ± 27 (35-132)	69 ± 27 (34-142)	0.27
LVMi	67 ± 12 (44-98)	60 ± 9 (43-75)	0.02
EDV (mL)	51 ± 14 (33-92)	49 ± 17 (27-94)	0.63
ESV (mL)	21 ± 10 (10-61)	19 ± 8 (8-43)	0.35
LV systolic function			
EF (%)	61 ± 7 (51-72)	61 ± 6 (50-70)	0.81
FS (%)	36 ± 5 (27-46)	36 ± 5 (25-51)	0.46
LVOT TVI (cm/s)	17.6 ± 3.2 (11.8-24.8)	17.3 ± 3.4 (11.3-23.8)	0.73
LVET (ms)	254 ± 24 (221-304)	252 ± 22 (208-300)	0.76
LV S' sep	8.4 ± 0.7 (7-9)	9.1 ± 1.3 (7-11)	0.70
LV S' ave (cm/s)	9.3 ± 1.1 (7.5-11.5)	9.1 ± 1.3 (7.0-11.5)	0.59
Global Strain (%)	–22.3 ± 3.2 (–16.2––30.7)	–21.1 ± 2.7 (–17.1––29.1)	0.13
LV diastolic function			
E wave (cm/s)	95 ± 14 (51-116)	89 ± 14 (54-115)	0.17
E/A ratio	2.1 ± 0.5 (1.0-3.2)	1.8 ± 0.4 (1.0-3.0)	0.09
Deceleration time (ms)	148 ± 21 (113-195)	144 ± 27 (111-192)	0.47
IVRT (ms)	55 ± 6 (44-66)	57 ± 11 (39-80)	0.38
E' sep (cm/s)	13.8 ± 2.1 (10-16)	13.6 ± 1.7 (10-16)	0.74
E' ave (cm/s)	16.3 ± 2.5 (11.8-21.5)	15.0 ± 2.2 (10.0-17.5)	0.03
E/E'	6.0 ± 1.0 (4.4-7.7)	6.1 ± 1.1 (3.5-8.4)	0.88
MPI	0.43 ± 0.12 (0.21-0.65)	0.4 ± 0.1 (0.29-0.58)	0.63

Values are mean ± SD. Range provided in parentheses. HIV: human immunodeficiency virus, HR: heart rate, bpm: beats per minute, SBP: systolic blood pressure, DBP: diastolic blood pressure, mmHg: mL of mercury, LV: left ventricle, LVM: left ventricular mass measured by M-mode echocardiography, EDV: end diastolic volume, ESV: end systolic volume, EF: ejection fraction, FS: fractional shortening, LVOT TVI: left ventricular outflow tract time velocity integral, LVET: left ventricular ejection time, S' sep: systolic myocardial velocity measured at septum, S' ave: systolic myocardial velocity averaged from septum and lateral wall, E wave: mitral inflow during early diastole measured by Doppler imaging, E/A ratio: early to late mitral inflow during diastole measured by Doppler imaging, E' sep: myocardial velocity during early diastole measured at septum, E' ave: myocardial velocity during early diastole averaged from septum and lateral wall, MPI: myocardial performance index.