High Prevalence of Echocardiographic Abnormalities among HIV-infected Persons in the Era of Highly Active Antiretroviral Therapy

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Background. In the era of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV)–infected persons have higher cardiovascular disease risk. Little is known about asymptomatic abnormalities in cardiac structure and function in this population.

Methods. The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) is a prospective, observational, multi-site cohort of 656 HIV-infected participants who underwent baseline echocardiography during 2004–2006. We examined prevalence of and factors associated with left ventricular systolic dysfunction (LVSD), diastolic dysfunction (DD), pulmonary hypertension (PHTN), left ventricular hypertrophy (LVH), and left atrial enlargement (LAE).

Results. Participant characteristics were as follows: median age, 41 years; 24% women; 29% non-Hispanic black; 73% receiving HAART; and median CD4+ cell count, 462 cells/μL. Among evaluable participants, 18% had LVSD, 26% had DD, 57% had PHTN (right ventricular pressure >30 mm Hg), 6.5% had LVH, and 40% had LAE. In multivariate analyses, significant factors ($P < .05$) associated with LVSD were history of MI, elevated highly sensitive C-reactive protein (hsCRP) level, and current tobacco smoking; for DD, elevated hsCRP level and hypertension; for PHTN, current use of ritonavir; for LVH, hypertension, diabetes, non-white race, female sex with elevated body mass index, calculated as the weight in kilograms divided by the square of height in meters, of ⩾25, elevated hsCRP level, and current use of abacavir; for LAE, hypertension and recent marijuana use.

Conclusions. In this large contemporary HIV cohort, the prevalence of subclinical functional and structural cardiac abnormalities was greater than expected for age. Abnormalities were mostly associated with expected and often modifiable risks. Lifestyle modification should become a greater priority in the management of chronic HIV disease.

Since the introduction of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) infection has evolved into a chronic disease in which patients may continue to receive HAART indefinitely [1]. Consequently, there is concern about long-term outcomes because of adverse effects of HAART and HIV infection. Atherogenic complications have been observed both among patients treated with HAART [2–4] and among untreated patients with low CD4+ cell counts [5]. Few studies have reported the prevalence of important abnormalities in cardiac structure and function among persons taking HAART [6, 7]. In the pre-HAART era, a large echocardiographic study involving 952 asymptomatic HIV-infected persons found that 8% of subjects had dilated cardiomyopathy, which was associated with lower CD4+ cell

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count, use of zidovudine, and the presence of myocarditis [8]. Another study with only 61 subjects suggested echocardiographic abnormalities were related to poor nutritional status [9].

In the HAART era, emerging data suggest that echocardiographic abnormalities may not be improved by HAART or immune reconstitution. The large, prospective P2C2 multicenter study involving HIV-infected children found a high prevalence (18%) of mild left ventricular (LV) dysfunction and progressive increase in LV mass over the course of the study, leading to a 12% 5-year cumulative incidence of congestive heart failure and overall higher risk of all-cause mortality in subjects with even mild cardiac abnormalities [10]. Case reports have linked nucleoside reverse-transcriptase inhibitor (NRTI) use to adverse cardiac function, possibly from mitochondrial toxicity [11–13]. Protease inhibitors (PIs) have also been implicated in adversely affecting cardiac function [6, 14]. One small study comparing HIV-infected persons receiving a PI-containing regimen with patients receiving a non–PI-containing regimen found a significant increase in LV hypertrophy and diastolic dysfunction in the group exposed to PIs [6]. However, most PI-exposed subjects were actively using illicit drugs or alcohol (cocaine use, 93%; alcohol use, 66%), and 42% of subjects were receiving first-generation PIs (eg, indinavir or high-dose ritonavir), which have been associated with pro-atherogenic complications [15, 16]. Studies have also found a higher prevalence of pulmonary hypertension among HIV-infected patients, compared with the general population, in both the pre-HAART and HAART eras [17, 18]. These results have conflicted with regard to the relative contribution of antiretroviral exposure to pulmonary hypertension risk [19–21].

The Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy (SUN Study) is a prospective, observational, multi-site closed cohort study designed to monitor the incidence of complications, such as cardiac disease, in contemporary HIV-infected patients and to identify risk factors for the development of such complications [22]. As part of the SUN study, we performed resting echocardiography, including Doppler tissue imaging, for SUN Study participants to determine the prevalence of 5 asymptomatic cardiac abnormalities: LV systolic dysfunction, diastolic dysfunction, pulmonary hypertension, LV hypertrophy, and left atrial (LA) enlargement. We also measured multiple other metabolic, clinical, and behavioral parameters in subjects to explore factors associated with these cardiac abnormalities.

METHODS

The SUN Study

The SUN Study is a prospective, observational cohort funded by the Centers for Disease Control and Prevention (CDC) that monitors the clinical course of HIV-infected individuals treated with HAART from 7 HIV-specialty clinics in 4 US cities: St. Louis, Missouri; Providence, Rhode Island; Minneapolis, Minnesota; and Denver, Colorado [22]. Data collection (except imaging) occurred at the clinic site and coincided with subjects' schedule of routine care. Imaging studies were obtained at a single site within each city. Seven hundred HIV-infected patients were enrolled from March 2004 through June 2006. The study's design, and its data collection and management methods have been described previously [22]. Participants were generally healthy HIV-infected patients receiving routine outpatient care whose entire antiretroviral experience consisted only of HAART. Patient data, including sociodemographic characteristics and all symptoms, signs, diagnoses, treatments, and laboratory data, were abstracted from medical charts and entered into an electronic database (Clinical Practice Analyst; Cerner) by trained staff. These data are reviewed for quality and are analyzed centrally. Additional data were collected through physical examination, noninvasive imaging (echocardiogram, carotid intima-media thickness [cIMT], coronary computed tomography, and dual-energy X-ray absorptiometry [DEXA]), comprehensive testing for sexually transmitted diseases, and validated audio computer-assisted self-interview (ACASI) [23, 24]. The ACASI collected behavioral risk data and other health information, including family history and use of tobacco, alcohol and recreational drugs. The study protocol has been approved and is reviewed annually by the CDC and each site's institutional review board.

Laboratory Evaluation

Clinical laboratory testing was performed for CD4+ cell count and fasting high-density lipoprotein, low-density lipoprotein, total cholesterol, glucose, and HIV RNA levels using commercial assays at each site according to the health care provider's usual standard-of-care. Laboratory tests used for research only (insulin, highly-sensitive C-reactive protein [hsCRP], and 25-OH vitamin D) were performed by the Diabetes Research and Training Center Radioimmunoassay Core Laboratory, Washington University School of Medicine (St Louis, MO), for all subjects. Serum and plasma used for these tests were aliquoted and stored at –70°C until time of batched assay. Fasting status was verified at the time of phlebotomy.

Echocardiographic Measurements

Echocardiograms were performed at the 4 participating sites according to standardized procedures described elsewhere [22, 25–28]. Studies were recorded on videotape and digitized offline on a commercially available workstation at a core laboratory (University of Maryland Medical Center, Baltimore). They were interpreted by a single experienced reader blinded to the study [22]. Of the total cohort of 700 participants, 656

(93.7%) of the patients had complete data for the present analysis.

The LV end diastolic and end systolic volumes were determined using the biplane modified Simpsons rule from apical 2- and 4-chamber views [26], after manual tracing of the endocardial borders by a single experienced reader. Ejection fraction was calculated as the difference between end diastolic and end systolic volume divided by end diastolic volume. Techniques for measurements and partition values for presence and degree of abnormality are described previously [26]. Briefly, LV mass was determined from anatomically correctly aligned linear measurements of LV cavity dimension and wall thickness; LA volume was computed from a modified biplane algorithm; pulmonary artery peak systolic pressure was determined from the highest peak velocity of the tricuspid regurgitant jet (present in 322 patients) obtained from several echocardiographic windows.

Functional and Structural Cardiac Outcomes

Five functional and structural cardiac outcomes were evaluated [26]. Systolic dysfunction was defined using the LV ejection fraction measurements from echocardiogram results and categorized as normal (≥55%), mildly decreased (45%–54%), moderately decreased (35%–44%), and severely decreased (<35%). Diastolic function was categorized [27] on the basis of values [28] of Doppler peak early (E) and late diastolic (A) mitral inflow velocity, mitral inflow deceleration time, and lateral mitral annular velocity (Em) on tissue Doppler. Normal diastolic function was defined as an E/A ratio of 1–2, deceleration time ≥220 msec, and Em > 8 cm/sec; abnormal relaxation (Grade 1 diastolic dysfunction) was defined as an E/A ratio < 1.0, deceleration time > 220 msec; pseudonormal (Grade 2 diastolic dysfunction) was defined as an E/A ratio 1–2, deceleration time 150–200 msec, and Em < 8 cm/sec; and restrictive (Grade 3 diastolic dysfunction) was defined as an E/A ratio > 2.0, deceleration time <150 msec, and Em < 8 cm/sec. Pulmonary hypertension was defined using right ventricular systolic pressure (RVSP) and calculated using the formula: $RVSP = 4V^2 + 10$ mm Hg, which was based on measurement of velocity of the systolic tricuspid regurgitation jet. Pulmonary hypertension was categorized as normal (15–30 mm Hg), borderline (31–35 mm Hg), mild (36–40 mm Hg), moderate (41–50 mm Hg), and severe (>50 mm Hg).

LV hypertrophy was defined based on LV mass calculated using a standard, validated formula [25, 26]. Values for LV mass were normalized to height [27] to adjust for influence of body size [29]. In men [26], LV hypertrophy was categorized as normal (<49 m^2), mild (49–55 m^2), moderate (56–63 m^2), and severe (≥64 m^2). In women [26], LV hypertrophy was categorized as normal (<45 m^2), mild (45–51 m^2), moderate (52–58 m^2), and severe (≥59 m^2).

LA enlargement was defined on the basis of LA volume calculated using the following formula: LA volume = (.85 A1 A2)/L)/BSA, where A1 = the area of the atrium in the 4-chamber view (cm^2), A2 = the area of the atrium in the 2-chamber view, L = the long axis length of the atrium (cm), and BSA = body surface area. LA enlargement was normalized for BSA and categorized [26] as normal (<29 mL/m^2), mild (29–33 mL/m^2), moderate (34–39 mL/m^2), and severe (>40 mL/m^2).

Statistical Analysis

For all analyses, cardiac outcomes of interest were redefined as dichotomized categorical variables where "normal" was evaluated versus all other categories. Univariate analyses of associations between cardiac outcomes and potential risk factors were performed using either Mantel-Hanzel X^2 or Fisher's exact test for categorical variables and Student's t test for continuous variables. Significant variables ($P < .10$) in univariate analysis or variables that had been found to be associated with functional and structural cardiac disease in previous studies were included in the multivariate logistic regression models. We first constructed full multivariate models, which included cardiac risk factors (eg, age, history of cardiovascular disease, and history of myocardial infarction) and all factors associated ($P \leq .10$) with the outcome of interest in univariate analyses. Using the backward elimination method, we then removed from the full model nonsignificant ($P > .05$) factors, starting with those having the highest P values, and constructed a parsimonious model, which included only variables independently ($P \leq .05$) associated with the outcome of interest. All analyses were performed using SAS statistical software, version 9.1 (SAS).

RESULTS

Patient Characteristics

Among the 656 participants with complete echocardiographic and clinical data, the mean age was 41 years (interquartile [IQR] range, 35–47 years), 24% were women, 29% were non-Hispanic black, and 10% were Hispanic. The median CD4+ cell count was 462 cells/mm^3 (IQR, 326–661 cells/mm^3), and 73% of subjects were currently prescribed HAART, of whom 91% had an HIV RNA level <400 copies/mL. Additional characteristics are shown in Table 1.

Prevalence of Echocardiographic Abnormalities

Eighteen percent and 26% of participants with available data had abnormal systolic and diastolic dysfunction, respectively. One participant (<1%) had severe systolic dysfunction (LV ejection fraction <35%), and 61 (9%) of participants had severe (Grade 3/restrictive) diastolic dysfunction. Of 322 participants with detectable tricuspid regurgitant flow, 50% had

Table 1. Baseline Characteristics of SUN Study Participants who Underwent Echocardiography

Characteristic	Participants (n = 656)
Age, median years (IQR)	41 (35–47)
Sex	
Male	501 (76)
Female	155 (24)
Race	
White	389 (59)
Black	187 (29)
Hispanic	66 (10)
Other/Unknown	14 (2)
Duration since HIV diagnosis, median years (IQR)	6.0 (2.3–8.1)
History of opportunistic infection	121 (19)
Co-infection with hepatitis B	21 (5)
Co-infection with hepatitis C	84 (13)
Diagnosis of hypertension	199 (30)
Diagnosis of diabetes	45 (7)
Diagnosis of chronic kidney disease	12 (2)
History of myocardial infarction	5 (1)
Diagnosis of congestive heart failure	1 (<1)
Diagnosis of pulmonary hypertension	3 (<1)
Receiving llipid-lowering therapy	65 (10)
Current smoker	280 (44)
Current drug use	
Cocaine	80 (13)
Marijuana	200 (31)
Inhaled nitrites	123 (10)
Heroin or methamphetamine	44 (7)
Receiving HAART	478 (73)
HIV RNA level <400 copies/mL	435 (91)
Type of HAART	
Ritonavir-boosted PI	181 (38)
Unboosted PI	40 (8)
NNRTI	230 (48)
Three or more NRTIs	41 (9)
Duration of HAART, median years (IQR)	2.3 (0.6–5.0)
CD4+ count, median cells/mm^3 (IQR)	
Current	462 (326–661)
Nadir	211 (93–324)
BMI, median value (IQR)	25.5 (22.8–28.6)
Glucose level, median mg/dL (IQR)	92 (84–99)
Total cholesterol level, median mg/dL (IQR)	180.5 (154–208)
LDL level, median mg/dL (IQR)	105 (84–130)
HDL level, median mg/dL (IQR)	40 (33–50)
TG level, median mg/dL (IQR)	138 (95–212)
Insulin level, median mg/dL (IQR)	8.7 (5.4–13.8)
hsCRP, median μg/L (IQR)	1.8 (0.8–4.5)
25-Hydroxy-vitamin D, median mg/dL (IQR)	23.2 (15.1–31.3)
Carotid IMT, median mm (IQR)	0.71 (0.65–.80)

NOTE. Data are no. (%) of participants, unless otherwise indicated. HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; IMT, intima media thickness; IQR, interquartile range; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; SEM, standard error of the mean; SUN study, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy; TG, triglyceride.

Table 2. Echocardiographic Characteristics of SUN Study Participants

Characteristic	No. (%) of participants	Mean value (±SD)	Range
Left ventricular systolic dysfunction (n = 652)			
Normal: ⩾55%	533 (82)	61.0 + 4.2	55.0–77.1
Mild: 45%–55%	116 (18)	53.3 + 1.5	45.4–55.0
Moderate: 35%–45%	2 (<1)	42.9 + 0.4	42.7–43.2
Severe: <35%	1 (<1)	31.4	–
Left ventricular diastolic function (n = 647)			
Grade 0: normal	477 (74)	–	–
Grade 1: impaired relaxation	97 (15)	–	–
Grade 2: pseudonormal	12 (2)	–	–
Grade 3: restrictive	61 (9)	–	–
Pulmonary hypertension (RVP mm Hg) (n = 322)			
Normal: < 31	139 (43)	27.1 + 2.9	14.4–30.97
Borderline abnormal: 31–35	109 (34)	33.2 + 1.4	31.06–35.99
Mildly abnormal: 36–40	52 (16)	38.2 + 1.4	36.1–40.9
Moderately abnormal: 41–50	17 (5)	44.9 + 3.0	41.1–49.9
Severely abnormal: ⩾50	5 (2)	67.8 + 16.9	54.8–90.3
Left ventricular mass (g/m$^{2.7}$) (n = 644)			
Normal: (<45 for women; <49 for men)	602 (93)	33.0 + 6.2	10.2–48.8
Mildly abnormal: (45–51 for women; 49–55 for men)	26 (4)	49.2 + 2.6	45.3–55.9
Moderately abnormal (52–58 for women; 56–63 for men)	8 (1)	58.0 + 3.0	54.0–62.7
Severely abnormal: (⩾59 for women; ⩾64 for men)	8 (1)	83.3 + 30.3	60.7–151.4
Left atrial volume (ml/m^2 BSA) (n = 631)			
Normal: <29	378 (60)	23.4 + 3.8	11.0–29.0
Mildly abnormal: 29–33	133 (21)	31.4 + 1.5	29.1–34.0
Moderately abnormal: 34–39	70 (11)	36.5 + 1.6	34.2–40.0
Severely abnormal: ⩾40	50 (8)	45.3 + 6.2	40.1–71.2

NOTE. SUN study, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

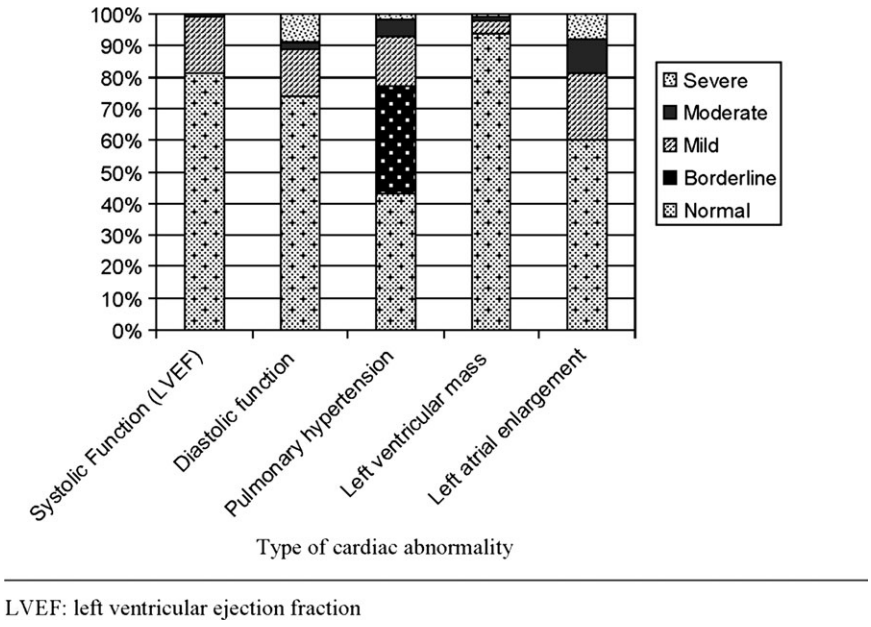

Figure 1. Distribution of cardiac abnormalities among Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy participants. LVEF, left ventricular ejection fraction.

Table 3. Predictors of Echocardiographic Abnormalities among SUN Study Participants

Abnormality, associated factor	Odds ratio	95% CI	*P*
Left ventricular systolic dysfunction			
History of myocardial infarction	15.9	1.94–329	.019
hsCRP level >5 μg/L	1.70	1.03–2.77	.033
Current tobacco smoking	1.57	1.03–2.34	.036
Diastolic dysfunction			
hsCRP level >5 μg/L	1.61	1.05–2.46	.027
Diagnosis/treatment of hypertension	1.87	1.24–2.82	.003
Pulmonary hypertension			
Current use of ritonavir	1.75	1.04–3.00	.037
Left ventricular hypertrophy			
Diagnosis/treatment of hypertension	3.56	1.57–8.25	.002
Diagnosis/treatment of diabetes	4.51	1.60–12.1	.003
Non-Hispanic black race or Hispanic	3.30	1.43–8.15	.006
Women with BMI > 25	3.40	1.43–8.05	.005
hsCRP level >5 μg/L	2.69	1.20–6.02	.015
Current use of abacavir	3.88	1.63–9.20	.002
Left atrial enlargement			
Diagnosis/treatment of hypertension	1.66	1.14–2.41	.008
Marijuana use within last 6 months	1.56	1.10–2.22	.013

NOTE. BMI, body mass index, calculated as the weight in kilograms divided by the square of height in meters; hsCRP: high sensitivity C-reactive protein; SUN study, Study to Understand the Natural History of HIV/AIDS in the Era of Effective Therapy.

borderline/mild pulmonary hypertension and 7% had moderate-to-severe pulmonary hypertension. No subjects had significant valvular disease other than tricuspid regurgitation. Six percent and 40% of participants had some degree of LV hypertrophy or LA enlargement, respectively. Further detailed listing of cardiac abnormalities is shown in Table 2, and distribution of cardiac abnormalities is shown in Figure 1. Only a third of participants had no abnormality detected on echocardiogram.

Factors Associated With Echocardiographic Abnormalities

In univariate analyses, factors significantly associated ($P \leq .05$) with systolic dysfunction were male sex, current tobacco smoking, ever having used cocaine, and hepatitis C co-infection. Factors significantly associated with diastolic dysfunction were diagnosis of hypertension, lower nadir CD4+ cell count, elevated fasting glucose level, and elevated hsCRP level. Factors significantly associated with pulmonary hypertension were current use of a ritonavir-boosted PI and higher cIMT (cIMT $\geq$ .80 mm). Factors significantly associated with LV hypertrophy were female sex, non-Hispanic black race, higher body mass index (BMI; calculated as the weight in kilograms divided by the square of height in meters), diagnosis of hypertension or diabetes, hepatitis C co-infection, elevated fasting glucose level, higher fasting insulin level, elevated hsCRP level, lower vitamin D level, lower nadir CD4+ cell count, higher visceral fat content by DEXA, higher cIMT level, and current use of abacavir. Factors significantly associated with LA enlargement were older age, non-Hispanic black race, diagnosis of hypertension, recent use of marijuana or cocaine, and lower triglyceride level; use of efavirenz was protective ($P = .004$).

In multivariate analyses, factors significantly associated with systolic dysfunction were having a history of a myocardial infarction, elevated hsCRP level, and current tobacco smoking (Table 3). Factors significantly associated with diastolic dysfunction were diagnosis of hypertension and elevated hsCRP level. Current ritonavir-boosted PI use was the only factor significantly associated with pulmonary hypertension. Hypertension, race other than non-Hispanic white, female sex with BMI $\geq$25, diagnosis of diabetes, current abacavir use, and elevated hsCRP level were significantly associated with LV hypertrophy. Factors significantly associated with LA enlargement were hypertension and recent marijuana use. Other immunologic and virologic variables (nadir/current CD4+ cell count, HIV RNA level, and prior AIDS diagnosis) were included in these multivariate analyses, but no significant associations were found. Analyses of participants with tobacco or drug use history, however, found low CD4+ cell count nadir (<200 cells/mm^3) to be a significant risk factor for systolic dysfunction (for current marijuana use: odds ratio [OR], 3.96; 95% confidence interval [CI], 1.76–9.64; for ever having used tobacco, OR, 1.77; 95% CI, 1.07–2.96). Only 16% of participants were HAART-naive; statistical power was inadequate to compare echocardiographic abnormalities between HAART-experienced and HAART-naive subjects.

DISCUSSION

In this large cohort of generally healthy HIV-infected patients, cardiac abnormalities were commonly detected by echocardiography, despite the relatively young age and high CD4+ cell counts of participants. The prevalence of diastolic and systolic dysfunction and pulmonary hypertension were particularly notable. In the general population, incidence of primary pulmonary hypertension is 1–2 cases per million persons [30]. Although prevalence estimates of asymptomatic diastolic or systolic dysfunction for younger adults are not established, in a study involving >2000 randomly selected persons (minimum age, 45 years), the prevalence of diastolic dysfunction was 28% [31]. Prevalence of mild-to-moderate systolic dysfunction was 3%–5% [31, 32]. SUN Study participants also had a high prevalence of LA enlargement, which is an independent predictor of risk for cardiovascular disease, heart failure, and stroke in the general population [33, 34]. In comparison, a recent general population estimate of LA enlargement (age range, 25–

74 years) was only 9.8% [35]. Unfortunately, echocardiographic data is lacking for tobacco smokers and recreational drug users within the general population.

Many factors associated with the echocardiographic abnormalities identified in the present study were traditional risk factors: these included hypertension, diabetes, tobacco smoking, and elevated BMI. Interestingly, women rather than men were at greater risk for LV hypertrophy due to BMI. In the SUN Study cohort, the majority of women with BMI $\geqslant$25 were also non-Hispanic black (60%).

Elevated hsCRP level, which is a risk factor for cardiovascular disease among HIV-seronegative persons [36, 37], was also associated with risk for echocardiographic abnormalities. The use of hsCRP level as a predictor of increased cardiovascular disease risk in HIV-infected persons, however, has yielded conflicting results [38–40]. HIV itself causes chronic immune activation and elevation in inflammatory biomarkers [41–43], but there are no studies suggesting hsCRP level adds to traditional risk factors in the evaluation of cardiovascular disease risk in this population [44].

When analyzing HAART as a contributor to echocardiographic abnormalities, we found that cumulative duration of therapy was not a significant factor. When analyzing the use of specific drugs, we found that current use of a ritonavir-boosted PI and abacavir were independently associated with pulmonary hypertension and LV hypertrophy, respectively. In the large Data Collection on Adverse Events of Anti-HIV Drugs Study, subjects taking abacavir had a nearly doubled relative risk of myocardial infarction over 5 years of follow-up [45]. This risk was restricted to recent or current use of abacavir and waned with its discontinuation. Importantly, the absolute risk of myocardial infarction remained quite low (1.6% over a 5-year period). Analyses from another large HIV cohort, the SMART study, found abacavir to be associated with increases in inflammatory biomarkers (interleukin 6 and C-reactive protein) among participants [43]. Whether these inflammatory and vascular effects of abacavir may affect cardiac remodeling requires additional investigation.

Studies that have examined the contribution of PI-containing HAART to pulmonary hypertension have yielded conflicting results [19–21]. An in vitro study found that specific antiretrovirals (including ritonavir) can impair endothelium-dependent relaxation of pulmonary artery endothelial cells [46]. Clinical trial data, however, suggest that endothelial function is impaired by HIV itself and improves with HAART [42]. In this study, we found no association of pulmonary hypertension with CD4+ cell count, HIV viremia, or length of time since HIV diagnosis.

Notably, in this study, age was not independently associated with any echocardiographic abnormality. The prevalence of pulmonary hypertension, systolic and diastolic dysfunction, and LA enlargement were higher than what would be expected on the basis of the mean age of this cohort [17, 18, 31]. Other traditionally aging-associated processes (osteoporosis, kidney dysfunction, and cardiovascular disease) have also been more prevalent among HIV-infected persons receiving HAART, compared with seronegative persons of similar age [47–50]. We hypothesize that HIV infection itself or exposure to antiretrovirals might accelerate the changes in cardiac morphology that typically occur later in life in response to effects of traditional risk factors (eg, age and hypertension). Such a hypothesis will require longitudinal study.

There were some limitations to this study. The current analysis was cross-sectional, but included a very large number of subjects, compared with most other echocardiographic studies of HIV infection [6,7,9]. We did not have a suitable HIV-seronegative control group, but we nonetheless found higher-than-expected prevalence rates for several cardiac outcomes, compared with general population data [17, 18, 31, 32, 35], thus suggesting important effects of HIV, HAART, or specific risk behaviors on cardiac function.

Variability may exist with methods used in estimating RVSP and diastolic function. RVSP was estimated using a fixed constant of 10 mm Hg added to the Doppler estimation of right ventricular-right atrial gradient, as is common clinical and investigative practice [51]. However, RA pressure may vary, and actual normal RA pressure is $<$10 mm Hg. Because few participants were expected to have medical conditions with an extreme RA pressure, additional adjustment of estimated RVSP was not necessary for this analysis.

In conclusion, in the current HAART era, we detected a significant prevalence of subtle yet important echocardiographic abnormalities in a large, generally healthy cohort of HIV-infected adults. Although the pathophysiologic mechanisms underlying these findings remain unknown, our results support lifestyle modifications, such as cessation of smoking and weight loss, as continued priorities in the chronic management of HIV infection. HAART substantially reduces both early and late morbidity and mortality from HIV infection and from a growing list of non–HIV-related conditions [52]. Recommendations to alter an individual's HAART regimen solely to prevent cardiac disease cannot be made on the basis of this study alone. Ongoing longitudinal studies will help determine whether our findings have any significant impact on future heart function and the relative contribution that treatment-related and non–treatment-related factors have on progression, incidence, and prevention of cardiac disease.

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