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ORIGINAL RESEARCH

Associations Between HIV Serostatus and Cardiac Structure and Function Evaluated by 2-Dimensional Echocardiography in the Multicenter AIDS Cohort Study

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BACKGROUND: We aimed to investigate whether there are differences in cardiac structure and systolic and diastolic function evaluated by 2-dimensional echocardiography among men living with versus without HIV in the era of combination antiretroviral therapy.

METHODS AND RESULTS: We performed a cross-sectional analysis of 1195 men from MACS (Multicenter AIDS Cohort Study) who completed a transthoracic echocardiogram examination between 2017 and 2019. Associations between HIV serostatus and echocardiographic indices were assessed by multivariable regression analyses, adjusting for demographics and cardiovascular risk factors. Among men who are HIV+, associations between HIV disease severity markers and echocardiographic parameters were also investigated. Average age was 57.1±11.9 years; 29% of the participants were Black, and 55% were HIV+. Most men who were HIV+ (77%) were virally suppressed; 92% received combination antiretroviral therapy. Prevalent left ventricular (LV) systolic dysfunction (ejection fraction <50%) was low and HIV serostatus was not associated with left ventricular ejection fraction. Multivariable adjustment models showed that men who were HIV+ versus those who were HIV– had greater LV mass index and larger left atrial diameter and right ventricular (RV) end-diastolic area; lower RV function; and higher prevalence of diastolic dysfunction. Higher current CD4+ T cell count ≥400 cell/mm^3 versus <400 was associated with smaller LV diastolic volume and RV area. Virally suppressed men who were HIV+ versus those who were HIV– had higher indexed LV mass and left atrial areas and greater diastolic dysfunction.

CONCLUSIONS: HIV seropositivity was independently associated with greater LV mass index, left atrial and RV sizes, lower RV function and diastolic abnormalities, but not left ventricular ejection fraction, which may herald a future predisposition to heart failure with preserved ejection fraction among men living with HIV.

Key Words: antiretroviral therapy ■ atria ■ cardiac remodeling ■ diastolic dysfunction ■ echocardiography ■ HIV/AIDS ■ subclinical cardiovascular disease

Combination antiretroviral therapy (cART) has transformed infection with HIV from a deadly condition into a chronic treatable disorder. As lifespans increase, people living with HIV (PLWH, HIV+) are increasingly susceptible to diseases associated with aging, particularly cardiovascular disease.[1] Increased cardiovascular disease risk in HIV is postulated to be multifactorial with potential

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CLINICAL PERSPECTIVE

What Is New?

- In a large cohort study of similar men living with and without HIV, compared with men who were HIV seronegative, we identified abnormalities in echocardiographic structure and function in men who were HIV seropositive consisting of greater left ventricular (LV) mass index, left atrial and right ventricular sizes, lower right ventricular function and diastolic abnormalities (e' velocity, E/e' ratio, and diastolic dysfunction), but not LV ejection fraction.
- Among the virally suppressed men who were HIV seropositive, there remained significant increases in indexed LV mass, left atrial diameter, and indexed left atrial area as well as decreased mitral e' velocity and increased E/e' ratio and a trend toward increased prevalence of diastolic dysfunction, compared with men who were HIV seronegative.

What Are the Clinical Implications?

- While LV systolic dysfunction is rare among people living with HIV, HIV infection remains an independent risk factor associated with small subclinical differences in cardiac structural and functional indices, despite HIV viral suppression and extensive multivariable adjustment, in the modern combination antiretroviral therapy era.
- Differences in LV mass and LV diastolic function and their upstream effects on left atrial and right ventricular indices among men who are HIV seropositive could be markers of increased risk for progression to heart failure with preserved ejection fraction that deserves further study.

Nonstandard Abbreviations and Acronyms

cART	combination antiretroviral therapy
CHART Study	Characterizing Heart Function on Antiretroviral Therapy Study
DD	diastolic dysfunction
HFpEF	heart failure with preserved ejection fraction
MACS	Multicenter AIDS Cohort Study
PLWH	people living with HIV

contributions from immune dysregulation and inflammation; accelerated aging; comorbidities; adverse metabolic side effects of older-generation ART; and environmental factors.[2–5] Recent studies suggest increased prevalence and incidence of heart failure (HF) among PLWH compared with matched controls who are HIV-uninfected (HIV–), with a shift towards HF with preserved ejection fraction (HFpEF), rather than historically more prevalent HF with reduced ejection fraction seen pre-cART.[6] There remains a residual, but poorly understood, association between HIV infection and HF risk not abrogated by HIV viral suppression that warrants further study.[7] In HIV-uninfected cohorts, early detection of subclinical abnormalities in cardiac structure and function by echocardiography can presage the occurrence of clinical events such as HF.[8] When applied to PLWH, echocardiography can add to our understanding of the extent to which HIV infection independently contributes to myocardial dysfunction in the cART era and help illuminate associated risk factors.

Prior studies investigating cardiac structure and function by echocardiography among PLWH have been small in size and/or lacking in a control group or comparable HIV-uninfected referents,[9–12] limiting conclusions. Comparison of subclinical myocardial abnormalities in a large, contemporary HIV community-based cohort of durably suppressed PLWH with comparable HIV-uninfected individuals has not been previously performed. Here, we hypothesized that there are differences in the association between HIV serostatus and adverse cardiac remodeling evaluated by 2-dimensional (2D) echocardiography, particularly for diastolic indices. We studied this hypothesis in a large multicenter, longitudinal study of men with and without HIV who have similar lifestyles and characteristics followed in the MACS (Multicenter AIDS Cohort Study). We focused on a salient HIV demographic in the United States, namely, predominantly middle-aged men who have sex with men, who comprise 86% of current HIV diagnoses in men,[13] are generally virally suppressed, and have high rates of traditional cardiovascular risk factors.

METHODS

Because of the sensitive nature of the data collected for this study, access to the data set from qualified researchers trained in human subject confidentiality protocols can be requested via the https://statepi.jhsph.edu/mwccs/ website or email address MWCCS@jhu.edu.

Study Population

The MACS[14] is a prospective observational cohort study of natural and treated histories of HIV-1 infection in men who have sex with men (with and without prevalent HIV at the time of enrollment) conducted at 5 US sites (Baltimore/Washington District of

Columbia; Chicago, Illinois; Pittsburgh, Pennsylvania; Columbus, Ohio; and Los Angeles, California). Men who have sex with men with and without HIV were recruited via combinations of media publicity, personal connections of both gay community groups and current participants in the study, promotional events or offerings (eg, raffles, medical screening), and previous clinical contacts with largely gay medical practices or through research on other conditions in gay men. MACS enrollment occurred over 4 enrollment waves: 1984 to 1985, 1987 to 1991, 2001 to 2003, and 2010 to 2018. Participants undergo biannual clinical research visits comprising standardized interviews, physical examinations, and blood specimen collection and storage. All active study participants were eligible and offered research echocardiograms. Institutional review boards from each field center and the coordinating center approved the study and all participants provided written informed consent. This cross-sectional analysis included 1195 men who completed a full transthoracic echocardiogram examination between October 2017 and January 2019. Echocardiograms were not obtained in 785 participants because of telephone/home rather than in-person visits (n=330), operational reasons (n=10), declined because of inconvenience (n=252), and no reason given (n=193). See Table S1 for clinical characteristics of the men who did and did not undergo the echocardiogram.

Covariates

Data collected included demographics (age, race), measured blood pressure, body mass index, smoking status, prescribed medications, alcohol use, cocaine use, history of cardiovascular disease, and laboratory values (fasting serum glucose, lipid levels, and estimated glomerular filtration rate). In PLWH, measures of HIV disease activity included plasma HIV RNA concentrations (quantified down to 20 copies/mL, COBAS AmpliPrep/COBAS TaqMan HIV-1 Test, version 2.0 [v2.0]), current and nadir CD4+ T cell counts, prior AIDS defining malignancy or opportunistic infection, and use of cART (duration and drug class including protease inhibitors, nucleoside reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, and integrase inhibitors).

Diabetes mellitus was defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes mellitus medications. Dyslipidemia was defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid-lowering medications. History of cardiovascular disease included a self-reported history of HF, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

Echocardiographic Assessment

Transthoracic echocardiography examinations were performed using an Artida ultrasound system (Toshiba Medical Systems, Otawara, Japan) by certified and centrally trained sonographers at all 5 MACS sites following standardized protocols based on the American Society of Echocardiography guidelines.[15] Briefly, participants were placed in a left lateral decubitus position for examination, utilizing parasternal long axis, parasternal short axis, apical 4-chamber, apical 2-chamber, and apical 3-chamber traditional views. The electrocardiographic tracing was recorded during the examination. All recording and measurements were done at end-expiration, with a full 3 cardiac cycle capture, increasing to 5 cardiac cycles if the heart rate exceeded 90 beats per minute or in the presence of arrhythmias.

Detailed quality control procedures were performed during the study period to assure adequate reproducibility and accuracy of the data. The echocardiograms were stored digitally and transferred electronically from each field center to the Johns Hopkins University Echo Reading Center using secure web-based technology, where experienced certified readers, using a standard software package (Digiview; Digisonics Systems, Houston, TX), analyzed the images following American Society of Echocardiography guidelines.[16]

Two-Dimensional Echocardiogram Acquisition and Analysis

A phased array PST-30BT 1.8 to 4.2 MHz transducer was used to acquire the 2D tissue harmonic imaging, color Doppler, pulse-wave Doppler, and continuous-wave Doppler. 2D LV end-diastolic volume, end-systolic volume, ejection fraction, left atrial (LA) area, and LA volumes were measured by the biplane disc method (modified Simpson's rule) in the 4- and 2-chamber views. LV mass was calculated using LV linear dimensions obtained from the parasternal long-axis view using the Devereux formula.[17] LA linear maximum anterior–posterior dimension was quantified in the parasternal long-axis view. Pulse wave Doppler echocardiography was used to measure the peak transmitral flow velocities from the early (E) and late (A) diastolic phases. Tissue Doppler imaging was applied to measure the early septal and lateral mitral annular diastolic peak velocities (septal and lateral e') and right ventricle (RV) annular S' peak velocity. Continuous-wave Doppler echocardiography was used to quantify the maximum tricuspid regurgitation jet velocity (TRJet). Right ventricular systolic pressure (RVSP) was estimated using the modified Bernoulli equation, assuming a right atrial pressure (RAP) estimate of 10 mm Hg ($RVSP=4\times[TRJet]^2+[RAP]$).

M-mode was applied to the lateral tricuspid annulus in the 4-chamber view to calculate the tricuspid annulus plane systolic excursion. Diastolic dysfunction was assessed using criteria proposed by the CHART (Characterizing Heart Function on Antiretroviral Therapy) study specifically for PLWH,[18] which comprise (1) left ventricular ejection fraction (LVEF) >50% and (2) septal e' <7 cm/s or lateral e' <10 cm/s; and (3) LA maximum volume index >28 mL/m^2 or LV hypertrophy (LV mass index >115 g/m^2) or concentric LV remodeling (relative wall thickness >0.42).

The intra- and interreader 2D echocardiography reproducibility was assessed by 2 readers in a random subset of 120 participants (≈10% of the total echocardiographic examinations). Re-readings were obtained 30 days after the initial analysis, blinded to the initial results.

Statistical Analysis

Continuous variables are described as medians (interquartile range [IQR]) and compared using the Wilcoxon rank-sum test. Categorical variables are presented as an absolute value (percentage) and compared using χ^2 statistics. Multivariable linear regression analyses were used to investigate the associations between HIV serostatus and cardiac structure and function, adjusting for the following:

Model 1: Age, race, body mass index (for echocardiographic metrics not normalized to body surface area), educational level, MACS site, and wave of MACS enrollment (before/after 2001);

Model 2: Model 1+further adjustment for heart rate, systolic blood pressure, antihypertensive medications, diabetes mellitus, dyslipidemia, smoking status, alcohol intake, history of cardiovascular disease, and history of cocaine consumption.

Using the same models above, we also performed an exploratory analysis among participants who were HIV+ to assess the association between the echocardiographic metrics and HIV disease severity factors and treatments.

A sensitivity analysis was also performed by excluding men with prior cardiovascular disease history. All statistical analyses were conducted using Stata 14.2 version for Windows (StataCorp LP, College Station, TX). A 2-tailed *P* value of <0.05 was considered statistically significant.

RESULTS

Participants' Characteristics

The study participants' characteristics by HIV serostatus are shown in Table 1; 55.4% of the cohort was HIV+. Compared with the HIV– group, men who were HIV+ were younger, more likely to be Black, had lower income, fewer years of traditional education, higher baseline heart rates, and lower systolic blood pressures. Most men who were HIV+ (509 [76.9%]) were virally suppressed (HIV RNA viral load <20 copies/mL), 609 (92.1%) were on cART, and the median nadir (before cART use) and most recent CD4+ T cell count were 320 cells/mm^3 (IQR 188.5–458) and 689 cells/mm^3 (IQR 496–885), respectively.

Two-Dimensional Echocardiogram Parameters

The 2D echocardiogram parameters by HIV serostatus are shown in Table 2. Median LVEF , LV end-diastolic volume index, LV end-systolic volume index, and LV mass index were normal at 61.4% (IQR, 58.5–64.3), 55.5 mL/m^2 (IQR, 48.8–63.0), 21.2 mL/m^2 (IQR, 18.1–25.0), and 87.7 g/m^2 (IQR, 75.4–100.1), respectively. The prevalence of LV systolic dysfunction (LVEF <50%) was low (2.2%).

Adjusted Association Between HIV Serostatus and Cardiac Structure and Function

In the final adjusted multivariable linear regression models (Table 3), men who were HIV+ had greater LV mass index (β=3.09 [95% CI, 0.62–5.56], *P*=0.014), greater LA diameter (β=0.08 [95% CI, 0.02–0.14], *P*=0.005), greater RV end-diastolic area (β=0.54 [95% CI, 0.06–1.01], *P*=0.027), lower tricuspid annulus plane systolic excursion (β=−0.05 [95% CI, −0.10 to −0.02], *P*=0.043), lower mitral annular e' velocity (β=−0.44 [95% CI, −0.71 to −0.18], *P*=0.001), and greater E/e' ratio (β=0.30 [95% CI, 0.02–0.59], *P*=0.048). HIV seropositivity was associated with diastolic dysfunction (DD) by CHART criteria using progressively adjusted logistic regression models (Model 1: odds ratio 1.53 [95% CI, 1.13–2.09], *P*=0.007; Model 2: odds ratio 1.43 [95% CI, 1.03–1.99], *P*=0.036) (Table 4).

Association Between HIV Disease Activity and Treatment and Cardiac Structure and Function

Among men who were HIV+, there were some associations between HIV viral load (VL), CD4+ count, and specific cART categories with cardiac structural and functional abnormalities (Table S2). Compared with men with VL ≥20 copies/mL, those with suppressed HIV VL <20 copies/mL had paradoxically larger LA areas and volumes, but lower RV annular S' peak velocity. Men with VL >500 copies/mL had lower early mitral annular diastolic peak velocities compared with men with VL <20 copies/mL. However, when comparing virally suppressed HIV seropositive (VL <20 copies/

Table 1. Clinical Characteristics of the Study Participants by HIV Serostatus

Clinical Characteristics	Total (n=1195)	HIV Seronegative (n=533)	HIV Seropositive (n=662)
Age, y	58.3 (50.6, 65.4)	62.2 (55.0, 68.8)	55.5 (48.9, 62.5)
Race			
White	744 (62.3)	386 (72.4)	358 (54.1)
Black	347 (29.0)	119 (22.3)	228 (34.4)
Other	104 (8.7)	28 (5.3)	76 (11.5)
Body mass index, kg/m^2	26.7 (23.8, 30.2)	26.7 (23.9, 30.4)	26.8 (23.6, 30.1)
Education <12th grade	271 (22.7)	84 (15.8)	187 (28.3)
Field center			
Baltimore	265 (22.2)	127 (23.8)	138 (20.9)
Chicago	270 (22.6)	105 (19.7)	165 (24.9)
Pittsburgh/Columbus	373 (31.3)	187 (35.1)	186 (28.1)
Los Angeles	287 (24.0)	114 (21.4)	173 (26.1)
Enrolled after 2001	637 (53.3)	198 (37.2)	439 (66.3)
Resting heart rate, bpm	66.2 (59.0, 74.0)	63.0 (57.7, 72.3)	68.0 (60.7, 75.3)
SBP, mm Hg	129 (117, 139)	132 (120, 142)	128 (118, 138)
On antihypertensive medication	481 (40.5)	224 (42.3)	257 (39.1)
Smoking status			
Never	374 (31.4)	178 (33.5)	196 (29.6)
Former and current smoking	818 (68.6)	353 (66.5)	465 (70.3)
Alcohol intake			
None	271 (22.7)	101 (19.0)	170 (25.7)
Low-heavy and binge drinking	921 (77.3)	430 (81.0)	491 (74.3)
Cocaine use	100 (8.5)	35 (6.6)	65 (10.0)
Diabetes mellitus*	169 (14.5)	68 (13.1)	101 (15.6)
Dyslipidemia†	829 (74.6)	370 (73.1)	459 (75.7)
History of cardiovascular events‡	70 (5.9)	36 (6.8)	34 (5.1)
HIV-specific disease activity and treatments			
Undetectable HIV RNA viral load (<20 copies/mL)			509 (76.9)
HIV RNA viral load (copies/mL)			
<20			509 (76.9)
20–499			99 (14.9)
≥500			54 (8.2)
Nadir CD4+ T cell count before cART (cells/mm^3) (absolute)			320 (188.5, 458.0)
Nadir CD4+ T cell count before cART (≥400 cells/mm^3)			227 (34.3)
Current CD4+ T cell count (cells/mm^3) (absolute)			689 (496, 885)
Current CD4+ T cell (≥400 cells/mm^3)			566 (85.5)
On cART			609 (92.1)
Duration of cART, y			13.4 (5.9, 17.6)
On PI			164 (24.8)
Cumulative years of PI use			5.3 (0, 12.5)
On NRTI			583 (88.2)
Cumulative years of NRTI use			14.1 (6.2, 19.6)
On NNRTI			196 (29.7)
Cumulative y of NNRTI			3.9 (0.1. 10.2)

(*Continued*)

Table 1. Continued

Clinical Characteristics	Total (n=1195)	HIV Seronegative (n=533)	HIV Seropositive (n=662)
On INSTI			386 (58.4)
Cumulative years of INSTI			1.2 (0, 3.6)
History of clinical AIDS			58 (8.8)

Data are presented as median (interquartile range) or n (%). bpm indicates beats per minute; cART, combination antiretroviral therapy; INSTI, integrase strand transfer inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitors; PI, protease inhibitor; and SBP, systolic blood pressure.

*Diabetes mellitus defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes mellitus medications.

†Dyslipidemia defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid-lowering medication.

‡History of cardiovascular events defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

mL) with HIV seronegative men, there remained significant increases in indexed LV mass (β=2.97 [95% CI, 0.31–5.63], *P*=0.029), LA diameter (β=0.08 [95% CI, 0.02–0.14], *P*=0.012), and indexed LA area (β=0.27 [95% CI, 0.06–0.48], *P*=0.011) as well as decreased mitral e' velocity (β=−0.42 [−0.70 to −0.14], *P*=0.004) and increased E/e' ratio (β=0.34, [95% CI, 0.03–0.66], *P*=0.033) and a borderline significant increased prevalence of DD (odds ratio 1.40 [95% CI, 0.99–2.00], *P*=0.06). The DD results are likely attenuated from the HIV seropositive versus HIV seronegative comparison because of the smaller sample size for men who were HIV+ and were virally suppressed.

Higher current CD4+ T cell count (≥400 versus <400 cells/mL) was associated with smaller LV end-diastolic volumes and RV end-diastolic areas. No other markers of HIV disease severity were associated with echocardiographic abnormalities. Current use of nucleoside reverse transcriptase protease inhibitors (NRTI) (compared with none) was associated with lower LV mass index and lower prevalence of DD. Current use of protease inhibitors (compared with none) was

Table 2. Two-Dimensional Echocardiogram Variables by HIV Serostatus

2D Echocardiogram Variables	Total (n=1195)	HIV Seronegative (n=533)	HIV Seropositive (n=662)
LV			
LV ejection fraction (%)	61.4 (58.5, 64.3)	61.7 (58.7, 64.3)	61.2 (58.4, 64.1)
LV EDV, indexed, mL/m^2	55.5 (48.8, 63.0)	55.3 (48.6, 62.7)	56.1 (49.3, 63.4)
LV ESV, indexed, mL/m^2	21.2 (18.1, 25)	21.0 (18.0, 24.5)	21.7 (18.2, 25.2)
LV mass, indexed, g/m^2	87.7 (75.4, 100.1)	87.3 (74.4, 99.4)	88.0 (76.0, 100.5)
Low ejection fraction (<50%)	26 (2.2)	10 (1.9)	16 (2.4)
Diastology			
E/A ratio	1.1 (0.8, 1.3)	1.1 (0.8, 1.3)	1.1 (0.9, 1.3)
e' velocity, cm/s	9.8 (8.5, 11.6)	9.7 (8.3, 11.4)	10.1 (8.5, 11.8)
E/e' ratio	7.3 (6.1, 8.7)	7.3 (6.2, 8.8)	7.2 (6.1, 8.7)
Diastolic dysfunction prevalence (CHART criteria)*	284 (23.8)	131 (24.6)	153 (23.1)
RV			
RV end-diastolic area, cm^2	19.1 (16.7, 21.3)	19.0 (16.5, 21.2)	19.2 (16.8, 21.3)
RV fractional area change (%)	42.8 (39.7, 47.2)	43.0 (39.7, 47.4)	42.8 (39.6, 47.1)
TAPSE, cm	2.2 (2.0, 2.5)	2.3 (2.0, 2.5)	2.2 (2.0, 2.5)
RV S', cm/s	13.3 (11.6, 14.9)	13.2 (11.5, 15.0)	13.3 (11.7, 14.9)
RVSP, mm Hg	31.6 (28.3, 35.0)	31.6 (28.3, 34.6)	31.4 (28.2, 35.1)
LA			
LA maximum AP diameter, cm	4.0 (3.7, 4.3)	4.0 (3.6, 4.3)	3.9 (3.7, 4.3)
LA maximum area index, cm^2/m^2	8.7 (7.9, 9.6)	8.7 (8.0, 9.6)	8.7 (7.9, 9.5)
LA maximum volume index, mL/m^2	24.3 (21.5, 27.9)	24.5 (21.6, 28.2)	24.2 (21.4, 27.7)

Data are presented as median (interquartile range). 2D indicates 2-dimensional; AP, anterior–posterior; CHART, Characterizing Heart Function on Antiretroviral Therapy Study; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium; LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; and TAPSE, tricuspid annular plane systolic excursion.

* Definition of diastolic dysfunction by CHART criteria: LVEF >50% and (septal e' <7 cm/s or lateral e' <10 cm/s) and (LA maximum volume index >28 mL/m^2 or LV hypertrophy [LV mass index >115 g/m^2] or concentric LV remodeling [relative wall thickness >0.42]).

Table 3. Association Between HIV Serostatus (HIV Seropositive Compared with HIV Seronegative) and 2D Echocardiogram Variables by Multivariable Linear Regression (β-Coefficients Represent Average Differences Between Men Who Were HIV Seropositive and Those Who Were HIV Seronegative)

2D Echocardiogram Variables	Differences (β) Between HIV Seropositive Compared with HIV Seronegative			
	Adjusted Model 1		Adjusted Model 2	
	β (95% CI)	*P* Value	β (95% CI)	*P* Value
LV				
LV ejection fraction (%)	−0.01 (−0.64, 0.62)	0.97	0.04 (−0.64, 0.70)	0.92
LV EDV, indexed, mL/m^2	−0.41 (−1.79, 0.96)	0.55	0.44 (−0.96, 1.83)	0.54
LV ESV, indexed, mL/m^2	−0.10 (−0.87, 0.67)	0.80	0.20 (−0.60, 1.00)	0.62
LV mass, indexed, g/m^2	1.69 (−0.74, 4.14)	0.17	3.09 (0.62, 5.56)*	
Diastology				
E/A ratio	−0.07 (−0.12, −0.02)*		−0.05 (−0.10, 0.01)	0.07
e' velocity, cm/s	−0.50 (−0.76, −0.25)*		−0.44 (−0.71, −0.18)*	
E/e' ratio	0.24 (−0.04, 0.52)	0.09	0.30 (0.02, 0.59)*	
RV				
RV end-diastolic area, cm^2	0.35 (−0.11, 0.81)	0.13	0.54 (0.06, 1.01)*	
RV fractional area change (%)	−0.40 (−1.18, 0.38)	0.31	−0.33 (−1.14, 0.49)	0.43
TAPSE, cm	−0.07 (−0.12, −0.02)*		−0.05 (−0.10, −0.02)*	
RV S', cm/s	0.08 (−0.28, 0.43)	0.67	0.07 (−0.30, 0.44)	0.29
RVSP	0.48 (−0.60, 1.56)	0.38	0.65 (−0.51, 1.81)	0.27
Left atrium (LA)				
LA maximum AP diameter, cm	0.05 (−0.001, 0.11)	0.05	0.08 (0.02, 0.14)*	
LA maximum area index, cm^2/m^2	0.08 (−0.99, 0.27)	0.37	0.18 (−0.01, 0.37)	0.07
LA maximum volume index, mL/m^2	0.04 (−0.78, 0.87)	0.92	0.47 (−0.38, 1.33)	0.28

Model 1: adjusted for age, race, education level, MACS (Multicenter AIDS Cohort Study) site, and wave of MACS enrollment (before/after 2001). Model 2: Model 1+further adjustment for heart rate, systolic blood pressure, antihypertensive medication, diabetes mellitus‡, dyslipidemia§, smoking status (never vs former or current), alcohol intake (none vs low-heavy or binge), history of cardiovascular events‖, and history of cocaine consumption. 2D indicates 2-dimensional; AP, anterior–posterior; EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrial; LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; and TAPSE, tricuspid annular plane systolic excursion.

*Significant results (*P*<0.05).

†Adjustment for body mass index was not performed if body surface area was used to index the echo parameter.

‡Diabetes mellitus defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes medication.

§Dyslipidemia defined as fasting total cholesterol ≥200 mg/dL or LDL ≥130 mg/dL or HDL ≤40 mg/dL or use of lipid-lowering medication.

‖History of cardiovascular events defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

associated with lower LVEF and greater LV volumes, though other indices were similar. Current use of integrase strand transfer inhibitors (compared with none) and their cumulative use were associated with greater LA maximum area index. Duration of cART of any category was not associated with subclinical myocardial disease.

Our results were unchanged with sensitivity analyses performed by excluding men with cardiovascular disease history from the multivariable models.

Two-Dimensional Echocardiography Reproducibility

Reproducibility of each of the echocardiographic metrics was excellent, with intra- and interreader interclass correlation coefficients ranging from 0.83 to 0.97 and 0.73 to 0.96, respectively (Table S3).

DISCUSSION

The main finding of this cross-sectional cohort analysis of men with and without HIV with similar risk factors for HIV acquisition and who were concurrently enrolled is that HIV seropositivity in the current cART era remains independently associated with small differences in subclinical cardiac structural and functional metrics with higher LV mass index, LV diastolic abnormalities (e' velocity, E/e' ratio, and DD), increased RV and LA sizes and lower RV function, after extensive covariate adjustment. There were fewer consistent associations between HIV viral load, CD4+ count, and

Table 4. Association Between Diastolic Dysfunction and HIV Serostatus

	LV Diastolic Dysfunction*			
	Model 1		Model 2	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
HIV serostatus (HIV+ vs HIV–)	1.53 (1.13, 2.09)	0.007†	1.43 (1.03, 1.99)	0.036†

Shown is the multivariable logistic regression model between HIV serostatus and diastolic dysfunction. Model 1: Adjusted for age, race, education level, MACS (Multicenter AIDS Cohort Study site), and wave of MACS enrollment (before/after 2001). Model 2: Model 1+further adjustment for body mass index, heart rate, systolic blood pressure, antihypertensive medication, diabetes mellitus‡, dyslipidemia§, smoking status, alcohol intake (none vs low-heavy), history of cardiovascular events‖, and history of cocaine consumption. OR indicates odds ratio.

*Definition of diastolic dysfunction by CHART criteria: left ventricular ejection fraction >50% & (septal e' <7 cm/s or lateral e' <10 cm/s) and (left atrial maximum volume index >28 mL/m^2 or left ventricle (LV) hypertrophy [LV mass index >115 g/m^2] or concentric LV remodeling [relative wall thickness >0.42]).

†Significant results (P<0.05).

‡Diabetes mellitus defined as glycosylated hemoglobin ≥6.5% or fasting glucose ≥126 mg/dL or use of diabetes mellitus medications.

§Dyslipidemia defined as fasting total cholesterol ≥200 mg/dL or low-density lipoprotein ≥130 mg/dL or high-density lipoprotein ≤40 mg/dL or use of lipid-lowering medication.

‖History of cardiovascular events defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

treatment with specific cART medications and myocardial abnormalities. However, differences in several cardiac metrics persisted among HIV seropostive but virally suppressed men compared with men who were HIV seronegative. Our results suggest an excess HIV-associated contribution to subclinical myocardial dysfunction, even among those virally suppressed, which could herald future predisposition to HFpEF among men who are HIV+.

The advent of cART has transformed the phenotype of HIV-associated cardiac dysfunction from one of symptomatic HF and dilated cardiomyopathy to one of subclinical changes in cardiac structure and function.[19–21] Among the men with HIV, we indeed found a low prevalence of LVEF <50% (2.4%), even lower than that described in a recent meta-analysis[19] (4.9% prevalence among the 7 studies for which ART use exceeded 81%, compared with 92% in our study). We found no association between HIV serostatus and LVEF. Among men who were HIV+, our finding that PI use was associated with lower LVEF and higher LV volumes is consistent with results from a recent retrospective study of PLWH hospitalized with HF.[22] These data add to results from the prospective Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study showing an association between PI use and greater incidence of major adverse cardiovascular events.[23] However, it is possible that these findings could be related to channeling bias rather than specifically or directly correlated with the medication.

DD generally precedes the development of HFpEF. Echocardiographic definitions of DD have evolved over time.[24,25] However, there remains no consensus regarding which echocardiographic definition of DD is most appropriate for analyses of population cohort studies.[26,27] This lack of agreement is especially relevant for PLWH because of the confounding effects of HIV-related pulmonary hypertension and high cardiac output associated with hepatitis C coinfection-related liver dysfunction on DD, leading several investigators to combine criteria for cardiac structural abnormalities and reduced diastolic relaxation.[18] Therefore, the reported prevalence of DD in PLWH will differ historically from study to study, depending on the DD criteria applied.[28] As a result, we assessed DD based on CHART criteria,[18] proposed specifically for PLWH. We found a prevalence of DD of 23.8% compared with previously reported rates ranging from 17% to 64% in smaller, older studies using prior DD definitions.[29] We showed a significant association between HIV serostatus and increased prevalence of DD. We further found an independent association between HIV serostatus and higher LV mass index, resting differences in diastolic functional components (e' velocity and E/e' ratio), and increased LA size, which may represent precursors to and support an increased predisposition to overt DD and eventual HFpEF among PLWH.

Our findings of HIV-associated increases in LV mass add to prior published results. Previous research showed an independent association between history of hypertension and CD4 count ≤200 cells/mm^3 and LV hypertrophy by echocardiography in PLWH.[30–32] In contrast to other studies, we did not find an association between markers of HIV disease activity and LVH. We did find an association between NRTI use and lower rather than higher LV mass among men with HIV, which differs from that of other studies.[30,33] NRTI use was also associated with lower prevalence of DD. While these results may reflect potential confounding by contraindication against NRTI as a class, our findings could support the lack of significant adverse effects of contemporary NRTIs on subclinical myocardial disease indices.

Previous studies have reported a higher prevalence of pulmonary hypertension among PLWH compared with the general population, leading to an increased risk of mortality even at pulmonary pressure levels below the threshold for invasive hemodynamic

evaluation.[34–36] A recent meta-analysis reported prevalence rates of 20.3%, 12.2%, and 11.3% for pulmonary artery systolic pressure thresholds of 30, 35, and 40 mm Hg, respectively among PLWH,[19] but was not further stratified by cART treatment. We found a low prevalence of pulmonary hypertension (3.7%), using a systolic pressure threshold of 40 mm Hg. However, the independent association between HIV serostatus with higher end-diastolic RV area and lower tricuspid annular plane systolic excursion might indicate a propensity for adverse RV remodeling as a result of elevated arterial pulmonary pressure, which might be underestimated from a single, resting measure of RV systolic pressure. Additionally, left ventricular DD and elevated left-sided filling pressures could contribute to RV structural alterations.

We acknowledge limitations of this study. Only men were enrolled in MACS, so our results cannot be extrapolated to women. MACS participants who did not undergo echocardiography tended to be older, had higher baseline risk for cardiovascular disease, and were less likely to be HIV+. Because of the observational study design, the potential for residual confounding remains and we cannot prove causation. We cannot completely separate HIV disease severity effects from those of ART medications, though we adjusted for ART use. Echocardiograms were only acquired at rest and thus, measures of provocable DD could not be obtained. Since this study was conceived as a discovery analysis with the primary aim to comprehensively describe cardiac structural and functional differences between men with and without HIV, we did not impose a correction for multiple comparisons when defining statistical significance. Nevertheless, we acknowledge that the comprehensive scope of the study, while one of its strengths, also presents more opportunities for spurious findings, and borderline significant results should be interpreted cautiously with this exploratory design in mind. Readers should consider the pathophysiological evidence supporting each association in addition to its effect size, CI, and *P* value when interpreting these findings. The fact that LV mass, LA and RV sizes, lower RV function, and diastolic abnormalities were all associated with HIV, and together support a phenotype that may predispose to HFpEF, strengthens our confidence in these results.

A strength of the study includes the large, multicenter cohort of men with HIV who were followed in the contemporary cART era with high rates of cART use, which facilitates a better understanding of the extent to which men with virally suppressed HIV remain at risk for subclinical myocardial disease. The concurrent enrollment of HIV– men with similar HIV risk behaviors and cardiovascular risk profiles improves adjustment for the multiple potentially confounding covariates that can also affect cardiac structure and function. The cohort was ethnically and socially diverse and well characterized with extensive covariate ascertainment and phenotyping. Finally, the use of a single ultrasound machine vendor with intensive pre-study technologist cross-training, standardized acquisition protocol, and centralized analyses minimized potential measurement variability.

CONCLUSIONS

In the era of cART and among a contemporary cohort of virally suppressed men living with and without HIV, HIV seropositivity remains an independent risk factor associated with small differences in subclinical cardiac structure and function. The combination of greater LV mass index, LV diastolic abnormalities and DD, larger RV sizes, lower RV systolic function, and larger LA sizes may be clinical markers of an increased propensity to develop HFpEF among PWLH, which deserves further study.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Clinical characteristics of the participants who did and did not undergo the echocardiogram exam.

Clinical Characteristics [1,*]	Underwent Echo (n=1,195)	Did not undergo Echo (n=785)
Age (years)	58.3 (50.6, 65.4)	62.8 (55.9, 68.6)
Race		
Non-White	468 (39.1)	178 (22.7)
Body Mass Index (kg/m^2)	26.7 (23.8, 30.2)	25.7 (23.1, 29.0)
College Degree	603 (50.5)	468 (59.6)
Field Center		
Baltimore	265 (22.2)	194 (24.7)
Chicago	270 (22.6)	117 (14.9)
Pittsburgh/Columbus	373 (31.3)	133 (16.9)
Los Angeles	287 (24.0)	341 (43.4)
SBP (mmHg)	129 (117, 139)	130 (119, 140)
On antihypertensive medication	481 (40.5)	315 (40.1)

Clinical Characteristics ǂ,*	Underwent Echo (n=1,195)	Did not undergo Echo (n=785)
Smoking status		
Never	374 (31.4)	233 (29.7)
Former and current smoking	818 (68.6)	552 (70.7)
Diabetes mellitus¥	157 (13.7)	84 (10.7)
On lipid-lowering medications	481 (40.3)	315 (41.3)
History of heart failure	9 (0.8)	12 (1.5)
History of myocardial infarction	23 (1.9)	24 (3.1)
History of cerebrovascular accident	7 (0.6)	2 (0.3)
History of atrial fibrillation	31 (2.6)	25 (3.2)
HIV seropositivity	662 (55.4)	338 (49.4)
HIV RNA (viral load), <20 copies/mL among HIV+	509 (76.9)	211 (75.4)

ǂ Data are presented as median (IQR) or n (%).

* Abbreviations: SBP: systolic blood pressure; ASCVD: atherosclerotic cardiovascular disease; HIV: human immunodeficiency virus; PLWH: people living with HIV; RNA: ribonucleic acid. ¥ Diabetes mellitus defined as HbA1C ≥ 6.5% or fasting glucose ≥ 126mg/dL or use of diabetes medications.

Table S2. Association between HIV disease activity and treatment and differences (deltas) in cardiac structure and function among HIV seropositive men (except for comparison between suppressed HIV RNA viral load vs. HIV seronegative) ǂ

	LV ejection fraction (%)		LV EDV, indexed (mL/m^2)		LV ESV, index (mL/m^2)		LV mass, indexed (g/m^2)	
HIV-specific disease activity and treatments	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Undetectable HIV RNA viral load (<20 copies/mL) (vs. ≥20)	-0.55 (-1.64, 0.54)	0.32	1.52 (-0.69, 3.73)	0.18	0.80 (-0.52, 2.11)	0.24	-1.49 (5.27, 2.29)	0.44
Undetectable HIV RNA viral load (<20 copies/mL) (vs. HIV seronegative)	-0.12 (-0.81, 0.56)	0.73	0.84 (-0.63, 2.31)	0.26	0.43 (-0.40, 1.26)	0.31	2.97 (0.31, 5.63)	**0.029**[p]
HIV RNA viral load (copies/mL)								
<20	ref	ref	ref	ref	ref	ref	ref	ref
20-499	0.98 (-0.30, 2.26)	0.13	-2.08 (-4.67, 0.50)	0.11	-1.40 (-2.93, 0.14)	0.08	-0.14 (-4.56, 4.28)	0.95
≥500	-0.32 (-2.01, 1.43)	0.72	-0.35 (-3.90, 3.20)	0.85	0.45 (-1.67, 2.56)	0.68	4.85 (-1.20, 10.90)	0.12
Nadir CD4+ T cell count before cART (≥400 cells/mm^3) (vs. <400)	-0.50 (-1.49, 0.49)	0.32	0.86 (-1.15, 2.87)	0.40	0.52 (-0.68, 1.71)	0.39	1.03 (-2.41, 4.47)	0.56

	LV ejection fraction (%)		LV EDV, indexed (mL/m^2)		LV ESV, index (mL/m^2)		LV mass, indexed (g/m^2)	
HIV-specific disease activity and treatments	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
CD4+ T cell count (cells/mm^3) (continuous)	-0.0001 (-0.002, 0.002	0.97	-0.003 (-0.006, -7.08)	**0.049** [p]	-0.001 (-0.003, 0.001)	0.15	-0.003 (-0.01. 0.001)	0.19
CD4+ T cell count (≥400 cells/mm^3) (vs. <400)	-0.14 (-1.46, 1.19)	0.84	-3.83 (-6.47, -1.19)	**0.005** [p]	-1.51 (-3.09, 0.07)	0.06	-3.23 (-7.76, 1.29)	0.16
History of AIDS (vs. no history)	-1.50 (-3.14, 0.14)	0.07	2.92 (-0.38, 6.21)	0.08	2.05 (0.09, 4.01)	**0.041** [p]	4.47 (-1.15, 10.09)	0.12
Duration of cART (years)	0.06 (-0.04, 0.14)	0.22	-0.14 (-0.32, 0.04)	0.13	-0.09 (-0.20, 0.02)	0.10	0.10 (-0.21, 0.41)	0.52
On protease inhibitors (PI) (vs. none)	-1.20 (-2.23, -0.16)	**0.023** [p]	2.68 (0.60, 4.77)	**0.012** [p]	2.01 (0.78, 3.25)	**0.001** [p]	2.97 (-0.62, 6.56)	0.11
Cumulative years of PI use	0.01 (-0.06, 0.09)	0.74	0.11 (-0.04, 0.26)	0.14	0.04 (-0.05, 0.13)	0.37	0.25 (-0.01, 0.50)	0.06
On nucleoside reverse transcriptase inhibitors (NRTI) (vs. none)	0.57 (-0.83, 1.97)	0.42	-2.17 (-5.01, 0.66)	0.13	-1.32 (-3.00, 0.37)	0.13	-5.48 (-10.3, -0.61)	**0.001** [p]
Cumulative years of NRTI use	0.07 (-0.01, 1.50)	0.09	-0.10 (-0.26, 0.06)	0.24	-0.09 (-0.18, 0.01)	0.08	0.23 (-0.05, 0.50)	0.11

	LV ejection fraction (%)		LV EDV, indexed (mL/m^2)		LV ESV, index (mL/m^2)		LV mass, indexed (g/m^2)	
HIV-specific disease activity and treatments	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
On non-nucleoside reverse transcriptase inhibitors (NNRTI) (vs. none)	0.63 (-0.37, 1.63)	0.21	-0.75 (-2.79, 1.28)	0.47	-0.77 (-1.98, 0.44)	0.21	-1.06 (-4.52, 2.41)	0.55
Cumulative years of NNRTI use	0.03 (-0.06, 0.11)	0.55	-0.11 (-0.28, 0.06)	0.20	-0.06 (-0.16, 0.04)	0.24	0.02 (-0.27, 0.31)	0.89
On integrase strand transfer inhibitor (INSTI) (vs. none)	-0.42 (-1.34, 0.51)	0.38	0.44 (-1.45, 2.33)	0.65	0.51 (-0.61, 1.63)	0.37	2.01 (-1.21, 5.25)	0.22
Cumulative years of INSTI use	-0.004 (-0.16, 0.16)	0.96	0.16 (-0.17, 0.48)	0.35	0.07 (-0.13, 0.26)	0.50	0.14 (0.43, 0.70)	0.64

	RV end-diastolic area (cm^2)		RV FAC (%)		TAPSE (cm)		LA maximum AP diameter (cm)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Undetectable HIV RNA viral load (<20 copies/mL) (vs. ≥20)	-0.10 (-0.84, 0.65)	0.80	0.53 (-0.69, 1.74)	0.40	0.04 (-0.04, 0.11)	0.36	-0.02 (-0.11, 0.06)	0.57

	RV end-diastolic area (cm^2)		RV FAC (%)		TAPSE (cm)		LA maximum AP diameter (cm)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Undetectable HIV RNA viral load (<20 copies/mL) (vs. HIV seronegative)	0.49 (-0.11, 0.99)	0.06	-0.22 (-1.10, 0.66)	0.62	-0.05 (-0.11, 0.002)	0.06	0.08 (0.02, 0.14)	**0.012[p]**
HIV RNA viral load (copies/mL)								
<20	ref	ref	ref	ref	ref	ref	ref	ref
20-499	0.25 (-0.64, 1.13)	0.59	-0.52 (-1.97, 0.92)	0.48	-0.01 (-0.10, 0.08)	0.86	0.01 (-0.09, 0.11)	0.81
≥500	-0.19 (-1.36, 0.98)	0.75	-0.53 (-2.43, 1.38)	0.59	-0.09 (-0.21, 0.03)	0.14	0.05 (-0.09, 0.19)	0.48
Nadir CD4+ T cell count before cART (≥400 cells/mm^3) (vs. <400)	-0.21 (-0.89, 0.46)	0.54	-0.01 (-1.11, 1.10)	0.99	-0.03 (-0.10, 0.04)	0.40	0.03 (-0.04, 0.10)	0.48
CD4+ T cell count (≥400 cells/mm^3) (vs. <400)	-1.26 (-2.15, -0.38)	**0.005 [p]**	-0.01 (-0.06, 0.04)	0.81	-0.01 (-0.10. 0.09)	0.90	0.003 (-0.10, 0.11)	0.96
History of AIDS (vs. no history)	0.81 (-0.27, 1.90)	0.14	0.28 (-1.50, 2.06)	0.76	-0.02 (-0.14, 0.09)	0.70	0.03 (-0.16, 0.10)	0.67

	RV end-diastolic area (cm^2)		RV FAC (%)		TAPSE (cm)		LA maximum AP diameter (cm)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Duration of cART (years)	-0.02 (-0.08, 0.04)	0.48	0.10 (0.003, 0.20)	0.05	-0.001 (-0.01, 0.01)	0.77	0.02 (-0.05, 0.01)	0.56
On protease inhibitors (PI) (vs. none)	-0.06 (-0.76, 0.65)	0.87	-0.48 (-1.63, 0.66)	0.41	0.004 (-0.07, 0.08)	0.92	0.01 (-0.07, 0.09)	0.79
Cumulative years of PI use	-0.01 (-0.06, 0.04)	0.62	0.05 (-0.03, 0.13)	0.25	-0.001 (-0.01, 0.004)	0.61	0.01 (-0.001, 0.01)	0.09
On nucleoside reverse transcriptase inhibitors (NRTI) (vs. none)	-0.17 (-1.13, 0.78)	0.72	0.41 (-1.15, 1.96)	0.61	-0.05 (-0.15, 0.06)	0.37	-0.02 (-0.13, 0.09)	0.76
Cumulative years of NRTI use	-0.04 (-0.10, 0.01)	0.13	0.05 (-0.04, 0.14)	0.25	-0.001 (-0.01, 0.005)	0.67	0.01 (-0.001, 0.01)	0.13
On non-nucleoside reverse transcriptase inhibitors (NNRTI) (vs. none)	-0.04 (-0.73, 0.64)	0.91	0.45 (-0.67, 1.56)	0.43	0.05 (-0.03, 0.12)	0.20	-0.001 (-0.08, 0.08)	0.97
Cumulative years of NNRTI use	-0.01 (-0.06, 0.05)	0.78	0.07 (-0.02, 0.16)	0.13	0.001 (-0.01, 0.01)	0.84	-0.003 (-0.01, 0.004)	0.43

	RV end-diastolic area (cm^2)		RV FAC (%)		TAPSE (cm)		LA maximum AP diameter (cm)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
On integrase strand transfer inhibitor (INSTI) (vs. none)	0.26 (-0.36, 0.89)	0.41	0.49 (-0.53, 1.51)	0.35	-0.06 (-0.12, 0.01)	0.08	0.06 (-0.02, 0.13)	0.13
Cumulative years of INSTI use	-0.05 (-0.17, 0.06)	0.48	0.13 (-0.05, 0.31)	0.14	-0.01 (-0.02, 0.002)	0.11	0.02 (0.002, 0.03)	**0.021** [p]

	LA maximum area index (cm^2/m^2)		LA maximum volume index (mL/m^2)		E/A ratio		E/average e' ratio	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Undetectable HIV RNA viral load (<20 copies/mL) (vs. ≥20)	0.30 (0.03, 0.58)	**0.030** [p]	1.31 (0.02, 2.60)	**0.047** [p]	0.02 (-0.06, 0.10))	0.57	0.11 (-0.36, 0.58)	0.66
Undetectable HIV RNA viral load (<20 copies/mL) (vs. HIV seronegative)	0.27 (0.06, 0.48)	**0.011** [p]	0.84 (-0.10, 1.78)	0.08	-0.04 (-0.10, 0.01)	0.12	0.34 (0.03, 0.66)	**0.033** [p]

	LA maximum area index (cm^2/m^2)		LA maximum volume index (mL/m^2)		E/A ratio		E/average e' ratio	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
HIV RNA viral load (copies/mL)								
<20	ref	ref	ref	ref			ref	ref
20-499	-0.24 (-0.56, 0.08)	0.14	-1.09 (-2.60, 0.42)	0.16			-0.003 (-0.09, 0.09)	0.96
≥500	0.43 (-0.87, 0.01)	**0.05** [p]	-1.76 (-3.82, 0.30)	0.09			-0.06 (-0.19, 0.06)	0.32
Nadir CD4+ T cell count before cART (≥400 cells/mm^3) (vs. <400)	0.16 (-0.10, 0.41)	0.22	0.81 (-0.37, 1.98)	0.18	0.02 (-0.05, 0.09)	0.66	-0.05 (-0.48, 0.37)	0.80
CD4+ T cell count (≥400 cells/mm^3) (vs. <400)	-0.24 (-0.57, 0.09)	0.16	-0.69 (-2.24, 0.87)	0.39	-0.01 (-0.10, 0.08)	0.84	-0.16 (-0.72, 0.40)	0.58
History of AIDS (vs. no history)	0.20 (-0.21, 0.61)	0.33	0.33 (-1.59, 2.25)	0.74	-0.06 (-0.18, 0.05)	0.27	-0.41 (-1.10, 0.29)	0.25
Duration of cART (years)	0.01 (-0.01, 0.03)	0.33	0.02 (-0.08, 0.13)	0.67	-0.01 (-0.01, 0.002)	0.16	0.01 (-0.03, 0.05)	0.62

	LA maximum area index (cm^2/m^2)		LA maximum volume index (mL/m^2)		E/A ratio		E/average e' ratio	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
On protease inhibitors (PI) (vs. none)	0.01 (-0.26, 0.27)	0.96	-0.38 (-1.61, 0.85)	0.47	-0.03 (-0.10, 0.05)	0.50	-0.20 (-0.65, 0.24)	0.37
Cumulative years of PI use (years)	0.003 (-0.02, 0.02)	0.74	-0.01 (-009, 0.07)	0.90	-0.003 (-0.01, 0.001)	0.15	-0.01 (-0.04, 0.02)	0.66
On nucleoside reverse transcriptase inhibitors (NRTI) (vs. none)	0.11 (-0.47, 0.25)	0.55	-0.32 (-1.99, 1.34)	0.70	0.07 (-0.03, 0.17)	0.15	0.30 (-0.30, 0.90)	0.33
Cumulative years of NRTI use	0.01 (-0.01, 0.03)	0.27	0.02 (-0.07, 0.12)	0.67	-0.003 (-0.01, 0.003)	0.38	0.01 (-0.02, 0.05)	0.30
On non-nucleoside reverse transcriptase inhibitors (NNRTI) (vs. none)	-0.20 (-0.45, 0.05)	0.12	-0.90 (-2.09, 0.28)	0.13	0.07 (-0.004, 0.14)	0.06	0.08 (-0.35, 0.51)	0.71
Cumulative years of NNRTI use	-0.0004 (-0.02, 0.02)	0.97	-0.01 (-0.11, 0.09)	0.82	-0.001 (-0.01, 0.004)	0.64	0.01 (-0.03, 0.04)	0.65
On integrase strand transfer inhibitors (INSTI) (vs. none)	0.38 (0.15, 0.62)	**0.001** [p]	1.66 (0.56 (2.75)	**0.003** [p]	-0.01 (-0.08, 0.05)	0.73	0.36 (-0.03, 0.76)	0.06

	LA maximum area index (cm^2/m^2)		LA maximum volume index (mL/m^2)		E/A ratio		E/average e' ratio	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Cumulative years of INSTI use	0.05 (0.01, 0.09)	**0.016** [p]	0.19 (-0.01, 0.38)	0.06	0.002 (-0.01, 0.01)	0.68	-0.01 (-0.08, 0.06)	0.86

	Average e' (cm/s)		LV DD[⊗]		RV S' velocity (cm/s)		RVSP (mmHg)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Undetectable HIV RNA viral load (<20 copies/mL) (vs. ≥20)	0.33 (-0.07, 0.74)	0.11	0.74 (0.44, 1.26)	0.27	-0.57 (-1.13, -0.01)	**0.047** [p]	0.94 (-1.05, 2.93)	0.35
Undetectable HIV RNA viral load (<20 copies/mL) (vs. HIV seronegative)	-0.42 (-0.70, -0.14)	**0.004** [p]	1.40 (0.99 to 2.00)	0.06	-0.06 (-0.45, 0.34)	0.78	0.67 (-0.54, 1.89)	0.28

	Average e' (cm/s)		LV DD[⊗]		RV S' velocity (cm/s)		RVSP (mmHg)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
HIV RNA viral load (copies/mL)								
<20	ref	ref	ref	ref	ref	ref	ref	ref
20-499	-0.16 (-0.63, 0.32)	0.52	1.12 (0.59, 2.12)	0.73	0.65 (-0.004, 1.31)	**0.05** [ᵽ]	-0.89 (-3.23, 1.44)	0.45
≥500	-0.68 (-1.31, 0.03)	**0.039** [ᵽ]	1.86 (0.85, 4.07)	0.12	0.39 (-0.52, 1.30)	0.40	-1.03 (-4.21, 2.15)	0.52
Nadir CD4+ T cell count before cART (≥400 cells/mm^3) (vs. <400)	0.18 (-0.18, 0.55)	0.31	1.01 (0.62, 1.65)	0.96	-0.11 (-0.62, 0.39)	0.66	-0.42 (-2.10, 1.26)	0.62
CD4+ T cell count (≥400 cells/mm^3) (vs. <400)	-0.20 (-0.69, 0.28)	0.41	0.94 (0.51, 1.74)	0.85	-0.27 (-0.95, 0.42)	0.44	0.19 (-1.89, 2.26)	0.86
History of AIDS (vs. no history)	-0.01 (-0.61, 0.59)	0.97	0.99 (0.48, 2.05)	0.98	-0.50 (-1.34, 0.33)	0.24	-1.12 (-3.60, 1.35)	0.37
Duration of cART (years)	-0.01 (-0.04, 0.02)	0.54	1.00 (0.96, 1.04)	0.83	-0.01 (-0.05, 0.04)	0.74	0.07 (-0.07, 0.22)	0.33

	Average e' (cm/s)		LV DD[⊗]		RV S' velocity (cm/s)		RVSP (mmHg)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
On protease inhibitors (PI) (vs. none)	0.07 (-0.31, 0.46)	0.71	0.91 (0.56, 1.48)	0.70	0.15 (-0.39, 0.68)	0.59	0.10 (-1.57, 1.78)	0.90
Cumulative years of PI use (years)	0.01 (-0.02, 0.04)	0.45	0.99 (0.96, 1.02)	0.65	-0.02 (-0.06, 0.02)	0.30	0.04 (-0.08, 0.16)	0.50
On nucleoside reverse transcriptase inhibitors (NRTI) (vs. none)	0.38 (-0.14, 0.90)	0.16	0.49 (0.26, 0.90)	**0.023** [p]	-0.48 (-1.21, 0.24)	0.19	0.73 (-1.53, 2.99)	0.52
Cumulative years of NRTI use	-0.01 (-0.04, 0.02)	0.33	0.99 (0.96, 1.03)	0.98	-0.01 (-0.05, 0.03)	0.63	0.02 (-0.11, 0.16)	0.71
On non-nucleoside reverse transcriptase (NNRTI) (vs. none)	0.20 (-0.17, 0.57)	0.29	1.03 (0.64, 1.66)	0.91	0.49 (-0.02, 1.00)	0.06	-0.62 (-2.30, 1.05)	0.47
Cumulative years of NNRTI use	-0.01 (-0.04, 0.02)	0.44	1.02 (0.98, 1.05)	0.42	0.01 (-0.03, 0.05)	0.62	-0.03 (-0.17, 0.11)	0.71
On integrase strand transfer inhibitor (INSTI) (vs. none)	-0.29 (-0.63, 0.02)	0.09	1.30 (0.82, 2.06)	0.27	-0,31 (-0.78, 0.17)	0.21	0.45 (-1.11, 2.00)	0.57

	Average e' (cm/s)		LV DD[Θ]		RV S' velocity (cm/s)		RVSP (mmHg)	
HIV-specific risk factors	**β (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
Cumulative years of INSTI use	-0.01 (-0.07, 0.05)	0.68	1.04 (0.97, 1.12)	0.29	0.01 (-0.07, 0.09)	0.87	-0.11 (-0.37, 0.14)	0.39

Each HIV disease factor was assessed in a separate multivariable linear or logistic model with adjustment for age, race, education level, MAC study site, wave of MACS enrollment (before/after 2001), heart rate, systolic blood pressure, antihypertensive medication, diabetes mellitus[¥], dyslipidemia[€], smoking status, alcohol intake, history of cardiovascular events[£], and history of cocaine consumption.

[A] Adjustments for BMI were also performed if the echo parameter was not indexed by BSA.

[¥] Diabetes Mellitus defined as HbA1C ≥ 6.5% or fasting glucose ≥ 126mg/dL or use of diabetes medications.

[€] Dyslipidemia defined as fasting total cholesterol ≥ 200mg/dL or LDL ≥ 130mg/dL or HDL ≤ 40mg/dL or use of lipid lowering medication.

[£] History of cardiovascular events defined as personal history of heart failure, myocardial infarction, cerebrovascular accident, or atrial fibrillation.

[ł] Abbreviations: LV: left ventricle, EDV: end-diastolic volume, ESV: end-systolic volume, RV: right ventricle, FAC: fractional area change, TAPSE: tricuspid annular plane systolic excursion, LA: left atrium, AP: anterior-posterior, RVSP: right ventricular systolic pressure, DD: diastolic dysfunction, RNA: ribonucleic acid, CD4: cluster of differentiation 4; cART: combination antiretroviral therapy; PI: protease inhibitor.

[Θ] Definition of diastolic dysfunction by CHART criteria: LVEF >50% & (septal e' < 7cm/s or lateral e' < 10cm/s) & (LA maximum volume index > 28mL/m^2 or LV hypertrophy [LV mass index >115g/m^2] or concentric LV remodeling [relative wall thickness >0.42]).

[þ] Significant results ($p < 0.05$) are indicated in bold.

Table S3. Reproducibility of the cardiac structure and function variables by 2D echocardiography.

n=120	**Intra reader**	**Inter reader**
2D echocardiogram variables ǂ	**ICC (95% CI)**	**ICC (95% CI)**
LV internal diameter - diastole (cm)	0.92 (0.88, 0.94)	0.86 (0.81, 0.90)
LV posterior wall diameter - diastole (cm)	0.84 (0.78, 0.89)	0.73 (0.64, 0.80)
LV interventricular septum - diastole (cm)	0.83 (0.77, 0.88)	0.75 (0.66, 0.82)
LV mass (g)	0.94 (0.92, 0.96)	0.89 (0.85, 092)
Aortic root diameter – diastole (cm)	0.97 (0.96, 0.98)	0.95 (0.93, 0.97)
LV ejection fraction (%)	0.87 (0.82, 0.91)	0.81 (0.73, 0.87)
LV end-diastolic volume (mL)	0.92 (0.89, 0.94)	0.80 (0.73, 0.86)
LV end-systolic volume (mL)	0.94 (0.91, 0.96)	0.89 (0.85, 0.92)
LA maximum volume (mL)	0.91 (0.88, 0.94)	0.84 (0.78, 0.88)
Mitral E peak velocity (cm/s)	0.97 (0.96, 0.98)	0.96 (0.94, 0.97)
Mitral A peak velocity (cm/s)	0.91 (0.88, 0.94)	0.95 (0.93, 0.97)
E/A ratio	0.91 (0.87, 0.94)	0.93 (0.90. 0.95)
E/e’ ratio - lateral	0.89 (0.85, 0.93)	0.91 (0.87, 0.93)

E/e’ ratio - septal	0.89 (0.84, 0.92)	0.92 (0.88. 0.94)

[ǂ] Abbreviations: 2D: two-dimensional, ICC: interclass correlation LV: left ventricle, LA: left atrium, TAPSE: tricuspid annular plane systolic excursion.