ORIGINAL RESEARCH

OUTCOMES AND QUALITY

Incidence and Progression of Diastolic Dysfunction in People With HIV in Tanzania

A Comparative Cohort

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ABSTRACT

BACKGROUND People living with HIV (PLWH) have a higher prevalence of diastolic dysfunction and left ventricular hypertrophy (LVH) in cross-sectional studies. Longitudinal data are lacking, especially from Africa.

OBJECTIVES The aim was to examine: 1) the incidence of diastolic dysfunction in PLWH compared to community controls in Tanzania; 2) the progression of diastolic function and LVH in PLWH after antiretroviral therapy initiation; and 3) traditional, endemic, and HIV-specific risk factors for diastolic function and LVH.

METHODS This was a prospective longitudinal cohort of PLWH and HIV-uninfected controls who had an echocardiogram at enrollment and in follow-up. Adjusted Cox proportional HR models were used to determine the incidence of diastolic dysfunction, and multivariable mixed effects regressions were used to determine the progression and risk factors for diastolic function.

RESULTS A total of 781 participants (367 PLWH) were followed for up to 5 years. There was no difference in incidence of diastolic dysfunction by HIV serostatus (aHR: 0.93 [95% CI: 0.61-1.42]). Baseline differences in echo parameters prior to antiretroviral therapy initiation resolved within 3 years of treatment for LVH (baseline difference $= 3.57$ g/m^2 [95% CI: 0.87-6.26]; no difference after 3 years) and other diastolic dysfunction markers. Hypertension and obesity were important modifiable risk factors for diastolic dysfunction (both $P < 0.001$), while subclinical kidney disease, anemia, and manual labor were predictors of LVH and diastolic dysfunction.

CONCLUSIONS The incidence of diastolic dysfunction was similar in PLWH and HIV-uninfected controls. Efforts to prevent diastolic heart failure in Africa must focus on addressing hypertension and obesity while also investigating nontraditional risk factors. (JACC Adv. 2024;3:101238) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ART = antiretroviral therapy

ASE = American Society of Echocardiography

BMI = body mass index

BP = blood pressure

CVD = cardiovascular disease

LVMI = left ventricular mass index

LVH = left ventricular hypertrophy

LA = left atrium

PLWH = people living with HIV

sST2 = serum soluble suppression of tumorigenicity 2

Recent studies have highlighted the burden of cardiovascular disease (CVD) in Africa,[1,2] however, few data describe the impact of traditional and endemic risk factors on incident disease. Diastolic dysfunction and increased left ventricular mass index (LVMI) are well-established echocardiographic measures of preclinical CVD and are strongly associated with heart failure and sudden cardiac death.[3,4] Recent cross-sectional studies of left ventricular diastolic function in Africa have shown strong associations between diastolic dysfunction and adiposity,[5] hypertension,[6] and HIV.[7,8] To date, no longitudinal data describe the evolution of diastolic function and left ventricular hypertrophy (LVH) in sub-Saharan Africa.

In high-income countries, HIV infection has been associated with a 2-fold increased risk of heart failure.[9,10] Prior cross-sectional studies assessing for preclinical echocardiographic markers of heart failure and CVD found a higher prevalence of diastolic dysfunction and increased LVMI in people living with HIV (PLWH) compared to HIV-uninfected community controls.[7,9,11] These studies have mostly focused on PLWH who have been treated with antiretroviral therapy (ART) and have not focused on the early ART period. Because most PLWH reside in sub-Saharan Africa, there is pressing need to understand the incidence and progression of diastolic dysfunction in this region.

The objectives of this prospective, observational study in Tanzania were to: 1) describe the incidence of diastolic dysfunction in PLWH compared to community controls; 2) describe the progression of diastolic function and LVMI in PLWH after ART initiation; and 3) explore the impact of traditional, endemic, and HIV-specific cardiovascular risk factors on diastolic function and LVH.

METHODS

STUDY POPULATION. This was a prospective study of PLWH and community controls in Mwanza, Tanzania. Study procedures were previously described.[7,12] Briefly, PLWH were enrolled from the HIV clinic and treatment center located at Bugando Medical Centre (BMC), the zonal referral hospital for Northwestern Tanzania. HIV-uninfected controls were enrolled from among all the HIV-treatment supporters registered at the BMC HIV clinic. Treatment supporters are close friends or relatives of PLWH that are named as alternative contacts and sources of support for PLWH enrolled in HIV care. We have previously shown that treatment supporters have similar sociodemographic characteristics as PLWH in Tanzania since they are drawn from the same source population.[7,12] According to the principles of frequency matching, we selected control participants from among all of the treatment supporters attending the HIV clinic during the study period with monitoring to ensure balanced enrollment by sex and age group. People were eligible for enrollment if they were between 18 and 65 years of age and did not have plans to move outside of Mwanza during the duration of the study. PLWH were ART-naïve at the time of enrollment. Enrolled participants provided informed consent and all study procedures were approved by the Institutional Review Boards at BMC, Weill Cornell Medicine, and the Tanzanian National Institute of Medical Research. Participants who were diagnosed with hypertension, diabetes, or CVD were provided free access to medications and clinical care at BMC.[13]

STUDY PROCEDURES. Participants were seen at enrollment and followed up 3, 6, and 12 months after enrollment and every 6 months thereafter. At each visit, participants completed the World Health Organizations STEPwise Surveillance survey. Participants underwent standard anthropometric measurement. Hypertension was defined as systolic blood pressure (BP) $\geq$140 mm Hg or diastolic BP $\geq$90 mm Hg per the International Society of Hypertension guidelines.[14]

Routine point-of-care testing was done at each visit and serum samples were collected and stored during the baseline study visit. At each visit, CD4 counts and hemoglobin levels were obtained using an automated BD FACSPresto System (BD Biosciences). Estimated glomerular filtration rate was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[15] Sickle cell status was with the RESOLVE hemoglobin kit and JB-2 staining system (PerkinElmer, Inc). Serum soluble suppression of tumorigenicity 2 [sST2] concentration was measured using R&D Systems Quantikine enzyme-linked immunosorbent assay (catalog number DST200).[7]

TABLE 1 Baseline Sociodemographic, Clinical, and Echocardiographic Data (n = 781)			
	PLWH (n = 367)	HIV-Uninfected Community Controls (n = 414)	P Value[a]
Traditional risk factors			
Age, y	37.0 (30.0-44.0)	37.0 (28.0-43.0)	0.227
Female	71% (262)	67% (276)	0.155
BMI, kg/m^2			
Underweight: <18.5	15% (54)	12% (51)	0.083
Normal: 18.5-24.9	57% (211)	52% (215)	
Overweight: 25-29.9	17% (64)	24% (101)	
Obese: ≥30	10% (38)	11% (47)	
Hypertension (SBP ≥140 or DBP ≥90), mm Hg	8% (29)	10% (42)	0.276
SBP	114.5 (105.0-125.0)	121.8 (111.5-132.5)	<0.001
DBP	73.5 (67.5-81.0)	77.5 (70.5-84.0)	<0.001
Diabetes	2% (9)	2% (7)	0.453
Current tobacco use	4% (14)	6% (26)	0.119
Current alcohol use	35% (129)	29% (122)	0.090
Exercise (days/week with at least 10 min)	0.0 (0.0-5.0)	2.0 (0.0-7.0)	<0.001
WHO CVD 10-year laboratory-based risk	0.9 (0.5-1.6)	1.1 (0.5-2.3)	0.038
Endemic risk factors			
Education			
Did not complete primary school	18% (66)	11% (46)	0.002
Completed primary	65% (240)	64% (266)	
Higher education	17% (61)	25% (102)	
Manual work [ref: office or domestic work]	26% (95)	27% (113)	0.657
Indoor or occupational smoke exposure (number of years)	10.0 (3.0-23.0)	7.0 (1.0-20.0)	
Vegetables, servings/week	4.0 (2.0-7.0)	5.0 (2.0-7.0)	0.200
Fruits, servings/week	2.0 (0.0-7.0)	2.0 (0.0-4.0)	0.095
Kidney function:			
eGFR: >60 mL/min/1.73 m^2	92% (335)	91% (378)	0.958
eGFR: 45-60 mL/min/1.73 m^2	6% (23)	7% (27)	
eGFR: <45 mL/min/1.73 m^2	2% (9)	2% (9)	
Urine: albumin to creatinine ratio (ACR)	7.0 (5.0-13.0)	6.0 (4.0-9.0)	
Anemia			
Normal (women: Hb ≥12 mg/dL; men: Hb >13 mg/dL)	58% (212)	83% (342)	<0.001
Mild (women: Hb 10-12 mg/dL; men: Hb 10-13 mg/dL)	27% (99)	12% (49)	
Moderate (Hb 8-10 mg/dL)	12% (43)	4% (17)	
Severe (Hb <8 mg/dL)	4% (13)	1% (6)	
Sickle cell trait	20% (74)	22% (91)	0.535

For PLWH, viral load and tuberculosis data were manually abstracted from medical records stored at government-run HIV-treatment centers.

ECHOCARDIOGRAPHY. All baseline echocardiograms were obtained using a Sonosite M-turbo machine and completed and read by a U.S. physician. All subsequent echocardiograms were completed and read by a U.S.-trained Tanzanian sonographer. Abnormal echocardiographs were reviewed prior to analysis; any discrepancies were adjudicated by an independent cardiologist. Separately, a U.S.-based cardiologist and specialist in echocardiography reviewed 10% of all echocardiograms to ensure adherence to the protocol throughout the study period and that echocardiograms were meeting quality standards. After study enrollment, echocardiography was performed annually; there was however variability in the timing of the measurements due to limitations on clinical research in Tanzania during the SARS-CoV-2 pandemic.

Measurements and classifications were made according to the 2016 American Society of Echocardiography (ASE) guidelines for the evaluation of left ventricular diastolic function and 2015 ASE guidelines for chamber quantification.[16,17] For each participant, we calculated left ventricular ejection fraction using the biplane method of disks and obtained measurements of the septal e' and lateral e' mitral valve

TABLE 1 Continued

	PLWH (n = 367)	HIV-Uninfected Community Controls (n = 414)	P Value[a]
HIV-specific risk factors			
History of TB	12% (44)	–	
CD4 count (cells/mL)	511.0 (284.0-734.0)	–	
CD4 percentage	25.5 (15.9-33.8)	–	
sST2 (ng/mL)	14.1 (10.8-19.8)	–	
First ART regimen			
Efavirenz based	79% (289)	–	
Dolutegravir based	21% (78)	–	
First ART NRTI combinations		–	
Tenofovir and lamivudine	99% (363)	–	
Lamivudine and abacavir	0% (1)	–	
Zidovudine and lamivudine	1% (3)	–	
Baseline echocardiographic data			
Baseline LV structure			
LV end-diastolic diameter (cm)	4.2 (3.8-4.5)	4.2 (3.9-4.5)	0.066
LV end-diastolic volume (mL)	76.8 (62.3-92.0)	79.0 (66.7-93.9)	0.045
LV mass (grams)	120.5 (99.1-143.2)	114.6 (97.9-138.2)	0.093
Baseline LV ejection fraction (%)	66.0 (61.0-72.0)	66.0 (60.0-73.0)	0.961
≥50%	97% (357)	97% (402)	1.000
40%-50%	2% (7)	2% (9)	
<40%	1% (3)	1% (3)	
Diastolic function			
Normal	96% (351)	95% (395)	0.883
Grade I	2% (9)	2% (9)	
Grade II	–	–	
Grade III	0% (1)	1% (3)	
Indeterminant	2% (6)	2% (7)	

Values are median (Q1-Q3) or % (n). [a]P value derived from chi-squared, Fisher's exact, or Mann-Whitney U (rank sum) statistical tests.

ART = antiretroviral therapy; BMI = body mass index; CVD = cardiovascular disease; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; LV = left ventricle; NRTI = nucleoside reverse transcriptase inhibitor; PLWH = people living with HIV; SBP = systolic blood pressure; sST2 = serum soluble suppression of tumorigenicity 2; TB = tuberculosis; WHO = World Health Organization.

annular velocities, mitral E and A velocities, and tricuspid regurgitation jet velocity, if detectable. We calculated the left atrial volume indexed to body surface area. Echocardiograms that had indeterminant diastolic function by ASE guidelines were considered normal. A sensitivity analysis was performed in which these echocardiograms were classified as having diastolic dysfunction.

We assessed the incidence of diastolic dysfunction using the definition of diastolic dysfunction described in the CHART (Characterizing Heart Function on Antiretroviral Therapy) study, which was developed to study diastolic dysfunction in PLWH with an ejection fraction >50% at baseline.[11] With the CHART definition, diastolic dysfunction is defined as evidence of impaired relaxation (septal e' <7 cm/s or lateral e' <10 cm/s) and evidence of chronically elevated filling pressures or LVH (left atrial volume index >28 mL/m², LVMI >95/m² in women or > 115 g/m² in men, or relative wall thickness >0.42). Participants with a baseline diastolic dysfunction and/or ejection fraction ≤50% were excluded from this analysis. As a secondary analysis, we used the ASE definition of diastolic dysfunction. This analysis excluded participants with diastolic dysfunction at baseline. We also explored the evolution of diastolic function by describing the proportion of participants that met at least one of the 4 ASE criteria for diastolic dysfunction.

LVMI was calculated using the Devereux equation.[18] All echocardiograms were reviewed by the study team to evaluate for underlying mitral valve stenosis or regurgitation, pericardial disease, or other pathology that would limit our ability to assess diastolic function. Electrocardiograms were reviewed; participants with atrial fibrillation or left bundle branch block were excluded.

TABLE 2 Change in LV Structure and Function

	PLWH (n = 367)			HIV-Uninfected Community Controls (n = 414)			P Value for Difference in Difference[a]
	Baseline	Final	Change	Baseline	Final	Change	
LV structure							
LV end-diastolic diameter (cm)	4.2 (3.8-4.5)	3.9 (3.6-4.2)	−0.3 (−0.7 to 0.1)	4.2 (3.9-4.5)	3.9 (3.6-4.2)	−0.3 (−0.7 to 0.1)	0.5484
LV end-diastolic volume (mL)	76.8 (62.3-92.0)	63.9 (53.3-78.6)	−10.1 (−28.8 to 4.4)	79.0 (66.7-93.9)	64.7 (53.1-79.5)	−15.4 (−28.2 to 2.0)	0.2012
LV mass (g)	120.5 (99.1-143.2)	137.1 (116.0-166.5)	15.9 (−3.4 to 38.6)	114.6 (97.9-138.2)	137.0 (115.4-159.7)	19.4 (2.6-40.9)	0.0604
LV ejection fraction (%)	66.0 (61.0-72.0)	60.0 (54.0-67.0)	−6.0 (−15.0 to 3.0)	66.0 (60.0-73.0)	62.0 (55.0-68.0)	−5.0 (−13.0 to 5.0)	0.3622

Values are median (IQR). [a]P values were calculated by t-tests.

Abbreviations as in **Table 1**.

STATISTICAL ANALYSIS. Descriptive statistics, including percentages, medians, and IQR, were calculated for baseline characteristics. As our study was primarily focused on the incidence of diastolic dysfunction and progression of diastolic dysfunction and LVMI, we excluded participants who only completed one echocardiogram. The analytic approaches used for the primary results, including survival analysis and mixed effect linear regressions, accounted for the variability in timing of follow-up echocardiography.

We described the incidence of diastolic dysfunction in the cohort and used Cox proportional HR models to estimate the unadjusted and adjusted HR for worsening of diastolic function; participants with prevalent diastolic dysfunction were excluded from these models. Models were adjusted for baseline age,

sex, body mass index (BMI), systolic BP, and smoking; these confounders were determined a priori.

We evaluated the impact of HIV infection, age, sex, BMI, systolic BP, and smoking on risk of developing one or more ASE criteria for diastolic dysfunction: 1) septal e' <7 cm/s or lateral e' <10cm/s; 2) average E/e' ratio >14; 3) left atrium (LA) volume index >34 mL/m²; or 4) peak tricuspid regurgitation velocity >2.8 m/s. Results were represented with Kaplan-Meier curves, and the differences of the curves by groups were assessed by a log-rank test.

In all time-to-event analyses, we accounted for the competing risk of death. Because there were very few deaths during the follow-up period (6 deaths), there was no difference between the original Cox proportional HR models and the competing risk regression models.

TABLE 3 Diastolic Dysfunction by HIV Serostatus (N = 781)

	PLWH (n = 367)	HIV-Uninfected Community Controls (n = 414)	PLWH Compared to Community Controls	
			HR	aHR
CHART study definition of diastolic dysfunction				
Excluded (baseline LV EF ≤50%)	13 (3.5%)	22 (5.3%)	–	–
Incident diastolic dysfunction	46 (12.5%)	50 (13.6%)	0.84 (0.56-1.26)	0.93 (0.61-1.42)
Improvement in diastolic function (diastolic dysfunction → normal function)	0 (0.0%)	0 (0.0%)	–	–
Normal diastolic function throughout study period	271 (73.8%)	311 (84.7%)	–	–
Stable diastolic dysfunction throughout study period	37 (10.1%)	31 (8.4%)	–	–
Incident rate ratio per 1,000 person-years	0.15 (0.11-0.20)	0.15 (0.11-0.20)	–	–
2016 American Society of Echocardiography (ASE) guidelines for diastolic dysfunction				
Incident diastolic dysfunction	50 (13.6%)	40 (9.7%)	1.07 (0.71-1.63)	1.09 (0.70-1.68)
Improvement in diastolic function (diastolic dysfunction → normal function)	9 (2.5%)	11 (2.7%)	–	–
Normal diastolic function throughout study period	307 (83.7%)	362 (87.4%)	–	–
Stable diastolic dysfunction throughout study period	1 (0.3%)	1 (0.2%)	–	–
Incident rate ratio per 1,000 person-years	0.14 (0.10-0.19)	0.11 (0.08-0.15)	–	–

HRs and adjusted HRs were derived from Cox proportional hazard regression models. Adjusted models included baseline age, sex, BMI, systolic blood pressure, smoking, and diabetes as covariates.

aHR = adjusted HR; CHART = characterizing heart function on antiretroviral therapy; other abbreviation as in **Table 1**.

FIGURE 1   Incidence of Diastolic Dysfunction by HIV Serostatus Among Participants Without Baseline Diastolic Dysfunction
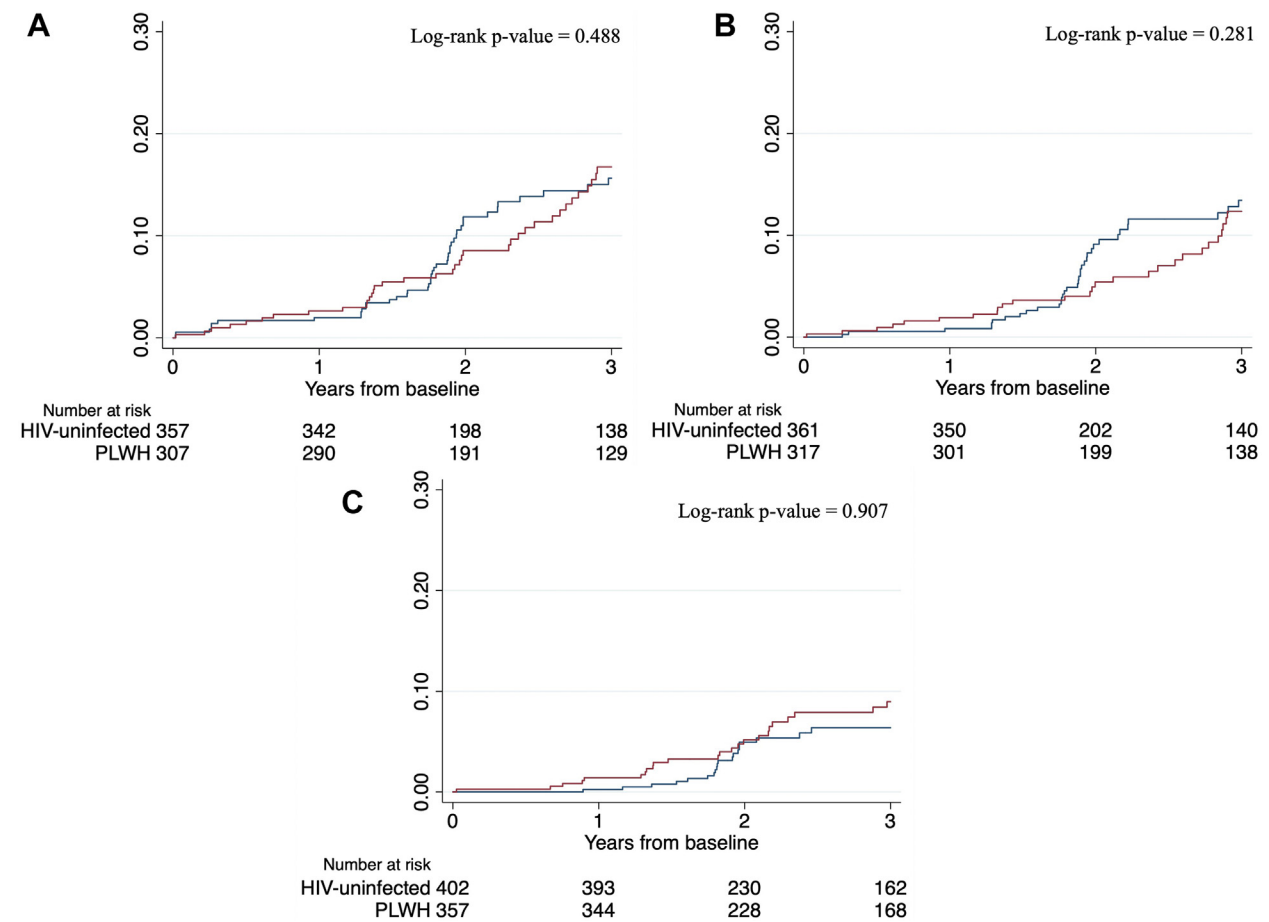
There was no difference in the incidence of diastolic dysfunction between PLWH and community controls. This was true using: (A) CHART study definition of diastolic dysfunction; (B) 2016 ASE definition of diastolic dysfunction; (C) time to meeting 1 or more ASE criteria for diastolic dysfunction. ASE = American Society of Echocardiography; CHART = characterizing heart function on antiretroviral therapy; PLWH = people living with HIV.

Mixed effects linear regression models were used to evaluate the effect of traditional, endemic, and HIV-specific risk factors on average echocardiographic measures of preclinical CVD, namely LVMI and 4 measures of diastolic dysfunction—E/e' average ratio, septal e' and lateral e' mitral valve annular velocities, and LA volume index. A random intercept was included in the model for each participant. Final models assessing the average impact of HIV infection were again adjusted for baseline age, sex, BMI, systolic BP, diabetes, smoking, and the amount of time elapsed from the enrollment echocardiogram. When LVMI and LA volume index were the outcomes of interest, BMI was not included since weight and height are included in the indexing of these variables. An interaction term between HIV serostatus and duration of follow-up was used to assess for effect

modification in the progression of LVMI and diastolic dysfunction. HIV-specific risk factors on diastolic dysfunction and LVMI were evaluated.

All analyses were performed using Stata, version 15 (StataCorp).

RESULTS

A total of 1,000 participants (496 PLWH and 504 community controls) were enrolled in the study between November 2016 and March 2020. Baseline differences in cardiac structure and function by HIV serostatus were previously reported.[7] Of the 1,000 participants enrolled in the study, 781 were included in the final analytic cohort, 46 died prior completing any follow-up echocardiography, and 173 did not return for repeat echocardiography

FIGURE 2 Traditional CVD Risk Factors for Meeting One or More Criteria for Diastolic Dysfunction by Baseline Age, Baseline Blood Pressure Status, and Baseline Body Mass Index
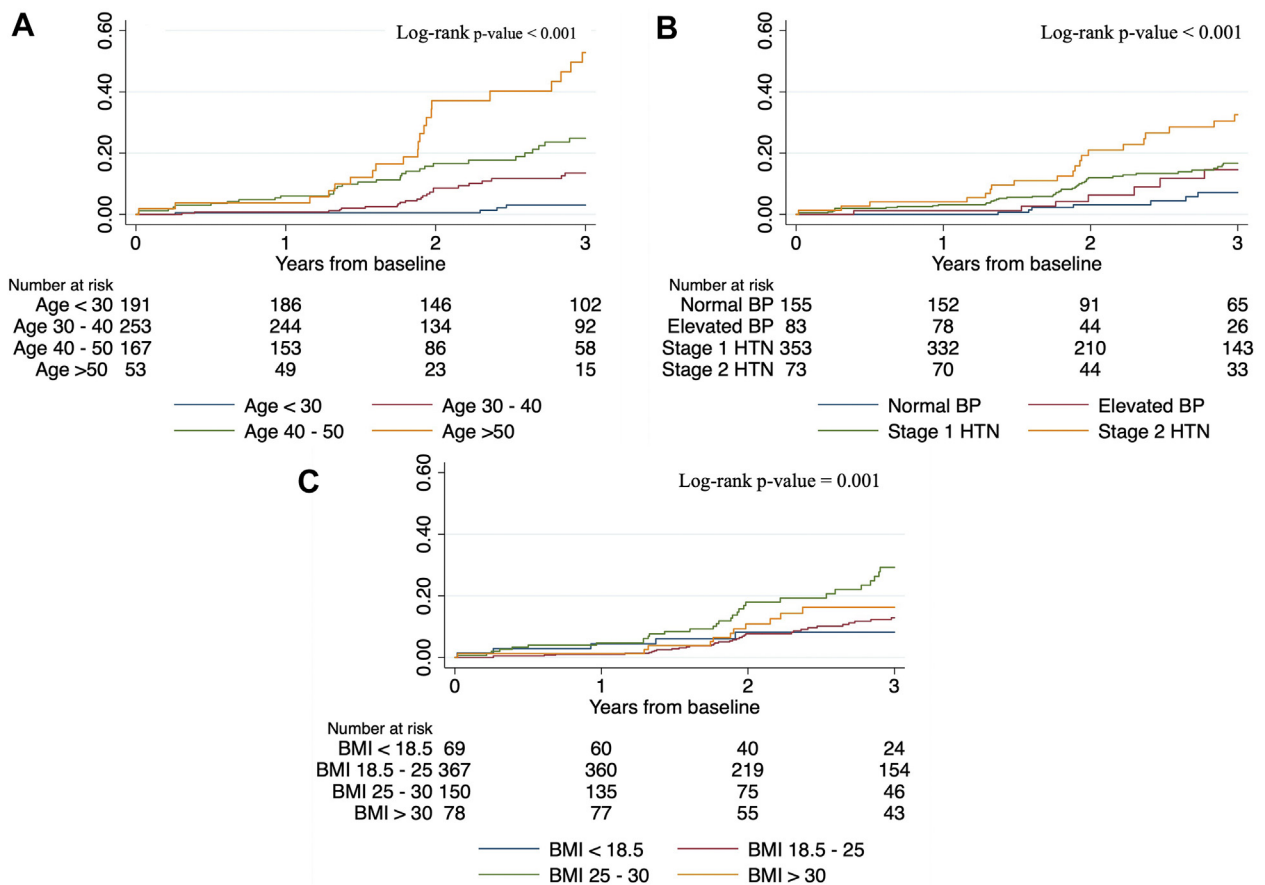

Traditional CVD risk factors for meeting one or more criteria for diastolic dysfunction by (A) baseline age, (B) baseline blood pressure status, and (C) baseline body mass index. Higher baseline age, higher baseline blood pressure, and higher baseline BMI preceded and predicted the incidence of at least 1 of the 4 2016 ASE criteria for diastolic dysfunction (log-rank $P < 0.001$). BMI = body mass index; CVD = cardiovascular disease; other abbreviation as in **Figure 1**.

(Supplemental Figure 1). A majority of those who died (43/46) were PLWH; 33 of the 43 deaths in PLWH were related to advanced HIV infection. Four out of 46 deaths were due to CVD and occurred in PLWH. The baseline characteristics between those included in the analytic cohort (n = 781) and those who contributed no echocardiograms during follow-up (n = 173) were largely similar and described in Supplemental Table 1.

The final analytic cohort consisted of 781 participants (367 [47%] PLWH). A total of 1,955 echocardiograms were completed (936 [48%] in PLWH). Of the 781 participants in the analytic cohort, 446 (57%) completed 2 echocardiograms, and 335 (43%) completed 3 or more echocardiograms. PLWH had a median of 2 [IQR: 2-3] echocardiograms performed, which was the same for HIV-uninfected community controls 2 [IQR: 2-3].

Baseline characteristics are described in **Table 1**. Baseline echocardiogram data are described in **Table 1**; changes in left ventricular structure and function are presented in **Table 2**. The median age was 36 in both PLWH and community controls. Participants were relatively healthy. Obesity was uncommon in PLWH (10%) and community controls (11%), as was hypertension (PLWH: 8%; community controls: 10%) and diabetes (PLWH: 2%; community controls: 2%). The median 10-year predicted risk of a cardiovascular event, using the 2017 World Health Organization lipid-based risk charts, was low (PLWH: 0.9%; community controls: 1.1%). At enrollment, 79% (289/367) of PLWH were initiated on tenofovir, lamivudine, and efavirenz and 21% (78/367) were started on tenofovir, lamivudine, and dolutegravir. Those started on efavirenz-based regimens were switched to dolutegravir when Tanzanian National guidelines

FIGURE 3 Evolution of LVMI and Diastolic Function by HIV Serostatus
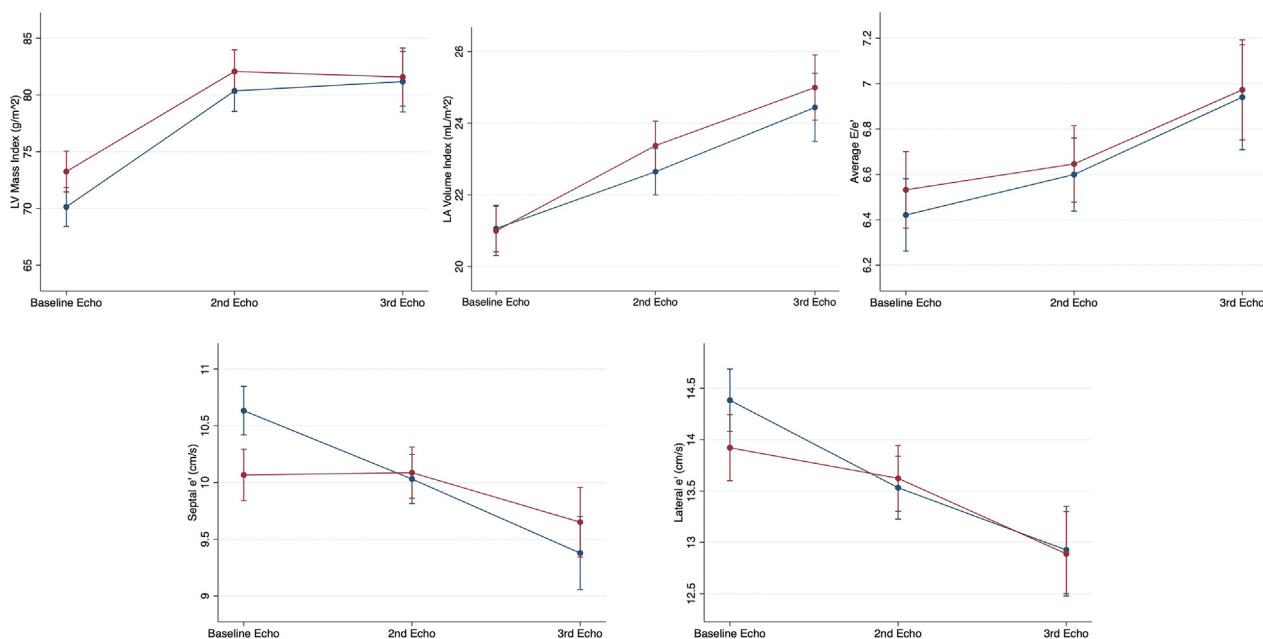
This figure displays differences between baseline, 2nd, and 3rd echocardiogram by HIV status. At the time of the baseline echocardiogram, PLWH had a higher LVMI than community controls and lower mitral valve annular velocities, but these differences resolved with time. LVMI = left ventricular mass index; other abbreviation as in **Figure 1**.

changed in 2019; all PLWH were on dolutegravir-based regimens by the end of the study period, except for 5 PLWH who transitioned to second-line PI-based ART. A majority of PLWH were virologically suppressed; only 15.5% (57/367) had a detectable viral load (>25 copies/mL) during the entirety of follow-up.
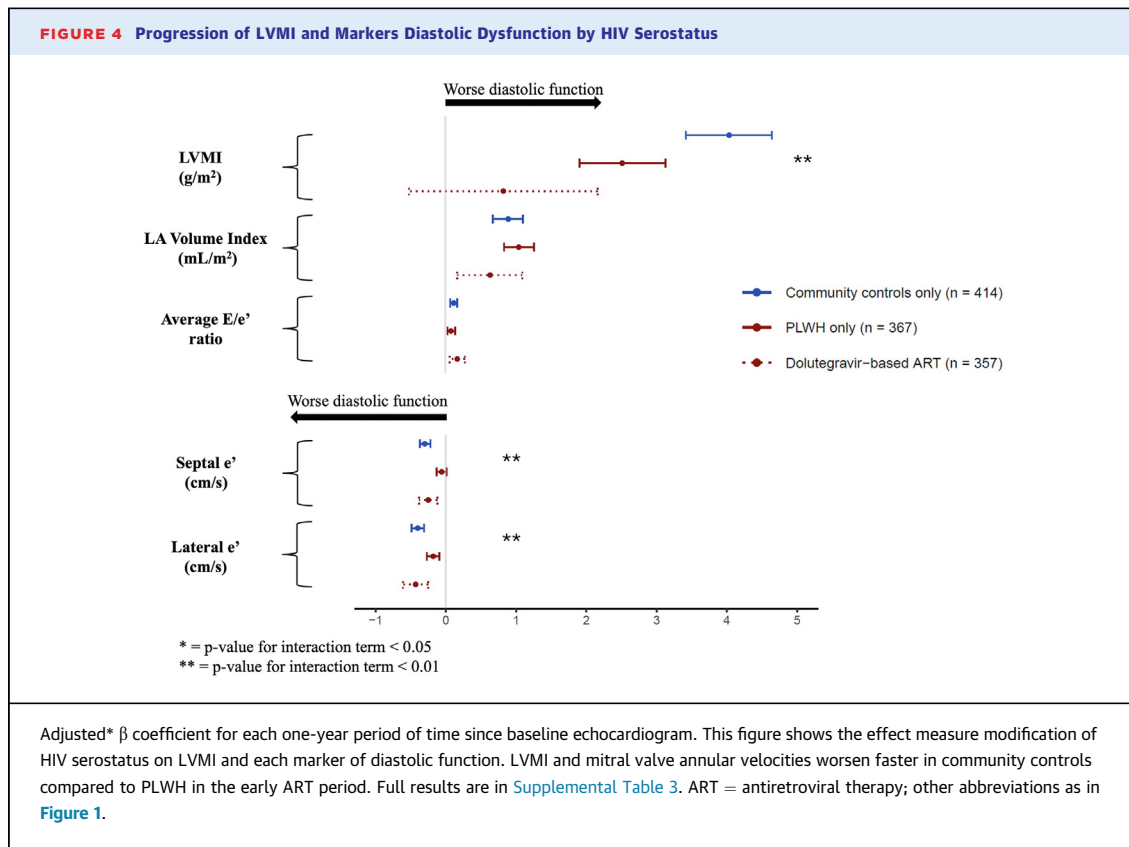
INCIDENCE OF DIASTOLIC DYSFUNCTION. The incidence of diastolic dysfunction did not differ between PLWH and HIV-uninfected adults using each of the 3 definitions of diastolic dysfunction used in this study. Specifically, using the CHART criteria for diastolic dysfunction, the incident rate ratio in PLWH 0.15 (0.11-0.20) per 1,000 person-years was the same as community controls 0.15 (0.11-0.20) per 1,000 person-years (**Table 3**). The time to incident diastolic dysfunction between PLWH and community controls is displayed in **Figure 1**.

Using the CHART criteria for diastolic dysfunction (**Table 3**), a total of 96 participants met the criteria for incident diastolic dysfunction (46/367 [12.5%] of PLWH vs 50/414 [13.6%] of community controls). There was no difference in the unadjusted or adjusted

HRs of incident diastolic dysfunction by HIV serostatus using the CHART definition (aHR: 0.93 [95% CI: 0.61-1.42]; PLWH vs HIV-uninfected).

Using the 2016 ASE diagnostic criteria for diastolic dysfunction, 90 participants had incident diastolic dysfunction (50/367 [13.6%] of PLWH vs 40/414 [9.7%] of community controls). There was no difference in the unadjusted and adjusted HRs for incident diastolic dysfunction (aHR: 1.09 [95% CI: 0.70-1.68] PLWH vs HIV-uninfected). In a sensitivity analysis, where echocardiograms that were indeterminant by ASE guidelines (n = 30) were categorized as having diastolic dysfunction, there was still no difference in the incidence of diastolic dysfunction (aHR: 1.16 [95% CI: 0.77-1.75] PLWH vs HIV-uninfected).

Significant risk factors for the incidence of at least one of the 4 2016 ASE criteria for diastolic dysfunction included: higher baseline age (log-rank $P <$ 0.001), higher baseline BP ($P <$ 0.001), and higher baseline BMI ($P <$ 0.001) (**Figure 2**). Among participants who were free from any markers of diastolic dysfunction at baseline, >50% of the participants over the age of 50 years and >25% of participants

FIGURE 4 Progression of LVMI and Markers Diastolic Dysfunction by HIV Serostatus

Adjusted* β coefficient for each one-year period of time since baseline echocardiogram. This figure shows the effect measure modification of HIV serostatus on LVMI and each marker of diastolic function. LVMI and mitral valve annular velocities worsen faster in community controls compared to PLWH in the early ART period. Full results are in Supplemental Table 3. ART = antiretroviral therapy; other abbreviations as in Figure 1.

with stage 2 hypertension met at least one criterion for diastolic dysfunction within 3 years of study enrollment.

PROGRESSION OF DIASTOLIC DYSFUNCTION AND LVMI BY HIV SEROSTATUS. Echocardiographic measures of diastolic function and LVMI worsened during the duration of study as expected. Over each 1-year period of follow-up time (Supplemental Table 2, final row): LVMI increased 3.30 gm/m^2/year of follow-up (95% CI: 2.86-3.74); LA volume index increased 0.98 mL/m^2/year of follow-up (95% CI: 0.82-1.13); average E/e' ratio increased 0.10/year of follow-up (95% CI: 0.06-0.14); and mitral valve annular velocities decreased: septal e' −0.18 cm/s/year of follow-up (95% CI: −0.23 to −0.12) and lateral e' −0.29 cm/s/year of follow-up (95% CI: −0.35 to −0.22).

There were several differences in the 1st echocardiogram measurements of diastolic dysfunction and LVMI between recently diagnosed PLWH and community controls (Figure 3). At the time of the baseline echocardiogram, PLWH had a 3.57 g/m^2 (95% CI: 0.87-6.26) higher LVMI than community controls and lower mitral valve annular velocities. Specifically, septal e' velocity was −0.57 cm/s (95% CI: −0.88 to −0.26) lower and lateral e' velocity

was −0.46 cm/s (95% CI: -0.90 to −0.02) lower in PLWH vs community controls.

By the 2nd and 3rd echocardiogram measurement, there were no statistically significant differences in diastolic function or LVMI between PLWH and community controls (Figure 3). Notably, the differences observed in baseline LVMI and mitral valve annular velocities between PLWH and community controls had resolved within 3 years of ART initiation.

After ART initiation, PLWH experienced slower rates of worsening of LVMI and mitral valve velocity compared to community controls. This was quantified in adjusted mixed effects models assessing for effect measure modification of HIV serostatus on LVMI and each marker of diastolic function (Figure 4, Supplemental Table 3). LVMI increased 1.52 gm/m^2/year of follow-up (95% CI: 0.66-2.38) faster in community controls compared to PLWH, septal e' velocity decreased 0.24 cm/s/year of follow-up faster (95% CI: 0.13-0.34) in community controls vs PLWH, and lateral e' velocity decreased 0.22 cm/s/year of follow-up faster (95% CI: 0.13-0.34) in community controls than PLWH. There were no statistically significant differences in baseline LA volume index or average E/e' and no evidence that these markers of diastolic dysfunction evolved differently by HIV serostatus.

TABLE 4   Endemic and HIV-Specific Risk Factors for Average Diastolic Function and LVMI, Adjusted[a] Mixed Effects Models

	LVMI (g/m²)	LA Volume Index (mL/m²)	Average E/e' ratio	Septal e' (cm/s)	Lateral e' (cm/s)
Endemic risk factors (n = 718, 1,995 echocardiograms)					
Manual labor[b] [ref: office or domestic]	**2.68 (0.07-5.29)**	**1.25 (0.31-2.19)**	0.00 (−0.22 to 0.22)	0.16 (−0.10 to 0.42)	0.20 (−0.15 to 0.54)
Baseline kidney disease (eGFR: <45 mL/min/1.73 m²)	**9.93 (2.67-17.20)**	2.54 (−0.08 to 5.16)	0.52 (−0.09 to 1.13)	0.11 (−0.61 to 0.83)	−0.01 (−0.99 to 0.96)
Baseline ACR (per 30 increase)	**0.47 (0.29-0.64)**	**0.13 (0.06-0.19)**	**0.02 (0.00-0.03)**	**−0.03 (−0.05 to −0.01)**	−0.02 (−0.04 to 0.00)
Moderate or severe anemia [ref: normal Hb or mild anemia][b]	**8.00 (5.34-10.66)**	**3.87 (2.93-4.80)**	**0.23 (0.00-0.45)**	0.14 (−0.16 to 0.44)	0.19 (−0.19 to 0.57)
Baseline sickle cell trait [ref: normal hemoglobin]	0.79 (−1.82 to 3.39)	0.17 (−0.78 to 1.11)	−0.09 (−0.31 to 0.13)	−0.08 (−0.34 to 0.17)	−0.01 (−0.35 to 0.34)
HIV-specific risk factors, (n = 367; 936 echocardiograms)					
Baseline sST2 (per 10 pg/mL increase)	2.67 (0.81-4.53)	**0.83 (0.19-1.47)**	0.09 (−0.06 to 0.25)	**−0.19 (−0.37 to −0.01)**	−0.16 (−0.41 to 0.09)
Current CD4 count (per 100 cells/mL increase)[b]	0.11 (−0.33 to 0.54)	−0.07 (−0.22 to 0.09)	0.01 (−0.02 to 0.05)	0.04 (−0.00 to 0.09)	0.05 (−0.01 to 0.11)
Viral load unsuppressed (VL ≥ 25 copies/mL)[b]	4.04 (−0.67 to 8.75)	1.07 (−0.54 to 2.68)	−0.10 (−0.51 to 0.30)	−0.15 (−0.62 to 0.32)	−0.62 (−1.27 to 0.04)

Values are β (95% CI). Statistically significant values (*P* value < 0.05) are **bolded**. [a]All mixed effects models were adjusted for baseline age, sex, BMI, systolic blood pressure, diabetes, smoking, and time elapsed since baseline echocardiogram and included a random intercept for each participant. With the exception of age and sex, all of these covariates were time varying and measured at each study visit. [b]Time varying covariates.

ACR = albumin to creatinine ratio; LVMI = left ventricular mass index; LA = left atrium; other abbreviations as in Table 1.

In a sub-group analysis of PLWH who were on dolutegravir-based ART regimens, there was no evidence diastolic function or LVMI progressed differently during study follow-up compared to the overall cohort of all PLWH (**Figure 4**, Supplemental Table 2).

HIV-SPECIFIC AND ENDEMIC RISK FACTORS FOR PRECLINICAL CVD. HIV-specific risk factors.

We used mixed effects regression models with time-varying covariates to examine HIV-specific risk factors for echocardiographic markers of diastolic dysfunction. None of the commonly measured laboratory markers of HIV severity or control (eg, nadir CD4 count, CD4 count, CD4 percentage, or viral load) were significantly associated with diastolic function or LVMI (**Table 4**, Supplemental Table 4). We similarly saw no difference in diastolic function or LVMI between PLWH who had a history of tuberculosis versus those who did not. Each 10 ng/mL increase in the baseline sST2 was independently associated with a 2.67 gm/m² (95% CI: 0.81-4.53) increase in average LVMI, an 0.83 mL/m² (95% CI: 0.19-1.47) increase LA volume, and a −0.19 cm/s (95% CI: −0.37 to −0.01) decrease in septal e' velocity.

Endemic risk factors. In adjusted mixed effect models, there were several risk factors that impacted diastolic function and LVMI (**Table 4**, Supplemental Table 5). Higher baseline ACR was associated with worse measures of diastolic function and higher LVMI. A baseline estimated glomerular filtration rate <45 mL/min/1.73 m² was associated with higher LVMI compared to those with normal renal function but had no impact on markers of diastolic function.

Moderate or severe anemia was associated with increases in both average E/e' ratio and LA volume index. Manual labor was associated with increased LA volume index and LVMI.
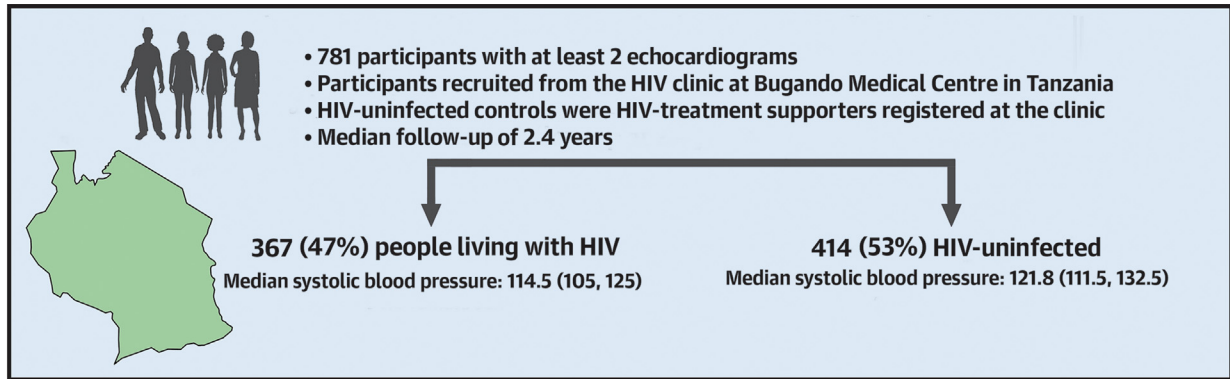
Traditional risk factors. In adjusted mixed effects models (Supplemental Table 2), baseline age, systolic BP, and obesity had the expected relationships with markers of diastolic dysfunction and LVMI, consistent with the results presented in **Figure 1**.

DISCUSSION

To our knowledge, this is the first study from sub-Saharan Africa to report longitudinal echocardiographic data for diastolic dysfunction. We observed no difference in the incidence of diastolic dysfunction between PLWH and community controls living in Tanzania (**Central Illustration**). Differences observed in individual markers of diastolic function and LVH between untreated PLWH and community controls resolved within 3 years of ART initiation. Hypertension and obesity were the 2 most important modifiable risk factors for incident diastolic dysfunction. Anemia was strongly associated with higher LVMI and LA volume index. Albuminuria was strongly linked with worse diastolic function and increased LVMI.

Our results offer reassurance that PLWH in Tanzania on stable ART do not appear to have a higher incidence of diastolic dysfunction than community controls. In a study of 781 participants followed for an average of 3 years, the incidence of diastolic dysfunction did not differ by HIV serostatus. We and others have previously reported an increased prevalence of diastolic dysfunction in cross-sectional

CENTRAL ILLUSTRATION Incidence and Progression of Diastolic Dysfunction and Left Ventricular Hypertrophy in People Living With HIV in Tanzania

- 781 participants with at least 2 echocardiograms
- Participants recruited from the HIV clinic at Bugando Medical Centre in Tanzania
- HIV-uninfected controls were HIV-treatment supporters registered at the clinic
- Median follow-up of 2.4 years

367 (47%) people living with HIV
Median systolic blood pressure: 114.5 (105, 125)

414 (53%) HIV-uninfected
Median systolic blood pressure: 121.8 (111.5, 132.5)

There was no difference in the incidence of disastolic dysfunction by HIV serostatus

Baseline differences in left ventricular mass index resolved within 3 years of antiretroviral therapy initiation

CHART study definition of diastolic dysfunction
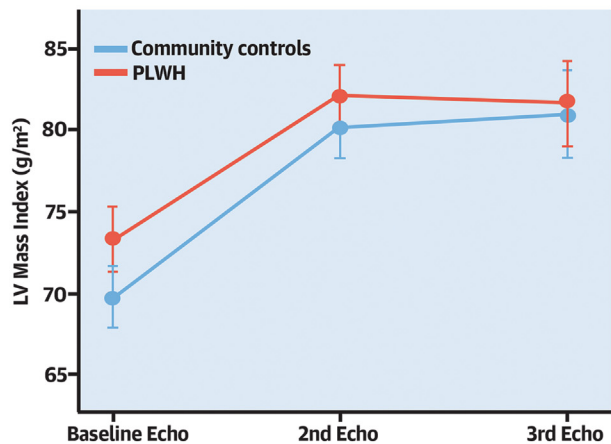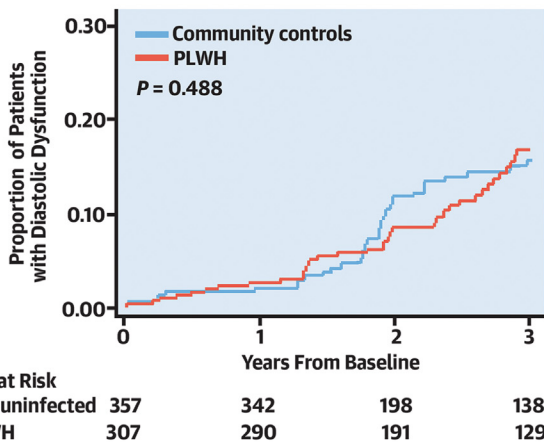
— Community controls
— PLWH
P = 0.488

No. at Risk
	0	1	2	3
HIV-uninfected	357	342	198	138
PLWH	307	290	191	129

- Hypertension and obesity were important modifiable risk factors for diastolic dysfunction
- Efforts to prevent diastolic heart failure in Africa must focus on addressing known factors associated with cardiovascular disease, while continuing to investigate non-traditional, endemic risk factors

Cichowitz C, et al. JACC Adv. 2024;3(12):101238.

Abbreviations as in **Figure 1**.

analyses of PLWH compared to community controls.[7,9,11] Based on these findings, many HIV research groups including our own have hypothesized that PLWH could suffer from an increased incidence and a faster progression of diastolic dysfunction. Our study failed to find any evidence to support this hypothesis. The results were largely similar when looking at multiple definitions of diastolic dysfunction and also when looking at individual markers of diastolic function.

A strength of our cohort is that, unlike most studies from the United States that have focused on those with long-standing HIV, our cohort enrolled newly diagnosed PLWH so as to investigate the incidence of diastolic dysfunction immediately after the initiation of ART.[9,11] Untreated HIV infection appears to have a

strong influence on cardiac structure and function, leading to deleterious changes in diastolic function and LVMI that we previously reported.[7] Promisingly, in this cohort, these differences between PLWH and community controls resolved within a few years of treatment, even when patients were enrolled with low CD4 counts and advanced immunosuppression.

Emerging evidence suggests that integrase strand inhibitors, which are now recommended as the first-line treatment for HIV globally, may be associated with excessive rates of major adverse cardiac events.[19] In our cohort, most participants either started on integrase strand inhibitors or were switched to integrase inhibitors when the national ART guidelines changed. In a subgroup analysis, we found no evidence that integrase inhibitor (dolutegravir) therapy was associated with diastolic dysfunction or LVH. These results offer some reassurance although long-term studies are needed to monitor the cardiovascular safety of integrase inhibitors across a variety of clinical CVD endpoints.

Regarding sST2, our results confirm and extend the findings of our baseline analysis.[7] Elevated sST2 at baseline predicted LVH and worse diastolic function throughout the follow-up period. Additional research is needed to examine whether sST2 levels are associated with clinical heart failure events in PLWH and may be a useful risk prediction tool following a new diagnosis of HIV.

Our data suggest that, beyond PLWH, diastolic dysfunction will be a general concern as the African population ages. In both PLWH and community controls, high BP was the most important modifiable risk factor for diastolic dysfunction. Systolic BP was associated with higher average LVMI and worse diastolic function. Hypertension was associated with incident diastolic dysfunction and there was a dose-dependent relationship between high BP and diastolic dysfunction. Compared to other modifiable risk factors—like smoking, exercise, alcohol consumption, and diet—hypertension had the largest and most consistent impact on diastolic function and LVMI. There is an urgent need to integrate hypertension management into primary HIV care and more broadly in primary care systems in Africa.[20,21]

Anemia and subclinical kidney disease may be important endemic risk factors for diastolic function in Africa. Countries in sub-Saharan Africa experience some of the highest rates of anemia in the world,[22] and the prevalence of severe anemia among PLWH in East Africa is as high as 20%.[23] In our population, moderate and severe anemia were more common in PLWH (15% in PLWH vs 5% in HIV-uninfected) and were associated with large increases in LMVI. Anemia is a well-established risk factor for heart failure and LVH in high-income settings.[24,25] Given the prevalence of anemia in East Africa and in PLWH, cardiovascular prevention efforts should incorporate ways to test and treat for anemia. Similarly, kidney disease, a known risk factor for CVD,[26] has been understudied in Africa and is an increasingly recognized as a major contributor to morbidity and mortality low-income countries.[27] In our study, elevated levels of urine albumin to creatinine were associated with worse diastolic function and elevated LVMI, a finding that was previously observed in high-income countries.[28] Additional research is needed to see evaluate whether these types of biomarkers, which are easy to obtain in resource-limited settings, can help identify the highest-risk patients and guide CVD prevention. In this study, manual labor was also associated with increased LVMI and LA volume index even after adjusting for BP. Finally, exposure to manual labor was common within our cohort (~30%). We previously showed manual labor was associated with persistently higher BP over time.[12] The deleterious changes observed in cardiac structure may be due to prolonged states of physical exertion and heat exposure.[29,30] On the other hand, the observed changes in LV mass and LV volume index could simply be markers of an athlete's heart in people engaging in manual labor. The relationship between endemic risk factors and CVD events and the best ways to mitigate their impact of cardiovascular health warrant further investigation.

STUDY LIMITATIONS. There are several important limitations to this study. First, due to COVID-19, echocardiograms were not performed at all regularly scheduled time points. Consequently, not all participants had the same number of echocardiograms performed nor were follow-up echocardiograms completed at uniform time intervals; however, the primary analytic methods accounted for the total amount of follow-up time each participant contributed. Second, the analytic cohort consisted of a healthier subgroup of those originally enrolled in the study because many PLWH died prior to completion of 2 or more echocardiograms. This high rate of mortality in the early ART period is a sad reality in resource-limited settings and is a common challenge for clinicians and studies focusing on the early ART period. Third, we could not directly quantify the effect of ART on diastolic dysfunction in PLWH since this study lacked an ART untreated control group. Finally, this cohort may not be generalizable older participants or wealthier subpopulations that have a higher prevalence of conditions like obesity and diabetes.

CONCLUSIONS

To the best of our knowledge, this is the first prospective study of incident diastolic function in PLWH and adults living in sub-Saharan Africa. Encouragingly, in a cohort drawn from a typical HIV clinic in Africa, the incidence of diastolic dysfunction was similar between PLWH and HIV-uninfected community controls. Our data reinforce the need for widespread screening and treatment of hypertension to prevent diastolic heart failure in Africa, particularly for older adults. Efforts to prevent diastolic heart failure in Africa should also include investigation of the best ways to mitigate endemic risk factors like anemia and subclinical kidney disease.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: HIV is a known risk factor for CVD. Prevention-focused interventions targeting obesity and BP in Africa are needed to address the growing burden of heart failure.

TRANSLATIONAL OUTLOOK: Additional research is needed to identify endemic risk factors for heart failure in low-income countries and the most cost-effective interventions to prevent the development of CVD.

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APPENDIX For supplemental tables and a figure, please see the online version of this paper.