Original Article

Prevalence and predictors of right ventricular dysfunction among adults living with HIV in northwest Nigeria

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Background: People living with the human immunodeficiency virus (PLWH) are at increased risk of cardiovascular diseases. Right ventricular (RV) function has important prognostic value in cardiac pathology, and advances in imaging modalities, such as transthoracic echocardiography have enabled in-depth RV studies. There is, however, a scarcity of multiparameter RV function studies in PLWH in low- and middle-income settings, such as Nigeria. The aim of this study is to determine the prevalence and predictors of RV dysfunction among adult PLWH in northwest Nigeria.

Methods: This is a retrospective cross-sectional study conducted between February 1, 2023 and August 31, 2023. We consecutively recruited 330 adults [median age 45 years, interquartile range (IQR), 38 to 52 years, 61% female] attending human immunodeficiency virus (HIV) and general outpatient clinics in a tertiary hospital in northwest Nigeria. They included 110 antiretroviral therapy (ART)-experienced PLWH, 110 ART-naïve PLWH, and 110 age- and sex-matched HIV-negative control subjects. All participants had conventional two-dimensional (2D), tissue Doppler (TDI), and speckle tracking (2D-STE) echocardiography to estimate left ventricular (LV) and RV systolic and diastolic function, peak systolic and diastolic myocardial velocities, RV and LV longitudinal strain, and chamber dimensions. All participants also underwent 12-lead electrocardiography. Multiple linear and Firth's logistic regression modeling were performed to assess for independent predictors of RV myocardial performance index (RVMPI) as a continuous and as a dichotomous variable, respectively.

Results: The prevalence of RV dysfunction, as determined by the RVMPI among HIV-positive participants was 14.5% [95% confidence interval (CI): 10.5–19.8%] compared to 0% (95% CI: 0.0–3.4%) for those without HIV. Among participants with HIV, RVMPI was associated with participant age (P<0.001) and left ventricular ejection fraction (LVEF) (P<0.001). Results were similar when RVMPI was dichotomized. The association between RV dysfunction and LVEF was modified by ART status: a 10% decrease in LVEF was associated with an average decrease of 0.08 in RVMPI among participants who were ART-experienced (β=–0.08, P<0.001) but a lesser decrease among those who were ART- naïve (β=–0.03, P=0.14).

Conclusions: This study highlights the complexity of RV dysfunction in PLWH and underscores the importance of LVEF and age as key factors influencing the risk of RV dysfunction in PLWH.

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Keywords: Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS); right ventricular dysfunction (RV dysfunction); non-communicable diseases; antiretroviral therapy (ART); Nigeria

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Introduction

Background

People living with the human immunodeficiency virus (PLWH) are at increased risk of cardiovascular diseases (CVDs) (1-3), such as human immunodeficiency virus (HIV)-associated cardiomyopathy, pulmonary hypertension, and congestive heart failure. This increased risk is attributed to reduced mortality and improved survival in PLWH due to the progress made in the availability and access to effective antiretroviral therapies. Several pathogenetic mechanisms have been proposed as the basis for the spectrum of CVDs seen in HIV. These include systemic chronic inflammation/ immune activation from the HIV virus itself, concomitant viral infections (e.g., *Cytomegalovirus*), exposure to endemic pathogens (e.g., *Mycobacterium tuberculosis*, parasitic infestations), myocarditis from secondary opportunistic infections, micronutrient deficiencies, autonomic dysfunction, tobacco and/or alcohol use, and exposure to specific antiretroviral medications, such as protease inhibitors (4).

Highlight box

Key findings
- Right ventricular (RV) dysfunction as assessed by right ventricular myocardial perfusion index is common among adult Nigerians with the human immunodeficiency virus (HIV).
- RV dysfunction was associated with participant age and left ventricular ejection fraction (LVEF) but not with antiretroviral therapy (ART) use or death.

What is known and what is new?
- The prevalence and association of RV dysfunction with ART and mortality in persons with HIV have been largely understudied.
- RV dysfunction is common in people with HIV and associated with age and LVEF.
- The association between RV dysfunction and LVEF among people living with HIV is modified by ART status.

What is the implication, and what should change now?
- The findings from this study could help inform future directions for improved therapeutic management of patients with HIV and cardiac dysfunction.

Rationale and knowledge gap

Right ventricular (RV) function estimated via echocardiography or radionuclide ventriculography is an important prognostic indicator in ischemic heart disease and dilated cardiomyopathy (5). Despite the prognostic utility and potential therapeutic target of RV dysfunction in many CVDs, its prevalence, predictors, and association with antiretroviral therapy (ART) and mortality have been largely understudied, especially in Nigeria. Earlier studies (6,7), some conducted in the pre-ART era, have attempted to determine the prevalence and presence of subclinical RV dysfunction in PLWH. However, it remains unclear whether there are ART-based differences in the occurrence of RV dysfunction and whether RV dysfunction impacts adverse clinical outcomes in HIV, specifically mortality and rehospitalization rates. In addition, previous studies in PLWH mostly focused on left ventricular (LV) function (8-11), and only a few reports focused on RV dysfunction in Nigeria (12). For decades, the RV has been thought to have limited significant value in cardiac function. The introduction of the Fontan procedure for complex congenital heart disease in 1968, a technique that directly connects the right atrium to the pulmonary artery, thus 'bypassing' the RV, reinforced this belief (13). As a result, the role of the RV in heart failure and other disease states has been largely understudied (14).

Objective

We propose to assess the prevalence of RV dysfunction in the resource-constrained and high HIV burden setting of northwest Nigeria using multiparameter variables, and to explore its association with duration of HIV disease and type of ART regimen. Our work has the potential of advancing our understanding of the pathophysiology of RV dysfunction among PLWH in Nigeria and informing future

directions for improved therapeutic management of patients with HIV and cardiac dysfunction. We present this article in accordance with the STROBE reporting checklist (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-165/rc).

Methods

Study design and setting

This is a retrospective cross-sectional study with participants drawn from adult patients attending the HIV clinic at Aminu Kano Teaching Hospital (AKTH), a public tertiary health facility located in Kano, northwest Nigeria. Kano is the most populous state in Nigeria and has an estimated HIV prevalence of 1.3% (15). The HIV clinic at AKTH is supported by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and provides care for more than 10,000 PLWH. The clinic is also a site for multiple ongoing clinical research studies funded by the U.S. National Institutes of Health (NIH).

Participants

We recruited 220 adult PLWH (18–65 years) from the HIV clinic at AKTH. One half of these adults (n=110) were ART-naïve, while the other half (n=110) were ART-experienced. An age- and sex-matched group of HIV-negative participants (n=110) was recruited from the AKTH general medical outpatient clinic, giving a final sample size of 330 participants. Matching was done using the optimal pair matching ratio of 2:1 (PLWH: controls respectively). Most participants self-referred after receiving information from printed flyers distributed during clinic visits. The ART-naïve participants were mostly referrals from other health facilities (private and public) that lack the capacity to care for PLWH.

We estimated that a minimum sample of 220 PLWH will allow us detect an estimated RV dysfunction prevalence of 16% (±5%) among PLWH (based on a range of 11–20% reported in prior studies) (15) with a confidence level of 95% and assuming a non-response rate of 5%. We assume that RV dysfunction prevalence among HIV-negative persons will be at least half of the prevalence in PLWH, resulting in an estimated minimum sample size of 110 HIV-negative persons.

We excluded persons with the following conditions: history of opportunistic infection within the past three months (using the medical records of the participants and thorough examination), current pregnancy, history of hypertension or on treatment for hypertension, history of diabetes mellitus, not willing to consent, and history of cancer/malignancy. Other exclusion criteria include history of illicit drug use and use of medications with potential for cardiotoxicity (e.g., anthracyclines, 5-fluorouracil, cyclophosphamide, etc.). Individuals with these conditions were excluded due to the potential of these conditions to confound the association between HIV status and right heart function.

Procedures

Eligible and consented participants were consecutively recruited using convenience sampling over a period of six months (February to August 2023). Participants in the control group were enrolled similarly but were recruited from the general outpatient department of the same hospital. Enrolled participants underwent a history and physical examination with emphasis on the cardiovascular and respiratory systems, in addition to a review of clinical records. Basic demographic information such as age, sex, ethnicity, cigarette smoking, and family history of CVD and diabetes mellitus were collected using a structured questionnaire. In addition to the thorough physical examination, control group participants also underwent HIV testing. Data on clinical indices including log viral load, current ART regimen, and duration on ART were extracted from the HIV-positive participants' medical records (*Figure 1*).

Cardiac measurements

Transthoracic echocardiography and 12 lead electrocardiography (ECG) were performed on all participants by an experienced cardiologist with formal training in cardiac imaging using the General Electric (GE) Vivid iq series machine with the 3.5-MHz transducer probe and Schiller AT-2 ECG machine, respectively. Standard Motion-mode (M-mode), two-dimensional (2D), pulse wave (PW), continuous wave (CW), and color Doppler echocardiography were conducted with the patient in the left lateral decubitus position with appropriate adjustments of gain settings, filters, and pulse repetition frequency (PRF) to optimize color saturation.

Right heart measurements

We diagnosed RV dysfunction using multiparameter echocardiographic variables, specifically: tricuspid annular

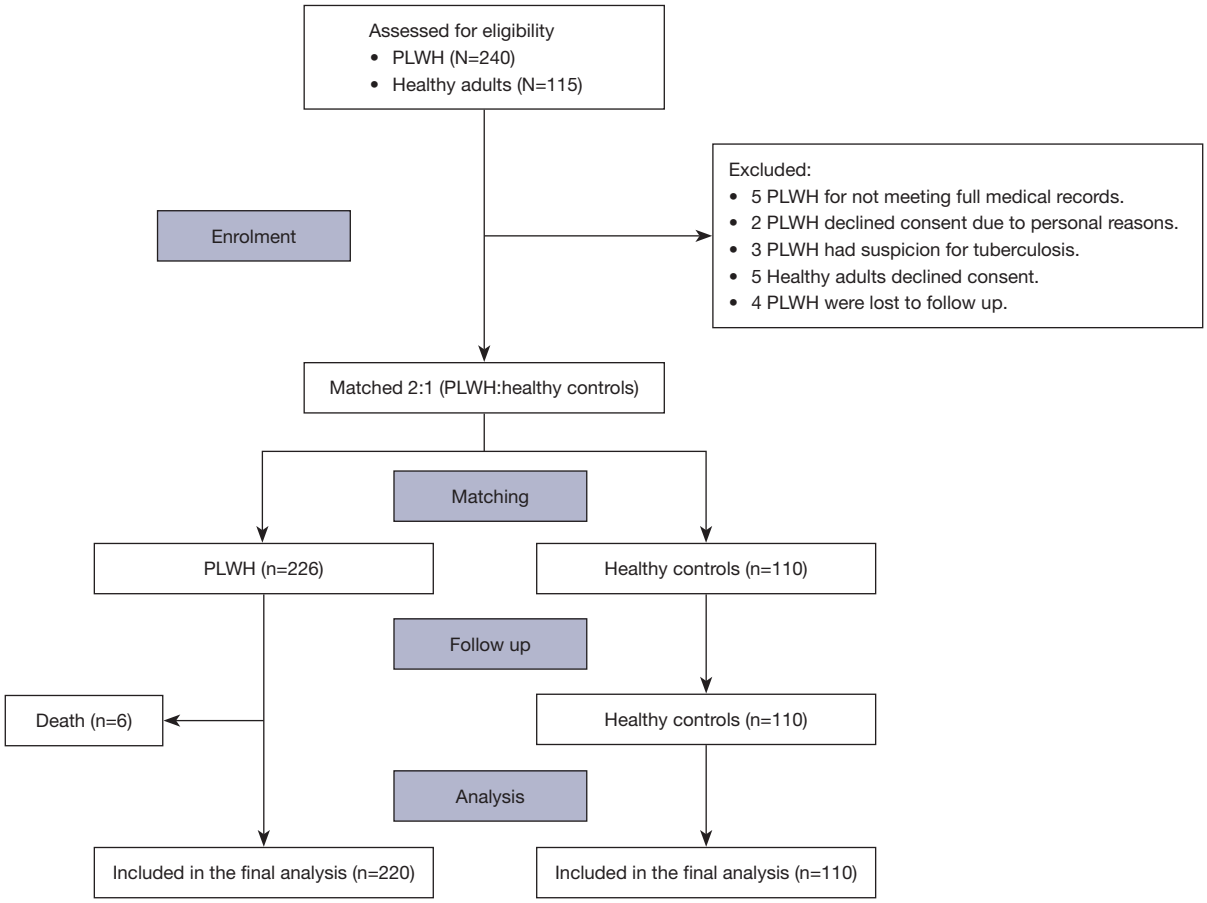

Figure 1 A flow diagram showing participants recruitment. PLWH, people living with human immunodeficiency virus.

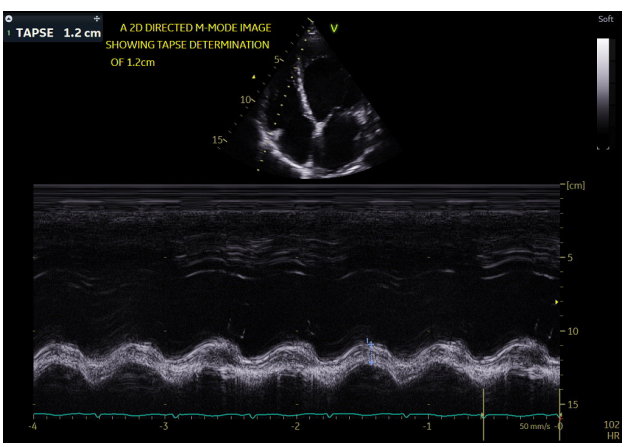

Figure 2 Echocardiographic image of one of the participants showing the 2D directed M-mode TAPSE of 1.2 cm measurement in the RV focused-apical four chamber view. TAPSE, tricuspid annular plane systolic excursion; M-mode, Motion mode; RV, right ventricle; HR, heart rate.

plane systolic excursion (TAPSE); right ventricular fractional area change (RVFAC); right ventricular peak systolic velocity (RV S'); right ventricular myocardial performance index (RVMPI) or Tei Index, and trans-tricuspid valve pulsed wave Doppler interrogation.

The TAPSE was recorded from the apical four-chamber view with the M-mode cursor placed through the lateral tricuspid annulus and the absolute systolic displacement of the annulus measured from peak to trough. Abnormal TAPSE was defined as a value <16 mm (*Figure 2*) (16). The RV area in both diastole and systole was obtained from the apical four-chamber view by planimetry and RVFAC calculated using the formula below:

$$RVFAC = \frac{RV\ end\ diastolic\ area - RV\ end\ systolic\ area}{RV\ end\ diastolic\ area} \times 100\% \quad [1]$$

Abnormal RVFAC was defined as RVFAC <35% (*Figures 3,4*) (16). RVMPI was determined using tissue

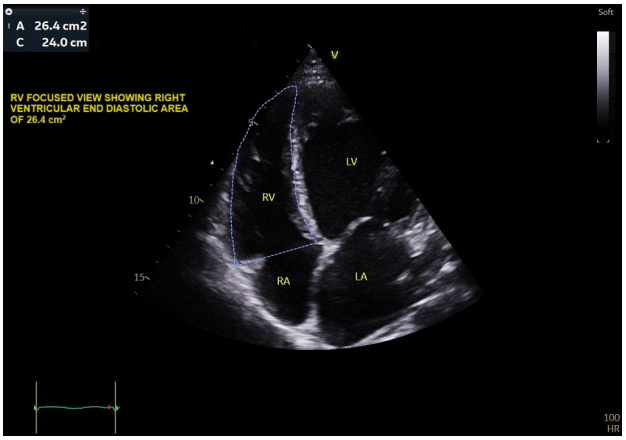

Figure 3 Echocardiographic still image of one of the participants showing determination of the RVEDA (26.4 cm^2) in the apical four chamber view used to determine the RVFAC. RVEDA, right ventricular end diastolic area; RVFAC, right ventricular fractional area change; RV, right ventricle; RA, right atrium; LA, left atrium; LV, left ventricle; HR, heart rate.

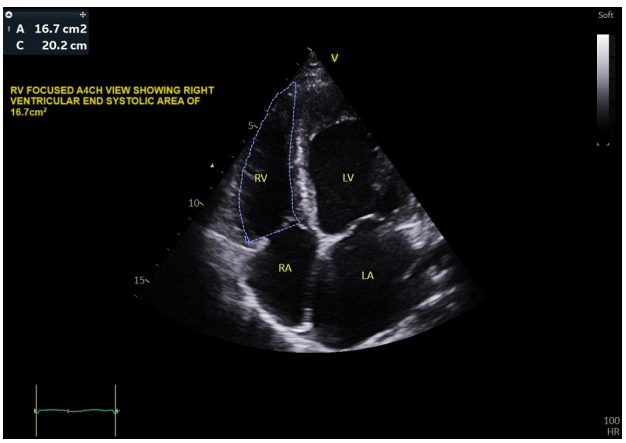

Figure 4 Echocardiographic still image of one of the participants showing determination of the RVESA (16.7 cm^2) in the apical four chamber view used to determine the RVFAC. RVEDA, right ventricular end diastolic area; RVFAC, right ventricular fractional area change; RV, right ventricle; RA, right atrium; LA, left atrium; LV, left ventricle; HR, heart rate.

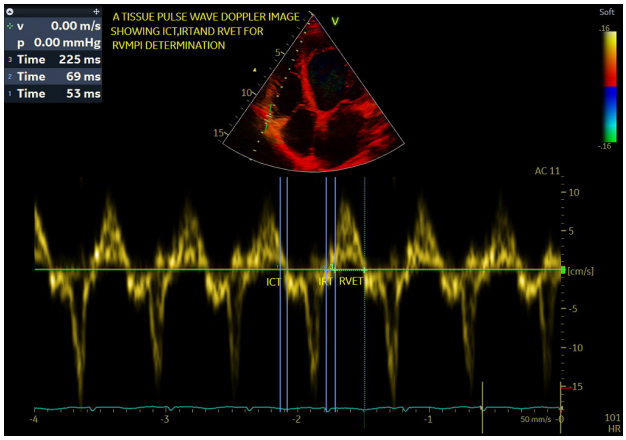

Figure 5 Tissue doppler image echocardiography of one of the participants showing measurement of the ICT, IRT and RVET to determine the RVMPI. Measurement 1 = ICT (53 ms), measurement 2 = IRT (69 ms), measurement 3 = RVET (225 ms). ICT, isovolumic contraction time; IRT, isovolumic relaxation time; RVET, right ventricular ejection time; RVMPI, right ventricular myocardial performance index; V, velocity; P, pressure, HR, heart rate.

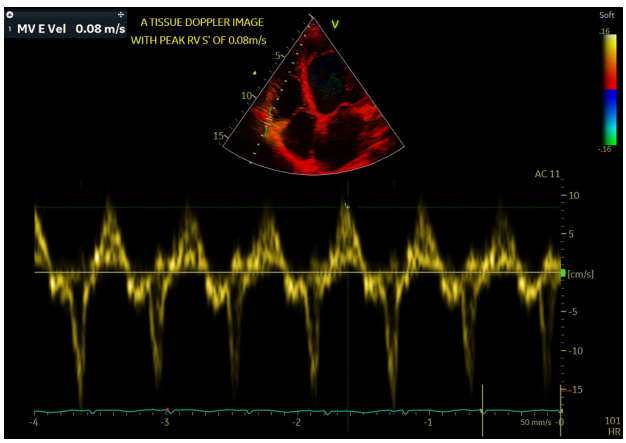

Figure 6 Tissue doppler image echocardiography of one of the participants showing measurement of the right ventricular peak systolic velocity (RV S'=0.08 m/s). E vel, E velocity, HR, heart rate.

Doppler-derived isovolumic (TDI) contraction time, isovolumic relaxation time, and RV ejection time (*Figure 5*). Abnormal RVMPI was defined as >0.55 (16). The pulsed Doppler RV S' at peak lateral annular contraction was determined by tissue Doppler method and abnormal RV S' defined as <10 cm/s (*Figure 6*) (16). From the apical four-chamber view, a 5-mm PW sample volume was placed just apical to the lateral tricuspid valve annulus for the TDI with the RV free wall to obtain a Doppler angulation of close to zero degrees between the interrogating Doppler beam and

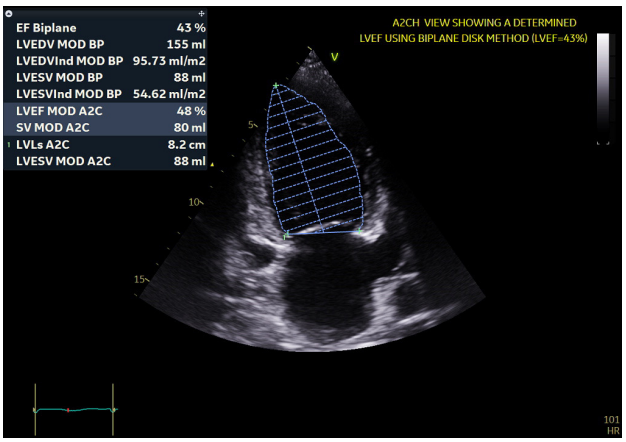

Figure 7 Echocardiographic still image of one of the participants showing determination of the LVEF using the biplane disk method in the apical two chamber view. A2CH, apical 2 chamber; LVEF, left ventricular ejection fraction; EF, ejection fraction; LVEDV, left ventricular end diastolic volume; LVEDVInd, LVEDV index; LVESV, left ventricular end systolic volume; LVESVInd, LVESV index; SV, stroke volume; LVLs, left ventricular length in systole; HR, heart rate.

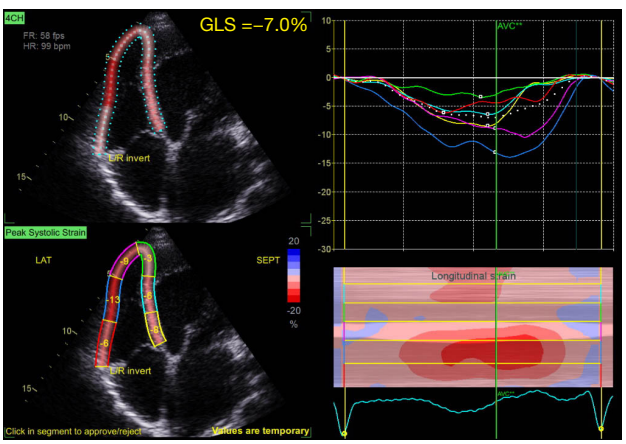

Figure 8 Echocardiographic images of one of the participants showing right ventricular global longitudinal strain (RV GLS= –7.0%) on the left panel, the strain curves and the strain map on the right panel respectively. 4CH, 4-chamber view; FR, frame rate; HR, heart rate; L/R, left/right invert; LAT, lateral; SEPT, septal; AVC, aortic valve closure line; RV, right ventricle; GLS, global longitudinal strain.

the longitudinal motion of the RV free wall. The pulmonary artery systolic pressure (PASP) was determined using the modified Bernoulli equation (16). Pulmonary hypertension was defined as mean pulmonary arterial pressure (mPAP) >20 mmHg (17). All other measurements were performed according to the American Society of Echocardiography (ASE) guidelines (16).

Left heart measurements

The left atrial size and left ventricular ejection fraction (LVEF) were determined using the left atrial volume index (LAVI) and Simpson's biplane disk summation method. The global longitudinal strain (GLS) of both ventricles was assessed to detect subclinical systolic dysfunction. The left atrial volume (LAV) was measured using the modified biplane area-length method and then corrected for body surface to derive the LAVI (18). The LAVI was categorized as either normal (<28 mL/m^2) or increased (mild 29–33 mL/m^2; moderate 34–39 mL/m^2; severe ≥40 mL/m^2) (18). The LVEF was determined using the Simpson's biplane disk summation method, where good 2D apical two-chamber (A2CH) and four-chamber (A4CH) views were obtained and care was taken to avoid apical foreshortening (*Figure 7*). Manual tracing of the endocardial border avoiding the papillary muscles was performed in both end-diastole and end-systole, from the lateral to septal borders of the annulus on the 4-chamber view and the anterior and inferior annular borders on the 2-chamber view. End-diastole was defined as the onset of the QRS complex and end-systole was defined as the end of the T-wave (18).

The GLS of the ventricles was assessed by two-dimensional speckle tracking echocardiography (2D-STE) with the automated function imaging (AFI) software of the vivid iq machine. All images were recorded at a frame rate of 58 cycles/second. The speckles were tracked on the standard grayscale 2D images. Myocardial strain was then calculated by measuring the change of the position of the speckles within the myocardial segment or region of interest during the cardiac cycle. The GLS assessment of the RV was performed using a good RV-focused apical four-chamber view by tracing the endocardial surface of the RV in the apical 4-chamber with a 3-point-and-click approach (*Figure 8*) (19). Care was taken to avoid RV trabeculations. Abnormal RV GLS was defined as –17 and below (19). The GLS of the LV was estimated using the apical two-, three-, and four-chamber views of the LV. A peak systolic longitudinal strain of greater than –18% was accepted as normal) (19).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Conference on Harmonization for Good Clinical Practice (ICH-GCP) (20) guidelines. Ethical approval for the study was obtained from the AKTH Ethics Review Committee and the Vanderbilt

University Medical Center (NHREC/28/01/2020/AKTH/EC/3494, AKTH/MAC/SUB/12A/P-3/VI/3594 and IRB-200119). Eligible participants were approached regarding potential participation in the study, and written informed consent was obtained from all individual participants.

Statistical analysis

We described baseline descriptive statistics for continuous variables using the median ± interquartile range (IQR), as well as percentages and frequencies for categorical variables. The prevalence of echocardiographic abnormalities was determined using simple proportions; 95% confidence intervals (CIs) were calculated with Wilson intervals. Differences between the prevalence of RV dysfunction were tested using Chi-square tests. Differences in function based on the continuous RV measure were assessed using the Wilcoxon rank-sum test. Multiple linear regression modeling was performed to assess for independent predictors of RVMPI as a continuous variable, as it serves as a comprehensive marker for both systolic and diastolic functions of the RV. One model was fit among all participants; a second model was fit among HIV-positive participants and a third with interaction term to evaluate the combined effect of ART status and LVEF. The models included variables deemed clinically meaningful in these analyses: age, sex, LVEF, HIV status (for model with all participants), and ART status (for model among HIV-positive participants). Firth's logistic regression models were fit to investigate predictors of RV dysfunction based on dichotomized RVMPI. R software was used for all computations, and a two-sided P value <0.05 was considered statistically significant.

Results

General clinical characteristics

From February 2023 to August 2023, we sought consent from 240 adults living with HIV who did not have a history of traditional risk factors for CVD and attended the AKTH HIV clinic, along with 115 healthy individuals at the general outpatient clinic. Of the 355 individuals approached, a total of 330 subjects (93%) agreed to participate in the study and provided consent. Among these 330 participants, 220 were PLWH (110 ART-experienced and 110 ART-naïve), and 110 were healthy individuals. The majority of the participants (98%) were urban dwellers residing in Kano.

Women comprised 61% (n=200) of the study population. The overall median age was 45 (IQR, 38–52) years, higher in the control group than in the ART-experienced and ART-naïve arms [48 (IQR, 40–55) *vs.* 43 (IQR, 35–50) *vs.* 42 (IQR, 38–50), respectively, P=0.002] (*Table 1*).

The control group had a higher median body mass index (BMI) [27.0 (IQR, 24.3–29.4) *vs.* 21.4 (IQR, 18.6–24.1) kg/m^2 for ART-naïve and 24.1 (IQR, 21.1–28.4) kg/m^2 for HIV-positive ART experienced participants, P<0.001]. The median systolic blood pressure (SBP) and diastolic blood pressure (DBP) were higher in the PLWH-ART experienced group than in the PLWH-ART naïve group and controls [SBP: 120 (IQR, 110–130) *vs.* 113 (IQR, 100–123) mmHg and 120 (IQR, 115–128) mmHg, P<0.001; DBP: 79 (IQR, 70–82) *vs.* 70 (IQR, 64–80) *vs.* 70 (IQR, 70–76) mmHg, P<0.001; respectively]. There were no differences in baseline pulse rate between the three groups.

Baseline 12-lead electrocardiographic findings

The electrocardiographic parameters of study participants are shown in *Table 2*. The QTc, PR intervals and QRS duration were similar across the three groups. However, the presence of left atrial enlargement (LAE) and voltage criteria for left ventricular hypertrophy (LVH) were observed in only one patient each in the HIV-ART naïve group (P>0.99). There were more patients in the HIV ART-naïve group with tachycardia compared to the other cohorts, and a higher proportion of patients in the HIV ART-experienced group exhibited bradycardia (5.5%, P=0.03).

Baseline echocardiographic findings

The proportion of participants with LVEF lower than 55% was significantly higher among ART-experienced HIV-positive subjects compared to ART-naïve participants and controls (15% *vs.* 0% and 0%) respectively (*Table 2*). The LAVI was also significantly higher in the PLWH-ART experienced cohort (11%) than in the PLWH-ART naïve and controls (0.9% and 0%, respectively). Other metrics such as left ventricular internal dimension in diastole and in systole (LVIDd, LVIDs), LV mass, and left ventricular mass index (LVMI) were all significantly higher in the HIV ART-experienced group compared to the HIV ART-naïve and control groups (*Table 2*).

The HIV ART-experienced group showed higher values for RV basal diameter (RV basal, 12%) and mean pulmonary artery pressure (MPAP, 8.2%) than the other two groups (P<0.001 in both instances). Only 4 participants (3.6%) in the

Table 1 Demographics and vital statistics of study participants by HIV status, Kano, Nigeria

Characteristics	Overall (N=330)	Control (N=110)	HIV$^+$, ART-naïve (N=110)	HIV$^+$, on ART (N=110)	P value
Age (years)	45 (38, 52)	48 (40, 55)	43 (35, 50)	42 (38, 50)	0.002*
Sex					0.02*
Female	200 (61%)	59 (54%)	63 (57%)	78 (71%)	
Marital status					<0.001*
Divorced	22 (6.7%)	3 (2.7%)	7 (6.4%)	12 (11%)	
Married	232 (70%)	97 (88%)	70 (64%)	65 (59%)	
Single	29 (8.8%)	1 (0.9%)	7 (6.4%)	21 (19%)	
Widowed	47 (14%)	9 (8.2%)	26 (24%)	12 (11%)	
Education					<0.001*
Missing/unknown	2 (0.6%)	0 (0%)	0 (0%)	2 (1.8%)	
None/informal education	70 (21%)	22 (20%)	28 (25%)	20 (18%)	
Primary	57 (17%)	27 (25%)	30 (27%)	0 (0%)	
Secondary	137 (42%)	43 (39%)	38 (35%)	56 (51%)	
Tertiary	64 (19%)	18 (16%)	14 (13%)	32 (29%)	
Occupation					<0.001*
Business	111 (34%)	46 (42%)	35 (32%)	30 (27%)	
Civil servant	71 (22%)	21 (19%)	17 (15%)	33 (30%)	
Pensioner	23 (7.0%)	13 (12%)	10 (9.1%)	0 (0%)	
Unemployed	85 (26%)	21 (19%)	25 (23%)	39 (35%)	
Missing	40 (12%)	9 (8.2%)	23 (21%)	8 (7.3%)	
Place of residence					0.008*
Rural	18 (5.5%)	5 (4.5%)	3 (2.7%)	10 (9.1%)	
Semi-urban	22 (6.7%)	7 (6.4%)	14 (12.7%)	1 (0.9%)	
Urban	290 (88%)	98 (89%)	93 (85%)	99 (90%)	
Body surface area (m^2)	1.68 (1.58, 1.79)	1.75 (1.67, 1.86)	1.61 (1.51, 1.70)	1.67 (1.56, 1.79)	<0.001*
Body mass index (kg/m^2)	24.2 (21.0, 27.8)	27.0 (24.3, 29.4)	21.4 (18.6, 24.1)	24.1 (21.1, 28.4)	<0.001*
Systolic blood pressure (mmHg)	120 (110, 128)	120 (115, 128)	113 (100, 123)	120 (110, 130)	<0.001*
Diastolic blood pressure (mmHg)	71 (68, 80)	70 (70, 76)	70 (64, 80)	79 (70, 82)	<0.001*

Data are presented as median (interquartile range) and n (%). *, significant P value. HIV, human immunodeficiency virus; ART, antiretroviral therapy.

HIV ART-experienced group had TR peak velocity >2.8 m/s, which was not significantly different from the other groups (P=0.13). Whereas a higher proportion of subjects in the HIV ART-experienced group showed abnormal RV GLS compared to the HIV-positive ART-naïve group and normal controls, this difference was not statistically significant (4.5% *vs.* 0.9% *vs.* 0.9%, respectively; P=0.20).

Prevalence of RV dysfunction among HIV-positive and HIV-negative groups

RV systolic and diastolic dysfunction, as determined by the RV myocardial performance index (RVMPI) was more prevalent among HIV-positive participants compared to HIV-negative individuals [prevalence =14.50% (95% CI: 10.5–19.8%) for HIV-positive *vs.* 0% (95% CI: 0.0–3.4%)

Table 2 Cardiac measurements of participants by HIV and ART status, Kano, Nigeria

Characteristics	Overall (N=330)	Control (N=110)	HIV$^+$, ART-naïve (N=110)	HIV$^+$, on ART (N=110)	P value
PR (bpm)	84 (76, 92)	86 (78, 92)	86 (76, 92)	80 (72, 93)	0.11
LVEF (%)	66 (61, 70)	66 (60, 69)	66 (62, 70)	66 (60, 71)	0.40
LVEF (<55%) abnormal	16 (4.8%)	0 (0%)	0 (0%)	16 (15%)	<0.001*
LAVI (>28 mL/m^2)	13 (3.9%)	0 (0%)	1 (0.9%)	12 (11%)	<0.001*
LVIDd (>5.5 cm)	27 (8.2%)	2 (1.8%)	3 (2.7%)	22 (20%)	<0.001*
LVIDs (>4.0 cm)	13 (3.9%)	0 (0%)	2 (1.8%)	11 (10%)	<0.001*
LV mass (g), abnormal (>162 in females and >224 in males)	14 (4.2%)	1 (0.9%)	2 (1.8%)	11 (10%)	0.003*
LVMI (g/m^2), abnormal (≥115 in males and ≥95 in females)	28 (8.5%)	2 (1.8%)	4 (3.6%)	22 (20%)	<0.001*
TAPSE (>1.6 cm)	5 (1.5%)	0 (0%)	0 (0%)	5 (4.5%)	0.01*
RV basal (>4.2 cm)	13 (3.9%)	0 (0%)	0 (0%)	13 (12%)	<0.001*
RAAs (>18 cm^2)	4 (1.2%)	2 (1.8%)	2 (1.8%)	0 (0%)	0.60
RV S' (<0.10 m/s)	1 (0.3%)	0 (0%)	0 (0%)	1 (0.9%)	>0.90
RVMPI	0.4 (0.3, 0.5)	0.3 (0.3, 0.4)	0.4 (0.4, 0.5)	0.4 (0.4, 0.5)	<0.001*
RVMPI (>0.55)	32 (9.7%)	0 (0%)	16 (15%)	16 (15%)	<0.001*
RVFAC (<35%)	26 (7.9%)	8 (7.3%)	4 (3.6%)	14 (13%)	0.04*
TR peak velocity (>2.8 m/s)	5 (1.5%)	1 (0.9%)	0 (0%)	4 (3.6%)	0.13
MPAP (>20 mmHg)	10 (3.0%)	1 (0.9%)	0 (0%)	9 (8.2%)	<0.001*
RV GLS (>−17%)	7 (2.1%)	1 (0.9%)	1 (0.9%)	5 (4.5%)	0.20
LV GLS (>−18%)	13 (3.9%)	0 (0%)	0 (0%)	13 (12%)	<0.001*
PASP: abnormal (>30 mmHg)	8 (2.4%)	1 (0.9%)	0 (0%)	7 (6.4%)	0.007*
LAE					>0.99
Normal (<2.5 mV)	329 (100%)	110 (100%)	109 (99%)	110 (100%)	
Present (≥2.5 mV)	1 (0.3%)	0 (0%)	1 (0.9%)	0 (0%)	
LVH					>0.99
Present (≥35 mm)	1 (0.3%)	0 (0%)	1 (0.9%)	0 (0%)	
Voltage criteria for LVH (≥35 mm)	1 (0.3%)	1 (0.9%)	0 (0%)	0 (0%)	
T wave inversion					0.04*
Normal	323 (98%)	110 (100%)	106 (96%)	107 (97%)	
v1–v3	1 (0.3%)	0 (0%)	1 (0.9%)	0 (0%)	
v1–v4	2 (0.6%)	0 (0%)	2 (1.8%)	0 (0%)	
v1–v5	2 (0.6%)	0 (0%)	0 (0%)	2 (1.8%)	
v1–v6	1 (0.3%)	0 (0%)	0 (0%)	1 (0.9%)	
v3–v6	1 (0.3%)	0 (0%)	1 (0.9%)	0 (0%)	
QTc interval (>440 ms)	8 (2.4%)	1 (0.9%)	3 (2.7%)	4 (3.6%)	0.50

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Overall (N=330)	Control (N=110)	HIV$^+$, ART-naïve (N=110)	HIV$^+$, on ART (N=110)	P value
PR interval					0.80
Shortened (<120 ms)	6 (1.8%)	1 (0.9%)	3 (2.7%)	2 (1.8%)	
Prolonged (>200 ms)	9 (2.7%)	3 (2.7%)	4 (3.6%)	2 (1.8%)	
QRS duration (>120 ms)	1 (0.3%)	0 (0%)	1 (0.9%)	0 (0%)	>0.90
HR					0.03*
Bradycardia (<60 bpm)	10 (3.0%)	3 (2.7%)	1 (0.9%)	6 (5.5%)	
Tachycardia (>100 bpm)	26 (7.9%)	6 (5.5%)	15 (14%)	5 (4.5%)	
TV E/A ratio					<0.001*
Grade 1	38 (12%)	7 (6.4%)	9 (8.2%)	22 (20%)	
Grade 2	285 (86%)	103 (94%)	101 (92%)	81 (74%)	
Grade 3	7 (2.1%)	0 (0%)	0 (0%)	7 (6.4%)	
E wave DT (ms), abnormal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	

Data are presented as median (interquartile range) and n (%). *, significant P value. HIV, human immunodeficiency virus; ART, antiretroviral therapy; PR, pulse rate; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; LVIDd, left ventricular internal diameter in diastole; LVIDs, left ventricular internal diameter in systole; LV mass, left ventricular mass; LVMI, left ventricular mass index; TAPSE, tricuspid valve trans-annular plane systolic excursion; RV basal, right ventricular basal diameter; RAAs, right atrial area in systole; RV S', right ventricular peak systolic pressure; RVMPI, right ventricular myocardial performance index; RVFAC, right ventricular fractional area change; TR peak velocity, tricuspid regurgitant jet peak velocity; MPAP, mean pulmonary artery pressure; RV GLS, right ventricular global longitudinal strain; PASP, pulmonary artery systolic pressure; LAE, left atrial enlargement; LVH, left ventricular hypertrophy; HR, heart rate; TV E/A ratio, tricuspid valve early to atrial contraction ratio; E wave DT, E wave deceleration time.

Table 3 Prevalence and average values of markers of right ventricular dysfunction by HIV status, Kano, Nigeria

Variable	Prevalence, %, (95% CI)			Median (IQR)		
	HIV$^+$	HIV$^-$	P value	HIV$^+$	HIV$^-$	P value
RVMPI	14.50 (10.5–19.8)	0.00 (0.0–3.4)	<0.001*	0.43 (0.36–0.49)	0.3 (0.30–0.40)	<0.001*
RVFAC (%)	7.70 (4.9–12.0)	7.27 (3.7–13.6)	0.88	48.6 (43.00–54.80)	43.0 (38.00–49.00)	<0.001*
RV S' (m/s)	0.50 (0.02–2.50)	0.90 (0.04–5.00)	>0.99	0.13 (0.12–0.14)	0.14 (0.12–0.15)	<0.001*
TAPSE (cm)	2.30 (1.00–5.20)	2.70 (0.90–7.70)	>0.99	2.20 (2.00–2.40)	2.10 (1.90–2.40)	0.09

*, significant P value. HIV, human immunodeficiency virus; CI, confidence interval; IQR, interquartile range; RVMPI, right ventricular myocardial performance index; RVFAC, right ventricular fractional area change; RV S', right ventricular peak systolic pressure; TAPSE, tricuspid valve trans-annular plane systolic excursion.

for HIV-negative controls; P<0.001]. The median RVMPI for the HIV-positive group was also higher than the value for HIV-negative participants at 0.43 (IQR, 0.36–0.49) *vs.* 0.3 (IQR, 0.30–0.40), P<0.001 (*Table 3*).

The prevalence of RV systolic dysfunction, as measured by the RVFAC was similar between HIV-positive and HIV-negative groups [prevalence =7.70% (95% CI: 4.9–12.0%) *vs.* 7.27% (95% CI: 3.7–13.6%) respectively, P=0.88]. However, the median RVFAC for PLWH was higher than in those without HIV: 48.6 (IQR, 43.00–54.80) *vs.* 43.0 (IQR, 38.00–49.00), respectively (P<0.001) (*Table 3*).

RV systolic dysfunction, as determined by the RV S' was low among participants who were HIV-negative [prevalence =0.90% (95% CI: 0.04–5.00%)] and among those who were HIV-positive [0.50% (95% CI: 0.02–2.50%); P>0.99]. The median RV S' for persons with HIV was 0.13 (IQR, 0.12–

Table 4 Markers of right ventricular dysfunction by ART status, Kano, Nigeria

Variable	Prevalence, % (95% CI)			Median (IQR)		
	ART-naïve	ART$^+$	P value	ART-naïve	ART$^+$	P value
RVMPI	14.5 (9.2–22.3)	14.5 (9.2–22.3)	>0.99	0.43 (0.36–0.50)	0.42 (0.36–0.47)	0.71
RVFAC (%)	3.6 (1.4–8.9)	11.8 (7.0–19.2)	0.04*	47.2 (42.2–52.1)	52.1 (44.5–56.4)	0.003*
RV S' (m/s)	0 (0–3.4)	0.9 (0.04–5.0)	>0.99	0.13 (0.12–0.14)	0.13 (0.12–0.14)	0.89
TAPSE (cm)	0 (0–3.4)	4.5 (2.0–10.2)	0.06	2.2 (2.03–2.40)	2.1 (2.0–2.40)	0.43
Duration of HIV (years)	–	–	–	0.25 (0.17–0.33)	10 (7–13)	<0.001
Duration of ART use (years)					10 (7–13)	
Viral load (cells/mL)	–	–	–	–	20 (20–35)	–

*, significant P value. ART, antiretroviral therapy; CI, confidence interval; IQR, interquartile range; RVMPI, right ventricular myocardial performance index; RVFAC, right ventricular fractional area change; RV S', right ventricular peak systolic pressure; TAPSE, tricuspid valve trans-annular plane systolic excursion; HIV, human immunodeficiency virus.

0.14) compared to 0.14 (IQR, 0.12–0.15) for people without HIV (P<0.001). RV systolic dysfunction, as assessed by the TAPSE was also similarly prevalent among participants with HIV compared to seronegative controls, [prevalence =2.30% (95% CI: 1.00–5.20%) *vs.* 2.70% (95% CI: 0.90–7.70%), respectively; P>0.99] (*Table 3*).

Association between markers of RV dysfunction (RVMPI, RVFAC, RV S', TAPSE) and ART use

HIV$^+$ participants on ART had a longer duration of HIV illness than those who were ART-naïve [10 (IQR, 7–13) *vs.* 0.25 (IQR, 0.17–0.33) years, respectively, P<0.001] (*Table 4*). The average viral load in participants on ART was 20 (IQR, 20–35) cells/mL (*Table 4*). Approximately 92.5% (99/107) of participants on ART were on a tenofovir-based regimen.

The prevalence of RV dysfunction as measured by RV fractional area change (RVFAC) was greater among HIV-positive participants on ART as compared to their HIV-positive ART-naïve counterparts [11.8% (95% CI: 7.0–19.2%) *vs.* 3.6% (95% CI: 1.4–8.9%), P=0.04] (*Table 4*). The median RVFAC was similarly higher among HIV-positive ART-experienced participants [52.1 (IQR, 44.5–56.4) *vs.* 47.2 (IQR, 42.2–52.1, P=0.003] (*Table 4*). There were no statistically significant differences between the two groups in the prevalence of RV dysfunction as measured by the other markers or in the average values of the other three markers of RV dysfunction (RVMPI, RV S' and TAPSE).

In initial analyses among people living with HIV that investigated factors associated with RVMPI (as a continuous variable), we found that older age and lower LVEF are good predictors of higher RVMPI (*Table 5*). In a multiple linear regression model among people with HIV including age, sex, LVEF, and ART-status, age (P=0.01) and LVEF (P<0.001) were associated with RVMPI (*Table 5*). A 10-year increase in age was associated with a 0.022 unit increase in RVMPI (95% CI: 0.005–0.039). A 10% increase in LVEF was associated with a 0.076 unit decrease in RVMPI (95% CI: −0.09, −0.06). However, we failed to demonstrate a statistically significant association between ART status and RV dysfunction using both multivariable linear and Firth's logistic regression models (*Table 5*). Controlling for ART status, sex, and LVEF, a 10-year increase in age was associated with an 81% increase in the odds of RV dysfunction [odds ratio (OR) 1.81; 95% CI: 1.16–2.84]. A 10% increase in LVEF was associated with a 61% decrease in the odds of RVMPI (OR 0.39, 95% CI: 0.26–0.58) (*Table 5*).

However, we saw a statistically significant interaction between LVEF and ART status (P=0.03; *Table 6*). Specifically, for people who were ART-experienced, a 10% increase in LVEF was associated with a 0.08 decrease in RVMPI (beta coefficient =−0.08, 95% CI: −1.10 to −0.07), whereas for those who were ART naïve, a 10% increase in LVEF was associated with a 0.03 decrease in RVMPI (beta coefficient =−0.03, 95% CI: −0.08 to 0.01) (*Table 6*). Results were similar when models were fit separately to ART-experienced and ART-naïve participants (Table S1) and when LVEF was included as a categorical variable (normal *vs.* abnormal) and interacted with ART status (Tables S2-S4). In analyses that categorized RVMPI as normal/abnormal, the interaction was not statistically significant (P=0.72).

Table 5 Predictors of RVMPI (marker of RV dysfunction) among HIV-positive participants in Kano, Nigeria, using both linear regression and Firth's logistic regression

Variable	Linear regression		Firth's logistic regression	
	β coef. (95% CI)	P value	OR (95% CI)	P value
Age (per 10 years)	0.022 (0.005, 0.039)	0.01*	1.81 (1.16, 2.84)	0.008*
Male *vs.* female (ref.)	−0.001 (−0.037, 0.035)	0.94	0.68 (0.27, 1.67)	0.39
ART$^+$ *vs.* ART-naïve (ref.)	−0.000 (−0.034, 0.034)	>0.99	0.40 (0.15, 1.02)	0.051
LVEF (per 10%)	−0.076 (−0.09, −0.06)	<0.001*	0.39 (0.26, 0.58)	<0.001*

*, significant P value. RVMPI, right ventricular myocardial performance index; RV, right ventricular; HIV-positive, human immunodeficiency virus; CI, confidence interval; OR, odds ratio; ART, antiretroviral therapy; LVEF, left ventricular ejection fraction.

Table 6 Predictors of RVMPI (marker of RV dysfunction) among HIV-positive participants including an interaction term between LVEF (continuous) and ART status, Kano, Nigeria

Variable	Linear regression	
	β coef. (95% CI)	P value
Age (per 10 years)	0.021 (0.004, 0.038)	0.01*
Male *vs.* female (ref.)	−0.003 (−0.038, 0.032)	0.86
ART$^+$ *vs.* ART-naïve (ref) (LVEF set at median of 66%)	−0.001 (−0.035, 0.032)	0.93
Interaction of ART status and LVEF	–	0.03*
LVEF (per 10%) among ART-naïve	−0.03 (−0.08, 0.01)	0.14
LVEF (per 10%) among ART$^+$	−0.08 (−0.10, −0.07)	<0.001*

*, significant P value. RVMPI, right ventricular myocardial performance index; RV, right ventricular; HIV-positive, human immunodeficiency virus; LVEF, left ventricular ejection fraction; ART, antiretroviral therapy; CI, confidence interval.

Table 7 Predictors of RVMPI (marker of RV dysfunction) among participants in Kano, Nigeria, using both linear regression and Firth's logistic regression models

Variable	Linear regression		Firth's logistic regression	
	β coef. (95% CI)	P value	OR (95% CI)	P value
Age (per 10 years)	0.010 (−0.002, 0.020)	0.09	1.79 (1.14, 2.81)	0.01*
Male sex *vs.* female (ref.)	0.002 (−0.024, 0.027)	0.89	0.78 (0.32, 1.91)	0.06
HIV$^+$ *vs.* HIV$^-$ (ref.)	0.105 (0.078, 0.132)	<0.001*	42.3 (2.68, 6.70)	<0.001*
LVEF (per 10%)	−0.06 (−0.07, −0.05)	<0.001*	0.45 (0.32, 0.64)	<0.001*

*, significant P value. RVMPI, right ventricular myocardial performance index; RV, right ventricular; CI, confidence interval; OR, odds ratio; HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction.

Association between HIV status and RV dysfunction

Table 7 shows the results of regression analyses examining factors associated with RVMPI and RV dysfunction as defined by dichotomized RVMPI. In a multiple linear regression model, HIV status (P<0.001) and LVEF (P<0.001) were associated with RVMPI. After adjusting for age, sex, and LVEF, participants with HIV had, on average, RVMPI scores that were 0.105 units higher than those without HIV (95% CI: 0.078, 0.132). A 10% increase in LVEF was associated with a 0.06 decrease in RVMPI (95% CI: −0.07, −0.05). With RVMPI dichotomized as RV dysfunction

Table 8 Markers of RV dysfunction stratified by RV GLS status, Kano, Nigeria

Characteristics	Overall (N=110)	Preserved RV strain (N=105)	Poor RV strain (N=5)	P value†
RVFAC (%)				<0.001*
Abnormal (<35)	14 (13%)	9 (8.6%)	5 (100%)	
Normal (≥35)	96 (87%)	96 (91.4%)	0 (0%)	
RV S' (m/s)				>0.99
Abnormal (<0.10)	1 (0.9%)	1 (1.0%)	0 (0%)	
Normal (≥0.10)	109 (99.1%)	104 (99%)	5 (100%)	
TAPSE (cm)				0.20
Abnormal (<1.6)	5 (4.5%)	4 (3.8%)	1 (20%)	
Normal (≥1.6)	105 (95.5%)	101 (96.2%)	4 (80%)	
RVMPI				0.001*
Abnormal (>0.55)	16 (15%)	12 (11%)	4 (80%)	
Normal (≤0.55)	94 (85%)	93 (89%)	1 (20%)	
PASP (mmHg)				0.002*
Abnormal (≥30)	7 (6.4%)	4 (3.8%)	3 (60%)	
Normal (<30)	103 (93.6%)	101 (96.2%)	2 (40%)	
MPAP (mmHg)				<0.001*
Abnormal (>20)	9 (8.1%)	5 (4.8%)	4 (80%)	
Normal (≤20)	101 (91.8%)	100 (95.2%)	1 (20%)	

†, Fisher's exact test. *, significant P value. RV, right ventricular; GLS, global longitudinal strain; RVFAC, right ventricular fractional area change; RV S', right ventricular peak systolic pressure; TAPSE, tricuspid valve trans-annular plane systolic excursion; RVMPI, right ventricular myocardial performance index; PASP, pulmonary artery systolic pressure; MPAP, mean pulmonary artery pressure.

(yes/no), in a model adjusting for HIV status, sex, age, and LVEF, a 10-year increase in age was associated with a 79% increase in the odds of RV dysfunction (OR 1.79; 95% CI: 1.14–2.81). The odds of RV dysfunction for people with HIV was 42 times higher than that for people without HIV (OR 42.3, 95% CI: 2.68–6.70). A 10% increase in LVEF was associated with a 55% decrease in the odds of RV dysfunction (OR 0.45, 95% CI: 0.32–0.64).

Relationship of RV GLS, PASP and RV dysfunction

Among the HIV on ART group, a total of 5 participants had poor strain and 105 had preserved strain (*Table 8*). When stratified by subclinical RV function as defined by RV GLS of greater than –17, the difference in estimated PASP was statistically significant (P=0.002). Similarly, RV strain varied significantly by RVFAC (P<0.001), MPAP (P<0.001) and RVMPI (P=0.001). However, when stratified by TAPSE (P=0.20) and RV S' (P>0.99), no statistically significant differences in RV strain were observed.

Discussion

Key findings

To our knowledge, this is the first study to use multiple echocardiographic parameters including GLS, to define RV dysfunction and to determine LVEF and left atrial size using Simpson's biplane disk method and LAVI respectively, among PLWH in Nigeria. We found a higher prevalence of RV dysfunction among PLWH compared to seronegative controls. Even though HIV positive status and LVEF were associated with abnormal RVMPI (a measure of both RV diastolic and systolic function), we did not observe an association between ART status and RV dysfunction.

PLWH face double the risk of developing CVDs, even with viral suppression, use of ART and the absence of major atherosclerotic CVD risks (21). RV function estimated at echocardiography or radionuclide ventriculography is an important prognostic indicator in ischemic heart disease and dilated cardiomyopathy (5). Nevertheless, the relationship

between ART regimens and RV dysfunction remains largely understudied, as is the prevalence of RV dysfunction in HIV, despite its clinical importance in the prognosis of many CVDs (5).

Comparison with similar research studies

The importance of the RV has been underestimated in the past, as previous HIV-related studies have primarily focused on LV function (8-10). In our study, we found that RV diastolic and systolic dysfunction as measured by RVMPI, was present in 14.5% of our HIV-positive participants, significantly higher than in our seronegative subjects. This finding aligns with a previous study that showed significantly impaired RVMPI in the HIV-positive group (13%) compared to healthy controls (22).

The prevalence of RV systolic dysfunction in PLWH as determined by RVFAC, RV S' and TAPSE in this study was 7.7%, 0.5%, and 2.3% respectively, which did not significantly differ from the normal controls. The prevalence of RV dysfunction (using RVFAC alone) in our study is lower than a report from the United States (11%) (23). Our TAPSE-derived figures are also lower than the numbers (7.0%) reported in a Nigerian study (12). These differences could stem from the different criteria used to define RV dysfunction. We used standardized cut-off values of abnormal TAPSE of <1.6 cm as recommended by the ASE guidelines (16), which have been shown to correlate well with radionuclide angiographically determined right ventricular ejection fraction (RVEF) (24). In contrast, the U.S. study used a TAPSE of <2.2 cm, defined by the lower quartile in the cohort, whereas the Nigerian study used the same criteria definition of abnormal TAPSE and RV S' but only included PLWH naïve to ART. In a similar study in South-South Nigeria, mean TAPSE was found to be similar between PLWH (both ART experienced and ART naïve) and normal controls (25).

The RV myocardial performance index (RVMPI) also called the Tei index, defines both systolic and diastolic functions of the RV. Using the RVMPI as the continuous response variable, we identified HIV status (P<0.0001) and LVEF (P<0.0001) as independent risk factors for RV dysfunction. Our finding contrasts with a previous study that showed only pulmonary infections as the primary predictor of RV dilatation and isolated RV heart failure (26). Another study failed to demonstrate associations between age, sex, dyslipidemia, $CD4^+$ cell count and mPAP and the outcome of RV dysfunction (27). Possible reasons for these differences include varied covariates used, the different markers used to define the outcome variables (we used RVMPI) and varied eligibility criteria (we excluded individuals with recent pulmonary infection in our study).

After controlling for age, LVEF, and sex, PLWH in our study had an RVMPI that was 0.105 units higher than seronegative controls (95% CI: 0.07–0.13). Consistent with our study, Hammoudi *et al.* (22) also reported impaired RVMPI in PLWH compared to healthy seronegative controls. Various pathologic mechanisms have been advanced to explain the myocardial involvement that could underlie isolated RV dysfunction in HIV, including repeated opportunistic infections, direct viral and drug toxicity, genetic susceptibility, altered autoimmune responses and autonomic dysfunction (2,3,28,29).

Our finding that LVEF independently predicted RV dysfunction (P<0.0001) is consistent with established knowledge that LV is a known cause of RV dysfunction (30). Pulmonary hypertension is also associated with HIV infection (23,31) and can result in RV dysfunction. Exaggerated ventricular interdependence and left heart dysfunction-related pulmonary hypertension could therefore explain our finding. Among the PLWH on ART in our study sixteen (15%) had LVEF <50%, 7 (6.4%) had abnormal PASP >35 mmHg, and 4 (3.6%) had abnormal TR peak velocity >2.8 m/s. In addition, abnormal RV GLS (which could indicate subclinical RV dysfunction) was present in 5 participants in the HIV ART-experienced cohort. This contrasts with the HIV-negative control group, where only 1 participant had abnormal PASP, abnormal TR peak velocity, or abnormal RV GLS, and there were no cases of LVEF <50%. However, not all of our participants with elevated TR peak velocity and PASP had RV dysfunction, and vice versa, suggesting that HIV has distinct effects on pulmonary hemodynamics and RV myocardial function, and indicating likely separate pathologic pathways for primary RV dysfunction and pulmonary hypertension.

Certain classes of antiretroviral drugs are known to be associated with myocardial dysfunction. For instance, Zidovudine, Stavudine and the protease inhibitors can cause myocardial mitochondrial toxicity and coronary artery disease, respectively (32). We failed to find a statistically significant association between ART status and the prevalence of RV dysfunction as measured by RVMPI, TAPSE and RV S'. Our results are in agreement with Robbertse *et al.*, who showed that compared to normal controls, PLWH on ART (tenofovir/lamivudine/dolutegravir) nine months after initiation did not exhibit changes in right and left

cardiac parameters (chamber volumes, dimensions and systolic function) as determined by cardiac magnetic resonance imaging (CMR) (33). This consistency in findings is reassuring given that CMR is considered the gold standard for evaluating the right heart more so than 2D-echocardiography.

The link between age and RV dysfunction is not surprising. Age-dependent cellular, structural, and functional changes in the heart are well-recognized. In one study (34), RVMPI was directly correlated with increasing participant age in both ventricles.

RV dysfunction is a negative prognostic factor in many CVDs, exacerbating heart failure, and posing a significant risk for sudden cardiac death (SCD) (35). In our HIV ART-experienced group, six participants died, but none of them exhibited RV dysfunction based on the markers we assessed. We therefore did not find evidence supporting our hypothesis that RV dysfunction is directly associated with death. However, our study's short-term follow-up of three to six months and its design are not suitable for determining long-term survival outcomes. In addition, the study was not powered for this purpose.

2D-STE offers several advantages over other strain imaging abnormalities like tissue Doppler imaging. Its sample volume angle independence and integration of artificial intelligence software for automated tracking coupled with the ability to detect early subclinical myocardial dysfunction make it particularly valuable. In this study, using 2D-STE, a frame rate of 58, and a RV GLS of less than –17 to define worse strain, we found statistically significant associations between RV GLS and RVFAC, RVMPI and PASP among participants in the ART-experienced group. In contrast to our study where no association was observed between RV GLS and TAPSE, a 2011 study found TAPSE to be lower in patients with decreased RV longitudinal mid wall strain below the median value of –27.3% (23). This difference with our findings could be explained by the variation in the wall segment used, frame rate and the cut-off value.

Strengths and limitations

Our study has several strengths. To our knowledge, this is the first large cross-sectional study of RV dysfunction among PLWH from a high HIV-burden setting of Nigeria classified by ART status and using multiple echocardiographic parameters, including RVMPI (a measure of both RV diastolic and systolic function). In addition, we employed 2D-STE to evaluate GLS, which has advantages over other methods for assessing strain imaging abnormalities. Transthoracic echocardiography and 12 lead ECG were also performed on all participants by an experienced cardiologist, increasing the validity of study findings. The study is also timely because of its potential of generating preliminary data that could be further tested with larger prospective studies.

A limitation of our study is the cross-sectional design, which limits causal inferences. Second, caution is warranted when interpreting the prevalence data due to the limited sample size and the non-random selection of cases and controls. Third, AKTH is the main referral tertiary hospital in the state—patients presenting there for care may differ in socioeconomic status and educational attainment from those seen in smaller facilities. We also excluded participants with current pregnancy, hypertension, diabetes mellitus, history of cancer/malignancy, illicit drug use and use of potentially cardiotoxic medications. This selection of participants from a single clinic and the relatively broad exclusion criteria potentially limits the generalizability of our findings. Finally, assessing measures of RV dysfunction in asymptomatic individuals remains of uncertain significance and warrants further study. We also did not power the study to detect differences in death outcomes and did not utilize advanced diagnostic techniques like CMR and right heart catheterization, which could provide more accurate measurements.

Conclusions

We found a high prevalence of RV dysfunction (14.5%) using the RVMPI among a group of HIV-positive, ART-experienced patients in Nigeria. In addition, we identified participants' age and LVEF as significant predictors of RV dysfunction using RVMPI, and no association between RV dysfunction and ART use and death. The findings from this study could inform future directions for improved therapeutic management of patients with HIV and cardiac dysfunction, such as the use of cardiac remodeling drugs, particularly in resource-constrained, high-HIV burden settings. They also highlight the complexity of RV dysfunction in PLWH, warranting further investigations into its underlying mechanisms and clinical implications. In light of our findings, we recommend considering baseline echocardiography for PLWH who are older than 45 years.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the International Conference on Harmonization for Good clinical Practice (ICH-GCP) guidelines. Ethical approval for the study was obtained from the AKTH Ethics Review Committee and the Vanderbilt University Medical Center (NHREC/28/01/2020/AKTH/EC/3494, AKTH/MAC/SUB/12A/P-3/VI/3594 and IRB/200119). Eligible participants were approached regarding potential participation in the study, and written informed consent was obtained from all individual participants.

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