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Human immunodeficiency viral infection and differences in interstitial ventricular fibrosis and left atrial size

Katherine C. Wu [1]*, Sabina A. Haberlen [2], Michael W. Plankey [3], Frank J. Palella [4], Damani A. Piggott [2,5], Gregory D. Kirk[2,5], Joseph B. Margolick [6], and Wendy S. Post [1,2]

[1]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Blalock 559, 600 North Wolfe Street, Baltimore, MD 21287, USA; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA; [3]Department of Medicine, Georgetown University Medical Center, Washington, DC, USA; [4]Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [5]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; and [6]Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

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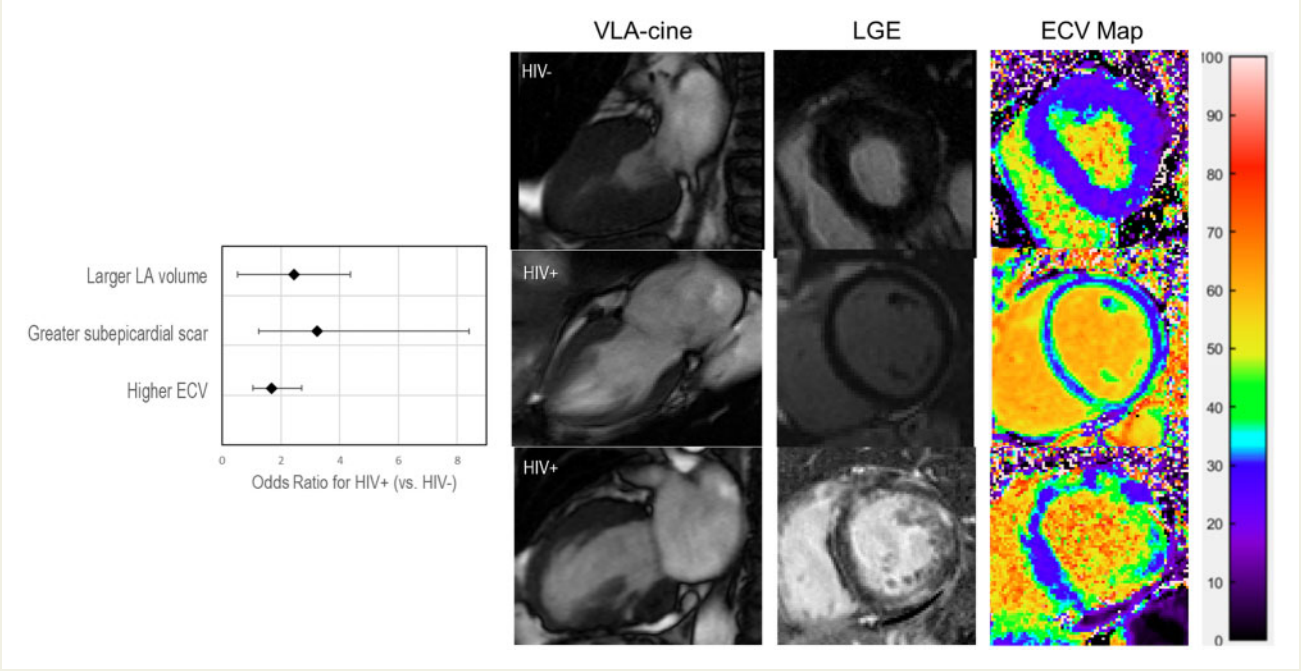
Aims The extent to which human immunodeficiency viral (HIV) infection is independently associated with myocardial disease in the era of combination antiretroviral therapy (cART) remains understudied. We assessed differences in cardiovascular magnetic resonance imaging (CMR) metrics among people living with HIV (PLWH) and without HIV (PWOH).

Methods and results Among 436 participants (aged 54.7 ± 6.0 years, 29% women) from three cohorts, we acquired CMR cines, late gadolinium enhancement (LGE), and T1 mapping. Multivariable linear regressions were used to evaluate associations between HIV serostatus and CMR metrics. Baseline characteristics were similar by HIV serostatus; 63% were PLWH of whom 88% received cART and 73% were virally suppressed. Median left ventricular ejection fraction was normal and similar by HIV serostatus (73%, PWOH vs. 72%, PLWH, $P = 0.43$) as were right ventricular function, biventricular volumes, and masses. LGE prevalence was similar (32%, PWOH vs. 36%, PLWH, $P = 0.46$) with low scar extents (4.1, PWOH vs. 4.9 g, PLWH, $P = 0.51$) and few ischaemic scars (3%, PWOH vs. 4%, PLWH, $P = 0.70$). Extracellular volume fraction (ECV) was higher among PLWH (29.2 ± 4.1% vs. 28.3 ± 3.7%, $P = 0.04$) as was indexed maximum left atrial (LA) volume (LAVI, 29.7 ± 10.3 vs. 27.8 ± 8.7 mL/m^2, $P = 0.05$). After multivariate adjustment, ECV was 0.84% higher among PLWH ($P = 0.05$) and LAVI was 2.45 mL/m^2 larger ($P = 0.01$). HIV seropositivity and higher ECV contributed to higher LAVI ($P < 0.02$). There were no associations between HIV disease severity and CMR metrics among PLWH.

Conclusion HIV seropositivity was independently associated with greater diffuse non-ischaemic fibrosis and larger LA volume but no other differences in CMR metrics.

*Corresponding author. Tel: +1 410 502 7283; Fax: +1 410 367 2151. E-mail: kwu@jhmi.edu



Keywords human immunodeficiency virus • cardiovascular magnetic resonance imaging • myocardial fibrosis • left atrial volumes

Introduction

Combination antiretroviral therapy (cART) in people living with human immunodeficiency virus (HIV) (PLWH) has resulted in durable viral suppression and increased lifespan. Consequently, PLWH are now at increased risk for chronic non-HIV-associated diseases of aging, including a significant increase in proportionate mortality due to cardiovascular disease.[1] Risk for sudden cardiac death is higher in PLWH compared with people without HIV (PWOH).[2] Excess morbidity from heart failure and atrial arrhythmias has also been described, compared with PWOH who were matched by age, sex, and race/ethnicity.[3] However, the mechanisms of increased cardiovascular disease risk among PLWH remain unclear, particularly among those with virologic cART-induced suppression. Traditional cardiac risk factors, direct HIV viral invasion, and cART treatment effects do not fully explain the increased risk. An under-investigated area is whether the use of potentially cardiotoxic recreational substances, a common behaviour in PLWH,[4] modulates cardiovascular risk. Prior CMR studies of PLWH are limited by lack of comparable PWOH who have similar risk factors for HIV acquisition.

Here, we used cardiovascular magnetic resonance imaging (CMR) to examine whether sub-clinical markers of abnormal cardiac structure and function that can precede heart failure and arrhythmias, differ by HIV serostatus and whether recreational substance use modifies this difference. We studied men and women with and without HIV but with similar risk behaviours for HIV acquisition, who were concurrently enrolled and followed in three established longitudinal cohort studies, the Multicenter AIDS Cohort Study (MACS), the AIDS Linked to the IntraVenous Experience (ALIVE) study, and the Women's Interagency HIV Study (WIHS).

Methods

We recruited active participants of MACS, ALIVE, and WIHS.[5–7] The MACS is a prospective, longitudinal study of men who have sex with men with and without HIV-1 infection.[7] It is conducted at 4 US sites including Baltimore, MD/Washington, DC, and Chicago, IL. The ALIVE study is a community-based cohort in Baltimore, MD, of men and women with a history of injection drug use.[5] The WIHS recruited HIV-seronegative and HIV-seropositive women from 10 US cities including Washington, DC.[6] See Supplementary data online for parent cohort details. Participants in these cohorts undergo semi-annual study visits with similar follow-up protocols including standardized interviews, physical examinations, and blood specimen collection and storage. Cohort participants aged 40–70 years were eligible to enrol in the present study if active in the MACS/ALIVE/WIHS Baltimore or Washington, DC or Chicago MACS sites; exclusion criteria included estimated glomerular filtration rate, eGFR < 45 mL/min/1.73 m^2, weight >350 pounds, known claustrophobia or contrast allergy, and contraindications to CMR. By design, we oversampled for PLWH, aiming for ~60%. Our target sample size was 400 with late gadolinium enhancement (LGE) to achieve 80% study power to detect a 14% difference in prevalent fibrosis between PLWH and PWOH. We screened 603 participants meeting age and initial eGFR eligibility criteria and enrolled 468 people, of whom 442 completed the CMR (see Supplementary data online, *Figure S1* for the cohort derivation). The Institutional Review Boards at all enrolment sites approved the study, and

all participants signed informed consent. Given the sensitive nature of data collected for this study, requests for data sharing from researchers certified in human subject confidentiality can be submitted to and will be reviewed by the parent cohorts: https://statepi.jhsph.edu/mwccs/ and https://www.jhsph.edu/research/affiliated-programs/aids-linked-to-the-intravenous-experience/.

Participants in this study completed an interviewer-administered structured questionnaire, biological measures, and CMR at a single study visit from March 2015 to February 2018. Prescribed medications, history of cardiovascular disease, and use of recreational drugs (marijuana, opiates, stimulant, erectile dysfunction agents, and/or nitrates), and alcohol during the 5 years preceding CMR were queried. These data were supplemented with data collected prospectively through the parent cohorts, including age, race, education, measured blood pressure, body mass index (BMI), smoking, fasting glucose level; total, low-density, and high-density cholesterol levels; serum creatinine, eGFR, haematocrit, and hepatitis C viral infection status. See Supplementary data onlinefor covariate definitions. In PLWH, measures of HIV disease activity included current plasma HIV RNA concentrations (quantified down to 50 copies/mL, Roche ultrasensitive assay), current and nadir CD4+ T-lymphocyte cell counts/μL (CD4), history of acquired immunodeficiency syndrome (AIDS)-defining malignancy, or opportunistic infection and use of cART.

CMR was performed at Johns Hopkins Hospital (Baltimore, MD, USA) or Northwestern Memorial Hospital (Chicago, IL, USA) on 1.5 T Siemens Avanto or Aera scanners (Erlangen, Germany) using a standardized protocol. Short- and long-axis cines (30 phases/cardiac cycle) were acquired with a steady-state free precession sequence. Two-dimensional LGE short- and long-axis images were acquired 15 min after intravenous administration of 0.2 mmol/kg of gadobutrol (Gadavist®, Bayer, Montville, NJ, USA) using an inversion-recovery fast gradient-echo sequence. T1 mapping with a modified Look-Locker inversion (MOLLI) recovery sequence was performed before and after gadolinium administration.

All CMR analyses were performed blinded to HIV serostatus and other participant characteristics. Analysis of biventricular structure, function, and LGE was performed with Segment v2.0 (http://segment.heiberg.se).[8] Biventricular volumes and mass were quantified by standard methods. All LGE images were reviewed for LGE presence, confirmed in two planes. If present, LGE was quantified into core and grey zone extents as described.[9] Core mass comprised all pixels with a signal intensity (SI) >50% of maximal SI within the hyperenhanced region. Grey zone mass comprised all pixels with SI >peak SI in the normal myocardium but <50% of maximal SI within the hyperenhanced region. Total scar mass comprised the sum of the grey zone and core extents. The scar pattern was categorized as ischaemic if the LGE location was distributed along with a coronary artery territory and involved the sub-endocardium with or without transmural involvement. Non-ischaemic LGE patterns were categorized according to major [midwall, sub-epicardial, or diffuse/patchy LGE in the setting of pathologic left ventricular (LV) hypertrophy] and minor (small foci or right ventricular insertion point) myocardial fibrosis patterns.[10]

Multimodality Tissue Tracking software (MTT; version 6.0, Toshiba, Japan) was used to quantify LV regional systolic and diastolic strain and strain rates as well as phasic left atrial (LA) volumes, function, strain, and strain rates.[11] LV peak circumferential systolic strain and strain rate and early circumferential diastolic strain rate were calculated from basal, mid, and apical cross-sections and averaged to derive global systolic LV strain. Maximum LA volume (Vmax), minimum LA volume (Vmin), and pre-atrial contraction LA volume (VpreA) were measured using the LA volume curve generated by the Simpson's method from the four-chamber and two-chamber views. The following LA functional metrics were calculated: LA total emptying fraction (LAef) = (Vmax - Vmin) × 100%/Vmax; LA passive ef = (Vmax - VpreA) × 100%/Vmax; and LA active ef = (VpreA - Vmin) × 100%/VpreA. Global longitudinal strain and strain rate curves were generated by averaging strains and strain rates in all LA segments. LA maximum strain (Smax), conduit strain (Se), and pre-atrial contraction strain (SpreA) were derived from the global longitudinal strain curve.

We used MRmap version 1.2 (Charite University Medicine, Berlin, Germany) to post-process the MOLLI images. After contouring of the LV endocardium and epicardium in the basal, mid, and apical slices, each slice was segmented into six sections. A three-parameter curve fit of the MOLLI source images was then performed with automatic calculation of per sector T1 values. The partition coefficient was determined by the slope of the linear relationship of $1/T1_{myocardium}$ vs. $1/T1_{blood}$ pre and post-contrast. Extracellular volume (ECV, %) was calculated as ECV = 100 × partition coefficient × [1 - haematocrit]).[12]

Statistical methods

We report continuous data as median values with interquartile ranges (IQRs), mean ± SD, and categorical and binary data as counts with percentages. Distributions of the CMR indices were compared by HIV serostatus using the Wilcoxon rank-sum test, *t*-test, or Pearson's χ^2 test for continuous and binary variables, respectively. We also compared prevalences of indexed LA volumes (LAVI) (≥normal mean of 40 mL/m^2 and ≥upper limit of normal of 53 mL/m^2)[13] and native T1 times and ECV ≥1 – 2 SD from normative data derived from the Multiethnic Study of Atherosclerosis (MESA) which had a similar CMR protocol. We used age-adjusted, gender-specific native T1 thresholds: ≥1076 (women) and ≥1044 (men) (≥2SD above mean) and ECV: ≥30 (≥1 SD) or ≥33 (≥2 SD) (women) and ≥28 (≥1 SD) or ≥30 (≥2 SD) (men).[14] We used multivariable linear and logistic regression to evaluate the associations between HIV serostatus and each continuous or binary CMR variable, sequentially adjusting for covariates as follows:

- Model 0: HIV serostatus only;
- Model 1: Model 0 + age, sex, race, parent cohort, and education level;
- Model 2: Model 1 + smoking, BMI (for CMR outcomes not indexed to body surface area), hypertension, diabetes, dyslipidaemia, and cardiovascular disease history; and
- Model 3: Model 2 + hazardous alcohol use, and use of marijuana, opioids, stimulants, erectile dysfunction drugs, or nitrates.

Analytic exclusion criteria specific to a CMR outcome are documented in the tables (e.g. atrial metrics exclude participants with atrial fibrillation, etc.). We assessed differences in the associations between HIV serostatus and the primary CMR outcomes by sex using multiplicative interaction terms (HIV×sex, HIV×cohort) in separate regression models. We also performed multivariable linear regressions among PLWH to explore HIV-specific disease severity factors, each in separate models including covariates from Model 3. Missing values led to slight sample size differences among each model.

A *P*-value <0.05 was defined as significant. All analyses were performed using Stata 15.

Results

Supplementary data online, *Figure S1* shows the study population derivation. Of the 442 participants who completed the CMR, 436 had complete covariate data and comprised the final analytic pool. See *Table 1* for participant characteristics by HIV serostatus and Supplementary data online, *Table S1* by parent cohort. Despite cohort differences, most characteristics were similar between PWOH

($n = 163$, 37%) and PLWH ($n = 273$, 63%) including age, sex, race, and cardiac risk factors. Education level was lower among PLWH with small absolute differences in creatinine, haematocrit, and lipid profile levels. Use rates of stimulant, opioid, and marijuana in the preceding 5 years were 39%, 32%, and 44%, respectively, and were similar by HIV serostatus. Among PLWH, 88% received cART for 10.8 ± 6.1 years, 73% were virally suppressed, and the median contemporaneous CD4 was 607/μL (IQR 393–826) with nadir CD4 of 270/μL (IQR 141–400).

Supplementary data online, *Table S2* compares the unadjusted cardiac structure and functional indices by HIV serostatus. Biventricular volumes, mass, and function were normal and similar between groups, with a low prevalence of LV systolic dysfunction [$n = 2$ with left ventricular ejection fraction (LVEF) ≤ 40%, both PLWH]. Maximum and minimum LAVI were larger in PLWH ($P \leq 0.05$) with a greater prevalence of PLWH with high normal maximal LAVI (≥40 mL/m^2) compared with PWOH (15.7% vs. 6.8%, $P = 0.006$). Compared with normal reference values for LA emptying fraction, strain and strain rates,[15] LA total and passive emptying fractions, maximal and conduit strain, and all strain rates were lower than that of age-matched healthy volunteers for both PLWH and PWOH. Supplementary data online, *Table S3* summarizes the unadjusted comparisons of LGE and T1 results by HIV serostatus. LGE prevalence was similar by HIV serostatus (PWOH, 32%, vs. PLWH, 36%, $P = 0.46$), regardless of ischaemic vs. non-ischaemic pattern, with low total scar burden (PWOH, 4.1 vs. PLWH, 4.9 g, $P = 0.51$). However, among people with non-ischaemic scar, more PLWH than PWOH had major sub-epicardial-pattern scar (35% vs. 57%, $P = 0.02$). While there were few ischaemic scars ($n = 15$), all were distributed in the right coronary or left circumflex coronary artery territories. Absolute ECV was significantly higher among PLWH ($P < 0.05$) and among participants without ischaemic scar, the prevalence of high ECV (≥1 SD above mean for sex) was also greater among PLWH (43.4% vs. 55.3%, $P = 0.03$). More men with HIV had high native T1 times (≥2SD above normal mean) vs. HIV-seronegative men (6.2% vs. 14.2%, $P = 0.03$); there was no significant T1 difference among women by HIV serostatus.

Fully adjusted analyses for representative CMR parameters are shown in *Table 2* (see Supplementary data online, *Table S4* for model derivations for all CMR metrics) and participant examples of the main findings are depicted in *Figure 1*. Biventricular volumes, mass, and function were similar by HIV serostatus, as were the prevalences of any scar, ischaemic pattern scar, and scar burden. However, among those with non-ischaemic scar, PLWH had a higher odds ratio (OR) than PWOH for major sub-epicardial scar pattern (OR = 3.22, $P = 0.02$) which generally affected the inferior, inferolateral, and/or septal walls. ECV also differed by HIV serostatus. After excluding ischaemic scars, ECV was significantly higher in PLWH vs. PWOH by 0.84% ($P = 0.05$) independent of covariates. Other significant risk factors for higher ECV included female sex, absence of dyslipidaemia, and non-significant trend with lower BMI (Supplementary data online, *Table S5*). When people with known cardiovascular disease were excluded from the ECV analyses, the adjusted association with HIV serostatus remained significant (mean ECV difference 0.84%, $P = 0.05$).

There were statistically significant, small increases in phasic LAVI after covariate adjustment in PLWH vs. PWOH (mean difference 2.45 mL/m^2 in maximum LAVI, $P = 0.01$) with a greater prevalence of high normal maximum LAVI (OR = 2.92, $P < 0.005$) among PLWH. Other covariates significantly associated with maximum LAVI included systolic blood pressure and ECV (Supplementary data online, *Table S6*). Among PLWH, no HIV disease severity factors or treatments were associated with any CMR metric. There were no statistically significant interactions between sex and HIV serostatus (Supplementary data online, *Table S7*). Cohort differences were weak with wide confidence intervals.

Discussion

In this contemporary, well-characterized cohort of well-treated PLWH with largely suppressed HIV-viremia, we found overall normal LV function and volumes and similarly low myocardial scar burden compared with a concurrently enrolled group of PWOH with similar risk behaviours. However, compared with HIV-seronegativity, HIV-seropositivity was independently associated with greater absolute ECV denoting more diffuse fibrosis and a larger proportion of PLWH had high normal ECV values. PLWH had larger adjusted phasic LAVI vs. PWOH. Indices of resting LV diastolic function and RV structure and function were similar between groups. Among PLWH, neither HIV disease severity nor treatment regimens were associated with CMR metrics.

Compared with previous smaller studies ($n = 125$–195)[16–18] that evaluated CMR differences by HIV serostatus, our cohort was more ethnically diverse, older in age by ∼5–10 years and most importantly, controlled for risk factors and behaviours associated with acquisition of HIV infection including substance use. Prior CMR studies of PLWH used healthy volunteers as PWOH comparators with fewer cardiac risk factors and did not investigate substance use. By incorporating PWOH with shared risk behaviours for HIV who were otherwise similar to concurrently enrolled PLWH, we can better isolate HIV-specific associations with sub-clinical myocardial disease while accounting for multiple confounding variables including potentially cardiotoxic recreational drug use. Differences in cohort characteristics and comparison group selection may explain disparities between our results and those of prior publications.

Among PLWH, we found less prevalent sub-clinical LV dysfunction than previously and corroborated prior reported similarities in LVEF[17] and LV strain.[16,18] The prevalence of focal LV scar among PLWH was intermediate to that of other studies (range 8–83%),[16–18] though closer to that of another US cohort[18] with more comparable demographics. Similar to other reports of PLWH,[16,19] among participants with non-ischaemic scar, we observed both midwall and sub-epicardial scar patterns, which have been associated with irreversible injury and fibrosis from sub-clinical myocarditis and worse prognosis in PWOH.[10] While we found no significant differences in native T1 by HIV serostatus compared with prior reports,[16–18] our findings add to data about higher ECV in PLWH.[18]

Although the HIV-associated differences in ECV were small in this generally middle-aged cohort, small mean group differences may herald significantly disparate risk for future cardiovascular events, as reported in observational studies of PWOH. Two recent large studies of PWOH referred clinically for CMR found linear relationships between increasing ECV and adverse outcomes.[20,21] Each 4–5%

Table 1 Participant characteristics by HIV serostatus

	n (%) or median (IQR)		
	PWOH (*n* = 163)	**PLWH (*n* = 273)**	***P*-value**
Age (years)	55.2 ± 5.9	54.4 ± 6.1	0.23
Female	44 (27)	83 (30)	0.45
Race			0.50
Caucasian	41 (25)	60 (22)	
Black	110 (67)	198 (73)	
Hispanic/other	12 (7)	15 (5)	
Cohort			0.32
MACS	72 (44)	123 (45)	
WIHS	26 (16)	57 (21)	
ALIVE	65 (40)	93 (34)	
Education level (<high school diploma)	39 (24)	85 (31)	0.04
Hazardous alcohol use	24 (15)	29 (11)	0.20
Never smoker	31 (19)	57 (21)	0.17
Pack-year smoking[a]	1.5 ± 0.5	1.5 ± 0.5	0.51
BMI (kg/m^2)	28.1 ± 6.0	27.1 ± 5.5	0.08
Average systolic blood pressure[a] (mmHg)	127 ± 16	126 ± 19	0.51
Hypertension	92 (56)	149 (55)	0.71
Diabetes	23 (14)	35 (13)	0.70
Dyslipidaemia	96 (59)	162 (59)	0.93
Known cardiovascular disease	9 (6)	19 (7)	0.55
Substance use[a]			
Marijuana	69 (42)	123 (45)	0.58
Opioids	55 (34)	85 (31)	0.57
Stimulants	59 (36)	113 (41)	0.28
Erectile dysfunction medications[b]	24 (20)	49 (26)	0.26
Nitrates	22 (13)	42 (15)	0.59
Chronic hepatitis C viral infection	35 (22)	73 (27)	0.18
Creatinine (mg/dL)	0.8 (0.7–1.1)	0.9 (0.8–1.1)	<0.001
eGFR < 60 mL/min/m^2	3 (2)	11 (4)	0.20
Haematocrit (%)	40.7 (37.6–43.4)	39.6 (36.5–42.2)	0.04
Fasting glucose (mg/dL)	92.0 (83.5–100.0)	90.0 (82.0–99.5)	0.39
Total cholesterol (mL/dL)	178.0 (150.0–210.0)	172.0 (151.0–193.0)	0.05
HDL (mL/dL)	57.0 (46.0–69.0)	51.0 (41.0–64.0)	<0.02
LDL (mL/dL)	99.0 (78.0–122.5)	93.0 (74.0–115.0)	0.07
HIV disease factors			
HIV RNA (viral load), <50 copies/mL		200 (73)	
HIV RNA copies/mL if detectable		279 (131–4373)	
CD4+ count (cells/mm^3)		607 (393–826)	
Nadir CD4+ (cells/mm^3)		270 (141–400)	
History of clinical AIDS[c]		39 (22)	
On cART		240 (88)	
cART duration (years)[c]		10.8 ± 6.1	
cART type			
Protease inhibitor-based		94 (35)	
Non-nucleoside reverse transcriptase inhibitor-based		75 (28)	
Integrase inhibitor-based		68 (25)	
Other cART		3 (1)	
No cART		32 (12)	

AIDS, acquired immunodeficiency syndrome; ALIVE, AIDS Linked to the IntraVenous Experience; BMI, body mass index; cART, combination antiretroviral therapy; CMR, cardiovascular magnetic resonance imaging; HIV, human immunodeficiency virus; IQR, inter-quartile range; MACS, Multicenter AIDS Cohort Study; PLWH, people living with HIV; PWOH, people living without HIV; WIHS, Women's Interagency HIV Study.

[a]Use/measurement in the 5 years preceding CMR.

[b]Among men.

[c]Data unavailable for ALIVE.

Table 2 Association between HIV serostatus and CMR indices in fully adjusted[a] multivariable linear or logistic regression models

		Model 3[a]	
	n	Mean difference or OR (95% CI)	*P*-value
LV indices			
LVEF (%)	436	-0.76 (-2.09 to 0.58)	0.27
LV mass, indexed (g/m^2)	436	1.02 (-0.88 to 2.92)	0.29
LV end-diastolic volume, indexed (mL/m^2)	436	3.09 (-0.01 to 6.19)	0.05
Global circumferential systolic strain (%)	422	0.48 (-0.35 to 1.31)	0.25
Average systolic strain rate (/s)	424	0.04 (-0.02 to 0.10)	0.21
Average diastolic strain rate (/s)	423	-0.02 (-0.08 to 0.04)	0.56
OR, LGE scar[b]	389	1.16 (0.73 to 1.84)	0.53
OR, ischaemic LGE[b]	389	0.44 (0.08 to 2.41)	0.35
Total scar mass[c] (log scale)	135	0.00 (-0.29 to 0.30)	0.99
OR, major non-ischaemic scar	120	2.61 (0.88 to 7.72)	0.08
OR, major sub-epicardial non-ischaemic scar	120	**3.22 (1.23 to 8.40)**	0.02
Native T1 (ms) (all participants)	423	-4.51 (-14.88 to 5.86)	0.39
ECV (%) (all participants)[b]	349	0.70 (-0.13 to 1.54)	0.10
OR, high ECV (≥30%, women and ≥28%, men) (all participants)	349	1.56 (0.98 to 2.50)	0.06
Native T1 (ms) (excluding ischaemic scar)	408	-3.89 (-14.47 to 6.68)	0.47
OR, highT1 (men)(≥1044)	289	2.50 (0.96 to 6.49)	0.06
ECV (%) (excluding ischaemic scar)	335	**0.84 (-0.01 to 1.70)**	0.05
OR, high ECV (ECV ≥ 30%, women and ECV ≥ 28%, men) (excluding ischaemic scar)	335	**1.68 (1.04 to 2.71)**	0.04
RV indices			
RVEF (%)	436	-0.72 (-2.21 to 0.77)	0.34
RV mass, indexed (g/m^2)	436	0.80 (-0.14 to 1.74)	0.10
RVEDV, indexed (mL/m^2)	436	0.66 (-2.32 to 3.65)	0.66
LA indices			
LAVI (max) (mL/m^2)	429	**2.45 (0.52 to 4.37)**	0.01
OR, LAVI (max) ≥40 mL/m^2	429	**2.92 (1.42 to 6.00)**	<0.005
LAVI (preA) (mL/m^2)	424	**2.04 (0.46 to 3.63)**	0.01
LAVI (min) (mL/m^2)	424	**1.38 (0.28 to 2.47)**	0.01
LA total ef (%)	424	-0.15 (-2.03 to 1.73)	0.88
LA passive ef (%)	424	-0.31 (-1.86 to 1.24)	0.70
LA active ef (%)	424	-0.16 (-2.30 to 1.99)	0.89
Smax	429	-0.08 (-0.22 to 0.06)	0.26
Se	427	-0.01 (-0.12 to 0.10)	0.90
SpreA	428	0.05 (-0.11 to 0.22)	0.53
Strain rate (max) (1/s)	420	-0.27 (-2.10 to 1.56)	0.77
Strain rate (e) (1/s)	420	0.34 (-0.99 to 1.68)	0.61
Strain rate (*a*) (1/s)	427	-0.56 (-2.36 to 1.23)	0.54

ALIVE, AIDS Linked to the IntraVenous Experience; BMI, body mass index; CMR, cardiovascular magnetic resonance imaging; ECV, extracellular volume fraction; HIV, human immunodeficiency virus; IQR, inter-quartile range; LA, left atrial; LAVI, indexed left atrial volume; LV, left ventricular; LGE, late gadolinium enhanced; LVEF, left ventricular ejection fraction; OR, odds ratio; Smax, LA maximum strain; Se, conduit strain; SpreA, pre-atrial contraction strain.

[a]Fully adjusted model incorporates: age, sex, race, cohort, education, cardiovascular disease history, hypertension, diabetes, dyslipidaemia, smoking, BMI (for CMR outcomes not indexed to body surface area), and substance use.

[b]Among participants with CMR-LGE and analysable post-contrast T1 images.

[c]Among participants with scar >0.

Values in bold denote significant associations.

(~1SD) ECV increment was associated with a hazard ratio (HR) of 1.28–1.41 for risk of heart failure hospitalization or death.[20,21] Furthermore, ECV but not native T1 was associated with outcomes.[20] In investigating covariates associated with higher ECV, our results were similar to those reported in PWOH. MESA also described a positive association between female sex and ECV, trend for negative association with BMI, and negative association with dyslipidaemia.[22] Contrary to MESA, we did not find an association

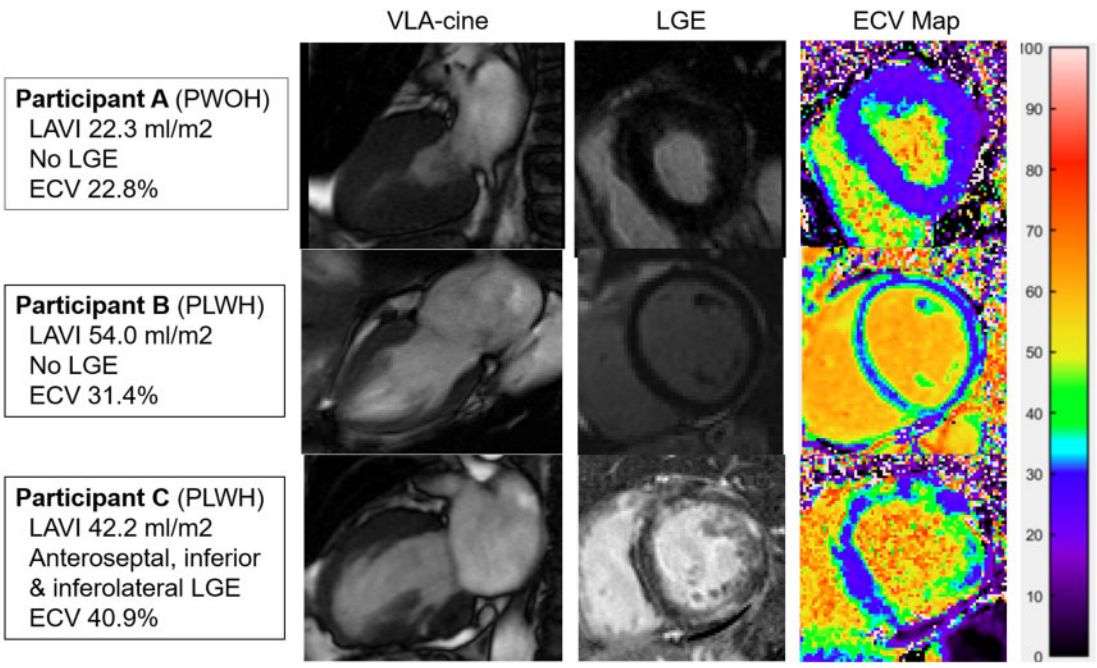


Figure 1 Representative VLA and LGE images and ECV maps from three participants are shown in this figure.
In the PWOH (Participant A), both LAVI and ECV were low and there was no LGE. One of the PLWH (Participant B) also had no LGE but elevated ECV consistent with diffuse myocardial fibrosis and an enlarged left atrium. The second PLWH (Participant C) had diffuse patchy fibrosis involving the anteroseptal, inferior, and inferolateral walls with sub-epicardial predominant pattern. The ECV map shows elevation with segmental pattern corresponding to that of the LGE images and left atrial size was enlarged. ECV, extracellular volume fraction; LAVI, indexed left atrial volume; LGE, late gadolinium enhanced; PLWH, people living with HIV; PWOH; people living without HIV, VLA, vertical long axis

between smoking and ECV, though our cohort had only 5-year cumulative histories of smoking rather than life-time. The relationship between age and ECV is controversial. We observed no age-dependence of ECV, though our participant age ranges were relatively narrow (majority between 44 and 65 years old). Prior studies either reported no age-association[23] or weak correlations ($r = 0.14$–0.28) over larger 40–60 year age spans.[22,24] We found no association between hypertension diagnosis and increased ECV, similar to MESA.[22] While hypertensive heart disease can increase ECV, our cohort did not have significant LV hypertrophy.

Higher ECV is a marker of adverse atrial remodelling and incident atrial fibrillation in PWOH.[22,25] The mechanisms linking diffuse LV fibrosis and LA dysfunction and dysrhythmia are speculative, though our observed association between high ECV and higher maximum LAVI is supportive. The relationship may arise from fibrosis-induced increased LV stiffness causing elevated LA pressures and subsequent LA dilation. Alternatively, diffuse LV fibrosis could mirror the LA fibrosis associated with adversely remodelled atria due to common risk factors.

Prior studies either did not evaluate LA structure and function[16,18] or only measured LA diameter in one plane.[17] Here, we comprehensively assessed all phasic LAVI and LA strain. We found greater LAVI among PLWH vs. PWOH. Small differences in mean LAVI can also translate into significant outcome disparities. In MESA, each SD increase in maximum LAVI was associated with HR = 1.38 for developing atrial fibrillation despite small variations in baseline mean LAVI (controls, $35 \pm 10\,mL/m^2$ vs. cases, $41 \pm 15\,mL/m^2$).[26] When modelled as a continuous variable, systolic blood pressure was associated with increasing LAVI, similar to prior reports.[26] We did not find an association between age and LAVI, consistent with a recent large meta-analysis.[27]

We found no differences by HIV serostatus in resting LA strain or strain rates. Interestingly, compared with published values from healthy HIV-seronegative volunteers aged 50–59 years with no cardiac risk factors,[15] maximal and conduit strains and all strain rates were lower here in both PLWH and PWOH. Notably, reduced maximal and conduit strain have been reported as strong predictors of heart failure risk in PWOH.[28] This may suggest that risk factors and behaviours common to people predisposed to HIV and PLWH could contribute to sub-clinical atrial dysfunction which can precede atrial dilation. Whether HIV infection or associated unstudied factors potentiate LA adverse remodelling with disproportionate increases in LA size perhaps in response to atrial dysfunction warrants further study.

We acknowledge limitations with our study. We did not measure intramyocardial fat or atrial fibrosis. CMR has lower temporal resolution to detect diastolic dysfunction than echocardiography and only resting diastology was assessed. Because this study was conceived as a discovery analysis, no corrections for multiple comparisons were performed but the findings are consistent pathophysiologically with and add to those of prior studies. We did not include an age-matched general population comparison group without risk factors for HIV.

In conclusion, PLWH, even those virally suppressed on cART, are susceptible to small HIV-associated increases in diffuse LV fibrosis and LA volumes. Both PLWH and PWOH with similar risk factors and behaviours appear to have abnormal sub-clinical LA dysfunction. Future studies should examine temporal progression of these sub-clinical findings and their impact on clinical outcomes.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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References

1. Feinstein MJ, Bahiru E, Achenbach C, Longenecker CT, Hsue P, So-Armah K *et al.* Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am J Cardiol* 2016;**117**:214–20.
2. Alvi RM, Neilan AM, Tariq N, Hassan MO, Awadalla M, Zhang L *et al.* The risk for sudden cardiac death among patients living with heart failure and human immunodeficiency virus. *JACC Heart Fail* 2019;**7**:759–67.
3. Alonso A, Barnes AE, Guest JL, Shah A, Shao IY, Marconi V. HIV infection and incidence of cardiovascular diseases: an analysis of a large healthcare database. *J Am Heart Assoc* 2019;**8**:e012241.
4. So-Armah K, Freiberg MH. and Cardiovascular disease: update on clinical events, special populations, and novel biomarkers. *Curr HIV/AIDS Rep* 2018;**15**:233–44.
5. Vlahov D, Anthony JC, Munoz A, Margolick J, Nelson KE, Celentano DD *et al.* The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of methods and characteristics of participants. *NIDA Res Monogr* 1991;**109**:75–100.
6. Barkan SE, Melnick SL, Preston-Martin S, Weber K, Kalish LA, Miotti P *et al.* The women's interagency HIV study. WIHS Collaborative Study Group. *Epidemiology* 1998;**9**:117–25.
7. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR. Jr., for the Multicenter AIDS Cohort Study. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987;**126**:310–8.
8. Heiberg E, Sjogren J, Ugander M, Carlsson M, Engblom H, Arheden H. Design and validation of segment–freely available software for cardiovascular image analysis. *BMC Med Imaging* 2010;**10**: 1.doi: 10.1186/1471-2342-10-1.
9. Schmidt A, Azevedo CF, Cheng A, Gupta SN, Bluemke DA, Foo TK *et al.* Infarct tissue heterogeneity by magnetic resonance imaging identifies enhanced cardiac arrhythmia susceptibility in patients with left ventricular dysfunction. *Circulation* 2007;**115**:2006–14.
10. Shanbhag SM, Greve AM, Aspelund T, Schelbert EB, Cao JJ, Danielsen R *et al.* Prevalence and prognosis of ischaemic and non-ischaemic myocardial fibrosis in older adults. *Eur Heart J* 2019;**40**:529–38.
11. Tao S, Ashikaga H, Ciuffo LA, Yoneyama K, Lima JAC, Frank TF *et al.* Impaired left atrial function predicts inappropriate shocks in primary prevention implantable cardioverter-defibrillator candidates. *J Cardiovasc Electrophysiol* 2017;**28**:796–805.
12. Moon JC, Messroghli DR, Kellman P, Piechnik SK, Robson MD, Ugander M *et al.* Myocardial T1 mapping and extracellular volume quantification: a Society for Cardiovascular Magnetic Resonance (SCMR) and CMR Working Group of the European Society of Cardiology consensus statement. *J Cardiovasc Magn Reson* 2013;**15**:92.
13. Kawel-Boehm N, Maceira A, Valsangiacomo-Buechel ER, Vogel-Claussen J, Turkbey EB, Williams R *et al.* Normal values for cardiovascular magnetic resonance in adults and children. *J Cardiovasc Magn Reson* 2015;**17**:29.
14. Liu CY, Liu YC, Wu C, Armstrong A, Volpe GJ, van der Geest RJ *et al.* Evaluation of age-related interstitial myocardial fibrosis with cardiac magnetic resonance contrast-enhanced T1 mapping: MESA (Multi-Ethnic Study of Atherosclerosis). *J Am Coll Cardiol* 2013;**62**:1280–7.
15. Truong VT, Palmer C, Wolking S, Sheets B, Young M, Ngo TNM *et al.* Normal left atrial strain and strain rate using cardiac magnetic resonance feature tracking in healthy volunteers. *Eur Heart J Cardiovasc Imaging* 2020;**21**:446–53.
16. Holloway CJ, Ntusi N, Suttie J, Mahmod M, Wainwright E, Clutton G *et al.* Comprehensive cardiac magnetic resonance imaging and spectroscopy reveal a high burden of myocardial disease in HIV patients. *Circulation* 2013;**128**:814–22.
17. Ntusi N, O'Dwyer E, Dorrell L, Wainwright E, Piechnik S, Clutton G *et al.* HIV-1-related cardiovascular disease is associated with chronic inflammation, frequent pericardial effusions, and probable myocardial edema. *Circ Cardiovasc Imaging* 2016;**9**:e004430.
18. Thiara DK, Liu CY, Raman F, Mangat S, Purdy JB, Duarte HA *et al.* Abnormal myocardial function is related to myocardial steatosis and diffuse myocardial fibrosis in HIV-infected adults. *J Infect Dis* 2015;**212**:1544–51.
19. Luetkens JA, Doerner J, Schwarze-Zander C, Wasmuth JC, Boesecke C, Sprinkart AM *et al.* Cardiac magnetic resonance reveals signs of subclinical myocardial inflammation in asymptomatic HIV-infected patients. *Circ Cardiovasc Imaging* 2016;**9**:e004091.
20. Treibel TA, Fridman Y, Bering P, Sayeed A, Maanja M, Frojdh F *et al.* Extracellular volume associates with outcomes more strongly than native or post-contrast myocardial T1. *JACC Cardiovasc Imaging* 2020;**13**:44–54.
21. Yang EY, Ghosn MG, Khan MA, Gramze NL, Brunner G, Nabi F *et al.* Myocardial extracellular volume fraction adds prognostic information beyond myocardial replacement fibrosis. *Circ Cardiovasc Imaging* 2019;**12**:e009535.
22. Ambale-Venkatesh B, Liu CY, Liu YC, Donekal S, Ohyama Y, Sharma RK *et al.* Association of myocardial fibrosis and cardiovascular events: the multi-ethnic study of atherosclerosis. *Eur Heart J Cardiovasc Imaging* 2019;**20**:168–76.
23. Rosmini S, Bulluck H, Captur G, Treibel TA, Abdel-Gadir A, Bhuva AN *et al.* Myocardial native T1 and extracellular volume with healthy ageing and gender. *Eur Heart J Cardiovasc Imaging* 2018;**19**:615–21.
24. Ugander M, Oki AJ, Hsu LY, Kellman P, Greiser A, Aletras AH *et al.* Extracellular volume imaging by magnetic resonance imaging provides insights into overt and sub-clinical myocardial pathology. *Eur Heart J* 2012;**33**:1268–78.
25. Imai M, Ambale Venkatesh B, Samiei S, Donekal S, Habibi M, Armstrong AC *et al.* Multi-ethnic study of atherosclerosis: association between left atrial function using tissue tracking from cine MR imaging and myocardial fibrosis. *Radiology* 2014;**273**:703–13.
26. Habibi M, Samiei S, Ambale Venkatesh B, Opdahl A, Helle-Valle TM, Zareian M *et al.* Cardiac magnetic resonance-measured left atrial volume and function and incident atrial fibrillation: results from MESA (Multi-Ethnic Study of Atherosclerosis). *Circ Cardiovasc Imaging* 2016;**9**(8):10.1161/CIRCIMAGING.115.004299
27. D'Ascenzi F, Piu P, Capone V, Sciaccaluga C, Solari M, Mondillo S *et al.* Reference values of left atrial size and function according to age: should we redefine the normal upper limits? *Int J Cardiovasc Imaging* 2019;**35**:41–8.
28. Chirinos JA, Sardana M, Ansari B, Satija V, Kuriakose D, Edelstein I *et al.* Left atrial phasic function by cardiac magnetic resonance feature tracking is a strong predictor of incident cardiovascular events. *Circ Cardiovasc Imaging* 2018;**11**:e007512.