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HIV, HIV-specific Factors and Myocardial Disease in Women

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Background: People with HIV (PWH) have an increased risk of cardiovascular disease (CVD). Cardiac magnetic resonance (CMR) has documented higher myocardial fibrosis, inflammation and steatosis in PWH, but studies have mostly relied on healthy volunteers as comparators and focused on men.

Methods: We investigated the associations of HIV and HIV-specific factors with CMR phenotypes in female participants enrolled in the Women's Interagency HIV Study's New York and San Francisco sites. Primary phenotypes included myocardial native (n) T1 (fibro-inflammation), extracellular volume fraction (ECV, fibrosis) and triglyceride content (steatosis). Associations were evaluated with multivariable linear regression, and results pooled or meta-analyzed across centers.

Results: Among 261 women with HIV (WWH, total n=362), 76.2% had undetectable viremia at CMR. For the 82.8% receiving continuous antiretroviral therapy (ART) in the preceding 5 years, adherence was 51.7%, and 71.3% failed to achieve persistent viral suppression (42.2% with peak viral load<200 cp/mL). Overall, WWH showed higher nT1 than women without HIV (WWOH) after full adjustment. This higher nT1 was more pronounced in those with antecedent or current viremia or nadir CD4+ count<200 cells/μL, the latter also associated with higher ECV. WWH and current CD4+ count<200 cells/μL had less cardiomyocyte steatosis. Cumulative exposure to specific ART showed no associations.

Conclusions: Compared with sociodemographically similar WWOH, WWH on ART exhibit higher myocardial fibro-inflammation, which is more prominent with unsuppressed viremia or CD4+ lymphopenia. These findings support the importance of improved ART adherence strategies, along with better understanding of latent infection, to mitigate cardiac end-organ damage in this population.

Keywords: HIV; cardiac magnetic resonance; myocardial fibro-inflammation; antiretroviral therapy; Women's Interagency HIV Study (WIHS)

People with HIV (PWH) have an outsized risk of cardiovascular disease (CVD), including heart failure (HF) and sudden cardiac death (SCD), compared with the general population [1]. Cardiac magnetic resonance imaging (CMR) increasingly suggests that myocardial inflammation, fibrosis, and steatosis play a role [2–4]. In male-predominant samples, CMR-assessed myocardial inflammation, fibrosis and/or steatosis were higher in PWH compared with their HIV-negative counterparts [3,5]. Among women, small studies have similarly reported higher myocardial fibrosis and steatosis in individuals with HIV than healthy controls [6,7].

Because PWH exhibit high prevalences of CVD risk factors [1], the true impact of HIV on the myocardium may not be captured by comparing to healthier HIV-negative groups [8]. These same potential biases apply to studies of clinical CVD. In particular, the contributions to myocardial disease of HIV and specific antiretroviral therapy (ART) previously linked to HF or weight gain – including protease inhibitors (PIs) [9], tenofovir disoproxil fumarate (TDF) [10] and integrase inhibitors [11] – remain unclear. Such knowledge gaps are especially true for women, who account for ~¼ of U.S. HIV cases [12].

We undertook CMR in the Women's Interagency HIV Study (WIHS) to evaluate the association of HIV and HIV-specific factors with myocardial native (n) T1, a measure of intracellular and extracellular edema (fibro-inflammation); extracellular volume fraction (ECV), a measure of extracellular fibrosis; and myocardial triglyceride content (MTG), a measure of cardiomyocyte steatosis. We tested the hypothesis that women with HIV (WWH) have higher myocardial fibro-inflammation, fibrosis and steatosis compared with women without HIV (WWOH); and that viremia, CD4+, and duration of specific ART influences these relationships.

METHODS

Study cohort

WIHS is a multicenter longitudinal investigation of U.S. WWH and HIV-negative women with similar social and behavioral risk factors for HIV enrolled in 1994-95, 2001-02 and 2011-12 [13]. Participants attended semiannual visits where extensive data were collected.

For the CMR study, all active participants at the Bronx, Brooklyn, and San Francisco (SF) WIHS sites were invited to participate irrespective of HIV status. Participants without contraindications to CMR were enrolled following informed consent (**eMethods**). The institutional review board of each center approved the study.

HIV-specific Variables

Assessment and definition of HIV-related variables are detailed in the **eMethods**.

CMR

A standardized CMR protocol was performed using 3T magnets in the Bronx and SF (**eMethods**) [14,15]. The primary phenotypes were myocardial nT1, ECV and MTG. Secondary phenotypes included left ventricular mass index (LVMI), LVEF, and LGE scar %.

Covariates

Definitions of covariates are given in the **eMethods**.

Statistical analysis

Nearly all cardiac phenotypes were evaluated as continuous measures, after removing outliers>4SD from mean. MTG and LVMI were log-transformed. LGE scar was categorized as 0%, 0-4.9%, and ≥5.0%. Adjusted associations of HIV or HIV-specific factors with cardiac phenotypes were evaluated with linear regression, except for LGE scar %, assessed with ordered logistic regression. Covariates were selected based on reported associations or known biology, with the goal of accounting for aggregate confounding. Model 1 adjusted for age, race/ethnicity and site. Model 2 additionally adjusted for BMI, smoking, heavy alcohol, ever heroin/cocaine, ever IDU and HCV status. Model 3 further adjusted for hypertension, diabetes, dyslipidemia, history of MI or HF, and eGFR. Model 3 was considered the main model, recognizing that some covariates could be partly downstream of HIV or HIV-specific factors. Sensitivity analyses involved additional adjustment for education, income, methamphetamine use, or menopausal status in Model 2, or heart rate in Model 3; exclusion of prior MI or HF or WWH off ART at the study visit; and limiting cumulative exposure of ART medications to the past 5 years. All analyses were first stratified by site. Because myocardial ECV and MTG exhibited substantial site dependence, we decided a priori to meta-analyze the results using fixed-effects and random-effects methods. For other phenotypes, we pooled individual-level data across sites. Additional sensitivity analyses evaluated associations of HIV serostatus with phantom-calibrated nT1 and ECV, available in up to n=266 participants scanned at SF and the primary Bronx magnet; primary phenotypes without exclusion of outliers; and results of pooled, fixed-effects, and random-effects meta-analysis for HIV serostatus and primary CMR phenotypes. Analyses used R, v2.14.1. P<0.05 defined statistical significance.

RESULTS

Participant characteristics

Participant selection and comparison to non-participants are described in **eFigure 1** and **eTable 1**, respectively. Participant characteristics are summarized in **Table 1 and eTable 2**. WWH were older and more frequently post-menopausal, but showed lower MI or eGFR, than WWOH. About ¼ of WWH had detectable viremia at the study visit but <1/3 achieved persistent viral suppression in the past 5 years, with all observed blips <200 cp/mL. Roughly ½ of WWH on continuous ART reported adherence, >2/5 of whom achieved persistent viral suppression, as compared with 1/8 among the non-adherent. Approximately 1/20 WWH had current CD4+ count <200 cells/μL, and 1/6 experienced such a nadir in the prior 5 years. WWH presented lower LVMI but higher nT1 than WWOH. SF participants were older, more often non-Hispanic White and users of heavy alcohol or drugs than Bronx/Brooklyn participants. WWH in Bronx/Brooklyn more commonly achieved persistent viral suppression, but had higher maximal viral load and lower nadir CD4+, than WWH in SF; they also showed differences in ART. There were site

differences in primary cardiac phenotypes, with higher ECV and MTG but lower nT1 in SF than Bronx/Brooklyn.

Bivariable associations

Table 2 presents unadjusted covariate associations with primary cardiac phenotypes. Myocardial ECV showed differences among race/ethnic groups. Higher income was associated with greater nT1, as were current smoking, HIV-positive status, heart rate and prior HF. Current smoking was also associated with higher ECV, along with heavy alcohol and heroin/cocaine use. As shown in **Figure 1**, myocardial nT1 and ECV were mild-moderately positively correlated. Each showed a mild positive correlation with LGE scar %, as did myocardial ECV with LVMI.

HIV and Primary Phenotypes

Meta-analysis showed no heterogeneity across sites for myocardial ECV and MTG. Because fixed and random-effects results were similar, only the former are presented in **Table 3** and **Figure 2**, along with pooled analyses for myocardial nT1. HIV-seropositive status showed marginally non-significant associations with higher nT1 in early models that became significant in the main model. WWH with and without current viremia had significantly higher nT1 than WWOH; among WWH on continuous ART in the past 5 years, this was only the case for unsuppressed viremia. WWH with a 5-year nadir, but not current, CD4+<200 cells/μL had significantly higher nT1 compared with WWOH. There were no significant associations between HIV serostatus or viremia with ECV or MTG at any level of adjustment. As compared with WWOH, WWH and nadir CD4+<200 cells/μL showed significantly higher ECV in the fully adjusted model, whereas WWH and current CD4+<200 cells/μL exhibited lower MTG at all levels of adjustment. Sensitivity analyses with additional covariate adjustments, exclusions of prevalent CVD or WWH off ART, or retention of outliers were consistent with the main findings (not shown), as were phantom-calibrated results for nT1 and ECV (**eTable 3**) or results of pooled and meta-analytic approaches for the primary cardiac phenotypes (presented for HIV serostatus in **eTable 4**).

Pooled/meta-analyzed results revealed no significant associations for duration of any PI, ritonavir, TDF, or integrase-inhibitor use with primary phenotypes at any level of adjustment (**eTable 5**). Findings were unchanged when exposure was limited to the past 5 years.

Site-stratified analyses of HIV and HIV-specific factors with primary phenotypes are presented in **eTables 6 and 7**. Positive associations of HIV and HIV-specific factors with nT1 were seen in SF, as was an inverse association between low current CD4+ and MTG in Bronx/Brooklyn, largely mirroring the pooled results.

HIV and Secondary Phenotypes

Pooled analyses of HIV serostatus, viremia, or CD4+ and secondary cardiac phenotypes are presented in **eTable 8**. HIV serostatus was not significantly associated with secondary phenotypes at any level of adjustment. Certain viremic or CD4+ categories did show significant inverse associations with LVMI in the minimally adjusted model, but only that for current viremia remained significant upon higher adjustment. There were otherwise no significant associations between viremia or CD4+ categories with LVEF or LGE scar % after full adjustment, which was almost entirely the case for earlier models. Specific ART showed no significant associations (**eTable 5**).

DISCUSSION

Main findings

In this multi-center study of women, we documented an association of HIV with higher myocardial nT1, but not ECV or MTG, after extensive adjustment for covariates. This association with nT1 was more evident with unsuppressed viremia or nadir CD4+<200 cells/μL during the preceding 5 years. WWH and nadir CD4+<200 cells/μL had higher ECV than WWOH, while WWH and current CD4+<200 cells/μL had lower MTG. Cumulative exposure to specific ART was not related to these primary phenotypes.

Previous literature

Studies of PWH have shown an increased risk of HF and SCD, associations that have been more pronounced at high viral loads (≥500 cp/mL) or immunosuppression [16,17]. CMR studies have likewise documented higher myocardial fibro-inflammation, fibrosis and steatosis in PWH [3,5,18]. Such findings included patchy fibrosis by LGE or diffuse interstitial fibrosis by post-contrast T1 mapping [3,5,6]; prolonged nT1 or T2, signaling myocardial edema/inflammation [18,19]; and increased MTG [3,7]. Higher myocardial fibrosis in persons with than without HIV was likewise documented in a postmortem study of SCD [20]. Yet a limitation of most existing studies, apart from their predominant focus on men, is their use of HIV-negative comparators lacking the adverse cardiovascular profiles characteristic of PWH [8]. This has been particularly the case for CMR studies, nearly all of which have used HIV-negative comparators matched on a limited number of factors [3,5–7,18,19]. Nor have such studies assessed the impact of antecedent HIV control on outcomes.

To our knowledge, this is the largest CMR study of HIV in women to date. A key strength is the inclusion of U.S. WWH and sociodemographically similar WWOH, permitting more meaningful assessment of the impact of HIV on cardiac phenotypes. Another is its regular longitudinal assessment of viremia, CD4+, and HIV treatment and adherence, allowing characterization of therapeutic effectiveness over time. Accordingly, the present findings provide new insights

regarding HIV, its control, and cardiac fibro-inflammation in this understudied population from a high-income country.

Potential explanations

The associations detected by HIV serostatus, viremia, and low nadir CD4+ with CMR phenotypes were limited to nT1, and for low nadir CD4+, ECV. These findings contrast with previous studies from high-income countries [3,5–7,18], which showed HIV-related differences not just in myocardial nT1, but also, where evaluated, ECV, patchy fibrosis by LGE, and MTG. These studies selected controls from populations who were not sociodemographically at risk for HIV, however, which may have accentuated the contributions of HIV-associated CVD risk factors to the differences observed.

Higher myocardial nT1 and ECV each correlate with increased collagen volume fraction in tissue, but the former measures intracellular and extracellular edema (reflecting inflammation, cellular injury and fibrosis), while the latter captures interstitial edema (extracellular collagen deposition). Both measures have been associated with diastolic dysfunction [21] and clinical events [22–24]. Notably, for nT1 the latter was specifically demonstrated in PWH, with each 10-ms-higher nT1 associated with 1.2-fold greater incidence of CVD [25]. Our finding of more salient differences for HIV and HIV-specific factors for nT1 than ECV could reflect an active myocellular inflammatory process that becomes more marked extracellularly when CD4+ lymphopenia supervenes.

The current findings are compatible with a prior longitudinal CMR investigation in ART-naïve PWH from South Africa before and after the initiation of therapy [19]. This study revealed that myocardial nT1 and ECV decreased significantly after ART in conjunction with lower viremia and improved CD4+ count [19]. This suggests that both nT1 and ECV in this ART-naïve group predominantly reflected myocardial inflammation pre-treatment, much as our findings seem to indicate for nT1 and ECV on treatment. Yet one prior large U.S. study (29% female) that included a comparison group at risk for HIV found a near-significantly higher myocardial ECV in PWH, but not nT1, with no differences by HIV severity [26]. Moreover, another CMR study of South African people with and without HIV (65% female) exhibiting similar risk factor profiles documented higher HIV-associated myocardial ECV, though not nT1, an association that appeared more pronounced in women [27]. The basis for these discrepant findings to ours is uncertain, but could owe to differences in populations and their trajectories of HIV control or treatment. Current viremic suppression in the previous U.S. study [26] was similar to ours, but persistent viral suppression was not reported. Unlike our study, the South African study excluded PWH with viremia≥200 cp/mL and prior CVD, including myocarditis/pericarditis, which may have made myocardial fibro-inflammation less likely [27]. IDU was not reported, but was presumably lower than seen herein, and CVD risk factors were ½ to ¼ as frequent [27]. Hence, background stimuli to fibrosis were much stronger in our participants with and without HIV, potentially making any HIV-related signal more difficult to detect.

The finding that low current CD4+ count was associated with lower MTG runs counter to our hypothesis that more severe HIV disease would increase cardiomyocyte oxidative stress, resulting in impaired fatty-acid oxidative capacity and intracellular triglyceride accumulation [8]. Instead, our findings support the view that WWH and WWOH with comparably high prevalences of obesity, diabetes and dyslipidemia have similar levels of cardiomyocyte triglyceride deposition. In this context, immune compromise, associated wasting, and dissipation of whole-body triglyceride excess – as indicated by the lower BMI seen here in WWH and low CD4+ – exert the dominant influence over mitochondrial impairment to reduce cardiomyocyte fat accumulation. Differences in obesity and dysmetabolism likely account for the contrary finding of higher MTG with lower nadir CD4+ documented in a predominantly male sample of PWH [28], whose much lower BMI would have removed the overriding contribution of excess adiposity to myocardial ectopic fat deposition observed here.

We did not find an association between duration of PI, TDF, or integrase-inhibitor use and cardiac phenotypes. This provides some reassurance about the potential adverse cardiac effects of PIs [9] and integrase inhibitors [11], but fails to support cardioprotective effects for TDF [10] in WWH. Overall ART adherence was suboptimal, however. It is recognized that PWH receiving ART experience chronic inflammation and immune activation, which are largely responsible for heightened non-infectious comorbidities [29,30]. Part of this inflammatory activation results from depletion of gut-associated lymphoid tissue during acute HIV [4], fostering recurrent microbial translocation. Even with ART, however, HIV persists in cellular reservoirs, and may retain the capacity to replicate [31,32]. The virus does not productively infect cardiomyocytes, but does infect immune or dendritic cells that reside or can migrate to the myocardium [33]. The resulting inflammation is compounded by the myocardial toxicity of viral proteins themselves [33].

Among WWH in our cohort receiving continuous ART, ~70% did not achieve persistent viral suppression. This played an important role in the observed myocardial fibro-inflammation, as did episodic, severe HIV-induced lymphopenia. A majority of women with unsuppressed viremia had maximal viral loads ≥200 cp/mL, levels reflecting active viral replication and its attendant tissue effects [32]. Yet a substantial number of WWH on ART and unsuppressed viremia had maximal viral loads <200 cp/mL, as did all who were persistently suppressed. The clinical implications of such low-level viremia, which could reflect release of non-replication competent virus, have been unclear [32]. But recent evidence has linked low-level viremia to subsequent virologic failure [31,32]. Our finding that even WWH with persistent viral suppression had a non-significant uptick in myocardial fibro-inflammation suggests that such modest viremic levels may also have adverse cardiac consequences.

Clinical implications

We previously documented a borderline association of HIV with echocardiographic LV systolic dysfunction WIHS-wide, with LV diastolic dysfunction observed with decreasing CD4+ [34].

The present findings from NY and SF further support these HIV-related differences, implicating myocardial fibro-inflammation as the underlying disease process. Our results are of particular importance because evidence suggests that HIV-associated HF risk may be higher in women than men [16], and that HIV-negative women from race/ethnic minority groups already experience an increased burden of HF [35,36].

Our proportion of WWH attaining persistent viral suppression is lower than the 58% reported for U.S. women, but that reflects one-time testing at a cutoff of <200 cp/mL [37]. In fact, high-level ART adherence in our cohort exceeds that documented nationally for PWH during a 12-month period (38.7% with ≥90% adherence) [38]. Hence, our rate of sustained viral suppression may be more favorable than for U.S. WWH generally. As such, our findings highlight contemporary gaps in HIV control in this population, and the need to improve compliance with ART to, among other benefits [39], prevent myocardial disease.

High adherence in our cohort substantially lowered unsuppressed viremia, achieving more low-level viremia in the latter group. But >½ of WWH who reported high adherence failed to achieve persistent suppression, a sizable fraction of whom had substantial viremic levels, suggesting that viral resistance could be a concern in this group. Nonetheless, the considerable proportion of low viral loads among participants with unsuppressed viremia, together with the suggestion of increased myocardial fibro-inflammation in their counterparts achieving persistent suppression, call for additional study of the cellular reservoir and its potential contributions to CVD in WWH.

Limitations

This cross-sectional observational study may be subject to residual confounding. Phantom calibration of MRI scans was conducted for nT1 and ECV, and not for MTG, but the former suggests that site differences predominantly relate to the different risk profiles of participants. MOLLI schemes for T1 mapping were updated in the course of scanning in the Bronx, but their effects are considered minimal [40]. We were only able to complete scans in a subset of participants. Women who received scans were broadly similar to those who did not, except for having lower BMI, and higher frequency of smoking or ever drug use. Our findings are not necessarily generalizable to other settings.

Conclusions

In U.S. women with and without HIV, we documented increased HIV-associated myocardial fibro-inflammation that was accentuated by unsuppressed viremia and lymphopenia. These findings highlight the need for strategies to enhance ART adherence, improve virologic suppression, and address the potential effects of low-level viremia to prevent cardiac end-organ damage and reduce CVD events in this vulnerable population.

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Author Contributions

J.R.K., J.A.C.L., R.C.K., and J.M.L. designed the study and obtained funding. Y.K. and J.R.K drafted the manuscript. M.N. and R.K. conducted the statistical analyses. All coauthors contributed to study conduct, and provided edits to the manuscript draft.

Conflicts of Interest

J.R.K. reports stock ownership in Abbvie, Abbott, Bristol Myers Squibb, Johnson & Johnson, Medtronic, Merck and Pfizer. K.O. is president of the Society for Cardiovascular Magnetic Resonance (2023-2024). There are no other relationships to disclose. YK reports receiving speaker fees from CANON Medical Systems. JML reports editing royalties for cardiovascular textbook from Oxford University Press. PCT reports grants from Merck and Gilead paid to their institution, payment for integritas CME presentation, participation on the STAR cohort Scientific Advisory Board, STAR cohort Scientific Advisory Board, BIRCWH K12 External Scientific Advisory Board

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FIGURE LEGENDS

Figure 1. Heat map of Spearman correlations for primary and secondary cardiac phenotypes. ECV = extracellular volume fraction; EF = ejection fraction; LGE = late gadolinium enhancement; LV = left ventricular; MTG = myocardial triglyceride content.

Figure 2. Forest plot of associations between HIV and HIV-specific factors (viremia and CD4+ T-cell count) and primary cardiac phenotypes.

Model 1. Adjusted for age, race/ethnicity, and site.
Model 2. Adjusted for Model 1 covariates and body mass index, current smoking, heavy alcohol use, use of heroin or cocaine, injection drug use, hepatitis C virus status
Model 3. Adjusted for Model 2 covariates and hypertension, diabetes, dyslipidemia, history of myocardial infarction, history of heart failure, and estimated glomerular filtration rate.
VL = viral load.

Table 1. Sociodemographic, Clinical and Cardiac Phenotype Characteristics* by Site and HIV Serostatus

Characteristics	All (n=362)	Site			HIV Serostatus		
		Bronx-Brooklyn (n=266)	San Francisco (n=96)	P†	Positive (n=261)	Negative (n=101)	P†
Sociodemographic Factors							
Age, y	53 (48, 58)	**52 (47, 58)**	**56 (50, 62)**	**<.001**	**54 (49, 59)**	**52 (45, 57)**	**0.002**
Race/ethnicity, n (%)				**<.001**			0.074
Hispanic	88 (24.3)	**80 (30.1)**	**8 (8.3)**		62 (23.8)	26 (25.7)	
Non-Hispanic Black	226 (62.4)	**170 (63.9)**	**56 (58.3)**		157 (60.2)	69 (68.3)	
Non-Hispanic White	29 (8.0)	**9 (3.4)**	**20 (20.8)**		26 (10.0)	3 (3.0)	
Other	19 (5.2)	**7 (2.6)**	**12 (12.5)**		16 (6.1)	3 (3.0)	
≥High school education, n (%)	228 (63.0)	**152 (57.1)**	**76 (79.2)**	**<.001**	104 (39.8)	30 (29.7)	0.073
Annual income ≥$12,000, n (%)	179 (49.4)	133 (50.0)	46 (47.9)		125 (47.9)	58 (57.4)	0.104
Clinical Factors							
BMI, kg/m^2	29.3 (25.1, 34.7)	29.6 (25.4, 34.7)	27.9 (23.9, 35.0)	0.358	29.2 (24.9, 34.4)	29.4 (25.3, 35.4)	0.991
Heart rate, bpm	67 (60, 74)	**66 (60, 73)**	**70 (62, 76.5)**	**0.011**	68 (60, 75)	66 (59, 72)	0.094
Current smoker, n (%)	154 (42.5)	112 (42.1)	42 (43.8)	0.780	106 (40.6)	48 (47.5)	0.233
Heavy alcohol use, n (%)	38 (10.5)	**18 (6.8)**	**20 (20.8)**	**<.001**	26 (10.0)	12 (11.9)	0.593
Menopause status, n (%)				0.353			**<.001**
Pre-menopausal	72 (19.9)	57 (21.4)	15 (15.6)		**39 (14.9)**	**33 (32.7)**	
Peri-menopausal	47 (13.0)	36 (13.5)	11 (11.5)		**32 (12.3)**	**15 (14.9)**	
Post-menopausal	243 (67.1)	173 (65.0)	70 (72.9)		**190 (72.8)**	**53 (52.5)**	
HIV, n (%)	261 (72.1)	195 (73.3)	66 (68.8)	0.393	261 (100.0)	0 (0.0)	N/A
HCV, n (%)	87 (24.0)	57 (21.4)	30 (31.2)	0.054	69 (26.4)	18 (17.8)	0.085
Ever IDU , n (%)	75 (20.7)	**39 (14.7)**	**36 (37.5)**	**<.001**	56 (21.5)	19 (18.8)	0.578
Ever heroin/cocaine , n (%)	241 (66.6)	**161 (60.5)**	**80 (83.3)**	**<.001**	173 (66.3)	68 (67.3)	0.850
Ever methamphetamine, n (%)	16 (4.4)	**0 (0)**	**16 (16.7)**	**<.001**	9 (3.4)	7 (6.9)	0.160
Hypertension, n (%)	246 (68.0)	181 (68.0)	65 (67.7)	0.952	181 (69.3)	65 (64.4)	0.361
Diabetes, n (%)	101 (27.9)	80 (30.1)	21 (21.9)	0.125	73 (28.0)	28 (27.7)	0.963
Dyslipidemia, n (%)	309 (85.4)	231 (86.8)	78 (81.2)	0.184	228 (87.4)	81 (80.2)	0.084

History of MI, n (%)	22 (6.1)	17 (6.4)	5 (5.2)	0.806	**11 (4.2)**	**11 (10.9)**	**0.017**
History of HF, n (%)	8 (2.2)	4 (1.5)	4 (4.2)	0.216	4 (1.5)	4 (4.0)	0.226
eGFR, mL/min/1.73m^2	90 (75, 106)	92 (76, 106)	86 (72, 105)	0.315	**85 (70, 101)**	**100 (86, 114)**	**<.001**
HIV-specific Factors (WWH Only)							
Detectable viremia at visit, n (%)	N/A	48 (24.6)	14 (21.2)	0.574	62 (23.8)	N/A	N/A
Current VL, when detectable, cp/mL	N/A	88 (43, 684)	64 (30, 511)	0.608	75 (40, 554)	N/A	N/A
Persistent viral suppression within 5 y,‡ n (%)				**0.021**			N/A
Viremia suppressed	N/A	**56 (34.8)**	**10 (18.2)**		66 (30.6)	N/A	
Unsuppressed viremia	N/A	**105 (65.2)**	**45 (81.8)**		150 (69.4)	N/A	
Maximum VL during period, cp/mL	N/A	**871 (87, 22100)**	**199 (107, 556)**	**0.026**	428 (93, 9970)	N/A	N/A
Proportion with maximal VL<200 cp/mL	N/A	38 (36.2)	23 (51.1)	0.088	61 (40.7)	N/A	N/A
Adherent with ART across prior 5 y,	N/A	80 (51.0)	27 (54.0)	0.708	107 (51.7)	N/A	N/A
Unsuppressed viremia	N/A	39 (48.8)	19 (70.4)	0.051	58 (54.2)	N/A	N/A
Proportion with maximal VL<200 cp/mL		23 (59.0)	13 (68.4)	0.486	36 (62.1)	N/A	N/A
Non-adherent with ART across prior 5 y	N/A	77 (49.0)	23 (46.0)	0.708	100 (48.3)	N/A	N/A
Unsuppressed viremia	N/A	63 (81.2)	22 (95.7)	0.103	85 (85.0)	N/A	N/A
Proportion with maximal VL<200 cp/mL		15 (23.8)	8 (36.4)	0.254	23 (27.1)	N/A	N/A
CD4+ T-cell count, cells/μL	N/A	665 (473, 883)	745 (603, 965)	0.061	700 (500, 925)	N/A	N/A
CD4+ categories, n (%)				0.512			N/A
CD4+ ≥500 cells/μL	N/A	144 (73.8)	52 (78.8)		196 (75.1)	N/A	
CD4+ 200-499 cells/μL	N/A	38 (19.5)	12 (18.2)		50 (19.2)	N/A	
CD4+ <200 cells/μL	N/A	13 (6.7)	2 (3.0)		15 (5.7)	N/A	
Nadir CD4+ categories, n (%)				**0.044**			N/A
CD4+ ≥500 cells/μL	N/A	**66 (33.8)**	**33 (50.0)**		99 (37.9)	N/A	
CD4+ 200-499 cells/μL	N/A	**91 (46.7)**	**26 (39.4)**		117 (44.8)	N/A	
CD4+ <200 cells/μL	N/A	**38 (19.5)**	**7 (10.6)**		45 (17.2)	N/A	
ART use at visit, n (%)	N/A	180 (92.3)	63 (95.5)	0.383	243 (93.1)	N/A	N/A
NRTI use at visit, n (%)	N/A	168 (86.2)	61 (92.4)	0.179	229 (87.7)	N/A	N/A
TDF use at visit, n (%)	N/A	**74 (37.9)**	**5 (7.6)**	**<.001**	79 (30.3)	N/A	N/A
NNRTI use at visit, n (%)	N/A	**60 (30.8)**	**12 (18.2)**	**0.048**	72 (27.6)	N/A	N/A
PI use at visit, n (%)	N/A	**66 (33.8)**	**8 (12.1)**	**0.001**	74 (28.4)	N/A	N/A

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Ritonavir use at visit, n (%)	N/A	**60 (30.8)**	**5 (7.6)**	**<.001**	65 (24.9)	N/A	N/A
INSTI use at visit, n (%)	N/A	**101 (51.8)**	**49 (74.2)**	**0.001**	150 (57.5)	N/A	N/A
Continuous ART prescription in past 5 y, n (%)	N/A	161 (82.6)	55 (83.3)	0.686	216 (82.8)	N/A	N/A
Cumulative TDF exposure, y	N/A	8.0 (5.5, 11.0)	6.8 (5.0, 9.2)	0.062	7.5 (5.0, 10.5)	N/A	N/A
Cumulative PI exposure, y	N/A	8.5 (4.5, 11.5)	7.5 (5.1, 9.5)	0.405	8.0 (4.8, 11.0)	N/A	N/A
Cumulative ritonavir exposure, y	N/A	8.5 (5.0, 11.5)	7.8 (6.1, 9.9)	0.702	8.5 (5.1, 11.0)	N/A	N/A
Cumulative INSTI exposure, y	N/A	7.5 (4.0, 10.5)	6.0 (3.8, 9.3)	0.088	7.0 (4.0, 10.0)	N/A	N/A
Cardiac Phenotypes							
LV mass index, g/m^2	44.1 (39.2, 50.2)	43.9 (39.1, 49.9)	45.7 (40.4, 50.4)	0.216	**43.7 (38.7, 49.9)**	**45.3 (41.9, 50.9)**	**0.026**
LVEF, %	57.0 (53.0, 60.0)	**56.0 (53.0, 60.0)**	**58.0 (53.3, 61.8)**	**0.023**	57.0 (53.0, 61.0)	56.0 (53.0, 59.0)	0.069
Raw native T1, ms	1271 (1243, 1304)	**1277 (1249, 1305)**	**1255 (1219, 1286)**	**0.002**	**1276 (1246, 1308)**	**1264 (1233, 1283)**	**0.038**
Phantom-calibrated native T1,§ ms	1271 (1245, 1304)	**1278 (1250, 1305)**	**1258 (1222, 1289)**	**0.007**	**1277 (1247, 1308)**	**1263 (1236, 1283)**	**0.022**
LGE scar, %	0.23 (0, 1.45)	0.42 (0, 1.51)	0 (0, 1.10)	0.019	0.15 (0, 1.30)	0.45 (0, 1.90)	0.067
Myocardial ECV, %	27.6 (25.5, 30.4)	**26.7 (24.9, 28.8)**	**30.5 (28.3, 33.5)**	**<.001**	27.4 (25.4, 30.3)	28.3 (26.2, 30.6)	0.253
Phantom-calibrated myocardial ECV,§ %	27.8 (25.5, 30.4)	**26.9 (25.0, 29.0)**	**30.1 (27.8, 33.1)**	**<.001**	27.8 (25.4, 30.3)	28.2 (26.2, 30.5)	0.399
Myocardial triglyceride content, %	0.57 (0.33, 0.93)	**0.52 (0.30, 0.83)**	**0.80 (0.43, 1.62)**	**<.001**	0.57 (0.31, 0.94)	0.52 (0.33, 0.84)	0.973

*Median (IQR) for continuous variables. Frequency (%) for categorical variables.

†Continuous variables were compared by the Wilcoxon rank-sum test, and categorical variables by the chi-square or Fisher's exact test.

‡Among women with HIV on continuous ART during the 5-year period.

§Calibration for T1 mapping measures involves participants from the main study (n=328) after exclusion of n=36 participants scanned at the secondary Bronx magnet, where phantom imaging was not performed.

ART = antiretroviral therapy; BMI = body mass index; ECV = extracellular volume fraction; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HF = heart failure; HIV = human immunodeficiency virus; INSTI = integrase strand transfer inhibitor; IQR = inter-quartile range; IDU = injection drug use; LGE = late gadolinium enhancement; LV = left ventricle; LVEF = LV ejection fraction; LVMI = LV mass index; MI = myocardial infarction; NNRTI =

Non-nucleoside reverse transcriptase inhibitor; NRTI = Nucleoside reverse transcriptase inhibitor; TDF = tenofovir disoproxil fumarate; PI = protease inhibitors; VL = viral load; WWH = women with HIV.

Table 2. Bivariable Associations* of Covariates with Primary Cardiac Phenotypes

	Myocardial Native T1		**Myocardial ECV**		**Myocardial Triglyceride Content**	
	R or Median (IQR)	**P**	**R or Median (IQR)**	**P**	**R or Median (IQR)**	**P**
Age‡	0	0.993	0.028	0.646	0.053	0.367
Race/ethnicity		0.318		**0.038**		0.085
Non-Hispanic Black	1277 (1244, 1305)		**26.7 (25, 29.5)**		0.55 (0.35, 0.92)	
Hispanic	1268 (1245, 1303)		**27.7 (25.4, 30.4)**		0.52 (0.29, 0.88)	
Non-Hispanic White	1255 (1208, 1285)		**28.2 (26, 30.3)**		0.87 (0.39, 1.75)	
Other	1279 (1254, 1335)		**30.5 (28.6, 32.9)**		0.74 (0.36, 0.93)	
Site		**0.002**		**<0.001**		**<0.001**
Bronx/Brooklyn	**1277 (1249, 1305)**		**26.7 (24.9, 28.8)**		**0.52 (0.3, 0.83)**	
San Francisco	**1255 (1219, 1286)**		**30.5 (28.3, 33.5)**		**0.80 (0.43, 1.62)**	
BMI‡	-0.099	0.091	**-0.262**	**<0.001**	0.098	0.095
Education		0.09		0.869		0.208
<High school	1278 (1248, 1311)		27.6 (25.9, 29.5)		0.52 (0.28, 0.88)	
≥High school	1267 (1238, 1301)		28 (25.4, 30.6)		0.6 (0.35, 0.98)	
Annual income		**0.036**		0.189		0.317
≤ $12,000	**1264 (1237, 1295)**		27.4 (25.1, 30.6)		0.61 (0.35, 0.94)	
>$12,000	**1280 (1248, 1313)**		28.3 (26.1, 30.1)		0.55 (0.28, 0.9)	
Current Smoking		**0.011**		**0.013**		0.442
No	**1265 (1237, 1292)**		**27.2 (25.1, 29.7)**		0.52 (0.33, 0.88)	
Yes	**1281 (1248, 1315)**		**28.7 (26.1, 30.9)**		0.63 (0.3, 0.97)	
Heavy alcohol use		0.911		**0.042**		0.985
No	1269 (1244, 1303)		**27.6 (25.4, 30.1)**		0.57 (0.33, 0.92)	

Yes	1275 (1228, 1309)		**29.4 (27.3, 32.02)**		0.57 (0.29, 0.96)	
Ever IDU		0.752		0.100		0.094
No	1271 (1244, 1304)		27.6 (25.4, 30)		0.55 (0.31, 0.88)	
Yes	1270 (1239, 1293)		28.5 (25.7, 31.5)		0.66 (0.38, 1.17)	
Ever use of heroin/cocaine		0.816		**0.003**		0.264
No	1267 (1243, 1303)		**26.9 (24.8, 29.2)**		0.52 (0.33, 0.82)	
Yes	1273 (1244, 1304)		**28.3 (25.8, 30.8)**		0.59 (0.31, 1)	
Ever use of methamphetamine†		0.115		0.428		0.842
No	1260 (1220, 1291)		30.6 (28.3, 33.7)		0.79 (0.42, 1.54)	
Yes	1237 (1192, 1274)		30.1 (27.9, 31.6)		1.01 (0.49, 1.87)	
Menopausal status		0.678		0.315		0.465
Pre-menopausal	1273 (1250, 1308)		28.1 (26.7, 30.6)		0.51 (0.35, 0.93)	
Peri-menopausal	1267 (1236, 1305)		28.7 (25.3, 30.5)		0.44 (0.23, 0.85)	
Post-menopausal	1271 (1243, 1302)		27.4 (25.2, 30.1)		0.59 (0.34, 0.96)	
HIV status		**0.038**		0.254		0.974
Negative	**1264 (1233, 1284)**		28.3 (26.2, 30.6)		0.52 (0.33, 0.84)	
Positive	**1277 (1246, 1308)**		27.4 (25.4, 30.3)		0.57 (0.31, 0.94)	
HCV status		0.572		0.669		0.655
Negative	1268 (1242, 1303)		27.7 (25.5, 30.0)		0.58 (0.32, 0.9)	
Positive	1274 (1247, 1307)		27.5 (25.2, 31.0)		0.53 (0.35, 1.02)	
Hypertension		0.616		0.525		0.562
No	1270 (1242, 1307)		27.6 (25.5, 30.1)		0.58 (0.34, 0.99)	
Yes	1272 (1245, 1301)		28.0 (25.5, 30.5)		0.56 (0.31, 0.92)	
Diabetes		0.113		0.09		0.391
No	1267 (1242, 1302)		27.6 (25.5, 29.9)		0.59 (0.33, 0.92)	
Yes	1281 (1246, 1311)		28.5 (25.5, 31.6)		0.49 (0.28, 0.94)	
Dyslipidemia		0.132		0.388		0.516
No	1282 (1253, 1310)		27.6 (26.3, 30.1)		0.65 (0.32, 0.92)	
Yes	1267 (1238, 1302)		27.7 (25.3, 30.4)		0.55 (0.33, 0.93)	
Heart rate‡	**0.24**	**<0.001**	0.102	0.1	0.02	0.744

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History of myocardial infarction		0.119		0.128		0.713
No	1268 (1242, 1303)		27.6 (25.4, 30.3)		0.57 (0.33, 0.93)	
Yes	1287 (1268, 1321)		29 (27.3, 30.9)		0.59 (0.21, 0.83)	
History of heart failure		**0.017**		0.14		0.271
No	**1268 (1242, 1303)**		27.6 (25.4, 30.4)		0.55 (0.32, 0.93)	
Yes	**1316 (1289, 1360)**		28.7 (27.7, 33.1)		0.76 (0.62, 0.94)	
eGFR‡	-0.027	0.642	0.107	0.083	-0.039	0.503

*The bivariable associations presented are unadjusted, and do not account for the potential influence of confounders. Correlations between variables were assessed with Spearman coefficients. Comparisons of CMR measures across levels of categorical variables were conducted with the Wilcoxon rank-sum test.
†For San Francisco site only (no women from Bronx or Brooklyn reported methamphetamine use).
‡Continuous variables. The remainder are categorical variables.
BMI = body mass index; CMR = cardiac magnetic resonance; ECV = extracellular volume fraction; eGFR = estimated glomerular filtration rate; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IDU = injection drug use; IQR = inter-quartile range.

Table 3. Associations of HIV Serostatus, Viremia and CD4+ T-cell Count with Primary Cardiac Phenotypes in Pooled Analysis or Meta-Analysis

	Model 1		**Model 2**		**Model 3**	
Myocardial Native T1 (Pooled Analysis)	**Mean Change (95% CI)**	**P**	**Mean Change (95% CI)**	**P**	**Mean Change (95% CI)**	**P**
HIV seropositive (ref. HIV-negative women)	11.3 (-1.3, 23.8)	0.080	12.6 (-0.14, 25.3)	0.054	**15.3 (2.5, 28.1)**	**0.020**
Current HIV viremia (ref. HIV-negative women)						
Viremia undetected	9.7 (-3.4, 22.9)	0.148	11.5 (-1.8, 24.8)	0.092	**13.9 (0.6, 27.2)**	**0.041**
Viremia detected	16.0 (-1.1, 33.1)	0.068	15.7 (-1.5, 32.9)	0.074	**19.8 (2.6, 37.1)**	**0.025**
HIV viremia in past 5y (ref. HIV-negative women)						
Persistent viral suppression*	2.9 (-14.1, 19.8)	0.742	6.1 (-11.0, 23.2)	0.487	8.8 (-8.2, 25.9)	0.310
Viremia unsuppressed*	11.0 (-2.6, 24.5)	0.114	10.9 (-2.8, 24.7)	0.121	**14.5 (0.5, 28.6)**	**0.044**
Current CD4+ count (ref. HIV-negative women)						

≥500 cells/μL	11.1 (-2.0, 24.1)	0.097	12.7 (-0.46, 25.9)	0.060	**15.4 (2.2, 28.6)**	**0.023**
200-499 cells/μL	12.5 (-6.8, 31.8)	0.205	13.1 (-6.4, 32.5)	0.190	16.1 (-3.1, 35.3)	0.102
<200 cells/μL	10.5 (-22.9, 43.9)	0.538	8.7 (-24.9, 42.3)	0.611	11.5 (-21.7, 44.8)	0.497
Nadir CD4+ count in past 5y (ref. HIV-negative women)						
≥500 cells/μL	8.9 (-6.0, 23.7)	0.243	11.4 (-3.7, 26.5)	0.139	14.1 (-1.1, 29.3)	0.070
200-499 cells/μL	10.3 (-4.3, 24.9)	0.168	11.1 (-3.6, 25.7)	0.139	13.6 (-0.9, 28.1)	0.066
<200 cells/μL	20.4 (0.05, 40.7)	0.050	20.4 (-0.3, 41.2)	0.055	**25.1 (4.3, 45.9)**	**0.019**
Myocardial ECV (Fixed Effects Meta-Analysis)	**Mean Change (95% CI)**	**P**	**Mean Change (95% CI)**	**P**	**Mean Change (95% CI)**	**P**
HIV seropositive (ref. HIV-negative women)	-0.27 (-1.16, 0.63)	0.561	-0.11 (-1.02, 0.79)	0.804	0.35 (-0.57, 1.27)	0.456
Current HIV viremia (ref. HIV-negative women)						
Viremia undetected	-0.28 (-1.21, 0.66)	0.562	-0.07 (-1.01, 0.87)	0.881	0.39 (-0.56, 1.35)	0.420
Viremia detected	-0.20 (-1.42, 1.02)	0.743	-0.20 (-1.43, 1.03)	0.751	0.27 (-0.97, 1.51)	0.665
HIV viremia in past 5y (ref. HIV-negative women)						
Persistent viral suppression*	-0.33 (-1.50, 0.84)	0.582	0.06 (-1.11, 1.23)	0.915	0.51 (-0.67, 1.69)	0.394
Viremia unsuppressed*	-0.24 (-1.23, 0.75)	0.682	-0.11 (-1.11, 0.89)	0.832	0.36 (-0.66, 1.39)	0.488
Current CD4+ count (ref. HIV-negative women)						
≥500 cells/μL	-0.28 (-1.22, 0.66)	0.558	-0.07 (-1.00, 0.87)	0.892	0.34 (-0.62, 1.29)	0.488
200-499 cells/μL	-0.36 (-1.72, 1.00)	0.606	-0.35 (-1.70, 1.01)	0.614	0.34 (-1.03, 1.72)	0.622
<200 cells/μL	0.03 (-2.19, 2.25)	0.976	-0.03 (-2.24, 2.19)	0.980	0.82 (-1.42, 3.05)	0.475
Nadir CD4+ count in past 5y (ref. HIV-negative women)						
≥500 cells/μL	-0.84 (-1.91, 0.23)	0.125	-0.58 (-1.66, 0.51)	0.298	-0.11 (-1.21, 0.99)	0.848
200-499 cells/μL	-0.19 (-1.22, 0.83)	0.713	-0.10 (-1.13, 0.92)	0.846	0.33 (-0.70, 1.36)	0.530
<200 cells/μL	0.78 (-0.62, 2.18)	0.276	0.83 (-0.58, 2.24)	0.249	**1.47 (0.03, 2.91)**	**0.045**
Myocardial Triglyceride Content (Fixed-Effects Meta-Analysis)	**Proportional Change† (95% CI)**	**P**	**Proportional Change† (95% CI)**	**P**	**Proportional Change† (95% CI)**	**P**
HIV seropositive (ref. HIV-negative women)	1.00 (0.81, 1.23)	0.988	1.00 (0.81, 1.23)	0.978	0.97 (0.77, 1.21)	0.773
Current HIV viremia (ref. HIV-negative women)						

Viremia undetected	0.99 (0.80, 1.22)	0.902	0.98 (0.79, 1.23)	0.889	0.94 (0.75, 1.19)	0.627
Viremia detected	1.04 (0.78, 1.40)	0.771	1.05 (0.78, 1.41)	0.771	1.06 (0.78, 1.43)	0.730
HIV viremia in past 5y (ref. HIV-negative women)						
Persistent viral suppression*	1.06 (0.81, 1.39)	0.650	1.04 (0.79, 1.37)	0.791	0.99 (0.74, 1.33)	0.960
Viremia unsuppressed*	0.99 (0.79, 1.25)	0.943	1.00 (0.79, 1.27)	0.996	0.99 (0.77, 1.27)	0.944
Current CD4+ count (ref. HIV-negative women)						
≥500 cells/μL	1.00 (0.81, 1.24)	0.995	0.99 (0.80, 1.24)	0.947	0.96 (0.77, 1.21)	0.745
200-499 cells/μL	1.18 (0.88, 1.57)	0.273	1.19 (0.88, 1.59)	0.259	1.13 (0.83, 1.53)	0.429
<200 cells/μL	**0.56 (0.34, 0.93)**	**0.025**	**0.60 (0.36, 1.00)**	**0.048**	**0.54 (0.32, 0.91)**	**0.020**
Nadir CD4+ count in past 5y (ref. HIV-negative women)						
≥500 cells/μL	1.02 (0.79, 1.31)	0.905	1.02 (0.78, 1.33)	0.895	1.02 (0.77, 1.34)	0.912
200-499 cells/μL	0.99 (0.78, 1.25)	0.912	0.97 (0.76, 1.24)	0.798	0.92 (0.71, 1.19)	0.523
<200 cells/μL	1.02 (0.76, 1.38)	0.898	1.06 (0.78, 1.44)	0.724	1.02 (0.74, 1.41)	0.894

*Among women with HIV on continuous antiretroviral therapy during the 5-year period.

†Ratio of geometric mean of index group to geometric mean of comparator (HIV-negative) group.

Model 1. Adjusted for age, race/ethnicity, and site.

Model 2. Adjusted for Model 1 covariates and body mass index, current smoking, heavy alcohol use, use of heroin or cocaine, injection drug use, hepatitis C virus status.

Model 3. Adjusted for Model 2 covariates and hypertension, diabetes, dyslipidemia, history of myocardial infarction, history of heart failure, and estimated glomerular filtration rate.

CI = confidence interval; ECV = extracellular volume fraction; HIV = human immunodeficiency virus; y = years.

FIGURES

Figure 1. Heat map of correlations of primary and secondary cardiac phenotypes.

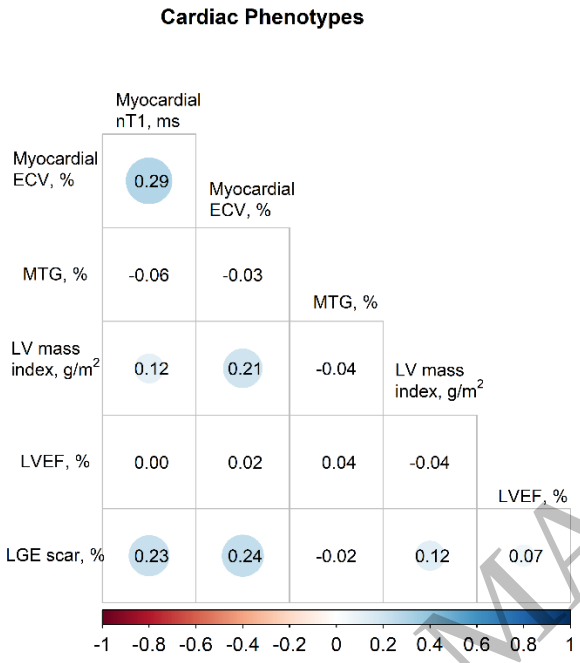
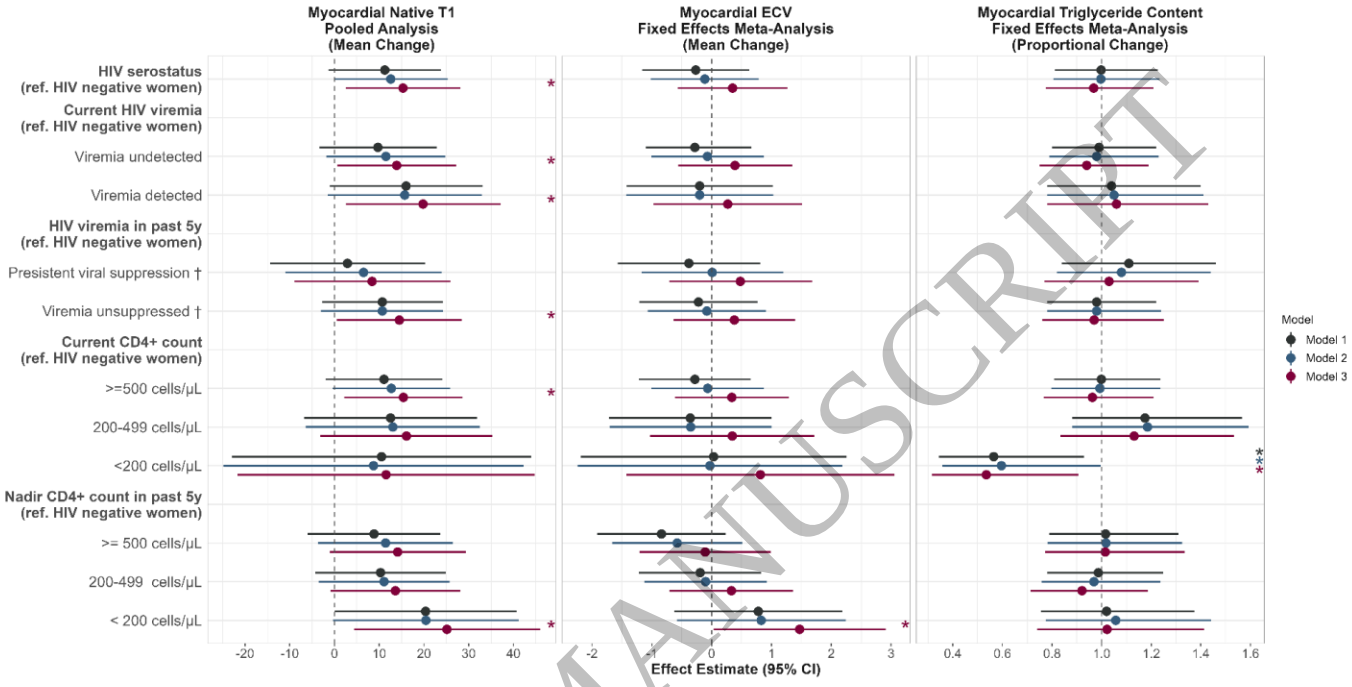


Figure 2. Forest plot of associations between HIV and HIV-specific factors (viremia and CD4+ T-cell count) and primary cardiac phenotypes.



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