Human Immunodeficiency Virus and Cardiac End-Organ Damage in Women: Findings From an Echocardiographic Study Across the United States

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Background. People with human immunodeficiency virus (HIV) have been reported to have increased risk of clinical and subclinical cardiovascular disease. Existing studies have focused on men and often have been uncontrolled or lacked adequate HIV-negative comparators.

Methods. We performed echocardiography in the Women's Interagency HIV Study to investigate associations of HIV and HIV-specific factors with cardiac phenotypes, including left ventricular systolic dysfunction (LVSD), isolated LV diastolic dysfunction (LVDD), left atrial enlargement (LAE), LV hypertrophy (LVH), and increased tricuspid regurgitation velocity (TRV).

Results. Of 1654 participants (age 51 ± 9 years), 70% had HIV. Sixty-three (5.4%) women with HIV (WWH) had LVSD; 71 (6.5%) had isolated LVDD. Compared with women without HIV (WWOH), WWH had a near-significantly increased risk of LVSD (adjusted relative risk = 1.69; 95% confidence interval = 1.00 to 2.86; $P = .051$). No significant association was noted for HIV seropositivity with other phenotypes, but there was a risk gradient for decreasing CD4+ count among WWH that approached or reached significance for isolated LVDD, LAE, and LVH. WWH with CD4+ count <200 cells/mm^3 had significantly higher prevalence of LAE, LVH, and high TRV than WWOH. There were no consistent associations for viral suppression or antiretroviral drug exposure.

Conclusions. This study suggests that WWH have a higher risk of LVSD compared with sociodemographically similar WWOH, but their risk for isolated LVDD, LAE, LVH, and high TRV is increased only with reduced CD4+ count. Although these findings warrant replication, they support the importance of cardiovascular risk-factor and HIV-disease control for heart disease prevention in this population.

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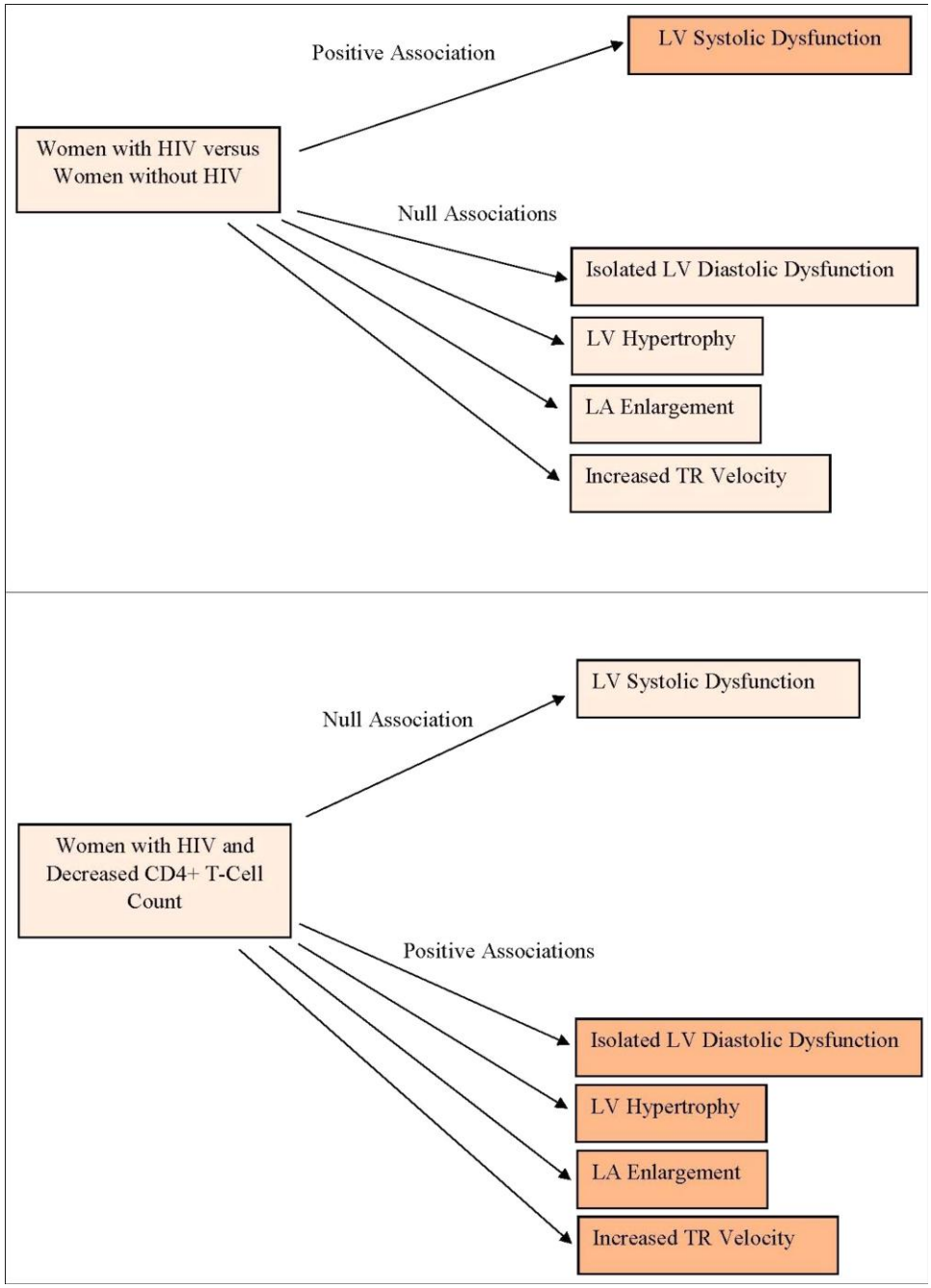
Graphical Abstract



Keywords. HIV; cardiac dysfunction; women.

Antiretroviral therapy (ART) has afforded marked gains in life expectancy for people with human immunodeficiency virus (HIV; PWH), but this has been counterbalanced by a high burden of chronic diseases [1]. Various studies have documented that, compared with people without HIV, PWH exhibit an elevated risk of cardiovascular disease [2–8]. As assessed in cohorts with less intensive ART use than in contemporary practice, such risks have been shown to be more pronounced in the setting of high viremic load or immunosuppression [3, 5, 6, 8].

Imaging studies have likewise reported a high frequency of cardiac functional abnormalities [9] and pulmonary hypertension (PH) [10] in PWH. A meta-analysis of echocardiographic studies of PWH from high- and low-income countries conducted pre- and post-ART reported on various cardiac phenotypes, documenting marked prevalences of left ventricular systolic dysfunction (LVSD), LV diastolic dysfunction (LVDD), right ventricular systolic dysfunction (RVSD), and PH [11]. There was substantial heterogeneity in the findings, but, after accounting for geographic region, LVSD was less common in more recent studies [11].

As with assessments of cardiovascular events, investigations of HIV-associated cardiac dysfunction have largely focused on men. Further, a common limitation of existing studies of HIV-related heart disease is that they have included as controls individuals without HIV who lacked the same high-risk behavior profiles overrepresented in PWH [12]. This makes unclear the extent to which the associated risk is attributable to HIV itself or relates instead to associated cardiovascular risk factors. This limitation has been a particular feature of imaging studies of HIV, many of which have been uncontrolled or selected age- and sex-matched healthy volunteers as comparators. While women account for half of cases with HIV worldwide and one-quarter in the United States, available data on adverse cardiac phenotypes in women remain sparse [13].

To address these gaps, we undertook an echocardiographic study within the Women's Interagency HIV Study (WIHS) to test the hypothesis that among women with (WWH) and without HIV (WWOH) having similar risk-factor profiles, HIV and HIV-specific factors are associated with various forms of cardiac end organ damage.

METHODS

WIHS is a US multicenter investigation of WWH and sociodemographically similar WWOH at increased risk of acquiring HIV [14]. Details of the study design; clinical, laboratory, and echocardiographic assessments; and covariate definitions are provided in the Supplementary Methods. Briefly, we performed a WIHS-wide echocardiographic study in 1654 women in 2014–2019 to evaluate the association between HIV and HIV-specific factors with adverse cardiac phenotypes. Persistent viral suppression and cumulative years of specific ART during the 4 years prior to echocardiography were examined. The echocardiographic study involved sonographer training and certification, a standardized imaging protocol, and centralized image interpretation. Primary phenotypes of interest were LVSD, isolated LVDD, left atrial enlargement (LAE), LV hypertrophy (LVH), and elevated tricuspid regurgitation velocity (TRV).

Characteristics of study participants were summarized using standard statistics. Relative risks (RRs) for the 5 main phenotypes were calculated via generalized linear models using a Poisson distribution with a log-link function and robust standard errors. We fit sequential models to adjust for possible confounders and also for potential causal intermediates. Model 1 adjusted for age, race–ethnicity, site, and echocardiographer. Model 2 (main model) additionally adjusted for body mass index, current smoking, heavy alcohol use, history of injection drug use, history of heroin or cocaine use, and hepatitis C virus (HCV) status. Model 3 further adjusted for factors plausibly on the causal pathway, including hypertension, diabetes, dyslipidemia, self-reported history of myocardial infarction (MI) and heart failure (HF), and estimated glomerular filtration rate (eGFR). Secondary analyses evaluated LA volume index (LAVI) and LV mass index (LVMI) as continuous outcomes. Because of nonnormal distributions and paucity of high and low values, LVEF and peak TRV were not examined continuously.

In addition to including site as a fixed-effect variable, we undertook a sensitivity analysis modeling site as a random-effect variable in generalized linear mixed models to assess consistency for the primary associations. Additional sensitivity analyses explored adjustment for menopausal status and exclusion of women with MI or HF, WWH who were not receiving ART, or WWH who qualified as elite controllers or long-term nonprogressors. Analyses used SAS 9.4 (Cary, NC); $P < .05$ defined statistical significance.

RESULTS

Of the 2096 WIHS participants in active follow-up, 1654 (78.9%) completed echocardiograms. Compared with participants who did not complete echocardiograms, those who did were more often non-Hispanic Black, pre- and perimenopausal, and hypertensive (Supplementary Table 1). Characteristics of the study sample, stratified by HIV, are presented in Table 1. Compared with WWOH, WWH were older; more often non-Hispanic White; more commonly enrolled in the fourth, but less frequently the second wave; more often postmenopausal, HCV-positive, or dyslipidemic; and less likely to report current smoking, heavy alcohol consumption, use of heroin or cocaine, or history of MI. They also exhibited lower eGFR.

Frequencies of echocardiographic phenotypes are summarized in Table 2. There were no significant differences between WWH and WWOH in these unadjusted comparisons. LVSD in both groups was largely mild. Most participants with LVH had normal relative wall thickness, consistent with eccentric hypertrophy (HIV-positive vs HIV-negative: 77% vs 68%, $P = .403$). Severe valvular or pericardial disease was rare or absent.

Multivariable-adjusted associations of HIV with cardiac phenotypes are detailed in Figure 1. There were near-significant and similar associations of HIV with LVSD in the

Table 1. Characteristics of the Study Cohort

Characteristic	Women With HIV (n = 1163)	Women Without HIV (n = 491)	*P* Value
General			
Age, y	53 (46–58)	51 (43–58)	.005
Race–ethnicity, n (%)			.028
Non-Hispanic White	103 (8.9)	25 (5.1)	
Hispanic	154 (13.2)	74 (15.1)	
Non-Hispanic Black	870 (74.8)	370 (75.4)	
Other	36 (3.1)	22 (4.5)	
Site, n (%)			.265
Atlanta, Georgia	107 (9.2)	41 (8.4)	
Birmingham, Alabama	72 (6.2)	19 (3.9)	
Bronx, New York	169 (14.5)	89 (18.1)	
Brooklyn, New York	195 (16.8)	76 (15.5)	
Chapel Hill, North Carolina	97 (8.3)	33 (6.7)	
Chicago, Illinois	130 (11.2)	62 (12.6)	
Washington, District of Columbia	132 (11.4)	61 (12.4)	
Miami, Florida	72 (6.2)	27 (5.5)	
Jackson, Mississippi	68 (5.9)	23 (4.7)	
San Francisco, California	121 (10.4)	60 (12.2)	
Enrollment wave			<.001
1994–1995	369 (31.7)	139 (28.3)	
2001–2002	251 (21.6)	155 (31.6)	
2011–2012	137 (11.8)	60 (12.2)	
2013–2015	406 (34.9)	137 (27.9)	
Body mass index, kg/m^2	30.7 (26.0–37.6)	32.0 (26.6–37.9)	.110
Current smoker, n (%)	429 (36.9)	212 (43.2)	.016
Heavy alcohol use, n (%)	84 (7.2)	53 (10.8)	.016
History of injection drug use, n (%)	183 (15.7)	78 (15.9)	.939
History of heroin or cocaine use, n (%)	631 (54.3)	297 (60.5)	.019
History of hepatitis C virus seropositivity, n (%)	256 (22.0)	79 (16.1)	.006
Menopause status			<.001
Premenopausal	254 (21.8)	168 (34.2)	
Perimenopausal	134 (11.5)	64 (13.0)	
Postmenopausal	775 (66.6)	259 (52.8)	
Hypertension, n (%)	950 (81.7)	392 (79.8)	.380
Diabetes, n (%)	368 (31.6)	169 (34.4)	.270
Dyslipidemia, n (%)	940 (80.8)	354 (72.1)	<.001
Estimated glomerular filtration rate, mL/min/1.73 m^2	88.6 (71.0–105.4)	96.4 (81.9–111.7)	<.001
History of myocardial infarction, n (%)	42 (3.6)	29 (5.9)	.035
History of heart failure, n (%)	32 (2.8)	16 (3.3)	.575
HIV-specific factors			
Detectable viral load, n (%)	324 (27.9)	NA	NA
CD4 count categories, n (%)			NA
<200 cells/mm^3	52 (4.5)	NA	
200–499 cells/mm^3	276 (23.7)	NA	
≥ 500 cells/mm^3	835 (71.8)	NA	
Antiretroviral therapy, n (%)	1058 (91.0)	NA	NA
Elite controllers, n (%)	9 (0.8)	NA	NA
Long-term nonprogressors, n (%)	10 (0.9)	NA	NA
Entry inhibitor			
Proportion on treatment at echo visit, n (%)	10 (1.0)	NA	
Cumulative use (n = 34), y	4.0 (1.5–5.5)	NA	NA
Integrase strand transfer inhibitor			
Proportion on treatment at echo visit, n (%)	689 (65.1)	NA	NA
Cumulative use (n = 765), y	3.0 (1.5–4.5)	NA	NA
Nonnucleoside reverse transcriptase inhibitor			
Proportion on treatment at echo visit, n (%)	276 (26.1)	NA	NA

Table 1. Continued

Characteristic	Women With HIV (n = 1163)	Women Without HIV (n = 491)	*P* Value
Cumulative use (n = 707), y	4.5 (2.5–8.0)	NA	NA
Nucleoside reverse transcriptase inhibitor			
Proportion on treatment at echo visit, n (%)	1002 (94.7)	NA	NA
Cumulative use (n = 1056), y	8.0 (4.5–16.0)	NA	NA
Protease inhibitor			
Proportion on treatment at echo visit, n (%)	260 (24.6)	NA	NA
Cumulative use (n = 649), y	6.5 (3.5–12.5)	NA	NA

Abbreviations: echo, echocardiography; HIV, human immunodeficiency virus; NA, not applicable.

Frequency (%) for categorical variables. Median (interquartile range) for continuous variables. Proportion on treatment and cumulative use for antiretroviral therapy (ART) drug classes apply only for participants on ART at echocardiography visit. Cumulative use for ART drug classes shown only for those who report any use.

minimally adjusted and main models, the latter characterized by an approximately 1.7-fold higher risk of LVSD. This relationship was not meaningfully changed after adjustment for putative mediators. We did not find significant associations of HIV with isolated LVDD, LAE, LVH, or high TRV at any level of adjustment. In secondary analyses, WWH had lower LAVI than WWOH at all levels of adjustment (model 2, mean difference = −0.86; 95% confidence interval [CI] = −1.63 to −.10 mL/m^2; P = .027), but no difference in LVMI was detected between serogroups (mean difference = 0.17; 95% CI = −1.54 to 1.88 g/m^2; P = .845; Supplementary Table 2).

In sensitivity analyses modeling site as a random-effect variable, a similar HIV-associated risk of LVSD approaching significance was observed (RR = 1.72; 95% CI = 1.00 to 2.95; P = .051), while risk estimates for the other primary phenotypes remained nonsignificant (Supplementary Table 3). In additional sensitivity analyses, further adjustment for menopausal status did not meaningfully alter the findings (Supplementary Table 4), nor did exclusion of women with a history of MI or HF, WWH who were not receiving ART, or WWH who were elite controllers or long-term nonprogressors, with 2 exceptions (Supplementary Tables 5–7). Stronger HIV-associated risks of LVSD that attained statistical significance were observed following removal of participants with MI or HF (RR = 2.54; 95% CI = 1.27 to 4.87; P = .008) and WWH off ART (RR = 1.84; 95% CI = 1.09 to 3.12; P = .024).

The relationships with cardiac phenotypes for HIV-associated factors are given in Table 3. After adjustment for main-model covariates, WWH with undetectable viral load had a significant, nearly 2-fold higher risk of LVSD but almost half the risk of isolated LVDD compared with WWOH, although the latter association did not reach significance. Yet, the risk estimates for WWH with detectable and undetectable viral load were generally similar for these cardiac phenotypes, as well as LVH and high TRV, without evidence of a corresponding risk gradient. Although this was also the case for categories of CD4+ T-cell count in relation to LVSD, there was evidence of a gradient of increased risk for lower CD4+ count categories and the other 4 phenotypes. After adjustment for main-model covariates, WWH with CD4+ counts ≥500 cells/mm^3 had a near-significant 32% lower risk of isolated LVDD compared with WWOH, which was of slightly higher magnitude and significant after additional adjustment for potential mediators. In turn, WWH with CD4+ counts <200 cells/mm^3 had roughly 1.5-fold, 3-fold, and 2.3-fold higher risk of LAE, LVH, and elevated TRV, respectively, compared with WWOH. These associations remained significant after further adjustment for putative mediators. Moreover, a test for trend across decreasing CD4+ count categories among WWH showed significant or near-significant gradients of increasing risk for isolated LVDD (P = .069), LAE (P = .002), and LVH (P = .003), though not for LVSD (P = .943) or elevated TRV (P = .264), after adjustment for main-model covariates.

Table 4 describes the RRs for adverse cardiac phenotypes per year of ART-class exposure within the WWH group on multivariable adjustment. There were largely no significant associations between cumulative exposure to specific ART classes and cardiac outcome measures. The one exception was integrase strand transfer inhibitors (INSTIs), which showed a 17% significantly higher risk for isolated LVDD per year of additional use in the main model that became nonsignificant after adjustment for potential mediators.

DISCUSSION

In this study of US women, we found that those with HIV had a near-significant 1.7-fold higher risk of echocardiographic LVSD but similar risk of isolated LVDD, LAE, LVH, and elevated TRV compared with WWOH after adjustment for potential confounders. The burden of RVSD, valve disease, and pericardial disease was low in this cohort and did not differ by HIV serostatus. We found no relationship between measures of HIV disease control or severity and LVSD, but such associations were present for the other adverse cardiac phenotypes. Specifically, there was a gradient of increasing risk for the remaining phenotypes with lower CD4+ T-cell count. Among WWH, declining

Table 2. Cardiac Phenotypes in the Study Cohort

Outcomes	Women With HIV (n = 1163)	Women Without HIV (n = 491)	*P* Value
Left ventricular systolic dysfunction, n (%)	63 (5.4)	17 (3.5)	.091
LVEF 45% to 53%	49 (77.8[a])	9 (52.9[a])	
LVEF 30% to 44%	11 (17.5[a])	5 (29.4[a])	
LVEF <30%	3 (4.8[a])	3 (17.7[a])	
Isolated left ventricular diastolic dysfunction, n (%)	71 (6.5)	38 (8.0)	.262
Left atrial enlargement, n (%)	254 (22.4)	122 (25.9)	.139
Left atrial volume index, mL/m^2	28.6 (23.8–33.7)	29.7 (25.0–34.6)	.005
Left ventricular hypertrophy, n (%)	53 (4.6)	25 (5.1)	.668
Left ventricular mass index, g/m^2	62.6 (53.4–73.9)	63.2 (53.7–74.6)	.598
Peak tricuspid regurgitation velocity >2.8 m/s, n (%)	96 (8.3)	41 (8.4)	.949
Right ventricular fractional area change <.35, n (%)	18 (1.6)	6 (1.3)	.610
Aortic valve regurgitation, n (%)			.687
None/minimal	1089 (94.2)	465 (95.1)	
Mild or moderate	66 (5.7)	24 (4.9)	
Severe	1 (0.1)	0 (0.0)	
Aortic valve stenosis, n (%)			1.000
None/minimal	1151 (99.0)	487 (99.6)	
Mild or moderate	4 (0.4)	2 (0.4)	
Severe	1 (0.1)	0 (0.0)	
Mitral valve regurgitation, n (%)			.651
None/minimal	924 (79.9)	384 (78.5)	
Mild or moderate	231 (20.0)	105 (21.5)	
Severe	1 (0.1)	0 (0.0)	
Tricuspid valve regurgitation, n (%)			.908
None/minimal	688 (59.5)	294 (60.1)	
Mild or moderate	467 (40.4)	195 (39.9)	
Severe	1 (0.1)	0 (0.0)	
Prosthetic aortic or mitral valve, n (%)			.370
No	1153 (99.1)	486 (99.0)	
Yes	3 (0.3)	3 (0.6)	
Pericardial effusion, n (%)			.453
No effusion	1106 (95.7)	461 (94.3)	
Minimal pericardial effusion	36 (3.1)	21 (4.3)	
Small pericardial effusion	14 (1.2)	7 (1.4)	

Abbreviations: HIV, human immunodeficiency virus; LVEF, left ventricular ejection fraction.

[a]Of those with left ventricular systolic dysfunction. Median (interquartile range) for continuous variables and frequency (%) for categorical variables.

CD4+ counts were or tended to be associated with increased risk for isolated LVDD, LAE, and LVH. WWH and CD4+ count in the lowest category had significantly higher LAE, LVH, and elevated TRV compared with WWOH. There was a positive association between duration of INSTI use and isolated LVDD but otherwise no relationship between cumulative ART use and cardiac phenotypes.

Previous studies have been crucial in illuminating high rates of adverse cardiovascular events in PWH and the role of uncontrolled viremia or immunosuppression in magnifying risk for such outcomes [3–8]. Assessment of clinical events in such studies is a notable strength. However, these investigations predominantly focused on men and often relied on administrative claims to define covariates and outcomes, which can lead to incomplete adjustment or misclassification. Moreover, such studies frequently selected controls matched on demographic characteristics but not on the high-risk behavioral or clinical risk factors that are enriched in PWH.

Imaging studies that involve echocardiography or cardiac magnetic resonance (CMR) have added to this understanding, highlighting elevated prevalences of cardiac dysfunction [9, 15–17] and PH [10] in PWH and the contributions of high viremic loads or lower CD4+ counts. However, like studies of clinical events, these reports primarily involved men and were frequently uncontrolled or relied on controls matched on a limited set of risk factors. Among echocardiographic studies, several drew on patients referred for imaging, rather than unselected samples, or relied on nonstandardized echocardiographic assessments obtained in clinical practice [16]. In addition, available studies, whether of clinical events or imaging phenotypes, often involved cohorts with HIV that were on less-than-optimal ART-induced viral suppression than currently recommended.

Although high frequencies of LVSD, LVDD, and RVSD were documented in a meta-analysis of echocardiographic studies in PWH [11], a large cohort study of men with and without HIV who have sex with men with similar risk profiles detected no difference in echocardiographic LVSD, whose prevalence was low [18]. Instead, there was a positive association of HIV seropositivity with LVMI and LVDD but no discernible impact of viremic load, immunosuppression, or specific ART. In an analysis of younger New York WIHS participants, HIV seropositivity was likewise associated with greater LVMI, with no notable influence of HIV-related factors [19].

To our knowledge, this is the largest echocardiographic investigation to date in people of either sex with and without HIV and the first to include a sample of women with and without HIV from sites across the United States. The current study also counts as key strengths the use of standardized echocardiography and the inclusion of WWH and WWOH drawn from the same clinics such that, by design, the HIV-negative comparison group exhibited a similarly high burden of behavioral and clinical risk factors.

Our findings suggest that even in comparison with sociodemographically similar high-risk WWOH, WWH mostly on ART exhibit an increased risk of LVSD. Notably, there was no accompanying increased risk of isolated LVDD, LAE, or LVH, nor elevated TRV, for participants with HIV relative to their counterparts without HIV. Yet, the presence of a lower CD4+ count was associated, or nearly so, with increased risk of isolated LVDD, LVH, LAE, and elevated TRV in WWH or in comparison with WWOH but showed no discernible relationship with LVSD. A possible explanation for the divergent

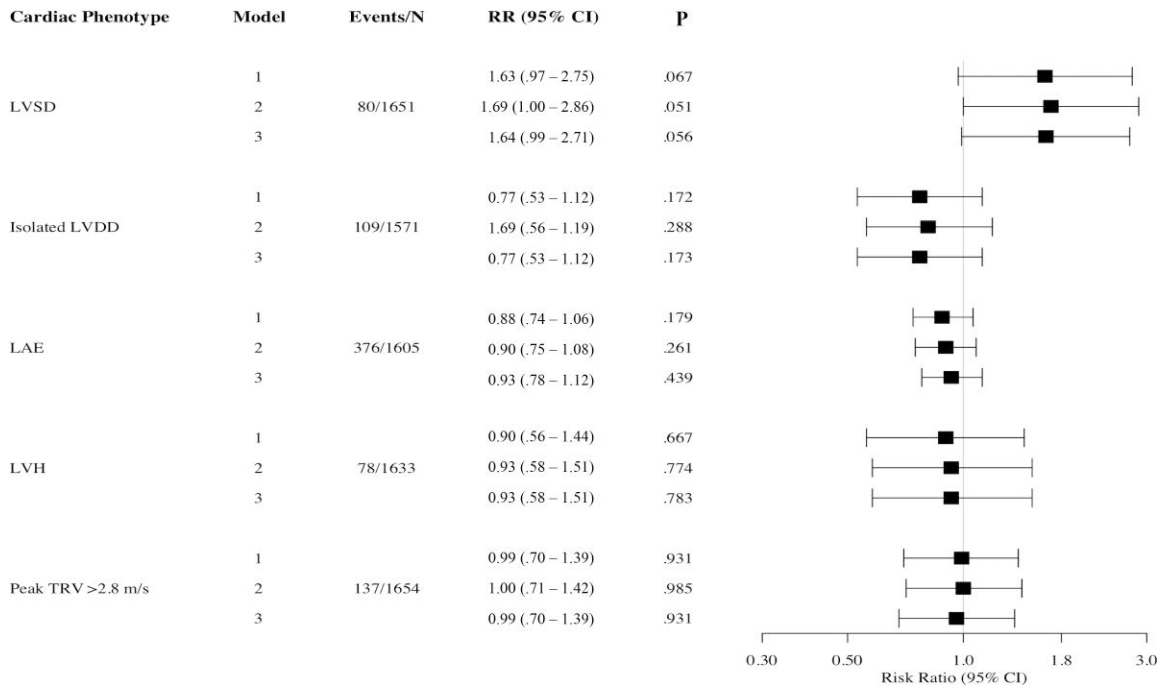


Figure 1. Association of human immunodeficiency virus (HIV) with adverse cardiac phenotypes. Relative risk for women with HIV compared with women without HIV calculated by generalized linear models using a Poisson distribution and log-link function with robust standard errors. Model 1 adjusts for age, site, race–ethnicity, and echocardiography interpreter. Model 2 additionally adjusts for body mass index, current smoker, heavy alcohol use, history of injection drug use, history of heroin or cocaine, and hepatitis C virus status. Model 3 additionally adjusts for hypertension, diabetes, dyslipidemia, history of myocardial infarction, history of heart failure, and estimated glomerular filtration rate. Abbreviations: CI, confidence interval; LAE, left atrial enlargement; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; RR, relative risk; TRV, tricuspid regurgitation velocity.

findings between LVSD and the other cardiac phenotypes may involve the nature of the study population, especially the comparison group.

Among mostly middle-aged women with a high burden of cardiovascular risk factors, as was the case in the group without HIV, cardiac dysfunction more frequently takes the form of isolated LVDD and, correspondingly, LAE, LVH, and PH, than of LVSD [20, 21]. This may account for the lack of increased risk for these phenotypes overall in our WWH, most of whom were receiving ART, compared with WWOH who exhibited higher adiposity, along with a greater frequency of smoking, substance use, and self-reported MI (and in whom LAVI was greater). In fact, WWH and high CD4+ count showed risk estimates <1.0 for these adverse phenotypes in comparison with WWOH, an inverse association that reached or approached significance in the case of LAE and isolated LVDD.

LVSD was less common than the other phenotypes in WWOH, although of considerable magnitude relative to population-based cohorts [22, 23], likely resulting from such factors as high substance use and coronary disease. Indeed, exclusion of self-reported MI or HF, the former more common among WWOH than WWH enrolled in WIHS, strengthened the association of HIV with LVSD and rendered it significant. The absence of a CD4+ associated gradient for LVSD is harder to explain, but the modest overall numbers of the phenotype may have made it difficult to detect. Still, the overall association with LVSD, but not other phenotypes, suggests that this may be a more distinctive feature of HIV-related cardiac disease in women after accounting for sociodemographic and behavioral factors. Of note, the association with LVSD for WWH on ART was stronger than for WWH overall and reached significance. However, the explanation for this finding is uncertain, as only a minority of WWH qualified as elite controllers and long-term nonprogressors.

We did not find an association between persistent viral suppression and any cardiac phenotype. This could relate to better overall viremic control of the group with HIV in comparison with earlier studies. Nor was there a relationship between specific ART and echocardiographic outcomes, with the exception of a positive association between cumulative INSTI use and isolated LVDD and (borderline) LVH. Use of INSTIs is associated with weight gain, but its cardiovascular implications remain unclear [24]. The association observed here must be interpreted with caution because an early switch to INSTIs among WIHS participants may have reflected failure of other therapies. Such confounding by indication prevents valid assessment of off-target cardiac effects of this drug class, and the association will require additional investigation.

Table 3. Association of Viral Load and CD4+ T-Cell Count With Adverse Cardiac Phenotypes

		Model 1		Model 2		Model 3	
Outcome	Exposure	RR[a] (95% CI)	*P* Value	RR[a] (95% CI)	*P* Value	RR[a] (95% CI)	*P* Value
Detectable viral load status							
LVSD	Undetectable viral load	1.82 (.97–3.42)	.061	1.94 (1.03–3.66)	.039	1.87 (1.01–3.49)	.048
	Detectable viral load	1.56 (.90–2.70)	.113	1.61 (.92–2.80)	.094	1.57 (.92–2.67)	.099
Isolated LVDD	Undetectable viral load	0.50 (.26–.96)	.037	0.56 (.29–1.06)	.073	0.53 (.28–1.00)	.050
	Detectable viral load	0.86 (.58–1.27)	.441	0.89 (.61–1.32)	.578	0.85 (.58–1.24)	.396
LAE	Undetectable viral load	0.82 (.63–1.07)	.149	0.86 (.66–1.13)	.278	0.90 (.68–1.18)	.431
	Detectable viral load	0.90 (.75–1.09)	.292	0.91 (.76–1.10)	.348	0.94 (.78–1.14)	.526
LVH	Undetectable viral load	0.64 (.30–1.39)	.267	0.69 (.32–1.50)	.352	0.70 (.32–1.52)	.369
	Detectable viral load	0.99 (.61–1.60)	.963	1.01 (.62–1.64)	.978	1.01 (.62–1.64)	.975
Peak TRV >2.8 m/s	Undetectable viral load	0.67 (.39–1.13)	.131	0.67 (.39–1.13)	.135	0.62 (.36–1.06)	.082
	Detectable viral load	1.09 (.77–1.56)	.613	1.12 (.79–1.59)	.536	1.08 (.76–1.53)	.667
CD4+ T-cell count categories							
LVSD	≥500 cells/mm^3	1.61 (.94–2.78)	.085	1.66 (.96–2.89)	.071	1.63 (.95–2.78)	.075
	200–499 cells/mm^3	1.70 (.86–3.36)	.128	1.80 (.91–3.56)	.093	1.63 (.85–3.11)	.139
	<200 cells/mm^3	1.57 (.48–5.13)	.459	1.65 (.51–5.30)	.401	1.80 (.56–5.79)	.326
Isolated LVDD	≥500 cells/mm^3	0.63 (.41–.96)	.033	0.68 (.45–1.04)	.077	0.65 (.43–.99)	.043
	200–499 cells/mm^3	1.03 (.63–1.67)	.920	1.07 (.66–1.73)	.797	0.95 (.59–1.53)	.839
	<200 cells/mm^3	1.49 (.64–3.48)	.351	1.43 (.60–3.42)	.426	1.75 (.79–3.85)	.166
LAE	≥500 cells/mm^3	0.79 (.64–.96)	.017	0.81 (.67–.99)	.038	0.84 (.69–1.03)	.086
	200–499 cells/mm^3	1.05 (.83–1.33)	.695	1.06 (.83–1.34)	.658	1.07 (.84–1.36)	.576
	<200 cells/mm^3	1.54 (1.07–2.20)	.020	1.45 (1.00–2.11)	.049	1.52 (1.05–2.22)	.028
LVH	≥500 cells/mm^3	0.71 (.42–1.20)	.199	0.74 (.44–1.25)	.264	0.78 (.46–1.33)	.357
	200–499 cells/mm^3	1.05 (.56–1.97)	.875	1.09 (.58–2.07)	.787	0.94 (.52–1.71)	.836
	<200 cells/mm^3	3.11 (1.46–6.64)	.003	3.06 (1.38–6.82)	.006	4.13 (1.90–8.98)	<.001
Peak TRV >2.8 m/s	≥500 cells/mm^3	0.95 (.66–1.37)	.780	0.97 (.67–1.40)	.861	0.93 (.64–1.35)	.711
	200–499 cells/mm^3	0.88 (.54–1.43)	.600	0.89 (.55–1.46)	.655	0.82 (.51–1.32)	.412
	<200 cells/mm^3	2.15 (1.08–4.26)	.029	2.30 (1.14–4.63)	.019	2.48 (1.28–4.82)	.007

Abbreviations: CI, confidence interval; LAE, left atrial enlargement; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; RR, relative risk; TRV, tricuspid regurgitation velocity.

[a]RR for viral load status or CD4+ T-cell categories in women with HIV compared with women without HIV calculated by generalized linear models using a Poisson distribution and log-link function with robust standard errors. Events/n for LVSD, isolated LVDD, LAE, LVH ,and peak TRV >2.8 m/s are 80/1651, 109/1571, 376/1605, 78/1633, and 137/1654, respectively. Model 1 adjusts for age, site, race–ethnicity, and echocardiography interpreter. Model 2 additionally adjusts for body mass index, current smoker, heavy alcohol use, history of injection drug use, history of heroin or cocaine, and hepatitis C virus status. Model 3 additionally adjusts for hypertension, diabetes, dyslipidemia, history of myocardial infarction, history of heart failure, and estimated glomerular filtration rate.

Our finding that immunosuppression was associated with all but 1 of the main outcomes supports the well-known impact of HIV-associated inflammation and immune activation on myocardial disease and dysfunction in proportion with loss of immunocompetence [1]. Previous CMR studies have documented increased cardiac fibrosis and steatosis in PWH [17], and this has been documented in small samples of women [25, 26]. Inflammation-related abnormalities in vascular and cardiomyocyte function [27] may also explain the HIV-related LVSD documented here. In the case of PH, the findings relate to the impact of elevated LV filling pressures (post-capillary PH) but likely also reflect HIV-associated lung disease (pre-capillary PH) [28].

Together, the present results contribute novel information regarding the cardiovascular consequences of HIV infection in women who receive contemporary ART. These results show that WWH currently have comparable overall risk of isolated LVDD, LAE, LVH, and PH as sociodemographically similar WWOH, as well as low and comparable prevalences of RVSD or serious valvular disease or pericardial effusion. The findings also underscore the importance of HIV control and preservation of immune competence for prevention of LVDD, LVH, and PH. Nonetheless, the current results show that despite widespread ART, LVSD tends to be more common in WWH, with more than 1 in 20 affected. This has salient implications for the care of WWH, highlighting the importance of cardiovascular risk factor management, particularly hypertension and diabetes, for prevention of cardiovascular disease and HF in this population [1, 29].

We acknowledge the following weaknesses. Although we accounted for important measured covariates, the possibility of residual confounding cannot be excluded. In order to maximize power, we did not adjust our analyses of HIV or HIV-specific factors for multiple comparisons. Although this may have inflated the false-positive rate, our cardiac phenotypes are correlated, and patterns in the data (as related to LVDD, LAE, LVH,

Table 4. Duration of Antiretroviral Drug Class Exposure and Adverse Cardiac Phenotypes in Women With Human Immunodeficiency Virus

		Model 1		Model 2		Model 3	
Outcome	Drug Class	RR[a] (95% CI)	*P* Value	RR[a] (95% CI)	*P* Value	RR[a] (95% CI)	*P* Value
LVSD	INSTI	0.91 (.78–1.06)	.209	0.91 (.79–1.06)	.233	0.90 (.77–1.04)	.158
Isolated LVDD	INSTI	1.17 (.02–1.35)	.027	1.17 (1.02–1.35)	.030	1.11 (.95–1.30)	.184
LAE	INSTI	1.01 (.94–1.08)	.887	1.00 (.93–1.08)	.964	1.00 (.93–1.08)	.907
LVH	INSTI	1.18 (1.00–1.39)	.055	1.18 (1.00–1.40)	.054	NR	NR
Peak TRV > 2.8 m/s	INSTI	1.06 (.94–1.19)	.344	1.05 (.94–1.19)	.396	1.02 (.91–1.17)	.676
LVSD	NNRTI	0.99 (.87–1.15)	.989	1.00 (.87–1.15)	.981	1.01 (.88–1.16)	.850
Isolated LVDD	NNRTI	0.94 (.82–1.08)	.373	0.95 (.83–1.09)	.508	0.95 (.83–1.10)	.512
LAE	NNRTI	1.02 (.96–1.09)	.445	1.03 (.97–1.09)	.389	1.03 (.97–1.10)	.385
LVH	NNRTI	0.84 (.69–1.01)	.062	0.83 (.68–1.01)	.059	NR	NR
Peak TRV > 2.8 m/s	NNRTI	1.08 (.97–1.20)	.155	1.08 (.97–1.20)	.178	1.08 (.97–1.21)	.172
LVSD	NRTI	0.96 (.72–1.27)	.761	0.96 (.72–1.29)	.807	0.99 (.74–1.33)	.944
Isolated LVDD	NRTI	0.95 (.75–1.19)	.645	0.99 (.78–1.27)	.949	1.02 (.80–1.31)	.857
LAE	NRTI	0.99 (.88–1.13)	.977	1.02 (.89–1.16)	.806	1.02 (.89–1.18)	.752
LVH	NRTI	0.91 (.67–1.25)	.558	0.91 (.66–1.24)	.537	NR	NR
Peak TRV > 2.8 m/s	NRTI	0.98 (.77–1.24)	.837	0.99 (.78–1.27)	.994	1.01 (.79–1.31)	.899
LVSD	PI	1.01 (.88–1.16)	.891	1.01 (.87–1.16)	.932	0.98 (.86–1.13)	.807
Isolated LVDD	PI	1.00 (.87–1.16)	.964	1.00 (.86–1.16)	.985	1.01 (.87–1.16)	.943
LAE	PI	1.00 (.94–1.07)	.960	1.00 (.93–1.07)	.963	0.99 (.93–1.07)	.896
LVH	PI	1.16 (.98–1.38)	.079	1.18 (.99–1.40)	.068	NR	NR
Peak TRV > 2.8 m/s	PI	0.92 (.81–1.05)	.221	0.93 (.82–1.06)	.295	0.93 (.82–1.06)	.286

Abbreviations: CI, confidence interval; INSTI, integrase strand transfer inhibitor; LAE, left atrial enlargement; LVDD, left ventricular diastolic dysfunction; LVH, left ventricular hypertrophy; LVSD, left ventricular systolic dysfunction; NNRTI, nonnucleoside reverse transcriptase inhibitor; NR, model "not run" due to few events and many covariates; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RR, relative risk; TRV, tricuspid regurgitation velocity.

[a]Relative risk per year of exposure to each drug class calculated via generalized linear models using a Poisson distribution and log-link function with robust standard errors. Model 1 adjusts for age, site, race–ethnicity, and echocardiography interpreter. Model 2 additionally adjusts for body mass index, current smoker, heavy alcohol use, history of injection drug use, history of heroin or cocaine, and hepatitis C virus status. Model 3 additionally adjusts for hypertension, diabetes, dyslipidemia, history of myocardial infarction, history of heart failure, and estimated glomerular filtration rate. Events/N for LVSD, isolated LVDD, LAE, LVH, and peak TRV >2.8 m/s are 63/1161, 71/1098, 254/1133, 53/1145, and 96/1163, respectively.

and high TRV) lend support to the validity of associations. Moreover, our findings stand against a background of considerable experimental and clinical data on HIV-related heart disease and are interpreted in this context. We recognize that the association of HIV with LVSD came close to, but did not meet, the conventional level of significance such that the finding can only be considered suggestive. Yet, sensitivity analyses focused on WWH who were receiving ART or participants free of self-reported MI or HF yielded stronger and significant relationships, supporting the presence of a true association. Regardless, the present results will require replication in similar populations of WWH receiving ART. Last, our findings in largely race–ethnic minority women are not necessarily generalizable to other ethnic groups, low-resource settings, or men.

In conclusion, in this nationwide study of US women with and without HIV, we found that HIV seropositivity was associated with a nearly significant 1.7-fold increased risk of LVSD. WWH did not have an increased risk of isolated LVDD, LVH, LAE, or PH compared with their counterparts without HIV, but there was a risk gradient for these phenotypes associated with progressive immunosuppression. Cumulative use of specific ART was not associated with cardiac phenotypes, with the exception of INSTI use with isolated LVDD, a finding that will require further study. In aggregate, these findings point to a contribution of HIV infection to LVSD in women despite ART, supporting the importance of careful management of cardiovascular risk factors, as well as the primacy of HIV-disease control in preventing cardiac remodeling, diastolic dysfunction, and PH.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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