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HIV, hepatitis C virus and risk of new-onset left ventricular dysfunction in women

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Background: HIV and HCV have each been linked with cardiac dysfunction. Studies of HIV have often lacked appropriate controls and primarily involved men, whereas data for HCV are sparse.

Methods: We performed repeat echocardiography over a median interval of 12 years in participants from the Women's Interagency HIV Study in order to evaluate the relationships of HIV and HCV with incident left ventricular (LV) dysfunction (systolic or diastolic).

Results: Of the 311 women included (age 39 ± 9), 70% were HIV-positive and 20% HCV-positive. Forty three participants (13.8%) developed LV dysfunction, of which 79.1% was diastolic. Compared with participants with neither infection, the group with HIV–HCV coinfection showed a significantly increased risk of incident LV dysfunction after adjustment for risk factors [RR = 2.96 (95% CI = 1.05–8.31)], but associations for the HCV monoinfected and HIV monoinfected groups were not statistically significant [RR = 2.54 (0.83–7.73) and RR = 1.66 (0.65–4.25), respectively]. Comparison of HCV-positive and HCV-negative women showed a significantly increased risk independent of covariates [RR = 1.96 (1.02–3.77)] but this was not the case for HIV-positive vs. HIV-negative women [RR = 1.43 (0.76–2.69)]. There was no evidence of HCV-by-HIV interaction. A more restrictive definition of LV diastolic dysfunction led to fewer incident cases, but a similar, though nonsignificant, risk estimate for HCV.

Conclusion: Among mostly middle-aged women, HCV but not HIV infection was associated with a pronounced risk of incident LV dysfunction. Although the influence of residual confounding cannot be excluded, these findings bolster the potential benefits that could be realized by adopting recent recommendations for expanding HCV screening and treatment.

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Introduction

Antiretroviral therapy (ART) has dramatically extended survival in people with HIV (PWH). Yet, for the 1.1 million PWH in the United States, as elsewhere, this enhanced longevity has been accompanied by pronounced comorbidities, including cardiovascular disease (CVD) [1]. PWH have been reported to have an increased risk of coronary heart disease (CHD) [2,3], heart failure [4–6] and sudden cardiac death [7]. Similarly, PWH have been documented to have high prevalences of left ventricular (LV) systolic and diastolic dysfunction, with pooled estimates of 12 and 29.3%, respectively [8].

Chronic infection with hepatitis C virus (HCV) is also common, affecting 2.7–3.9 million Americans [9], and occurs more frequently in PWH [10]. Direct-acting antiviral (DAA) medications have made HCV curable [11], prompting increased screening [12]. Apart from its hepatic sequelae, HCV has been linked to various extrahepatic manifestations, including atherosclerotic CVD [13], with HIV–HCV coinfection associated with a higher risk of CHD than HIV monoinfection [14]. Some reports have identified myocardial HCV in dilated and hypertrophic cardiomyopathy but this has not been supported by others [15]. Moreover, longitudinal studies have not documented consistent associations between HCV and risk of heart failure [4,16].

To date, most studies linking HIV to myocardial dysfunction have focused predominantly on men, and corresponding investigations of HCV are sparse. Available echocardiographic studies are primarily cross-sectional, and have either been uncontrolled or relied on healthy controls who lack cardiovascular risk factors enriched in PWH. Furthermore, race–ethnic minorities, who bear a disproportionate burden of HIV and HCV in the United States [17,18], remain understudied. To address these gaps, we undertook a longitudinal echocardiographic study within the Women's Interagency HIV Study (WIHS) to test the hypothesis that HIV and HCV, alone and especially in combination, are associated with new-onset LV dysfunction.

Methods

WIHS is a multicenter study that enrolled women with, or at risk for, HIV infection in 1994–1995 and 2001–2002 at six United States sites [19,20]. As previously detailed [19,20], participants attended semiannual core visits where sociodemographic, lifestyle, and medical information was collected, along with biospecimens.

In a previous study, $n = 661$ women from Bronx and Brooklyn underwent echocardiographic examinations in 2004–2005 [21]. We invited all women from this initial study to complete a follow-up echocardiogram, first as part of a pilot study (2014–2016), and then as part of the main study (2016–2018). Overall, $n = 371$ participant women returned for follow-up echocardiography. The study received institutional review board approval.

WIHS participants received testing for HIV by immunoassay at every core visit and, if positive, confirmation by western blot. Two women who seroconverted within 3 years of baseline were considered HIV positive for the present analyses. Women underwent testing for HCV serostatus and, if positive, HCV RNA at study entry in 1994–1995 ($n = 167$) or 2001–2002 ($n = 144$). A minority ($n = 22$) underwent repeat HCV RNA testing in 1996–2005. We considered participants positive for HCV infection if they were seropositive at the baseline echocardiogram, irrespective of HCV RNA result.

Procedures for baseline echocardiography (2004–2005) have been reported [21]. Briefly, transthoracic echocardiograms were performed by a trained sonographer at the Bronx and Brooklyn sites using a Philips Sonos 5500 machine. Acquisition of two-dimensional, M-mode, and Doppler images followed a standardized protocol [22]. The follow-up echocardiographic examination (2014–2018) was conducted by trained sonographers using a similar protocol with Philips iE33 machines.

In both examinations, LV ejection fraction and left atrial volume were determined by the biplane method of discs [23]. Transmitral Doppler imaging was performed at the leaflet tips. Tissue Doppler imaging was obtained at the septal mitral annulus at baseline, and septal and lateral mitral annulus at follow-up echocardiography. Interpretations were completed blinded to clinical characteristics by a single echocardiographer for baseline (J.M.L.), and by two echocardiographers (J.M.L. and J.R.K.) for follow-up echocardiograms. Inter-reader agreement was good to excellent: LVEF [intraclass correlation coefficient (ICC) 0.81], left atrial volume index (ICC 0.91), mitral E velocity (ICC 0.91), mitral A velocity (ICC 0.97), septal *e'* velocity (ICC 0.90), peak tricuspid regurgitation velocity (ICC 0.78).

The outcome of interest was new-onset LV dysfunction, constituting systolic or diastolic dysfunction. LV systolic dysfunction (LVSD) was defined as LVEF less than 50%. For our primary outcome, given the young age of the population, we chose the less restrictive definition of LV diastolic dysfunction (LVDD) recommended by the ASE 2009 guidelines [24]. LVDD was defined as septal *e'* less than 8 cm/s or lateral *e'* less than 10 cm/s and left atrial volume index at least 34 ml/m^2. For our secondary outcome, we applied the stricter ASE 2016 recommendations to define LVDD [25]. Indeterminate cases with LV end-diastolic volume index greater than 61 ml/m^2 or LV mass index greater than 95 g/m^2 were classified as having LVDD.

Covariates were measured at the closest visit preceding baseline echocardiography. Race–ethnicity was defined by self-report, as was ever-history of drug use. Current smoking was defined by self-report of any ongoing smoking, and heavy alcohol use as more than seven drinks/week. Hypertension, diabetes and dyslipidemia were defined as previously reported [26]. History of myocardial infarction was obtained by self-report. Estimated glomerular filtration rate (eGFR), and aspartate-aminotransferase-to-platelet ratio and fibrosis-4 scores were calculated using established formulas [27–29]. Plasma HIV RNA was measured by commercial immunoassay (lower limit of detection: 80 copies/ml). Plasma $CD4^+$ T cells were quantified by flow cytometry. HCV seropositivity and viremia were assessed by commercial assays.

We divided the cohort into neither-infected, HCV-monoinfected, HIV-monoinfected and HIV–HCV-coinfected groups, as done elsewhere [30]. We employed relative risk regression using a Poisson working model with a log-link function and robust standard errors to calculate risk ratios of new-onset LV dysfunction with the neither-infected group as referent. We adjusted for baseline covariates as follows. Model 1 adjusted for age, race–ethnicity and site. Model 2 additionally adjusted for current smoking, history of intravenous drug use (IDU) and history of heroin or cocaine use. (There was no self-reported methamphetamine use). Model 3 further adjusted for hypertension, diabetes and dyslipidemia. Subsequent models also adjusted for interval between scans, heavy alcohol use, eGFR or liver fibrosis indices. We repeated the analyses comparing HIV-positive versus HIV-negative participants adjusting for HCV status, and vice versa. To assess for interaction between HIV and HCV, we included a cross-product term in Model 3. We used SAS 9.4 (Cary, North Carolina, USA) for all analyses. Two-tailed P less than 0.05 defined statistical significance.

Results

Of the $n = 290$ original participants who did not return for follow-up echocardiography, $n = 86$ died and $n = 204$ were alive but did not participate. Compared with participants who completed a follow-up echocardiogram, those who died were older, had lower measures of body size and eGFR, more smoking and drug use, greater hypertension and liver fibrosis indices, and were more frequently HCV and HIV seropositive, the latter of greater severity and less well controlled (Supplementary Table 1, http://links.lww.com/QAD/C127). Participants who were alive but did not complete a follow-up echocardiogram were more comparable with those who did but had lower heavy alcohol use, hypertension, dyslipidemia and use of ART.

After exclusion of $n = 18$ participants with baseline LV dysfunction and $n = 32$ with incomplete baseline echocardiographic data, incident LV dysfunction was examined in $n = 321$. Echocardiographic data were incomplete at follow-up in $n = 10$, leaving $n = 311$ for primary analyses.

Table 1 presents baseline characteristics stratified by HIV and HCV status. Compared with the neither-infected group, the HCV-monoinfected group was older, with higher current smoking, history of IDU and hypertension, Bronx-site enrollment, liver-fibrosis scores and use of renin–angiotensin–aldosterone system antagonists, along with lower eGFR. In a similar comparison, the HIV-monoinfected group had greater dyslipidemia and liver fibrosis scores, whereas the HIV–HCV-coinfected group was older and had more ever-drug use. In comparison to neither-infected women, HIV–HCV-coinfected women also had lower eGFR, higher liver-fibrosis indices and were mostly from the Bronx. Among participants with HIV monoinfection and HIV–HCV coinfection, more than four of five were on ART, median $CD4^+$ T-cell counts were ~450 cells/μl, and more than half had detectable viremia. Of HCV-monoinfected women at baseline ($n = 16$), $n = 6$ (37%) had cleared HCV without treatment whereas $n = 10$ (63%) had HCV viremia. For women with HIV–HCV coinfection at baseline ($n = 45$), $n = 15$ (33%) had cleared HCV without treatment whereas $n = 30$ (67%) were HCV viremic.

The characteristics of the cohort by HIV and HCV status at follow-up echocardiography are given in Supplementary Table 2, http://links.lww.com/QAD/C127. The prevalence of cardiovascular, liver or kidney disease or their risk factors, along with use of renin–angiotensin–aldosterone system antagonists and beta-blockers, generally increased as compared with baseline. By contrast, current smoking and heavy alcohol intake showed a decline between baseline and follow-up. Compared with baseline, HIV-monoinfected and HIV–HCV-coinfected women showed numerically higher figures for ART use at 93 and 98%, median [interquartile range (IQR)] $CD4^+$ T-cell counts at 674 (453–858) and 571 (392–697) cells/μl, and undetectable viral load at 72 and 71%, respectively.

The use of specific ART at baseline and follow-up is detailed in Supplementary Table 3, http://links.lww.com/QAD/C127. Among HIV-monoinfected and HIV–HCV-coinfected women at baseline, 70.5 and 79.6% were receiving nucleoside reverse transcriptase inhibitors (NRTIs), 26.6 and 29.6% nonnucleoside reverse transcriptase inhibitors (NNRTIs) and 45.7 and 59.1% protease inhibitors, respectively. These proportions were numerically higher for NRTIs and NNRTIs, but lower for protease inhibitors at follow-up. In HIV-monoinfected and HIV–HCV-coinfected participants, follow-up use was 85.1 and 86.7% for NRTIs; 34.5 and

Table 1. Baseline characteristics of the cohort.

	Neither infected ($n = 76$)	HCV monoinfected ($n = 16$)	HIV monoinfected ($n = 174$)	HIV-HCV coinfected ($n = 45$)
Age (years)	38 (29–43)	47 (41–53)[a]	39 (33–43)	47 (42–53)[a]
Race–ethnicity [*n* (%)]				
Non-Hispanic white	2 (2.6)	0 (0.0)	8 (4.6)	2 (4.4)
Hispanic	17 (22.4)	8 (50.0)	36 (20.7)	20 (44.4)
Non-Hispanic black	57 (75.0)	8 (50.0)	121 (69.5)	22 (48.9)
Other	0 (0.0)	0 (0.0)	9 (5.2)	1 (2.2)
Site [*n* (%)]				
Bronx	24 (31.6)	11 (68.8)[a]	49 (28.2)	25 (55.6)[a]
Brooklyn	52 (68.4)	5 (31.3)[a]	125 (71.8)	20 (44.4)[a]
BMI (kg/m^2)	27.9 (24.7–33.0)	31.0 (27.2–40.2)	28.3 (24.8–34.7)	26.6 (24.2–28.9)
Current smoker [*n* (%)]	35 (46.1)	13 (81.3)[a]	83 (47.7)	29 (64.4)
Heavy alcohol use [*n* (%)]	8 (10.5)	1 (6.3)	14 (8.1)	2 (4.4)
History of injection drug use [*n* (%)]	2 (2.6)	8 (50.0)[a]	1 (0.6)	31 (68.9)[a]
History of heroin or cocaine use [*n* (%)]	32 (42.1)	11 (68.8)	71 (40.8)	36 (80.0)[a]
Diabetes [*n* (%)]	17 (22.4)	7 (43.8)	44 (25.3)	14 (31.1)
Hypertension [*n* (%)]	36 (47.4)	13 (81.3)[a]	96 (55.2)	26 (57.8)
Dyslipidemia [*n* (%)]	50 (65.8)	9 (56.3)	137 (78.7)[a]	35 (77.8)
History of myocardial infarction [*n* (%)]	1 (1.3)	2 (12.5)	1 (0.6)	0 (0.0)
eGFR (ml/min per 1.73 m^2)	109 (102–125)	100 (85–112)[a]	110 (94–124)	95 (77–114)[a]
APRI	0.14 (0.11–0.17)	0.35 (0.20–0.55)[a]	0.17 (0.13–0.26)[a]	0.40 (0.24–0.53)[a]
FIB-4	0.57 (0.48–0.73)	1.15 (0.85–1.74)[a]	0.79 (0.55–1.05)[a]	1.31 (0.91–1.92)[a]
RAAS-antagonist use [*n* (%)]	7 (9.2)	5 (31.3)[a]	17 (9.8)	9 (20.0)
Beta-blocker use [*n* (%)]	3 (4.0)	3 (18.8)	12 (6.9)	4 (8.9)
HIV-specific characteristics[b]				
CD4$^+$ T-cell count (cells/μl)	NA	NA	480 (336–737)	444 (261–585)
ART use [*n* (%)]	NA	NA	145 (83.8)	39 (88.6)
Detectable viral load [*n* (%)]	NA	NA	107 (61.9)	25 (56.8)

Median (IQR) for continuous variables; *n* (%) for categorical variables. APRI, aspartate aminotransferase to platelet ratio index; ART, antiretroviral therapy; eGFR, estimated glomerular filtration rate; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; IQR, interquartile range; NA, not applicable; RAAS, renin–angiotensin–aldosterone system.
[a]*P* less than 0.05 when compared with neither-infected.
[b]$n = 2$ HIV seroconverters between baseline and follow-up dropped; pairwise differences in characteristics were determined using the Wilcoxon rank-sum, chi-square or Fisher's exact test, as appropriate.

33.3% for NNRTIs; and 33.9 and 37.8% for protease inhibitors. There was also a corresponding shift to newer agents with lower side-effects.

There were 43 cases of new-onset LV dysfunction after a median (range) of 12.1 (8.1−13.6) years between scans. Of these incident cases, 9 (20.9%) had LVSD and 34 (79.1%) had isolated LVDD (ASE 2009 definition). Among women with incident LVSD, median (range) LVEF was 42% (37−49%). In those with isolated LVDD, 24 (70.6%) had grade I, 8 (23.5%) had grade II and 2 (5.9%) had indeterminate grade. Figure 1 shows the proportions of incident LV dysfunction by HIV and HCV status. In comparison to the neither-infected group, the HCV-monoinfected and HIV–HCV-coinfected groups experienced significantly greater isolated LVDD and LVSD or LVDD.

Adjusted relative risks for the primary outcome of new-onset LV dysfunction for participants with HIV or HCV or both compared with neither infection are shown in Fig. 2. The HCV-monoinfected group was three-fold more likely than the referent group to experience LV dysfunction in the minimally adjusted model. This risk estimate was attenuated to 2.5-fold and became nonsignificant after full adjustment. Meanwhile, the HIV-monoinfected group showed a risk ∼1.7-times higher, which remained virtually unchanged and nonsignificant at all levels of adjustment. As for women with HIV–HCV-coinfection, this group was nearly three times more likely to experience LV dysfunction across the models, an association that remained significant after full

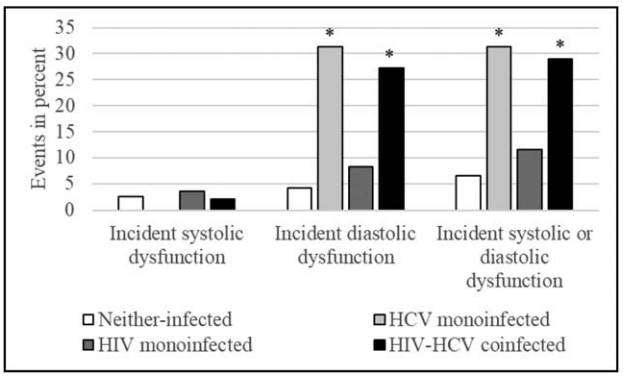

Fig. 1. Cumulative incidence of left ventricular dysfunction – systolic, diastolic or either. $*P < 0.05$ versus neither-infected group.

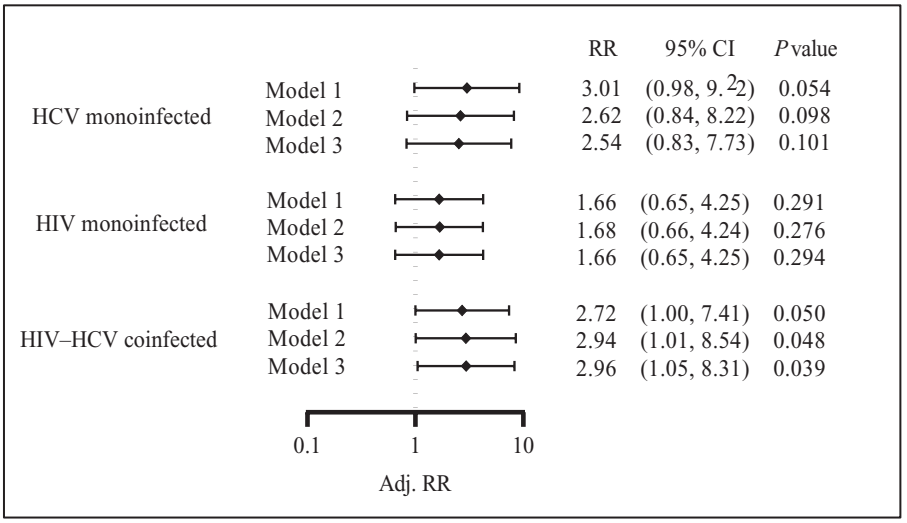

Fig. 2. Relative risk estimates of new-onset left ventricular dysfunction (primary outcome) for hepatitis C virus-infected and/or HIV-infected groups versus the neither-infected group. Model 1 adjusts for age, race–ethnicity, site; model 2 additionally adjusts for smoking, injection drug use, heroin or cocaine use; model 3 additionally adjusts for hypertension, diabetes, dyslipidemia. CI, confidence interval; EF, ejection fraction; HCV, hepatitis C virus; LV, left ventricular; RR, relative risk.

adjustment. In these analyses, additional adjustment for time between scans, heavy alcohol use, eGFR or liver fibrosis indices did not attenuate the risk estimates (not shown).

For the secondary outcome of LV dysfunction (using the ASE 2016 definition for LVDD), $n = 346$ baseline participants were included. Of these participants, $n = 28$ developed new-onset LV dysfunction [$n = 9$ (32.1%) LVSD, and $n = 19$ (67.9%) isolated LVDD]. Relative risks for the secondary outcome are shown in Supplementary Figure, http://links.lww.com/QAD/C127. The HCV-monoinfected group had a risk estimate 1.8 times higher than the neither-infected group in the minimally adjusted model, which was attenuated to 1.4 times higher in the fully adjusted model but was nonsignificant at any level of adjustment. Compared with the referent, the HIV-monoinfected group had nonsignificant relative risks ranging from 0.9 to 1.0 across adjusted models. In turn, the HIV–HCV-coinfected group exhibited risk estimates approaching two-fold higher than the neither-infected group across levels of adjustment, but these were not statistically significant.

Adjusted comparisons of HCV-positive or HIV-positive participants with their HCV-negative or HIV-negative counterparts for the primary outcome are shown in Table 2. After full adjustment, HCV was significantly associated with a two-fold higher risk of new-onset LV dysfunction. The corresponding risk for HIV was ~1.4-fold higher but this was not statistically significant. There was no evidence of interaction between HIV and HCV ($P_{\text{interaction}} = 0.572$).

Table 2. Relative risk estimates by hepatitis C virus and HIV infection status for the primary outcome of new-onset left ventricular dysfunction [systolic dysfunction (ejection fraction <50%] or isolated diastolic dysfunction (American Society of Echocardiography 2009)].

Models	New-onset LV systolic or diastolic (ASE 2009) Dysfunction			
	HCV-positive versus HCV-negative		HIV-positive versus HIV-negative	
	RR (95% CI)	*P*	RR (95% CI)	*P*
Model 1	1.90 (1.05–3.44)	0.035	1.29 (0.68–2.45)	0.441
Model 2	1.96 (1.00–3.83)	0.049	1.41 (0.75–2.65)	0.287
Model 3	1.96 (1.02–3.77)	0.044	1.43 (0.76–2.69)	0.271

Model 1 adjusts for age, race–ethnicity, site; model 2 additionally for smoking, intravenous drug use, heroin or cocaine use, HIV status (or HCV status); model 3 additionally for hypertension, diabetes, dyslipidemia. ASE, American Society of Echocardiography; CI, confidence interval; EF, ejection fraction; HCV, hepatitis C virus; LV, Left ventricular; RR, relative risk.

Findings for the secondary outcome are presented in Supplementary Table 4, http://links.lww.com/QAD/C127. HCV was associated with a 1.7-fold risk of LV dysfunction, whereas HIV was associated with 1.1-fold risk but neither was statistically significant. No evidence of HIV-by-HCV interaction was detected ($P_{\text{interaction}} = 0.714$).

Discussion

In this study of mostly middle-aged women, we found that participants with HIV–HCV coinfection exhibited a

three-fold significantly greater risk of incident LV dysfunction after adjustment for risk factors than those with neither infection. Women with HCV monoinfection and HIV monoinfection showed 2.5-fold and 1.7-fold higher corresponding risks, respectively, but these were not statistically significant. Comparison of women with and without HCV, however, revealed a two-fold significantly higher adjusted risk of new-onset LV dysfunction independent of, and without effect modification by, HIV. Similar comparison of women with and without HIV showed a 1.4-fold higher risk of incident LV dysfunction independent of HCV status, which was not statistically significant.

Previous clinical studies have linked HCV to risk of atherosclerotic CVD [31], and document a stronger association with incident CVD for HIV–HCV coinfection than HCV monoinfection [13]. A relationship between HCV and cardiac dysfunction was previously suggested by detection of HCV RNA in cardiac specimens from Japanese patients with dilated or hypertrophic cardiomyopathy but subsequent cross-sectional studies in larger cohorts from Greece and Italy failed to confirm an HCV–cardiomyopathy association [15]. In a longitudinal United States study constituting mostly men with CHD, HCV seropositivity was positively associated with incident heart failure [16], but this was not replicated among United States veterans without prevalent CHD [4].

PWH have likewise been shown to have increased risk of CVD [2–7], with imaging studies documenting high prevalences of LVSD and, particularly, LVDD [8]. Apart from a small study that found high incidence of LVDD in a small sample ($n = 60$) of PWH who underwent echocardiograms 4 years apart, existing imaging data are cross-sectional [32].

To our knowledge, this is the first long-term evaluation of LV function by repeat echocardiography among people with and without HIV or HCV, and the first of its kind in women. HIV–HCV-coinfected women emerged as the only group with a significant and strong association with new-onset LV dysfunction but the corresponding risk estimate for HCV monoinfection, while not significant, was also of large magnitude. The comparison of HCV-positive and HCV-negative women also revealed a significant and sizable association with incident LV dysfunction, without evidence of interaction by HIV status. Hence, the present findings do not support a stronger risk for HIV–HCV coinfection than HCV monoinfection but the relatively modest sample size precludes decisive evaluation.

Potential explanations for the documented HCV-associated risk of incident LV dysfunction include HCV's association with high-risk behaviors [33]. HCV-positive participants in our study had higher smoking and substance use than HCV-negative participants but the association persisted after adjustment for these factors. HCV is also associated with glucose dysregulation, which may in part account for its reported link to atherosclerosis [15]. Such atherosclerotic disease, together with HCV-associated vasculitis [34], can eventuate in cardiac dysfunction. Although diabetes did not differ significantly by HCV status at baseline, there was significantly more diabetes in the HCV-positive than HCV-negative group (47.5 vs. 29.6%, $P = 0.008$) at follow-up. Self-reported myocardial infarction, which was infrequent at baseline, was near-significantly higher in HCV-positive than HCV-negative women (8.2 vs. 2.8%, $P = 0.064$) at follow-up. As these events were not adjudicated, however, and their timing relative to the onset of LV dysfunction indeterminate, the contribution of CHD to the incident LV dysfunction observed is uncertain.

Another possible mechanism is HCV-induced kidney disease [34]. Although adjustment for baseline eGFR did not meaningfully affect risk estimates, differences in eGFR persisted at follow-up. In addition, HCV cardiotropism and direct cytotoxic damage could play a role, as may immune-mediated mechanisms or inflammation affecting cardiomyocytes, coronary endothelium, or both [15]. Liver fibroinflammatory disease may also be important [35]. Liver fibrosis scores were higher at baseline and follow-up in HCV-positive women but adjustment for baseline levels did not dampen the effect estimates.

We did not find a significant association for HIV and incident LV dysfunction. Although risk estimates were increased, 95% confidence intervals (CIs) were wide, indicating limited power. Although multiple studies have linked HIV to LV dysfunction (cross-sectionally) [8] and heart failure (longitudinally) [4–6], these have included small proportions of women. Imaging studies, in particular have lacked HIV-negative controls with the closely matched behavioral and clinical risk profiles available in WIHS. Moreover, the relationship of HIV with CVD has been shown especially among people with low $CD4^+$ T-cell counts or lacking viremic suppression [4–6]. Women not receiving ART, or having $CD4^+$ T-cell depletion or unsuppressed viremia, were a minority at follow-up echocardiography.

Certain ART medications have adverse metabolic and cardiovascular effects, particularly early generation protease inhibitors and NRTIs [1]. Among the latter, drugs such as zidovudine, stavudine and didanosine have been linked to mitochondrial toxicity and LV dysfunction [36]. But such medications were largely replaced with newer agents during follow-up in our study. And, notwithstanding its off-target effects, ART has been shown to reduce cardiovascular events in HIV [1]. Thus, the predominance of ART use in our sample likely contributed to the lack of an observable association between HIV and new-onset LV dysfunction, presumably by lessening the potential effects

of HIV-related inflammation and immune activation on LV myocardium [36].

Given the young age of our population, we applied for our primary outcome the 2009 ASE definition of LVDD, which may involve a tradeoff of greater sensitivity for lower specificity compared with the 2016 ASE definition [25]. Still, our secondary outcome involving the 2016 ASE definition, with two-thirds as many cases of new-onset LV dysfunction, yielded increased, if attenuated and nonsignificant, risk estimates for HCV. Less restrictive definitions of LVDD have been applied previously in a population-based setting, showing that new-onset or progression of LVDD predicts development of heart failure [37]. Comparison to the foregoing cohort is limited by differences in demographic and clinical profiles, duration of follow-up and assessment of LVDD. Yet, if we consider the frequencies of cumulative LVDD of 6.7% (ASE 2009 definition) and LVSD of 2.2% among participants with neither infection from our entire sample of $n = 371$ women at follow-up echocardiography [median age 53 (IQR 47–58)], these are broadly similar to the cross-sectional prevalences of LVDD of 9.6% and LVSD of 1.0% reported for women aged 45–64 years in that population [38].

Hence, our findings are of clinical significance, suggesting that women in early middle-age infected with HCV carry a substantial risk of future heart failure. Although HCV may be a surrogate for adverse factors that may have gone unmeasured or incompletely measured in our analysis, the present findings tend to validate recent recommendations for expanding HCV screening to all United States adults aged 18 to 79 years [12]. Given the implications of chronic HCV not just for liver disease but for cardiac dysfunction, the high sustained virologic responses achievable by direct antiviral agents [11], and evidence that such responses improve liver-related [39] and cardiovascular outcomes [40], our findings further support the public health mission to eradicate HCV through increased allocation of resources for screening and treatment efforts.

The corresponding lack of association for HIV among mostly immunocompetent, virally suppressed women receiving ART at follow-up is also important. This finding suggests that as compared with similar women at risk of HIV, women with well controlled HIV may be subject to lower risk of cardiac dysfunction and its consequences, as supported by prior studies mostly of men [4,5].

Several limitations merit attention. Given its observational design, the present study cannot demonstrate causality. Our study's sample size was relatively modest, such that our risk estimates lacked precision, and our comparisons had insufficient power to detect moderate effects for HIV or HIV–HCV interaction. Nor could we meanigfully evaluate the impact of HIV-specific factors on risk in the HIV-positive group. The small number of events also limited the number of covariates that could be fitted in multivariable models, and evaluation of causal intermediates. Even upon broad inclusion of covariates, there was no evidence of model overfitting but we cannot exclude the influence of residual confounding on our findings.

We defined HCV status as both exposure and active infection in order to enhance power. Hence, our findings are likely to underestimate the association between chronic HCV infection and LV dysfunction as HCV exposure without chronic infection or successful HCV treatment would tend to bias our results toward the null hypothesis.

For LV dysfunction, we combined both LVDD and LVSD, distinct but related forms of myocardial disease [41], to maximize power. Although moderate/severe LVSD does represent a different subtype of heart failure than its counterpart with preserved LV systolic function [42], most of the incident cases of LVSD were of mild severity. Further, most incident cases constituted LVDD, consistent with its greater prevalence in general cohorts and in PWH [8]. Thus, the present findings support the view that HIV, HCV and associated risk factors lead primarily to early perturbations in cardiomyocyte function and myocardial interstitium in middle-aged women, manifest as abnormalities in LV relaxation and stiffness [43]. Absent ischemic or other insults resulting in major cardiomyocyte loss, such LV diastolic abnormalities largely predate development of reductions in LVEF, as is the case for preclinical stages of heart failure generally [41].

It is possible that some women may have developed incident LVSD or LVDD between the baseline and follow-up echocardiograms, which might have resolved before the follow-up assessment. We are unable to capture such instances because of the nature of the study design. Last, participants who returned for follow-up echocardiography were in better health, such that our findings are not necessarily generalizable to the broader population.

In conclusion, we found that HIV–HCV-coinfected women had markedly higher risk of incident LV dysfunction than uninfected women, an association that was seen generally for women with HCV, but not for women with HIV receiving ART. Additional study is warranted in larger populations to evaluate the association of HIV and HCV monoinfection with incident LV dysfunction, and to elucidate underlying mechanisms.

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Conflicts of interest

J.R.K., stock ownership in Bristol-Myers Squibb, Johnson & Johnson, Medtronic, Merck and Pfizer. S.G.S., J.M.L., D.B.H., R.S.K., K.A., M.J.G., P.C.T., J.A.C.L., and R.C.K. have no conflicts of interest.

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