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Association of hepatitis C virus and HIV infection with subclinical atherosclerosis in the women's interagency HIV study

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Abstract

Whether hepatitis C virus coinfection might accelerate atherosclerosis in HIV-infected individuals is unclear. We examined the relationship of HIV and hepatitis C virus with carotid artery intima media thickness and the presence of carotid plaques in the Women's Interagency HIV Study. Hepatitis C virus infection was not associated with greater carotid artery intima media thickness after adjustment for demographic and traditional cardiovascular risk factors. Further follow-up is needed to clarify whether HIV/hepatitis C virus coinfection may be associated with a greater risk of carotid plaque.

Recent evidence suggests that HIV-infected individuals may be at increased risk for premature atherosclerosis [1,2] and cardiovascular disease (CVD) [3–5]. Whether hepatitis C virus (HCV) coinfection might further accelerate atherosclerosis and CVD is unclear. Few studies have examined the association of HIV/HCV-coinfection with CVD [6]; none have examined the association with atherosclerosis. We determined the relationship between HIV and HCV infection with carotid artery intima media thickness (CIMT) and carotid plaques among participants from the Women's Interagency HIV Study, a multisite prospective cohort of United States women with and at risk for HIV [7,8].

CIMT data were collected at one study visit from 2004 to 2005 on 1865 participants enrolled in a carotid ultrasound substudy [9]. HCV antibody (anti-HCV) and confirmatory HCV RNA status was available in 1767 (95%) (1349 anti-HCV negative, 94 anti-HCV positive/HCV RNA negative and 324 anti-HCV positive/HCV RNA positive). Of these, 36 with hepatitis B surface anti-genemia and 56 reporting HCV therapy were excluded, yielding a final study population

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of 1675 (220 HIV/HCV-coinfected, 53 HCV-monoinfected, 950 HIV-monoinfected, 452 controls).

High-resolution B-mode carotid artery ultrasound was used to image the far wall of the right common carotid artery (CCA), internal carotid artery, and the bifurcation according to a standardized protocol (patents 2005, 2006) [9–14]. The CCA CIMT and the presence of carotid plaques (focal CIMT > 1.5 mm in any of the imaged segments) were measured centrally. Image analysis and reproducibility of CIMT measures have been described [9–11,13,14].

Linear regression models quantified the association of HIV and HCV with the logarithm of CIMT as a continuous outcome. The ratio of the median CIMT values of two groups with different exposures were obtained by exponentiation of appropriate model coefficients and used as the measure of association between exposure and outcome [15]. Logistic regression models quantified the association of HIV and HCV with the presence of at least one carotid plaque as a binary outcome. Multiple regression models adjusted for demographic and traditional cardiovascular risk factors.

Hepatitis C virus-infected women were older (medians of 48 and 49 years in HIV/HCV-coinfected and HCV-monoinfected, respectively, versus 39 and 36 years in HIV-monoinfected and controls, respectively); more likely to report a longer median duration of smoking (26 and 27 years versus 5 and 7 years), to have diabetes mellitus (23% and 26% versus 14%- and 6%), and to have a higher median systolic and diastolic blood pressure (123/76 and 123/74 mmHg versus 115/70 and 116/69 mm/Hg), but lower median LDL-cholesterol level (78 and 81 mg/dl versus 104 and 99 mg/dl). Among HIV-infected women, those with HCV-coinfection had a lower median CD4 cell count (367 versus 442 cells/μl) and higher median HIV RNA (2.92 versus 2.32 $\log_{10}$-copies/ml), and were less likely to be on highly active antiretroviral therapy (58% versus 67%).

The median CIMT was similar between HIV/HCV-coinfected and HCV-monoinfected women; both HCV-infected groups had higher CIMT than HIV-monoinfected and those with neither infection (Table 1). The prevalence of carotid plaques was higher in HIV/HCV-coinfected than HCV-monoinfected women; both were higher than the prevalence in HIV-monoinfected and control women.

After adjustment, HCV infection was no longer associated with greater CIMT, regardless of HIV status compared to controls. Additionally, the 4.28-fold and the 2.40-fold higher odds of carotid plaques among HIV/HCV-coinfected and HCV-monoinfected women, respectively, was attenuated and not statistically significant after adjustment.

Our findings of a lack of an association between HCV infection and greater CIMT are contrary to prior studies [16–19]. On the contrary, HIV/HCV coinfection may be associated with higher odds of carotid plaques than those with neither infection. There are several potential reasons for the differences between our study and other studies.

First, our study is the first to examine the association of HIV/HCV coinfection with CIMT and includes a large sample of individuals with confirmed HCV infection. Prior CIMT studies have been in HCV-monoinfected individuals and have mainly used large population-based health-screening examinations to identify anti-HCV-positive cases and controls. In our study, women with and without HIV infection had similar high-risk behaviors for HIV and HCV transmission.

Second, our study controlled for smoking duration; other studies controlled for smoking history. Smoking duration has been associated with CIMT [20]. It is noteworthy that HCV-infected women in our study, on average, reported smoking for 20 more years than HCV-uninfected women (beyond the difference in the median age for the groups). Diabetes

determined using fasting glucose parameters was also highly prevalent in our HCV cases. Previous studies indicate that traditional cardiovascular risk factors (rather than HIV infection itself) account for CIMT differences between HIV-infected and HIV-uninfected individuals [10,11]. These factors may also account for the CIMT differences between HCV-infected and HCV-uninfected individuals, although the attenuation in the association between HCV infection and CIMT occurred mainly after adjustment for age and race.

Interestingly, the association of HIV/HCV coinfection and HIV monoinfection with carotid plaques was in a positive direction, whereas the association with CCA CIMT was in a negative direction. A study comparing HCV-monoinfected with uninfected individuals found that HCV core protein was strongly associated with carotid plaques and weakly associated with CCA CIMT [18]. Similar to our study, carotid plaque was defined as the presence of focally increased CIMT in any of the CCA, internal carotid artery or bifurcation. These data could suggest a differential affect of HCV infection on the different segments of the carotid artery.

A limitation of our study is its cross-sectional design, which included few HCV-monoinfected cases and so the association of HCV monoinfection with CIMT and carotid plaques should be interpreted with caution. Our findings may also represent confounding by other factors associated with HCV infection, such as injection drug use. Nonetheless, our study included large numbers of participants, used a robust definition of HCV infection, and had a rich database of biologic, demographic, and behavioral characteristics.

In summary, contrary to prior studies, we did not find an association of HCV infection with greater CIMT after adjustment for demographic and traditional cardiovascular risk factors. HIV/HCV coinfection may be associated with a greater risk of carotid plaques; further follow-up over time should clarify this question. Additionally, whether HCV infection might differentially affect the development and progression of subclinical atherosclerosis in the different segments of the carotid artery should be evaluated.

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Table 1

Comparison of median CIMT and presence of carotid artery plaques by HIV and HCV infection status among 1675 Women's Interagency HIV Study participants studied between April 2004 and September 2005.

		CIMT				Carotid artery plaques			
			Ratio of median values (95% CI)				OR (95% CI) of presence of ≥ 1 plaque		
	N	Median (μm IQR)	Unadjusted	Adjusted for age and race	Adjusted for age, race and CVD risk factors[a]	Prevalence	Unadjusted	Adjusted for age and race	Adjusted for age, race and CVD risk factors[a]
HCV+/HIV+	220	748 (691, 829)	1.08 (1.05, 1.10)	0.98 (0.96, 0.99)	0.97 (0.95, 0.99)	21%	4.28 (2.58, 7.09)	1.87 (1.10, 3.19)	1.64 (0.91, 2.94)
HCV+/HIV−	53	753 (672, 834)	1.08 (1.03, 1.12)	0.97 (0.94, 1.01)	0.97 (0.93, 1.00)	13%	2.40 (0.99, 5.81)	0.96 (0.38, 2.42)	0.77 (0.29, 2.07)
HCV−/HIV+	950	698 (642, 764)	1.00 (0.98, 1.02)	0.97 (0.96, 0.99)	0.98 (0.97, 0.99)	8%	1.33 (0.84, 2.10)	1.00 (0.62, 1.61)	1.10 (0.66, 1.82)
HCV−/HIV−	452	701 (641, 767)	1 (reference)	1 (ref)	1 (ref)	6%	1 (ref)	1 (ref)	1 (ref)

CI, confidence interval; CIMT,carotid artery intima-media thickness; CVD, cardiovascular disease; HCV, hepatitis C virus; IQR, interquartile range; OR, odds ratio.

[a]Adjusted for enrollment cohort (1994–1995 or 2001–2002), age (per 10 years), race (African-American, Hispanic, Caucasian), enrollment cohort, menopause status, number of years reporting smoking, systolic and diastolic blood pressure, total cholesterol, HDL-cholesterol, and diabetes status.

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