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Short Communication
Risk of Elevated Total Cholesterol/High-Density Lipoprotein Cholesterol Ratio After Antiretroviral Therapy in HIV/Hepatitis C Virus Patients

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Abstract

Dyslipidemia from highly active antiretroviral therapy (HAART) use has been reported to be less severe among persons with HIV and hepatitis C (HCV) compared to those with HIV monoinfection. However, the effect on lipoprotein ratios is less clear. The total cholesterol/high-density lipoprotein ratio (TC/HDL-C ratio) is a robust measure of cardiovascular disease (CVD) risk but has not been examined in the context of HIV/HCV-coinfected patients. We compared the TC/HDL-C ratio before HAART initiation and after at least 6 months on HAART between patients monoinfected with HIV and coinfected with HIV and HCV. Pre- and post-HAART TC, HDL-C, and non-HDL-C were also assessed. Although TC, HDL-C, and non-HDL-C significantly increased after HAART initiation in both HIV and HIV/HCV patients, the TC/HDL-C ratio did not. In addition, although the pre- and post-HAART TC, HDL-C, non-HDL-C, and TC/HDL-C ratio were significantly different between HIV and HIV/HCV patients, the magnitude in the change from pre- to post-HAART was not significantly different between infection groups. These results persisted after controlling for age, sex, race, current pharmacotherapy for lipoproteins, body mass index, and current CD4 cell count. The magnitude of change in the TC/HDL-C ratio after HAART initiation is not significantly different between HIV and HIV/HCV patients, suggesting subsequent CVD risk in HIV/HCV patients may be greater than currently appreciated.

Many highly active antiretroviral therapies (HAART) lead to increased lipoprotein levels in HIV-infected patients.[1,2] However, lipoprotein increases after HAART have been reported to be attenuated among persons coinfected with HIV and hepatitis C (HCV) compared to those with HIV alone,[3–6] resulting in HCV coinfection having a "protective effect" against hyperlipidemia.[7,8] Nevertheless, cardiovascular disease (CVD) events among HIV/HCV persons have been noted to be higher than those with HIV, suggesting a better predictor of CVD is needed.[9–12] Previously, lipoprotein comparisons of total cholesterol (TC), or high-density lipoprotein cholesterol (HDL-C) from pre- to post-HAART between HIV and HIV/HCV groups were primarily assessed separately, a reportedly less accurate depiction of CVD risk than lipoprotein ratios. Because the TC/HDL-C ratio is a significant predictor of future CVD,[13] and has minimal variability in nonfasting states,[14] the objective of this cohort study was to investigate the changes of the TC/HDL-C ratio before and after HAART. Our study was designed (1) to determine if the TC/HDL-C ratio significantly changed 6 months after HAART initiation in either the HIV or the HIV/HCV group, and (2) to determine if the change in the TC/HDL-C ratio from pre- to post-HAART initiation significantly differed between patients in these groups. Changes in TC and HDL and non-HDL-C were also assessed.

This research study was a retrospective cohort study of HIV and HIV/HCV patients receiving medical care at one of three sites (University of Rochester Medical Center's Infectious Disease Clinic, AIDS Community Health Center, and Unity Health System's Infectious Disease Clinic) from Monroe County in Rochester, NY. Approximately 85% of all patients with known HIV in Monroe County receive their care from one of these three clinics. Patients were identified through an internal database and were assessed for eligibility. To be

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eligible, patients had to be over the age of 18, and had to be either HAART naive, or not on HAART therapy for 60 days prior to a baseline lipoprotein measurement. HIV/HCV patients had to be chronically infected with HCV. For patients with multiple lipoprotein profile measurements, the measurement that was closest, but not after the initiation of HAART, was used for the baseline measurement. Patients were followed after starting HAART, and a post-HAART lipoprotein assessment was obtained after at least 6 months on HAART. HIV patients were randomly sampled from Monroe County's primary HIV service care provider (University of Rochester's Infectious Diseases); however, due to smaller clinic sample sizes, all HIV/HCV patients receiving care from the three study sites were sampled. The study was approved by the University of Rochester Research Subjects Review Board.

Data collected from electronic and paper medical records included demographic characteristics, metabolic and lipoprotein profiles, anthropometric measurements, blood pressure, history of current or past smoking or drug use, and indicators of HIV severity (CD4 cell counts and viral load) and HCV severity (HCV viral load, fibrosis score). Because the fasting status of the patients was not always known, diabetes was conservatively defined as a single measurement of blood sugar ≥ 200 mg/dl, or self-report of current or former diagnosis of diabetes or pharmacotherapy. Hypertension was defined as a single measurement of systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, self-report of current or former diagnosis of hypertension, or pharmacotherapy for hypertension. Non-HDL-C was defined as TC-HDL-C.

The HIV and HIV/HCV groups were compared at baseline for differences in demographic and health characteristics with *t*-tests and chi-squares for continuous and categorical variables, respectively. The change in metabolic measures (TC, HDL, non-HDL-C, and TC/HDL-C ratio) from baseline to follow-up was assessed with paired *t*-tests for within group

Table 1. Sociodemographic Characteristics of the Study Population at Baseline

Subject characteristics[a]	*HIV only* (n = *132*)	*HIV/HCV* (n = *62*)	p
Age, mean (SD)[b]	40.6 (10.8)	45.9 (7.8)	0.0001
Male	91 (69%)	39 (63%)	0.40
Body mass index, mean (SD)	27.1 (5.4)	24.8 (5.0)	0.005
Ethnicity			
White	65 (49%)	14 (23%)	0.001
Black	53 (40%)	31 (50%)	
Hispanic	12 (9%)	17 (27%)	
Other	2 (1%)	0 (0%)	
Marital status			
Single	82 (62%)	35 (56%)	
Married	29 (22%)	12 (19%)	0.62
Divorced/widowed	21 (16%)	13 (21%)	
Current smoker	48 (36%)	36 (58%)	0.004
Current or former drug use	38 (29%)	55 (89%)	< 0.0001
HIV risk behavior			
Heterosexual contact	64 (48%)	26 (42%)	
MSM	59 (45%)	1 (1%)	
IDU	3 (2%)	26 (42%)	< 0.0001
MSM and IDU	1 (1%)	4 (6%)	
Other	5 (4%)	1 (1%)	
Hypertensive[c]	21 (16%)	9 (14%)	0.80
Hyperglycemic[d]	1 (1%)	5 (8%)	0.01
On lipoprotein medications	6 (4%)	2 (3%)	0.67
On blood pressure medications	18 (14%)	7 (11%)	0.65
On glucose medications	8 (6%)	6 (10%)	0.36
Family history of CHD[e]	68 (51%)	25 (40%)	0.38
Family history of diabetes	50 (38%)	22 (35%)	0.17
Duration of HIV, mean years (SD)	3.79 (5.26)	7.4 (6.1)	< 0.0001
CD4 count, mean cells/μl, (SD)	250 (216)	215 (199)	0.28
HIV viral load, mean log (SD)	5.13 (5.3)	5.11 (5.3)	0.85
Previous HAART use	48 (37%)	24 (39%)	0.75
Duration of previous HAART, mean years (SD)	3.20 (2.07)	2.78 (1.90)	0.40
Time since last on HAART, mean years (SD)	0.7 (1.0)	1.5 (1.8)	0.04

[a]*N* (%) unless otherwise indicated. Not all % add up to 100 due to rounding or missing values.
[b]SD, standard deviation.
[c]Hypertension: systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg or self-report of current or former diagnosis of hypertension or pharmacotherapy for hypertension.
[d]Hyperglycemic: random glucose ≥ 200 mg/dl or self-report of current or former diagnosis of diabetes or pharmacotherapy for diabetes.
[e]Family history available for 80 and 32 HIV and HIV/HCV participants, respectively, for CHD and 60 and 31 HIV and HIV/HCV participants, respectively, for diabetes.

HCV, hepatitis C virus; MSM, men who have sex with men; IDU, intravenous drug use; CHD, coronary heart disease; HAART, highly active antiretroviral therapy.

comparisons, and *t*-tests for between group comparisons. Covariates controlled for in the multivariable linear regression analyses included age, sex, race, current use of lipoprotein lowering medications, post-HAART CD4 cell count, change in body mass index (BMI) from pre- to post-HAART, and duration of current HAART use. Analyses were performed with SAS 9.2 (SAS, Cary, NC).

There was no evidence of heterogeneity across clinics, thus we did not control for clinic. The characteristics of the study population ($n=194$) at baseline are presented (Table 1). The HIV/HCV participants were on average 5 years older than the HIV group (45.9 vs. 40.6 years, respectively, $p=0.0001$) and were more likely to be smokers (58% vs. 36%, p = 0.004) and current or former drug users (89% vs. 29%, $p<0.0001$). The groups were comparable in CD4 cell count, HIV viral load, sex, marital status, medication use for hypertension or hyperlipidemia, previous HIV therapy use including duration, and time since last HIV medication. Among the HIV/HCV patients, approximately half of the HIV/HCV patients previously had a biopsy performed (data not shown). Of these patients, two-thirds had no signs of fibrosis ($n=9$) or low fibrosis (fibrosis score of 1 or 2, $n=10$). Five patients had a moderate fibrosis score of 3 or 4, and the remaining five patients had cirrhosis. Excluding patients with cirrhosis did not affect our results (data not shown). Five HIV/HCV patients had ever received HCV antiviral therapy; three discontinued therapy more than 5 years prior to study follow-up, one discontinued therapy 6 months prior to study follow-up, and one was currently on treatment. Excluding these five participants did not affect our results (data not shown).

At baseline, the TC/HDL-C ratio was significantly higher in the HIV patients (4.39) than in the HIV/HCV patients (3.68, $p<0.0001$). The mean TC was significantly higher in the HIV group compared to the HIV/HCV group (175.3 mg/dl vs. 150.7 mg/dl, respectively, $p=0.0003$) (Table 2), as was non-HDL-C (132.9 mg/dl vs. 106.9 mg/dl, $p<0.0001$), but HDL cholesterol was not significantly different (42.4 mg/dl vs. 43.9 mg/dl, $p=0.55$).

All patients had been placed on HAART for a minimum of 6 months, but average duration was approximately 12 months for both HIV (383 days) and HIV/HCV patients (391 days, $p=0.81$). At follow-up, the HIV and HIV/HCV groups were comparable in terms of their statins or lipoprotein lowering medication use, as well as their HAART regimen, with similar proportions on protease inhibitors and nonnucleoside reverse transcriptase inhibitors-based regimens ($p>0.10$, data not shown).

After a minimum of 6 months of HAART, mean TC, HDL-C, and non-HDL-C significantly changed after HAART initiation within both HIV-monoinfected and HIV/HCV-coinfected patients (all $p<0.05$). However, the TC/HDL-C ratio did not significantly increase in either group, and the *magnitude* of the changes in TC, HDL-C, non-HDL-C, and the TC/HDL-C ratio following HAART was not significantly different between infection groups ($p=0.08$, 0.93, 0.05, and 0.61, respectively). A sensitivity analysis using median values, rather than mean values, did not affect our main findings (data not shown).

After adjusting for age, sex, race, current use of lipoprotein lowering medications, current CD4 cell count, BMI, and duration of current HAART use, the mean change in the TC/HDL-C ratio was 0.04 greater among patients with HIV/HCV

Table 2. Comparison of Lipoprotein Levels in HIV and HIV/Hepatitis C Virus Patients at Baseline and After at Least 6 Months of Highly Active Antiretroviral Therapy

	HIV				*HIV/HCV*				*HIV vs. HIV/HCV*		
	Baseline	*Follow-up*	*Delta*	p	*Baseline*	*Follow-up*	*Delta*	p	p *of comparison at baseline*	p *of comparison at follow-up*	p *of delta comparison*
Total cholesterol	175.3 (46.3)	202.2 (47.9)	26.9 (45.5)	<0.0001	150.7 (41.2)	165.8 (45.0)	15.1 (40.3)	0.004	0.0003	<0.0001	0.08
HDL cholesterol	42.4 (14.9)	47.2 (14.7)	4.9 (12.5)	<0.0001	43.9 (17.2)	48.5 (18.5)	4.7 (15.4)	0.02	0.55	0.61	0.93
TC/HDL-C ratio	4.39 (1.2)	4.53 (1.2)	0.1 (1.1)	0.13	3.68 (0.9)	3.74 (1.4)	0.06 (1.1)	0.68	<0.0001	0.0003	0.61
Non-HDL-C	132.9 (39.6)	155.0 (44.6)	22.0 (40.0)	<0.0001	106.9 (32.5)	117.3 (42.8)	10.4 (33.3)	0.02	<0.0001	<0.0001	0.05

Data presented are unadjusted mean values (standard deviation). Unless otherwise noted, *p*-values are for the differences in baseline to follow-up.
HCV, hepatitis C virus; HDL, high-density lipoprotein; TC/HDL-C, total cholesterol/high-density lipoprotein cholesterol.

compared to HIV patients ($p = 0.86$), the mean change in TC was 5.64 mg/dl lower ($p = 0.49$), and the mean change in HDL was 0.22 mg/dl higher ($p = 0.93$) (data not shown).

Consistent with the literature, TC, HDL-C, and non-HDL-C significantly increased after HAART exposure in our study.[15,16] However, our study improves upon the existing literature with the inclusion of the well-validated TC/HDL-C ratio. We found that the TC/HDL-C ratio did not change significantly after HAART use in either HIV or HIV/HCV persons. In addition, although the post-HAART TC, non-HDL-C and HDL-C were significantly different between HIV and HIV/HCV groups, the *magnitude* of the change from pre- to post-HAART was not significantly different. These results suggest that while post-HAART lipid values may have different absolute values between infection groups, the magnitude of the changes post-HAART is similar, possibly reflecting a delayed, but not significantly different CVD risk in those with HIV/HCV compared to HIV monoinfection. Increased CVD events and poorer surrogate markers in HIV/HCV patients compared to HIV patients have already been noted,[9–12,17] and further research should be conducted to compare other traditional risk measures (such as the Framingham risk score) between HIV and HIV/HCV patients.

This study has a number of limitations. Sample size limited our ability to analyze specific HIV treatment regimens, and follow-up for this study may have been inadequate to observe large changes in lipoprotein profiles over time. Although all subjects were on HAART for an average of 12 months, the longitudinal effects of HAART as well as the effects of HAART interruption in these populations should be assessed with longer periods of follow-up time.[18] In addition, the power to detect significant differences in our multivariable analyses may have been limited by our relatively small sample size. Severity of liver disease was not assessed for all persons with HIV/HCV and the association between cirrhosis and CVD remains unclear. Results may not be generalizable on a national level, however, the ethnicities of our participants are similar to that of the nationally infected populations.[19] Lastly, because the fasting status of our subjects was oftentimes unknown, we focused our study on the lipids that have been shown to be stable between fasting and nonfasting states.

This study aimed to improve our understanding of the impact of coinfection with HIV and HCV on lipoproteins. With the advent of HAART, HIV-infected patients are living longer, with CVD accounting for 25% of the deaths due to non-AIDS-related causes.[20] However, the risk of CVD among people with HIV/HCV is still largely unknown.[9–11] As approximately 2–4 million Americans are coinfected with HIV and HCV, chronic diseases such as CVD in this population represent a significant public health burden. Lower lipoprotein profiles in persons with HIV/HCV may incorrectly influence clinicians and patients into believing there is little risk of CVD, and additional studies on the risk of CVD among HIV/HCV persons are needed.

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Author Disclosure Statement

No competing financial interests exist.

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