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Treatment-related changes in serum lipids and inflammation: clinical relevance remains unclear. Analyses from the Women's Interagency HIV Study

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Summary

Among 127 HIV-infected women, the magnitude of HDLc increases after HAART initiation predicted the magnitude of concurrent decreases in inflammation biomarkers. After HAART initiation, changes in LDLc and inflammation were unrelated. In the same population, predicted risk of coronary heart disease based upon levels of standard clinical risk factors was similar before and after HAART treatment. Thus, it remains unknown whether short-term treatment-related changes in standard risk factors may appreciably change risk of CVD.

Keywords

lipids; HAART; HIV infection; inflammation

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A recent article in *AIDS* by Piconi et al [1] reported that among HIV-infected individuals, pro-thrombotic and inflammation factors were lower and metabolic factors (i.e. serum cholesterol and lipoproteins) were higher in persons on antiretroviral therapy (ART) compared to untreated persons. The authors concluded that HIV replication and inflammatory/thrombotic factors may be an important pathway to atherosclerosis in untreated HIV-infected individuals, while changes in metabolic factors may be important atherosclerosis risk factors in those using ART. While an important contribution, the Piconi study lacked data on women, was limited by a cross-sectional study design, and made no conclusions about changes after ART initiation in widely-used clinical measures of future cardiovascular disease (CVD) risk.

We confirmed and extended the key conclusions of Piconi et al using longitudinal data from the Women's Interagency HIV Study (WIHS). Using data from a WIHS substudy of 127 HIV-infected women who initiated highly active ART (HAART) while enrolled in the WIHS [2], we measured levels of lipids and inflammation factors at three semi-annual visits prior to first use of HAART and again at three semi-annual visits after first use of HAART. These data were used to examine the association between changes in serum lipids, and concurrent changes in levels of inflammation-related biomarkers. Levels of high-density lipoprotein cholesterol (HDLc) increased after initiation of HAART (from 48 mg/dL to 54 mg/dL), while low-density lipoprotein cholesterol (LDLc) increased only among the 67 women who initiated protease inhibitor (PI)-based HAART regimens (in PI-HAART users, 92 mg/dL to 109 mg/dL, and in non-PI based HAART users, 101 mg/dL to 103 mg/dL). Regardless of the type of HAART regimen used, the magnitude of increase in HDLc was correlated with the magnitude of decrease in soluble CD14 (sCD14), tumor necrosis factor alpha (TNF-a), soluble interleukin 2 receptors (sIL-2R), interleukin 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) (**Figure**). Change in LDLc level was not associated with changes in inflammation biomarker levels, suggesting a largely inflammation-independent mechanism for increased LDLc with PIHAART.

Among the same patient population, we also investigated the net effect of changes in lipid profile and other vascular risk factors after ART initiation on predicted risk of clinical CVD events. Hence, we calculated predicted coronary heart disease risk in HIV-infected women at visits shortly before initiating HAART, and again 18 months after beginning HAART. The Framingham risk score for estimating the 10-year risk of total coronary heart disease (including angina and fatal and non-fatal acute coronary events) [4] was calculated based upon age, TC, HDLc, diastolic and systolic blood pressures, diabetes and current smoking status. We grouped women into low (10-year risk <15%), moderate (15%-25%) or high risk (≥25%) categories, while placing all diabetics into the high risk category [5,6]. We then determined the proportion of women who were reclassified after HAART initiation. Among all HIV-infected women prior to treatment, 84% had low predicted risk of coronary heart disease, 1% had moderate risk and 15% had high risk. After HAART initiation, 97% remained in the same risk category, 1% moved into a lower risk category, and 2% moved into a higher risk category.

In summary, consistent with the findings from Piconi et al [1], our data demonstrate the reciprocal relationship of inflammation and lipid perturbation in HIV-infected patients, while also suggesting that LDLc and inflammation are biologically discrete pathways that may alter atherosclerosis risk. We [2,3] and Piconi et al [1], among others, have demonstrated that in HIV-infected patients, inflammation and lipid levels are associated with common carotid artery intima-media thickness, a measure of subclinical atherosclerosis. However, it can be difficult to translate findings from this subclinical atherosclerosis measure into clinically meaningful information on risk of CVD. At least

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among middle-aged HIV-infected women, we find little evidence that the net balance of short-term metabolic alterations related to HAART initiation would appreciably change future risk of CVD as measured by standard clinical risk factors. Therefore, as research into novel CVD biomarkers and long-term treated HIV natural history continues to mature, it will become increasingly important to evaluate the clinical relevance of changes in intermediate biomarkers.

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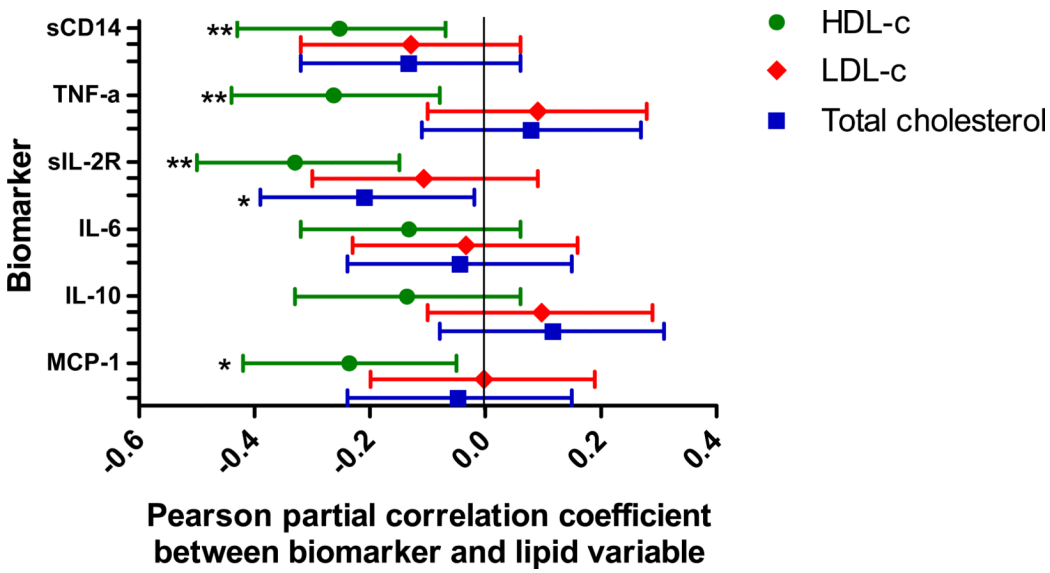

Figure. Correlations of post-HAART changes in high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc) and total cholesterol (TC) with post-HAART changes in inflammation-related biomarkers among HIV-infected women

Pearson partial correlations were computed between change variables, adjusting for change in HIV RNA and change in CD4+ T cell count.