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Association of subclinical atherosclerosis with lipid levels amongst antiretroviral-treated and untreated HIV-infected women in the Women's Interagency HIV study

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ABSTRACT

Objective: We examined serum lipids in association with carotid artery intima-media thickness (CIMT) in HIV-infected and HIV-uninfected women.
Methods: In 2003–4, among 1827 Women's Interagency HIV Study participants, we measured CIMT and lipids (high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), total cholesterol (TC), non-HDL-c). A subset of 520 treated HIV-infected women had pre-1997 lipid measures. We used multivariable linear regression to examine associations between lipids and CIMT.
Results: In HIV-uninfected women, higher TC, LDL-c and non-HDL-c were associated with increased CIMT. Among HIV-infected women, associations of lipids with CIMT were observed in treated but not untreated women. Among the HIV-infected women treated in 2003–4, CIMT was associated both with lipids measured a decade earlier in infection, and with late lipid measurements.
Conclusion: Among HIV-infected women, hyperlipidemia is most strongly associated with subclinical atherosclerosis in treated women. Among treated women, the association appeared strongest early in the disease course.

1. Introduction

The advent of antiretroviral therapy (ART) has increased the life expectancy of persons infected with HIV. Increased duration of exposure to HIV, as well as to ART, has prompted the question of whether patients with HIV have an increased risk of cardiovascular disease (CVD). HIV infection results in dyslipidemia, which presents as low HDL-cholesterol (HDL-c), LDL-cholesterol (LDL-c), total cholesterol (TC), and high triglyceride (TG) levels, and may be associated with increased CVD risk [1–4]. Initiation of highly active antiretroviral therapy (HAART) in HIV-infected persons has been shown to increase HDL-c, LDL-c and TC compared to pre-treatment levels [2,5–8]. Dyslipidemia associated with HAART has also been linked to increased CVD risk and decreased life expectancy [6]. Prior studies have reported varying associations between lipids and subclinical atherosclerosis in HIV-infected and HIV-uninfected populations [9–13].

In this study, we examined the association of serum lipid levels with subclinical atherosclerosis, measured as carotid artery intima-

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media thickness (CIMT), in HIV-infected and HIV-uninfected women. Among HIV-infected women who were treated at the time of the CIMT, we also examined the ability of lipids measured about 10 years earlier, when most women were untreated, to predict subclinical atherosclerosis.

2. Methods

We studied 1827 women (1305 HIV-infected and 522 HIV-uninfected) who were enrolled in WIHS during 2 waves of recruitment (1994–1995 and 2001–2002). All women had CIMT and lipids measured approximately concurrently during 2004–2005. Among those women enrolled during 1994–1995, there were 520 HIV-infected women who had blood specimens from the early period of study participation (1994–1997), and who were ART-treated (mostly HAART) at the 2004–2005 visit when CIMT was measured. In the early period of study participation, less than 1% of participants received HAART, 10% received combination therapy, and 31% received monotherapy.

As previously described, standardized B-mode carotid artery ultrasound images were acquired with superimposed simultaneous electrographic tracing and CIMT was centrally measured with in-house developed automated computerized edge detection software (Patents, 2005, 2006, 2011) [14]. Quality control procedures included centralized training of sonographers and repeat imaging and CIMT measurements obtained on the same individual separated by several weeks conducted throughout the study; this yielded a coefficient of variation of 1.8% and an intraclass correlation coefficient of 0.98. All sites performed periodic calibration using a phantom (Gammex, Middleton WI) to assure consistency of images over time and to harmonize measurements collected using different instrumentation. TC and HDL-c were measured at the early study visits and concurrent with CIMT, while LDL-c was only available for the visits concurrent with CIMT. Non-HDL-c was calculated by subtracting HDL-c from TC. If direct LDL-c was unavailable, we used calculated LDL-c, only if the participant was fasting and had TG levels of 400 mg/dL or below. Of the 1827 participants included in the study, 84% ($N = 440$) of HIV-uninfected women and 85% ($N = 1105$) of HIV-infected women were fasting at the visit concurrent with CIMT. Fasting status was not available for the early visits. Treatment was defined as use of HAART, combination therapy or monotherapy at the time of the lipid measurement concurrent with CIMT.

We used multivariable linear regression to examine whether HDL-c, LDL-c, TC and non-HDL-c were associated with concurrent CIMT. Models were run separately in HIV-infected and HIV-uninfected women. Among the HIV-infected women, we further stratified analyses by ART treatment status (treated versus untreated). Then, among only the treated HIV-infected women who had both early and concurrent lipid measurements, we ran separate models for lipid levels obtained during the early years of study participation and those measured concurrently with CIMT. All models were adjusted for age at time of cholesterol measure and race/ethnicity. Models were further adjusted for smoking status and BMI (and CD4+ T cell count and log-transformed HIV RNA in HIV-infected women), to control for potential confounding. Fewer than 6% of women reported lipid-lowering medication, so we did not adjust for this. Analyses were performed using SAS software (version 9.2, SAS Systems, Cary, NC).

3. Results

3.1. Characteristics of HIV-infected and HIV-uninfected women

The majority of study participants were Black/African–American and nearly half were current smokers (Table 1). Mean age was between 38.0 and 42.2 years in HIV-uninfected, untreated HIV-infected, and treated HIV-infected groups ($P < 0.0001$, Table 1). Compared to untreated HIV-infected women, treated HIV-infected women had higher levels of HDL-c, LDL-c, TC and non-HDL-c (all $P < 0.0001$, Table 1). Compared to HIV-uninfected women, treated HIV-infected women had higher levels of TC and non-HDL-c ($P = 0.03$ and $P < 0.0001$, respectively) and lower HDL-c levels ($P < 0.0001$, Table 1).

3.2. Association of lipid values and CIMT measured concurrently

Adjusted for age and race/ethnicity, among 522 HIV-uninfected women, higher TC, LDL-c and non-HDL-c levels were statistically significantly associated with higher CIMT (Table 2). Adjusted for age and race/ethnicity, among 836 HIV-infected women receiving ART, higher LDL-c level was significantly associated with higher CIMT, higher non-HDL-c level had a borderline significant association with higher CIMT, and TC level had no significant association with CIMT (Table 2). After adjustment for BMI and smoking, in HIV-uninfected women these significant associations persisted at $P < 0.05$, but in treated HIV-infected women the associations between lipids and CIMT became non-significant ($P = 0.14$ for LDL-c and $P = 0.20$ for non-HDL-c) (data not shown). Among 469 untreated HIV-infected women, we did not find a significant association of lipid measures with CIMT (Table 2). HDL-c levels were not associated with CIMT in either HIV-infected or HIV-uninfected groups.

3.3. Lipids measured during pre-HAART and post-HAART era

Among 520 of the 836 antiretroviral-treated HIV-infected women, lipid levels had been measured both during the pre-HAART era and at the time of CIMT (2003–2004). Mean age was 36 years at the time of the pre-HAART lipid measurements and 46 years at the time of CIMT. Among these women, 41% received any HIV treatment (mainly monotherapy) at the time of early lipid measurement (Table 1). Among these women, at pre-HAART visits higher TC level was significantly associated with higher CIMT (adjusted for age and race/ethnicity, difference in CIMT per 10 mg/dL increment in TC = 3.39 μm, 95% CI 0.57–6.22, $P = 0.02$). At visits during the HAART era, the difference in CIMT per 10 mg/dL increment in TC level was 2.01 μm (95% CI −0.17 to 4.19, $P = 0.07$). There was a significant association between non-HDL-c level and CIMT at pre-HAART visits (difference in CIMT per 10 mg/dL non-HDL-c increment = 3.44 μm, 95% CI 0.34 to 6.54, $P = 0.03$) and a non-significant trend suggesting an association between non-HDL-c and CIMT during the HAART era (difference in CIMT per 10 mg/dL non-HDL-c increment = 2.08 μm, 95% CI = −0.16–4.32, $P = 0.07$). HDL-c level measured either in the pre-HAART or HAART era had no association with CIMT (data not shown).

4. Discussion

As is well-known, among HIV-uninfected women higher levels of TC, LDL-c and non-HDL-c are risk factors for atherosclerosis, which we confirmed in our data using CIMT as a measure of subclinical atherosclerosis. Among HIV-infected women, we made several important observations about lipids and CIMT. First, in untreated HIV-infected women, we did not find a significant association between lipid levels and concurrent CIMT; the point estimates actually suggested less rather than more atherosclerosis in women with higher lipid levels. Second, among ART-treated HIV-infected women, higher levels of LDL-c and non-HDL-c were associated with higher CIMT. These associations appeared weaker than those observed in the HIV-uninfected women. TC levels were also significantly associated with CIMT only in the HIV-uninfected