Postprandial Lipoprotein Changes in Patients Taking Antiretroviral Therapy for HIV Infection

James H. Stein, Michelle A. Merwood, Jennifer B. Bellehumeur, Patrick E. McBride, Donald A. Wiebe, James M. Sosman

Objective—Dyslipidemia is common among patients receiving antiretroviral therapy for HIV infection. The purpose of this study was to determine whether postprandial lipemia contributes to the dyslipidemia observed in HIV-positive patients taking antiretroviral therapy.

Methods and Results—A standardized fat load was administered to 65 subjects (group 1 35 HIV-positive subjects receiving protease inhibitors [PIs]; group 2 20 HIV-positive subjects not receiving PIs; group 3 10 HIV-negative controls). Serum triglycerides, retinyl palmitate, and lipoproteins were measured using enzymatic and nuclear magnetic resonance spectroscopic techniques. Compared with HIV-negative controls, peak postprandial retinyl palmitate and large very low-density lipoprotein (VLDL) levels occurred later in both HIV-positive groups, and a delayed decrease in serum triglycerides was observed. However, postprandial areas under the curve (AUCs) for triglycerides, retinyl palmitate, chylomicrons, and large VLDL were similar. Postprandial AUCs for intermediate-density lipoproteins (IDLs) and low-density lipoproteins (LDLs) were higher in group 1 than groups 2 and 3 (all P<0.035).

Conclusions—Postprandial clearance of triglyceride-rich lipoproteins is delayed in HIV-positive individuals receiving antiretroviral therapy. Compared with HIV-positive individuals not on PIs, those taking PIs do not have increased postprandial triglyceride-rich lipoproteins but do have increased postprandial IDLs and LDLs. (Arterioscler Thromb Vasc Biol. 2005;25:1-7.)

Key Words: human immunodeficiency virus ■ lipids ■ lipoproteins ■ metabolism ■ protease inhibitors

The dramatic immunologic and clinical benefits associated with use of highly active antiretroviral therapy (HAART) have led to its widespread acceptance for treatment of patients with HIV infection. Although many patients taking HAART develop metabolic changes that may increase cardiovascular risk, it is unclear whether HAART, its pharmacological components, HIV infection per se, or aging-associated risk factors account for the increased risk of cardiovascular disease observed in patients taking antiretroviral therapy.

Patients taking HAART frequently have hypercholesterolemia and hypertriglyceridemia, and increased concentrations of very low-density lipoproteins (VLDLs) and intermediate-density lipoproteins (IDLs) have been observed in patients taking HIV protease inhibitors (PIs). In the pre-HAART era, decreases in cholesterol-containing lipoproteins were observed with hypertriglyceridemia that was, at least in part, related to disease progression and impaired clearance of triglycerides. Triglyceride-rich lipoproteins and their cholesterol-rich remnants promote accumulation of cholesterol in the arterial wall and adversely affect high-density lipoprotein (HDL) and low-density lipoprotein (LDL) composition and cholesterol concentrations. In individuals without HIV infection, postprandial lipemia is a risk factor for the development and progression of coronary artery disease (CAD). Subjects with CAD have delayed clearance of triglyceride-rich lipoproteins and their remnants, resulting in postprandial lipemia.

Several potential mechanisms by which HAART could lead to dyslipidemia have been proposed, including some related to decreased lipoprotein clearance; however, it is not known whether postprandial lipemia contributes to the dyslipidemia and increased cardiovascular risk observed in patients on HAART.

Methods

The University of Wisconsin institutional review board approved this study. Subjects included adults with HIV infection on a stable antiretroviral regimen for ≥3 months who had evidence of dyslipidemia, including serum triglycerides >150 mg/dL and either HDL cholesterol <40 mg/dL or LDL cholesterol >130 mg/dL. These subjects were recruited into 2 groups: group 1 (HIV positive and on antiretroviral therapy, including PIs) and group 2 (HIV positive and on antiretroviral therapy without PIs for ≥6 months). A control set of HIV negative subjects also was recruited (group 3). Exclusion criteria included current use of lipid-lowering therapy, diabetes...
oral lipid load

After a minimum of 12 hours of fasting (except medications), subjects were admitted to the general clinical research center at 7:00 AM and drank 236 mL of water. Vital signs were measured and an 18-gauge intravenous catheter was placed. After blood was drawn for fasting tests, subjects consumed a milkshake composed of heavy whipping cream (190 g; Sysco Grade A), ice cream (90 g; Babcock vanilla 12% butterfat), chocolate-flavored syrup (30 g; Richardson’s or Hershey’s), concentrated protein supplement (25 g; nonfat dry milk powder), safﬂower oil (22 g), Lactaid (McNeil-PPC), and Aquasol (Amur Pharmaceuticals). The milkshake composition was adjusted to a body surface area of 2.0 m². On average (SD), each milkshake contained 1175 (98) calories, with 101 (9) g of fat, 55 (5) g of carbohydrate, and 17 (1) g of protein. The average fat composition included 51 (5) g saturated, 6 (1) g polyunsaturated, and 38 (3) g monounsaturated fat, with 296 (25) g of cholesterol and 51 (4) g of sugar. Laboratory tests were repeated 2, 4, 6, 8, and 10 hours later.

Measurement of Lipids and Lipoproteins

Serum triglycerides were measured using a glycerol kinas-based enzymatic procedure on a Hitachi Modular DP. Retinyl palmitate levels were measured by high-performance liquid chromatography. Apolipoprotein E genotyping was performed using the polymerase chain reaction withﬂuorescent monitoring. A blood sample was collected into a lavender-topped tube and immediately centrifuged at 3000 rpm for 15 minutes. Plasma was transferred to a cryovial, refrigerated at 4°C, and shipped within 24 hours in a refrigerated box to LipoScience, Inc. for NMR spectroscopic lipoprotein analysis, which was performed within 48 hours of sample collection.

Other Laboratory Tests

Serum glucose levels were measured using a colorimetric enzymatic procedure on a Hitachi Modular DP. Fasting serum insulin was measured using a chemiluminescent immunoassay on a Diagnostic Products Corporation Immulite 2000 analyzer. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum insulin (µU/mL)/fasting plasma glucose (after conversion to mmol/L) (22.5). CD4 cell counts were measured by ﬂow cytometry. Plasma HIV RNA titers were measured by b-DNA hybridization.

Data Analysis

All variables are described by mean ± SE unless otherwise noted. Baseline comparisons between the 3 groups initially were performed using 1-way repeated-measures ANOVA; however, subjects in group 3 were younger than in groups 1 and 2, so baseline between-group differences were re-evaluated using analysis of covariance and Tukey–Kramer multiple comparison tests, adjusted for age. χ² or Fisher exact tests for proportions were performed for categorical data. Student t tests were used to compare pre-HAART data between groups 1 and 2. To evaluate response to the oral fat load, areas under the curve (AUCs) were calculated from plots of lipid and lipoprotein values that were measured at baseline and every 2 hours through hour 10. Between-group AUC differences were evaluated by repeated-measures ANOVA, with group contrasts determined using the general linear model, adjusted for age. In addition, incremental AUCs were determined sequentially in a similar fashion (ie, hours 2 through 10, 4 through 10, 6 through 10, and 8 through 10). Preliminary analysis after recruitment of 49 subjects led to a revised sample size estimate that 62 subjects (including 32 in group 1) would provide 80% power to show signiﬁcant between-group differences in AUCs for chylomicrons and serum triglycerides (α=0.05).

Results

Subject Characteristics

Of 65 subjects, 35 were HIV positive and receiving PIs (group 1), 20 were HIV positive and not receiving PIs (group 2), and 10 were HIV negative (group 3) (Table 1). The mean age was 40.4±1.1 years, 54 (83%) subjects were men, 52 (80%) were white, 7 were black (11%), and the remainder were Hispanic or Asian. Subjects in group 3 were younger than those in groups 1 and 2 (P<0.001); therefore all subsequent between-group comparisons were adjusted for age. Distributions of sex and race did not differ signiﬁcantly between groups. A family history of premature CAD was reported in 11 (17%) subjects, 29 (45%) currently used cigarettes, and 12 (18%) had hypertension. The prevalences of these CAD risk factors were similar in all groups. Insulin levels and HOMA-IR were lower in group 3 than in either HIV-positive group; however, these differences were only signiﬁcant compared with group 1. Group 1 also had the highest waist circumference (P=0.028 versus group 2). The most common apolipoprotein E genotype was ε3/ε3 (52%) followed by ε3/ε4 (22%). No subjects had the ε2/ε2 genotype. Apolipoprotein E allele frequencies did not differ between groups.

The average duration of HIV treatment, CD4 cell count, and median HIV RNA titer, including the percentage completely suppressed (<50 copies/mL; 46%), were similar in groups 1 and 2. In group 1, the most commonly used PI was ritonavir (n=20), which, in all subjects, was used to boost serum levels of another PI (12 lamivudine; 5 indinavir; 2 amprinavir, and 1 saquinavir). Remaining group 1 subjects were receiving nelfinavir,10 indinavir,11 and amprinavir.1 In group 1, 5 subjects also were taking nevirapine, and 1 was taking efavirenz. The most commonly used nucleoside reverse transcriptase inhibitors were lamivudine (83%), stavudine (57%), and abacavir (23%). Less than 20% were taking zidovudine, didanosine, or tenofovir. In group 2, 6 subjects were taking nevirapine (30%), and 7 were taking efavirenz (35%). The most commonly used nucleoside reverse transcriptase inhibitors in group 2 were similar to group 1: lamivudine 95%; stavudine 40%; zidovudine 50%; and abacavir 35%. Less than 20% were taking didanosine or tenofovir. There were no signiﬁcant differences between groups 1 and 2 in the frequency of use of any individual nucleoside or non-nucleoside reverse transcriptase inhibitors.

Before starting on HAART, total cholesterol levels (149.5±6.1 versus 152.5±10.1 mg/dL; P=0.250), glucose levels (89.7±6.1 versus 85.5±4.1 mg/dL; P=0.372), weight (74.0±3.1 versus 68.4±3.7 kg; P=0.303), and body mass index (23.5±0.9 versus 22.4±1.1 kg/m²; P=0.491) were similar in both groups of HIV-positive subjects (group 1 versus group 2).

Baseline Lipids and Lipoproteins

Baseline serum triglycerides and retinyl palmitate levels in groups 1 and 2 were not signiﬁcantly different (P>0.100) (Table 2). Serum triglycerides in group 1 were greater than in group 3 (P=0.040). Retinyl palmitate levels were low in all groups but were marginally higher in group 1 than in group 3.
Postprandial Changes in Lipids and Lipoproteins

All 3 groups experienced parallel rises in serum triglycerides, retinyl palmitate, and large VLDL, with peak triglycerides and chylomicron concentrations observed at hour 4 (Figure 1 and Table 3). After hour 4, concentrations of these parameters decreased rapidly in group 3 but remained elevated in groups 1 and 2, with peak retinyl palmitate and large VLDL concentrations not occurring until hour 6 (Figure 1). The postprandial concentration curves for groups 1 and 2 were nearly superimposable for these parameters. Postprandial AUCs did not differ significantly between groups 1 and 2. However, the serum triglycerides postprandial AUC for group 1 was higher than for group 3 (P=0.049). Baseline lipoprotein concentrations also were similar in groups 1 and 2. The only significant difference was in the concentration of LDL particles (P=0.042), with significantly higher values in group 1 than in group 3 (P=0.014) and a trend for higher values than in group 2 (P=0.091). Other significant between-group differences were only when compared with the control group (group 3). Baseline particle sizes were similar in groups 1 and 2, with smaller LDL and HDL particles than group 3.

**Significant between-group differences** were noted in the postprandial AUCs for IDL (P=0.020) and LDL particles (P=0.031; Table 3). For these parameters, the postprandial AUCs for group 1 were higher than for groups 2 and 3. For LDL particles, the postprandial curves were relatively flat, with slight decreases in the second and fourth postprandial hours. Postprandial differences seemed to reflect baseline values; however, the differences between groups 1 and 2 increased enough to reach statistical significance (P=0.032; Figure 2). For IDL, postprandial levels increased in both HIV-positive groups, but more in group 1 than 2 (P=0.020) or group 3 (P=0.017; Figure 2). This difference was especially notable between the fourth and sixth postprandial hours, when IDL increased in group 1 but decreased in groups 2 and 3. The postprandial AUC for small LDL particles was highest among subjects in group 1 and was significantly higher than in group 3 (P=0.030) but did not differ significantly from group 2.

**Incremental Postprandial AUC Differences Between Groups 1 and 2**

In incremental AUC analyses (numerical data not shown), differences in triglycerides, retinyl palmitate, chylomicrons, large VLDL, and small VLDL were not seen between groups 1 and 2 across any time increment. Between-group differences in medium VLDL postprandial AUCs trended toward significance at hours 2 through 10 and 4 through 10 only. Postprandial AUC differences in IDL and LDL particle concentrations between groups 1 and 2 remained statistically significant throughout each time increment because of con-

-----

**TABLE 1. Subject Characteristics**

<table>
<thead>
<tr>
<th>Group 1 (HIV+, on PIs)</th>
<th>Group 2 (HIV+, not on PIs)</th>
<th>Group 3 (HIV−)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>35</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>42.5±1.3</td>
<td>41.6±1.8</td>
<td>31.1±2.5</td>
</tr>
<tr>
<td>(1 vs 3, &lt;0.001)</td>
<td>(2 vs 3, 0.001)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>83</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>Body surface area (kg/m²)</td>
<td>1.93±0.03</td>
<td>1.87±0.03</td>
<td>1.97±0.05</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>128.0±2.4</td>
<td>128.3±3.2</td>
<td>124.8±4.6</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>26</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>96.6±1.9</td>
<td>95.0±2.4</td>
<td>89.8±3.4</td>
</tr>
<tr>
<td>Insulin (µU/mL)</td>
<td>12.8±1.3</td>
<td>10.6±1.7</td>
<td>5.6±2.5</td>
</tr>
<tr>
<td>HOMA-IR (units)</td>
<td>3.2±0.4</td>
<td>2.5±0.5</td>
<td>1.2±0.7</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>90.9±1.6</td>
<td>83.8±2.1</td>
<td>89.3±2.9</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>3</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Current smoking (%)</td>
<td>46</td>
<td>55</td>
<td>0</td>
</tr>
<tr>
<td>Family history of premature CAD (%)</td>
<td>23</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Duration of HIV treatment (years)</td>
<td>5.7±0.5</td>
<td>5.1±0.7</td>
<td>—</td>
</tr>
<tr>
<td>CD4 cell count (cells/mL)</td>
<td>423±45</td>
<td>474±59</td>
<td>—</td>
</tr>
<tr>
<td>HIV RNA titer (median copies/mL, % undetectable)</td>
<td>75(45.7)</td>
<td>67(45.8)</td>
<td>—</td>
</tr>
</tbody>
</table>

*Statistically significant between-group differences (P<0.05) are in parentheses.*
In this study, postprandial serum triglycerides, retinyl palmitate, chylomicrons, and large VLDL concentrations in HIV-positive individuals taking PIs were similar to HIV-positive individuals not taking PIs. However, compared with HIV-negative subjects, both HIV-positive groups had more persistent peak serum triglyceride concentrations and later peak concentrations of retinyl palmitate and large VLDL. For these markers of triglyceride metabolism, postprandial concentration curves for groups 1 and 2 were nearly superimposable, and the postprandial AUCs did not differ significantly. Between the fourth and sixth postprandial hours, the decreasing chylomicron concentrations with increasing large VLDLs/remnants and IDLs suggest that clearance of postprandial lipoproteins is delayed in HIV-positive patients on antiretroviral therapy, with chylomicron triglycerides being hydrolyzed by lipoprotein lipases and subsequent conversion to chylomicron remnants, large VLDLs, and IDLs, with delayed hepatic removal. The delayed peak in retinyl palmitate levels (at hour 6) in groups 1 and 2 also supports this conclusion.

Exploratory Analyses
Exploratory analyses to determine whether there were differences in baseline and postprandial responses between the 12 subjects taking lopinavir/ritonavir (the most commonly used nonritonavir-boosted PI) and the 10 subjects taking nelfinavir (the most commonly used nonritonavir-boosted PI) were performed. These subjects were of similar age. Subjects taking ritonavir (the PI most implicated in hyperlipidemia), and the 10 subjects taking nelfinavir had higher CD4 cell counts (P=0.001) and a higher prevalence of hypertension (P=0.028); however, no significant differences or trends (P<0.010) between the groups taking these PIs were observed for lipids or lipoproteins at baseline or after the fat load. Similar results were obtained when comparing all 20 subjects in group 1 who were taking ritonavir (the PI most implicated in hyperlipidemia), with the remaining 15 not taking this PI. Also, use of stavudine did not significantly influence postprandial AUCs for the parameters in Figures 1 and 2.

Discussion

In this study, postprandial serum triglycerides, retinyl palmitate, chylomicrons, and large VLDL concentrations in HIV-positive individuals taking PIs were similar to HIV-positive individuals not taking PIs. However, compared with HIV-negative subjects, both HIV-positive groups had more persistent peak serum triglyceride concentrations and later peak concentrations of retinyl palmitate and large VLDL. For these markers of triglyceride metabolism, postprandial concentration curves for groups 1 and 2 were nearly superimposable, and the postprandial AUCs did not differ significantly. Between the fourth and sixth postprandial hours, the decreasing chylomicron concentrations with increasing large VLDLs/remnants and IDLs suggest that clearance of postprandial lipoproteins is delayed in HIV-positive patients on antiretroviral therapy, with chylomicron triglycerides being hydrolyzed by lipoprotein lipases and subsequent conversion to chylomicron remnants, large VLDLs, and IDLs, with delayed hepatic removal. The delayed peak in retinyl palmitate levels (at hour 6) in groups 1 and 2 also supports this conclusion.

Evaluating postprandial chylomicron and triglyceride metabolism by measuring retinyl palmitate levels is based on the observation that in humans, retinyl esters circulate with chylomicrons and their remnants, are taken up by hepatocytes, and do not recycle in VLDLs. Because of experimental evidence that retinyl esters can be transferred from chylomicrons to other lipoprotein fractions, we also assessed lipoprotein concentrations using NMR spectroscopy, another validated technique for assessing triglyceride-rich lipoproteins after an oral fat load. In agreement with the findings using retinyl palmitate levels, NMR assessment of
postprandial chylomicron and large VLDL remnant concentrations showed similar postprandial AUCs among both groups of HIV-positive patients. These findings also suggest that postprandial metabolism of chylomicrons and their remnants do not differ significantly between patients with HIV infection currently using or not using PIs.

The only postprandial AUC differences observed between HIV-positive subjects receiving and not receiving PIs were in the concentrations of IDL and LDL particles. Postprandial curves for LDL particles initially reflected baseline differences between groups and were higher in group 1. Although this general relationship was maintained throughout the postprandial period, differences between groups 1 and 2 increased, whereas the differences between groups 2 and 3 tended to decrease, so the postprandial AUCs for LDL particles were significantly higher in group 1 than in group 2 or 3. The LDL particle concentration is the most powerful of the NMR-derived lipoprotein concentrations for predicting cardiovascular risk in the fasting state; however, associations between CAD and postprandial lipoprotein measured using NMR spectroscopy have not been described previously. Similarly, baseline IDL concentrations were highest among subjects taking PIs. After the lipid load, the increase in IDLs was most dramatic and sustained in group 1, and the postprandial AUC for IDLs was significantly higher than in groups 2 and 3. Although disorders associated with increased IDL levels (measured using other techniques) have been associated with atherosclerosis, associations with CAD have not been described between IDL concentrations measured by NMR spectroscopy or postprandial IDL levels. Nevertheless, as a cholesterol-rich remnant lipoprotein, it is likely that increased IDL levels contribute to atherosclerosis.

Overall, these findings suggest that HIV-positive subjects receiving antiretroviral therapy have impaired clearance of postprandial triglyceride-rich lipoproteins, but that the dyslipidemia observed in patients receiving PIs also may be related to impaired clearance of IDLs and LDLs. Increased postprandial lipemia predicts the development and progression of atherosclerosis.

### Table 3. Postprandial AUC Values

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum triglycerides (mg/dL)</td>
<td>3389 ± 362</td>
<td>3092 ± 478</td>
<td>1565 ± 677</td>
<td>0.114 (1 vs 3, 0.021)</td>
</tr>
<tr>
<td>Retinyl palmitate (mg/dL)</td>
<td>15.2 ± 1.4</td>
<td>15.2 ± 1.3</td>
<td>10.6 ± 2.6</td>
<td>0.355</td>
</tr>
<tr>
<td>Chylomicrons (mg/dL)</td>
<td>447 ± 75</td>
<td>408 ± 99</td>
<td>267 ± 140</td>
<td>0.688</td>
</tr>
<tr>
<td>Large VLDL (mg/dL)</td>
<td>1231 ± 201</td>
<td>1026 ± 266</td>
<td>447 ± 376</td>
<td>0.265</td>
</tr>
<tr>
<td>Medium VLDL (mg/dL)</td>
<td>768 ± 84</td>
<td>653 ± 111</td>
<td>240 ± 157</td>
<td>0.036 (1 vs 3, 0.004) (2 vs 3, 0.035)</td>
</tr>
<tr>
<td>Small VLDL (mg/dL)</td>
<td>100 ± 15</td>
<td>113 ± 20</td>
<td>96 ± 28</td>
<td>0.841</td>
</tr>
<tr>
<td>LDL particles (mmol/L)</td>
<td>14362 ± 693</td>
<td>11846 ± 917</td>
<td>10824 ± 1297</td>
<td>0.031 (1 vs 2, 0.032) (1 vs 3, 0.019)</td>
</tr>
<tr>
<td>IDL (mg/dL)</td>
<td>56 ± 10</td>
<td>15 ± 14</td>
<td>5 ± 19</td>
<td>0.020 (1 vs 2, 0.017) (1 vs 3, 0.020)</td>
</tr>
<tr>
<td>Large LDL (mg/dL)</td>
<td>417 ± 66</td>
<td>314 ± 88</td>
<td>445 ± 124</td>
<td>0.588</td>
</tr>
<tr>
<td>Medium LDL (mg/dL)</td>
<td>360 ± 57</td>
<td>492 ± 75</td>
<td>487 ± 106</td>
<td>0.321</td>
</tr>
<tr>
<td>Small LDL (mg/dL)</td>
<td>387 ± 66</td>
<td>208 ± 87</td>
<td>78 ± 123</td>
<td>0.082 (1 vs 3, 0.030)</td>
</tr>
<tr>
<td>Large HDL (mg/dL)</td>
<td>255 ± 27</td>
<td>239 ± 30</td>
<td>215 ± 42</td>
<td>0.732</td>
</tr>
<tr>
<td>Small HDL (mg/dL)</td>
<td>138 ± 7.0</td>
<td>160 ± 9.3</td>
<td>160 ± 13.1</td>
<td>0.126</td>
</tr>
</tbody>
</table>

*Statistically significant between-group differences (P<0.05) are in parentheses.
tion of CAD; however, postprandial lipoprotein metabolism is complex, and most studies have focused only on postprandial triglyceride metabolism.14–16,20–22 Patients with increased postprandial hypertriglyceridemia have disordered handling not only of exogenous-derived triglyceride-rich lipoproteins but also hepatic-derived triglyceride-rich lipoproteins.26,27 Postprandial hypertriglyceridemia in hypertriglyceridemic patients with CAD appears to be attributable to impaired metabolism of VLDLs rather than accumulation of chylo- micon and their remnants.27 In this context, it is interesting that postprandial medium VLDL concentrations were higher in both HIV-positive groups than in HIV-negative controls. These findings also are consistent with a previous report of decreased triglyceride clearance in patients with advanced HIV infection not on HAART.13

Strengths of this study include the use of an HIV-negative control group, demonstration of the expected postprandial curves for serum triglycerides and retinyl palmitate, and verification and elucidation of postprandial lipoprotein metabolism by the newer NMR technology.23 Other strengths include statistical validation of the AUC data by incremental AUC analysis and similar apolipoprotein E genotypes in all 3 groups. Also, age, body surface area, systolic blood pressure, glucose, duration of HIV treatment, CD4 cell count, and HIV RNA titer (including percentage completely suppressed) were similar between both HIV-positive groups. Although subjects in group 1 had larger waist circumferences, their fasting insulin and HOMA-IR levels were not significantly different from group 2.

Limitations
Because subjects with diabetes mellitus or on lipid-lowering medications were excluded, the magnitude of the dyslipidemia in this study was not as severe as in previous studies of HAART and lipoproteins. It is possible that differences in postprandial lipoprotein metabolism among patients taking HAART with more significant metabolic abnormalities were not detected.11 In this study, levels of apolipoprotein B-48, apolipoprotein B-100, and “triglyceride-rich remnant lipoproteins” using newer assays were not measured because they were in several previous studies of postprandial lipemia.12,20,21,26–28 Similarly, levels and activity of enzymes involved in triglyceride metabolism were not assayed. Although the HIV-negative controls were significantly younger than both HIV-positive groups, all between-group comparisons were adjusted statistically for age. A fourth arm of HIV-positive individuals not on HAART was not included because impaired triglyceride clearance has already been demonstrated in this group, and the sample size for a 4-way comparison would have been prohibitive.13 Finally, the prevalence of stavudine use in this study was somewhat higher than current usage patterns; however, it did not appear to affect postprandial lipoprotein metabolism in group 1 or 2 and was reflective of nucleoside reverse transcriptase inhibitor use when this study started (summer 2002).

Conclusions
Postprandial clearance of triglyceride-rich lipoproteins is delayed in HIV-positive individuals receiving antiretroviral therapy. Compared with HIV-positive individuals not on PIs, those taking PIs do not have increased postprandial triglyceride-rich lipoproteins but do have increased postprandial IDLs and LDLs. In this regard, postprandial hypertriglyceridemia does not contribute to the increased cardiovascular risk observed among HIV-positive patients receiving PIs relative to HIV-positive subjects not taking PIs but may contribute to the increased cardiovascular risk observed in patients with HIV infection per se. The finding that subjects taking HIV PIs had increased postprandial concentrations of atherogenic IDL and LDL particles is unique and merits further study.

Acknowledgments
This work was funded in part by the National Center for Research Resources (K23 RR16716) and the University of Wisconsin General Clinical Research Center (M01 RR03186-1551).

References


Postprandial Lipoprotein Changes in Patients Taking Antiretroviral Therapy for HIV Infection
James H. Stein, Michelle A. Merwood, Jennifer B. Bellehumeur, Patrick E. McBride, Donald A. Wiebe and James M. Sosman

Arterioscler Thromb Vasc Biol. published online December 2, 2004;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/early/2004/12/02/01.ATV.0000152233.80082.9c.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/