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HIV Infection and High Density Lipoprotein Metabolism

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Abstract

HIV infection and its treatment are associated with dyslipidemia, including hypoalphalipoproteinemia, and increased risk of cardiovascular disease. Parameters of HDL metabolism in HIV-positive patients were investigated in a cross-sectional study. The following groups of subjects were selected: *i*) 25 treatment-naïve HIV-infected patients or HIV-infected patients on long therapy break, *ii*) 28 HIV-infected patients currently treated with protease inhibitors, and *iii*) 33 HIV-negative subjects. Compared to the HIV-negative group, all groups of HIV-infected patients were characterized by significantly elevated triglyceride and apolipoprotein B levels, mass and activity of lecithin cholesterol acyl transferase and cholesteryl ester transfer protein ($p < 0.01$). Total and LDL cholesterol was lower in treatment-naïve HIV-infected group only. HDL cholesterol and pre β_1 -HDL were significantly lower in all HIV-infected groups ($p < 0.05$), while mean levels of apolipoprotein A-I (apoA-I) and ability of plasma to promote cholesterol efflux were similar in all groups. We found a positive correlation between apoA-I and levels of CD4+ cells ($r^2 = 0.3$, $p < 0.001$). Plasma level of phospholipid transfer protein was reduced in the group on antiretroviral therapy. Taken together these results suggest that HIV infection is associated with modified HDL metabolism re-directing cholesterol to the apoB-containing lipoproteins and likely reducing the functionality of reverse cholesterol transport.

Keywords

HIV; dyslipidemia; high density lipoprotein; atherosclerosis

1. Introduction

Both asymptomatic HIV infection and AIDS are consistently associated with a higher risk of coronary artery disease (CAD) [1,2]. The introduction of highly active anti-retroviral therapy (HAART) has resulted in a dramatic improvement in morbidity and mortality of HIV-infected patients [3]. It was expected that successful control of HIV infection would also reduce the

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risk of CAD associated with HIV infection. However, the existing data suggest the opposite: despite treatment, or possibly because of it, HIV infection is associated with an increased risk of development of atherosclerosis [4] and at least a 3-fold increase of the risk of CAD [4,5]. Cardiovascular complications are rapidly becoming one of the prevalent causes of morbidity and mortality in HIV-infected patients [2], however, the relative contribution of HIV infection itself and adverse effects of the anti-retroviral treatment is not clear.

Treatment of HIV infection with a protease inhibitor (PI)-containing regimens causes severe dyslipidemia, which could be a key contributor to the elevated risk of CAD in HIV-infected patients [6]. The proposed mechanisms mainly deal with elevation of total and low density lipoprotein (LDL) cholesterol levels, however, other pathways of lipoprotein metabolism may also contribute to the significant rise in cardiovascular risk in HIV-infected patients. High density lipoprotein (HDL) metabolism is also affected in such patients, as HIV-induced dyslipidemia includes low levels of HDL cholesterol (HDL-C) [7,8]. Among HIV-negative individuals, HDL levels consistently and strongly correlate negatively with the incidence of CAD, independently of other risk factors [9]. While elevation of LDL is likely to be caused by HAART [10,11], the relative contributions of HAART and HIV infection itself to low HDL-C levels, as well as the mechanisms of hypoalphalipoproteinemia in HIV-infected patients remain to be determined. The only study that tested the effect of an antiretroviral drug, Ritonavir, on lipoprotein levels in HIV-negative subjects demonstrated a significant effect on LDL level with only a marginal effect on HDL level [12]. Moreover, treatment with two antiretroviral compounds, Efavirens and Nevirapine, was associated with elevation of plasma HDL [13]. DAD study has demonstrated that the effect of HAART on HDL is too limited to have a significant contribution to cardiovascular risk [8]. Studies from our [14,15] and other [11] laboratories indicate that HIV infection might play a key role in the impairment of HDL metabolism and in increased risk of atherosclerosis and CAD.

In this study, we report that the likely mechanism of hypoalphalipoproteinemia in HIV-infected patients is the enhanced transfer of HDL cholesterol to apoB-containing lipoproteins due to elevated activity of cholesteryl ester transfer protein (CETP) and higher levels of triglycerides. This finding has significant implications for both the treatment of CAD in HIV-infected patients and understanding of basic mechanisms of the effect of HIV on lipid metabolism.

2. Materials and Methods

2.1. Study Participants

The following groups of patients were recruited by the Clinical Research Unit of the Department of Infectious Diseases, the Alfred Hospital. 1) Eleven HIV-infected males who were ARV treatment naïve. 2) Fourteen HIV-infected males that were treated for several years before, but had not received treatment with antiretroviral therapy for at least 3 months. The reason for the break in treatment was patient choice. 3) Twenty eight HIV-infected males, who had received continuous treatment with an antiretroviral regimen containing a protease inhibitor for at least 3 months (HIV PI). In this group 9 patients were prescribed a ritonavir-boosted regimen, 7 were receiving lopinavir/ritonavir, 5 were receiving atazanavir, 3 were receiving amprenavir/ritonavir, 2 were receiving ritonavir, and 2 were receiving nelfinavir. All compounds were prescribed at the standard regimen doses. These groups were compared with a group of 33 HIV-negative healthy male volunteers recruited through the Baker Heart Research Institute (Control group). Because of the limited difference in lipid parameters between groups 1 and 2 and to assess the acute effect of treatment, we also included in the analysis a combined group of HIV-infected patients that were currently untreated.

All subjects have answered a questionnaire about their diet, drinking and exercise, habits. All subjects were exercising once or twice a week, but were not engaged in any competitive

sporting activity; all consumed less than 2 standard drinks a day. All participants had BMI of less than 27 and were not on any form of lipid lowering medication. All subjects were fasting for at least 12 h before blood collection. The protocol was approved by the Alfred Hospital Ethics Committee, and conducted in accordance with the Declaration of Helsinki of the World Medical Association. All volunteers provided written informed consent prior to participation.

2.2. Blood collection

Blood (20 ml) was collected by venipuncture into tubes containing streptokinase (Sigma, final concentration 150 units/ml). This was placed immediately onto ice for transport to the laboratory, and plasma was isolated by centrifugation for 15 min at 4°C. Plasma was then aliquoted, snap-frozen in liquid nitrogen and kept at -80°C until assayed. It was demonstrated previously that these conditions fully preserve the activity of plasma enzymes and the distribution of apoA-I among HDL subfractions [16].

2.3. Lipids, Lipoproteins, CETP, PLTP and LCAT

Plasma total cholesterol, triglyceride (TG), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (apoB), high density lipoprotein cholesterol (HDL-C) and apolipoprotein A-I (apoA-I) were measured with a Cobas-FARA centrifugal analyzer (Roche Diagnostic Systems, Basel, Switzerland). Pre β ₁-HDL concentration was measured by ELISA [17] (Daiichi Pure Chemicals, Tokyo, Japan). Standard samples were included in each round of determinations to account for the effect of inter-experimental variations. Plasma concentrations of CETP and lecithin cholesterol acyl transferase (LCAT) were measured by ELISA (Daiichi) according to the manufacturer instruction. As changes in LCAT and CETP concentrations are not unambiguously related to changes in their activities, the latter were also measured. CETP activity was measured by fluorometric assay (Roar Biomedical, NY, NY). This assay uses external substrate, is independent from plasma triglyceride concentration and therefore reflects the true activity of CETP rather than cholesteryl ester transfer rate in plasma. LCAT activity was measured by the method of Bielicki et al [18] using internal substrate; this method reflects the rate of cholesterol esterification in plasma. Phospholipid transfer protein (PLTP) activity was measured using the radiometric assay according to Jauhiainen et al [19]. The coefficient of variation in all assays was below 5%.

2. 4. HIV-related parameters

The CD4⁺ cell count and the percentage of CD4⁺ cells were determined by flow cytometric analysis of cells stained with a range of fluorescently-labelled antibodies against lymphoid markers. The plasma HIV viral load was measured by RT-PCR.

2.5. Cholesterol Efflux

Cholesterol efflux to 2% patient plasma from RAW 264.7 mouse macrophages activated with LXR agonist TO-901317 (final concentration 1 μ mol/L) was measured as described previously [16].

2. 6. Statistics

Group characteristics were compared by One Way ANOVA with post-hoc Bonferroni adjustments. Correlations were calculated as Pearson Product Moment correlation.

3. Results

3.1. Study Participants

The following groups of HIV-infected patients were compared in this study: 11 treatment-naïve patients, 14 patients who were treated previously, but were on a treatment break at the time of

the study, and 28 HIV-infected patients currently on treatment with a protease inhibitor-containing regimen (HIV-PI). All HIV-infected patients were Caucasian males with mean age 40 ± 8 years. To assess the acute effect of the treatment, the combined group of treatment-naïve patients and patients on treatment break (designated as “currently untreated HIV-infected patients (HIV-UT)”) was also included in the analysis. The control group was composed of 33 HIV-negative Caucasian males with a mean age of 34 ± 6 years (age difference between the groups was not statistically significant). Physical activity, alcohol consumption and BMI, the factors known to affect HDL metabolism, were similar in all groups; none of the participants were on lipid-lowering medication.

3. 2. HIV parameters, Lipids and Lipoproteins

The mean and standard deviation of the surrogate markers of the severity of HIV infection, and the plasma lipid and lipoprotein values for each group are presented in Table 1. The HIV-negative control group had TC and LDL-C levels that were respectively 30% and 50% higher than the treatment-naïve HIV-infected group ($p < 0.01$), but were similar to all other groups. TC and LDL-C levels in treatment-naïve HIV-infected patients were respectively 24% ($p < 0.01$) and 50% lower ($p < 0.01$) than in patients that were on the treatment break. Among all parameters measured TC and LDL-C were the only statistically significant differences between these two groups. Treatment-naïve and “on a treatment break” groups were therefore combined into one “currently untreated” group, however values and statistical analysis are presented for both the combined group and two groups of currently untreated patients separately. Total cholesterol levels in the HIV-PI group were significantly higher (10–18%) compared to the HIV-UT groups ($p < 0.05$). VLDL cholesterol levels had a tendency for higher values in all HIV-infected groups, but the difference reached statistical significance ($p < 0.05$) in HIV-PI versus HIV-negative groups only. Triglyceride levels were 23% and 81% higher ($p < 0.05$) and apolipoprotein B levels 26% and 38% higher ($p < 0.05$) in the HIV-UT groups and in HIV-PI group, respectively, when compared to the HIV-negative group. HOMA values were close to normal in control and HIV UT groups and as expected slightly elevated in HIV-PI group.

Plasma levels of HDL cholesterol in all groups of HIV-infected patients were almost half those of the HIV-negative group ($p < 0.001$) (Table 1). Interestingly, there was no statistically significant difference among all groups in the mean levels of plasma apolipoprotein A-I (apoA-I) ($p = 0.4$; Table 1, Fig. 1A). There was, however, a considerable (4-fold) variation in the levels of apoA-I in HIV-infected patients (Fig. 1A) compared to a tighter distribution of apoA-I levels in HIV-negative patients. This variation may be indicative of an additional factor affecting apoA-I levels in HIV-infected, but not in HIV-negative groups. A statistically significant positive correlation was observed between the CD4⁺ cell count and the apoA-I concentration in the combined group of HIV-infected patients ($r^2 = 0.3$, $p < 0.001$) (Fig. 1B). This correlation remained statistically significant even when HIV-infected groups were analysed separately or outlay points were removed ($r^2 = 0.2$, $p < 0.02$). This finding indicates that severity of HIV infection may be a factor contributing to the variation in the number of HDL particles (which is proportional to the apoA-I concentration), as lower CD4⁺ cell counts indicate a more advanced HIV disease. We have previously found that HDL-C also correlates with CD4⁺ cell count [14], however, we did not find such correlation in this study (not shown), presumably due to a smaller number of subjects. The calculated mean HDL-C/apoA-I ratio in all groups of HIV-infected patients was half that of the HIV-negative group (Table 1), indicating a direct contribution of HIV infection to the formation of cholesterol-poor HDL particles.

Plasma levels of pre β_1 -HDL, the primary discoidal HDL particle, were approximately 50% lower in all HIV-infected groups compared to the HIV-negative controls ($p < 0.05$) (Table 1).

3. 3. LCAT, Triglycerides, CETP and PLTP

LCAT mass was 40% and 80% higher and LCAT activity was 49% and 77% higher in all HIV-UT and HIV-PI groups, respectively, compared with the HIV-negative group (Table 2). The HIV-infected groups had on average 50% greater LCAT per HDL particle than the HIV-negative group (Table 2).

The CETP activity levels were significantly higher ($p < 0.05$) in all HIV-infected groups, compared with the HIV-negative group (Table 2). CETP mass was higher in the HIV-infected currently untreated and combined HIV-infected untreated group, compared to HIV-negative group (Table 2). To assess the contribution of elevated TG level and CETP activity to the HDL-C levels we related these three parameters in all groups. In combined population there was a negative relationship between HDL-C levels and both TG levels ($r^2 = -0.2$, $p < 0.001$) and CETP activity ($r^2 = -0.4$, $p < 0.001$) indicating that both TG and CETP are strong determinants of HDL-C levels (Fig. 2 A, B). In the HIV-negative group there was a negative correlation between HDL-C and TG levels ($r^2 = -0.1$, $p < 0.05$) (Fig. 2 A, open symbols), but no relationship between HDL-C and CETP activity (Fig. 2 B, open symbols). However, in the combined HIV-infected group there was a significant negative correlation ($r^2 = -0.3$, $p < 0.01$) between CETP activity and HDL-C levels (Fig. 2 B, closed symbols) and no correlation between HDL-C and TG levels (Fig. 2 A, closed symbols). These findings indicate that while TG level was a determinant of HDL-C in the HIV-negative, normotriglyceridemic group, a major determinant of hypoalphalipoproteinaemia in HIV-infected hypertriglyceridemic groups was activity of CETP.

The activity of plasma PLTP was similar between the HIV-UT and HIV-negative groups, but was 50% lower ($p < 0.01$) in the HIV-PI group (Table 2) indicating that PLTP is most likely affected by the therapy rather than by HIV infection itself.

3. 4. Cholesterol efflux

The ability of plasma to promote cholesterol efflux from activated RAW 264.7 mouse macrophages was similar for all groups: $10.1 \pm 3.6\%$, $10.5 \pm 3.9\%$ and $9.2 \pm 1.1\%$ for the HIV-UT, HIV-PI and HIV-negative groups, respectively.

4. Discussion

Hypoalphalipoproteinemia is a consistent feature of the HIV-induced dyslipidemia and may contribute significantly to the risk of CAD in HIV-infected patients. The most significant finding of this study is unravelling a mechanism that may be responsible for the hypoalphalipoproteinaemia in HIV-infected patients. Firstly, mass and activity of LCAT were significantly higher in HIV-infected patients. An increase in LCAT activity would enhance maturation of HDL and increase the rate of cholesterol transfer through reverse cholesterol transport (RCT). LCAT converts pre β_1 -HDL to spherical α -HDL and is a major determinant of the pre β_1 -HDL concentration [20]. Consistent with higher LCAT activity, the concentration of pre β_1 -HDL was lower in HIV-infected patients. However, increase in LCAT activity is generally associated with higher HDL-C levels [16], whereas the opposite was found in the HIV-infected patient groups. The likely explanation is our second finding that the activity of CETP was also increased in HIV-infected patients. Higher activity of CETP, especially when associated with hypertriglyceridemia, would increase the transfer of cholesteryl esters from HDL to apoB-containing lipoproteins. Consistent with this finding, the ratio of cholesterol to apoA-I in HDL was 50% lower in HIV-infected patients, indicating the presence of cholesterol poor (and presumably triglyceride-rich) HDL particles, a finding consistent with that of Rimland et al [21]. Moreover, in HIV-infected patients, the level of HDL-C correlated negatively with CETP levels, suggesting that the higher activity of CETP is an important

contributor to the low HDL-C levels. Higher activity of CETP in HIV-infected patients was accompanied by high levels of triglycerides, which would further increase the rate of cholesteryl ester–triglyceride exchange. Interestingly, the rise of CETP activity was disproportional to the rise of CETP mass implying a change in CETP specific activity. This discrepancy was observed by us before [16] and the likely explanation is the presence of “active” and “inactive” forms of CETP [22]; the mechanism of altering this ratio in HIV-infected patients is unclear.

By combining the observations in this study, the following model describing the biochemical mechanism of the effect of HIV infection on reverse cholesterol transport is proposed (Fig. 3). The initial plasma step of RCT, the conversion of pre β_1 -HDL to α -HDL and further maturation of HDL is most likely enhanced in HIV-infected patients. However, the combination of hypertriglyceridemia and high activity of CETP diverts the latter steps of RCT from delivery of cholesterol directly to the liver towards delivery of cholesterol to atherogenic VLDL and LDL. Although the liver through LDL receptors will take up the majority of transferred cholesterol, the amount of cholesterol available for modification and uptake by extrahepatic tissues will also increase proportionally. This is likely to result in more cholesterol being delivered to extrahepatic cells in absolute terms. If this situation persists over long period of time, it may contribute to the increased risk of atherosclerosis.

Changes in HDL remodelling also lead to the alteration of HDL composition. Although the ability of HDL particles from HIV-infected patients to promote cholesterol efflux remained intact, the increased triglyceride content of HDL may impact on binding and uptake of these particles by liver scavenger receptors, impairing cholesterol delivery through these receptors [23] and making HDL particles less protective against atherosclerosis [24]. It was suggested by Boekholdt et al [25] and Foger et al [26] that higher levels of CETP are associated with hypoalphalipoproteinemia and higher risk of CAD, but only in subjects with hypertriglyceridemia. HIV-infected patients may represent such a situation, and the combination of hypertriglyceridemia with significantly elevated CETP activity may contribute considerably to the risk of CAD in these patients.

The second important finding of this study is that HIV-related hypoalphalipoproteinemia and impairment of reverse cholesterol transport are more likely to be caused by HIV infection itself than by the antiretroviral treatment. This conclusion is based on two observations. First, we observed a strong positive correlation between apoA-I levels and CD4+ cell counts indicating that more severe infection is associated with lower levels of apoA-I. This finding is consistent with recent reports from our [14] and other [11] laboratories. Second, with the exception of PLTP activity, all changes in RCT were similar between treatment-naïve, currently untreated and currently treated HIV-infected groups. The only long-term effect of treatment on lipoprotein metabolism found in this study was on the TC and LDL-C levels. Thus, while changes in “forward” cholesterol transport may be long-lasting and related to the antiretroviral treatment, especially by protease inhibitors [27], changes in RCT are more likely to result from HIV infection itself. The combination of atherogenic changes in plasma lipoproteins caused by the antiretroviral treatment and the weakening of the defence pathway, RCT, caused by the HIV infection itself may be a primary cause of the elevated risk of CAD in HIV-infected patients receiving antiretroviral therapy.

The only factor which differed between the HIV-UT and HIV-PI groups was the activity of PLTP and HOMA. PLTP is generally considered a pro-atherogenic factor [28], although it was shown recently that PLTP stabilizes ABCA1 thus enhancing cholesterol efflux [29]. Higher HOMA values in HIV-PI group indicate insulin resistance, which may contribute to the higher TG level.

A limitation of this study is that HIV-infected patients were treated with various antiretroviral regimens that may have different impact on lipid metabolism [30]. Most parameters of HDL metabolism, however, were not affected by the treatment regimens used in this study, suggesting a limited impact of these compounds on HDL metabolism. This finding is consistent with other reports [30,31], but cannot be extended to all classes of antiretroviral therapy. Another limitation is that only males were included in this study; differences between males and females in responding to HAART have been described [31].

Our findings have significant implications for treatment of metabolic disorders in HIV-infected patients. First, they indicate that adequate control of the infection, in addition to choosing the appropriate antiretroviral therapy, is critical for maintaining anti-atherogenic lipoprotein profile. Second, they point to CETP as a key target to treat dyslipidemia and cardiovascular complications in HIV-infected patients. CETP inhibitor Torcetrapib failed to improve cardiovascular outcomes in HIV-negative population [32]. However, the outcome may be different in HIV-infected patients, as high CETP activity in this group may specifically contribute to the hypoalphalipoproteinemia. Alternatively, triglyceride-lowering medication, such as niacin, may be beneficial for this group of patients. It must be recognized however that hypoalphalipoproteinemia and disturbances of lipoprotein metabolism are not the only cardiovascular risk factors in HIV-infected patients [8] and dyslipidemia needs to be managed together with other risk factors.

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Figure 1. Scatter diagram of plasma apoA-I levels (A) and correlation between CD4+ cell levels and plasma apoA-I levels (B)

Percent of CD4+ cells and apoA-I levels were measured in 25 HIV-infected currently untreated, 28 HIV-infected treated and 33, HIV-negative subjects as described in the Methods section. ○ – HIV-negative group; ■ – HIV-infected treatment-naïve; • – HIV-infected currently untreated group; ▲ – HIV-infected treated group. $r^2=0.3$, $p<0.001$.

Figure 2. Correlation between plasma level of HDL-C and triglyceride concentration (A) or CETP activity (B)

CETP activity and plasma HDL-C and TG concentration were measured as described in the Methods section. ○ – HIV-negative group; ■ – HIV-infected treatment-naïve; ● – HIV-infected currently untreated group; ▲ – HIV-infected treated group. Regression curves shown are for HIV-negative group (A) and HIV-infected (B) groups.

Figure 3. Schematic representation of HIV-induced changes in RCT

In HIV-negative subjects (top) cholesterol is removed from the cells mainly by the action of ABC transporters, with the formation of discoidal $\text{pre}\beta_1\text{-HDL}$ particles. These particles can be acted upon by lecithin cholesterol acyl transferase (LCAT) to form spherical mature $\alpha\text{-HDL}$. The subsequent remodelling of mature $\alpha\text{-HDL}$ includes *i*) selective uptake of HDL-derived cholesteryl esters by the liver SR-B1; *ii*) uptake of whole HDL particles by liver through LDL receptor-related protein or other receptors; *iii*) exchange of cholesteryl esters for triglyceride from apoB-containing lipoproteins by the action of cholesteryl ester transfer protein (CETP). In HIV-infected subjects (bottom) combination of hypertriglyceridemia and high activity of LCAT and CETP enhance maturation of HDL particles but re-directs the later steps of RCT toward delivering cholesterol to atherogenic VLDL and LDL. That would likely result in more cholesterol delivered to extrahepatic cells.

Table 1

HIV- and lipid-related plasma parameters

Parameter	HIV-negative (n=33)	HIV-infected treatment-naïve (n=11)	HIV-infected currently untreated (n=14)	HIV-infected untreated combined (n=25)	HIV-infected treated with PI regimen (n=28)
CD4+ cell count(cells/ μ l)	N/D	514 $\pm$ 236	315 $\pm$ 74	409 $\pm$ 270	362 $\pm$ 279
CD4+ cells (%)	N/D	22 $\pm$ 10	14 $\pm$ 6	18 $\pm$ 9	19 $\pm$ 12
Viral Load ($\times 10^4$ /ml)	N/D	5.9 $\pm$ 4.0	7.0 $\pm$ 3.9	6.5 $\pm$ 4.0	2.2 $\pm$ 3.5
TG (mmol/L)	1.3 $\pm$ 0.8	1.6 $\pm$ 0.6*	1.7 $\pm$ 0.6*	1.7 $\pm$ 0.6*	2.3 $\pm$ 0.9*
Total cholesterol(mmol/L)	4.9 $\pm$ 0.8	3.8 $\pm$ 1.4*	4.7 $\pm$ 1.0 [#]	4.1 $\pm$ 1.1*	4.5 $\pm$ 1.2 ^{#^A}
LDL-C (mmol/L)	2.9 $\pm$ 0.9	1.9 $\pm$ 0.8*	2.8 $\pm$ 1.0 [#]	2.4 $\pm$ 1.0	2.3 $\pm$ 0.6 [#]
apoB (mg/dL)	73 $\pm$ 17	95 $\pm$ 25*	90 $\pm$ 20*	93 $\pm$ 17*	102 $\pm$ 17*
VLDL-C (mmol/L)	0.6 $\pm$ 0.4	0.8 $\pm$ 0.3	0.8 $\pm$ 0.3	0.8 $\pm$ 0.3*	1.1 $\pm$ 0.4*
HDL-C (mmol/l)	1.4 $\pm$ 0.4	0.8 $\pm$ 0.3*	0.8 $\pm$ 0.3*	0.8 $\pm$ 0.2*	0.8 $\pm$ 0.2*
apoA-I (mg/dL)	128 $\pm$ 17	128 $\pm$ 45	130 $\pm$ 24	129 $\pm$ 27	136 $\pm$ 22
HDL-C/apoA-I	0.4 $\pm$ 0.1	0.2 $\pm$ 0.1*	0.2 $\pm$ 0.1*	0.2 $\pm$ 0.1*	0.2 $\pm$ 0.1*
pre β -HDL (μ g/ml)	40 $\pm$ 5	17 $\pm$ 8*	26 $\pm$ 9*	23 $\pm$ 2*	26 $\pm$ 3*
HOMA	2.61 $\pm$ 1.71	2.11 $\pm$ 0.69	2.03 $\pm$ 0.54	2.07 $\pm$ 0.60	2.75 $\pm$ 1.07 [^]

Means $\pm$ SD are shown.

* p<0.05 versus HIV-negative;

^

p<0.05 versus HIV-infected untreated combined;

#

p<0.05 versus HIV-infected treatment naïve; N/D – not determined.

Table 2

Plasma levels and activity of LCAT, CETP and PLTP

Parameter	HIV-negative (n=33)	HIV-infected treatment-naïve (n=11)	HIV-infected currently untreated (n=14)	HIV-infected untreated combined (n=25)	HIV-infected treated with PI regimen (n=28)
LCAT mass (µg/mL)	4.3±1.6	5.9±1.4*	6.1±2.2*	6.0±1.9*	7.8±2.5*
LCAT activity (nmol/µL/h)	0.24±0.08	0.32±0.13	0.39±0.16*	0.36±0.15*	0.43±0.17*
LCAT mass/apoA-1 × 10 ²	3.4±1.5	4.6±1.6*	4.7±1.7*	4.7±1.5*	5.6±1.6*
CETP mass (µg/mL)	1.8±0.5	2.0±0.9	2.4±0.8*	2.2±0.9*	1.8±0.5
CETP activity (nmol/mL/h)	88±12	135±40*	138±23*	137±27*	126±20*
PLTP activity (µmol/mL/h)	31±0.3	33±7	30±7	30±7	20±1.6*

Means ± SD are shown.

* p<0.05 versus HIV-negative