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HIV infection and high-density lipoprotein: the effect of the disease vs the effect of treatment

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Abstract

HIV infection is commonly associated with hypoalphalipoproteinemia. It is not clear how much the HIV infection and/or treatment contribute to the changes in high-density lipoprotein (HDL) levels. Blood lipids of HIV-positive males were assessed in a retrospective study. The following groups of patients were studied: (1) untreated for at least 6 months; (2) treatment with highly active antiretroviral therapy (HAART) without protease inhibitor (PI); (3) treatment with a HAART regimen that includes a PI (HAART/PI); (4) treatment with HAART that includes low-dose ritonavir and a PI (HAART/PI/boost). Lipoprotein levels were compared with those of age-matched HIV-negative healthy subjects. Compared with the control group, HDL-cholesterol (HDL-C) levels were 22%, 11%, 14%, and 11% lower for currently untreated HIV, HAART, HAART/PI, and HAART/PI/boost groups, respectively. Negative correlations were found among HDL-C level, peak and current viral load, and duration of the disease and the treatment. A positive correlation was found between HDL-C and current and nadir CD4 cell count and CD4 percentage. When patients were divided into subgroups based on duration of antiretroviral therapy, patients treated with HAART and HAART/PI for 3 to 6 years were significantly less likely to have high HDL-C levels compared with the control group and patients treated for 1 to 3 years. A 5-fold decrease in the proportion of subjects with high HDL-C and a 3-fold increase in those with low HDL-C were found in the group treated with HAART/PI/boost. These data suggest that hypoalphalipoproteinemia in patients with HIV is likely to be secondary to HIV infection itself.

1. Introduction

HIV infects and depletes CD4 lymphocytes, resulting in immunodeficiency and a slowly progressive disease. HIV is associated with dyslipidemia, namely, hypocholesterolemia, hypertriglyceridemia, and low levels of both low- and high-density lipoproteins (LDL and HDL, respectively) [1,2]. The latter is likely to contribute to the elevated risk of coronary artery disease (CAD) in patients with HIV [3,4] despite low levels of plasma total cholesterol (TC) and LDL-cholesterol (LDL-C). With highly active antiretroviral therapy (HAART) intervention, mortality due to HIV was greatly reduced [5]. However, there have been several reports of increases in cardiovascular complications in patients with HIV. It is now established that some HAART regimens cause severe dyslipidemia, characterized by high levels of TC and LDL-C, hypertriglyceridemia, and hypoalphalipoproteinemia [2]. This clearly pro-atherogenic lipoprotein profile is associated with a rise in incidence of CAD [6].

HAART is composed of antiretroviral drugs from 3 classes: nucleoside reverse transcription inhibitors (NRTIs), non–nucleoside reverse transcription inhibitors (NNRTIs), and protease inhibitors (PIs). The therapy regimen usually contains NRTIs in combination with either NNRTIs or PIs or both. There are well-documented links between the treatment of patients with HAART, specifically with PI, and significant changes in lipid and lipoprotein levels [7]. Remarkably, however, most of the treatment regiments return TC and LDL-C levels to the preinfection level or above,

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Table 1
Characteristics of study subjects

	Uninfected	HIV-untreated	HIV HAART	HIV HAART/PI	HIV HAART/PI + boost
n	33	36	75	38	21
Age (y)	30.0 ± 1.0	40.0 ± 2.0	42.0 ± 1.0	42.0 ± 1.0	39.0 ± 2.0
Duration of HIV infection (y)	0	7.0 ± 1.0	8.0 ± 1.0	8.0 ± 1.0	10.0 ± 1.0
Duration of antiretroviral therapy (y)	0	0	3.0 ± 0.2	2.0 ± 0.3	4.0 ± 0.4
Nadir CD4 cell count recorded (cells/μL)	NA	243 ± 181	208 ± 184	155 ± 137	123 ± 121*
Current CD4 cell count (cells/μL)	NA	418 ± 250	464 ± 349	337 ± 199	393 ± 280
Current CD4 percentage	NA	24 ± 10	23 ± 12	19 ± 10	21 ± 11

NA indicates not applicable.
* $P < .05$ vs HIV-untreated.

whereas HDL-cholesterol (HDL-C) levels remain low [2]. The exception is nevirapine: several studies reported that nevirapine, although being equally effective in treating HIV infection, raises HDL-C levels resulting in an improvement of atherogenecity index [8-10]. Another NNRTI, efavirenz, may also normalize HDL levels [11]. Thus, it remains unclear what is the relative contribution of infection with HIV itself, its treatment with antiretroviral therapy, and the interaction of the two to dyslipidemia and risk of CAD in patients with HIV.

In this article, we investigate the effect of HIV and different types of antiretroviral therapy on levels of HDL-C. We provide evidence that the likely cause of hypoalphalipoproteinemia is HIV infection itself, with high exposures to PI, generated by the addition of a second PI (ritonavir, which inhibits the breakdown of the other PIs by the hepatic cytochrome P450 3A4 enzymes) (PI + boost), having an additional effect.

2. Methods

2.1. Patients

The Alfred Hospital HIV database was searched for men between the ages of 30 and 50 years, with documentation of their antiretroviral treatment history and fasting lipid levels. One hundred seventy suitable individuals were subdivided into the following groups: (1) currently untreated (this group included individuals not receiving any type of antiretroviral therapy for at least 6 months; all subjects, however, had received prior antiretroviral therapy for an average of 3.6 years); (2) current treatment with a non–PI-based HAART regimen; (3) current treatment with a PI-based HAART regimen (HAART/PI); (4) current treatment with a ritonavir-boosted PI-based HAART (HAART/PI + boost) (this regimen contains 2 PIs, resulting in higher plasma drug concentrations and exposure [12]). Compliance of the patients with the treatment was regularly monitored as part of duty of care. A group of 30 HIV-negative healthy male volunteers were recruited among Alfred Hospital staff. Volunteers were whites, without documented medical problems, with moderate exercise habits, not taking any medication, not smoking, and not drinking excessively. The characteristics of the subjects are presented in Table 1.

2.2. Biochemical data

Lipoprotein and lipid levels were measured by the Alfred Hospital Clinical Biochemistry Department using automated colorimetric techniques. Additional details such as duration of illness and duration of treatment were collected from the hospital records. CD4 cell count was determined by flow cytometric analysis of cells stained by immunofluorescence with a range of antibodies against lymphoid markers. Viral load was measured by reverse transcription–polymerase chain reaction. Current CD4 count, CD4 percentage, and viral load refer to the values measured either at the same occasion (54% of samples) or within several days (average of 14 days) of measurements of lipid parameters.

2.3. Statistical analysis

The TC, triglycerides (TGs), LDL-C, and HDL-C measurements for each subject group were averaged and analyzed by 1-way analysis of variance (with post hoc

Table 2
Lipid levels in study groups

Mean values (mmol/L)	Uninfected	HIV-untreated	HIV HAART	HIV HAART/PI	HIV HAART/PI + boost
n	33	36	75	38	21
Total cholesterol	4.89 ± 0.14	4.56 ± 1.28	4.89 ± 1.51	5.53 ± 1.47*	5.52 ± 1.18
TG	1.58 ± 0.14	2.39 ± 2.36	2.33 ± 2.70	2.26 ± 1.22	3.35 ± 3.40
LDL-C	2.90 ± 0.9	2.56 ± 1.04	2.66 ± 1.16	3.39 ± 1.28*	2.96 ± 1.03
HDL-C	1.37 ± 0.35	1.07 ± 0.42†	1.22 ± 0.44†	1.18 ± 0.41†	1.16 ± 0.29†

* $P < .05$ vs HIV-untreated.
† $P < .05$ vs uninfected.

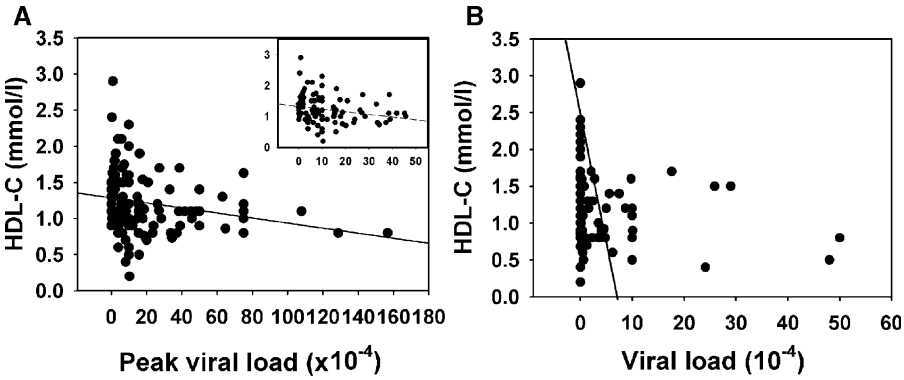

Fig. 1. Correlation between HDL-C levels and peak (A) and current (B) viral load. HDL-C correlated negatively to peak viral load ($r = -0.23$, $P < .02$) (A) and to current viral load ($r = -0.21$, $P < .03$) (B). Inset, Correlation between HDL-C levels and peak viral load in subjects with peak viral load below 5×10^5 ($r = -0.23$, $P < .03$).

Bonferroni adjustments). Means ± SD are shown. Pearson correlation analysis was used for correlations.

3. Results

3.1. Plasma lipids and HIV status

The subject groups were matched with respect to their age (within a decade), duration of illness and treatment, and CD4 cell count and CD4 percentage (Table 1). Nadir CD4 cell count was significantly lower in the HAART/PI + boost group when compared with currently untreated patients (Table 1). The values of serum TC, TG, and LDL-C are presented in Table 2. Total cholesterol levels were similar in all groups except for higher levels in the HAART/PI group ($P < .05$). All 4 HIV groups had hypertriglyceridemia. LDL-C was significantly higher in HAART/PI than in both currently untreated and HAART groups.

The average HDL-C concentration in uninfected patients was 1.37 ± 0.35 mmol/L. This is consistent with values described for the males of the same [13] or older age [14] in Australia and Europe [15]. All patients with HIV

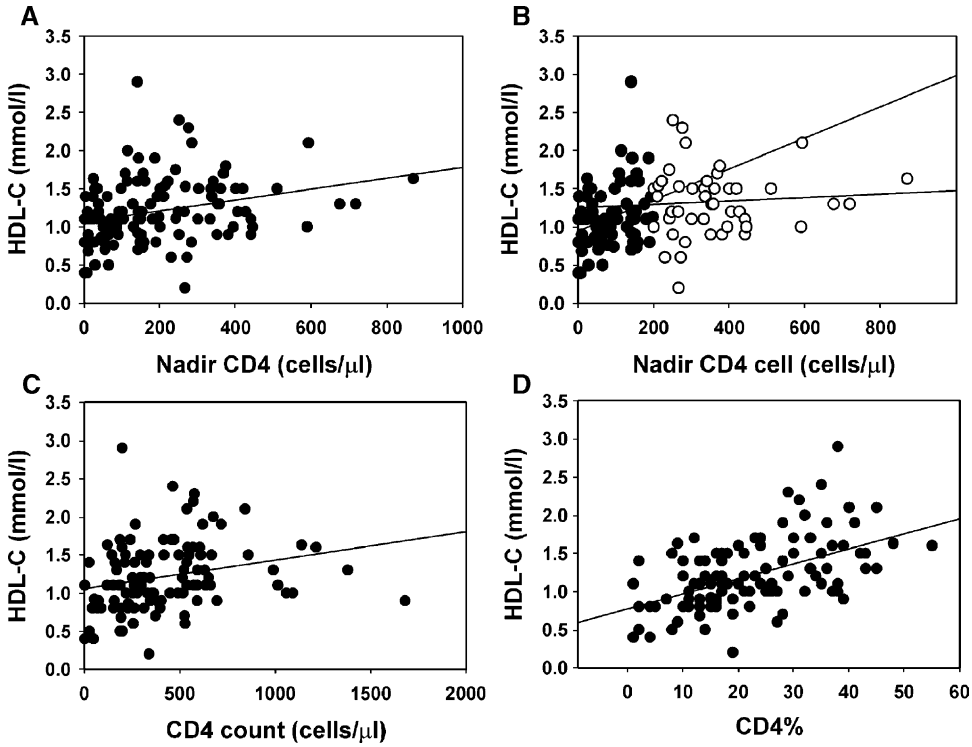

Fig. 2. Correlation between HDL-C levels and CD4 counts. A, Correlation between HDL-C levels and nadir CD4 cell count ($r = 0.28$, $P < .002$). B, Correlation between HDL-C levels and nadir CD4 counts more than and less than 200 cells/μL. The subjects were divided into groups with CD4 cell count above (○) and below (●) 200 cells/μL; statistically significant correlation remained only in subjects with CD4 cell count of less than 200 cells/μL ($r = 0.30$, $P < .01$). C, Correlation between HDL-C levels and current CD4 counts ($r = 0.247$, $P < .01$). D, Correlation between HDL-C levels and CD4 percentage ($r = 0.518$, $P < .001$).

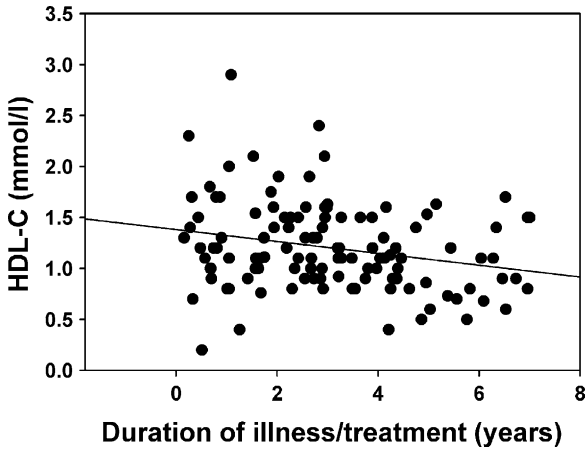

Fig. 3. Correlation among HDL-C levels, duration of the illness, and therapy. HDL-C negatively correlated with the duration of disease (for untreated patients) and disease + therapy (for treated patients) ($r = -0.24$, $P < .01$).

have marked hypoalphacholesterolemia compared with uninfected subjects. HDL-C levels were 22%, 11%, 14%, and 11% lower in HIV-untreated, HAART, HAART/PI, and HAART/PI/boost groups, respectively (Table 2).

3.2. Relationship between duration and severity of HIV infection and HDL-C levels

Two sets of values were used to analyze the relationship between severity of HIV infection and HDL-C levels. Firstly, nadir CD4 count and peak viral load were used as a value reflecting the severity of the disease at its peak. These values were correlated with HDL-C to establish a possible long-term effect of the infection at its peak. It was suggested by Hsue et al [16] that nadir CD4 count is an independent predictor of severity of atherosclerosis in patients with HIV. The average interval between measurements of nadir CD4 count, peak viral load, and lipid parameters was 761 days. Secondly, CD4 count, CD4 percentage, and viral load at the time of lipid measurements were correlated with HDL-C to establish the effect of the status of the infection.

The relationship between peak viral load and HDL-C levels is shown in Fig. 1A. HDL-C correlated negatively with peak viral load ($r = -0.23$, $P < .02$). The correlation was analyzed separately for viral loads below 5×10^5 to exclude a possibility of disproportional contribution to the correlation of few patients with very high viral load. The correlation remained statistically significant for subjects with viral loads below 5×10^5 ($r = -0.23$, $P < .03$) (Fig. 1A, inset).

HDL-C also positively correlated with nadir CD4 count (Fig. 2A) ($r = 0.28$, $P < .002$). When subjects were divided into 2 groups based on their CD4 cell count, the correlation remained significant only for subjects with nadir CD4 cell counts of less than 200 cell/μL ($r = 0.30$, $P < .01$), indicating a possible existence of a threshold in the relationship (Fig. 2B).

The viral loads measured at the time of lipid measurement were significantly lower than peak viral loads (Fig. 1A and B) despite that the distribution of HDL-C values did not change and there still was a statistically significant correlation between viral load and HDL-C (Fig. 1B, $r = -0.21$, $P < .03$). When HDL-C levels were related to the current values of CD4 count and CD4 percentage, again, a statistically significant correlation was observed (Fig. 2C, D). HDL-C correlated with the current CD4 count (Fig. 2C, $r = 0.247$, $P < .01$) and CD4 percentage (Fig. 2D, $r = 0.518$, $P < .001$). It has to be noted that there was a statistically significant correlation between nadir and current CD4 count ($r = 0.655$, $P < .001$) and between peak and current viral load ($r = 0.518$, $P < .001$) (not shown).

Finally, HDL-C negatively correlated with the duration of the disease and treatment ($r = -0.24$, $P < .01$) (Fig. 3).

In contrast to HDL-C, LDL-C levels only correlated negatively to peak viral load ($r = -0.25$, $P < .05$) (not shown).

3.3. Relationship among treatment regimen, duration, and HDL-C levels

To study the effect of treatment regimen and duration on HDL-C levels, we divided each of the subject groups into 2 subgroups based on the duration of the treatment: 1 to 3 years of therapy and 3 to 6 years of therapy. HDL-C levels in each subgroup were classified as low (<0.91 mmol/L), medium (0.91-1.37 mmol/L), or high (>1.37 mmol/L) HDL-C. The predetermined HDL-C classification levels were based on those from similar studies [17].

The distribution of subjects among subgroups is shown at Fig. 4. The following observations could be made from these data. First, treatment of patients with HIV with HAART (no PI) and HAART/PI resulted in a similar time-dependent decrease in the number of subjects with high HDL-C. Although in the patient group treated with

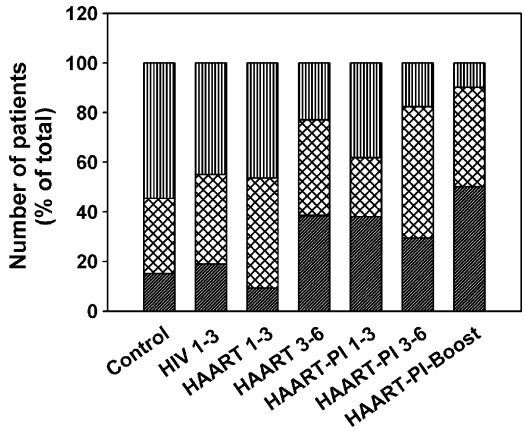

Fig. 4. Proportions of patients with low, medium, and high HDL-C levels according to therapy type and duration. Each of the subject groups was divided into 2 subgroups based on the duration of the treatment. HDL-C levels in each subgroup were classified as low (<0.91 mmol/L, lower part of the bar), medium (0.91-1.37 mmol/L, middle part of the bar), or high (>1.37 mmol/L, top part of the bar).

HAART, we found a proportional increase in the number of subjects in the low–HDL-C group, in the HAART/PI group, we found the increased proportion of patients in the medium–HDL-C group. Second, in the HAART/PI group, we found an increased proportion of patients in low–HDL-C group after 3 years, whereas the same values were observed in patients treated with HAART without PI only after 6 years of treatment. However, in patients treated for more than 6 years, there was little difference between the HAART and HAART/PI groups. Third, profound changes were found in the group treated with HAART/PI/booster (in which 2 PIs are used in conjunction). We found a 5-fold decrease in the proportion of subjects with high HDL-C and a 3-fold increase in those with low HDL-C in this group.

4. Discussion

This study provides evidence that hypoalphalipoproteinemia in patients with HIV is more likely to be caused by the HIV infection itself rather than by the therapy. This suggestion is consistent with the finding that HIV infection itself is an independent predictor of progression of atherosclerosis [16] and the recent finding of a negative correlation between viral load and HDL-C levels in treatment-naïve patients [18]. The following findings support this hypothesis. (1) HDL-C levels were reduced significantly in both currently untreated and all HIV-treated groups. The reduction in treated groups was half of that in the currently untreated subjects. This is consistent with the findings of van der Valk and Reiss [19] and Riddler et al [2]. (2) HDL-C correlates negatively with current and peak viral load and positively with current and nadir CD4 cell count and CD4 percentage. Importantly, the correlation remained significant for groups both with and without the HAART/PI category (data not shown). Thus, HDL-C levels are reduced proportionally to the severity of HIV infection with type of the therapy having a limited impact. These data are consistent with the findings of significant association between HDL-C and time of undetectable viral load [20]. It remains unresolved however whether a peak and a current severity of the disease have an independent impact on HDL-C. The correlation between HDL-C and current parameters of HIV infection may reflect the effect of current infection or can result from a correlation between peak and current parameters of the infection. (3) HDL-C negatively correlated with the duration of disease and treatment. (4) Changes in HDL-C levels were in discord with changes of TC and LDL-C. Changes in TC and LDL-C levels are likely to be caused by therapy, especially by PI-containing HAART regimens [21-23]. This is consistent with the findings of Riddler et al [2], who observed changes of LDL-C, but not HDL-C levels during various therapy regimens. (5) The proportion of subjects with low HDL-C levels increased with increased duration of the infection and the therapy. Patients treated with HAART for 3 to 6 years were 4 times more likely to have low HDL-C levels (<0.91) than those who had been on treatment for 1 to 3 years. Interestingly, patients treated for 3 to 6 years on HAART/PI were less likely to have low HDL-C than those treated for 1 to 3 years; however, they were half as likely to have high HDL-C.

Contradicting this conclusion, however, is the fact that subjects treated with HAART/PI-booster regimen had significantly lower proportion of subjects with high HDL-C and higher proportion of subjects with low HDL-C. The likely explanation is a higher prevalence of hypertriglyceridemia in this group; however, the direct contribution of this treatment regimen to hypoalphacholesterolemia cannot be excluded. An example of how treatment could interfere with HDL-C levels are recent findings of van der Valk et al [8], van Leth et al [9], and Negredo et al [10], describing return to normoalphalipoproteinemia in patients with HIV treated with nevirapine. The HDL-raising effect of nevirapine may be related to the retarded degradation of HDL [24]. No information is available on how nevirapine affects HDL-C levels in HIV-negative subjects; therefore, it is not clear if this effect is related to nevirapine antiretroviral properties. Nevertheless, these studies clearly demonstrate that HIV-induced hypoalphalipoproteinemia is reversible. No patients in our study were currently treated with nevirapine, and we did not observe an HDL-raising effect of treatment.

The suggestion that HIV infection is primarily responsible for hypoalphalipoproteinemia brings a question on how HIV infection may affect HDL-C levels. Liver cells are responsible for forming most HDL-C particles in plasma [25], with extrahepatic cells including lymphocytes contributing very little [26]. Although liver cells are not targets for viral replication, it is conceivable that a soluble protein secreted into plasma by HIV may reduce cholesterol mobilization from these cell types, reducing the pool of HDL-C. It has been recently suggested that the HIV-secreted transactivator protein (Tat) is linked with HIV-associated dementia, demonstrating the ability of HIV to be involved in pathological developments outside the infected host cell [27]. The effect may also be mediated by inducing general or local inflammatory responses [4] or other indirect effects of HIV on liver [28]. It is important to note that blood $CD4^+$ T-cell levels may not accurately represent the reduction of $CD4^+$ T cells in other tissues [29]. Therefore, correlations between CD4 cell count and HDL-C levels seen in this study may be an underestimate.

An important caveat of this study is that, being a retrospective study, it has limited access to data on the background clinical condition, medication not related to HIV treatment, and lifestyle of the subjects. Thus, we could not evaluate the possible influence of a number of confounding factors, such as insulin resistance, smoking, and drinking habits. We also were unable to evaluate the frequency of cardiac events in different groups of patients. It is also important to recognize that the HIV-untreated group was not treatment-naïve, but included previously treated patients

with an average duration of antiretroviral therapy exposure of 3.2 years. Hence, a long-term influence of the treatment cannot be excluded. However, the most important long-term lipid-related effect of the treatment, lipodystrophy, is mainly linked to the altered lipolysis of TGs without an evident effect on HDL metabolism [30]. Another drawback was that subjects in the uninfected group were on average 10 years younger than those in the HIV-infected groups. However, HDL-C levels measured by us and others [13] in 30-year-old men were similar to those in 60-year-old men [14], indicating that 10-year age difference would unlikely contribute to the differences in HDL-C levels between the groups.

In conclusion, it is reasonable to suggest that HIV infection is likely to play a major role in reduction of HDL-C levels, but this may be additionally affected by the use of antiretroviral therapy regimens including PIs over prolonged periods.

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