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Nevirapine Increases High-Density Lipoprotein Cholesterol Concentration by Stimulation of Apolipoprotein A-I Production

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Submitted for publication
Abstract

**Objective:** To identify the mechanism by which the non-nucleoside reverse transcriptase inhibitor nevirapine (NVP) increases high-density lipoprotein cholesterol in treatment-experienced HIV-1 infected patients.

**Methods:** Fourteen HIV-1 infected patients, with stably suppressed HIV-1 viral load (plasma HIV-1-RNA <50 copies/ml) using AZT/3TC/abacavir for ≥6 months, added NVP to their current antiretroviral regimen. Patients received a primed bolus infusion of the stable isotope L-[1-13C]-valine for 12 hours before, as well as 6 and 24 weeks after the addition of NVP in order to study apolipoprotein A-I (apoA-I) kinetics. Absolute production rate (APR) and fractional catabolic rate (FCR) of apoA-I were calculated using SAAM-II modelling. Major HDLc-modulating enzymes were also assessed.

**Results:** Plasma ApoA-I (14±4%) and HDLc (19±5%) levels increased significantly after 24 weeks of NVP treatment. Concomitantly, apoA-I production rate at 24 weeks increased by 16±6% (p=0.03), whereas apoA-I catabolism did not change. Slight increases were observed in activity of lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein.

**Conclusions:** NVP increases apoA-I production which contributes to the marked HDLc increase following introduction of NVP-containing regimens. Changes in apoA-I and HDLc plasma levels could not be accounted for by the observed changes in HDLc-modulating enzymes. In view of the potent anti-atherogenic effects of apoA-I, the observed apoA-I increase may contribute to the favorable cardiovascular profile of NNRTIs such as NVP.
Introduction

Combination antiretroviral therapy (CART) for HIV-1 infection, comprising protease-inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and nucleoside reverse transcriptase inhibitors, has led to a dramatic reduction in HIV-related morbidity and mortality. However, most of the PIs have been shown to induce lipid changes, predominantly increases in low-density lipoprotein cholesterol (LDLc) and/or triglycerides (TG) levels which have a pro-atherogenic effect [1]. The clinical impact of these PI-induced lipid changes has recently been substantiated, as HIV infected individuals treated with PI-based CART were shown to have an increased risk of developing cardiovascular disease (CVD), in part due to changes in lipids [2]. In contrast, in the same study, NNRTI-based CART, which is characterized by an increase in high-density lipoprotein cholesterol (HDLc)[3, 4], was not found to be associated with a greater CVD risk.

HDL is a key player in the anti-atherogenic reverse cholesterol transport. In addition, HDL has several other protective properties, including anti-inflammatory, anti-oxidative and anti-coagulant effects [5]. NNRTIs have consistently been associated with an increase in HDLc, the magnitude of which varies from 20% to 49% dependent upon the characteristics of the patient population investigated [3, 4, 6-8]. Overall, the HDLc increase has been shown to be most pronounced with the use of nevirapine as compared to efavirenz [3, 9]. Since it has proven difficult to develop selective HDLc increasing compounds [10], the significant increase in HDLc following NNRTIs is clearly of interest. The mechanisms, however, by which NNRTIs mediate these changes, have not yet been unraveled. While HDLc increase can be the result of increased production of apolipoprotein (apo) A-I [11], the most common mechanism responsible for increasing HDLc levels is due to decreased HDLc catabolism via modulation of transfer proteins involved in HDL-remodeling and degradation [12].

To evaluate the mechanism by which NVP increases HDLc, we measured the in vivo kinetics of apoA-I using stable isotope infusion both before, as well as 6 and 24 weeks after adding NVP to the existing antiretroviral regimen of HIV-1 infected patients, characterized by stably suppressed plasma HIV-1-RNA levels to < 50 copies/mL for ≥ 6 months. Concomitantly, we measured plasma lipid concentrations as well as the activity of transfer proteins involved in HDL-metabolism.
Methods

Between December 2003 and September 2005, 14 male HIV-1 infected patients 18 years or older were included in this multicenter trial. Patients were recruited from the outpatient clinics of the Academic Medical Center and the Onze Lieve Vrouwe Gasthuis hospital, both located in Amsterdam, and from the HIV outpatient clinic of the University College London in the United Kingdom. Patients were included if they had been using a triple combination drug regimen of zidovudine, lamivudine and abacavir for at least 6 months prior to study entry while having an undetectable viral load, i.e. plasma HIV-1 RNA ≤50 copies/mL, during that period. Patients were excluded from the study if they met any of the following criteria: previous exposure to NNRTI, fasting hypertriglyceridemia (>5.65 mmol/L), a documented history of diabetes mellitus or hypertension, or CD4 counts > 250 cells/mm³ (women) or > 400 cells/mm³ (men).

The study lasted for 24 weeks. None of the patients were taking medication known to affect plasma lipid levels. Compliance of study drug intake was verified by measuring NVP plasma levels at week 2, 6 and 24 of the study. The study protocol was approved by the institutional review boards of all 3 participating hospitals. All subjects provided written informed consent.

Experimental protocol

ApoA-I kinetic studies using stable isotopes were performed at 0 weeks (baseline), 6 weeks and 24 weeks after adding NVP to the antiretroviral regimen. After an overnight fast subjects were given a primed constant intravenous infusion of L-[1-13C]-valine. A bolus of 15 µmol per kilogram body weight of L-[1-13C]-valine was administered intravenously followed by a 12 hour constant infusion of 15 µmol/kg/h. Subjects remained fasting throughout the entire study day having free access only to drinking water. Blood samples (20 ml) were collected from an antecubital vein of the contralateral arm at regular intervals (-5 minutes, prior, and 15, 30 and 45 minutes as well as 1, 1.5, 2, 3, 4, 5, 6, 8, 10 and 12 hours after start of the isotope infusion) in tubes containing EDTA and heparin, respectively.

Plasma was separated by centrifugation at 3,500 rpm for 15 min at 4 °C. HDL was purified by means of density gradient ultracentrifugation. ApoA-I was purified by SDS-PAGE using 12.5% gels. ApoA-I bands were excised from the polyacrylamide gels, hydrolyzed in 12 N HCl at 110°C for 18 hours. The tracer-to-tracee ratio of L-(1-13C)-valine was measured on an isotope ratio mass spectrometer (Delta Plus, Thermo Scientific, Bremen Germany) at the different time points. The tracer-to-tracee ratio of α-ketoisovalerate in plasma was measured on a GC-MSD system (Agilent technologies, Palo Alto, CA, USA) as described previously [13].

Kinetic Analysis

Kinetic analysis of tracer-to-tracee ratios was achieved using computer software for Simulation, Analysis and Modeling (SAAM) II (version 1.2, University of Washington, Seattle, WA). HDL apoA-I kinetics were assessed using a one-compartmental model as described previously.
The fractional synthetic rate (FSR), i.e. the proportion of apoA-I entering the pool per unit of time (pool d^{-1}), and the absolute production rate (APR), i.e. the amount of apoA-I entering the pool per unit of time (mg kg^{-1} d^{-1}), were calculated. Absolute production rate was determined using the formula: 

\[
\text{APR} = (\text{FSR}) \times (\text{plasma apoA-I concentration}) \times (\text{plasma volume}) \times \frac{1000}{\text{body weight}}
\]

The apoA-I pool size was calculated by multiplying plasma apoA-I by 0.045 (L kg^{-1}), assuming a plasma volume of 4.5% of body weight [17]. The apoA-I pool was considered to be constant during the experiment. If one assumes steady-state conditions [17], FSR equals the fractional catabolic rate (FCR). To estimate the apoA-I synthesis we used the plateau of \(\alpha\)-ketoisovalerate tracer-to-tracee ratio as precursor pool enrichment. ApoA-I kinetics were calculated using the following function: 

\[
A(t) = Ap(1-\exp^{-k(t-d)})
\]

where \(A(t)\) is the apolipoprotein enrichment at time \(t\), \(Ap\) the enrichment at the plateau of the \(\alpha\)-ketoisovalerate, \(d\) the delay between the beginning of the experiment and the appearance of tracer in the apolipoprotein and \(k\) the fractional synthetic rate of the apolipoprotein [18].

**Lipid and lipoprotein modifying proteins and enzymes**

Phospholipid transfer protein (PLTP) activity was measured in a liposome vesicles-HDL system as described previously [19]. PLTP mass was determined as published previously [20]. Lecithin:cholesterol acyltransferase (LCAT) activity was determined using excess exogenous substrate containing \([\text{H}]\)-cholesterol as described [19, 21]. LCAT and PLTP activities were expressed as percentage of normal human reference plasma pool, which was set at 100% (equivalent to 65 nmol/ml plasma/h for LCAT and 13.9 \(\mu\)mol/ml per h for PLTP-activity). Cholesteryl ester transfer protein (CETP) concentration was determined using two-antibody ELISA. A combination of monoclonal antibodies TP1 and TP2 was employed as coating antibodies and monoclonal antibody TP20, labeled with digoxigenine, as the secondary antibody. CETP activity was determined after removal of VLDL+LDL from each sample, as published previously [22].

**Biochemical analyses**

Total cholesterol, HDLc and triglycerides were determined with commercially available enzymatic methods (Roche Diagnostics GmbH, Mannheim, Germany). LDLc was calculated using the Friedewald formula. ApoA-I and apoB were determined by nephelometric immunochemistry (Behring, Marburg, Germany).

**Statistical analysis**

In order to detect a change in FSR exceeding 20% (\(\alpha=0.01, \beta=0.2\)), at least 10 patients had to be included in the study. All analyses were performed using the percent change from baseline in all patients who took at least one dose of NVP (modified intention to treat). Initially the FSR measurements were planned to be tested only at week 0 and week 6. Therefore, changes in the FSR and APR outcomes from week 0 to week 6 were tested by the Wilcoxon signed rank test. After inclusion of the first 2 patients, the study protocol was amended to additionally
measure FSR and APR at week 24 given the delayed onset increase in HDLc and apoA-I. The changes over the full 24 week period were analyzed using a generalized linear model that takes repeated measurements into account (PROC MIXED in SAS). The most appropriate covariance structure was selected based on the likelihood ratio test using a restricted maximum likelihood model for estimations. In this model, missing data for a particular patient were imputed with a value based on the mean value of all available data of all patients for a given parameter, given the specified covariate structure.

If the outcome parameters were normally distributed a generalized linear model was used as described before. If they were not normally distributed, the Wilcoxon signed rank test was performed. Regarding the Wilcoxon signed rank test, missing data were treated as missing. The data in figures and tables are described as means and standard errors or as medians and interquartile ranges or numbers and percentages, as appropriate.

### Table 1  Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>NVP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (%)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Male, n(%)</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Age, years</td>
<td>44 (34-50)</td>
</tr>
<tr>
<td>Race, n(%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>13 (92.9)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179 (174-184)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>75.5 (69.0-92.0)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24 (22-26)</td>
</tr>
<tr>
<td>History of alcohol use, n(%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (14.3)</td>
</tr>
<tr>
<td>Yes</td>
<td>12 (85.7)</td>
</tr>
<tr>
<td>Smoking history, n(%)</td>
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<tr>
<td>Never smoked</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Ex smoker</td>
<td>7 (50.0)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>3 (21.4)</td>
</tr>
<tr>
<td>Ex smokers</td>
<td></td>
</tr>
<tr>
<td>years since stopping smoking</td>
<td>38 (19-43)</td>
</tr>
<tr>
<td>HIV RNA, log10 copies/mL</td>
<td>1.69 (1.69-2.12)</td>
</tr>
<tr>
<td>CD4+ count, cells/m³</td>
<td>515 (200-840)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range) unless specified otherwise. BMI denotes body mass index.
Results

Fourteen male HIV-1 infected patients were included, 13 of whom were Caucasian and 1 was black. The baseline characteristics of the patients are shown in Table 1. The median (interquartile range) age of the patients was 44 (34-50) years. Median HIV RNA at study-entry was 1.69 (1.69-2.12) log_{10} copies/mL, and the median CD4+ count was 515 (200-840) cells/mm³. Nevirapine had to be discontinued in one patient who experienced transaminase elevations which exceeded 5 times the upper limit of normal within the first 2 weeks of therapy. Discontinuation of nevirapine resulted in normalization of his liver transaminases within 3 weeks. Another patient had a rash which was assessed to be caused by the use of nevirapine leading to discontinuation of drug use.

ApoA-I kinetics

ApoA-I plasma levels increased from 1.19 g/L at baseline to 1.34 g/L at 24 weeks, a mean (±SE) increase of 14 ± 4% (p=0.005). We observed a gradual increase in mean apoA-I pool size between 6 and 24 weeks of therapy with NVP. When analyzing each patient separately all patients except one showed increases in apoA-I pool size at 24 weeks of NVP therapy (data not shown). ApoA-I FCR did not change significantly throughout the study (Figure 1).

The median (interquartile range) APR of apoA-I increased from 9.88 (8.20 to 10.59) mg/kg/day at baseline to 10.05 (8.78 to 11.23) mg/kg/day at 24 weeks of NVP treatment (16±6% increase; p=0.03). The absolute increase (SE) of apoA-I APR of 1.36 mg/kg/day was also significant using a mixed models analysis (p=0.02). At week 6 no significant change was seen in APR. We performed an exploratory post-hoc analysis comparing the changes between week 6 and week 24 showing an increase (interquartile range) of 22% (10% - 31%) using the wilcoxon signed rank test (p=0.0273).

| Table 2 Lipid changes after 6 and 24 weeks of nevirapine treatment |
|-----------------|----------------|-----------------|----------------|----------------|----------------|----------------|
| Baseline | Week 6 | Week 24 | % change bl to wk 6 | p-value week 6 | % change bl to wk 24 | p-value week 24 |
| TC, mmol/L | 4.16 (3.78-4.53) | 4.42 (4.24-4.84) | 4.42 (4.01-5.46) | 6 (4) | 0.163 | 11 (4) | 0.012 |
| HDLc, mmol/L | 1.13 (0.95-1.37) | 1.15 (1.06-1.34) | 1.38 (0.98-1.46) | 4 (4) | 0.334 | 19 (5) | 0.003 |
| LDLc, mmol/L | 2.41 (2.07-2.80) | 2.68 (2.34-2.93) | 2.86 (2.19-3.36) | 5 (5) | 0.370 | 13 (5) | 0.034 |
| TG, mmol/L | 1.35 (0.87-1.71) | 1.55 (1.14-2.06) | 1.04 (0.91-1.32) | 53 (36) | 0.166 | -6 (11) | 0.583 |
| ApoA-I, g/L | 1.19 (1.10-1.35) | 1.17 (1.07-1.39) | 1.34 (1.13-1.57) | -4 (7) | 0.570 | 14 (4) | 0.005 |
| ApoB, g/L | 0.83 (0.77-0.98) | 0.91 (0.75-0.98) | 0.94 (0.81-1.07) | -7 (7) | 0.323 | 9 (4) | 0.074 |

Data are presented as median (interquartile range). TC denotes total cholesterol, HDLc high-density lipoprotein cholesterol, LDLc low-density lipoprotein cholesterol, TG triglycerides, ApoA-I apolipoprotein A-I, and ApoB apolipoprotein B. % change bl to wk 6 denotes percent change from baseline to week 6 of nevirapine treatment, % change bl to wk 24 denotes percent change from baseline to week 24 of nevirapine treatment.

To convert cholesterol values from mmol/L to mg/dL multiply by 38.67. To convert triglycerides values from mmol/L to mg/dL multiply by 88.57. Lipid parameters were analyzed using an intention-to-treat analysis (n=14) in which missing values were imputed with a value based on the mean value of all available data of all patients for a given parameter.
**Lipids**

Baseline median (interquartile range) plasma total cholesterol, HDLc, LDLc and TG were 4.16 (3.78-4.53), 1.13 (0.95-1.37), 2.41 (2.07-2.80) mmol/L and 1.35 (0.87-1.74) mmol/L respectively. After 6 weeks of NVP treatment, no significant changes were observed in plasma levels of apoA-I or HDLc. At 24 weeks, however, HDLc levels had increased significantly by 19±5% to 1.38 (0.98-1.46) mmol/L (p=0.003) while LDLc increased by 13±5% to 2.86 (2.19-3.36) mmol/L. As a consequence, total cholesterol increased with 11±4%, while triglyceride levels remained unaffected (Table 2).

**Lipid and lipoprotein modifying proteins and enzymes**

Table 3 shows data on the effect of nevirapine treatment on lipid and lipoprotein modifying proteins and enzymes. CETP activity and LCAT activity increased significantly at 24 weeks. PLTP activity was unaffected during the entire treatment period (Table 3).

Data are presented as mean percent change. Bars represent standard errors.

* not significant
# p=0.03
Discussion

To our knowledge the present study is the first to show that in patients receiving NVP, the increase in HDLc and its major apolipoprotein, apoA-I, results from a stimulation of the apoA-I production rate. In contrast, apoA-I catabolism remained largely unaffected. In view of the potent anti-atherogenic effect of apoA-I, this effect is likely to contribute to the lack of adverse cardiovascular effects of NNRTI as opposed to PI-containing CART regimens in HIV-1 infected subjects.

ApoA-I kinetics

The observed absolute production rates of apoA-I at baseline are comparable with the production rates reported in healthy individuals [18, 23, 24], subjects with metabolic syndrome [25], and CETP-inhibitor treated subjects [26, 27]. After 24 weeks of NVP treatment, apoA-I APR had increased significantly by 16%. Although the latter may seem modest, it compares favorably to changes reported for other drugs. Peroxisome proliferator-activated receptor alpha (PPARα) stimulation has been reported to increase APR by approximately +10% [28]. In this respect, the effect of NVP clearly exceeds that of fibrates, which have been designed as lipid modulating drugs targeting low HDLc and high TG levels [29]. The fractional catabolic rate of apoA-I remained unchanged. Of note, a constant fractional clearance combined with an increased pool size indicates that the absolute clearance rate of apoA-I is also increased. Since a primary increase in absolute clearance, however, cannot account for an increased apoA-I plasma concentration, the change in apoA-I clearance likely reflects a secondary increase following increased apoA-I production.

The mechanism of action leading to enhanced apoA-I production cannot be directly addressed by the present study. In comparison, several PPARα agonists are being developed which mainly increase production of ApoA-I as well as of ApoA-II [30] [31], but also decrease plasma TG levels by decreasing apoCIII and lipoprotein lipase expression. However in the present study no obvious changes in TG metabolism have been observed which is not in favor for a PPAR alpha mediated process. Alternatively, apoA-I can be increased by stimulating the expression of the nuclear receptor, liver X receptor (LXR). These LXR agonists, however, also strongly affect hepatic TG metabolism, as a direct consequence of fatty acid synthase stimulation [32], resulting in a strong increase in hepatic secretion of TG-rich lipoproteins. In view of the absence of any effect on triglycerides, a major role for LXR activation also does not seem to be a likely explanation for the present results. Finally, 1-hydroxyalkyl-3-phenylthioureas, compounds based on benzodiazepines, have also been shown to increase apoA-I production through a non-PPAR/non-LXR mechanism [33, 34]. The mechanism of action for these compounds however has not been elucidated. Clearly, further research is needed to identify the exact molecular mechanism contributing to the increased apoA-I production rates when various drugs are used.
Table 3  Percent change in activity and/or mass of HDL-modifying enzymes after 24 weeks of nevirapine treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% change from baseline at week 24</th>
<th>p-value week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCATa</td>
<td>9 (3)</td>
<td>0.02</td>
</tr>
<tr>
<td>CETPm</td>
<td>10 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>CETPa</td>
<td>14 (4)</td>
<td>0.003</td>
</tr>
<tr>
<td>PLTPm</td>
<td>-7 (4)</td>
<td>NS</td>
</tr>
<tr>
<td>PLTPa</td>
<td>4 (2)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are presented as mean (±SE). LCATa denotes lecithin:cholesterol cytltransferase activity, NS not significant, CETPm cholesteryl ester transfer protein mass, CETPa cholesteryl ester transfer protein activity, PLTPm phospholipid transfer protein mass, PLTPa phospholipid transfer protein activity

**NVP and HDL increase**

We previously observed that changes in HDLc reached steady state approximately 24 weeks following NVP initiation [4, 35]. In the present study, a 19% increase in HDLc levels and a 14% increase in plasma apoA-I levels were observed 24 weeks after NVP initiation. These findings are in accordance with previous studies in CART-experienced patients in whom replacement of PIs with NVP was associated with a 20% HDLc increase [6, 8]. In contrast, early and larger increases in HDLc up to 49% have been reported following the initiation of NVP in antiretroviral naïve subjects [3]. Since HDL is an inverse acute phase reactant, a substantial part of the increase in treatment naïve patients has been attributed to a ‘return-to-health’ phenomenon following effective first time suppression of HIV-1 infection [36]. Interestingly, the observation that 6 weeks of NVP had not yet significantly affected HDLc levels suggests the absence of a ‘return-to-health’ phenomenon in the present study. The latter is in line with the fact that we only included patients with durably suppressed HIV-1 infection. However, it should be noted that the apparent decrease in APR at week 6 was predominantly caused by a single individual, showing an unexplained profound decrease. Exclusion of this subject resulted in a more stable pattern of a progressive increase in APR. Conversely, the onset of HDLc increase between 6-24 weeks following NVP initiation implies a delayed mechanism of action. However, since the exact mechanism by which NVP elicits HDLc increase cannot be addressed in the present in vivo study, further experimental studies are required to elucidate the causes for the late onset.

**Lipid and lipoprotein modifying proteins and enzymes**

Changes in HDLc levels can be a result of changes in the activity of lipid and lipoprotein modifying proteins and enzymes [12]. We measured several principal parameters that are known to affect changes in HDL metabolism. At 24 weeks, we observed a modest increase in both LCAT and CETP-activity. While increased LCAT activity can be expected to increase HDLc, an increased CETP activity causes a decrease in HDLc. These minor changes should, however, not be used to delineate causal relations with regard to systemic HDLc concentrations in the patients studied.
Clinical implications
The importance for cardiovascular prevention in HIV-infected patients has been widely acknowledged. Recent data from the DAD study support the need to appropriately manage traditional cardiovascular risk factors in HIV, and to refrain from using PI-based CART regimens in patients at increased CVD risk whenever this is possible without jeopardizing appropriate and sustained control of HIV replication [2]. The DAD study also suggested that NNRTI-based regimens may be an appropriate alternative in that context. The SMART study, which looked at the effect of treatment interruption on patient’s health, supported this notion in a recent presentation of their data [37]. It was demonstrated that patients on NNRTI therapy (n=1980) had a hazard ratio (treatment interruption arm/continuous therapy arm) for CVD events of 2.07 (0.89-4.84). The risk appeared to be exclusively related to patients in the drug conservation arm. In further analysis the SMART study also showed that patients in the treatment interruption arm suffered the greatest decline in HDLc, especially if they had been on NNRTI therapy at the time they entered the study. This leads to the speculation that the mechanism of increased risk for CVD in patients taking NNRTIs in the SMART study is the precipitous decline in HDLc which occurs when these drugs are stopped.

Study limitations
In the SMART study increased levels of IL-6 and amyloid P in the drug conservation group were associated with increased incidence of CVD [38] Whether these pro-inflammatory changes are specifically inhibited by NVP and may also contribute to cardiovascular protection should be investigated in future studies. In the present study, we only evaluated the effect of NVP on apoA-I kinetics. As such, it remains to be established whether other NNRTIs, such as EFV, exert similar effects.

NVP also increase pro-atherogenic lipid fractions. However, the numerically greater increase in HDL and apoAI (19% and 14%, respectively), as compared to LDL and apoB (13% and 9% respectively) can be expected to provide an overall benefit on cardiovascular risk, which has been substantiated in the DAD study [2]. In line, a net anti-atherogenic effect of NVP is supported by recent findings from our group, in which NVP was associated with less thickening of carotid intima-media thickness, an established surrogate marker for CVD, when compared with the use of protease inhibitors in HIV-1 infected patients [39]

Conclusion
The present study shows a clear increase in plasma levels of HDLc and apoA-I following the administration of nevirapine in HIV-1 infected patients with durable virus suppression during prior treatment with a combination of zidovudine, lamivudine and abacavir. These effects were shown to result from an increased production of apoA-I. The finding of a stimulation of apoA-I production by nevirapine may assist ongoing efforts aimed at unraveling novel therapeutics to increase apoA-I/HDLc levels in patients at increased cardiovascular risk in general.
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Reference List


