Objective—The purpose of this study was to investigate the mechanism by which the nonnucleoside reverse transcriptase inhibitor (NNRTI) nevirapine (NVP) increases high-density lipoprotein cholesterol (HDLc) in treatment-experienced human immunodeficiency virus-1 (HIV-1)-infected patients.

Methods and Results—Twelve HIV-1 infected patients, with stably suppressed HIV-1 viral load 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 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 modeling. Major HDLc-modulating enzymes were assessed. Plasma apoA-I and HDLc levels increased significantly after 24 weeks of treatment by, respectively, 13±4% (P=0.01) and 16±6% (P=0.015). Concomitantly, apoA-I production rate at 24 weeks increased by 17±7% (P=0.04). ApoA-I catabolism did not change. A modest increase of lecithin:cholesterol acyltransferase and cholesteryl ester transfer protein activity was observed.

Conclusions—NVP increases apoA-I production, which contributes to the HDLc increase after introduction of NVP-containing regimens. In view of the potent antiatherogenic effects of apoA-I, the observed increase may contribute to the favorable cardiovascular profile of NVP. (Arterioscler Thromb Vasc Biol. 2009;29:1336-1341.)

Key Words: nevirapine ■ high-density lipoprotein cholesterol ■ apolipoprotein A-I ■ metabolism ■ stable isotopes
patients interrupting NNRTIs may be causally related to the increased CVD risk in these patients.

HDL is a key player in the antiatherogenic reverse cholesterol transport. In addition, HDL has other protective properties.6 NNRTIs have consistently been associated with an increase in HDLc, the magnitude of which varies from 20% to 49% dependent on the characteristics of the patient population investigated4,7–9 Overall, the HDLc increase has been shown to be most pronounced with the use of nevirapine (NVP) as compared to efavirenz.3,10 Because it has proven difficult to develop selective HDLc increasing compounds,11 the increase in HDLc after NNRTIs is of clear interest. The mechanisms, however, by which NNRTIs mediate these changes have not been addressed. Although HDLc increase can be the result of increased production of apolipoprotein (apo) A-I,12 the most common mechanism responsible for increasing HDLc is attributable to decreased HDL catabolism via modulation of transfer proteins involved in HDL remodeling and degradation.13

To evaluate the mechanism by which NVP increases HDLc, we measured the in vivo kinetics of apoA-I using stable isotope infusion of L-[1-13C]-valine. A bolus of (apo) A-I12, the most common mechanism responsible for changes have not been addressed. Although HDLc increase can be the result of increased production of apolipoprotein (apo) A-I, the most common mechanism responsible for increasing HDLc is attributable to decreased HDL catabolism via modulation of transfer proteins involved in HDL remodeling and degradation.13

To evaluate the mechanism by which NVP increases HDLc, we measured the in vivo kinetics of apoA-I using stable isotope infusion of L-[1-13C]-valine. A bolus of (apo) A-I12, the most common mechanism responsible for increasing HDLc is attributable to decreased HDL catabolism via modulation of transfer proteins involved in HDL remodeling and degradation.13

**Experimental Protocol**

**Methods**

Between December 2003 and September 2005, 12 male HIV-1–infected patients 18 years or older were included. Patients were recruited from the outpatient clinics of the Academic Medical Center and the Onze Lieve Vrouwe Gasthuis hospital, Amsterdam, and 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 before study entry while having an undetectable viral load, ie, plasma HIV-1 RNA ≤50 copies/mL. Patients were excluded in case of: previous exposure to NNRTI; fasting hypertriglyceridemia (>225 mg/dL), use of lipid-lowering drugs, diabetes mellitus, or hypertension.

After the introduction of new guidelines on CD4 cell count, only men with CD4 >400 cells/mm³ were included. Compliance of study drug intake was verified by measuring NVP plasma levels. The study protocol was approved by the institutional review boards of all 3 participating hospitals. All subjects provided written informed consent.

**Statistical Analysis**

All analyses were performed using the percent change from baseline in all subjects who completed the study on NVP (as treated analysis). The changes in FSR and APR at baseline, week 6, and week 24 were analyzed using a linear model that takes repeated measurements into account (PROC MIXED in SAS). The most appropriate covariate structure was selected based on the likelihood ratio test using a restricted maximum likelihood model for estimations. If the outcome parameters were normally distributed a linear model was used. If they were not normally distributed, the Wilcoxon signed rank test was used. Regarding the Wilcoxon signed rank test, missing data were treated as missing. The data in the figure and tables are described as medians and interquartile ranges or numbers and percentages, as appropriate.

**Results**

The baseline characteristics of the 12 HIV-1–infected patients that entered the study are listed in Table 1. The median (interquartile range) age of the patients was 43 (33 to 49) years. HIV RNA was ≤50 copies/mL in all patients at baseline visit. Median CD4+ count was 433 (373–718) cells/mm³ with the majority of patients (n = 10) having been included before the update CD4+–exclusion criterion (<400 cells/mm³). During the course of the study there were no significant changes in BMI, smoking behavior, or alcohol consumption (data not shown). Eight patients completed the entire study protocol, whereas 4 patients were excluded from analysis because of discontinuation of nevirapine within 3 weeks in 2 patients and 12.5% gels under nonreducing conditions. 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) at the different time points. The tracer-to-tracee ratio of α-ketoisovalerate in plasma was measured on a GC-MSD system (Agilent technologies) as described previously.14
hepatic transaminase elevations and development of a rash, both transient. One patient lost stable viral suppression (HIV RNA copies/mL from 50 at screening; 285 during the first infusion with subsequent further increase to 1069 copies/mL). The fourth patient withdrew informed consent after the 6th week because of personal reasons.

**ApoA-I Kinetics**

Median 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 13% (P = 0.010). When analyzing each patient separately, all patients except 1 showed increases in apoA-I pool size at 24 weeks of NVP therapy (supplemental Table I). ApoA-I FCR did not change significantly throughout the study (Figure).

The median (interquartile range) APR of apoA-I increased from 9.88 (8.03 to 10.59) mg/kg/d at baseline to 10.05 (8.78 to 11.23) mg/kg/d at 24 weeks of NVP treatment (a mean [±SE] increase of 17±7%; P = 0.04; Figure). The absolute increase of apoA-I APR of 1.42 (0.36 to 1.66) mg/kg/d was also significant using a mixed models analysis (P = 0.04). At week 6 no significant change was seen in APR. An exploratory posthoc analysis comparing APR at week 6 and 24 revealed an increase of 23%±8% (P = 0.01).

**Lipids**

Baseline median (interquartile range) plasma total cholesterol, HDLc, LDLc, and TG were 159 (144–175), 44 (37–53), 92 (75–108), and 120 (75–191) mg/dL, respectively. After 6 weeks of NVP treatment, no significant changes were observed in plasma levels of apoA-I or HDLc. At 24 weeks, HDLc levels had increased significantly by 16±6% to 53 (39–55) mg/dL. (P = 0.015), whereas LDLc increased by 13±7% to 109 (85–116) mg/dL. Total cholesterol increased with 10±4%, whereas triglyceride levels remained unaffected (Table 2).

**HDL-NMR**

HDL particle number and HDL cholesterol increased significantly during the 24 weeks of NVP treatment by, respectively, 7.9% (P = 0.021) and 19.4% (P = 0.002; Table 3). With respect to the distribution of particle size, predominantly the large HDL particles increased by 104%, whereas medium and small-sized HDL particles remained unaffected.

**Lipid and Lipoprotein Modifying Proteins and Enzymes**

Table 4 shows the effect of NVP treatment on lipid and lipoprotein modifying proteins and enzymes. CETP activity and LCAT activity increased modestly at 24 weeks. PLTP activity was unaffected during the entire treatment period (Table 4).

**Discussion**

In the present study we show that in patients receiving NVP, the increase in HDLc and its major apolipoprotein, apoA-I, is associated with an increased apoA-I production rate, whereas apoA-I catabolism remained unchanged. In view of the potent antiatherogenic 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.

**ApooA-I Kinetics**

The observed absolute production rates of apoA-I at baseline are comparable with production rates reported in healthy individuals,19–21 subjects with metabolic syndrome,22 and CETP-inhibitor treated subjects.23–24 After 24 weeks of NVP treatment, apoA-I APR had increased significantly by 17%. Although such an increase is modest, it compares favorably to changes reported for targeted HDL-modulating drugs. For example, peroxisome proliferator-activated receptor alpha (PPARα) stimulation increased APR by 10%.25 The effect of NVP also exceeds that of fibrates, which have been designed as lipid modulating drugs targeting low HDLc and high TG levels.26 The fractional catabolic rate of apoA-I did not change significantly. A constant fractional clearance combined with an increased pool size automatically indicates an increased absolute production rate of apoA-I. However, because a primary increase in absolute clearance is incompatible with an increase in apoA-I plasma levels, the change in absolute apoA-I clearance most likely reflects a secondary increase after increased apoA-I production. A direct effect of NNRTIs on hepatic apoA1 production was recently corroborated by Tohyama et al.27 These investigators showed in mice that NNRTIs, both NVP as well as efavirenz, elicited increased apoA-I mRNA expression in the liver, which corresponded to increased circulating apoA-I levels.27 These findings provide a biological substrate for the increased APR observed in HIV patients treated with NVP in our study.

**NVP and HDL Increase**

We previously observed that changes in HDLc reached steady state approximately 24 weeks after NVP initiation.4,28 In the present study, a 16% increase in HDLc levels and a 13% 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 HDLc increase around 20% which persisted for at least 2 years.7,9,29 In contrast, early and larger increases in HDLc up to 49% have been reported after the initiation of NVP in antiretroviral naïve subjects.1 Because 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 after effective first-time suppression of HIV-1 infection.30 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. The onset of HDLc increase between 6 to 24 weeks after NVP initiation implies a delayed mechanism of action. The reason for the delayed onset requires further experimental studies.

**Table 2. Lipid Changes After 6 and 24 Weeks of Nevirapine Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 6</th>
<th>Week 24</th>
<th>% Change bl to wk 6</th>
<th>P Value 6</th>
<th>% Change bl to wk 24</th>
<th>P Value 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC, mg/dL</td>
<td>159.3</td>
<td>167.4</td>
<td>170.2</td>
<td>4 (4)</td>
<td>0.449</td>
<td>10 (4)</td>
<td>0.036</td>
</tr>
<tr>
<td>HDLc, mg/dL</td>
<td>43.7</td>
<td>44.5</td>
<td>53.4</td>
<td>5 (5)</td>
<td>0.325</td>
<td>16 (6)</td>
<td>0.015</td>
</tr>
<tr>
<td>LDLc, mg/dL</td>
<td>92.0</td>
<td>97.8</td>
<td>108.7</td>
<td>2 (5)</td>
<td>0.782</td>
<td>13 (7)</td>
<td>0.075</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>119.6</td>
<td>137.3</td>
<td>87.7</td>
<td>54 (43)</td>
<td>0.237</td>
<td>-7 (13)</td>
<td>0.633</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.19</td>
<td>1.17</td>
<td>1.34</td>
<td>-4 (8)</td>
<td>0.612</td>
<td>13 (4)</td>
<td>0.010</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>0.83</td>
<td>0.79</td>
<td>0.91</td>
<td>-9 (8)</td>
<td>0.284</td>
<td>9 (5)</td>
<td>0.126</td>
</tr>
<tr>
<td>ApoB/ApoA-I ratio</td>
<td>0.66</td>
<td>0.62</td>
<td>0.65</td>
<td>-7 (3)</td>
<td>0.041</td>
<td>-0.1</td>
<td>0.991</td>
</tr>
</tbody>
</table>

Table 3: HDL-NMR Changes After 6 and 24 Weeks of Nevirapine Treatment

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 6</th>
<th>Week 24</th>
<th>% Change bl to wk 6</th>
<th>P Value 6</th>
<th>% Change bl to wk 24</th>
<th>P Value 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL particles, umol/L</td>
<td>28.3</td>
<td>31.3</td>
<td>4.7</td>
<td>26.3 (3.9)</td>
<td>0.263</td>
<td>7.2 (2.68)</td>
<td>0.021</td>
</tr>
<tr>
<td>Large, umol/L</td>
<td>4.8</td>
<td>6.3</td>
<td>63.0</td>
<td>56.3 (56.3)</td>
<td>0.300</td>
<td>104.7 (50.5)</td>
<td>0.077</td>
</tr>
<tr>
<td>Medium, umol/L</td>
<td>6.9</td>
<td>8.8</td>
<td>31.4</td>
<td>37.4 (37.4)</td>
<td>0.434</td>
<td>17.9 (26.0)</td>
<td>0.517</td>
</tr>
<tr>
<td>Small, umol/L</td>
<td>19.5</td>
<td>17.8</td>
<td>-5.2</td>
<td>9.9 (9.9)</td>
<td>0.616</td>
<td>-7.2 (10.4)</td>
<td>0.508</td>
</tr>
<tr>
<td>HDL size, nm</td>
<td>8.7</td>
<td>8.9</td>
<td>2.6</td>
<td>0.9 (0.9)</td>
<td>0.026</td>
<td>2.1 (0.9)</td>
<td>0.052</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>40.3</td>
<td>46.8</td>
<td>13.7</td>
<td>(4.7)</td>
<td>0.022</td>
<td>19.4 (4.2)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data (n=8) are presented as median (interquartile range) and percentages as estimated means (standard error). TC indicates total cholesterol; HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B. % change bl to wk 6 denotes percent change from baseline to week 6 of nevirapine treatment, and % change bl to wk 24 denotes percent change from baseline to week 24 of nevirapine treatment.
HDL-NMR Changes
The observed increase in HDLc is predominantly attributable to an increase in the large HDL particles with stable levels of intermediate and small HDL particles. Combined with the increased apoA-I production rate, these data imply that maturation of HDLc is unimpaired in these patients, because newly formed prebeta HDL particles are rapidly converted to spherical large HDL particles by a concerted action of ABCA1 and LCAT, respectively.31,32 These data are in full concordance with observations in mice, in which NNRTI also result in a selective increase in large HDL particles.27

Lipid and Lipoprotein Modifying Proteins and Enzymes
Changes in HDLc levels can also be a result of changes in the activity of lipid and lipoprotein modifying proteins and enzymes.13 Increased activity of LCAT as well as decreased activity of PLTP and CETP results in HDLc increase. At 24 weeks, we observed a modest but significant increase in both CETP and LCAT-activity. Because increased CETP activity is associated with decreased HDLc levels, CETP is not involved in the HDLc increase after NVP. In contrast, increased LCAT activity does associate with an HDLc increase. Whereas the increased LCAT activity may have contributed, an increased apoA-I production rate is not a recognized feature of increased LCAT activity. Therefore, factors beyond changes in LCAT are likely to have contributed to the increase in APR.

Besides an increase in HDLc and apoA-I we also observed a decrease in plasma triglycerides at 24 weeks. Although not significant, an improved hydrolysis of triglyceride-rich lipoproteins may affect the formation of large HDL particles.33 However, we observed no relation between changes in plasma triglycerides and changes in HDLc in the present study. Finally, newly-synthesized lipid-poor apoA-I is rapidly stabilized by ABC-A1-mediated efflux of phospholipids. To evaluate a potential role of NVP-mediated ABC-A1 stimulation, Mukhamedova et al recently studied the impact of different antiretroviral agents, among which was NVP, on ABCA1 mediated macrophase cholesterol efflux.34 Because no changes in ABCA1 functionality was observed, the later is unlikely to have contributed to the HDL-c increase in the present study.

Study Limitations
In the present study, several issues deserve closer attention. First, because we only evaluated the effect of NVP on apoA-I kinetics, it remains to be established whether other NNRTIs, such as EFV, exert similar effects. In fact, experimental data from Tohyama et al imply that the impact of NNRTI may be a class rather than a compound effect.27 Second, the study design used, with repetitive infusions in patients serving as their own controls, is not a randomized clinical trial because all subjects were treated with NVP. However, in view of the consistency of our findings with recent experimental data,27 our findings provide insight into the mechanism of HDLc increase in patients. Finally, besides increasing HDLc and apoA-I, NVP also increased proatherogenic apoB containing lipid fractions, which makes it difficult to predict its effect on atherogenis. However, recent analyses in the DAD study as well as cross-sectional data obtained at our center show that, in spite of a stable apoBrapoA-I ratio, the net effect of NVP favors the antiatherogenic side. Thus, use of NNRTIs was associated with thinner IMT and decreased risk of myocardial infarction compared to PI based regimens.2,29

Acknowledgments
We thank our trial nurse Hans-Erik Nobel for administrative support, Joram van Miert for his assistance with the kinetics, Geesje Dallinga and Jan Albert Kuivenhoven for laboratory advice, and Matti Jauhiainen for the PLTP measurements.

Sources of Funding
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Disclosures
Dr Reiss has received honoraria from companies including Boehringer Ingelheim, Hoffmann LaRoche, Merck, Tibotec, Gilead Sciences, GlaxoSmithKline, Pfizer, Bristol Myers Squibb, and Theratechnologies. Dr Storfer is employed by Boehringer Ingelheim.

References

Table 4. Percent Change in Activity and/or Mass of HDL-Modifying Enzymes After 6 and 24 Weeks of Nevirapine Treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>% Change From Baseline at Week 6</th>
<th>P Value</th>
<th>% Change From Baseline at Week 24</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LCATa</td>
<td>8 (5) NS</td>
<td>0.02</td>
<td>10 (3) NS</td>
<td></td>
</tr>
<tr>
<td>CETPm</td>
<td>8 (10) NS</td>
<td></td>
<td>10 (9) NS</td>
<td></td>
</tr>
<tr>
<td>CETPa</td>
<td>9 (4) NS</td>
<td>0.007</td>
<td>14 (4) NS</td>
<td></td>
</tr>
<tr>
<td>PLTPm</td>
<td>−6 (2) 0.01</td>
<td>NS</td>
<td>−6 (4) NS</td>
<td>NS</td>
</tr>
<tr>
<td>PLTPa</td>
<td>4 (3) NS</td>
<td>NS</td>
<td>4 (3) NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data (n=8) are presented as estimated means (standard error). LCATa indicates lecithin:cholesterol acyltransferase activity; NS, not significant; CETPa, cholesteryl ester transfer protein activity; CETPm, cholesteryl ester transfer protein mass; PLTPm, phospholipid transfer protein mass; PLTPa, phospholipid transfer protein activity.


Nevirapine Increases High-Density Lipoprotein Cholesterol Concentration by Stimulation of Apolipoprotein A-I Production
Remco Franssen, Raaj R. Sankatsing, Elly Hassink, Barbara Hutten, Mariette T. Ackermans, Kees Brinkman, René Oesterholt, Alejandro Arenas-Pinto, Stephen P. Storfer, John J. Kastelein, Hans P. Sauerwein, Peter Reiss and Erik S. Stroes

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Supplement Material

**Lipid and lipoprotein modifying proteins and enzymes**

Phospholipid transfer protein (PLTP) activity was measured in a liposome vesicles-HDL system as described previously. PLTP mass was determined as published previously. Lecithin:cholesterol acyltransferase (LCAT) activity was determined using excess exogenous substrate containing $[^3]$H]-cholesterol as described. 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 a double-antibody sandwich enzyme-linked immunosorbent assay. A combination of monoclonal antibodies TP1 and TP2 was employed as coating antibodies and monoclonal antibody TP20, labeled with digoxigenine, as the secondary antibody (all antibodies were supplied by the University of Ottawa). CETP activity was determined after removal of VLDL+LDL from each sample, as published previously.

**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).

**NMR**

Lipoprotein subclass particle concentrations and average size of particles were measured by proton NMR spectroscopy (Lipo-Science, Raleigh, North Carolina) as previously described.
In brief, we obtained particle concentrations of lipoprotein subclasses of different size directly from the measured amplitudes of their spectroscopically distinct lipid methyl group NMR signals. Summation of the HDL subclass levels provides total HDL particle concentration. We calculated NMR spectroscopy–measured HDL size as the mass-weighted average diameter of the HDL particles in a particular plasma sample. The average HDL particle size is computed as the sum of the diameter of each subclass multiplied by its relative mass percentage as estimated from the amplitude of its measured NMR signal.

Reference List


Supplemental table I. Individual data on changes in apolipoprotein A-I absolute production rate after 6 and 24 weeks of nevirapine treatment

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Baseline</th>
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<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.2</td>
<td>8.7</td>
<td>10.1</td>
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<tr>
<td>2</td>
<td>4.8</td>
<td>9.1</td>
<td>8.3</td>
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<td>3</td>
<td>9.5</td>
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<td>4</td>
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<td>9.1</td>
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<td>8</td>
<td>12.2</td>
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