Atherogenic Dyslipidemia in HIV-Infected Individuals Treated With Protease Inhibitors

Daniel Périard, MD; Amalio Telenti, MD; Philippe Sudre, MD, PhD; Jean-Jacques Cheseaux, MD; Patricia Halfon, MD; Marianne J. Reymond, PhD; Santica M. Marcovina, PhD; Michel P. Glauser, MD; Pascal Nicod, MD; Roger Darioli, MD; Vincent Mooser, MD, for the Swiss HIV Cohort Study

Methods and Results—Plasma lipoprotein levels were quantified in 93 HIV-infected adults receiving PIs. Comparison was done with pretreatment values and with 28 nonPI-treated HIV-infected subjects. An elevation in plasma cholesterol levels was observed in all PI-treated groups but was more pronounced for ritonavir (2.0±0.3 mmol/L [mean±SEM], n=46, versus 0.1±0.2 mmol/L in nonPI treated group, P<0.001) than for indinavir (0.8±0.2 mmol/L, n=26, P=0.03) or nelfinavir (1.2±0.2 mmol/L, n=21, P=0.01). Administration of ritonavir, but not indinavir or nelfinavir, was associated with a marked elevation in plasma triglyceride levels (1.83±0.46 mmol/L, P=0.002). Plasma HDL-cholesterol levels remained unchanged. Combination of ritonavir or nelfinavir with saquinavir did not further elevate plasma lipid levels. A 48% increase in plasma levels of lipoprotein(a) was detected in PI-treated subjects with pretreatment Lp(a) values >20 mg/dL. Similar changes in plasma lipid levels were observed in 6 children receiving ritonavir.

Conclusions—Administration of PIs to HIV-infected individuals is associated with a marked, compound-specific dyslipidemia. The risk of pancreatitis and premature atherosclerosis due to PI-associated dyslipidemia remains to be established. (Circulation. 1999;100:700-705.)

Key Words: AIDS • atherogenesis • drugs • hyperlipoproteinemia • lipoproteins
Methods

Patients

All HIV-infected individuals who attended the local HIV-outpatient clinic between February 1 and March 31, 1998, were informed about the study (n = 157). A total of 129 individuals were treated with ritonavir, indinavir, or nelfinavir, alone or in combination with saquinavir, at doses recommended by the manufacturers. Only PI-treated subjects who had been on the same PI-regimen for at least 4 consecutive weeks before information visit were invited to participate. Thirty-six PI-treated individuals were not eligible or declined participation to the study, so that 93 PI-treated persons were included in the study. Among the 157 contacted HIV-infected individuals, 28 patients had not been given PI therapy because of less advanced and more slowly progressive disease (CD4 cell count >500 cells/mm$^3$) (n=21) or refusal of PI therapy (n=7). These individuals were also recruited and served as a comparison group. All participants gave their informed consent. Each subject completed a structured questionnaire focusing on cardiovascular risk factors as well as personal and family history of diabetes, lipid disorders, or cardiovascular diseases. None were on lipid-lowering therapy. Alcohol consumption and the use of drugs known to affect lipid metabolism (diuretics, sex hormones, steroids, β-blockers) were also recorded. A limited physical examination was performed and venous blood was obtained after a 10-hour fast. Six HIV-infected children aged 4 to 18 years who had received ritonavir for 6 to 25 weeks were also included in this study. These subjects were not asked to be fasting at the time of blood collection. Blood was collected on EDTA, maintained on ice, and plasma was isolated within 2 hours.

Adult subjects were participants of the Swiss HIV Cohort Study, and plasma samples collected 1 to 3 months before initiation of PI therapy (nonfasting) were also available for all of them. These plasma samples had been stored at −80°C for an average of 531±22 days (mean±SEM) and had never been thawed before. Measurements done on these samples were considered as baseline values. For PI-naive individuals, samples collected 628±61 days before enrollment were retrieved and analyzed.

Laboratory Methods

Plasma concentrations of cholesterol and triglycerides were determined using the Unimate5-CHOL and Unimate7-TRIG kits, respectively (Roche). Quality controls were performed on a monthly basis by the Swiss Quality Control Program for Standardization of Lipid Measurements. Intra-assay coefficient of variations (CV) for total cholesterol and triglycerides were 0.4% and 1%, respectively. For subjects with plasma triglycerides levels ≤ 4.5 mmol/L, plasma HDL-cholesterol levels were measured after precipitation of apolipoprotein B (apoB)-containing lipoproteins using the phosphotungstate-magnesium chloride method (Boehringer-Mannheim; CV: 0.7%); plasma LDL-cholesterol levels were calculated using the Friedewald formula. Ultracentrifugation of lipoproteins was performed for 5 of 14 individuals who had plasma triglycerides levels >4.5 mmol/L at study period and plasma HDL- and LDL-cholesterol levels were quantified on fractionated lipoproteins. Plasma apoB levels were determined by nephelometry (Behring; CV: 5.8%). Plasma Lp(a) levels were quantified using an ELISA assay and a commercially available nephelometric method (Behring Diagnostic; CV: 6.7%). The Lp(a) ELISA assay was performed exactly as described using mouse monoclonal antibodies IgG-a6 as capture antibody and IgG-a40 as detecting antibody. The calibrator and the quality controls for this assay were provided by the Northwest Lipid Research Laboratories, University of Washington, Seattle. CV was 11% for plasma Lp(a) levels ≤5 mg/dL, 8% for plasma Lp(a) levels between 5 and 50 mg/dL, and 12% for values >50 mg/dL. Plasma samples used in the ELISA assay had been heated at 56°C for 30 minutes to inactivate HIV. This treatment had no effect on plasma levels of Lp(a) or apo(a) fragments. Plasma levels of insulin were quantified using a radioimmunoassay (Pharmacia). Plasma levels of thyroid-stimulating hormone (TSH) were measured by microparticle enzyme immunoassay (MEIA) using the Abbott Assay system and reagents. Levels of glucose in plasma were determined using the Granutest 250 assay (Merck).

Statistical Analysis

We used logistic regression analysis to assess the PI-associated risk of developing a >0.6 mmol/L increase in plasma levels of total cholesterol, any increase in plasma levels of triglycerides or Lp(a), or any decrease in plasma levels of HDL-cholesterol. These cut-off points were selected on the basis of the distribution of changes in plasma lipid concentrations (tertiles) during administration of PIs. The association between treatment, gender, age, family history of cardiovascular disease, diabetes or lipid disorders, presumed mode of HIV acquisition, baseline CD4 T-cell counts and initial body mass index (predictor variables), and changes in lipid concentration (outcome variable) was assessed by the odds ratio (OR) and its 95% CI. All statistical analysis were conducted using SPSS, version 7.5 (SPSS Inc., 1989 to 1996).

Results

Clinical Characteristics of the HIV-Infected Adults at Study Period

A total of 93 PI-treated and 28 PI-naive adults were included in the study. Forty-six individuals were receiving ritonavir, 26 were given indinavir, and 21 nelfinavir. Ritonavir and nelfinavir were administered alone (n=9 and 10, respectively), or in combination with saquinavir (n=37 and 11, respectively). Addition of saquinavir to ritonavir or nelfinavir was not associated with any further increase in plasma lipid levels (see below), so that subjects receiving ritonavir or nelfinavir alone or in combination with saquinavir were grouped under the headings ritonavir or nelfinavir, respectively. The mean (± SEM) duration of PI therapy was 470±22 days. PI-treated and PI-naive groups were similar for age (Table 1). The

| TABLE 1. Clinical Characteristics of the Subjects at Study Period |
|--------------------------|----------------------|----------------------|----------------------|----------------------|
|                         | Ritonavir*           | Indinavir†           | Nelfinavir‡          | PI-Naive            |
| n (male/female)         | 46 (32/14)           | 26 (21/5)            | 21 (15/6)           | 28 (18/10)          |
| Age, y‡                 | 39.0±1.1             | 38.2±1.7             | 38.8±1.8            | 38.0±1.7            |
| BMI, kg/m²§§            | 22.3±0.4             | 22.4±0.5             | 22.4±1.1            | 22.2±0.6            |
| Waist-to-hip ratio‡     | 0.88±0.01            | 0.92±0.011           | 0.87±0.02           | 0.86±0.01           |
| HIV-RNA copies/mL (Log 10)¶ | 2.79±0.18          | 2.92±0.22            | 3.47±0.32           | 3.62±0.21¶          |
| CD4 cells/mm³‡‡         | 369±36               | 404±40               | 352±52              | 389±41              |
| Duration of PI-therapy, d‡‡| 444±34              | 509±33               | 479±42              | ...                 |

*Group includes 37 subjects receiving ritonavir + saquinavir and 9 receiving ritonavir alone.
†Group includes 11 subjects receiving neflinavir + saquinavir and 10 receiving nelfinavir alone.
‡Mean±SEM; §body mass index; ¶P<0.05; ¶¶P<0.01 vs ritonavir group.
proportion of males ranged from 64% in the PI-naive group to 80% in the indinavir group. No difference in body mass index was observed between groups; however, indinavir-treated individuals had a higher waist-to-hip ratio than the other 2 PI-treated groups (0.92±0.01 versus 0.88±0.01 for ritonavir, P=0.03 and 0.87±0.02 for nelfinavir, P=0.03), possibly owing to a higher proportion of males in this group or to the development of lipodystrophy. None of the subjects presented evidence for nephrotic syndrome. The clinical staging of the disease was similar for the 3 PI-treated groups with 70%, 73%, and 62% of the ritonavir-, indinavir-, or nelfinavir-treated subjects being in CDC stages B or C, respectively. As expected, the majority (57%) of PI-naive subjects were in CDC stage A and the number of HIV-RNA copies was higher in PI-naive than in PI-treated groups. The proportion of subjects within each group who reported a personal history of diabetes, lipid disorders, cardiovascular disease, or pancreatitis was <10%. The estimated alcohol consumption was similar between groups. No statistically significant differences were noticed between groups with respect to mode of acquisition of HIV-infection and the proportion of use of diuretics, β-blockers, oral contraceptive, or steroids.

**Plasma Lipid Levels**

Baseline plasma levels of total, HDL- and LDL-cholesterol, triglycerides, and apoB did not differ significantly between PI-treated groups (Table 2). However, PI-naive subjects tended to have higher baseline plasma HDL-cholesterol levels (1.2±0.1 mmol/L versus 1.0±0.0 mmol/L, P=0.05) and lower triglycerides levels (1.53±0.16 mmol/L versus 1.98±0.13 mmol/L, P=0.07) than PI-treated subjects. Administration of PIs was associated with a significant elevation in plasma total cholesterol levels. The increase in plasma total cholesterol levels was more pronounced with ritonavir (2.0±0.3 mmol/L versus 0.1±0.2 mmol/L in PI-naive group, P<0.001) than with indinavir (0.8±0.2 mmol/L, P=0.03) or nelfinavir (1.2±0.2 mmol/L, P=0.01). The proportion of subjects with total cholesterol level >6.2 mmol/L (a threshold above which the incidence of coronary artery disease increases exponentially in large prospective epidemiological studies) rose from 7% at baseline to 44% at study period in the ritonavir group, from 12% to 35% in the indinavir group, from 5% to 33% in the nelfinavir group, and from 11% to 14% in the PI-naive group during a similar duration of follow-up. Changes in plasma total cholesterol levels were mainly accounted for by an elevation in nonHDL-cholesterol levels because HDL-cholesterol levels remained unchanged during PI therapy. A statistically significant (P<0.05) increase in plasma levels of LDL-cholesterol was observed in the ritonavir and the nelfinavir group, whereas the increase in plasma LDL-cholesterol levels was borderline significant (P=0.06) for indinavir. Changes in plasma LDL-cholesterol levels were paralleled by increases in plasma apoB levels. In addition, treatment with ritonavir, unlike indinavir or nelfinavir, was associated with a significant increase in plasma triglycerides levels (1.83±0.46 mmol/L, P=0.002). Although only 1 in 126 subjects presented at baseline a highly atherogenic lipid profile (as defined by the simultaneous presence of plasma levels of total cholesterol >6.2 mmol/L, triglycerides >2.3 mmol/L and HDL-cholesterol <0.9 mmol/L), this specific profile was found in 9 of 46 (20%) subjects in the ritonavir group, 2 of 26 (8%) in the indinavir group, 1 of 21 (5%) in the nelfinavir, and 1 of 28 (4%) in the PI-naive groups at study period.

To determine whether adjunction of saquinavir to nelfinavir or ritonavir was associated with more pronounced dyslipidemia, plasma lipid levels were compared among subjects who received nelfinavine alone (n=10) or nelfinavir in combination with saquinavir (n=11) and ritonavir alone (n=9) or ritonavir and saquinavir (n=37). Subjects on nelfinavir or ritonavir alone had slightly more elevated plasma total cholesterol levels than those on combination therapy (nelfinavir, 5.9±0.5 mmol/L versus 5.1±0.4 mmol/L, P=0.03; ritonavir, 7.4±0.6 mmol/L versus 6.4±0.3 mmol/L, P=0.16). In addition, the increase in plasma total cholesterol levels between baseline and study period was more pronounced for ritonavir alone than for ritonavir-saquinavir–treated subjects (2.7±0.3 mmol/L versus 1.8±0.3 mmol/L, P=0.05), presumably as a consequence of lower dosage of

**TABLE 2. Plasma Levels of Lipids, Glucose, Insulin, and TSH**

<table>
<thead>
<tr>
<th></th>
<th>Ritonavir*</th>
<th>Indinavir</th>
<th>Nelfinavir†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Study Period</td>
<td>Change</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.6±0.2</td>
<td>6.8±0.3</td>
<td>2.0±0.3</td>
</tr>
<tr>
<td>HDL-cholesterol, mmol/L</td>
<td>1.0±0.1</td>
<td>1.0±0.0</td>
<td>0.0±0.0</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.8±0.2</td>
<td>4.2±0.2</td>
<td>1.4±0.3</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.81±0.14</td>
<td>3.64±0.48</td>
<td>1.83±0.46</td>
</tr>
<tr>
<td>Apo B, g/L</td>
<td>0.91±0.04</td>
<td>1.38±0.07</td>
<td>0.47±0.06</td>
</tr>
<tr>
<td>Lp(a), mg/dL</td>
<td>2.4</td>
<td>4.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>5.2±0.1</td>
<td>5.2±0.2</td>
<td>5.2±0.1</td>
</tr>
<tr>
<td>Insulin, U/L</td>
<td>11.3±0.7</td>
<td>15.2±1.4</td>
<td>13.4±1.5</td>
</tr>
<tr>
<td>TSH, μIU/L</td>
<td>1.98±0.22</td>
<td>1.86±0.23</td>
<td>1.45±0.09</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SEM or median for Lp(a).

*Group includes 37 subjects receiving ritonavir + saquinavir and 9 subjects receiving ritonavir alone.
†Group includes 11 subjects receiving nelfinavir + saquinavir and 10 subjects receiving nelfinavir alone.
‡P<0.05; §P<0.01; ||P<0.001 vs change in PI-naive group; ¶P<0.05 vs PI-naive group.
ritonavir when combined with saquinavir (400 mg BID versus 600 mg BID).

We next examined retrospectively the plasma lipid levels in 7 hyperlipidemic subjects for whom ritonavir had been replaced by nelfinavir (n = 6) or indinavir (n = 1). Plasma lipid levels obtained 8 to 47 days before termination of ritonavir therapy were compared with values obtained 29 to 63 days after initiation of nelfinavir or indinavir therapy. A reduction in plasma cholesterol (from 7.7±0.7 mmol/L to 6.4±0.5 mmol/L, *P* = 0.004) and triglycerides levels (from 9.35±2.57 mmol/L to 3.51±0.69 mmol/L, *P* = 0.02) was observed in all subjects. Taken together, these data provide additional evidence that ritonavir is associated with more pronounced disturbances in plasma lipid levels than indinavir or nelfinavir and indicate that ritonavir-associated lipid disorders are partly reversible over a limited period of time.

To gain insight into the mechanism responsible for disturbances in lipid metabolism observed during administration of PI therapy, we measured the levels of glucose, insulin, and TSH, a marker for hypothyroidism, in plasma samples collected at study period (Table 2). Plasma glucose levels were similar in all groups. In contrast, compared with PI-naive group, plasma insulin levels were slightly more elevated in the indinavir-treated group (15.2±1.4 U/L versus 11.5±1.2 U/L in PI-naive group, *P* = 0.04), but not in the ritonavir (11.3±0.7 U/L) or nelfinavir groups (13.4±1.5 U/L). No relationship was observed between plasma lipid levels and insulin levels. None of the participants presented clinical signs of overt hypothyroidism. In addition, plasma TSH levels were similar between groups, and no relationship was observed between plasma TSH and lipid levels. These data suggested that PI-associated lipid disorders were not due to thyroid dysfunction or alteration in glucose metabolism.

### Plasma Lp(a) Levels

The distribution of plasma Lp(a) levels at baseline was highly skewed toward lower values with >70% of the subjects having plasma Lp(a) levels <10 mg/dL. Plasma levels of Lp(a) increased in all 4 groups between baseline and study period (Table 2). The absolute increase in plasma Lp(a) levels was modest in PI-treated subjects with baseline plasma Lp(a) levels <20 mg/dL (from 1.8 to 3.5 mg/dL, median, *P* = NS) and was similar to the elevation observed in the comparison group (from 3.2 to 6.4 mg/dL, *P* = NS) (Figure 1). However, for 11 PI-treated subjects with baseline plasma Lp(a) levels ≥20 mg/dL, a marked increase in plasma Lp(a) levels was observed (from 45.3 to 67.2 mg/dL, *P* = 0.03) and this elevation was higher (*P* = 0.05) than the change noticed in 7 PI-naive subjects with baseline Lp(a) levels >20 mg/dL (from 24.7 to 24.6 mg/dL, *P* = NS). These observations were confirmed when plasma Lp(a) levels were measured independently and blindly using a commercial nephelometric method and different antibodies. No relationship was observed between changes in plasma Lp(a) levels and changes in plasma levels of other lipoproteins or duration of PI therapy.

### PI-Associated Risk of Dyslipidemia

In an attempt to identify factors which may predispose PI-treated individuals to develop lipid disorders, we performed a multivariate logistic regression analysis. This analysis indicated that none of the following factors was independently and significantly associated with changes in plasma lipid concentration during PI therapy: presumed mode of HIV-acquisition; family history of cardiovascular diseases, diabetes or lipid disorder; baseline plasma lipid level; baseline CD4 T-cell counts; initial body mass index; and age. To account for differences among treatment groups, CD4 T-cell counts, body mass index, and age were adjusted in the final model. Using this model, patients receiving ritonavir were 19.6 times more likely to develop a >0.6 mmol/L increase in plasma total cholesterol levels (95% CI: 4.7 to 80.6) compared with PI-naive patients. The risk was increased 8.5-fold (1.9 to 38.3) with nelfinavir and 3.8-fold (0.9 to 15.3) with indinavir. In addition, administration of ritonavir, but not nelfinavir or indinavir, was associated with a 7.2-fold increase risk (1.9 to 27.1) of developing any elevation in plasma triglycerides levels.
Plasma Lipid Levels In Six HIV-Infected Children Administered Ritonavir

To determine whether lipid abnormalities observed during administration of PI therapy were specific to adults, plasma lipid levels were measured in 6 HIV-infected children who had been on ritonavir for 6 to 25 weeks (Figure 2). None of the subjects received saquinavir. These 6 children had baseline plasma total cholesterol levels ≤4.0 mmol/L. Plasma levels of total cholesterol increased in all but 1 child. In addition, plasma triglycerides levels increased on average by 2-fold during ritonavir therapy. In 1 child, plasma triglycerides level rose from 5.7 mmol/L at baseline to 14.0 mmol/L at study period. As was observed for adults, plasma Lp(a) levels remained relatively stable in 4 children with low plasma Lp(a) levels and increased from 25.7 to 43.9 mg/dL and 39.7 to 62.3 mg/dL in the other 2 children. None of the children presented any sign of nephrotic syndrome.

Discussion

The major finding of this study is that administration of ritonavir or ritonavir-saquinavir to HIV-infected subjects is associated with a marked and frequent increase in plasma levels of total cholesterol and triglycerides. Administration of indinavir, nelfinavir, or nelfinavir-saquinavir was associated with a more modest yet significant increase in plasma total cholesterol levels; there was no change in plasma triglycerides levels. However, as fasting plasma lipid levels at study period were compared with nonfasting values at baseline, our analysis may underestimate the elevation in plasma lipid levels observed between baseline and study period.

In our study, ritonavir and nelfinavir-treated subjects had plasma insulin levels which were similar to PI-naive individuals, and no correlation was observed between plasma insulin and lipid levels. These data suggested that ritonavir- and nelfinavir-associated dyslipidemia may occur independently from abnormalities in glucose homeostasis. It is interesting to note, however, that plasma insulin levels were higher in indinavir-treated individuals, and these individuals had higher waist-to-hip ratio. This finding may be consistent with a link between glucose intolerance and lipodystrophy.4

Administration of PIs was associated with an increase in plasma levels of Lp(a) for subjects who had elevated pretreatment plasma Lp(a) levels. This observation was unexpected, as plasma Lp(a) levels are highly genetically determined.10 The increase in plasma Lp(a) levels was not due to prolonged storage of plasma samples, as storage only minimally affects plasma Lp(a) levels,17 and was observed using 2 different Lp(a) assays. Accordingly, elevation in plasma Lp(a) levels was most probably a result of administration of PI therapy, to progression of the disease or to a combination of both. Elevated plasma levels of Lp(a) may be due to increased synthesis of the particle by the hepatocytes. Alternatively, the clearance of Lp(a) may be retarded in PI-treated subjects. Fragments of apo(a) are present in plasma and appear to result from a proteolytic cleavage of Lp(a)/apo(a).15 To determine whether this process was blocked by PIs, we measured the amount of apo(a) fragments in plasma from 10 PI-naive and 10 PI-treated individuals with plasma Lp(a) levels ranging from 15 to 35 mg/dL. No difference was observed, making this scenario unlikely to account for the excess in plasma Lp(a) levels in PI-treated subjects.

Should PI-associated lipid abnormalities be treated and if so, using which therapeutic modalities? Preliminary retro-
spective analysis indicates that PI-associated disturbances in plasma lipid levels do not attenuate over time. Replacing one PI with another may be beneficial, as suggested by our observation of 7 hyperlipidemic subjects for whom ritonavir was replaced by neflavin or indinavir. Recent evidence indicates that dietary intervention and exercise can be beneficial in selected subjects. In subjects who failed to normalize plasma lipid levels, administration of statins (in this particular case atorvastatin starting at 10 mg daily) and fibrates (gemfibrozil 600 mg BID), alone or in combination, was shown to represent an effective and safe lipid-lowering intervention. However, the possibility of interaction between PI and lipid-lowering agents at the level of cytochrome P450 system could lead to inadequate viral suppression or to greater drug toxicity and should be carefully addressed before recommending such interventions in the routine management of PI-associated dyslipidemia.

The major concern raised by PI-associated elevation in plasma levels of triglycerides and atherogenic lipoproteins [LDL-cholesterol-rich particles and Lp(a)] relates to the risk of acute pancreatitis and premature development of atherosclerosis, respectively. HIV infection, per se, appears to be associated with a high incidence of pancreatitis. Whether ritonavir-associated hypertriglyceridemia will further increase this risk remains to be established. As for atherosclerosis, for a given plasma lipid profile, PI-treated HIV-infected individuals may even be at higher risk of acute cardiovascular events than estimated from large population-based prospective studies. Indeed, rapidly evolving plaques may be particularly unstable and thus prone to rupture, generating an acute coronary event. Furthermore, an inflammatory state, which constitutes an independent cardiovascular risk factor, is frequently encountered in HIV-infected subjects.

Appendix

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