Dyslipidaemia associated with antiretroviral therapy in HIV-infected patients

Leonardo Calza*, Roberto Manfredi and Francesco Chiodo

Highly active antiretroviral therapy (HAART) has had a significant impact on the natural history of human immunodeficiency virus (HIV) infection, leading to a remarkable decrease in its morbidity and mortality, but is frequently associated with clinical and metabolic complications. Fat redistribution or lipodystrophy, hypertriglyceridaemia, hypercholesterolaemia, insulin resistance and diabetes mellitus have been extensively reported in subjects treated with protease inhibitor (PI)-based antiretroviral regimens. In particular, dyslipidaemia occurs in up to 70–80% of HIV-infected individuals receiving HAART and can be associated with all the available PIs, although hypertriglyceridaemia appears to be more frequent in patients treated with ritonavir, ritonavir–saquinavir, or ritonavir–lopinavir. The potential long-term consequences of HAART-associated hyperlipidaemia are not completely understood, but an increased risk of premature coronary artery disease has been reported in young HIV-positive persons receiving PIs. Dietary changes, regular aerobic exercise and switching to a PI-sparing regimen may act favourably on dyslipidaemia. Lipid-lowering therapy is often required with statins or fibrates. The choice of hypolipidaemic drugs should take into account potential pharmacological interactions with antiretroviral agents.

Keywords: HIV infection, antiretroviral therapy, hyperlipidaemia, fibrates, statins

Prevalence and risk factors

Highly active antiretroviral therapy (HAART) has changed the natural history of human immunodeficiency virus (HIV) infection, leading to a significant decrease in morbidity and mortality, and a notable extension of life expectancy. However, the benefits of antiretroviral combinations are tempered by a broad spectrum of side effects, including a wide range of laboratory and clinical disturbances.

Fat redistribution syndrome or lipodystrophy, hyperlipidaemia, insulin resistance and hyperglycaemia have been extensively reported in subjects treated with protease inhibitors (PIs) and nucleoside-reverse transcriptase inhibitors (NRTIs). However, it remains uncertain whether these complications are related to each other, and whether they are exclusively associated with PI administration. A classification of morphological and metabolic abnormalities following HAART administration is summarized in Table 1.

During the course of HIV infection and acquired immunodeficiency syndrome (AIDS), disturbances of lipid metabolism were observed long before the introduction of PI-based antiretroviral regimens, and included hypertriglyceridaemia and a decrease in total and high-density lipoprotein (HDL) cholesterol, occurring in advanced phases of HIV infection. Moreover, Savès et al. and Grunfeld et al. reported lower levels of HDL-cholesterol in HIV-positive individuals with or without antiretroviral therapy compared with the general population.

On the other hand, anomalies of lipid metabolism have been increasingly recognized among HIV-infected persons since the introduction of HAART. Even though therapy with zidovudine, lamivudine, stavudine, or non-nucleoside-reverse transcriptase inhibitors (NNRTIs) has been associated with the occurrence of dyslipidaemia, abnormalities of plasma lipid levels appear to be prevalent among patients receiving a PI-based regimen. In fact, treatment with ritonavir in healthy volunteers results in hypertriglyceridaemia which is apparently not mediated by impaired lipoprotein lipase activity or the defective removal of remnant lipoproteins, but could be caused by enhanced formation of very low-density lipoproteins (VLDL). At the same time, therapy with indinavir may decrease total and non-oxidative insulin-stimulated glucose disposal, leading to insulin resistance and lipid metabolism dysregulation even in the absence of HIV infection.

In patients who receive a PI-containing antiretroviral regimen, the prevalence of hyperlipidaemia ranges from 28% to 80%, and it includes hypertriglyceridaemia in the majority of cases (40–80%), followed by hypercholesterolaemia (10–50%).

Although elevations in serum triglyceride and cholesterol levels have been associated with all the available PIs, hypertriglyceridaemia seems more frequent in patients receiving a ritonavir or ritonavir–saquinavir combination therapy, and may sometimes be extreme, reaching a triglyceride plasma concentration >1000 mg/dL. A mild-to-moderate increase in serum cholesterol levels seems more frequent among patients treated with ritonavir and probably nelfinavir,
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### Table 1.
Classification of morphological and metabolic alterations associated with antiretroviral therapy, as proposed by the Antiretroviral-Associated Lipodystrophy European Comparative Study (ALECS) Group

<table>
<thead>
<tr>
<th>Type</th>
<th>Main morphological features</th>
<th>Subclassification</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>fat loss (lipoatrophy)</td>
<td>a) without Bichat fat pad reduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b) with Bichat fat pad reduction</td>
</tr>
<tr>
<td>II</td>
<td>fat accumulation (lipohypertrophy)</td>
<td>c) involvement of one site (excluding lipoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>d) involvement of more than one site</td>
</tr>
<tr>
<td>III</td>
<td>combined form</td>
<td>e) lipomatosis</td>
</tr>
<tr>
<td>IV</td>
<td>isolated metabolic alterations</td>
<td>a/b + c/d/e</td>
</tr>
</tbody>
</table>

as opposed to indinavir.12,13 With regard to newer PIs, the real incidence of metabolic abnormalities has not yet been defined for amprenavir,14 whereas the occurrence of hyperlipidaemia seems more frequent in subjects receiving a lopinavir/ritonavir-based treatment.15,16 On the other hand, preliminary studies have shown that atazanavir, a novel azapeptide PI, is not associated with increases in total cholesterol, low density-lipoprotein (LDL)-cholesterol, or triglyceride serum levels.17

In a cohort of 212 HIV-positive patients who started a new PI-based antiretroviral regimen, we found an incidence of hypertriglyceridaemia and hypercholesterolaemia of 38.2% and 25%, respectively, after a 12 month follow-up. The frequency of increased serum triglyceride levels proved to be significantly higher in subjects treated with ritonavir or lopinavir/ritonavir, in conformity with previous published studies (Figure 1).18

The development of hyperlipidaemia during PI administration appears to be dose- and probably time-related. Serum lipid abnormalities occur shortly after beginning therapy, usually between 3 and 12 months, but their onset may be faster in subjects receiving a ritonavir-containing regimen (weeks to months).12,14

In recent studies, hyperlipidaemia was also related to a longer cumulative exposure to stavudine, nevirapine and efavirenz.10,19 Mauss et al.20 showed that PIs and the NNRTI efavirenz were associated with an increase in total and LDL-cholesterol, whereas treatment with NRTIs only did not seem to cause a profound alteration of serum lipid profile. Switch studies in PI-treated patients with lipodystrophy and hyperlipidaemia, have shown conflicting results. Estrada et al.21 showed that substituting efavirenz for a PI did not improve the lipid profile. On the other hand, Bonnet et al.22 described the occurrence of severe hyperlipidaemia in subjects receiving efavirenz-based treatments.

Previous reports have shown increased serum HDL-cholesterol level and elevated apolipoprotein A1 (which is associated with HDL-cholesterol) in patients taking nevirapine or efavirenz.20,23,24 The potential impact of this effect on cardiovascular risk is at present uncertain.

### Pathogenic mechanisms

The mechanism of PI-induced dyslipidaemia is not fully understood, but is probably multifactorial. One proposed pathway is based upon the structural similarity between the catalytic region of HIV-1 protease and two homologous human proteins involved in lipid metabolism: cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) and low density lipoprotein-receptor-related protein (LRP). The amino acid sequence of the C-terminal region of CRABP-1 is 58% homologous to the catalytic region of HIV-1 protease, whereas LRP shares 63% amino acid homology with the HIV viral protease.

CRABP-1 usually binds intracellular retinoic acid and presents it to cytochrome P450 (CYP) 3A enzymes, which convert retinoic acid to cis-9 retinoic acid. This molecule subsequently binds to a heterodimer (including retinoid X receptor, or RXR, and peroxisome-proliferator-activated receptor type γ, or PPARγ) in adipocyte nuclei. The heterodimer RXR-PPARγ associated with the cis-9 retinoic acid inhibits adipocyte apoptosis and stimulates adipocyte proliferation and differentiation. PIs probably bind to CRABP-1, which is homologous to the viral protease, and erroneously inhibit the formation of cis-9 retinoic acid, leading to a reduced RXR-PPARγ activity, increased apoptosis and diminished proliferation of peripheral adipocytes. Such events would cause peripheral lipodystrophy syndrome and hyperlipidaemia, because of adipocyte loss, decreased lipid storage, and lipid release into the bloodstream.2,3,6

Recent data indicate that PIs may directly suppress the breakdown of the nuclear form of sterol regulatory element binding proteins (nSREBP) in the liver and adipocytes, leading to hepatic accumulation of nSREBP, increased fatty acid and cholesterol biosynthesis, lipodystrophy, reduced leptin expression, and insulin resistance. PIs also seem to inhibit the proteasome-mediated breakdown of nascent apolipoprotein (apo) B, therefore resulting in the overproduction and secretion of triglyceride-rich lipoproteins.25

Finally, PI-related dyslipidaemia probably involves a genetic predisposition. Recent data document an evident association between hypertriglyceridaemia (with low serum HDL-cholesterol levels), and several polymorphisms found in the apo C-III gene.26

### Clinical complications

The potential clinico-pathological consequences of HIV-associated hyperlipidaemia from an epidemiological, a pathogenic and a clinical point of view remain currently unclear.

Anecdotal reports suggest that premature cardiovascular events (coronary artery disease and myocardial infarction), may be associated with HAART and abnormal plasma lipid values, but large, prospective, controlled studies have not yet demonstrated a significantly increased cardiovascular morbidity and mortality in association with the PI use.

However, in retrospective analysis, significant increases in the incidence of myocardial infarction were found among HIV-positive...
subjects after the introduction of PI-containing regimens, compared with patients treated in the pre-HAART era.27,28

Hypertriglyceridaemia, elevated total and low-density lipoprotein (LDL) cholesterol levels, decreased serum HDL-cholesterol levels, insulin resistance syndrome, diabetes mellitus, and truncal adiposity are known to increase cardiovascular risk in the general population, and may similarly predispose HIV-infected subjects to accelerated coronary illness.19,29-31

A large proportion of middle-aged HIV-infected individuals examined by high-resolution B-mode ultrasound arterial imaging had one or more atherosclerotic plaques within the femoral or carotid arteries. However, some authors have observed that the presence of peripheral atherosclerosis within this population was not associated with the use of PIs, but rather with other classic cardiovascular risk factors, such as hyperlipidaemia and cigarette smoking. At the same time, some recent studies have showed that premature carotid artery lesions (such as arterial calcifications), and an increased erythrocyte volume have a higher prevalence in HIV-positive subjects treated with PIs, compared with PI-naive patients.32,33

Prolonged and extremely high serum triglyceride concentrations (>1000 mg/dL), such as those following ritonavir administration, are associated with the occurrence of acute pancreatitis, especially in patients with a history of alcoholism and gallstones.13,14

Larger studies with extensive follow-up periods are certainly required in order to determine the exact risk index of cardiovascular diseases and other clinical complications associated with prolonged PI administration.

**Management**

Dietary therapy and increased physical activity may act favourably on dyslipidaemia, but they are often inadequate to correct metabolic alterations, and other interventions are generally needed. At the same time, cessation of tobacco smoking and reduction in alcohol intake are requested in order to reduce the cardiovascular disease risk in patients with dyslipidaemia.

Switching from a PI-based treatment to a PI-sparing regimen (including two NRTIs associated with nevirapine, efavirenz, abacavir, or possibly tenofovir), or a different PI are two options that have been evaluated.

Several studies have demonstrated that an antiretroviral regimen in which a PI is replaced with nevirapine, efavirenz or abacavir in patients with long-lasting viral suppression maintains antiviral activity. However, the rate of virological failure might eventually increase among patients who have previously received prolonged non-suppressive antiretroviral regimens, such as dual NRTI therapy, as a result of the re-emergence of archived resistance.19,34

With regard to alterations of serum lipid metabolism, some authors have reported a significant improvement in hyperlipidaemia. However, some authors have not found beneficial effects on lipid levels after substitution of PIs with nevirapine or efavirenz, and the long-term efficacy of switching antiretroviral therapies is not yet understood.34

Lipid-lowering therapy becomes necessary when dietary changes, physical exercise and switching treatment are ineffective or not applicable. Drug therapy for dyslipidaemia in HIV-infected persons receiving HAART is problematic, because of potential drug interactions, toxicity, intolerance and decreased patient adherence to multiple pharmacological regimens.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitors, or statins, are considered the current first-line therapy for primary hypercholesterolaemia. Most of these compounds are metabolized by cytochrome P450 3A4 and may cause clinically relevant interactions with other agents that are changed by this enzymic complex, such as ciclosporin, erythromycin, itraconazole, ketoconazole, oral anticoagulants, PIs and NNRTIs. Simvastatin, lovastatin and atorvastatin are extensively metabolized by CYP 3A4; these notable drug interactions cause elevated plasma levels of statins, leading to a significantly increased risk of liver and skeletal muscle toxicity (acute hepatitis, myopathy and rhabdomyolysis). On the other hand, fluvastatin is metabolized by CYP 2C9 and pravastatin is not significantly metabolized by the CYP enzyme system, with a very low risk of drug interactions.

Consequently, it is reasonable to recommend the use of pravastatin as first-line treatment for hypercholesterolaemia in PI-treated patients, and the use of fluvastatin (characterized by a slightly lower efficacy), as second-line regimen. On the other hand, simvastatin, lovastatin and atorvastatin should be avoided, because they present a great risk of pharmacological interactions with PIs.35,36

Fibrates represent the cornerstone of drug therapy for hypertriglyceridaemia and mixed hyperlipidaemia. These compounds are also metabolized by hepatic cytochrome P450 enzymes, but they appear to primarily affect only CYP 4A, and do not show clinically relevant interactions with PIs. However, concomitant use of both fibrates and statins can increase the risk of skeletal muscle toxicity and should be avoided. Treatment with gemfibrozil, bezafibrate or fenofibrate generally results in a significant reduction in triglyceride and cholesterol levels in HIV-infected patients receiving a PI-containing therapy, with a more evident improvement of hypertriglyceridaemia.37

In a cohort of 106 HIV-infected individuals on PI-based antiretroviral therapy and with hyperlipidaemia of at least 6 months duration, we investigated treatment with bezafibrate, gemfibrozil, fenofibrate, pravastatin or fluvastatin. After a 12 month follow-up, fibrates gave a reduction of 41% and 22% versus baseline triglyceridaemia and cholesterololemia, respectively, and statins obtained a reduction of 35% and 25% versus baseline triglyceride and total cholesterol levels, respectively. There were no significant differences in efficacy between drugs, and all fibrates and statins used have shown a favourable tolerability profile.38

The National Cholesterol Education Program (NCEP) Guidelines for the pharmacological treatment of PI-related hypercholesterolaemia focus on LDL-cholesterol levels, as summarized in Table 2. Suggested cholesterol levels for dietary and drug interventions are
variable according to the presence of cardiovascular disease risk factors. The first-line therapy is represented by pravastatin or fluvastatin. Fibrates are reasonable alternative agents.

Hypertriglyceridaemia requires drug treatment in patients with plasma triglyceride levels above 1000 mg/dL, but subjects with a history of pancreatitis may represent a group for whom a lower threshold of triglyceride increase is opportune, such as >500 mg/dL. Fibrates are considered the cornerstone of drug therapy for hypertriglyceridaemia, whereas statins represent the second-choice treatment line.

To conclude, larger studies are warranted to compare the effects of switching antiretroviral treatment with those of adding lipid-lowering agents, in order to produce specific recommendations and guidelines for the management of HAART-associated dyslipidaemia.

References


