Hyperlipidaemia in patients with HIV-1 infection receiving highly active antiretroviral therapy: epidemiology, pathogenesis, clinical course and management

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Abstract

A wide range of abnormalities of lipid metabolism have been recently described in HIV-infected patients receiving a protease inhibitor (PI)-based highly active antiretroviral treatment, including hypertriglyceridaemia and hypercholesterolaemia. The increase of plasma lipid concentrations may involve up to 70–80% of HIV-positive subjects treated with a PI-containing regimen and are frequently (but not always) associated with the fat redistribution or the lipodystrophy syndrome. Multiple pathogenetic mechanisms by which antiretroviral agents lead to dyslipidaemia have been hypothesized, but they are still controversial. The potential clinicopathological consequences of HIV-associated hyperlipidaemia are not completely known, but several anecdotal observations report an increased risk of premature coronary artery diseases in young HIV-positive individuals receiving PIs, besides peripheral atherosclerosis and acute pancreatitis. A limited-to-significant improvement of increased triglyceride and cholesterol plasma levels was described in patients who replaced PIs with nevirapine, efavirenz or abacavir, but the risks of long-term toxicity and virological relapse of this treatment switching are not completely defined. A hypolipidaemic diet and regular physical exercise may act favorably on dyslipidaemia, but pharmacological therapy becomes necessary when hyperlipidaemia is severe or persists for a long time. The choice of hypolipidaemic drugs is problematic because of potential pharmacological interactions with antiretroviral compounds and other antimicrobial agents, associated with an increased risk of toxicity and intolerance. Statins are considered the first-line therapy for the PI-related hypercholesterolaemia, while fibrates are the cornerstone of drug therapy when predominant hypertriglyceridaemia is of concern.

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Keywords: HIV infection; Highly active antiretroviral therapy; Protease inhibitors; Hypertriglyceridaemia; Hypercholesterolaemia

1. Introduction

Despite the profound impact of protease inhibitor (PI)-based antiretroviral treatment (highly active antiretroviral therapy or HAART) on the natural history of human immunodeficiency virus type 1 (HIV-1) infection, leading to a remarkable decrease of its morbidity and mortality, this pharmacological association has frequently been associated with a wide range of clinical and metabolic complications.

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The fat redistribution syndrome or lipodystrophy (characterized by either localized fat loss in the face or limbs, or fat accumulation in the abdomen, breasts or dorso-cervical region), hyperlipidaemia, insulin resistance and hyperglycaemia have been extensively reported in subjects treated with PIs and nucleoside reverse transcriptase inhibitors (NRTIs). However, it remains uncertain if the occurrence of hyperlipidaemia, abnormal body fat distribution and glucose metabolism alteration are interrelated and associated with PI clinical use only [1–4].

Classification of morphological and metabolic abnormalities following PI administration is summarized
in Table 1, while the severity of metabolic alterations is reported in Table 2.

Although lipid metabolism imbalances have been increasingly recognized since the introduction of HAART in clinical practice, disturbances in lipid metabolism during the course of HIV infection and acquired immunodeficiency syndrome (AIDS) had been observed long before the advent of new PI-based antiretroviral regimens [2,5]. Briefly, this therapy-unrelated dyslipidaemia was characterized by initial decreased plasma levels of total, HDL and LDL cholesterol, followed by elevations in triglyceride levels during advanced stages of HIV disease. These plasma lipid level alterations are comparable with those observed in chronic infections sustained by bacteria, parasites and other viruses, and are associated with an increased blood concentration of the cytokine interferon-α (IFN-α). Therefore, circulating levels of IFN-α are elevated in the advanced phase of HIV disease and probably correlate with an increased production and a reduced clearance of triglyceride, even though it is unclear whether IFN-α directly affects the lipid metabolism or whether it is an indirect marker of these metabolic disturbances [1,2,6–8].

At the same time, tumour necrosis factor (TNF) is likely to be involved in HIV-related dyslipidaemia. Although TNF levels are not elevated during HIV infection, they increase during concomitant opportunistic infections occurring in patients with AIDS and this elevation may exacerbate reductions in total, HDL and LDL cholesterol serum concentrations. On the other hand, significant interleukin-1 (IL-1) plasma levels are usually undetectable in the circulation of subjects with AIDS and they do not seem to be associated with decreased cholesterolemia or increased triglyceridaemia [6,9–11].

Hypocholesterolaemia and hypertriglyceridaemia were also considered a marker of HIV disease progression, with both frequency and severity of dyslipidaemia inversely related to decreased CD4+ lymphocyte count. Particularly, patients with a CD4+ cell count below 200 lymphocytes/mm³ show significantly lower total cholesterol levels than the HIV-negative subjects and those below 400 lymphocytes/mm³ have significantly higher triglyceride concentrations, when compared with matched HIV-negative controls. A multivariate analysis performed in HIV-positive individuals naïve to all antiretroviral agents showed that the hypertriglyceridaemia was correlated to acute opportunistic infections and to IFN-α levels, while reduced serum LDL cholesterol concentration was associated with hypoalbuminemia [11].

Moreover, nutritional alterations are commonly observed in patients with advanced HIV infection long before the usual PI administration, including in most cases weight loss with protein and body cell mass depletion. The development of malnutrition was generally multifactorial and occurred through changes in calorie intake, nutrient absorption or energy expenditure. Clinically, malnutrition usually led to cachexia and was often favored by concurrent hormonal alterations [9,12].

The clinical course of HIV infection and AIDS may be complicated by a variety of endocrine abnormalities such as hypopituitarism, hypotestosteronemia and thyroid dysfunction (hypothyroidism or thyroiditis with thyrotoxicosis). Endocrine function could be altered because of the complex relationship between immune and endocrine systems or through the direct involvement of these glands by HIV itself, opportunistic infections (Pneumocystis carinii, Toxoplasma gondii, mycobacteria, cytomegalovirus) or malignancies (Kaposi’s sarcoma, lymphoma). Hormonal alterations occurring during HIV disease may lead also to extensive

Table 1
Classification of morphological and metabolic alterations under antiretroviral therapy 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>
</thead>
<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 1 site (excluding lipoma)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(d) Involvement of &gt; 1 site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(e) Lipomatosis</td>
</tr>
<tr>
<td>III</td>
<td>Combined form</td>
<td>(a/b)+(c/d/e)</td>
</tr>
<tr>
<td>IV</td>
<td>Isolated metabolic alterations</td>
<td></td>
</tr>
</tbody>
</table>

Table 2
Grading of severity in metabolic abnormalities associated with antiretroviral therapy

<table>
<thead>
<tr>
<th>Severity</th>
<th>Serum cholesterol levels (fasting) (mg/dl)</th>
<th>Serum triglyceride level (fasting) (mg/dl)</th>
<th>Serum glucose levels (fasting) (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0 (normal)</td>
<td>Total &lt; 200, LDL &lt; 160</td>
<td>&lt; 200</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>Total 200–239, LDL 160–189</td>
<td>200–399</td>
<td>110–125 (intermittent)</td>
</tr>
<tr>
<td>Grade 2 (moderate)</td>
<td>Total 240–300, LDL 190–220</td>
<td>400–1000</td>
<td>110–125 (persistent)</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Total &gt; 300, LDL &gt; 220</td>
<td>&gt; 1000</td>
<td>&gt; 125</td>
</tr>
</tbody>
</table>
metabolic and nutritional abnormalities, aside from antiretroviral treatment [11–14].

2. Risk factors for HAART-associated hyperlipidaemia

A wide range of anomalies of lipid metabolism has been increasingly recognized among HIV-infected persons since the introduction of HAART in current clinical practice [2,4,15–17]. Even though therapy with zidovudine, lamivudine, stavudine or non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been sometimes associated with the occurrence of dyslipidaemia, abnormalities of plasma lipid levels sometimes associated with the occurrence of dyslipidaemia (5–30%) and hyperglycaemia, raised C-peptide concentrations, diabetes mellitus and the lipodystrophy syndrome [4,16,20–22].

In patients receiving 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%) and hyperglycaemia–hyperinsulinaemia (5–30%), with the prevalence of fat redistribution syndrome ranging from 10 to 80% in different studies [4,15,16,22–24]. The so-called lipodystrophy syndrome is frequently (but not always) associated with dyslipidaemia; although metabolic alterations are more common among patients with lipodystrophy, they are also present in those without these morphological changes. It has been observed that metabolic abnormalities usually precede the body fat redistribution [17,22,25]. Particularly, fat depletion or lipoatrophy syndrome is often related to the hypertriglyceridaemia, while fat accumulation or lipohypertrophy syndrome is accompanied by dyslipidaemia, peripheral insulin resistance, raised C-peptide levels and diabetes mellitus in an elevated number of cases [26–28].

In several studies, hypertriglyceridaemia has been found in association with the following factors: male gender, more advanced age (>36 years), higher body mass index, greater weight (>65 kg), being homosexual, diagnosis of AIDS, higher mean CD4+ lymphocyte count, and elevated cholesterol and triglyceride plasma levels prior to the PI therapy initiation [1,9,22,29–31]. However, in some studies, gender, baseline lipid levels, stage of HIV disease and body weight do not appear to be related to the occurrence of hypertriglyceridaemia [2,17,32].

On the other hand, none of the following predictors is usually associated with the appearance of hypercholesterolaemia: lipid levels at the start of the PI treatment, gender, age, mean CD4+ lymphocyte count, mean plasma viral load, weight or body mass index [2]. Nevertheless, some authors pointed out an association of increased cholesterol concentration with higher values of age, body mass index and CD4+ cell count [22,32,33]. Therefore, epidemiological, clinical and laboratory risk factors for the PI-related hyperlipidaemia are still controversial today when comparing different published researches.

Even though elevations in serum triglyceride and cholesterol levels have been associated with all the available PIs, hypertriglyceridaemia seems more frequent in patients receiving a ritonavir, ritonavir–saquinavir or ritonavir–lopinavir combination therapy, compared with indinavir-, nelfinavir- and amprenavir-based ones, and may sometimes be extreme, reaching a triglyceride plasma concentration >1000 mg/dl in subjects on ritonavir therapy [3,4,32,34–40]. At the same time, a mild to moderate increase of cholesterol levels seems more frequent among patients treated with ritonavir and probably nelfinavir, as opposed to indinavir [35,41,42]. In a retrospective analysis, indinavir seems PI associated with the lowest risk of hypercholesterolaemia and hypertriglyceridaemia [2].

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) [2,19,20]. Ritonavir, alone or in combination with saquinavir or lopinavir, appears to be associated with the most frequent and severe lipid level elevations, while available data are limited and remain insufficient to evaluate the real effect of indinavir, nelfinavir, saquinavir and amprenavir on plasma lipid concentrations [2,4,40,42].

In recent studies, hyperlipidaemia was also related to a longer cumulative exposure to stavudine, although the exact effect of NRTIs on lipid metabolism is still being debated [22,32,33]. Moreover, some authors have found out that hypertriglyceridaemia is more frequent among patients with concurrent hyperglycaemia or diabetes mellitus [43], while chronic hepatitis C virus infection seems inversely associated with the development of hypercholesterolaemia [22,44]. Finally, lipid metabolism alterations have also been frequently reported in HIV-infected paediatric patients receiving HAART. Hyperlipidaemia was found in 70% of children treated with ritonavir and in approximately 50% of those receiving nelfinavir [45].
3. Pathophysiology

The broad spectrum possibly supporting pathogenetic pathways that potentially underlie PI-associated dyslipidaemia is not fully understood. The most convincing proposed mechanism is based upon the structural similarity to the catalytic region of HIV-1 protease and two homologous human proteins involved in the 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, while LRP shares 63% amino acid homology with the 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 (RXR) and peroxisome-proliferator-activated receptor type γ (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 [2–4].

Another possible mechanism underlying these metabolic abnormalities involves the inhibition of CYP 3A induced by PIs and particularly by ritonavir, which is the most potent inhibitor of these enzymes and proved associated with the most frequent and severe hyperlipidaemia. The inhibition of CYP 3A would be responsible for a reduced formation of cis-9-retinoic acid and a decreased activity of RXR–PPARγ enzymes [4,46].

During normal lipid metabolism, LRP is bound to lipoprotein lipase (LPL) on capillary endothelium and this LRP–LPL complex cleaves fatty acids from triglycerides, thereby promoting free fatty acid accumulation in peripheral adipocytes. Some authors hypothesize that PIs binding to LRP may inhibit the LRP–LPL complex normal function and interfere with fatty acid storage, leading to hyperlipidaemia [2–4]. The elevation in cholesterol levels is principally in the LDL and VLDL cholesterol fractions, since fatty acids released into the bloodstream subsequently reach the liver and promote a secondary hepatic synthesis of triglycerides and VLDL [4,21,47–49]. Moreover, new experimental results suggest that PIs may directly stimulate hepatic triglyceride synthesis. Several PIs up-regulate the mRNA production in hepatic cells for key enzymes involved in the triglyceride biosynthetic pathway, leading to the hepatic accumulation of triglyceride-rich lipoparticles [3,50–52].

A recent report hypothesizes that mitochondrial alterations found in HIV-infected patients receiving HAART could also play a role in the development of antiretroviral therapy-related lipodystrophy and dyslipidaemia. It could be speculated that HAART (especially when conducted with multiple NRTIs) would cause mitochondrial abnormalities by inhibiting the mitochondrial DNA polymerase γ, leading to a mitochondrial DNA depletion, a respiratory chain dysfunction and a reduced cell energy production.

Mitochondrial respiratory chain inhibition could be responsible for several abnormalities in different cell types, such as adipocytes, promoting lipodystrophy syndrome and increased plasma lipid levels. Moreover, interference between PIs and cellular protease could also trigger the development of metabolic alterations, because some proteases are essential for mitochondrial biogenesis and metabolic function [53].

Finally, PI-related dyslipidaemia probably involves a genetic predisposition, too. Recent experimental searches document an evident association between hypertriglyceridaemia (with low serum HDL cholesterol levels) and several polymorphisms found in the apo C-III gene. Variations at nucleosides –455 and –482 are both associated with increased levels of triglyceride-containing lipoproteins (VLDL) and low HDL values. Carriers of the –455 genetic variant had 30% lower levels of HDL cholesterol for those without this polymorphism and plasma lipid concentrations increase according to the number of these variant alleles [54].

In conclusion, pathogenetic mechanisms underlying PI-related dyslipidaemia are very complex and probably involve multiple drug-induced lipid metabolism anomalies, in association with a broad range of hormonal and immunological imbalances and genetic predisposing factors.

4. Clinical course and complications

Since the introduction of HAART into clinical practice has remarkably changed the natural history of HIV disease and led to a notable extension of life expectancy, prolonged metabolic alterations could significantly act on the long-term prognosis and outcome of HIV-infected persons. Therefore, these metabolic imbalances are causing increasing concern, particularly those linked with elevated risk of cardiovascular complications.

The potential clinicopathological consequences of HIV-associated hyperlipidaemia are still not completely known and controlled studies have not yet demonstrated an increased risk of cardiovascular events in
association with the PI-based antiretroviral therapy. However, some anecdotal observations reported an increased incidence of premature coronary artery disease and myocardial infarction in young HIV-infected individuals treated with HAART, besides peripheral atherosclerosis, acute pancreatitis and cutaneous xanthomas [16,36–38,55–61].

Hypertriglyceridaemia, elevated total and LDL cholesterol levels, decreased HDL cholesterol levels, insulin resistance syndrome, diabetes mellitus and truncal adiposity are known to increase cardiovascular risk in the HIV-negative population, and may similarly predispose HIV-infected subjects to accelerated coronary illness [58–61].

A large proportion of the 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 smoking [62,63]. At the same time, two 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-naïve patients [64,65].

Even though an increased risk of coronary artery events has not yet been demonstrated in patients treated with HAART, subjects receiving PI-based antiretroviral regimens frequently present a rapid deterioration of a pre-existing coronary artery illness, which often becomes symptomatic only after the initiation of antiretroviral treatment [61].

The constellation of metabolic abnormalities (including dyslipidaemia and hyperinsulinaemia) suggestive of a significant insulin resistance syndrome among HIV-positive patients with concurrent fat redistribution syndrome leads to a notable increase of cardiovascular disease risk factors already known in HIV-negative population. On the other hand, these predisposing factors are markedly lower in patients without lipodystrophy syndrome [60]. In addition, prolonged and extremely high triglyceride concentrations (>1000 mg/dl), such as those following the ritonavir administration, are associated with the occurrence of acute pancreatitis, especially in patients with a history of alcoholism and gallstones [59,66].

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

5. Non-pharmacological management

Prior to instituting an antihyperlipidaemic pharmacological treatment, clinicians should exclude secondary causes of dyslipidaemia, such as familial hyperlipidaemia, drug therapy (β-blockers, diuretics, steroid derivatives and oral contraceptives), diabetes mellitus, obesity, alcoholism, hypothyroidism, and liver or kidney chronic diseases.

Attention must be given to other correctable risk factors for cardiovascular diseases, such as cigarette smoking, physical inactivity, arterial hypertension and concomitant medications. For women with early menopause, oestrogen or oestrogen–progestin replacement therapy can be considered where appropriate and may lead to a reduced LDL and increased HDL serum cholesterol levels, but can exacerbate hypertriglyceridaemia and should be used with great caution.

A hypolipidaemic diet and an increased physical exercise may act favorably on dyslipidaemia, but they are often inadequate to correct metabolic alterations, and other pertinent interventions are generally requested. However, hypolipidaemic nourishment and regular physical activity should be general and usual components of a healthy lifestyle for all HIV-infected individuals.

Switching from the PI-based treatment to a PI-sparing regimen (including two NRTIs associated with nevirapine, efavirenz or abacavir) or a different PI are two options that have been evaluated. Several clinical studies have shown that, for the antiretroviral-naïve HIV-infected patients, antiretroviral combinations including one NNRTI or abacavir and two NRTIs are at least as potent as PI-based regimens [67–70].

These PI-sparing antiretroviral associations containing nevirapine, efavirenz or abacavir are being employed to reduce toxicity and complexity of HAART and to improve the long-term therapeutic adherence. Preliminary searches support the role of NNRTIs and abacavir for therapy simplification strategies and metabolic correction in patients receiving PI-based treatments, but most of these studies have been uncontrolled and relatively short [71–76].

A lot of 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 has antiviral activity similar to that of prior PI-based combination. In the great majority of cases, full plasma HIV-RNA suppression is maintained and a significant increase in the CD4+ lymphocyte count is reported [67–69,72–74,76]. Efavirenz in particular has shown the greatest antiviral efficacy in switched patients (with undetectable plasma viral load maintained in 92–100% of cases) [68,72,77–80], followed by abacavir (85–90%) [76,81,82] and nevirapine (79–90%) [71,72,74,83].
However, the rate of virological failure might eventually increase among patients who have previously received prolonged non-suppressive antiretroviral regimens as dual NRTI therapy. According to current knowledge, patients previously treated with isolated NRTI therapy may eventually harbor drug-resistant virus variants with multiple mutations in the reverse transcriptase gene, despite subsequent prolonged viral suppression during the HAART administration. Therefore, because of the intrinsically low genetic barrier of the NNRTI class, the safest strategy is probably to replace PI with nevirapine, efavirenz or abacavir only in patients with prolonged undetectable plasma HIV-RNA levels and who have previously exclusively received a PI-based antiretroviral association [71,77].

With regard to the lipid metabolism alterations, several authors have reported similar results in patients switched from HAART to a PI-sparing regimen, which is generally able to significantly improve the concurrent hyperlipidaemia. The nevirapine-containing simplification therapies have obtained the most remarkable reductions both in triglyceride and in cholesterol plasma levels after a 12-month follow-up. The efavirenz- or abacavir-based associations also lead frequently to a significant improvement of hyperlipidaemia [70–74,76,77,79–82]. On the other hand, the effect of the replacement of a PI with an NNRTI or abacavir on the HAART-related lipodystrophy syndrome is still controversial. Even though some studies have reported an improvement in the fat redistribution syndrome [72–74], the majority of authors failed to detect any significant change in morphological alterations after the switch from HAART to a PI-sparing regimen [71,75,77,84]. Results of the most recent studies concerning switch therapy with nevirapine, efavirenz or abacavir are summarized in Table 3.

To conclude, two studies have also evaluated the effects on dyslipidaemia of switching a PI-based antiretroviral regimen from ritonavir, ritonavir–saquinavir or indinavir to nelfinavir. These authors have reported that switching to nelfinavir leads to a significant decrease of the concurrent hypertriglyceridaemia after a 6- or 12-month follow-up, without significant variations in the viral suppression drug activity [85,86].

### 6. Drug therapy

A pharmacological hypolipidaemic therapy becomes necessary when the HAART-related hyperlipidaemia is remarkable or persists for a long time and if 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 drug regimens.

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitors, or statins, are considered the current first-line therapy for primary hypercholesterolaemia. Considerable evidence demonstrates their beneficial effects in reducing both total and LDL cholesterol levels in HIV-negative population, leading to a decreased risk of coronary artery events, in the primary and secondary prevention of the heart diseases [87].

These compounds inhibit the key rate-controlling enzyme in the de novo synthesis of cholesterol, responsible for production of >50% of total body cholesterol. By the inhibition of HMG-Co A reductase, statins can also promote an increased synthesis of hepatic LDL receptors and a reduced production of VLDL lipoproteins. Most statin agents may provide comparable lowering of LDL cholesterol, even though simvastatin and atorvastatin can more remarkably influence these cholesterol levels [87–89].

### Table 3

<table>
<thead>
<tr>
<th>Authors</th>
<th>Drug used</th>
<th>Number of patients</th>
<th>Follow-up (months)</th>
<th>Virological relapse (%)</th>
<th>Effect on hyperlipidaemia</th>
<th>Effect on lipodystrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barreiro et al. [74]</td>
<td>NVP</td>
<td>104</td>
<td>6</td>
<td>11</td>
<td>Unchanged</td>
<td>Reduced</td>
</tr>
<tr>
<td>Ruiz et al. [71]</td>
<td>NVP</td>
<td>52</td>
<td>12</td>
<td>21</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Martinez et al. [72]</td>
<td>NVP</td>
<td>23</td>
<td>6</td>
<td>4</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Negredo et al. [77]</td>
<td>NVP</td>
<td>25</td>
<td>12</td>
<td>4</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Moyle [68]</td>
<td>EFV</td>
<td>26</td>
<td>12</td>
<td>0</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Negredo et al. [77]</td>
<td>EFV</td>
<td>25</td>
<td>12</td>
<td>8</td>
<td>Unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Martinez et al. [72]</td>
<td>EFV</td>
<td>20</td>
<td>6</td>
<td>5</td>
<td>Reduced</td>
<td>Reduced</td>
</tr>
<tr>
<td>Opravil et al. [76]</td>
<td>ABC</td>
<td>84</td>
<td>8</td>
<td>15</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Clumeck et al. [81]</td>
<td>ABC</td>
<td>105</td>
<td>12</td>
<td>13</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Walli et al. [82]</td>
<td>ABC</td>
<td>16</td>
<td>12</td>
<td>12</td>
<td>Reduced</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

NVP, nevirapine; EFV, efavirenz; ABC, abacavir.
Most of these compounds are metabolized by cytochrome P450 3A4 and may cause clinically relevant interactions with other agents that are changed by this enzymatic complex, such as cyclosporin, erythromycin, itraconazole, ketoconazole, oral anticoagulants, PIs and NNRTIs. An additional complicating feature is that individual statins are metabolized to differing degrees, in some cases producing active metabolites. They are also substrates for P-glycoprotein, a drug transporter present in the small intestine, which may influence their oral bioavailability [87,88].

Simvastatin, lovastatin and atorvastatin are extensively metabolized by CYP 3A4; co-administration of ritonavir plus saquinavir to HIV-negative volunteers resulted in an increased exposure to simvastatin by 3059% and to atorvastatin by 347%. 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 [88–90]. 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.

Given these potential interactions, it is opportune to administer low initial doses of either pravastatin (10 mg daily) or fluvastatin (20 mg daily), with a monthly monitoring of plasma aminotransferase and creatine-phosphokinase levels in patients who are taking PIs. On the other hand, simvastatin, lovastatin and atorvastatin should be avoided, because they present a great risk of pharmacological interactions with PIs [91–98]. Moreover, in a recent study, pravastatin had the lowest binding to plasma proteins of the statin agents and dietary advice associated with this statin compound significantly reduced total cholesterol levels in HIV-infected patients treated with HAART, without significant adverse events [99].

Fibrates represent the cornerstone of drug therapy for hypertriglyceridaemia and mixed hyperlipidaemia. These compounds are characterized by an extended activity on the hepatic synthesis of both triglycerides and cholesterol, LPL and acetyl-CoA-carboxylase, as well as the favorable effects on peripheral lipolysis inhibition and glycemic control. Fibrates are also metabolized by hepatic cytochrome P450 enzymes, but they appear primarily to 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 [100–103].

Treatment with gemfibrozil (600 mg twice daily), bezafibrate (400 mg daily) or fenofibrate (200 mg daily) 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 [91,101,103]. With regard to other hypolipidaemic agents, niacin should be avoided as first-line therapy in subjects treated with PIs, because it often causes cutaneous rash, pruritus and insulin resistance. Bile sequestering resins should be discouraged because they may produce elevated triglyceride levels and bind several co-administered medications, with a reduction in their oral bioavailability. Fish oils (omega-3 fatty acid supplements) show a variable effect on plasma triglyceride concentrations and their efficacy has not been fully demonstrated [91,101–104].

The National Cholesterol Education Program (NCEP) Guidelines for the pharmacological treatment of PI-related hypercholesterolaemia focus on LDL cholesterol levels, as summarized in Table 4. Suggested cholesterol levels for dietary and drug interventions are variable according to the presence of cardiovascular disease risk factors (including men age ≥45 years, women age ≥55 years, familial history of coronary artery disease, cigarette smoking, arterial hypertension, serum HDL cholesterol level < 35 mg/dl and diabetes mellitus). The first-line therapy is represented by pravastatin or fluvastatin; fibrates are reasonable alternative agents [91,98].

Hypertriglyceridaemia requires drug treatment in patients with a plasma triglyceride level of > 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 the hypertriglyceridaemia, while statins represent the second-choice treatment [91,96,100]. A hypolipidaemic diet and a regular aerobic physical exercise should be always recommended in association with this pharmacological treatment.

### Table 4

<table>
<thead>
<tr>
<th>Risk factors for cardiovascular diseases</th>
<th>Hypolipidaemic diet (mg/dl)</th>
<th>Drug therapy (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without CAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 2 risk factors</td>
<td>LDL ≥ 160</td>
<td>LDL ≥ 190</td>
</tr>
<tr>
<td>≥ 2 risk factors</td>
<td>LDL ≥ 130</td>
<td>LDL ≥ 160</td>
</tr>
<tr>
<td>With CAD</td>
<td>LDL ≥ 100</td>
<td>LDL ≥ 130</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; LDL, plasma LDL cholesterol concentration.
Hyperlipidaemia is emerging as a frequent and considerable problem in HIV-infected individuals receiving a PI-containing antiretroviral therapy.

Although the long-term clinicopathological consequences of dyslipidaemia are today still unknown, persistent increased levels of triglycerides and/or cholesterol, often associated with truncal adiposity and insulin resistance syndrome, may predispose the HIV-infected population to develop cardiovascular diseases or other clinical complications.

Therefore, when dietary advice, physical activity or general health measures did not result in a significant improvement of plasma lipid levels, a more effective therapeutic intervention is generally indicated in order to correct this severe or prolonged dyslipidaemia.

At present, to the best of our knowledge, there are no clinical studies which have addressed the effects of treatment switch from HAART to a PI-sparing regimen with those of adding lipid-lowering pharmacological agents such as statins or fibrates. The risks of new treatment-related toxicity and the possible virological failure occurring when replacing a PI with an NNRTI or abacavir should be weighed against the risk of potential drug interactions and new drug-associated adverse events caused by the hypolipidaemic compounds.

To conclude, further, enlarged and controlled studies are certainly required in order to produce specific guidelines for the management of HAART-related hyperlipidaemia.

References


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