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HIV Protease Inhibitors and Dyslipidemia

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Abstract

Highly active antiretroviral therapy (HAART) significantly prolongs the lives of HIV-infected patients. Current regimens may consist of a protease inhibitor (PI) combined with at least two or more other antiretroviral drugs. PI administration has been shown to be associated with alterations in plasma lipids (i.e. prompt and sustained increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides) and insulin levels that place PI-treated patients at risk for coronary heart disease (CHD). Because PI-associated dyslipidemia is generally asymptomatic and occurs in patients who are often younger than those traditionally at risk for CHD, the need for primary prevention of acute coronary events in these patients is often unappreciated. Statins form a significant component of pharmacotherapy for PI-associated dyslipidemia. However, because PIs and all statins except pravastatin are metabolized by the cytochrome P450 (CYP) system, co-administration of these agents produces a significant risk of drug interactions and statin-induced hepatotoxicity and myopathy. This risk can be greatly reduced by administering a statin not metabolized by CYP. The need for lipid reduction therapy may be minimized with the use of new PIs that are comparable in efficacy to current PIs but do not negatively affect lipid levels.

Key words

HIV. Protease inhibitors. Dyslipidemia.

Introduction

HIV disease may be associated with maldistribution of fat, manifested by peripheral lipoatrophy, central fat accumulation, and lipomatosis, collectively known as the lipodystrophy syndrome[1,2]. HIV-associated lipodystrophy is strongly associated with the administration of protease inhibitors (PIs), although reverse transcriptase inhibitors have also been implicated in its pathogenesis[3,4]. Commonly accompanying this syndrome are elevated concentrations of triglycerides (TGs), elevations in total cholesterol (TC), elevated TC : high-density lipoprotein cholesterol (HDL-C) ratio, and insulin resistance[1,5]. These metabolic abnormalities are not usually observed in patients treated with non-PI-containing regimens. The dyslipidemia develops rapidly after initiation of PI therapy, and the associated hyperlipidemia is marked and sustained. Thus, lipid alterations appear to be an adverse event related to all current PIs used in HIV therapy[6-8].

Patients with HIV infection are surviving longer and with an improved quality of life as a result of the institution of highly active antiretroviral therapy (HAART), regimens for which usually consist of a PI combined with at least two other antiretroviral drugs[9,10]. The lipid abnormalities noted in PI-treated

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patients have raised concerns, however, regarding the risk of treatment-related atherosclerosis and coronary heart disease (CHD). Because PI-associated dyslipidemia is generally asymptomatic and occurs in a population younger than that traditionally considered to be at risk for CHD, the need for primary prevention of acute coronary events in these patients is often unappreciated[11]. Consequently, PI-associated dyslipidemia has the potential to be a "silent killer" in the HIV+ population treated with these important agents.

This review describes the pathophysiology of dyslipidemia in PI-treated patients as the basis for a discussion of the management strategies currently recommended for treating lipid elevations. Selection of antihyperlipidemic interventions in patients receiving HAART requires an understanding of the risks and benefits associated with adding these pharmacotherapies to PI-based antiretroviral regimens.

Risk factors for coronary heart disease

At present, CHD is the primary cause of death for men and women in the United States[12]. Each year, approximately 650,000 people in this country experience a first CHD event (i.e. acute myocardial infarction or fatal CHD event); most will have been previously asymptomatic, and approximately 40% will die within 12 months[12].

Major risk factors for CHD are both modifiable and non-modifiable. Although age, family history, and gender cannot be modified, other risk factors such as cigarette smoking, hypertension, and dyslipidemia (increased low-density lipoprotein cholesterol [LDL-C], elevated TG, and low HDL-C levels) can be corrected and can reduce an individual's risk for CHD and its complications[13]. Elevated cholesterol is the most important of these modifiable CHD risk factors, with LDL-C, the major atherogenic lipoprotein, being the primary focus of lipid-modifying interventions. Clinical trials have shown that lowering LDL-C levels reduces not only the incidence of CHD and mortality from CHD but also overall mortality[14].

Elevated TG levels are also an independent risk factor for CHD[13]. Some TG-rich (remnant) lipoproteins, such as partially degraded very low density lipoprotein (VLDL), appear to be particularly atherogenic.

Need for aggressive lipid management in PI-treated patients

PI-associated dyslipidemia places patients at risk for acute myocardial infarction, unstable angina pectoris, and sudden CHD-related death. These patients require early and aggressive risk factor modification. The importance of primary prevention of CHD events in HIV+ patients receiving PI therapy is underscored by the silent nature of CHD in patients without a previous history of heart disease. Given the relatively young age of the HIV+ population, heart disease in these patients may be neither clinically apparent nor suspected. Furthermore, antiretroviral therapy appears to have the potential to accelerate the development of CHD, and, in the general population at least, lipid-modifying interventions have less than satisfactory effectiveness. One survey showed that 18- to 34-year-old HIV+ men who were receiving antiretroviral therapy were more likely to develop CHD than were non-HIV+ men of similar age[15]. In addition, most of the CHD events in these patients occurred during the first 2 years of drug therapy.

Despite the public health emphasis on reducing the risk of CHD through the use of cholesterol screening and risk modification strategies, many at-risk patients are either not treated or fail to reach the LDL-C goals established by the National Cholesterol Education Program (NCEP) Expert Panels (Table 1)[13,16]. Data from the updated National Health and Nutrition Examination Survey III suggest that more than 28 million adults in the United States require drug therapy for elevated cholesterol levels[17]. However, even when elevated cholesterol levels are recognized, treatment is often insufficient. A study of primary care physicians who regularly treat HIV patients for dyslipidemia found that only 38% of those patients succeed in achieving NCEP Adult Treatment Panel II (ATP II) target lipid values. This percentage increases to 68% among patients with fewer than two CHD risk factors and no history of CHD[18]. Because so many PI-treated patients are unlikely to succeed using current approaches, there is a need for alternative management strategies for treatment of dyslipidemia in the HIV+, PI-treated population. This need for alternative strategies may be particularly acute in HIV+ women, as the metabolic abnormalities associated with HAART appear to be greater, and the overall rate of success in reducing the atherogenic profile appears to be lower, among women [9].

Table 1. *Lipid classification. National Cholesterol Education Program[13]*

Lipid (mg/dl)	Classification
Total cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
LDL-C	
<100	Optimal
100-129	Near or above optimal
130-159	Borderline high
160-189	High
≥190	Very high
HDL-C	
<40	Low
≥60	High
Triglycerides	
<150	Normal
150-199	Borderline high
200-499	High
≥500	Very high

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Pathophysiology of PI-associated dyslipidemia

HIV infection itself is associated with specific lipid abnormalities. This HIV-related dyslipidemia, which is believed to be independent of medication effects, is manifested by a tumor necrosis factor-dependent decrease in cholesterol and cholesterol-containing lipoproteins, including HDL-C[19]. With the onset of AIDS-defining symptoms, levels of plasma TG and free fatty acids increase, possibly as a result of increased concentrations of circulating interferon-α[20].

Currently marketed PIs have specific metabolic effects that can induce dyslipidemia and produce a proatherogenic state[21]. These effects are independent of the medication's antiretroviral activity or drug-related immune reconstitution. Instead, they have been postulated to be the result of PI-induced abnormalities of retinoic acid metabolism and chylomicron clearance. The 12 amino acids of the catalytic domain of the HIV protease have a 58% homology with the C-terminal region of cytoplasmic retinoic acid-binding protein type 1 (CRABP-1) and a 63% homology with a lipid-binding domain of LDL receptor-related protein (LRP)[1].

CRABP-1 is widely distributed in tissues, binding virtually all retinoic acid in cells. It is responsible for transport of retinoic acid to the cytochrome P450 3A isoform (CYP-3A) for metabolism[1]. By interfering with binding of retinoic acid to CRABP-1, PIs alter the metabolism of retinoic acid. In addition, PIs also are potent inhibitors of CYP-3A. As a consequence of these two related properties, there is insufficient synthesis of 9-cis retinoic acid, the principal activator of the retinoid X receptor (RXR), and the peroxisome proliferator-activated receptor type γ (PPAR-γ) heterodimer in patients treated with currently marketed PIs. Down-regulation of the activity of the RXR/PPAR-γ heterodimer results in decreased differentiation, reduced proliferation, and increased apoptosis of peripheral adipocytes. Consequently, fatty tissue is unable to clear circulating TGs, while apoptotic lipocytes release lipids into the blood[1].

LRP is present on hepatocytes and capillary endothelial cells[1]. In the liver, LRP facilitates clearance of chylomicrons. Endothelial LRP, in conjunction with co-expressed lipoprotein lipase, helps to cleave fatty acids from circulating TGs. The free fatty acids can then enter lipocytes to be stored as fat. PIs, as a result of their ability to bind to LRP, can contribute to hyperchylomicronemia and hypertriglyceridemia. The resultant hyperlipidemia contributes to the morphologic redistribution of fat characteristic of PI-induced lipodystrophy.

Dual-PI therapy (i.e. a saquinavir-ritonavir combination) has been associated with the rapid development of hypertriglyceridemia. In one study, the hypertriglyceridemia occurred within 2 weeks[22]. Treatment was initiated with saquinavir (hard-gel capsules, 400 mg twice daily) and ritonavir (300 mg twice daily, increasing over 6 days to a maintenance dose of 500 mg twice daily) for a period of 48 weeks; no other antiretroviral agents were administered. By week 4 of the trial, mean TG concentrations had increased more than 160%. Cholesterol concentrations also increased significantly, peaking after 8 weeks[22]. A significant correlation was found between higher trough levels of each of the PIs and elevated TG level at week 4 (saquinavir, $p = .02$; ritonavir, $p = .03$).

Hypertriglyceridemia is the dominant feature of PI-induced dyslipidemia. Other abnormalities in lipid metabolism in PI-treated patients include an increase in the TC:HDL-C ratio, which is characterized by elevated levels of intermediate-density lipoprotein (IDL) and VLDL, the characteristics that make the lipid aberrations highly atherogenic, and a decrease in the HDL_2:HDL_3 ratio[5,23]. Lipid abnormalities in PI-treated patients are also associated with impaired flow-mediated vasodilation of the brachial artery, which is an indication of significant endothelial cell dysfunction, a marker of CHD risk, and an index of the angiographic extent of CHD[23-25].

The dyslipidemia in PI-treated patients is consistent with the lipid profile associated with insulin resistance and is what makes it highly atherogenic[5]. Patients treated with PI therapy have been reported to develop insulin resistance and new-onset diabetes mellitus[26]. In a study of the effects of PI therapy on glucose metabolism in HIV+ patients, both PI-treated and PI-*naïve* patients were evaluated for insulin sensitivity and glucose tolerance[27]. All PI-*naïve* patients had normal insulin sensitivity, whereas those treated with PIs demonstrated a significant decrease in insulin sensitivity ($p < 0.001$). A subset of patients in the study was also evaluated using oral glucose tolerance tests. Results showed impaired glucose tolerance in 17% of PI-treated subjects and diabetic-level glucose tolerance in 38%.

Insulin resistance in PI-treated subjects appears to be a direct effect of the drug rather than the result of changes in weight or body fat distribution[28]. Among healthy HIV– men treated with indinavir, insulin resistance was not associated with increases in visceral adipose tissue or alterations in lipids or lipoproteins[29]. Although the exact etiology of PI-related insulin resistance remains to be fully elucidated, PI-treated patients exhibit increased secretion of insulin, proinsulin, and C-peptide in the fasting and post-glucose-ingestion states. This suggests that PI therapy is associated not only with insulin resistance but also with beta cell dysfunction[26]. The combination of dyslipidemia, insulin resistance, and impaired glucose tolerance is a feature of the metabolic syndrome, a constellation of lipid and nonlipid risk factors that identifies patients at increased risk for CHD who can benefit from intensive lipid-lowering therapy[13].

General considerations in the management of PI-associated dyslipidemia. When to initiate lipid management in the PI-treated patient

Because there is no direct evidence that PI-induced alterations in lipids translate into an increase in CHD events, the decision of when to institute lipid-lowering treatment in PI-treated patients remains somewhat controversial. However, there is substantial evidence from patients with other types of dyslipidemia that the lipid abnormalities observed in patients treated with PIs are associated with an increase in the 10-year risk of cardiovascular events, particularly when additional risk factors such as smoking and hypertension are present[13].

In 2000, the Adult AIDS Clinical Trial Group (ACTG) issued preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy[30]. Their guidelines were based both on recommendations of the NCEP ATP II regarding the management of dyslipidemia in the general population and on the pharmacokinetics of hypolipidemic agents in non-HIV-infected patients. However, after considering the prevalence and treatment of dyslipidemia in HIV-infected patients and the implications of treatment-related dyslipidemia in other chronically ill populations, the ACTG refined its guidelines. In line with the NCEP guidelines, the ACTG recommends that pharmacologic treatment of the HIV-infected patient with dyslipidemia be based on the results of the patient's initial lipid profile tests and risk factor stratification[30]. The initial lipid profile tests should be performed before instituting therapy and should include measurement of fasting TC, HDL-C, and TG levels. Even though the primary goal of the NCEP guidelines is to reduce LDL-C levels, LDL-C values are unreliable in patients with PI-induced and other types of hypertriglyceridemia (i.e. TG > 400 mg/dl). Therefore, the clinician can use either TC or HDL-C values (TC > 240 mg/dl; HDL-C < 40 mg/dl) as a "signal" to prompt intervention[13].

Role of statins in dyslipidemic patients

The initial lipid-modifying intervention should consist of therapeutic lifestyle changes such as alterations in diet, increased physical activity, and weight loss. However, even with these modifications, many PI-treated patients will require pharmacologic treatment for dyslipidemia.

Statins are competitive inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA), the enzyme that catalyzes the last regulated step in cholesterol synthesis[31]. The various statins have been shown to reduce elevated LDL-C levels by about 50%[24]. Although it may be difficult to estimate LDL-C levels in hypertriglyceridemic patients, reduction in LDL-C remains the foundation of treatment to prevent CHD morbidity and mortality. Statins also lower elevated TG levels by 10 to 29%[31]. These novel agents may also decrease the risk of CHD events through a variety of nonlipid mechanisms, including plaque stabilization, antiinflammatory and antioxidant activity, and restoration of endothelial cell function[31-33]. Statin therapy has been shown to significantly reduce morbidity and mortality in a wide range of patients with either average or elevated TC and LDL-C levels[31,34-39]. Unfortunately, however, despite the efficacy of statins in correcting dyslipidemia and reducing CHD-associated morbidity and mortality, many patients do not receive the appropriate drugs in adequate doses[40].

Role of other agents in the treatment of dyslipidemic patients

The role of other agents in the treatment of dyslipidemic patients who are receiving PI therapy is limited. Bile acid sequestrants have limited utility owing to their lack of effect on HDL-C and their potential to increase TG levels[31]. In addition, they cause a variety of abdominal complaints and can elevate aminotransferase levels. Nicotinic acid decreases TG levels and elevates HDL-C values, but it is hepatotoxic, can produce hyperglycemia, and can cause abdominal symptoms.

Managing the risk of drug interactions in PI-treated patients with dyslipidemia

The selection of pharmacologic interventions for lipid lowering in the HIV-infected patient treated with PIs must take into account the unique aspects of these drugs, particularly their potential for drug interactions. All currently marketed PIs interfere with the activity of CYP-3A but to varying degrees. In humans, this CYP subfamily has been shown to be responsible for the metabolism of the widest range of drugs and endogenous compounds of any metabolic system[41,42]. Consequently, therapy with current PIs raises a host of potential pharmacokinetic issues in patients receiving HAART, who may also be taking a variety of other medications. Among the PIs, ritonavir has the highest potential for CYP-3A interactions[43]. In addition, it also inhibits the CYP-2D6 and CYP-2C9/10 isoforms and induces the CYP-1A2 isoform.

Drug interactions between PIs and statins are predicted by their mechanisms of metabolism. With the exception of pravastatin, all of the current statins are metabolized by CYP (Table 2)[31,44]. PIs that inhibit the CYP-3A or -2C isoforms slow the metabolism of statins and other medications such as antibiotics and antifungal agents, which are commonly administered to HIV-infected patients[45]. In patients who are being treated with drugs metabolized by the CYP system, significantly elevated statin levels may occur, with the potential to produce hepatotoxicity or myotoxicity, or both[31]. Manifestations of statin-induced hepatotoxicity include fatigue, sluggishness, anorexia, weight loss, and elevated aminotransferase levels. Although symptoms can resolve overnight after discontinuation of statin therapy, abnormal liver function test results may persist for weeks[31]. Clues to the presence of myopathy include myalgias and elevated levels of creatine phosphokinase. Although myotoxicity is less common than hepatotoxicity, rhabdomyolysis is potentially life threatening[46]. Symptoms include contraction of intravascular volume, shock, metabolic derangements (including acidosis), hyperkalemia, hypocalcemia, and pigment-induced acute renal failure. The risk of rhabdomyolysis from a statin-induced drug interaction led to the withdrawal of cerivastatin from the market. Because neither pravastatin nor fluvastatin is significantly metabolized by CYP-3A, the risk of statin-related drug interactions is lower with these HMG-CoA reductase inhibitors than with other statins[47]. However, because fluvastatin carries a potential for CYP-2C drug interac-

Table 2. *Metabolic pathways (+) of currently available statins[31]*

Statin	Metabolic pathway CYP-3A4	CYP-2C9	Sulfation
Atorvastatin	+		
Fluvastatin		+	
Lovastatin	+		
Pravastatin			+
Simvastatin	+		

CYP, cytochrome P450

tions, pravastatin is the more favorable agent in terms of potential drug interactions and safety.

The safety and efficacy of statin therapy have been recently evaluated in 26 HIV-infected, dyslipidemic patients, most of whom were being treated with PIs[7]. A total of 30 courses of statin therapy were given; patients may have received more than one statin. Statins administered were pravastatin (patient n = 5), lovastatin (n = 13), simvastatin (n = 10), or atorvastatin (n = 2)[7]. Statin therapy reduced median baseline TC levels by 26% (from 354 to 263 mg/dl; median duration of treatment, 8.2 months) and TG levels by 15% (from 513 to 438 mg/dl; median duration of treatment, 7.2 months). Myopathy (n = 2) and hepatotoxicity (n = 2) occurred only in patients treated with a statin metabolized by CYP-3A[7].

In a randomized, open-label comparative trial of 31 patients receiving PI-based combination treatment, pravastatin plus dietary advice did not produce significant clinical or laboratory adverse events[48]. Treatment with pravastatin alone significantly reduced TC levels ($p < 0.05$). The magnitude of change in PI-treated patients was comparable to that achieved in patients with endogenous hyperlipidemia. However, in clinical practice, it is important to monitor statin levels to ensure that blood levels do not exceed those documented in clinical trials to be safe. This is particularly important at the initiation of therapy and when medications are changed.

Future Prospects In PI-related dyslipidemia

Optimal intervention in patients with PI-induced dyslipidemia remains undefined. Selection of therapy is particularly problematic in patients receiving HAART, as the probability of CHD events must be balanced with the risk of drug interactions introduced with lipid therapy[30]. For patients with severe dyslipidemia, switching from a PI-based regimen to a non-nucleoside reverse transcriptase inhibitor or to 3 nucleoside reverse transcriptase inhibitors could be of use, although the overall benefit of such a switch has not been determined[49].

Newer PIs in development need to be investigated for their effects on lipid levels to determine whether these agents offer an alternative to current PIs and reduce the need for lipid-lowering therapy. For example, atazanavir, a PI in phase III trials, has not been associated with changes in lipid profiles, and elevations that have occurred have not been clinically significant and its efficacy in reducing HIV RNA is comparable to or better than that of nelfinavir[50,51]. Atazanavir does not produce the prompt, marked, and sustained elevations in lipid levels commonly associated with nelfinavir and also with other PIs[52]. Consistently in the clinical studies, treatment with atazanavir has resulted in substantially lower levels of total cholesterol, LDL-C, and TG than has treatment with nelfinavir[50]. Thus, use of an agent such as atazanavir in the HAART regimen could potentially obviate the need for treatment of dyslipidemia[50,53,54].

Conclusions

PI-containing HAART regimens significantly prolong life in HIV+ patients. However, PI administration has been associated with dyslipidemia, insulin resistance, and beta cell dysfunction, all features associated with an increased risk of CHD in the non-HIV-infected population. This is of particular concern for HIV-infected patients, as they are often younger than the traditional population at risk for CHD, and the progression of atherosclerosis is clinically silent. The ACTG has recommended that HIV-infected, dyslipidemic patients be treated using a protocol based on guidelines developed by the NCEP.

The keystone of pharmacologic management of dyslipidemia is statin therapy. However, with the exception of pravastatin, all currently marketed statins are metabolized by the CYP-3A system, with which the PIs interact. Thus, the potential for drug interactions, already a major concern in patients receiving the multiple-medication regimens characteristic of HAART, is significant. Therefore, patients receiving intensive drug therapy for HIV infection who develop dyslipidemia should be treated with an agent that minimizes the risk for adverse drug events. New PIs that are comparable in efficacy to conventional agents but have a superior lipid-altering profile may obviate the need to specifically treat drug-induced dyslipidemia in patients receiving HAART.

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