ABSTRACT

HIV-infected patients who are naive to antiretroviral therapy usually demonstrate decreased lipid levels as a consequence of infection. Treatment with antiretroviral agents may be generally associated with a "return-to-baseline phenomenon" that should be considered when evaluating clinical trial findings. The older protease inhibitors (PIs)—saquinavir, indinavir, ritonavir, nelfinavir, and amprenavir—have been associated with the development of hypertriglyceridemia, insulin resistance, and dyslipidemia. New PIs have been developed that have more favorable lipid profiles, offer more dosing options, and are associated with fewer short-term side effects. This article summarizes the complications associated with the older and newer PIs and offers guidance for the clinical management of metabolic complications in patients taking antiretroviral therapy.

ing characteristics—obesity, elevated triglycerides, low high-density lipoprotein (HDL) cholesterol, blood pressure greater than 130/85 mm Hg, and a fasting glucose level exceeding 110 mg/dL. The overall age-adjusted prevalence of the metabolic syndrome is 32% in the general population of uninfected individuals. This prevalence rises with advancing age, differs somewhat between men and women, and is higher among those of African descent, especially women, compared with those of Caucasian lineage.

**LIPID CHANGES IN HIV-INFECTED PATIENTS**

HIV infection is associated with a drop in total cholesterol, an early and marked decrease in HDL cholesterol, and a later reduction in low-density lipoprotein (LDL) cholesterol, which parallels the decline in CD4 cell count (Figure). Highly elevated triglyceride levels are a late manifestation of disease particularly associated with the occurrence of AIDS.

Data from the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study reinforce the concept that the higher a patient’s CD4 count, the higher his or her total cholesterol level. Cholesterol levels in patients with high CD4 counts were lowest in patients naive to treatment, and increased in order from patients taking therapy with NRTIs to treatment with NRTI/non-NRTI (NNRTI), NRTI/PI, and NRTI/PI/NNRTI. The same pattern of elevated cholesterol is seen in relation to viral load.

**LIPODYSTROPHY**

The Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study, a large study supported by the National Institutes of Health, is evaluating an HIV-infected population of patients from around the United States. Controls were subjects from the Coronary Artery Risk Development in Young Adults (CARDIA) database, a prospective cohort of patients 33 to 45 years of age. The main findings reported from the FRAM study are that the major difference between HIV-infected patients and control subjects is the presence of lipoatrophy in the HIV-positive patients. Lipoatrophy is a rare occurrence in HIV-negative individuals, unlike the metabolic syndrome. Patients who reported fat loss in the FRAM study did not have any more central fat compared with controls. In addition, buffalo humps were not more prevalent among HIV-infected patients in the FRAM study, although they were larger than those seen in controls.

**PIs AND LIPID LEVELS**

Indinavir and nelfinavir are believed to promote both insulin resistance and a dyslipidemic profile similar to that seen in patients with diabetes, with high levels of triglycerides, low HDL levels, and the presence of triglyceride-rich particles. In contrast, ritonavir has been linked to hypertriglyceridemia and increased hepatic very-low-density lipoprotein and apolipoprotein B production with no or little effect on insulin resistance. This profile may increase vascular risk. The precise effect on this profile and on vascular risk of using ritonavir at lower doses in boosted regimens, as with lopinavir/ritonavir, is to be determined. However, increased levels of total cholesterol as well as triglycerides were observed in patients treated with lopinavir/ritonavir for 48 weeks.

In general, compared with the older PIs, phase 3 data for new PIs show that atazanavir and 908 have favorable lipid profiles.

**EVALUATING THE NEWER PIS**

**LIPIDS**

Atazanavir, approved by the US Food and Drug Administration (FDA) in June 2003, has been associated with minimal lipid abnormalities or improvements compared with efavirenz in a pivotal phase 3 trial. Switching from nelfinavir to atazanavir was also associated with an improvement in lipid levels in earlier studies. Favorable lipid effects of atazanavir have also been observed in trials of this new PI in antiretroviral therapy.
(ART)-experienced patients.\textsuperscript{23,24} Especially notable is the good lipid profile when atazanavir was boosted with ritonavir.\textsuperscript{24} In this study, more patients who received the comparator, lopinavir/ritonavir, required lipid-lowering therapy compared with those who received a combination of atazanavir and ritonavir. For 908 (fosamprenavir, approved by the FDA in October 2003), its unboosted twice-daily use in a 48-week phase 3 trial resulted in comparable lipid levels to those seen in ART-naive patients treated with nevirapine and remained within acceptable National Cholesterol Education Program (NCEP) guidelines.\textsuperscript{25}

Boosting 908 with ritonavir in a once-daily regimen also resulted in minimal lipid elevations.\textsuperscript{26} Levels of total cholesterol and LDL cholesterol did not exceed the NCEP cutoffs for initiating lipid-lowering therapy; however, mean triglyceride levels remained between “borderline high” and “high.” Nevertheless, these results are notable given the use of low-dose ritonavir in this phase 3 trial. Furthermore, such lipid elevations in general may in part reflect the “return-to-baseline phenomenon” that often occurs when ART-naive patients initiate treatment. A similarly good lipid profile with both once-daily and twice-daily boosted 908 was also observed in interim results of a third phase 3 trial evaluating 908 in ART-experienced patients, with generally more favorable results observed in both 908 arms compared with lopinavir/ritonavir.\textsuperscript{27}

\textbf{NONMETABOLIC EFFECTS}

In addition to their more favorable lipid profiles, new PIs also differ from the older PIs with respect to their nonmetabolic (eg, short-term) effects. The older agents in this class were frequently associated with diarrhea, gastrointestinal intolerance/nausea, retinoid side effects, and hyperbilirubinemia—short-term side effects that can make a regimen intolerable and potentially lead to discontinuation of therapy. Among the newer PI agents, atazanavir treatment has consistently been associated with elevated bilirubin levels with a lower, but steady, occurrence of jaundice and scleral icterus. Of potentially greater immediate clinical concern is that levels of atazanavir may be lowered by tenofovir disoproxil fumarate as well as by efavirenz.\textsuperscript{28} Ritonavir-boosted atazanavir (300/100 mg daily) is recommended for concurrent use with either of these 2 drugs. Regarding other drug interactions, the use of H\textsubscript{2} blockers and proton pump inhibitors is restricted in patients taking atazanavir. Moreover, food restrictions apply. For fos-

\textbf{Table 1. Some Advantages and Disadvantages of the Newer PIs}

<table>
<thead>
<tr>
<th>Atazanavir</th>
<th>Fosamprenavir (“908”)</th>
<th>Tipranavir</th>
<th>TMC-114</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADVANTAGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 (soon to be 1)</td>
<td>Dosing flexibility</td>
<td>Good activity</td>
<td>Good activity in multiple-PI-experienced patients (phase 2 results)</td>
</tr>
<tr>
<td>cap/dose/day</td>
<td>(4 pills/day; bid ± RTV, qd + RTV)</td>
<td>in multiple-PI-experienced patients (phase 2 results)</td>
<td></td>
</tr>
<tr>
<td>Minimal/improved lipid abnormalities vs EFV (unboosted in A1424-034), LPV/RTV (boosted in A1424-045)</td>
<td>Good GI tolerability</td>
<td>Minimal lipid perturbation vs NFV (boosted in SOLO), LPV/RTV (boosted in CONTEXT)</td>
<td></td>
</tr>
<tr>
<td>Improved lipids when switched from NFV</td>
<td>Comparable lipids unboosted vs NFV (N EAT)</td>
<td>No food restrictions</td>
<td></td>
</tr>
<tr>
<td><strong>DISADVANTAGES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role in PI-experienced patients not fully defined</td>
<td>RTV boosting required for qd dosing (increased triglycerides when used with RTV (minimal)</td>
<td>Poor bioavailability</td>
<td>Activity not yet well defined</td>
</tr>
<tr>
<td>Relative potency</td>
<td></td>
<td>High incidence of GI side effects</td>
<td>Risk of short-term side effects</td>
</tr>
<tr>
<td>Commonly associated with hyperbilirubinemia (potential for jaundice)</td>
<td></td>
<td>Induces metabolism of RTV</td>
<td>No clinical data in ART-naive patients</td>
</tr>
<tr>
<td>H\textsubscript{2} blockers, proton pump inhibitor use restricted</td>
<td></td>
<td>No clinical data in ART-naive patients</td>
<td></td>
</tr>
<tr>
<td>TDF and EFV each lower levels of ATV</td>
<td></td>
<td>Formulation not yet determined</td>
<td></td>
</tr>
</tbody>
</table>

PIs = protease inhibitors; EFV = efavirenz; LPV = lopinavir; RTV = ritonavir; NFV = nelfinavir; GI = gastrointestinal; TDF = tenofovir; ATV = atazanavir; ART = antiretroviral therapy.
amprenavir ("908"), concerns that this new prodrug of amprenavir would retain the side-effect profile of its active metabolite are likely overestimated. The side-effect profile of 908 is substantially improved, and diarrhea, gastrointestinal intolerance, and nausea were significantly lower with 908 in all phase 3 trials to date. There are also no food restrictions with 908, in contrast to amprenavir.29 Fewer data are available for both tipranavir and TMC-114. Tipranavir has poor bioavailability, and gastrointestinal intolerance/nausea is associated with its use.30,31 Tipranavir induces the metabolism of ritonavir; thus, boosting of tipranavir requires a higher ritonavir dose of 400 mg daily. The most commonly reported side effects in patients treated with TMC-114 were gastrointestinal events.32 A summary of some of the relative advantages and disadvantages among the newer PIs are listed in Table 1.

**Clinical Management of Metabolic Abnormalities**

Before initiating ART, it is a good idea to obtain fasting lipid measurements, keeping in mind the effects of HIV infection on lowering lipid levels (Table 2). An elevated LDL cholesterol level prior to initiating therapy is worrisome and may indicate preexisting dyslipidemia. Before starting treatment, it is also important to exclude diabetes mellitus and assess the patient's overall cardiovascular risk. Once a patient begins ART, it is necessary to monitor changes in lipids as well as fasting glucose. A minimal assessment of lipids should include fasting total cholesterol, HDL cholesterol, and triglycerides. Treatment of hypertension can be helpful in reducing cardiovascular risk. Treatment with statins is warrant-

<table>
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<th>Table 2. Clinical Management of Metabolic Abnormalities</th>
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**Before Choosing/Commencing ART**
- Obtain fasting lipids
  - Consider effect of HIV per se (especially with HDL cholesterol, low LDL cholesterol)
  - ↑ LDL cholesterol likely to be significant, suggestive of preexisting dyslipidemia
- Exclude diabetes mellitus
  - Oral glucose tolerance test to exclude impaired glucose tolerance
- Assess overall cardiovascular risk (NCEP III or similar "risk calculator")
  - Age
  - Family history (vascular disease, diabetes mellitus)
  - Smoking
  - Hypertension
- Assess risk of metabolic abnormalities associated with older PI therapy
  - Exercise; dietary history

**After Choosing/Commencing ART**
- Monitor fasting lipids (every 6 to 12 months)
  - Consider "recovery" effect with lipids/lipoproteins returning to normal levels
  - Minimal assessment includes total cholesterol, HDL cholesterol, triglycerides
  - Importance of non-HDL cholesterol in metabolic syndrome
- Monitor fasting glucose (+ oral glucose tolerance test)
- Manage overall cardiovascular risk
  - Interventions for smoking, hypertension
  - Treatment with statins when 10-year vascular risk >20%
- Encourage lifestyle changes to reduce risk of metabolic abnormalities associated with older PIs
  - Exercise; dietary history
- Monitor nonmetabolic side effects and adherence

**If Metabolic Complications Occur**
- Characterize phenotype
  - Comparison with baseline levels (preexisting dyslipidemia)
  - Predominantly ↑ triglycerides or "metabolic syndrome" phenotype?
  - Evidence of diabetes mellitus or impaired glucose tolerance?
- Assess impact on overall cardiovascular risk
  - Interventions for smoking, hypertension may be effective for decreasing cardiovascular risk
  - Treatment with statins supported when 10-year vascular risk >20%
- Encourage lifestyle changes to reduce risk of metabolic abnormalities associated with older PIs
  - Exercise; dietary history
- Consider other management options
  - Adjunctive therapy (statins, fibrates, insulin-sensitizing agents)
  - Switching (intraclass or switching PI to NNRTI/NRTI)

**ART = antiretroviral therapy; HDL = high-density lipoprotein; LDL = low-density lipoprotein; NCEP = National Cholesterol Education Program; PI = protease inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.**
ed when the 10-year vascular risk exceeds 20%. It is necessary to encourage modification of lifestyle-associated factors, such as smoking, exercise, and diet, to help manage overall vascular risk as well as the risk of metabolic abnormalities.

If metabolic complications occur, the physician has the option to add a lipid-lowering agent or an insulin-sensitizing agent, such as metformin, or to consider switching therapy. Addition of a lipid-lowering agent will not interfere with the antiretroviral sequencing strategy but does introduce the potential for drug interactions with PIs. Switching agents may also introduce drug interactions, which must be considered when devising alternative regimens. It is important to keep in mind that the diabetic dyslipidemia profile is fairly resistant. Lipid-lowering therapy may produce only a moderate effect in these patients. Intensification of the lipid-lowering treatment does not yield a substantially greater effect but does increase side effects. Therefore, if a patient had good lipid levels before starting ART and experiences a return to baseline values, management with a switch strategy may be preferable. Statins are not very effective in treating the profiles induced by some of the older PIs, whereas switch strategies may improve these profiles.

**CONCLUSION**

Continued research is important in refining our understanding of the metabolic complications of PI therapy. Rather than focusing on so-called class effects of PIs, the results of more recent studies have made possible a more individualized approach that distinguishes modifiable from unmodifiable risk factors, emphasizes prevention and monitoring, and tailors treatment to the specific patient. In general, the newer PIs offer important advantages over the older agents, with improved lipid profiles and fewer short-term side effects, characteristics that improve tolerability of new PI-based regimens. Ongoing research efforts will help assess the long-term cardiovascular risk associated with these agents.

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