Management of HIV-associated Hyperlipidemia

Douglas G. Fish, M.D. Albany Medical College, New York, EE.UU.

Disorders of lipid metabolism have been increasingly observed in patients with HIV infection, particularly as a result of highly active antiretroviral therapy (HAART). In the beginning of the HIV epidemic when patients were dying of wasting syndrome in large numbers, the pattern of lipid disturbance was different from that seen in the HAART era. Typically cholesterol was low and triglycerides were high. This was thought to be due, at least in part, to increases in tumor necrosis factor alpha (TNFα).

Today, disorders of lipid metabolism fall under the larger category of HIV-associated metabolic abnormalities that includes insulin resistance, lactic acidosis and the lipodystrophy syndrome. Some of these conditions, such as lactic acidosis, suggest a role for mitochondrial dysfunction, yet these theories don't seem to account for the dyslipidemias seen in HIV-infected patients on antiretroviral therapy. Changes in body morphology, or lipodystrophy, have been seen both with and without concomitant hyperlipidemia.

It is clear that much of the current hyperlipidemia seen in HIV-infected patients is related to HAART. Some antiretroviral drugs are lipid-friendly while others appear to be strongly associated with lipid abnormalities, though not in all patients. Ritonavir appears to be most strongly associated with lipid disorders, and it can be dose-dependent. The lower doses of ritonavir commonly used to boost drug levels of other protease inhibitors are often associated with fewer lipid problems, though some patients are clearly more sensitive and can get large increases of cholesterol and/or triglycerides. Moderate to occasionally severe increases of lipids have also been seen with other protease inhibitors and the non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz. Other antivirals such as nevirapine and atazanavir are lipid neutral, and can even be associated with lipid improvements, such as increased high-density lipoprotein (HDL)-cholesterol. Until recently nucleoside reverse transcriptase inhibitors (NRTIs) were felt to have little role in HIV-associated lipid disorders, but data with stavudine now suggest it can play a significant role in hyperlipidemia.[1,2]

The mechanism(s) by which antiretroviral therapies interfere with lipid metabolism is poorly understood. HAART seems to induce a "normalization" of the HIV effects that lower cholesterol, yet this does not fully account for the sometimes large increases seen in LDL-cholesterol and triglycerides. As patients live longer, the effects of aging on lipid metabolism also need to be kept in mind.

Treatment of lipid disorders in patients on HAART has become common practice in order to maintain patients on their suppressive therapy. One strategy can be antiretroviral substitutions with agents more lipid-friendly. More commonly these patients are treated with lipid-lowering agents to try to normalize or at least improve their lipid profile. The long-term risks of HAART-

associated hyperlipidemia are not clear, though there is obvious concern for cardiac and cerebrovascular complications down the road.

Studies to date have yielded conflicting results on cardiac morbidity and mortality, though one of the most recently published studies that followed over 23,000 patients on combination antiretroviral therapy for a median of 1.9 years found a 26 percent relative increase in the rate of myocardial infarction per year of exposure.[3] This was independent of other known cardiac risk factors, however, the absolute risk of myocardial infarction was low. Other well-established cardiac risk factors were present, as well. 56.2 percent of patients were current or former smokers, 2.8 percent had diabetes, 7.2 percent hypertension, and 45.9 percent dyslipidemia. Another complication of hypertriglyceridemia is pancreatitis, especially if it occurs in the presence of drugs, including alcohol, with known potential to induce pancreatitis.

Deciding whom and when to treat are the biggest issues we face clinically. Referral to a dietitian experienced in lipid management is indicated when hyperlipidemia occurs. Some patients will be successful with this intervention alone, especially when accompanied by an exercise program. These therapeutic lifestyle changes are always appropriate first steps in managing lipid abnormalities. Many patients, however, will require medical therapy in addition. Several sets of guidelines have been published to assist with the management of lipid disorders, though these are not specific to HIV-infected patients. One such guideline, that of the National Cholesterol Education Project in the United States, takes a risk-stratification approach.[4] Any patient with a low-density lipoprotein (LDL)-cholesterol $\geq$190 mg/dl is recommended to consider lipid-lowering therapy. Patients with 2 or more cardiac risk factors, such as a family history of premature coronary heart disease and smoking, are recommended to start therapy if the LDL-cholesterol is $\geq$160 mg/dl, with the goal LDL <130 mg/dl. A subgroup whose calculated risk of coronary heart disease is 10-20% is recommended to consider lipid-lowering therapy for LDL-cholesterol $\geq$130 mg/dl. Patients with a history of coronary heart disease or a coronary heart disease risk equivalent are recommended to start treatment if the LDL-cholesterol is $\geq$130 mg/dl, with the goal of treatment being an LDL <100 mg/dl.

The fibrates and niacin compounds work to lower triglycerides, and can be used in patients in HAART. The potential for drug-drug interactions is an obvious concern, and routine monitoring of liver enzymes and creatine kinase levels is recommended. For elevations in cholesterol, pravastatin and atorvastatin appear safest, having the least interaction with the cytochrome P450 system. Other statin drugs are not recommended in patients on protease inhibitors. Combination therapy is sometimes indicated, where a patient requires both a statin-type drug and a fibrate or niacin, in addition to diet and exercise. Omega-3 fatty acids, available as fish oil capsules, can also be helpful in lowering triglycerides. If patients are overweight, an exercise program geared at weight loss can help significantly with lipid control.

In summary, disorders of lipid metabolism have become commonplace among HIV-infected patients on antiretroviral therapy. Many infectious disease practitioners have had to familiarize themselves with lipid-lowering guidelines in order to maintain their patients on HAART. This is a challenge we welcome, as a small price to pay, for the life-saving effects of HAART. It is

clear that the benefits of HAART significantly outweigh the risks. Ongoing and additional prospective studies will help us answer questions regarding the long-term consequences of antiretroviral therapy, and how to avoid or at least better control these adverse events..

1. Kumar P *et al.* Determinants of hyperlipidemia in ART-naïve subjects treated with trizivir, combivir/nelfinavir, or stavudine/lamivudine. In: Programs and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, Feb. 8-11, San Francisco, CA 2004. Abstract 713.
2. Powderly W *et al*. Lipid abnormalities and body habitus in a double-blind, randomized, controlled trial comparing emtricitabine to stavudine in HIV+ ART-naïve patients. In: Programs and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, Feb. 8-11, San Francisco, CA 2004. Abstract 717.
3. The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl. J Med 2003;349:1993-2003.
4. National Heart, Lung, and Blood Institute, National Institutes of Health. National Cholesterol Education Program: Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III); September, 2002.