SAFETY AND TOLERABILITY OF CURRENTLY AVAILABLE ANTIRETROVIRAL AGENTS*

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ABSTRACT

Safety and tolerability are important factors to consider when instituting or modifying therapy with antiretroviral drugs because they are major determinants of adherence to therapy and, by extension, of long-term clinical outcome.

Because each of the 3 classes of antiretroviral agents are associated with different manifestations of toxicity, it is possible to choose regimens that minimize the occurrence of certain adverse effects and to consider switching regimens if certain side effects occur. Short-term complications of antiretroviral therapy may be unpleasant and lead to early noncompliance or partial compliance with therapy, thereby lessening the efficacy of therapy; however, long-term complications, such as lipodystrophy and various metabolic abnormalities, are most troublesome. Recent studies have shown that switching regimens can favorably alter fat distribution in patients with lipoatrophy and that lipoatrophy is not irreversible.

With regard to increased risk for cardiovascular disease in patients taking antiretroviral therapy—many of whom have lipid and other metabolic abnormalities—one recent study has shown that HIV-infected patients are far less likely to die from a cardiovascular event compared with the general population. Moreover, a meta-analysis involving more than 15,000 patients with HIV has found that the adjusted relative risk for a myocardial infarction is lower for each additional year of combination antiretroviral therapy than it is for each 5-year increment in age, male sex, smoking, and previous cardiovascular disease.


Safeg and tolerability of antiretroviral regimens are major issues in the management of HIV and AIDS because of their considerable impact on adherence to therapy and, ultimately, on clinical outcome. Of particular concern are the short-term side effects that often lead to early noncompliance or partial compliance with therapy, as well as long-term effects, such as lipodystrophy and alterations in the lipid profile and other metabolic parameters that can lower the likelihood of long-term adherence to therapy and long-term success. Thus, choosing initial antiretroviral regimens with less toxicity and better tolerability is crucial.

TOXICITY, TOLERABILITY, AND ADHERENCE TO THERAPY

Video Commentator: In our clinic, we are now trying to choose initial regimens that promote adherence to therapy, are user-friendly, and are easy to take. I think the...
outcome of an initial regimen is very much dependent on its short-term tolerability—in other words, how easy is it for the patient to start taking it without any side effects, particularly gastrointestinal side effects—and its long-term tolerability. Both of these factors are incredibly important in promoting adherence to therapy.

Each of the 3 classes of antiretroviral drugs is associated with different manifestations of toxicity, with the manifestations differing by degree within each class. The nucleoside reverse transcriptase inhibitors (NRTIs) are associated with mitochondrial toxicity, which may manifest as neuropathy, myopathy, pancreatitis, hepatitis, myelotoxicity, lactic acidosis, and lipoatrophy. The nonnucleoside reverse transcriptase inhibitors (NNRTIs) are associated with hypersensitivity reactions, such as exanthems, fever, mycoses, and multiorgan dysfunction. The protease inhibitors (PIs) are associated with metabolic abnormalities, such as hyperlipidemia, insulin resistance, type 2 diabetes, increased visceral fat, and possible bone disease.

Adverse events associated with antiretroviral therapy are typically underestimated in clinical trials. Only recently have investigators been taking a closer look at lipodystrophy and metabolic parameters, such as lipid and lipoprotein fractions, glucose, insulin, and lactate. In the few clinical trials that have addressed these problems, the approach has been inconsistent. Moreover, there has been no guidance, and no recommendations from public health and regulatory agencies have been issued on this point. Side effects that are not addressed in clinical trials and are therefore rarely studied include dermatitis and retinoid effects on the skin, osteopenia, osteonecrosis, and loss of libido. Nevertheless, the overall tolerability of an antiretroviral regimen, along with its potency, is a major determinant of long-term success (Figure 1).

**LONG-TERM COMPLICATIONS**

**Video Commentator:** The dominant clinical issues at this time are how to ensure long-term adherence to therapy despite long-term complications of treatment. The most obvious long-term complication of antiretroviral therapy is loss of fat, particularly in the arms and legs, which occurs after a certain limited period of time. Lipodystrophy results not only from antiretroviral therapy with NRTIs and PIs, but also from genetic and environmental factors in the host and from the chronic inflammation and immune reconstitution of HIV itself. Therefore, modifying the drug regimen and/or one or more of the other contributing factors may modify lipodystrophy.

In the ACTG 384 study, patients with similar clinical status were randomized to 1 of 4 treatment arms: NRTI therapy with zidovudine plus lamivudine, NRTI therapy with didanosine plus stavudine, NNRTI therapy with efavirenz, or PI therapy with nelfinavir. As shown in Figure 2, the median percentage change in limb fat from baseline was an increase of approximately 10% during the first 16 weeks of therapy and a steady decline in limb fat from week 16 through week 80 in all 4 treatment arms. The only difference between the NRTI arms (Figure 2A) and the NNRTI and PI arms (Figure 2B) was the rapidity and degree of fat loss after week 16.

Loss of abdominal fat also occurs over time with antiretroviral therapy. In Study 006, for example, intra-abdominal and subcutaneous fat was measured by abdominal computed tomography (CT) scan in 108 patients completing 1 year of therapy with the NNRTI/NRTI regimen of efavirenz plus zidovudine plus lamivudine, in 89 patients completing 1 year of therapy with the NRTI/NRTI regimen of zidovudine plus lamivudine, and in 94 patients completing 1 year of therapy with the PI regimen of nelfinavir plus zidovudine plus lamivudine.

**Figure 1. Impact of Regimen Tolerability and Potency on Long-term Success**

- Lack of Minor & Persistent Drug-Associated Symptoms
- Ease of Dosing
- Long-term Success
therapy with the NNRTI/PI regimen of efavirenz plus indinavir, and in 80 patients completing 1 year of therapy with the PI/NRTI regimen of indinavir plus zidovudine plus lamivudine. A second abdominal CT scan taken 1 year after the first showed that patients on each of the 3 regimens lost large amounts of subcutaneous fat and smaller amounts of intra-abdominal fat over the course of the year.

The results of this study echo the results of other studies that have evaluated fat loss in patients receiving antiretroviral therapy. All currently available data indicate that fat loss can be expected, either soon after the start of treatment or at 1 year.

**Switching Therapies**

To address the issue of lipodystrophy, some studies have investigated switching regimens, their impact on fat loss and gain, and the potential for improvement in patients with lipoatrophy.

In the MITOX study, which evaluated changes in limb fat for 72 weeks after the initiation of therapy, some patients remained on abacavir, some remained on stavudine plus zidovudine, and some switched at week 24 from stavudine plus zidovudine to abacavir. As shown in Figure 3, the patients who were switched did not continue to gain limb fat at the same rate as those who had been on abacavir therapy from the beginning, but did gain more limb fat than those who remained on stavudine plus zidovudine. The change in the abacavir-only group is a big one, representing about one third of the fat in the limb and a beneficial effect on reversing lipoatrophy. The major finding of the study is that lipoatrophy is not irreversible, which is very important from the patient's point of view and in terms of new therapies to be developed.

Another study exploring the effects of switching therapy on fat distribution is the Perth Switching Study, a randomized, controlled trial in which patients with clinical lipoatrophy, as measured by dual-energy x-ray absorptiometry scans, were switched from regimens containing stavudine and/or a PI to lamivudine/zidovudine plus abacavir, whereas those with apparently normal fat distribution remained on stavudine and/or a PI and served as controls. As shown in Figure 4, patients who were switched gained fat, whereas the controls lost fat after 1 year. Although the amount of fat gained over 1 year is low, the study demonstrates that changing the regi-

* Figure 2. Median Percentage Change in Limb Fat from Baseline by Treatment Arm (ACTG 384)

Adapted from Dubé et al.1

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NRTI = nucleoside reverse transcriptase inhibitor; AZT = zidovudine; 3TC = lamivudine; ddI = didanosine; d4T = stavudine; PI = protease inhibitor; EFV = efavirenz; NFV = nelfinavir.

Adapted from Dubé et al.1
men can change the distribution of fat in a positive direction. It also suggests that more time is needed to reverse lipoatrophy.

**CARDIOVASCULAR RISKS**

**Video Commentator:** Another issue that comes up more and more is how to manage the hyperlipidemia seen with some of the agents used to treat HIV infection. When infectious disease was a hospital-based specialty dealing primarily with short-term bacterial infections, little thought was given to the long-term implications of elevated cholesterol and triglyceride levels. However, advances in the past few years have deepened our understanding of the impact of lipid abnormalities on cardiovascular disease and resulted in the development of effective lipid-lowering agents to reduce risk when used in conjunction with diet and exercise. How do you manage lipid abnormalities in your patients on antiretroviral therapy?

The first step is to review the evidence regarding the risk for cardiovascular disease in HIV-infected patients. In the general population, the risk factors for cardiovascular disease are well known, are multifactorial, may be present for many years before cardiovascular symptoms develop, and are not drug induced. There is also unequivocal evidence that intervention with lipid-lowering agents is beneficial. Although it seems reasonable to say that lipid-lowering therapy would be similarly beneficial in HIV-infected patients, there are not yet any long-term intervention studies on lipid-lowering therapy in these patients.

What is known is that the prevalence of metabolic abnormalities is higher in HIV-infected patients—whether they are on antiretroviral therapy or not—compared with the general population. These patients are therefore at higher risk for changes in body fat distribution, which are often worsened by antiretroviral therapy. However, it is unclear whether antiretroviral therapy itself increases the risk for cardiovascular disease.

A recent study investigating the causes of death in a cohort of 163 HIV-infected patients and 38,859 persons between 16 and 64 years of age residing in the Catalonia region in Spain...
(ie, the general population) found that death due to a cardiovascular event was nearly 4 times as likely in the general population (19%) than in persons infected with HIV (5%). Another study, a meta-analysis involving more than 15,000 patients treated at various institutions in many countries, found that the adjusted relative risk for a myocardial infarction (MI) was lower per each additional year of combination antiretroviral therapy (1.26) than the adjusted relative risks per each 5-year increment in age (1.9), male sex (3.6), smoking (3.8), and previous cardiovascular disease (13.8). The study underscores both the relative safety of combination antiretroviral therapy and the danger of smoking with regard to cardiovascular risk. These findings serve as a reminder that it is perhaps more important to encourage patients who smoke to recognize the dangers of smoking and quit than it is to try to design an antiretroviral regimen that minimizes cardiovascular risk.

Assessing a patient’s risk for cardiovascular disease, choosing an antiretroviral regimen, and deciding whether—and which—lipid-lowering therapy is appropriate should be counterbalanced against the proven benefits of highly active antiretroviral therapy (HAART). Recognizing that HIV infection is a chronic disease should also be factored into the assessment. As a recent study has shown, the absolute risk of MI remains low in patients receiving HAART.

REFERENCES

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