Getting Smarter — The Toxicity of Undertreated HIV Infection
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Soon after the benefits of potent combination antiretroviral therapy were recognized in the late 1990s, clinicians understood that patients would need to be highly adherent to antiretroviral therapy and treated continuously with combination regimens. If this mark were not met, there was a real likelihood that a resistant virus would emerge. As experience with combination regimens expanded, data became available on long-term toxic effects, including dyslipidemia, changes in body fat, possibly increased cardiovascular risk, and hepatitis. Although infection with the human immunodeficiency virus (HIV) became a more manageable chronic disease, concerns about side effects led both patients and investigators to consider options for limiting exposure to antiretroviral therapy.

Several small, mostly uncontrolled studies suggested that antiretroviral therapy might be safely interrupted for varying periods of time, especially among patients with CD4+ counts of more than 350 cells per cubic millimeter and in whom HIV replication had been suppressed. On the basis of these findings, a number of investigators tested the use of both limited interruptions of antiretroviral therapy and treatment strategies guided by the CD4+ count. However, these studies also indicated that patients with AIDS or low nadir CD4+ counts would probably not be able to tolerate long interruptions of treatment. Whether withholding therapy for long periods would result in HIV-associated complications remained unknown.

To answer this question, the Strategies for Management of Antiretroviral Therapy (SMART) trial, presented in this issue of the Journal by the SMART study group, was designed.

The design of the SMART trial was controversial. In 2000 through 2002, when the study was on the drawing board, the scientific community was divided as to the appropriateness of the question. Some believed that it was hazardous to stop antiretroviral therapy in patients with a history of AIDS, whereas others thought there was equipoise between the risk of disease progression and the risk of toxic effects from the use of medication in the setting of close monitoring. In the end, the majority of the scientific community agreed that answering the question was critical, and the National Institutes of Health concurred.

The SMART study tested the strategy of intermittent antiretroviral therapy, guided by the CD4+ count, in patients with chronic infection with HIV. In this open-label study, more than 5400 volunteers infected with HIV who had CD4+ counts greater than 350 cells per cubic millimeter were randomly assigned to either continuous antiretroviral therapy (the viral suppression group) or to intermittent antiretroviral therapy (the drug conservation group), administered when the CD4+ count fell to less than 250 cells per cubic millimeter and stopped when the count rose to more than 350 cells per cubic millimeter. Patients in the viral suppression group received antiretroviral therapy 94% of the time, as compared with 33% of the time in the drug conservation group. It was estimated that an average of 6 years of follow-up would be required to reach the desired number of end points. The study was terminated early, with an average of 16 months of follow-up, owing to a significant increase in the hazard ratios for the drug conservation group to 2.6 for opportunistic disease or death from any cause and to 1.7 for major cardiovascular, renal, or hepatic disease. This definitive finding of the superiority of continuous treatment over intermittent treat-
ment is important for the field and should strengthen current efforts to promote adherence to therapy once it has been started.

Why was the drug conservation strategy inferior? The rate at which opportunistic diseases, most commonly esophageal candidiasis, developed in patients in the drug conservation group was not completely unexpected. However, the overall rate of death and the higher-than-expected rate of major cardiovascular, renal, or hepatic disease in the drug conservation group exceeded predictions. The precipitous decline in the CD4+ count and the rapid loss of virologic control (as evidenced by an increase in the percentage of patients with a detectable plasma HIV RNA level from 6% to 72%) — within 2 months after the cessation of antiretroviral therapy in the drug conservation group — largely explain the higher event rates. (On average throughout follow-up, the CD4+ count was 206 cells per cubic millimeter lower than that in the viral suppression group.) It is notable that the increase in mortality in the drug conservation group as compared with the viral suppression group was not clearly associated with traditional HIV-related events; the cause of more than a quarter of the deaths in the drug conservation group was unknown. The benefit of the viral suppression strategy relative to the drug conservation strategy was shown consistently in all subgroups evaluated — even among patients in whom CD4+ counts of more than 350 cells per cubic millimeter were maintained throughout follow-up and among those who had a loss of virologic control that was independent of the CD4+ count — and is consistent with the results of early studies examining the relation between viral load and the risk of opportunistic disease. This finding shows that we still have much to learn regarding the detrimental effects of uncontrolled HIV replication.

The results of the SMART study remind us of the benefit of using adequately powered randomized trials to evaluate new treatment strategies in clinical medicine. The most unexpected finding was that the rates of nonopportunistic disease and death were higher in the drug conservation group than in the viral suppression group. The drug conservation group should have been relatively protected from events that are usually relatively protected from events that are usually less toxic.

Should the findings of the SMART trial end the study of intermittent therapy in patients infected with HIV? Perhaps, but it is still unknown whether intermittent antiretroviral strategies may be appropriate in certain circumstances, such as in the setting of acute HIV infection, in women with CD4+ counts of more than 350 cells per cubic millimeter who receive antiretroviral therapy to prevent mother-to-child transmission of the virus, or with the use of shorter episodes of treatment interruption in patients with chronic HIV infection. We may learn that the only people in whom therapy can be safely interrupted for long periods are those who do not require it in the first place. Given the deleterious effects of uncontrolled HIV replication, we must continue to reevaluate the optimal criteria for the initiation of antiretroviral therapy. In the future, we can only hope to be smart enough to identify ways to make antiretroviral therapy less costly and less toxic.

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Thiazolidinediones for Nonalcoholic Steatohepatitis — Promising but Not Ready for Prime Time

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Mostly unrecognized before 1980, nonalcoholic fatty liver disease now affects all fields of clinical medicine and is the most common form of chronic liver disease in the United States.1 The prevalence of this disorder is expected to increase with the epidemic of obesity and type 2 diabetes mellitus. Its prevalence in non-Western countries is also increasing,2 in large part because of globalization of the Western diet. Data based on ultrasonographic studies and serum enzyme measurements indicate that the prevalence of nonalcoholic fatty liver disease in the general U.S. population is approximately 30%.3,4 This suggests that there may be as many as 90 million cases of nonalcoholic fatty liver disease in the United States. There are no reliable data on the prevalence of nonalcoholic steatohepatitis — the most severe form of nonalcoholic fatty liver disease. However, a review of the literature3 suggests a prevalence of approximately 5 to 6%.

Nonalcoholic steatohepatitis represents the extreme end of a large clinical spectrum of nonalcoholic fatty liver disease.4 The histologic features of nonalcoholic fatty liver disease range from fat alone to fat plus inflammation to fat plus hepatocyte injury (ballooning degeneration) with or without fibrosis, polymorphonuclear infiltrates, or Mallory’s hyaline. These histologic categories are important because they are associated not only with the prevalence of the disorder but also with the clinical outcomes.

Cirrhosis develops in 9 to 25% of patients with nonalcoholic steatohepatitis.5 Once it develops, 30 to 50% of these patients die from a liver-related cause during a 10-year period.4 This mortality rate is similar to6 or worse than7 that for cirrhosis associated with hepatitis C. Cirrhosis in patients with nonalcoholic steatohepatitis can also decompensate into subacute liver failure, progress to hepatocellular cancer, and recur after liver transplantation.3 Steatosis alone is reported to have a more benign clinical course, with cirrhosis developing in only 1 to 3% of patients.3,4

Currently, the most widely accepted pathophysiological model of nonalcoholic fatty liver disease is a two-hit process. The first hit is the development of steatosis caused by insulin resistance. Insulin resistance has been closely linked to nonalcoholic fatty liver disease in both clinical trials and laboratory-based studies.7 Insulin clamp studies8,9 have shown insulin resistance in muscle, adipose tissue, and liver in patients with nonalcoholic fatty liver disease. Alterations in several cytokines (including elevated levels of tumor necrosis factor [TNF] and interleukin-6 and decreased adiponectin levels) have been proposed as mediators of insulin resistance, although the precise mechanism remains incompletely defined. This close association between insulin resistance and nonalcoholic fatty liver disease has led to the concept that this disease is the hepatic component of the metabolic or insulin resistance syndrome, which is defined by increased waist circumference, elevated triglyceride levels, decreased high-density lipoprotein levels, hypertension, and glucose intolerance. The second hit involves the processes in the progression from steatosis to nonalcoholic steatohepatitis, which occur in a substantial but yet-to-be-determined percentage of patients. The major processes in the second hit that have been identified to date include cytokine-mediated inflammation, lipid peroxidation, and apoptosis.7

On the basis of this concept, a number of