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EDITORIAL COMMENT

Nutritional Therapy to Prevent Dyslipidemia in Patients Starting Antiretroviral Therapy for Human Immunodeficiency Virus*

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> *"As long as a person exercises and exerts himself a lot, takes care not to eat to the point of being completely full, and keeps his bowels soft, illness will not come upon him and his strength will increase."*
> —Maimonides, Hilchot Deot 4:15, 12th Century

With the advent of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) infection has become a chronic disease. As patients with HIV live longer, they are at increasing risk for more common diseases of Western society such as cardiovascular disease (CVD). Indeed, CVD has the highest age-adjusted mortality rate among individuals with HIV, second only to complications of HIV (1). Although aging and traditional risk factors such as tobacco use and dyslipidemia are major CVD risk factors for patients with HIV, it is likely that other factors, including persistent inflammation, viremia, and immune activation as well as specific HAART medications increase HIV patients' risk of CVD. It also is well

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recognized that initiation of HAART is associated with dyslipidemia (2,3). Dyslipidemia appears to be most dramatic after initiation of ritonavir-boosted protease inhibitor regimens, although newer protease inhibitors such as atazanavir and darunavir have relatively less adverse lipid effects. Non-nucleoside reverse transcriptase inhibitors also cause dyslipidemia, and most patients on HAART receive protease inhibitors or non-nucleoside reverse transcriptase inhibitors as the backbone of their multidrug HAART regimen. Newer agents such as maraviroc (an entry inhibitor) and raltegravir (an integrase inhibitor) seem to have minimal lipid effects, but these agents are less commonly used in the United States and worldwide. Guidelines for dyslipidemia emphasize dietary therapy; however, there is little information about the efficacy of dietary interventions among patients with HIV (3,4). Previous studies suggested that the effects of dietary interventions in HIV-infected patients were modest, but those studies were observational or small.

In this issue of the *Journal*, Lazzaretti et al. (5) describe the important results of a prospective, randomized clinical trial of a dietary intervention involving 83 HIV-infected patients beginning their first HAART regimen. The dietary intervention was based on recommendations from the National Cholesterol Education Program (NCEP), which primarily lower total and low-density lipoprotein (LDL) cholesterol levels (4). The prescribed diet limited calories to maintain or reduce weight, restricted fat intake to 25% of total calories, prescribed an especially low intake of saturated fat, and was high in fiber. The investigators provided quarterly nutritional guidance from a registered dietician—an important component of the intervention that should not be overlooked, because standard clinical practice usually involves simple dietary recommendations ("eat less fat"). Behavioral health intervention research emphasizes that long-term behavioral changes are more likely to occur when there is repeated reinforcement though contact with healthcare providers. Methodologically, the authors improved the reliability of 24-h food records by supplementing them with photographic food records. Their robust statistical analysis focused on the interaction of time by treatment group.

Participants in this study most commonly were prescribed a HAART regimen that included zidovudine and lamivudine, nucleoside reverse transcriptase inhibitors that do not have major lipid effects, and efavirenz. Efavirenz was used in 80% of the patients assigned to diet and 85% of the patients assigned to the control regimen, with the remaining subjects predominantly receiving boosted protease inhibitors. The control group had expected increases in total cholesterol that were significantly blunted with the dietary intervention group ($p < 0.001$). In the control group, LDL cholesterol levels increased with HAART initiation, on average, from 85 to 106 mg/dl, but did not change in diet group ($p < 0.001$). Similarly, triglycerides increased in the control group from 134 to 160 mg/dl, but decreased in the dietary intervention group from 135 to 101 mg/dl ($p < 0.001$). Both groups experienced similar increases in HDL cholesterol levels. These lipid changes are relevant clinically. On a population basis, a 1% reduction in total cholesterol reduces coronary heart disease risk by approximately 2%, so the 15% between arms difference in total cholesterol levels observed after 12 months would be expected to lead to a long-term CVD risk reduction of approximately 25% to 30% (4).

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Participants prescribed the interventional diet had significantly lower intakes of total calories, total fat, and saturated fat, with a striking reduction in cholesterol intake, from an average of 406 to 144 mg daily. The average daily intake of total cholesterol among the participants was much higher than consumed in the average American diet. Thus, it is likely that the high baseline dietary intake of cholesterol accentuated the reductions in total and LDL cholesterol levels observed with the intervention, because baseline *saturated fat* intake and its reduction were typical of patients who start a reduced-fat diet. The other dramatic change was the significant increase in fiber intake, which increased from a fairly common intake level of approximately 19 g/day to slightly above that recommended by the NCEP (30 g/day). Increasing dietary fiber intake by 10 g daily would be expected to lower LDL cholesterol by approximately 5%.

The observed triglycerides reduction was surprising, because carbohydrate intake increased. These findings suggest that the hypertriglyceridemia observed with HAART initiation may not be solely due to insulin resistance. However, the increase in BMI observed after starting HAART was significantly blunted in patients on the interventional diet and the waist-to-hip ratio did not appear to increase as much, either. These changes would be expected to have salutary effects on triglycerides as well as inflammation. It would have been useful if the authors had evaluated changes in inflammation and markers of immune activation, which are hypothesized to influence CVD risk in patients with HIV. Effects on immune activation are especially important during the immune reconstitution phase of ART initiation.

The insights provided by the dietary intervention are an important addition to the literature and re-emphasize that dietary interventions can be as effective as low-dose statin therapy for preventing and treating dyslipidemia associated with HAART. The authors hypothesized that the significant lipid improvements they observed may have been due to the patients starting HAART rather than being on chronic therapy, as in previous lifestyle intervention studies. That is a plausible and testable hypothesis. It also is likely that the quality of the dietary intervention (i.e., repeated contact with dieticians and significant increases in dietary fiber), the subjects' high baseline intake of dietary cholesterol, and the larger sample size may explain why they were able to observe improvements in lipids when others did not. I would not be as sanguine as the authors in suggesting that exercise training does not improve the lipid profile. Previous studies suggesting that exercise interventions in HIV-infected patients are ineffective were small and did demonstrate other salutary effects of exercise on markers of CVD risk, including cardiovascular fitness, endurance, and in one study, blood pressure and hemoglobin A_1C. Patients who are able to perform regular aerobic exercise would be expected to have better lipids if the intervention assists with weight loss or prevents weight gain.

Thus, like the medieval Jewish philosopher and physician Maimonides suggested, it is likely that patients living with HIV infection who do not eat too much (i.e., calorie restriction) and who eat fruits, vegetables, nuts, and whole grains (i.e., high-fiber, low-cholesterol, and low-fat foods that keep the "bowels soft") will benefit by avoiding illness and improving quality of life. For patients living with HIV infection, avoiding dyslipidemia also avoids, or at least delays, use of lipid-lowering medications, which are expensive and are complicated to use in patients on HAART. In conclusion, the authors are correct; nutritional interventions can prevent adverse changes in the lipid profile of HIV-infected patients who start HAART. Their findings emphasize the importance of nutritional interventions at the time of HAART initiation to improve CVD risk factors.

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