Alterations in Serum Levels of Lipids and Lipoproteins with Indinavir Therapy for Human Immunodeficiency Virus–Infected Patients

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Alterations in lipid metabolism have been associated with the use of protease inhibitors. Sequential lipid analyses were performed on serum samples from human immunodeficiency virus–infected antiretroviral-naive patients who received indinavir in combination with two nucleoside reverse transcriptase inhibitors. Serum levels of cholesterol, triglycerides, high-density lipoproteins (HDLs), and low-density lipoproteins (LDLs) were measured at baseline and at periodic intervals. After 48 weeks of indinavir therapy, mean serum levels ± SD rose as follows: cholesterol, from 167.2 ± 36.0 to 206.3 ± 32.4 mg/dL (P < .0005); triglycerides, from 110.4 ± 47.5 to 158.4 ± 72.5 mg/dL (P < .0010); and LDLs, from 106.6 ± 35.1 to 136.1 ± 31.6 mg/dL (P = .0029). There was no significant change in the serum HDL fraction. Mean serum lipoprotein (a) levels ± SD rose from 6.5 ± 1.4 to 9.6 ± 2.0 mg/dL after 30 weeks (P = .0695). Potential mechanisms for the noted increases include alterations in serum lipoprotein lipase activity or changes in hepatic lipid metabolism. The clinical significance of these changes remains to be determined.

Protease inhibitors are pivotal components of highly active antiretroviral therapy and when combined with other antiretroviral agents provide effective means of reducing plasma concentrations of HIV. As experience with their use broadens, the array of adverse effects observed in patients who are receiving treatment with these agents grows. Among the wide variety of idiosyncratic and toxic effects associated with protease inhibitors has been increasing evidence of abnormalities in lipid and carbohydrate metabolism. Both hyperlipidemia and elevated serum glucose concentrations have been recognized in patients receiving protease inhibitor therapy.

Abnormalities in fat distribution, including enlargement of the dorsocervical fat pad, increased abdominal fat, and, in women, breast enlargement, have been described by several investigators [1–5]. Carr and co-workers [6] studied patients receiving treatment with protease inhibitors who developed peripheral lipodystrophy characterized by central adiposity combined with fat wasting of the face and limbs. They suggested that this body habitus, as well as the observed hyperlipidemia and diabetes mellitus seen in such patients, may be due to abnormal lipid release or storage via adipocyte apoptosis. They also noted that there was significant homology between the catalytic site of protease inhibitors and two proteins that regulate lipid metabolism [7].

Materials and Methods

Antiretroviral-naive HIV-infected patients who were referred to the Infectious Diseases Clinical Trials Unit (The George Washington University Medical Center, Washington, D.C.) for inclusion in a clinical study of indinavir with either of two combinations of nucleoside reverse transcriptase inhibitors (zidovudine/lamivudine or stavudine/didanosine) were invited to participate in a prospective analysis of serum lipids. None of the patients had a history of lipid disorders. There was only one female patient in the study. Serum lipid levels in all patients were measured sequentially at 0, 4, 8, 18, 30, and 48 weeks of therapy while the patients were fasting. All lipid analyses were done in the Lipid Research Laboratory at The George Washington University Medical Center. Cholesterol and triglyceride levels were measured enzymatically, and high-density lipoprotein (HDL) levels were measured by the procedure of Gidez et al. [8]. Serum lipoprotein (a) levels were measured at baseline and at week 30 by an ELISA with use of monoclonal antibody (Wampole Laboratories, Cranberry, NJ).

A two-tailed Student’s t test for paired samples was used for data analysis.

Results

There were 17 patients who completed the 48-week study. At 48 weeks, nine of the 17 patients had received the nucleosides zidovudine and lamivudine in combination with indinavir, whereas the remainder of the patients had received stavu-
dine and didanosine in combination with indinavir. There were no statistically significant differences in any of the measured parameters between the individuals who received zidovudine/ lamivudine and indinavir and those who received stavudine/ didanosine and indinavir. At baseline, the patients had a mean CD4 cell count ± SD of 379.4 ± 157.0/mm³ and a mean plasma HIV RNA concentration ± SD of 62,816.1 ± 54,376.9 copies/mL; after 48 weeks, the mean CD4 cell count ± SD was 575.8 ± 215.0/mm³, and all patients had plasma HIV RNA concentrations of <500 copies/mL. There was a trend toward weight gain in the 17 patients, but the differences were not statistically significant. The mean weight ± SD at initiation of therapy was 80.9 ± 14.0 kg, which increased to 82.0 ± 13.8 kg after 48 weeks. No assessment of lipodystrophy in our patients was done.

The changes in serum levels of cholesterol, triglycerides, HDLs, and low-density lipoproteins (LDLs) in antiretroviral-naive HIV-infected patients receiving treatment with indinavir at weeks 0, 8, 18, 30, and 48 are shown in figure 1. During the 48-week study period, mean serum cholesterol levels ± SD steadily increased from 167.2 ± 36.0 to 206.3 ± 32.4 mg/dL (P < .0005), and mean serum triglyceride levels ± SD rose from 110.4 ± 47.5 to 158.4 ± 72.5 mg/dL (P < .0101). There was no significant change in mean serum HDL concentrations ± SD during the 48-week study period (from 39.1 ± 7.6 mg/dL at week 0 to 38.5 ± 9.1 mg/dL after 48 weeks). However, mean serum LDL levels ± SD rose from 106.6 ± 35.1 to 136.1 ± 31.6 mg/dL (P = .0029). We also found that mean serum lipoprotein (a) levels ± SD after 30 weeks were higher than those at baseline, although these results failed to achieve statistical significance (increase from 6.5 ± 1.4 to 9.6 ± 2.0 mg/dL [P = .0695]).

![Figure 1](https://academic.oup.com/cid/article-abstract/29/2/441/274398)

**Figure 1.** Changes in serum concentrations (mg/dL) of cholesterol (●), triglycerides (○), high-density lipoproteins (■), and low-density lipoproteins (▲) in antiretroviral-naive HIV-infected patients receiving indinavir treatment in combination with two nucleoside reverse transcriptase inhibitors.

**Discussion**

Antiretroviral protease inhibitors effectively lower plasma HIV concentrations and have been shown to have a demonstrably beneficial effect on the progression of HIV disease [9]. However, the use of these agents has been paralleled by an increasing array of adverse effects. In this study, indinavir treatment was associated with a statistically significant increase in mean serum cholesterol, triglyceride, and LDL levels ± SD, while mean serum HDL concentrations ± SD remained essentially unchanged. Similar increases in cholesterol and triglyceride concentrations in patients treated with ritonavir were reported by other investigators [10]. The observed changes in the serum lipid concentrations occurred as early as 8 weeks after initiation of therapy and generally increased over time.

Abnormalities in lipid metabolism were noted in association with HIV infection before the use of protease inhibitors. Most frequently, HIV-infected individuals, especially those with advanced disease, have depressed serum cholesterol concentrations, which is typical of cachexia (i.e., wasting syndrome) [11]. These patients, like ours, often have elevated serum triglyceride levels, although the mechanism of hypertriglyceridemia may be quite different. In patients with advanced AIDS, elevations in serum triglyceride levels may be due, at least in part, to TNF-mediated inhibition of serum lipoprotein lipase activity [11].

The mechanisms whereby serum lipid levels are increased in patients receiving treatment with protease inhibitors remain unclear. Carr et al. [7] found homology between the catalytic site of protease inhibitors and two proteins that regulate lipid metabolism. They proposed that binding to one of these proteins (cytoplasmic retinoic-acid binding protein type 1) affects the regulation of peripheral adipocyte differentiation and apoptosis, while binding to the other (LDL receptor–related protein) impairs hepatic chylomicron uptake and triglyceride clearance. This binding results in hyperlipidemia and contributes to central fat deposition.

The clinical significance of these elevations in serum lipid levels remains to be determined. The possibility exists that prolonged therapy with these agents might lead to accelerated atherosclerotic disease or pancreatitis. We have seen two young men with acute coronary symptoms who received protease inhibitors for 8 months and 1 year. Whether these agents had any role in the development of coronary artery disease in these patients is speculative at this point. Nevertheless, the trend toward increased lipoprotein (a) concentrations observed in our study suggests that these agents may have a significant role in promoting lipid deposition in coronary vessels since this protein is thought to be a risk factor for the development of premature coronary artery disease in men [12].
References


