Lipid disorders in antiretroviral-naive patients treated with lopinavir/ritonavir-based HAART: frequency, characterization and risk factors

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Objectives: The aim of this study was to evaluate the frequency, characteristics and risk factors of lipid changes associated with lopinavir/ritonavir treatment in antiretroviral-naive patients.

Methods: A prospective cohort of 107 antiretroviral-naive HIV-infected patients was followed for 12 months after starting lopinavir/ritonavir-based highly active antiretroviral therapy.

Results: At 12 months, percentages of patients with hypercholesterolaemia and hypertriglyceridaemia were 17.4% and 40%, respectively. Mean increases in total cholesterol and triglycerides were 40.7 and 73.3 mg/dL. There was a significant increase in both low-density and high-density (HDL) cholesterol, and no increase in the total cholesterol/HDL ratio (from 4.16 at baseline to 4.49 after 12 months). Baseline cholesterol > 200 mg/dL and triglycerides > 150 mg/dL were independent risk factors for dyslipidaemia, while hepatitis C coinfection appeared to be protective.

Conclusions: Patients with elevated lipid values at baseline have the greatest risk of developing hypercholesterolaemia and hypertriglyceridaemia after starting lopinavir/ritonavir. Antiretroviral-naive patients coinfected with hepatitis C have a low risk of developing hyperlipidaemia after starting lopinavir/ritonavir.

Keywords: antiretroviral therapy, hypercholesterolaemia, hypertriglyceridaemia, cholesterol, triglycerides, high-density cholesterol, low-density cholesterol

Introduction

Lopinavir/ritonavir is a boosted protease inhibitor that has been recommended as one of the preferred combinations with which to start antiretroviral treatment in HIV-infected patients. Dyslipidaemia is an important adverse event of lopinavir/ritonavir. In the pivotal clinical trial of lopinavir/ritonavir in antiretroviral-naive patients, significant increases in serum cholesterol and triglycerides were seen. There is no information about lipid changes after starting lopinavir/ritonavir in patients outside of clinical trials.

In the present study, we evaluated lipid changes associated with lopinavir/ritonavir-based highly active antiretroviral therapy...
Hyperlipidaemia after lopinavir/ritonavir

Patients and methods

This prospective study was carried out in five hospitals in Madrid. Antiretroviral-naive patients were enrolled if they had started an antiretroviral regimen that included lopinavir/ritonavir (400 mg and 100 mg, respectively, twice daily). Approval for the study protocol was obtained from the local ethics committee.

Patients remained on the study as long as lopinavir/ritonavir therapy was not discontinued. For patients who discontinued lopinavir/ritonavir therapy before the end of the study, data were censored at the last visit.

Laboratory parameters were measured at each participating site. Serum samples were drawn in the morning after 12 h of fasting. Total cholesterol, high-density cholesterol (HDL) and triglyceride levels were measured enzymically in serum. Low-density cholesterol (LDL) was calculated using the Friedwald formula or directly measured by ultracentrifugation of lipoproteins if the triglyceride level was > 350 mg/dL. Cholesterol fractions were measured only in centres in which this determination was carried out routinely.

Hypercholesterolaemia and hypertriglyceridaemia were defined according to cut-off values recommended in the US National Cholesterol Education Program guidelines. A cut-off value for the total cholesterol:HDL ratio was chosen as ≥ 6.5 to define a group at high risk of coronary heart disease.

Statistical analysis

Comparisons of quantitative variables at each time point were performed using repeated-measures analysis of variance and the Wilcoxon signed rank test. For the comparison of qualitative variables, the McNemar test was used. The time from the start of lopinavir/ritonavir to development of hyperlipidaemia was analysed with the use of the Kaplan–Meier method and Cox proportional hazards models. A multivariate Cox proportional hazards model was constructed with age, sex, baseline lipid levels, baseline CD4 cell count, use of stavudine, hepatitis C coinfection status and viral load < 400 copies/mL as predictive variables.

A two-tailed P value < 0.05 was considered significant and 95% confidence intervals (CIs) are provided when relevant. All statistical analyses were performed with the use of the SPSS package for Windows v.10.0.

Results

The inclusion period was from June 2001 until November 2002. Of the 107 patients included (Table 1), 21 did not complete the programmed follow-up: there were four AIDS-related deaths, seven patients were lost to follow-up and there were 10 discontinuations of treatment (four owing to gastrointestinal intolerance, three owing to simplification of antiretroviral treatment, two owing to pregnancy and one owing to tuberculosis).

At least one follow-up lipid profile was available in 99 patients. Total cholesterol and triglyceride levels increased significantly after starting lopinavir/ritonavir (Figure 1a and b). The main increase in total cholesterol occurred from baseline to month 2, with lower increases from month 2 to month 6. No further significant increases were seen after month 6. Likewise, triglycerides increased significantly from baseline to month 2. However, after month 2 no further significant increases were seen. At 12 months the mean increases in total cholesterol and triglycerides were 40.7 ± 5 and 73.3 ± 21.7 mg/dL, respectively (P = 0.001). Accordingly, the percentage of patients with total cholesterol ≥ 240 mg/dL increased significantly from baseline (4%) compared with month 2 (16% P = 0.004) and 12 months (17.4% P = 0.001). The increase in the percentage of patients with total cholesterol ≥ 240 mg/dL after 2 months of treatment was non-significant. The percentage of patients with hypertriglyceridaemia (≥ 200 mg/dL) increased significantly from baseline (22%) compared with month 2 (40% P = 0.001) and 12 months (40% P = 0.015). The increase in the percentage of patients with triglycerides ≥ 200 mg/dL after 2 months of treatment was non-significant. Only a minority of patients (1–6%) developed very high triglycerides at each time point. Mean absolute increases in total cholesterol and triglycerides at 12 months were not significantly different in those patients with or without baseline total cholesterol > 200 mg/dL and baseline triglycerides > 150 mg/dL, respectively. A minority of patients (six; 5.6%) started lipid-lowering drugs during follow-up.

Cholesterol fractions were performed in 48 (45%) patients. After 2, 6 and 12 months of treatment, mean increases in LDL were 14, 27 and 24 mg/dL, respectively. Significant increases in LDL occurred from baseline to month 6 (P = 0.002) and to month 12 (P = 0.003). Percentages of patients with an LDL > 160 mg/dL at baseline, month 2, month 6 and month 12 were 4%, 6%, 7% and 7%, respectively (differences non-significant). We observed a significant increase in HDL levels from baseline to month 2 (mean increase 9.8 mg/dL; P = 0.002), to month 6 (12.2 mg/dL;
There was a significant decrease in the percentage of patients with HDL < 40 mg/dL from baseline (69%) to month 2 (36% $P = 0.003$) and to month 6 (26% $P = 0.002$), but not to month 12 (35% $P = 0.065$). Accordingly, with these changes median ratios of total cholesterol:HDL at baseline, 2 months, 6 months and 12 months were 4.16, 4.58, 3.83 and 4.49, respectively (differences non-significant). Percentages of patients with a total

![Figure 1](https://academic.oup.com/jac/article-abstract/55/5/800/691135/14-November-2018)

Figure 1. (a and b) Lipid changes in antiretroviral-naive patients treated with lopinavir/ritonavir. Each box shows the median, quartiles and extreme values for total (a) cholesterol and (b) triglycerides. (c) Kaplan–Meier estimates of the likelihood of developing hypercholesterolaemia depending on baseline hepatitis C status.
Kaplan–Meier analyses showed that the probabilities of developing hypercholesterolaemia and hypertriglyceridaemia after 12 months of treatment were 0.24 and 0.68, respectively. Total cholesterol > 200 mg/dL and triglyceride > 150 mg/dL at baseline were associated with the risk of hypercholesterolaemia and hypertriglyceridaemia: the hazard ratios were 3.9 (95% CI 1.4–10.6; P = 0.008) and 3 (95% CI 1.3–7; P = 0.008), respectively. Patients infected with hepatitis C at baseline were significantly less likely to develop hypercholesterolaemia (hazard ratio 0.1; 95% CI 0.01–0.8; P = 0.027) (Figure 1c) and hypertriglyceridaemia (hazard ratio 0.4; 95% CI 0.16–0.98; P = 0.046). Concomitant stavudine therapy appeared to be inversely correlated with the risk of hypertriglyceridaemia but not with the risk of hypercholesterolaemia. The relative hazard ratio for hypertriglyceridaemia in patients treated with stavudine was 0.1 (95% CI 0.2–0.95; P = 0.038).

**Discussion**

We have found that antiretroviral-naive patients treated with lopinavir/ritonavir experience significant increases in fasting serum total cholesterol and triglyceride levels. These increases tended to occur promptly after initiation of lopinavir/ritonavir and reached a plateau after 2–6 months. After 12 months of treatment, the mean increase in total cholesterol was similar to the increase reported in the pivotal trial of lopinavir/ritonavir. In contrast, 12 month increases in triglycerides were almost 40% lower in our cohort. The most likely explanation for this difference is that in the clinical trial most of the serum samples for lipid measurements were obtained in the non-fasting state, while in our cohort all serum samples were obtained after fasting.

We have found that patients with increased baseline levels of serum cholesterol and triglycerides had the highest risk of developing clinically significant hypercholesterolaemia and hypertriglyceridaemia. Since absolute increases in total cholesterol and triglycerides were similar regardless of baseline levels, this finding probably only means that patients with baseline lipid levels near the upper limit of normal are more likely to exceed it. In mainly antiretroviral-experienced patients, two groups have found that both high baseline serum cholesterol and triglycerides were strong predictors of development of hypercholesterolaemia and hypertriglyceridaemia.

There is little information about the impact of lopinavir/ritonavir-based HAART on cholesterol lipid fractions. In healthy volunteers, 4 weeks of treatment with lopinavir/ritonavir did not produce changes in LDL or HDL. Interestingly, in our study, lopinavir/ritonavir increased significantly both the LDL and HDL. As a consequence, the total cholesterol:HDL ratio did not change significantly. These results are in agreement with those reported by Gathe et al.

Patients coinfected with hepatitis C had a significantly lower risk of developing hyperlipidaemia (especially hypercholesterolaemia). The lower risk of hyperlipidaemia persisted after adjusting for having an undetectable HIV viral load after 12 months of therapy, suggesting that lower adherence to HAART in coinfected patients was not a confounding factor. Other cohorts have also reported an apparent protective effect of hepatitis C in the development of hypercholesterolaemia after starting antiretroviral treatment. The mechanism underlying the protective effect of hepatitis C in the risk of developing hyperlipidaemia is not known.

In our study, treatment with stavudine was negatively correlated with the risk of developing hypertriglyceridaemia. This finding is surprising since stavudine has been shown to have an increased risk of hypertriglyceridaemia in a clinical trial that compared stavudine versus tenofovir (both in combination with lamivudine and efavirenz) in antiretroviral-naive patients. Compared with the patients reported by Staszewski et al., patients included in our cohort were clearly more advanced. It is possible that the short-term impact of stavudine on lipid values might be different in very advanced HIV-infected patients such as those included in our study. In addition, it is possible that the net effect of stavudine on lipid values might vary depending on the other drugs used in the antiretroviral regimen.

In summary, our study shows that patients with high baseline serum cholesterol and triglycerides have the greatest risk of developing dyslipidaemia after starting lopinavir/ritonavir, while patients with normal baseline lipid values and hepatitis C coinfection have only a modest risk. In antiretroviral-naive patients with advanced HIV infection, lopinavir/ritonavir increased triglycerides and LDL, and also HDL. As a consequence, the total cholesterol:HDL ratios did not change significantly.

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**References**


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