### Pharmacokinetics and hepatotoxicity of lopinavir/ritonavir in non-cirrhotic HIV and hepatitis C virus (HCV) co-infected patients


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**Keywords:** drug monitoring, antiretroviral therapy, liver function tests, protease inhibitors

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The clinical use of lopinavir/ritonavir, as a component of antiretroviral regimens, was found to be associated with an incidence of hepatotoxicity ranging from 1% to 9.5% in clinical trials. In this setting, an additional factor contributing to the likelihood of developing hepatotoxicity while on highly active antiretroviral therapy (HAART) is represented by the concomitant presence of HCV infection, which was found to be associated with a 4.7-fold increase in LFT abnormalities in lopinavir/ritonavir intakes compared with HCV-free subjects. However, generalization from clinical trial data has limited informative value, since no studies specifically addressed to evaluate lopinavir/ritonavir hepatotoxicity have been carried out in geographical areas with high prevalence rates of HIV/HCV co-infection. Among the possible mechanisms accounting for lopinavir/ritonavir hepatotoxicity in HIV/HCV co-infected patients, a role for higher drug concentrations resulting from reduced cytochrome P450 activity has been suggested. In patients with HIV/HCV co-infection, various degrees of liver function impairment were found to be proportionally associated with higher pharmacokinetic parameters of amprenavir, nelfinavir, indinavir, ritonavir and nevirapine. In HIV-infected patients with mild to moderate HCV-related liver cirrhosis, Arribas et al. found lopinavir and ritonavir area-under-the-curve (AUC) increases of 20% and 148–280%, respectively. However, few data are available on the pharmacokinetics of lopinavir/ritonavir in non-cirrhotic HIV/HCV co-infected patients. In an observational, comparative, prospective study at the Department of Infectious Diseases of the University of Torino, in a high prevalence area for HIV/HCV co-infection, 149 treatment-naive HIV-infected patients were consecutively administered an antiretroviral regimen consisting of lopinavir/ritonavir and two nucleoside/nucleotide reverse transcriptase inhibitors.

Seventy-eight patients (52.3%) were HIV+/HCV— (group A) and 71 were HIV+/HCV+ (group B). Self-reported poor adherence (<90%), liver cirrhosis and concomitant intake of drugs potentially interfering with the CYP450 enzymic system were the main exclusion criteria. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values were measured at 1, 3, 6 and 12 months. Hepatotoxicity was classified according to

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**Table 1. Alteration of liver function tests (LFTs) over the study period**

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Study group* (n)</th>
<th>cumulative, n (%)</th>
<th>moderate to severe, n (%)</th>
<th>AST elevation</th>
<th>cumulative, n (%)</th>
<th>moderate to severe, n (%)</th>
<th>ALT elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>cumulative, n (%)</td>
<td>moderate to severe, n (%)</td>
<td>P value&lt;sup&gt;c&lt;/sup&gt;</td>
<td>cumulative, n (%)</td>
<td>moderate to severe, n (%)</td>
<td>P value&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>A (43)</td>
<td>4 (9.3)</td>
<td>0</td>
<td>0.143</td>
<td>3 (7.0)</td>
<td>0.011</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B (42)</td>
<td>9 (21.4)</td>
<td>3</td>
<td>7.1</td>
<td>12 (28.6)</td>
<td>4 (9.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>3</td>
<td>A (38)</td>
<td>3 (7.9)</td>
<td>0.010</td>
<td>1 (2.6)</td>
<td>4 (10.5)</td>
<td>0.001</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B (40)</td>
<td>13 (32.5)</td>
<td>4 (10)</td>
<td>2 (5.7)</td>
<td>18 (45.0)</td>
<td>10 (25.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>A (35)</td>
<td>2 (5.7)</td>
<td>0.008</td>
<td>1 (2.9)</td>
<td>2 (5.7)</td>
<td>0.000</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td></td>
<td>B (41)</td>
<td>13 (31.7)</td>
<td>5 (12.2)</td>
<td></td>
<td>22 (53.6)</td>
<td>12 (29.3)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>A (24)</td>
<td>1 (4.1)</td>
<td>0.005</td>
<td>0</td>
<td>3 (12.5)</td>
<td>0.003</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>B (33)</td>
<td>16 (48.5)</td>
<td>5 (15.1)</td>
<td></td>
<td>20 (60.6)</td>
<td>9 (8.0)</td>
<td></td>
</tr>
</tbody>
</table>

*Group A, HIV infected patients; Group B, HIV/HCV co-infected patients.

<sup>a</sup>AST and ALT increases were classified as mild (<2-fold), moderate (2–5-fold) and severe (>5-fold) according to baseline values.

<sup>b</sup>χ² was used for comparative analysis between the two groups at every time point (level of significance P < 0.05).
ALT and AST increases relative to baseline values as follows: mild (<2-fold), moderate (2–5-fold), and severe (>5-fold). Steady-state lopinavir $C_{\text{trough}}$ values were obtained at 1, 3, 6 and 12 months. Lopinavir plasma levels were measured by validated HPLC with UV detection. Baseline demographic, virological and immunological characteristics were matched in the two groups [median values (range): age, 41 (26–71) years; sex ratio (M/F), 3.51; HIV-RNA (log), 4.85 (1.3–6.0); LTCD4+/mm$^3$, 202 (3–739)]. Baseline AST and ALT values were significantly higher in co-infected patients [median values (range): 44.5 (13–206) versus 22 (14–176) IU/L ($P=0.033$); and 54 (17–149) versus 25 (9–308) IU/L ($P<0.0001$), respectively]. Cumulative toxicity at 3, 6 and 12 months was significantly higher in co-infected subjects (Table 1).

Incidences of moderate to severe hepatotoxicity (ALT value) at 3, 6 and 12 months was significantly higher in group B than in group A (Table 1). No patient developed an LFT elevation more than 10-fold compared with baseline values. The discontinuation rate was lower in co-infected patients (2.8% versus 12.8%, $P=0.052$) and was not related to hepatotoxicity. Median lopinavir and ritonavir $C_{\text{trough}}$ levels were not statistically different between groups A and B [median values (range): 6563.5 (1143–18 581) versus 6805 (1916–15 318) ng/mL; and 315 (87–1697) versus 314 (0–523), respectively]. No correlation was found between both lopinavir and ritonavir $C_{\text{trough}}$ and ALT values in either group.

In our series, the incidence of LFT increase was significantly higher in HIV/HCV co-infected subjects. A similar finding has recently been reported by Chihirin et al., who identified the duration of treatment with lopinavir/ritonavir as a risk factor associated with grade 3/4 ALT increase (odds ratio: 3.18) in co-infected patients. No patient in our study developed a very severe hepatotoxicity (ALT increase >10-fold) and LFT increase did not have a significant impact on treatment discontinuation. The pharmacokinetics of lopinavir/ritonavir, as assessed by serial measurements of $C_{\text{trough}}$, showed no differences in the two groups and no association was found between the concentration of lopinavir and ritonavir and the development of hepatotoxicity. These data confirm the observations by Gonzalez de Requena et al., who found no differences in lopinavir pharmacokinetics between non-cirrhotic HIV/HCV co-infected and HCV-free patients. The authors, however, did not determine the pharmacokinetics of ritonavir, a drug which was repeatedly found to be associated with hepatotoxicity when administered at full dosage (600 mg twice a day). Our findings thus indicate that the pharmacokinetics of ritonavir, when given at doses of 100 mg twice a day as booster, are not influenced by the presence of HCV infection in non-cirrhotic patients and that ritonavir is not associated with the development of hepatotoxicity. According to these data, no dosage adjustment is required for lopinavir/ritonavir in non-cirrhotic patients with HIV/HCV co-infection, information of particular value for those settings where the prevalence of subjects carrying this dual condition is high.

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