Comment on: Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children

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Keywords: HIV, AIDS, paediatrics

Sir,

With interest we read the paper on low-dose lopinavir/ritonavir in HIV-infected, protease-inhibitor-naive children by Puthanakit et al.1 The authors report that after 4–6 weeks of liquid lopinavir/ritonavir (80/20 mg/mL) dosed either according to WHO guidelines for weight-band dosing2 or at a reduced (70% of recommended dose) dose (n = 12), lopinavir and ritonavir pharmacokinetic (PK) characteristics were not significantly different between the two groups. These characteristics included maximum concentration (Cmax), time to maximum concentration (Tmax), trough concentration (Crough) and area under the 12 h time–concentration curve (AUC12). The calculated PK parameters clearance (CL) and half-life (t1/2) were also not significantly different.

The standard-dose lopinavir PK data and measured concentrations in the study by Puthanakit et al.1 agree closely with our own published lopinavir data in 49 children.3 See Table 1. The median dose was higher in our study, yet the AUC12 and Cmax were slightly lower. Note that CL was nearly identical, suggesting that the minor peak and overall exposure differences may have been due to disparities in absorption and/or bioavailability, perhaps related to formulation. In our study 60% of the patients were dosed with capsules prior to the PK assessment. It is unlikely that population-based factors, e.g. genetic polymorphisms, played a role, since these generally affect clearance and none, to date, has been identified that has much influence on lopinavir PK.

In the study by Puthanakit et al.,1 the virological and immunological outcomes after 48 weeks of treatment were similar between the standard- and reduced-dose groups. However, six of the patients were excluded from the on-treatment analysis due to adherence problems, and eight in the standard arm and four in the reduced-dose arm switched from liquid to fixed-dose combination soft gel capsules (133 mg/33 mg) after the PK study. Therefore, the relationships of liquid dose, capsular dose and outcome are unclear. We also noted that the lower dose of lopinavir/ritonavir conferred no benefit on the average lipid profile. This is probably because the lower dose was different from standard dosing by only 30%, and indeed, the plasma concentration profiles, while trending lower, were not statistically significantly different except the week 24 Crough. In other words, the inter-patient variability in lopinavir/ritonavir PK obscured the 30% reduction in plasma exposure in this small population.

We strongly agree with the authors’ statement that reduced-dose lopinavir/ritonavir is not appropriate for children who have already been exposed to protease inhibitors in the past. The distribution of achievable lopinavir inhibitory quotients, simulated from our lopinavir population PK model, suggests that two-thirds of children with even moderately resistant virus (>10-fold increase in lopinavir 50% inhibitory concentration) will be unable to consistently reach therapeutic lopinavir trough concentrations with standard dosing, let alone reduced dosing.3

Given the inter-patient PK variability and the lack of reduced toxicity or increased adherence, one therefore must raise the question of whether a 30% reduction in dose is worth the reduction in the cost of treatment and the risks of developing resistance by under-dosing a patient who needs higher lopinavir concentrations. We are also unclear exactly how a 30% reduction would be achieved with capsules or tablets, and we would be most interested in some analysis of the economic benefit anticipated from such a modestly reduced dose.

The important conclusion from both studies1,3 is that recommended doses of lopinavir/ritonavir, whether according to WHO or US prescribing guidelines, result in concentrations of lopinavir that are adequate for most patients as part of combination therapy to suppress viral replication in medication-adherent HIV-infected children—if that child is naive to protease inhibitor therapy and the target trough concentration is >1 mg/L.4 However, reduced-dose lopinavir/ritonavir is not appropriate for protease-inhibitor-experienced children. In general, due to

Table 1. Comparison of lopinavir pharmacokinetics

<table>
<thead>
<tr>
<th>Study</th>
<th>Rakhmanina et al.3</th>
<th>Puthanakit et al.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose (mg)</td>
<td>320 (256–400)</td>
<td>279 (263–294)</td>
</tr>
<tr>
<td>AUC12 (mg.h/L)</td>
<td>96.1 (62.7–114.3)</td>
<td>117.6 (74.0–128.5)</td>
</tr>
<tr>
<td>Cmax (mg/L)</td>
<td>10.3 (7.9–12.3)</td>
<td>11.9 (10.6–14.4)</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.1 (2.0–4.0)</td>
<td>2.0 (2.0–4.0)</td>
</tr>
<tr>
<td>Crough (mg/L)</td>
<td>5.9 (3.8–7.4)</td>
<td>4.9 (2.7–8.0)</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>1.8 (1.0–2.6)</td>
<td>1.7 (1.0–3.5)</td>
</tr>
</tbody>
</table>

All values are median and interquartile range.

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**Transparency declarations**

None to declare.

**References**
