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

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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 (Ctrough) 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, capsule 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 Ctrough. 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>
<thead>
<tr>
<th>Study</th>
<th>Rakhmanina et al.³</th>
<th>Puthanakit et al.¹</th>
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<tbody>
<tr>
<td><strong>Dose (mg)</strong></td>
<td>320 (256–400)</td>
<td>279 (263–294)</td>
</tr>
<tr>
<td><strong>AUC12 (mg·h/L)</strong></td>
<td>96.1 (62.7–114.3)</td>
<td>117.6 (74.0–128.5)</td>
</tr>
<tr>
<td><strong>Cmax (mg/L)</strong></td>
<td>10.3 (7.9–12.3)</td>
<td>11.9 (10.6–14.4)</td>
</tr>
<tr>
<td><strong>Tmax (h)</strong></td>
<td>3.1 (2.0–4.0)</td>
<td>2.0 (2.0–4.0)</td>
</tr>
<tr>
<td><strong>Ctrough (mg/L)</strong></td>
<td>5.9 (3.8–7.4)</td>
<td>4.9 (2.7–8.0)</td>
</tr>
<tr>
<td><strong>CL (L/h)</strong></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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significant risks of under-dosing, we believe that dose reduction should be considered for individual patients only, guided by measurement of plasma concentrations, and coupled with expert interpretation, all of which may be difficult in a resource-limited setting.

**Transparency declarations**
None to declare.

**References**


**Pharmacokinetics and 48 week efficacy of low-dose lopinavir/ritonavir in HIV-infected children—authors’ response**

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Sir,

We thank Neely and Rakhmanina for their helpful comments on our article. We agree that these are pilot data on the use of low-dose lopinavir/ritonavir in children that need larger efficacy trials before implementation in practice and also emphasize that the clinical implication of this study is limited to HIV-infected children who are naïve to protease inhibitors (PIs).

However, we strongly believe that the concept of lower dosing of lopinavir/ritonavir is a valid research agenda especially for low and middle income countries. By the end of 2008, UNAIDS reported that 730000 children were in need of antiretroviral therapy. Only 275500 children, or ~38%, had access to lifesaving medications, showing that cost issues still have a significant impact on public health programmes. According to WHO guidelines, the recommended first-line regimen is a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen; PI-based regimens are used for second-line therapy.

However, based on reports from Asia and Africa, 16%–26% of children experienced treatment failure and subsequently needed to switch to a second-line regimen, so the demand for a PI drug regimen is in the range of 50000–100000 children. The 70% dose reduction simply means that for every three children, one child is treated for free.

The report from the Liverpool therapeutic drug monitoring (TDM) registry with data from 439 HIV-infected adults in Europe showed that >50% of patients had a lopinavir trough level >5000 ng/mL. The Kaledose trial also showed that reducing the dose of lopinavir/ritonavir from 400/100 to 266/66 mg among HIV-infected adult patients who were stable on the lopinavir/ritonavir regimen and had a high lopinavir trough level (defined as >5000 ng/mL) had no effect on treatment efficacy but significantly reduced the triglyceride level at 48 weeks. These studies support the need for optimization of lopinavir dosage not only for resource-limited settings but also globally in both adults and children.

The heat-stable lopinavir/ritonavir tablet formulation, comprising either 100/25 or 200/50 mg lopinavir/ritonavir, has less pharmacokinetic variability compared with a soft gel or oral solution.

The lopinavir TDM data derived from 54 Thai children showed a median lopinavir trough concentration of 6700 ng/mL, with 96% of children having lopinavir levels >4000 ng/L. A pharmacokinetic study of a low-dose lopinavir/ritonavir tablet formulation among Thai children is underway. The study plans to enrol 24 children with body weight >25 kg. Children weighing between 25 and 35 kg will be the subject of two pharmacokinetic studies comparing standard dosing using three tablets of 100/25 mg lopinavir/ritonavir and low dosing using two tablets. Children weighing >35 kg will be evaluated in a pharmacokinetic study comparing four versus three tablets.

**Transparency declarations**
None to declare.

**References**