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Chapter 13:
Pharmacokinetics and 24-week efficacy/safety of dual boosted saquinavir/lopinavir/ritonavir in nucleoside-pretreated children

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Pharmacokinetics and 24-Week Efficacy/Safety of Dual Boosted Saquinavir/Lopinavir/Ritonavir in Nucleoside-Pretreated Children

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Objective: To assess the pharmacokinetics and 24-week efficacy and safety of dual boosted saquinavir/lopinavir/ritonavir combination in children.

Design: Twenty reverse transcription inhibitor-pretreated children at 2 centers in Thailand were treated with saquinavir/lopinavir/ritonavir in an open label, single arm, 6-month prospective study. The dosage was 50 mg/kg twice daily (bid) for saquinavir and 230/57.5 mg/ml bid for lopinavir/ritonavir. Ten children also received lamivudine.

Methods: Samples were collected for a 12-hour pharmacokinetic profile in all children. Plasma concentrations of saquinavir, lopinavir and ritonavir were determined using a validated high performance liquid chromatography technique.

Results: At baseline, the median age was 8.5 years, with human immunodeficiency virus (HIV) RNA 4.9 log_{10} copies/ml, CD4 count 129 cells/µL and CD4%, 6.5%. Median area under the concentration curve at 0–12 hours and C_{max} were 39.4 mg/L · h and 1.4 mg/L for saquinavir and 118 mg/L · hr and 5.9 mg/L for lopinavir. After 24 weeks of treatment, HIV RNA was suppressed below 400 copies/ml for 16 of 20 (80%) children (intent-to-treat analysis) and below 50 copies/ml for 12 of 20 children (60%), and CD4% (count) rose by a median of 6% (216 cells/µL). Median changes of triglyceride and total cholesterol were 56 and 36.5 mg/dL, respectively (P = 0.01). Lopinavir C_{min} <1 and saquinavir C_{min} <0.28 mg/L correlated with HIV RNA >400 copies/ml, and lopinavir C_{max} >15 mg/L correlated with rises in cholesterol (P < 0.05).

Conclusion: Plasma drug concentrations of saquinavir, lopinavir and ritonavir were at the higher limits of expected ranges for adult treatment at approved dosages (1000/100 mg bid for saquinavir, 400/100 mg bid for lopinavir/ritonavir). The regimen was well-tolerated and had good efficacy at 24 weeks. This dual boosted protease inhibitor combination should be assessed in larger trials of reverse transcription inhibitor-experienced children.

Key Words: protease inhibitors, salvage therapy, resistance, nucleoside reverse transcription inhibitors, nonnucleoside reverse transcription inhibitors, human immunodeficiency virus, highly active antiretroviral therapy


Combination antiretroviral therapy including protease inhibitors has significantly improved survival for human immunodeficiency virus (HIV)-infected children. Current guidelines suggest first line treatment of children with 2 nucleoside reverse transcription inhibitors (NRTIs) plus either a nonnucleoside reverse transcription inhibitor (NNRTI) or protease inhibitor (PI). The palatability of liquid or powder formulations of protease inhibitors limits their use in younger children, especially because large dosages are required owing to more rapid metabolism than in adults.

For children treated first line with NRTI/NNRTI-based highly active antiretroviral therapy (HAART), resistance to reverse transcription inhibitors (RTIs) has been detected at treatment failure. NNRTI resistance might also be maternally acquired. For heavily RTI-experienced children, response to a second line treatment containing a single PI might be suboptimal because the NRTI component contributes little to efficacy. In addition, there is the potential for acute and progressive toxicity to NRTIs from continued usage.

Saquinavir and lopinavir have been evaluated in clinical trials of HIV-infected children. Lopinavir/ritonavir has been evaluated at the twice daily (bid) dosage of 230/57.5 mg/kg for children between 6 months and 12 years; this dosage is an estimate of the adult equivalent (400/100 mg bid) pediatric dosage on the basis of body surface area. Saquinavir at the dosage of 50 mg/kg bid with low dose ritonavir was predicted to provide saquinavir plasma concentrations similar to the currently approved adult dosage of 1000/100 mg bid. PI double boosting involves the use of ritonavir to increase drug concentrations of 2 protease inhibitors simultaneously. Stable pharmacokinetics has been shown for the
combination of saquinavir/lopinavir/ritonavir, and this combination shows synergistic interactions in vitro. Pilot studies of this combination in NRTI-experienced adults showed promising results.

Given the potential need for multiple PI treatment to overcome RTI-resistant virus, a pilot study of saquinavir plus lopinavir/ritonavir at their approved dosages was conducted in 20 RTI-pretreated children.

**METHODS**

**Clinical Assessment.** This single arm, open label, prospective 24-week trial, HIV-NAT 017, was conducted in 2 centers in Thailand (HIV-NAT in Bangkok and Khon Kaen University, Khon Kaen, Northeast Thailand). Ethics committees at both institutions approved the study, and all parents or caregivers of enrolled children signed written informed consent at screening. The trial enrolled 20 HIV-1-infected children who were PI-naive and failing NRTI- or NRTI/NRTI-based treatment. Children needed to be younger than 16 years of age, with results of biochemistry and hematological evaluations within prespecified ranges. Children had to be able to swallow pills. The dosage of lopinavir/ritonavir was 230/57.5 mg/m² bid, provided primarily as adult capsules (lopinavir 133/ritonavir 33 mg) but supplemented with oral solution containing lopinavir/ritonavir 80/20 mg/mL when necessary. For saquinavir, the dosage was 50 mg/kg bid provided as 200-mg hard gel capsules. Lamivudine was added in patients who had never taken it. Concurrent use of other inducers or inhibitors of cytochrome P4503A4 metabolism was not permitted.

After baseline assessment, children attended clinical follow-up visits at weeks 4, 8, 12 and 24 of the study. Children were assessed for CD4 count and percent, HIV RNA (Roche AmpliSeq Ultrasensitive assay, Palo Alto, CA), fasting lipids, hematology, clinical chemistry and adverse events. HIV RNA was summarized by visit week, using the intent-to-treat missing equals failure method. Clinical and laboratory adverse events were graded by severity.

**Pharmacokinetics.** Each child underwent a pharmacokinetic assessment, between 10 days and 4 weeks after starting trial medication for those not using an NNRTI in the previous regimen and after week 4 for those switched from an NNRTI-containing regimen at baseline (to allow for potential NNRTI induction effects to diminish). For pharmacokinetic assessments, children were hospitalized from 7 PM the preceding day, with the evening dose observed. At 7 AM the next morning, blood was drawn into heparinized tubes just before drug intake (predose) and at 2, 4, 6, 8, 10 and 12 hours after drug intake. Medication was taken with standardized meals and was observed. Blood samples were then centrifuged at 3800 rpm and 10 minutes at 4°C on the day of sample collection. Plasma concentrations of lopinavir, saquinavir and ritonavir were measured in all available samples by means of a validated high performance liquid chromatography method. Determination of pharmacokinetic factors [area under the concentration curve (AUC) at 0–12 hours, Cmax, Ctrough, t1/2] of the PIs was made by noncompartmental methods.

**Statistical Analysis.** Descriptive statistics were generated for all pharmacokinetic measures. Statistical analysis was performed with SPSS version 9 (SPSS, Chicago, IL). The Wilcoxon signed rank test and the McNemar test with a 2-tailed P value of 0.05 were used to evaluate the clinical outcomes.

**RESULTS**

**Baseline Characteristics.** Twenty children were enrolled (8 at the Bangkok center, 12 at the center in Khon Kaen), with a median age of 8.5 years. Six were male, and 14 were female. Fifteen patients (75%) were between 5 and 10 years of age, and 5 (25%) were older than 10 years at baseline. Other baseline characteristics are shown in Table 1. Prior NRTI treatment included zidovudine for 90%, lamivudine for 50%,

**TABLE 1.** Characteristics at Baseline and at Week 24

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline</th>
<th>Wk 24</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample size</td>
<td>20</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Gender</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>6 (30%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Female</td>
<td>14 (70%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Disease stage</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>A</td>
<td>1 (5%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>B</td>
<td>2 (10%)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>C</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medium age (yr); IQR</td>
<td>8.5, 6.9–9.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% with prior NRTI treatment</td>
<td>100</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medium NNRTI duration (yr); IQR</td>
<td>3.4, 2.0–4.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>% with prior NNRTI treatment</td>
<td>35</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medium NNRTI duration (yr); IQR</td>
<td>1.3, 0.5–2.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Medium wt (kg); IQR</td>
<td>19.5, 17.3–24.5</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Median, Q1, Q3</td>
<td>116, 111–125</td>
<td>117.5, 112.5–128.8</td>
<td>0.002</td>
</tr>
<tr>
<td>Medium HIV RNA (log10); IQR</td>
<td>4.9, 4.5–5.4</td>
<td>2.6, 1.7–2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median CD4 count (cells/μL); IQR</td>
<td>129, 35–243</td>
<td>378, 240–540</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median CD4%; IQR</td>
<td>6.5, 3.3–8.0</td>
<td>11.5, 10–14.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>111, 80.3–169.3</td>
<td>161, 135.5–249.8</td>
<td>0.014</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>150, 130.8–179.3</td>
<td>188, 184.5–225.3</td>
<td>0.012</td>
</tr>
</tbody>
</table>

*P value represents comparisons of individual changes overtime of weight, height, CD4, HIV RNA and lipids.

Numbers in parentheses, percent.
stavudine for 45% and didanosine for 80%. Seven of the 20 children (35%) were NNRTI-pretreated; all 7 had received nevirapine, and 1 child received efavirenz as well. Six children (30%) had received coformulated stavudine/lamivudine/nevirapine. The median number of nucleoside-associated mutations was 4, with 63% having at least 4 nucleoside-associated mutations, which signified resistance to all NRTI except for 3TC. In addition, multi-NRTI mutations were seen: T215Y (n = 7); Q151M (n = 1). All 20 children continued to receive lopinavir/saquinavir/ritonavir at 24 weeks. The 10 children who had not previously received lamivudine took this in addition for the duration of the trial. Efficacy and Safety: An individual patient’s body weight increased by a median of 1.5 kg during the trial (P = 0.002), and height increased by a median of 2 cm (Table 1), but weight for age (P = 0.08) and height for age (P = 0.28) Z scores were not different. The median CD4 count and CD4% rise were 216 cells/µL [interquartile range (IQR), 143–360] and 6% (IQR 3–9), respectively, at week 24 (P < 0.001) with the total count and percent shown in Table 1. HIV RNA titers fell from baseline by −2.5 log10 copies/mL (IQR −2.9 to −1.9, P < 0.001) with HIV RNA suppressed below 400 copies/mL for 16 of 20 children (80%) and <50 copies/mL for 12 of 20 children (60%). More children at the Bangkok site had HIV RNA <50 copies/mL (7 of 8) than at the Khon Kaen site (5 of 12). There were no differences in baseline characteristics at the 2 sites. Lamivudine use did not affect HIV RNA suppression (P = 0.17).

Of the 4 children with HIV RNA >400 copies/mL at week 24, 1 child was treated with combination antiretroviral medications containing efavirenz for presumed Mycobacterium tuberculosis within the first month of the study and had abnormally low concentrations of lopinavir and saquinavir. Efavirenz was subsequently stopped at week 8, but at week 24 the patient had undetectable lopinavir and saquinavir concentrations because of poor adherence resulting in an HIV RNA of 67,900 copies/mL. Genotyping of the protease gene showed L62S. After adherence reinforcement 1 month later, her HIV RNA was 532 copies/mL. Another child had underlying Mycobacterium avium complex (MAC) infection, salt-wasting nephropathy and HIV encephalopathy with seizure and was receiving multiple drugs in addition to the dual PI regimen. During the study, she had seizures, which were treated with phenytoin sodium. Her lopinavir and saquinavir concentrations at week 24 were low, and her HIV RNA was 35,900 copies/mL with K20R on genotyping. A third child, with M. tuberculosis during the first month treated with a non-rifampin-containing antituberculosis regimen, had low lopinavir concentrations and at week 24 had an HIV RNA of 3650 copies/mL, with emergence of the F22F mutation, which is associated with early PI failure. Finally a teenager with a history of poor adherence had an HIV RNA of 552 copies/mL at week 24 but a subsequent HIV RNA of <50 copies/mL at a follow-up visit.

One child had a serious adverse event (grade 3 diarrhea, vomiting, back pain and convulsions), which was judged by the investigator to be at least possibly related to study medication. This is the second child mentioned above with MAC, nephropathy and seizure. Lopinavir and saquinavir were briefly interrupted twice during her hospitalization, and at week 19 the lopinavir and saquinavir dosing were reduced by 20% with some improvement of diarrhea and back pain.

During the 24 weeks of the trial, serum triglyceride rose in individual patient from a median of 111 mg/dl to 161 mg/dl (P = 0.014), with a rise in total cholesterol from 150 mg/dl to 188 mg/dl (P = 0.012) (Table 1). The proportion of patients with total cholesterol above 200 mg/dl rose from 0% at baseline to 30% at week 24 (P = 0.031), whereas the proportion with triglycerides above 150 mg/dl rose from 25% at baseline to 60% at week 24 (P = 0.031). Alanine aminotransferase values showed a significant reduction during the trial, from 24 units/L at baseline to 14 units/L at week 24 (P < 0.001).

**Pharmacokinetics: Correlation With Efficacy and Safety.** Table 2 and Figure 1 show the summary pharmacokinetic profiles for saquinavir, lopinavir and ritonavir for the 19 children. One child with concurrent rifampin treatment was excluded from analyses correlating plasma PI pharmacokinetics with efficacy and safety.

Overall the pharmacokinetic measurements were within accepted ranges for all PIs. Of 3 children with saquinavir Cₘ₉₅ below 0.28 mg/L, 2 had HIV RNA >400 copies/mL at week 24, compared with 1 of 16 children with saquinavir Cₘ₉₅ above 0.28 mg/L (P = 0.008). Of 2 children with lopinavir Cₘ₉₅ below 1 mg/L, both had HIV RNA >400 copies/mL at week 24, compared with 1 virologic failure among 17 children with lopinavir concentrations above 1 mg/L (P = 0.001). The 2 children with lopinavir Cₘ₉₅ <1 mg/L also had low saquinavir Cₘ₉₅ (<0.28 mg/L). There were no significant correlations between virologic response and other measures of saquinavir or lopinavir pharmacokinetics (AUC, Cₘ₉₅). Ritonavir concentrations were within expected ranges.

**TABLE 2.** Summary Statistics of Lopinavir, Saquinavir and Ritonavir Pharmacokinetics (n = 19)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Units</th>
<th>Saquinavir</th>
<th>Lopinavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUₙ½</td>
<td>mg/L·h</td>
<td>30.4 (20.7–51.6)</td>
<td>115 (90.5–147.2)</td>
<td>6.8 (4.9–10.6)</td>
</tr>
<tr>
<td>Tₐₚ</td>
<td>h</td>
<td>4.4 (4–6)</td>
<td>11.8 (8.9–16.4)</td>
<td>0.9 (0.7–1.3)</td>
</tr>
<tr>
<td>Cₘ₉₅</td>
<td>mg/L</td>
<td>4.9 (0.7–2.0)</td>
<td>5.9 (4.1–7.1)</td>
<td>0.3 (0.1–0.6)</td>
</tr>
<tr>
<td>fₚₚ</td>
<td>h</td>
<td>3.2 (2.7–4.2)</td>
<td>6.0 (3.8–6.1)</td>
<td>4.8 (2.0–6.5)</td>
</tr>
</tbody>
</table>

*Values are median ± interquartile range (numbers in parentheses).*
There was also evidence for a correlation between PI pharmacokinetics and lipid elevations. Of 6 children with lopinavir $C_{\text{max}}$ above 15 mg/L, 4 developed total cholesterol elevations, compared with 2 of 13 with lopinavir $C_{\text{min}}$ below 15 mg/L ($P = 0.03$). Of 6 children with lopinavir $C_{\text{max}}$ above 5.5 mg/L, 5 developed triglyceride elevations at week 24, compared with 3 of 13 with lopinavir $C_{\text{min}}$ below 5.5 mg/L ($P = 0.06$). Correlations between saquinavir pharmacokinetics and lipid elevations did not reach statistical significance.

**DISCUSSION**

In this pilot study of dual boosted lopinavir/saquinavir/ritonavir in NRTI-pretreated children, 16 of 20 (80%) patients showed reductions in HIV RNA to $<400$ copies/mL after 24 weeks of treatment. This response is comparable with results in previous trials of PI treatment, with either boosted or unboosted PIs. In addition, significant improvements in CD4%, weight and height occurred. The elevated lipids seen are consistent with other studies in children using PIs. The National Cholesterol Education Program recommends stepwise dieting and bile acid sequestrants if the former fails. These measures often are inadequate in lowering lipids in children treated with PI. Other lipid-lowering agents such as atorvastatin have been successfully used in a small number of children with familial hypercholesterolemia, but these are approved only for postpubescent children. Data on the management of this problem in PI-treated children are unavailable.

The relative contribution of boosted saquinavir and lopinavir on antiretroviral efficacy cannot be determined from this trial. There is in vitro evidence for synergy between saquinavir and lopinavir, and the plasma concentrations of both PIs in children are within the ranges expected for the drugs used at their individual standard dosages. Randomized clinical trials in PI-pretreated adults have shown improved clinical efficacy using 2 unboosted protease inhibitors, relative to using 1 unboosted PI; however, the difference in efficacy for double versus single boosted PIs has not been evaluated in randomized clinical trials. Boosted saquinavir and lopinavir have antiretroviral effects in short term PI monotherapy trials, but these early trends have yet to be evaluated in large randomized trials.

Saquinavir plasma concentrations were higher in this trial than for previous studies of unboosted saquinavir in children. The Thai children in this trial had a median AUC 0–12 of 39.4 mg/L·h, which is significantly higher than previously seen for children given unboosted saquinavir 50 mg/kg/3 times a day, where the AUC$_{0-24}$ was 5.8 mg/L·h. The concentrations also appear higher than for Caucasian adults, in whom the 1000/100 mg bid dosage with lopinavir led to a saquinavir AUC of 17 mg/L·h. However, there may be a racial effect on saquinavir concentrations. For 10 Thai adults treated with saquinavir/ritonavir 1000/100 mg bid, the median AUC$_{0-24}$ was 55.3 mg·h/mL, which is higher than for any trial in Caucasian patients. The mechanism of this potential racial correlation is unknown; lower body weight for Thai adults may partially explain this difference.

Lopinavir AUC concentrations from this trial also appeared to be higher than from previous trials in Caucasian children. The median AUC concentration for lopinavir from this trial 118 mg/L·h (dosage, 230/57.5 mg/m$^2$), compares with a mean value of 72.6 mg/L·h for 12 mainly Caucasian children given lopinavir/ritonavir at the 230/57.5 mg/m$^2$ dosage without nevirapine and 116.4 mg/L·h for 15 children given lopinavir/ritonavir at 300/75 mg/m$^2$ with nevirapine. The differences appear to be consistent for $C_{\text{max}}$ and $C_{\text{min}}$ with these comparisons. The lopinavir $C_{\text{max}}$ and $C_{\text{min}}$ from this trial are in the upper 75th percentile of the adult pharmacokinetic values for the 400/100 mg bid dosage given without saquinavir and are higher than those from the adult trial of ritonavir.

The apparently higher plasma concentrations of saquinavir, lopinavir and ritonavir in this trial are unlikely to
be a result of adherence, given that pharmacokinetic ass-
assessments were made after observed dosage in both this trial and those used for comparison. Standardized meals were also taken in this and previous trials. The correlations between PI pharmacokinetics, efficacy and safety are interesting but need to be reevaluated in larger trials or cohort studies, given the small sample sizes and number of statistical tests performed. Several of the chil-
dren with low plasma PI levels also had intercurrent opportunistic infections, and it is unclear whether these low PI concentrations would have been observed other-
wise. Retrospectively, when caregivers of the children with virologic failure were asked about adherence. 3 of 4 admitted to missing dosages and not taking medications on time. It is difficult to predict whether use of additional nucleoside analogs could have improved efficacy in this trial. Significant correlations between lopinavir Cmin and virologic response have been observed in a previous study of PI-pre-treated children receiving lopinavir/ritonavir without saquinavir23; however, for PI naive adults, a recent study has shown no correlation between lopinavir or sa-
quinar pharmacokinetics and reductions in HIV RNA 24,25.

Currently, however, with widespread first line use of NRTI/NRTI combinations in children, it is important to have a reliable second line strategy. A regimen that is used frequently for salvage of NRTI/NRTI failure is recycling of NRTI and combination with a PI. Good efficacy with Kaletra has been shown.26 The regimen in this study would especially benefit children who have significant resistance to NRTIs and NRTIs and who can swallow pills. The pill burden for the treatment given in this trial is high and may have limited adherence for some children; however, a new 500-mg for-
mulation of saquinavir would reduce the saquinavir pill burden by 60%.27 Because saquinavir can be used only in children who can swallow pills, exploring the pharmacoki-
netics of saquinavir given as an open capsule would help widened the use of this regimen.

Both dual boosted and single boosted PI failures can lead to PI mutations affecting further options. Fortunately PI failure, if detected early, is usually associated with few mutations and ability to reexpress HIV RNA.28 Two of our patients with virologic failure had lower HIV RNA after adherence counseling. With any second regimen failure, the salvage option becomes more limited. Options for children with dual boosted PI failure include recycling of previously used antiretrovirals based on genotyping, using new classes of antiretrovirals and adding T-20 (HIV-1 infusion inhibitor). The latter 2 choices are currently difficult to access in the developing world.

We believe that the combination of lopinavir-ritona-
vir and saquinavir should be evaluated in larger random-
ized clinical trials as a potential second-line option for children with resistance or intolerance to the NRTI and NRTI classes. In addition, to save cost and possibly to minimize PI-related metabolic complication, our observa-
tions of higher pharmacokinetic profiles of both saquinavir and lopinavir than to those in Caucasians should lead to further studies to investigate whether a dose reduction of boosted PI among Thai population will be cost-effective.

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17. NCEP Expert Panel on Blood Cholesterol Levels in Children and Adolescents. National Cholesterol Education Program (NCEP) high-


APPENDIX: THE HIV-NAT 017 STUDY TEAM

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