Pharmacological Assessment of Efavirenz Weight-Band Dosing Recommendations in HIV-Infected Thai Children

To the Editors:
Efavirenz (EFV) plus a dual–nucleoside reverse transcriptase inhibitor (NRTI) backbone combination is recommended for HIV-infected treatment-naive children aged 3 years or older.1 EFV prescribing recommendations use weight-band dosing. Accumulating drug concentration data in HIV-infected children has raised concerns that the current dosing recommendations in the package insert, which is currently equivalent to the dosing recommendations in the US Department of Health and Human Services (US-DHHS) guidelines,1 may lead to subtherapeutic concentrations.2–5 It is unknown if the lower efavirenz clearance described in Thai adults compared with other populations4 reduces the risk of underdosing in Thai children. We evaluated the steady-state pharmacokinetics of efavirenz prescribed according to conventional weight-band dosing guidelines in 40 HIV-infected Thai children.

The pharmacokinetic data reported were collected within an ongoing prospective, single-arm, open-label, multicenter trial investigating the safety and pharmacokinetics of a once daily regimen of tenofovir/lamivudine/efavirenz in virologically suppressed HIV-infected children. Eligible patients were aged between 3 and 18 years, weighing 15 kg or more, receiving a first-line antiretroviral regimen composed of 2 NRTIs (without tenofovir) plus non-NRTI and a plasma HIV-1 RNA <50 copies/mL within 6 months before study entry. Patients were enrolled after providing informed consent by their legal guardian(s). Assent from the child was obtained following local ethical guidelines. Patients were excluded if they had opportunistic infections or other significant medical diagnosis required ongoing therapy, had history of psychological or neurological illnesses, had impaired baseline renal function (defined as a creatinine clearance <60 mL/min and calculated using the Schwartz equation), or were pregnant. At enrollment, their antiretroviral regimen was modified to tenofovir/lamivudine/efavirenz once daily. The dosage for efavirenz was 250, 300, 350, 400, and 600 mg once daily for children with body weights of 15–20, 20–25, 25–32.5, 32.5–40, or ≥40 kg, respectively, as recommended in US-DHHS guidelines (February 23, 2009). Efavirenz was prescribed using STOCRIN 50 mg and 600 mg tablets and/or a generic 200 mg capsule [World Health Organization (WHO) prequalified product by Matrix Laboratories Limited, Maharashtra, India] titrated according to weight to the nearest 50 mg. Intensive 24-hour blood sampling for pharmacokinetic assessment was


performed after 4 weeks. Blood samples were drawn predose and following an observed dose at 0.5, 1, 2, 4, 8, 12, and 24 hours postdose. Efavirenz was given as an observed dose without regard to food, but the last food intake was documented. Study participants were recruited from Siriraj Hospital in Bangkok and Chiang Mai University Hospital. The study was approved by the institutional review board at each clinical site.

All blood samples were centrifuged and the plasma was frozen at −20°C until analysis. Efavirenz plasma drug concentrations were measured using a validated high-performance liquid chromatography assay at the Program for HIV and Treatment—Chiang Mai laboratory, which participates in the AIDS Clinical Trials Group, USA, Pharmacology Quality Control program. The assay was validated over the concentration range of 0.078–10.0 µg/mL. The average accuracy was 102%–105% and precision (both inter- and intra-assay) was <5% of the coefficient of variation. Data were analyzed with WinNonLin (Version 5.2; Pharsight Corporation, Mountain View, CA) using noncompartmental methods. All data are presented as median (range).

Forty children (43% male) completed the intensive 24-hour PK sampling. At enrollment, median age was 12.5 (3.1–17.7) years, weight was 33.2 (16–56) kg, CD4 cell count was 757 (415–2675) cells/mm³, and 36 (90%) of 40 children had an HIV RNA level of <50 copies/mL. Four children had a viral load between 96 and 635 copies/mL at entry. Before enrollment, the median duration on highly active antiretroviral therapy (HAART) was 383 (76–815) weeks, and the median duration of efavirenz-containing treatment was 4 (4–434) weeks. The median EFV dose was 12.7 (10.3–19.4) mg/kg. One child received the incorrect EFV dose at the time of the PK sampling and was excluded from the PK analysis.

Overall, the median area under concentration time curve (AUC) was 54.6 (28.0–248.7) µg·h/mL, and the C₂₄ was 1.45 (0.68–10.23) µg/mL. Among the 39 children, 6 (15%) had an efavirenz 24-hour postdose concentration (C₂₄) <1.0 µg/mL, the suggested minimum target trough concentrations in the US-DHHS guidelines. Efavirenz PK parameters per dose weight band are presented in Table 1. The percentage of children with an EFV C₂₄ less than 1.0 µg/mL differed depending on the weight band. Within the 2 highest weight bands (ie, children more than 32.5 kg), 1 of 22 (5%) children had an EFV C₂₄ <1.0 µg/mL compared to 5 (26%) of 19 in the children less than 32.5 kg. In the lowest weight band, 2 (50%) of 4 children did not achieve target trough concentrations. An efavirenz concentration more than 4.0 µg/mL between 12 and 24 hours postdose has been associated with higher central nervous toxicity, and 2 children in this study had a C₂₄ more than this limit, and both had an efavirenz AUC >140 µg·h/mL, without any apparent toxicity.

All subjects, including those with low C₂₄, maintained their HIV RNA viral load <400 copies/mL at 12 weeks. Two children had a viral load between 50 and 400 copies/mL at 12 weeks, in one child the viral load returned to <50 copies/mL, and in the other increased to 3941 copies/mL at 24 week (C₂₄ of this child was 1.54 µg/mL at the week-4 PK visit). Pill counts were performed at each study visit and indicated good adherence by all study subjects.

Overall, we found that 85% of HIV-infected Thai children, weighing 15 kg or more, with median age 12.5 years, receiving efavirenz prescribed according to US-DHHS weight band, achieved target trough concentrations. This result is consistent with preliminary data assessing efavirenz “middose” concentrations in Thai children that found that 13% had concentrations less than target. However, in the present study the percentages of children with subtherapeutic concentrations in 2 of the weight bands, 15 to <20 kg and 25 to <32.5 kg, were relatively high with 50% and 33% of children having a C₂₄ less than the target threshold, respectively. Although the number of children in both weight bands was relatively low, these data indicate a possible trend for under dosing in these weight ranges.

A study in South Africa was the first to highlight the potential risk of underdosing of efavirenz in children following current dosing recommendations with 6 (40%) of 15 children (median age 6.8 years) having subtherapeutic trough concentrations. Recently, a larger study in Uganda reported 15 (38%) of 39 children (median age 7.6 years) having a C₂₄ less than 1.0 µg/mL. It is important to highlight that the median age of the Thai children in the present study was 12.5 years, and we must be cautious when making direct comparison between studies.

Efv is primarily metabolized by CYP2B6 and the CYP2B6 516 G>T genetic polymorphism is strongly associated with slower efavirenz clearance. Using a population pharmacokinetic approach, a study in Europe predicted that 50%–70% of children,

### TABLE 1. Summary of Efavirenz Pharmacokinetics in HIV-Infected Thai Children by Weight-Band Dosing Recommendations

<table>
<thead>
<tr>
<th>Weight Range (kg)</th>
<th>15–20</th>
<th>20–25</th>
<th>25–32.5</th>
<th>32.5–40</th>
<th>&gt;40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz dose, mg</td>
<td>250</td>
<td>300</td>
<td>350</td>
<td>400</td>
<td>600</td>
</tr>
<tr>
<td>No. children, n</td>
<td>4</td>
<td>9</td>
<td>6</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>AUC₀–₂₄ (µg·h/mL)</td>
<td>44.9  (41.2–66.2)</td>
<td>55.1  (42.8–248.7)</td>
<td>52.5  (28.0–241.4)</td>
<td>52.3 (44.7–89.3)</td>
<td>59.4 (38.9–99.8)</td>
</tr>
<tr>
<td>C₉₀ (µg/mL)</td>
<td>3.51  (2.49–5.38)</td>
<td>3.71  (3.0–11.4)</td>
<td>3.26 (1.77–13.45)</td>
<td>3.45 (2.70–5.75)</td>
<td>4.53 (3.14–6.01)</td>
</tr>
<tr>
<td>C₂₄ (µg/mL)</td>
<td>1.04  (0.87–1.69)</td>
<td>1.35  (0.74–10.23)</td>
<td>1.45 (0.74–9.35)</td>
<td>1.54 (1.30–2.89)</td>
<td>1.59 (0.68–3.40)</td>
</tr>
</tbody>
</table>

Values are expressed as median (range).

*The trough >1 mg/L are presented as number of subjects/total number of subjects (percentage).

| AUC₀–₂₄, area under concentration time curve; C₂₄, the 24-hour postdose concentration, after an observed dose; C₉₀, the maximum concentration; T₉₀, the time to maximum concentration. |
carrying the common CYP2B6 516 G/G genotype, would be at risk of subtherapeutic efavirenz concentrations following standard dosing. The frequency of the CYP2B6 TT genotype in Thai children is approximately 10%.1,3,11 Unfortunately, the CYP2B6 516 G>T genotype was not determined in the present study, but 2 (5%) of 39 children had high efavirenz exposure (ie, >140 μg·h/mL), suggesting a slow metabolizer genotype. The frequency of the CYP2B6 516 TT genotype could significantly influence the number of children with subtherapeutic concentrations and should be considered when comparing different ethnic pediatric populations.

The number of Thai children with subtherapeutic concentrations were highest in the 15 to <20 kg and 25 to <32.5 kg weight bands. The new WHO 2010 guidelines recommend increasing the efavirenz dose by 50 mg in both of these weight bands (ie, to 300 and 400 mg, respectively)12 and thus seems appropriate. However, these new WHO guidelines also increase the dose for children between 35 and 40 kg from 400 to 600 mg; no Thai children had an efavirenz C\text{\textsubscript{ss}} less than 1.0 μg/mL in this weight band. The change in the WHO guidelines also aims to simplify dosing and balance optimizing treatment with practical implementation in challenging clinical settings. The data reported in the present study suggest that these proposed higher dose in the 15 to <20 kg and 25 to <32.5 kg weight bands may be preferable for Thai children and should be assessed.

Our study enrolled virologically suppressed children and some of them had been receiving an efavirenz-containing HAART regimen before enrollment. Thus, despite possible subtherapeutic efavirenz concentrations, particularly in children with the lowest weight, sustained viral suppression was observed. The small number of children in the 10 to <15 kg weight band is a limitation of the present study, and additional data is needed in Thai children.

In conclusion, the percentage of Thai children with subtherapeutic concentrations was lower than other populations but remained high among children receiving 250 and 350 mg efavirenz dose. The higher doses recommended by the WHO in 2010 may minimize the risk of low efavirenz concentrations for children within these weight ranges.

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REFERENCES