Original article

Pharmacokinetics of darunavir/ritonavir in Asian HIV-1-infected children aged ≥7 years

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Introduction

Darunavir is a new protease inhibitor (PI) approved for the treatment of HIV in children age ≥6 years. Adult studies have shown that darunavir boosted with low-dose ritonavir has superior efficacy to lopinavir/ritonavir in both first-line antiretroviral therapy (ART) and salvage ART settings [1–3]. Heavily ART pretreated children in group B of the Darunavir Evaluation in Paediatric, HIV-Infected, treatment-experienced patients (DELPHI) study receiving 20–30% higher darunavir dosing than that calculated to provide an adult-equivalent dose of twice daily darunavir/ritonavir 600/100 mg had equivalent darunavir pharmacokinetic exposure to adults, as well as excellent virological and immunological responses [4]. This dosing was subsequently selected as the manufacturer-recommended dosing for children.
As access to ART has increased worldwide and more patients have now been on treatment for several years, treatment failure is becoming more common. A regional Asian cohort study showed that at present 20% of children are already on second-line therapy [5]. Lopinavir/ritonavir is currently the main PI option for children failing first-line non-nucleoside reverse transcriptase inhibitor (NNRTI)-based treatment in the 2010 World Health Organization guidelines [6]. The guidelines, however, do not have specific recommendations for ART when lopinavir/ritonavir-based regimens fail. With data supporting the high potency of darunavir/ritonavir in PI-experienced adults and children [7], darunavir/ritonavir is likely to be the mainstream of third-line therapy in children; however, pharmacokinetic data from developing countries are lacking.

Drug exposure to PIs might differ according to ethnicity. It is well documented that Thai children have higher drug exposure to several PIs, including lopinavir, indinavir and saquinavir, than non-Asian children [8–11]. High drug concentrations could lead to higher toxicity and unnecessary cost [12]. Further complicating the issue, children who weigh <40 kg require a ritonavir solution of 50–60 mg according to the manufacturer’s prescribing information [13]. Ritonavir solution needs to be stored at 20–25°C without refrigeration, demands large space in pharmacies and is poorly tolerated by patients. Large-scale procurement of liquid formulation for national programmes is often not feasible owing to the higher cost and shorter shelf life (6 months when stored at 20–25°C) compared with pills (12 months when stored at 5°C) [14]. In Thailand, 100 mg ritonavir capsules are used for children of all weight bands, which could further raise the darunavir and ritonavir plasma concentrations.

We assessed the darunavir and ritonavir pharmacokinetic parameters by extensive blood sampling over 12 h in Thai children who used darunavir at standard doses but with ritonavir 100 mg boosting. We assessed darunavir and ritonavir concentrations in relation to adverse events and compared the concentrations with those in children from the DELPHI study, conducted in the US, Europe and Argentina. This study is important to ascertain whether the recommended darunavir dosing used with 100 mg ritonavir boosting is appropriate in Asian children.

Methods

The HIV-NAT 113 study is an observational cohort study of third-line antiretroviral therapy in Thai children (www.clinicaltrials.gov identification number NCT01225406). This pharmacokinetic substudy of the HIV-NAT 113 study included 19 HIV-infected Thai children aged 7 to 16 years old and with body weight ≥20 kg who had been on darunavir/ritonavir-based ART for ≥2 weeks. Children with anaemia, defined as haemoglobin ≥ grade 2 according to the US National Institute of Allergy and Infectious Diseases, Division of AIDS toxicity grading table, were excluded. All eligible children from the HIV-NAT 113 study at two tertiary care sites in Bangkok (HIV-NAT/The Thai Red Cross AIDS Research Centre and Siriraj Hospital, Mahidol University) were enrolled in this pharmacokinetic substudy. The number of children in each weight band is reflective of the available population at these two sites. The study was approved by the Institutional Review Boards of Chulalongkorn and Mahidol Universities. All caregivers gave consent and children who knew their HIV status gave assent.

Darunavir and ritonavir dosing was based on recommendations by their respective manufacturers, except that a ritonavir 100 mg soft gel capsule (Norvir®) was used as a booster in children of all body weight bands owing to the difficulty in accessing ritonavir solution in Thailand. The two lower weight bands had higher ritonavir dosing than recommended by the manufacturer (50 mg ritonavir for 20 to <30 kg and 60 mg ritonavir for 30 to <40 kg) [13]. Therefore, in this study, children used the following twice daily darunavir/ritonavir dosing: 375/100 mg (20 to <30 kg), 450/100 mg (30 to <40 kg) and 600/100 mg (≥40 kg). On the day of pharmacokinetic sampling, all children received an observed dose of darunavir/ritonavir immediately after eating a breakfast that had approximately 30% fat content. Blood samples for drug concentration analysis were collected just before drug intake (t=0) and subsequently at 2, 4, 6, 8, 10 and 12 h after drug intake. Levels of fasting total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL), low-density lipoproteins (LDL) and alanine aminotransferase (ALT) were also determined. Plasma samples for pharmacokinetics were centrifuged at 3,000 rpm for 10 min at 20°C within 2 h of sample collection and then stored at -20°C until analysis at the HIV-NAT laboratory. Plasma concentrations of darunavir and ritonavir were measured by a validated HPLC method with UV detection based on methods used for measuring amprenavir concentration (detailed by one of our co authors) [15]. The darunavir concentration was linear over the range of 0.105–30.0 mg/l with the percentage accuracy being 103% at 0.15 mg/l, 106% at 1.5 mg/l and 105% at 7.5 mg/l darunavir concentration. The percentages of coefficient of variation (CV) of precision within the same day and between days, respectively, were 9.6% and 7.6% at 0.15 mg/l, 3.1% and 3.7% at 1.5 mg/l and 3.7% and 2.3% at 7.5 mg/l darunavir concentration. The lower limit of quantification for darunavir was 0.105 mg/l. For ritonavir, the concentration was linear over the range of 0.045–30.0 mg/l with the
percentage accuracy being 84% at 0.15 mg/l, 97% at 1.5 mg/l and 99% at 7.5 mg/l ritonavir concentration. The percentages of CV of precision within the same day and between days, respectively, were 8.5% and 2.1% at 0.15 mg/l, 2.4% and 2.4% at 1.5 mg/l and 3.1% and 1.3% at 7.5 mg/l ritonavir concentration. The lower limit of quantification for ritonavir was 0.045 mg/l. The validated assay used has successfully passed requirements set by the International Quality Control Program for Measurement of Antiretroviral Drugs in Plasma of the Radboud University Nijmegen Medical Center, the Netherlands [16].

Pharmacokinetic parameters were derived by using non-compartmental methods with WinNonlin 5.2 (Pharsight Corporation, Mountain View, CA, USA). Area under the concentration–time curve at 0–12 h (AUC_{0-12}) was calculated using a linear extension with the trapezoidal rule; oral clearance (Cl/F) was calculated by dividing the dose by the AUC, and the last three time points were used to calculate the elimination rate constant and half-life (t_{1/2}). Other parameters calculated were the maximum concentration (C_{max}), concentration prior to the next dose (C_{tr}) and time to reach maximum plasma concentration (t_{max}). Descriptive statistics were calculated for pharmacokinetic parameters of darunavir and ritonavir, including the number of patients with C_{12} above the protein binding adjusted 50% effective concentration (EC_{50}) of PI-resistant virus (0.55 mg/l). Statistical analysis was performed using Stata version 11.2 (StataCorp, College Station, TX, USA). The geometric mean, CV and 95% CI for darunavir and ritonavir pharmacokinetic parameters were calculated. Median (IQR) and frequency (%) were used to describe the patient demographic characteristics for continuous and categorical data, respectively. Log-transformed pharmacokinetic parameters were used as outcome variables in regression models to assess the effect of different darunavir doses and age, sex, weight and ritonavir exposure. Parameters considered to be significant in univariate analysis (P<0.15) were entered into stepwise backwards models and covariates were retained if P<0.05. Statistical tests were two-sided and performed at a significance level of 0.05. As ritonavir AUC_{0-12} was the most significant factor influencing the pharmacokinetic values of darunavir after adjusting for darunavir dose, we further assessed the effect of sex, age and weight of children on the log-transformed AUC_{0-12}, C_{max} and C_{12} of ritonavir. Geometric mean ratios of darunavir and ritonavir AUC_{0-12}, C_{max} and C_{12} between our study and the DELPHI study were calculated using raw data provided by Tibotec Inc., Titusville, NJ, USA. Associations between darunavir and ritonavir AUC_{0-12} and abnormal lipid levels were assessed using logistic regression models. Abnormal lipids were defined as TC>200 mg/dl, TG>130 mg/dl, HDL<40 mg/dl and LDL>130 mg/dl [17].

Results

All 19 children who enrolled completed the 12 h pharmacokinetic sampling. The numbers of children in the three darunavir/ritonavir weight band twice-daily dosing groups were 12 children for 375/100 mg (20 to <30 kg), 2 children for 450/100 mg (30 to <40 kg) and 5 children for 600/100 mg (≥40 kg). The median (IQR) duration on darunavir/ritonavir was 11 months (6–13). Other antiretroviral drugs in the regimen were tenofovir (63%), zidovudine (58%), abacavir (5%), lamivudine (95%) and etravirine (42%). In total, 11 children were male and 8 female. The median age was 13 years (IQR 10–15, range 7–16) and the median body weight was 29.4 kg (IQR 24.4–43.4, range 20–67.6). The median CD4+ T-cell count was 695 cells/mm$^3$ (IQR 466–928, range 22–1,127) and median HIV RNA was 1.60 log$_{10}$ copies/ml (IQR 1.60–1.81, range 1.60–6.28). Overall, 17 (89.5%) children had HIV RNA<400 copies/ml and 12 (63%) had HIV RNA<50 copies/ml. Median values for lipids were 187 mg/dl (IQR 162–208, range 82–295) for TC, 144 mg/dl (IQR 111–237, range 90–1,658) for TG, 98 mg/dl (IQR 80–121.4, range 39.4–168) for LDL and 38 mg/dl (IQR 31–49, range 19–61) for HDL. Median for ALT was 22 mg/dl (IQR 14–33, range 11–48). Eight adverse events ≥ grade 2 comprised two cases of acute bronchitis, five children presenting with hypercholesterolaemia (TC>200 mg/dl) and one child with hypertriglyceridaemia (TG>1,000 mg/dl). The pharmacokinetic parameters in this last patient were darunavir AUC_{0-12} 92 h×mg/l, C_{max} 12.8 mg/l and C_{12} 3.4 mg/l and ritonavir AUC_{0-12} 7.6 h×mg/l, C_{max} 1.24 mg/l and C_{12} 0.12 mg/l.

The median darunavir and ritonavir concentration–time curves in children receiving different dosing of darunavir/ritonavir by weight band are depicted in Figure 1A and 1B. Exposure to darunavir was comparable between the three dosing groups throughout the 12 h dosing cycle, whereas the ritonavir concentrations were generally higher for the darunavir/ritonavir 375/100 mg dosing group.

Table 1 shows the summary data for darunavir and ritonavir pharmacokinetic parameters. Overall the children had adequate darunavir and ritonavir pharmacokinetic parameters; all had darunavir C_{12}>0.55 mg/l, the protein binding adjusted EC_{50} of PI-resistant virus. There was high interpatient variability, as evidenced by large CVs (>50%). Between dosing groups, no significant differences were seen for darunavir pharmacokinetic parameters. Geometric mean clearance of ritonavir was significantly higher in the darunavir/ritonavir 375/100 mg dosing group.
Figure 1. Median plasma concentrations of darunavir and ritonavir by darunavir/ritonavir dosing groups

![Figure 1](image)

Table 1. Pharmacokinetic parameters in Thai children taking darunavir/ritonavir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>BW 20 to &lt;30 kg (n=12)</th>
<th>BW 30 to &lt;40 kg (n=2)</th>
<th>BW ≥40 kg (n=5)</th>
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</thead>
<tbody>
<tr>
<td>Darunavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_0–12 h×mg/l</td>
<td>60.3 (68)</td>
<td>58.5 (85)</td>
<td>58.5 (18)</td>
<td>65.8 (44)</td>
</tr>
<tr>
<td>C_{max}, mg/l</td>
<td>8.3 (55)</td>
<td>8.1 (65)</td>
<td>8.2 (1)</td>
<td>9.0 (46)</td>
</tr>
<tr>
<td>C_{12}, mg/l</td>
<td>3.1 (76)</td>
<td>3.0 (96)</td>
<td>3.2 (60)</td>
<td>3.1 (44)</td>
</tr>
<tr>
<td>Clearance, l/h</td>
<td>7.0 (69)</td>
<td>6.3 (83)</td>
<td>7.2 (27)</td>
<td>9.1 (44)</td>
</tr>
<tr>
<td>Median half-life, h (range)</td>
<td>6.8 (4.7–40.2)</td>
<td>6.5 (4.7–11.6)</td>
<td>6.6 (5.2–8.0)</td>
<td>7.0 (5.3–40.2)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_0–12 h×mg/l</td>
<td>1.2 (90)</td>
<td>12 (108)</td>
<td>9.5 (21)</td>
<td>6.8 (51)</td>
</tr>
<tr>
<td>C_{max}, mg/l</td>
<td>1.7 (96)</td>
<td>2.2 (98)</td>
<td>1.5 (29)</td>
<td>0.9 (66)</td>
</tr>
<tr>
<td>C_{12}, mg/l</td>
<td>0.37 (75)</td>
<td>0.39 (83)</td>
<td>0.51 (103)</td>
<td>0.27 (49)</td>
</tr>
<tr>
<td>Clearance, l/h</td>
<td>5.9 (116)</td>
<td>4.1 (108)</td>
<td>5.9 (33)</td>
<td>14.7 (51)</td>
</tr>
<tr>
<td>Median half-life, h (range)</td>
<td>3.9 (2.9–16.5)</td>
<td>3.5 (2.9–4.2)</td>
<td>10.6 (4.6–16.5)</td>
<td>4.9 (4.3–5.2)</td>
</tr>
</tbody>
</table>

Data are geometric mean (% coefficient of variation) unless indicated otherwise. *Ritonavir 100 mg boosting was used for all dosing groups. †Darunavir dosing was 375, 450 and 600 mg twice daily for body weight (BW) 20 to <30 kg, 30 to <40 kg and ≥40 kg, respectively. ‡P<0.05. AUC_{0–12 h}, area under the concentration–time curve at 0–12 h; C_{max}, maximum concentration; C_{12}, concentration prior to the next dose.

ritonavir 600/100 mg group (14.7 l/h) versus the other two groups (4.1 l/h in the 375/100 mg group and 5.9 l/h in the 450/100 mg group). Of note, there were two children in the darunavir/ritonavir 375/100 mg dosing group with very high darunavir C_{12} values of 12.20 and 11.20 mg/l (ritonavir C_{12} values of 0.18 and 2.00 mg/l, respectively); however, these children did not display any adverse events except for low HDL. There were two patients on anticonvulsants for >10 months prior to the pharmacokinetics sampling. One child (body weight 20.3 kg, 375/100 mg dosing) was on phenytoin 100 mg once daily and had an AUC_{0–12} of 210 h×mg/l and C_{12} of 8.6 mg/l. The other child (body weight 35 kg, 450/100 mg dosing) was on phenobarbital 60 mg...
once daily and had a darunavir \(A_{0-12}^{\text{P}}\) of 51.6 \text{h} \times \text{mg/l} and \(C_{12}\) of 2.2 \text{mg/l}. Both children were adherent to the anticonvulsant and ART.

Table 2 shows the geometric mean \(A_{0-12}^{\text{P}}\), \(C_{\text{max}}\) and \(C_{12}\) in Thai children from this study compared with non-Asian children in the DELPHI study. All Thai children received 100 mg ritonavir boosting regardless of weight band, whereas the DELPHI children received <100 mg of ritonavir if they weighed <40 kg. There were no statistically significant differences between the darunavir and ritonavir pharmacokinetic values between the two groups in all weight bands, except for higher ritonavir pharmacokinetic values in Thai children weighing 20 to <30 kg.

In the regression models assessing the effect of covariates (age, sex, weight, darunavir dose and ritonavir \(A_{0-12}^{\text{P}}\)) on darunavir pharmacokinetic parameters, only ritonavir \(A_{0-12}^{\text{P}}\) significantly influenced darunavir \(A_{0-12}^{\text{P}}\) (coefficient 1.03 [95% CI 1.01, 1.05]; \(P=0.01\)), \(C_{\text{max}}\) (coefficient 1.02 [95% CI 1.0, 1.0]; \(P=0.04\)), \(C_{12}\) (coefficient 1.03 [95% CI 1.01, 1.03]; \(P=0.01\)) and clearance (coefficient 0.98 [95% CI 0.96, 0.99]; \(P=0.01\)). There was a trend for faster darunavir clearance with increasing weight (coefficient 1.04 [95% CI 0.99, 1.08]; \(P=0.07\)). In separate regression models we assessed whether patient age, sex or weight influenced the \(A_{0-12}^{\text{P}}\), \(C_{\text{max}}\) and \(C_{12}\) of ritonavir. In these models, increasing weight was associated with a significant reduction in the \(C_{\text{max}}\) of ritonavir (coefficient 0.96 [95% CI 0.94, 0.98]; \(P=0.008\)). There were no significant associations between abnormal lipid levels, use of other antiretrovirals and pharmacokinetic parameters of darunavir and ritonavir.

**Discussion**

Our study shows that Thai children aged 7 to 16 years who used a ritonavir 100 mg capsule with standard doses of darunavir had appropriate pharmacokinetic values that were similar to those in non-Asian children from the DELPHI study [4]. All children had \(C_{12}\) concentrations above the protein binding adjusted \(E_{50}\) of PI-resistant virus, as also seen in the DELPHI study [18]. This is consistent with the high genetic barrier to resistance of darunavir/ritonavir [3]. To our knowledge, this is the first published study using the ritonavir 100 mg capsule for children with body weight 20–<40 kg rather than a lower dose of ritonavir.

The darunavir pharmacokinetic parameters were similar across dosing groups in our study children. The longer ritonavir half-life in the darunavir/ritonavir 450/100 mg group and higher ritonavir clearance in the darunavir/ritonavir 600/100 mg group require confirmation with a larger sample size, as there were only two and five children in these groups, respectively. We had expected Thai children to have higher darunavir concentrations than non-Asian children in the DELPHI study for two reasons: previous studies had shown Thai children to have higher PI concentrations in the Darunavir/ritonavir 600/100 mg group compared with Western children [8,10]; and a higher ritonavir boosting dose was used in children weighing <40 kg, which accounted for 74% of the study population. By contrast, we found no differences in darunavir pharmacokinetic parameters between our study and children in the DELPHI study. Additionally, the overall geometric mean darunavir \(A_{12}^{\text{P}}\) in our children was similar to that in US children from another study, most of whom received darunavir/ritonavir 600/100 mg twice daily [19]. This could be due to pharmacogenomic differences, which also accounted for lower drug exposure to darunavir in Asian adults in the Artemis study [20], and the fact that darunavir is boosted equally well with lower versus higher doses of ritonavir [21]. Moreover, the characteristics of pediatric patients differ across studies and there is large

| Table 2. \(A_{0-12}^{\text{P}}\), \(C_{\text{max}}\) and \(C_{12}\) in our study compared to the DELPHI study |
|-------------------------------|----------------|----------------|
| Pharmacokinetic parameters   | \(A_{0-12}^{\text{P}}\) | \(C_{\text{max}}\) |
| Darunavir                     | 0.72 (0.38, 1.39) | 0.86 (0.50, 1.47) |
| Ritonavir                     | 2.57 (1.08, 6.13) | 3.30 (1.41, 7.74) |
|                              | 2.01 (0.21, 19.35) | 3.6 (1.12, 9.53) |
|                              | 1.69 (0.58, 4.95) | 5.6 (0.84, 36.5) |
|                              | 1.84 (0.60, 5.67) | 4.5 (0.72, 28.7) |
|                              | 2.02 (0.21, 19.35) | 3.6 (0.26, 49.9) |
|                              | 1.21 (0.73, 2.02) | 0.94 (0.33, 2.64) |
|                              | 1.26 (0.73, 2.18) | 1.01 (0.35, 2.86) |
|                              | 1.40 (0.67, 2.89) | 1.34 (0.25, 7.37) |

Data in this table represent the geometric mean ratios (95% CI) of raw data of drug concentrations from Thai children in this study and those from non-Asian children in the DELPHI study [4]. Ratios <1 signify lower concentrations in Thai children and ratios >1 signify higher concentrations in Thai children. The non-Asian children in the DELPHI study received the same darunavir doses as the Thai children in this study: darunavir 375, 450 and 600 mg twice daily for body weight (BW) 20 to <30 kg, 30 to <40 kg and ≥40 kg, respectively. However, the ritonavir dosing differs for weight bands 20 to <30 kg and in this study, and 30 to <40 kg [80 and 100 mg twice daily, respectively, in the DELPHI study and in this study]. Both studies used ritonavir 100 mg twice daily for BW=40 kg. The number of children in each of these weight bands in the DELPHI study was 7, 6 and 7, respectively. \(^{a}\)P=0.05. \(A_{0-12}^{\text{P}}\) area under the concentration–time curve at 0–12 h; \(C_{\text{max}}\) maximum concentration; \(C_{12}\) concentration prior to the next dose.
interpatient variability in darunavir plasma concentrations [19]. Comparison of pharmacokinetic parameters between Thai and non-Asian adults on darunavir/ritonavir 600/100 mg twice daily showed only darunavir \( C_{\text{max}} \) to be higher in Thai patients [22].

Similar to other studies, a strong association between ritonavir and darunavir pharmacokinetic parameters was seen [21]. It is, therefore, unclear why there was a trend towards lower darunavir concentrations in the 375/100 mg darunavir/ritonavir group that exhibited the highest ritonavir concentrations. These findings could be the indigenous host factors of younger children. The DELPHI study showed no correlation between darunavir concentrations and virological response and adverse events. Our study showed similar findings, but the cross-sectional nature of this study and the small sample size limits the strength of the analyses. Age, sex, body weight and other antiretrovirals had no association with darunavir pharmacokinetic parameters. Hyperlipidaemia was not associated with darunavir concentrations, except for low HDL witnessed in two patients with 20\( \times \) the desired darunavir \( C_{12} \). Our study included two children treated with anticonvulsants, which could lower PI concentration [14]. Compared with the suggested target median \( C_{12} \) of 3.3 (range 1.2–7.3) mg/l for darunavir 600 mg twice daily, one child on standard dosing of phenytoin had high darunavir \( C_{12} \) probably due to low body weight. The other had darunavir \( C_{12} \) within the published ranges but lower than the median, probably because the phenobarbital dosing was only half of the recommended dose.

The US Department of Health and Human Services guidelines now recommend two nucleoside reverse transcriptase inhibitors plus darunavir/ritonavir as an alternative initial therapy for children, but this is unlikely to be the case in developing countries mainly due to cost [23]. Darunavir/ritonavir will be needed, however, for treating children failing PIs worldwide. This could be in a second-line setting in children who received a PI as first-line therapy or in a third-line setting in children who have failed first-line NNRTI and second-line PI-based HAART. Increasing evidence of darunavir/ritonavir efficacy in treating children who have failed other PIs [4,24] confirms findings previously shown in adults [2,3].

Alarmingly, large treatment cohorts in Africa and Asia have shown one-fifth of children requiring second-line PI regimens [5,25]. Children face specific treatment challenges, one of which is limited paediatric formulations and pharmacokinetic studies, contributing to incomplete dosing recommendations. This is particularly true for new antiretrovirals that are needed for managing treatment failure [7].

Our data are encouraging in that they document appropriate darunavir concentrations in non-Western children who are generally younger and need to take ritonavir 100 mg capsule boosting due to lack of appropriate ritonavir formulation. In the future it will be important to obtain more darunavir pharmacokinetic data from children of other ethnic groups and a concerted effort will be needed to plan and procure ART such as darunavir for treatment-experienced children in resource-limited settings.

Acknowledgements

We are grateful to the children and their families for participating in this study. We thank Sabrina Spinoso-Guzman and Thomas Kakuda from Tibotec Pharmaceuticals for providing data from the DELPHI study. Tibotec Pharmaceuticals provided darunavir (Prezista®) and etravirine (Intelenza®) for our children through their compassionate use programme. The other antiretrovirals were supported by the Thai Health Security Office. We thank Pirapon June Ohata for her help in preparing this manuscript.

Disclosure statement

DB has received honoraria and/or study grants from Tibotec, Merck, Abbott, BMS, Roche, Gilead and GSK. JA has received speakers’ fees or honorarium from Gilead, Abbott and ViV. VS is an employee of Tibotec. Remaining authors declare no competing interests.

Additional file


References


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Pharmacokinetics of DRV/r in children


