Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Darunavir (DRV, Prezista)  

(Last updated May 22, 2018; last reviewed May 22, 2018)

For additional information see Drugs@FDA: http://www.accessdata.fda.gov/scripts/cder/daf

Dosing Recommendations

Note: Darunavir should not be used without a pharmacokinetic (PK) enhancer (i.e., boosting agent): ritonavir (for children and adults) or cobicistat (for adults only).

Neonate/Infant Dose:
• Not approved for use in neonates/infants.

Pediatric Dose
Aged <3 Years:
• **Do not use darunavir in children aged <3 years or weighing ≤10 kg** because of toxicity concerns based on seizures and death observed in infant rats and attributed to immaturity of the blood-brain barrier and liver metabolic pathways.

Aged ≥3 Years:
• See table below for children aged ≥3 years who are antiretroviral treatment-naive and treatment-experienced with or without 1 or more darunavir resistance-associated mutations.

Aged 3 to <12 Years and Weighing ≥10 kg

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (Twice Daily with Food)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;11 kg²</td>
<td>Darunavir 200 mg (2.0 mL) plus ritonavir 32 mg (0.4 mL)</td>
</tr>
<tr>
<td>11 kg to &lt;12 kg²</td>
<td>Darunavir 220 mg (2.2 mL) plus ritonavir 32 mg (0.4 mL²)</td>
</tr>
<tr>
<td>12 kg to &lt;13 kg²</td>
<td>Darunavir 240 mg (2.4 mL) plus ritonavir 40 mg (0.5 mL²)</td>
</tr>
<tr>
<td>13 kg to &lt;14 kg²</td>
<td>Darunavir 260 mg (2.6 mL) plus ritonavir 40 mg (0.5 mL²)</td>
</tr>
<tr>
<td>14 kg to &lt;15 kg²</td>
<td>Darunavir 280 mg (2.8 mL) plus ritonavir 48 mg (0.6 mL²)</td>
</tr>
<tr>
<td>15 kg to &lt;30 kg</td>
<td>Darunavir 375 mg (combination of tablets or 3.8 mL²) plus ritonavir 48 mg (0.6 mL²)</td>
</tr>
<tr>
<td>30 kg to &lt;40 kg</td>
<td>Darunavir 450 mg (combination of tablets or 4.6 mL²) plus ritonavir (100 mg tablet or 1.25 mL²)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>Darunavir 600 mg (tablet or 6 mL) plus ritonavir 100 mg (tablet or 1.25 mL)</td>
</tr>
</tbody>
</table>

Selected Adverse Events

• Skin rash, including Stevens-Johnson syndrome and erythema multiforme
• Hepatotoxicity
• Diarrhea, nausea
• Headache
• Hyperlipidemia, transaminase elevation, hyperglycemia
• Fat maldistribution

Special Instructions

• In patients with 1 or more darunavir-associated mutations, darunavir should only be used twice daily. **Darunavir resistance-associated mutations are:** V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.
• Darunavir must be administered with food, which increases plasma concentrations by 30%.
• Darunavir contains a sulfonamide moiety. Use darunavir with caution in patients with known sulfonamide allergy.
• Pediatric dosing requires co-administration of tablets with different strengths to achieve the recommended doses for each weight band. Careful instructions to caregivers when recommending a combination of different-strength tablets is very important.
• Store darunavir tablets and oral suspension at room temperature (25°C or 77°F). Suspension must be shaken well before dosing.

Metabolism/Elimination

• Cytochrome (CYP) P450 3A4 inhibitor and substrate.
Boosting darunavir with cobicistat is currently not recommended in children aged <18 years; PK, efficacy, and safety of darunavir/ cobicistat is currently under investigation in children aged 12 to 18 years.

**Adolescent (Weighing \( \geq 40 \) kg)** and **Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations):**
- Darunavir 800 mg (tablet or combination of tablets) plus ritonavir 100 mg **once daily**

**Adult Dose (Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations):**
- Darunavir 800 mg (tablet) plus cobicistat 150 mg (tablet) or coformulated as Prezobix **once daily with food**

**Adolescent (Weighing >30 to <40 kg; Treatment Naive or Treatment-Experienced with or without at Least 1 Darunavir Resistance-Associated Mutation):**
- Darunavir 450 mg (combination of tablets) plus ritonavir 100 mg both **twice daily with food**

**Adolescent (Weight \( \geq 40 \) kg) and Adult Dose (Treatment-Experienced With at Least 1 Darunavir Resistance-Associated Mutation):**
- Darunavir 600 mg plus ritonavir 100 mg, both **twice daily with food**
- The use of cobicistat is **not recommended** with darunavir 600 mg twice daily.

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**Darunavir Dosing in Patients with Hepatic Impairment:**
- Darunavir is primarily metabolized by the liver. Caution should be used when administering darunavir to patients with hepatic impairment. Darunavir is not recommended in patients with severe hepatic impairment.

**Darunavir Dosing in Patients with Renal Impairment:**
- No dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).

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^ Once-daily dosing is Food and Drug Administration (FDA)-approved, but the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) does not recommend it for children (see Frequency of Administration section below).

^ Note that the dose in children weighing 10 kg to 15 kg is 20 mg/kg darunavir and 3 mg/kg ritonavir per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.

^ Ritonavir 80 g/mL oral solution.

^ The **volumes for the** 375-mg and 450-mg darunavir doses are rounded for suspension-dose convenience.

^ Some Panel members recommend the FDA-approved dose of once-daily darunavir 675 mg (combination of tablets) plus ritonavir 100 mg once daily for adolescents weighing ≥30 kg to <40 kg (see Table B below).

^ See **cobicistat section** for important information about toxicity, drug interactions, and monitoring patients who receive cobicistat.
**Drug Interactions** (see also the [Adult and Adolescent Guidelines](https://aidsinfo.nih.gov/guidelines) and [HIV Drug Interaction Checker](https://aidsinfo.nih.gov/guidelines))

- **Metabolism:** Darunavir is primarily metabolized by cytochrome P (CYP) 3A4. Both ritonavir and cobicistat are inhibitors of CYP3A4, thereby increasing the plasma concentration of darunavir. Co-administration of darunavir/ritonavir (DRV/r) or darunavir/cobicistat (DRV/c) with drugs that are highly dependent on CYP3A clearance creates potential for multiple drug-drug interactions and may be associated with serious and/or life-threatening events or suboptimal efficacy.

- Co-administration of several drugs, including protease inhibitors and rifampin, is **contraindicated** with ritonavir- or cobicistat-boosted darunavir. A recent study involving adults with HIV suggested that etravirine may reduce serum darunavir concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent. Before administration, a patient’s medication profile should be carefully reviewed for potential drug interactions.

**Major Toxicities**

- **More common:** Diarrhea, nausea, vomiting, abdominal pain, headache, and fatigue.

- **Less common:** Skin rash, including erythema multiforme and Stevens-Johnson syndrome, fever and elevated hepatic transaminases, lipid abnormalities, and crystalluria.

- **Rare:** New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, and spontaneous bleeding in hemophiliacs. Hepatic dysfunction, particularly in patients with underlying risk factors such as hepatitis B or hepatitis C virus coinfection.

**Resistance**

The International Antiviral Society-USA (IAS-USA) maintains a list of [updated resistance mutations](https://aidsinfo.nih.gov/guidelines) and the [Stanford University HIV Drug Resistance Database](https://aidsinfo.nih.gov/guidelines) offers a discussion of each mutation.

**Pediatric Use**

**Approval**

Darunavir co-administered with ritonavir is approved by the Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naive and treatment-experienced children aged ≥3 years.

**Efficacy in Clinical Trials**

- Data from a randomized, open-label, multicenter pediatric trial, which evaluated darunavir co-administered with ritonavir twice daily among 80 treatment-experienced children aged 6 to <18 years, demonstrated that 66% of patients had plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL at Week 24.

- In an international, multisite clinical trial (TMC114-TiDP29-C228) involving treatment-experienced children aged 3 to <6 years, 81% of children (17/21) had viral load <50 copies/mL at Week 48.

**Pharmacokinetics and Dosing**

**Pharmacokinetics in Children Aged 3 to <6 Years**

Twenty-one children aged 3 to <6 years and weighing 10 kg to <20 kg received twice-daily DRV/r oral suspension. These children had experienced failure of their previous ART regimens and had fewer than three darunavir resistance mutations on genotypic testing. The darunavir area under the curve [AUC(0–12h)], measured as a percent of the adult AUC value, was 128% overall: 140% in children weighing 10 kg to <15 kg and 122% in children weighing 15 kg to <20 kg.
Pharmacokinetics in Children Aged >6 Years

Initial pediatric pharmacokinetic (PK) evaluation of darunavir tablets and ritonavir liquid or tablets was based on a Phase 2 randomized, open-label, multicenter study that enrolled 80 treatment-experienced children and adolescents aged 6 years to <18 years and weighing ≥20 kg. Part 1 of the trial used a weight-adjusted dose of darunavir 9 mg/kg to 15 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily, equivalent to the standard adult dose of DRV/r 600/100 mg twice daily. This dose resulted in inadequate drug exposure in the pediatric population studied, with 24-hour AUC (AUC$_{24h}$) of 81% and pre-dose concentration (C$_{0h}$) of 91% of the corresponding adult PK parameters. A pediatric dose 20% to 33% higher than the directly scaled adult dose was needed to achieve drug exposure similar to that found in adults, and this was the dose selected for Part 2 of the study. The higher dose used for the safety and efficacy evaluation was darunavir 11 mg/kg to 19 mg/kg and ritonavir 1.5 mg/kg to 2.5 mg/kg twice daily. This resulted in darunavir AUC$_{24h}$ of 123.3 mcg*h/mL (range 71.9–201.5 mcg*h/mL) and C$_{0h}$ of 3,693 ng/mL (range 1,842–7,191 ng/mL), 102% and 114% of the respective PK values in adults. Doses were given twice daily and were stratified by body weight bands of 20 kg to <30 kg and 30 kg to <40 kg. Based on the findings in the safety and efficacy portion of the study, current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected (see Table A).

Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Backbone (Children Aged 3 Years to 18 Years and Adults Aged >18 Years)

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Dose of DRV/RTV</th>
<th>AUC$_{12h}$ (mcg*h/mL) Median$^a$</th>
<th>C$_{0h}$ (ng/mL) Median$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;15 kg$^a$</td>
<td>13</td>
<td>20/3 mg/kg</td>
<td>66.0</td>
<td>3,533</td>
</tr>
<tr>
<td>10 kg to &lt;15 kg$^a$</td>
<td>4</td>
<td>25/3 mg/kg</td>
<td>116.0</td>
<td>8,522</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg$^a$</td>
<td>11</td>
<td>20/3 mg/kg</td>
<td>54.2</td>
<td>3,387</td>
</tr>
<tr>
<td>15 kg to &lt;20 kg$^a$</td>
<td>14</td>
<td>25/3 mg/kg</td>
<td>68.6</td>
<td>4,365</td>
</tr>
<tr>
<td>Aged 6 Years to &lt;12 Years$^b$</td>
<td>24</td>
<td>Weight bands$^b$</td>
<td>56.4</td>
<td>3,354</td>
</tr>
<tr>
<td>Aged 12 Years to &lt;18 Years$^b$</td>
<td>50</td>
<td>Weight bands$^b$</td>
<td>66.4</td>
<td>4,059</td>
</tr>
<tr>
<td>Adults Aged &gt;18 Years (3 studies)$^c$</td>
<td>285/278/119</td>
<td>600/100 mg</td>
<td>54.7–61.7</td>
<td>3,197–3,539</td>
</tr>
</tbody>
</table>


$^b$ Weight band dosing was with DRV/r at doses of 375/50 mg twice daily for body weight 20 kg to <30 kg, 450/60 mg twice daily for 30 kg to <40 kg, and 600/100 mg twice daily for ≥40 kg. Data from FDA pharmacokinetics review 2008. Available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf


Key to Acronyms: AUC$_{12h}$ = 12-hour area under the curve; C$_{0h}$ = pre-dose concentration; DRV = darunavir; DRV/r = darunavir/ritonavir RTV = ritonavir

Dosing

Pharmacokinetic Enhancers

Darunavir should not be used without a PK enhancer (boosting agent): ritonavir (for children and adults) or cobicistat (for adults only).

A study in 19 Thai children used the ritonavir 100-mg capsule twice daily as the boosting dose with twice-daily darunavir doses of 375 mg (body weight 20 kg to <30 kg), 450 mg (body weight 30–40 kg), and 600 mg twice daily (body weight ≥40 kg). The darunavir exposures with 100-mg ritonavir twice daily were similar to those obtained in the studies with lower (<100 mg) liquid-preparation-based ritonavir doses.
tolerability and PK data from this small study support the higher doses of ritonavir boosting with 100-mg capsule or tablet in children weighing ≥20 kg, particularly when lower-dose formulations are unavailable or if a child does not tolerate the liquid ritonavir formulation. Data are not available to evaluate the safety and tolerability of using ritonavir 100-mg tablet/capsule formulations in children weighing <20 kg.

Data on the dosing of cobicistat with darunavir are available in adult patients only. Data on a fixed-dose combination of DRV/c 800/150 mg once daily showed comparable bioavailability to that obtained with 800/100 mg of DRV/r once daily.

**Frequency of Administration**

In February 2013, the FDA approved the use of once-daily darunavir for treatment-naive children and for treatment-experienced children without darunavir resistance-associated mutations (see Table B). To derive once-daily pediatric dosing recommendations for younger pediatric subjects aged 3 years to <12 years and weighing 10 kg to <40 kg, population PK modeling and simulation were used. A dedicated pediatric trial evaluating once-daily DRV/r dosing in children aged 6 years to <12 years was not conducted. No efficacy data have been obtained regarding use of once-daily DRV/r in treatment-naive or treatment-experienced children aged <12 years. Therefore, the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years (see Once-Daily Dosing section). The Panel recommends that once-daily DRV/r be used only in treatment-naive and treatment-experienced adolescents weighing ≥40 kg who do not have darunavir resistance-associated mutations. If darunavir and ritonavir are used once daily in children aged <12 years, the Panel recommends conducting PK (measurement of plasma concentrations) evaluation and closely monitoring viral load.

FDA approval was based on results from two small pediatric trials: TMC114-C230, which evaluated once-daily dosing in treatment-naive adolescents aged 12 to 18 years and weighing ≥40 kg (see below), and the TMC114-C228 sub-trial, which evaluated once-daily dosing in treatment-experienced children aged 3 years to <6 years (see below).

**Table B. Food and Drug Administration-Approved Dosing for Pediatric Patients Aged ≥3 Years and Weighing >10 kg who are Treatment-Naive or Treatment-Experienced with No Darunavir Resistance-Associated Mutations**

**Note:** The Panel generally recommends dosing darunavir with ritonavir twice daily in children aged ≥3 years to <12 years.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Dose (Once daily with food)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 kg to &lt;11 kg</td>
<td>DRV 350 mg (3.6 mL) plus RTV 64 mg (0.8 mL)</td>
</tr>
<tr>
<td>11 kg to &lt;12 kg</td>
<td>DRV 385 mg (4 mL) plus RTV 64 mg (0.8 mL)</td>
</tr>
<tr>
<td>12 kg to &lt;13 kg</td>
<td>DRV 420 mg (4.2 mL) plus RTV 80 mg (1 mL)</td>
</tr>
<tr>
<td>13 kg to &lt;14 kg</td>
<td>DRV 455 mg (4.6 mL) plus RTV 80 mg (1 mL)</td>
</tr>
<tr>
<td>14 kg to &lt;15 kg</td>
<td>DRV 490 mg (5 mL) plus RTV 80 mg (1 mL)</td>
</tr>
<tr>
<td>15 kg to &lt;30 kg</td>
<td>DRV 600 mg (tablet or combination of tablets or 6 mL) plus RTV 100 mg (tablet or 1.25 mL)</td>
</tr>
<tr>
<td>30 kg to &lt;40 kg</td>
<td>DRV 675 mg (combination of tablets or 6.8 mL plus RTV 100 mg (tablet or 1.25 mL)</td>
</tr>
<tr>
<td>≥40 kg</td>
<td>DRV 800 mg (tablet or combination of tablets or 8 mL plus RTV 100 mg (tablet or 1.25 mL)</td>
</tr>
</tbody>
</table>

- The dose in children weighing 10 kg to 15 kg is 35 mg/kg DRV and 7 mg/kg RTV per kg body weight per dose, which is higher than the weight-adjusted dose in children with higher weight.
- RTV 80 mg/mL oral solution.
- The 350-mg, 385-mg, 455-mg, 490-mg, and 675-mg DRV doses are rounded for suspension-dose convenience.
- The 6.8-mL and 8-mL DRV doses can be taken as 2 administrations (3.4 mL and 4 mL, respectively) with the included oral dosing syringe, or as one syringe when provided by pharmacy or medical office.

**Key to Acronyms:** DRV = darunavir; RTV = ritonavir
Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg

During the TMC114-C228 trial, the researchers investigated once-daily dosing of darunavir for 2 weeks with PK evaluation in treatment-experienced children aged 3 years to <12 years as part of a sub-study. After the conclusion of the sub-study, the participants switched back to a twice-daily regimen.9,12 The DRV/r dose for once-daily use in the trial, based on PK simulation (which did not include a relative bioavailability factor), was 40 mg/kg of darunavir co-administered with approximately 7 mg/kg of ritonavir once daily for children weighing <15 kg, and DRV/r 600/100 mg once daily for children weighing ≥15 kg.9,12 The PK data obtained from 10 children aged 3 to 6 years in this sub-study (Table C) were included as part of the population PK modeling and simulation, which proposed the FDA-approved dose for once-daily DRV/r in children aged 3 years to <12 years. Despite the FDA dosing guidelines, and because of the small set of data used for modeling and the lack of efficacy data on once-daily DRV/r in treatment-naive or treatment-experienced children aged <12 years, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years.

Table C. Pharmacokinetics of Once-Daily Darunavir in Children Aged 3 Years to 6 Years After 2 Weeks of Therapy with Ritonavir and Optimized Backbone12

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Once-Daily Darunavir Sub-Study (n = 10) Children Aged 3–6 years</th>
<th>Adult Study (n = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRV AUC_{24h} geometric mean, ng*h/mL (SD)</td>
<td>115 (40.6)</td>
<td>89.7 (27.0)</td>
</tr>
<tr>
<td>DRV C_{0h} geometric mean, ng/mL (SD)</td>
<td>3,029 (1,715)</td>
<td>2,027 (1,168)</td>
</tr>
</tbody>
</table>

Key to Acronyms: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

Once-Daily Administration in Adolescents Aged ≥12 and Weighing ≥40 kg

A sub-study of once-daily dosing of darunavir 800 mg with ritonavir 100 mg in 12 treatment-naive adolescents (aged 12–17 years and weighing ≥40 kg) demonstrated darunavir exposures similar to those seen in adults treated with once-daily darunavir (see Table D).10 In this study, the proportion of patients with viral load <50 copies/mL and <400 copies/mL at 48 weeks was 83.3% and 91.7%, respectively.11 Interestingly, no relationship was observed between darunavir AUC_{24h} and C_{0h} and virologic outcome (HIV RNA <50 copies/mL) in this study. Darunavir exposures were found to be similar to those in adults with once-daily dosing in another study in which a single dose of darunavir 800 mg with ritonavir 100-mg tablets was administered to 24 subjects with median age 19.5 years (range 14–23 years).13 However, darunavir exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting the potential need for higher doses in younger adolescents. A single case report suggests the potential therapeutic benefit of virologic suppression using an increased darunavir dose with standard ritonavir booster following therapeutic drug monitoring (TDM) in a highly treatment-experienced adolescent patient.14

Table D. Darunavir Pharmacokinetics with Once-Daily Administration (Adolescents Aged ≥12 Years and Adults Aged >18 Years)

<table>
<thead>
<tr>
<th>Population</th>
<th>N</th>
<th>Dose of DRV/RTV</th>
<th>AUC_{24h} (mcg*h/mL) median</th>
<th>C_{0h} (ng/mL) median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aged 12–17 Years (mean 14.6 years)</td>
<td>12</td>
<td>800/100 mg</td>
<td>86.7</td>
<td>2,141</td>
</tr>
<tr>
<td>Aged 14–23 Years (mean 19.5 years)</td>
<td>24</td>
<td>800/100 mg</td>
<td>69.5</td>
<td>1,300</td>
</tr>
<tr>
<td>Adults Aged &gt;18 Years (2 studies)</td>
<td>335/280</td>
<td>800/100 mg</td>
<td>87.8–87.9</td>
<td>1,896–2,041</td>
</tr>
</tbody>
</table>


Key to Acronyms: AUC_{24h} = 24-hour area under the curve; C_{0h} = pre-dose concentration; DRV = darunavir; RTV = ritonavir

Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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The efficacy of once-daily darunavir has been established within a limited number of studies in small cohorts of adolescents that reported long-term data on virologic and immunologic outcomes.11,15

Co-Administration with Other Antiretrovirals

Nucleotide Reverse Transcriptase Inhibitor

When twice-daily DRV/r was used in combination with tenofovir disoproxil fumarate (TDF) in 13 patients with HIV aged 13 to 16 years, both TDF and darunavir exposures were lower than those found in adults treated with the same combination.16 No dose adjustment is recommended for use of the combination of DRV/r with either of these drugs, but caution is advised and therapeutic drug monitoring (TDM) may be potentially useful.

Non-Nucleoside Reverse Transcriptase Inhibitors

Data from the IMPAACT protocol P1058A report that the co-administration of once-daily DRV/r with etravirine administered once or twice daily to children, adolescents, and young adults aged 9 through <24 years did not have a significant effect on darunavir plasma exposure.17 When DRV/r was co-administered with etravirine twice daily in pediatric patients, target concentrations for both darunavir and etravirine were achieved.18 When co-administered once daily, darunavir PKs have not been affected by co-administration of rilpivirine in adolescents and young adults.19 DRV/r co-administration increased rilpivirine exposure two- to three-fold, indicating that drug-related adverse effects should be closely monitored.

References


