Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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Darunavir (DRV, Prezista)  

Formulations  
Oral Suspension: 100 mg/mL  
Tablets: 75 mg, 150 mg, 600 mg, 800 mg  

Fixed-Dose Combination Tablets:  
• [Prezcobix] Darunavir 800 mg/cobicistat 150 mg  
• [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg  

When using fixed-dose combination (FDC) tablets, refer to other sections of the Drug Appendix for information about the individual components of the FDC. See also Appendix A, Table 2, Antiretroviral Fixed-Dose Combination Tablets: Minimum Body Weights and Considerations for Use in Children and Adolescents.  

For additional information, see Drugs@FDA or DailyMed.  

Dosing Recommendations  
Note: Darunavir (DRV) should not be used without a pharmacokinetic (PK) enhancer (boosting agent). Ritonavir (RTV) may be used as the boosting agent in children and adults. Cobicistat (COBI) may be used as a boosting agent with DRV in children weighing ≥40 kg and in adults.  

Neonate/Infant Dose:  
• DRV is not approved for use in neonates/infants.  

Child Dose  
Aged <3 Years:  
• Do not use DRV in children aged <3 years or weighing ≤10 kg. In juvenile rats, DRV caused convulsions and death, and these events have been attributed to immaturity of the blood-brain barrier and liver metabolic pathways.  

Aged ≥3 Years to <12 Years:  
• Dosing recommendations in the table below are for children aged ≥3 years to <12 years and weighing ≥10 kg who are antiretroviral therapy (ART)-naive or treatment-experienced and with or without resistance testing results that demonstrate that they have at least one mutation that is associated with DRV resistance.  

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

Special Instructions  
• Once-daily DRV is not generally recommended for use in children aged <12 years or weighing <40 kg. Dosing estimates for these patients were based on limited data, and there is limited clinical experience with this dosing schedule in this age group.  

• Once-daily DRV should not be used if any one of the following resistance-associated mutations are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, or L89V.  

• DRV must be administered with food, which increases DRV plasma concentrations by 30%.  

• DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.  

• Pediatric dosing requires coadministration of tablets with different strengths to achieve the
Child and Adolescent (Aged ≥12 Years and Weighing ≥30 to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With Darunavir Resistance:
- DRV 450 mg (using a combination of tablets) plus RTV 100 mg, both twice daily with food

Child and Adolescent (Aged ≥12 years and Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with No Mutations Associated With Darunavir Resistance:
- DRV 800 mg (using a tablet or combination of tablets) plus RTV 100 mg once daily with food

Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients with at Least One Mutation Associated with Darunavir Resistance:
- DRV 600 mg plus RTV 100 mg, both twice daily with food
- The use of COBI is not recommended with DRV 600 mg twice daily.

Metabolism/Elimination
- Cytochrome P450 3A4 substrate and inhibitor.

Darunavir Dosing in Patients with Hepatic Impairment:
- DRV is primarily metabolized by the liver. Caution should be used when administering DRV to patients with hepatic impairment. DRV 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 30–60 mL/min).
Drug Interactions (see also the Adult and Adolescent Antiretroviral Guidelines and HIV Drug Interaction Checker)

- **Metabolism:** Darunavir (DRV) is primarily metabolized by cytochrome P450 (CYP) 3A4. Both ritonavir (RTV) and cobicistat (COBI) are inhibitors of CYP3A4, thereby increasing the plasma concentration of DRV. Coadministration of DRV plus RTV (DRV/r) or DRV plus COBI (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.

- Coadministration of several drugs, including other protease inhibitors and rifampin, is contraindicated with DRV/r and DRV/c. A study involving adults with HIV suggested that etravirine (ETR) may reduce serum DRV concentrations by induction of CYP3A5, which is more commonly expressed in individuals of African descent.1 Before administering DRV with a pharmacokinetic (PK) enhancer (boosting agent), a patient’s medication profile should be carefully reviewed for potential drug interactions.

- 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 DRV darunavir exposures were lower than those found in adults treated with the same combination.2 No dose adjustment is recommended when using DRV/r with TDF, but caution is advised and therapeutic drug monitoring (TDM) may be useful. Data from the IMPAACT protocol P1058A indicate that coadministering once-daily DRV/r with once-daily or twice-daily ETR in children, adolescents, and young adults aged 9 years to <24 years did not have a significant effect on DRV plasma concentrations.3 When DRV/r was coadministered with ETR twice daily in pediatric patients, target concentrations for both DRV and ETR were achieved.4 DRV PKs were
not affected when DRV was coadministered with rilpivirine (RPV) in a study of adolescents and young adults. DRV/r coadministration increased RPV exposure two-fold to three-fold; close monitoring for RPV-related adverse events is advisable.

**Major Toxicities**

- **More common:** Diarrhea, nausea, vomiting, abdominal pain, headache, fatigue.
- **Less common:** Skin rash, including erythema multiforme and Stevens-Johnson syndrome, fever and elevated levels of 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**

DRV/r is approved by the Food and Drug Administration (FDA) as a component of antiretroviral (ARV) therapy in treatment-naive and treatment-experienced children aged ≥3 years.

COBI (as Tybost) is approved by the FDA to be coadministered with DRV in pediatric patients weighing ≥40 kg. COBI is also approved by the FDA as a component of Symtuza (DRV/c/emtricitabine/tenofovir alafenamide) in pediatric patients weighing ≥40 kg. Although the FDA has not approved the use of COBI coformulated with DRV (as Prezcobix), the Panel on Antiretroviral Therapy and Medical Management of Children Living with HIV (the Panel) recommends the use of this fixed-dose combination (FDC) tablet in pediatric patients weighing ≥40 kg based on FDA approval of the component drugs.

**Efficacy in Clinical Trials**

In an international, multisite clinical trial (TMC114-TiDP29-C228) that enrolled treatment-experienced children aged 3 years to <6 years, 17 of 21 children (81%) who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.6,7

A randomized, open-label, multicenter pediatric trial that evaluated twice-daily DRV/r among 80 treatment-experienced children aged 6 years to <18 years reported that 66% of patients had plasma HIV RNA <400 copies/mL and 51% had HIV RNA <50 copies/mL at Week 24.7,8

Once-daily DRV/r has been investigated in a small study involving 12 treatment-experienced children aged 6 to 12 years who had maintained HIV viral loads <50 copies/mL for at least 6 months. All but one child continued to have undetectable viral loads during a median of 11.6 months of follow-up (range 0.5-14.2 months). The remaining child had detectable viral load measurements between 20 copies/mL and 200 copies/mL on three occasions during a 3-month period before again becoming undetectable, without a change in regimen.

In one study, 12 participants aged 12 to 17 years received DRV/r once daily.10 After 48 weeks, all but one participant had viral loads <50 copies/mL.

**Pharmacokinetics and Dosing**

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

Twenty-one children aged 3 years to <6 years and weighing 10 kg to <20 kg received twice-daily DRV/r oral suspension. These children had experienced virologic failure on their previous ARV regimens and had fewer than three DRV resistance mutations, confirmed by genotypic testing. The DRV area under the curve (AUC0–12h), 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.\textsuperscript{6-8}

**Pharmacokinetics in Children Aged >6 Years**

Initial pediatric PK evaluation of DRV tablets and RTV oral solution 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 \( \geq 20 \) kg.\textsuperscript{11} Part 1 of the trial used a weight-adjusted dose of DRV (9 mg/kg to 15 mg/kg) and RTV (1.5 mg/kg to 2.5 mg/kg) twice daily, approximating the standard adult dose of DRV/r 600 mg/100 mg twice daily on a per-weight basis. This dose resulted in inadequate drug exposure in the pediatric population studied, with a 24-hour AUC (AUC\textsubscript{24h}) that was 81\% of the AUC\textsubscript{24h} observed in adults and a pre-dose concentration (C\textsubscript{0h}) that was 91\% of the C\textsubscript{0h} observed in adults. A pediatric dose that was 20\% to 33\% higher than the directly scaled adult dose was needed to achieve a drug exposure that was 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 DRV 11 mg/kg to 19 mg/kg and RTV 1.5 mg/kg to 2.5 mg/kg twice daily. This dose resulted in a DRV AUC\textsubscript{24h} of 123.3 mcg·h/mL (range 71.9–201.5 mcg·h/mL) and a C\textsubscript{0h} of 3,693 ng/mL (range 1,842–7,191 ng/mL), representing 102\% and 114\% of the respective values in adults. Doses were given twice daily and were stratified into body-weight bands of 20 kg to <30 kg and 30 kg to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 kg to <40 kg were selected using the findings from the safety and efficacy portion of this study (see Table A).

A small study that involved 12 treatment-experienced children aged 6 to 12 years examined the PKs and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine.\textsuperscript{9} All participants had maintained HIV plasma viral loads <50 copies/mL for at least 6 months prior to beginning this regimen. The weight-based doses used for once-daily DRV/r were based on a prior modeling study:\textsuperscript{12} 600 mg/100 mg for patients weighing 15 kg to 30 kg, 675 mg/100 mg for patients weighing 30 kg to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The geometric mean AUC\textsubscript{0-24} was below the study target of 80\% of the value seen in adults (63.1 mg·h/L vs. 71.8 mg·h/L), but the trough values that were observed at 23.1 hours to 25.1 hours after the previous dose exceeded the trough plasma concentration recommended for treatment-experienced adults (0.55 mg/L).\textsuperscript{13} One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to DRV; the AUC\textsubscript{0-24} was 47.8 mg·h/L.

### Table A. Darunavir Pharmacokinetics with Twice-Daily Administration with Ritonavir and Optimized Background Therapy in Children, Adolescents, and Adults

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


\textsuperscript{b} DRV/r was administered at doses of 375 mg/50 mg twice daily for patients weighing 20 kg to <30 kg, 450 mg/60 mg twice daily for patients weighing 30 kg to <40 kg, and 600 mg/100 mg twice daily for patients weighing >40 kg. Data from the 2008 FDA pharmacokinetics review. Available at: [http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf).

\textsuperscript{c} Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: [https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017bldt.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017bldt.pdf).

Key: AUC\textsubscript{12h} = 12-hour area under the curve; C\textsubscript{0h} = pre-dose concentration; DRV/r = darunavir/ritonavir; FDA = Food and Drug Administration.
**Dosing**

**Pharmacokinetic Enhancers**

DRV should not be used without a PK enhancer (boosting agent). RTV may be used as a boosting agent in children and adults. **COBI may be used as a boosting agent in children weighing ≥40 kg and adults.**

A study that enrolled 19 Thai children used the RTV 100-mg capsule twice daily as the boosting dose for twice-daily DRV 375 mg (in children weighing 20 kg to <30 kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing ≥40 kg). The DRV exposures with RTV 100 mg twice daily were similar to those obtained in the studies with lower (<100 mg) doses of liquid RTV. The tolerability and PK data from this small study support the use of RTV 100 mg for boosting, using either the powder or tablet formulation, in children weighing ≥20 kg, particularly in instances where the lower-dose formulations are unavailable or a child does not tolerate the liquid RTV formulation. There are no data available on the safety and tolerability of using the RTV 100-mg tablet or powder formulation in children weighing <20 kg.

Data on the dosing of DRV/c are available primarily for adult patients. Data on once-daily use of the FDC tablet DRV/c 800 mg/150 mg (Prezcoibix) showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.

In an open-label switch study, eight adolescent patients with a median age of 14 years (range 12–17 years) who received DRV/c had DRV exposures (AUC_{τ}) that were similar to those observed in adults, except for a lower trough concentration at the end of the dosing interval (C_{τ}). The median DRV C_{τ} (494 ng/mL) was above the protein binding-adjusted half-maximal inhibitory concentration for wild-type virus (55 ng/mL). Adolescent patients in this study received the adult dose of COBI 150 mg daily. DRV dosing was based on weight, with patients who weighed ≥40 kg receiving DRV 800 mg once daily and patients who weighed 30 kg to <40 kg receiving DRV 675 mg once daily. In this small sample, 95.5% of patients had HIV RNA <50 copies/mL at Week 12. COBI appeared to be well tolerated with no discontinuations due to adverse events.

**Frequency of Administration**

In February 2013, the FDA approved the use of once-daily DRV for treatment-naive children and for treatment-experienced children without DRV resistance-associated mutations. Population PK modeling and simulation were used to develop recommendations for once-daily dosing in younger pediatric subjects aged 3 years to <12 years and weighing 10 kg to <40 kg. Currently, there is limited data on the efficacy of once-daily DRV/r dosing in treatment-naive or treatment-experienced children aged <6 years. Therefore, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years (see Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg below). 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 mutations that are associated with DRV resistance. If DRV and RTV are used once daily in children aged <12 years, the Panel recommends conducting a PK evaluation of plasma concentrations of DRV and closely monitoring viral load.
Once-Daily Administration in Children Aged <12 Years and Weighing <40 kg

During the TMC114-C228 trial, the researchers investigated once-daily dosing of DRV for 2 weeks; DRV PKs were evaluated in treatment-experienced children aged 3 years to <12 years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen. The DRV/r dose for once-daily use, which was based on PK simulation and which did not include a relative bioavailability factor, was DRV 40 mg/kg coadministered with approximately 7 mg/kg of RTV for children weighing <15 kg, and DRV/r 600 mg/100 mg once daily for children weighing ≥15 kg. The DRV data obtained from 10 children aged 3 to 6 years in this substudy (see Table C) were included as part of the population PK modeling and simulation that was used to determine the FDA-approved dose for once-daily DRV/r in children aged 3 years to <12 years.

In a small study in which DRV/r was administered once daily to 12 treatment-experienced children aged 6 to 12 years, the geometric mean AUC_{24h} achieved was below the study target of 80% of the value seen in adults (63.1 mg·h/L vs. 71.8 mg·h/L). Trough values exceeded the plasma concentration that is recommended for treatment-experienced patients (0.55 mg/L). Despite the FDA dosing guidelines, the Panel generally recommends dosing DRV/r twice daily in children aged ≥3 years to <12 years. The Panel makes this recommendation because of the small set of data used for once-daily DRV/r PK modeling and the limited amount of data on the use of once-daily DRV/r in children aged <12 years.

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

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Children Aged 3 Years to 6 Years (n = 10)</th>
<th>Adults (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: 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 substudy of once-daily dosing of DRV/r 800 mg/100 mg demonstrated that DRV exposures in 12 treatment-naive adolescents (aged 12 to 17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily DRV (see Table D). After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL. Interestingly, no relationship was observed between DRV AUC$_{24h}$ and C$_{0h}$ and virologic outcome (HIV RNA <50 copies/mL) in this study. DRV exposures were found to be similar to those observed in adults with once-daily dosing in another study in which a single dose of DRV 800 mg with RTV 100 mg was administered to 24 subjects with a median age of 19.5 years (range 14–23 years). However, DRV exposures were slightly below the lower target concentrations in adolescent patients aged 14 to 17 years (n = 7) within the cohort, suggesting that higher doses may be needed in younger adolescents. A single case report involving a highly treatment-experienced adolescent patient suggests that using an increased DRV dose with standard RTV boosting and employing TDM can lead to virologic suppression.

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

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

*Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017bldt.pdf

Key: AUC$_{24h}$ = 24-hour area under the curve; C$_{0h}$ = pre-dose concentration; DRV/r = darunavir/ritonavir

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

References


