Darunavir (DRV, Prezista)

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Formulations

Oral Suspension: 100 mg/mL

Tablets: 75 mg, 150 mg, 600 mg, 800 mg

Fixed-Dose Combination (FDC) Tablets

- [Prezcobix]
  - Darunavir 800 mg/cobicistat 150 mg
  - Darunavir 675 mg/cobicistat 150 mg
  - Darunavir 600-mg/cobicistat 90-mg dispersible tablet
- [Symtuza] Darunavir 800 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir alafenamide 10 mg

When using FDC tablets, refer to other sections of Appendix A. Pediatric Antiretroviral Drug Information for information about the individual components of the FDC. See also Appendix A, Table 2. Antiretroviral Fixed-Dose Combination Tablets and Co-packaged Formulations: 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 enhancer (boosting agent).

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; 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 ≥20 kg who are antiretroviral therapy 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 limited clinical experience exists with this dosing schedule in this age group.
- Once-daily DRV **should not be used** if any one of the following resistance-associated mutations is 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 about 30%.

Twice-Daily DRV and Ritonavir (RTV) Doses for Children Aged ≥3 Years to <12 Years and Weighing ≥20 kg

Weight	Dose (Twice Daily with Food)[a]
20 kg to <30 kg[b]	DRV 375 mg (combination of tablets or 3.8 mL)[d] plus RTV 100 mg (tablet or powder)[c]
30 kg to <40 kg[b]	DRV 450 mg (combination of tablets or 4.6 mL)[c,d] plus RTV 100 mg (tablet or powder)
≥40 kg[b]	DRV 600 mg (tablet or 6 mL) plus RTV 100 mg (tablet or powder)

Child and Adolescent (Aged ≥12 Years and Weighing ≥30 kg to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With or Without at Least One Mutation Associated With DRV 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)[d] and Adult Dose for Treatment-Naive or Treatment-Experienced Patients With No Mutations Associated With DRV Resistance

- DRV 800 mg (using a tablet or combination of tablets) plus RTV 100 mg, both once daily with food

Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients With No Mutations Associated With DRV Resistance

- DRV 800 mg plus cobicistat (COBI)[e] 150 mg coformulation Prezcobix, once daily with food

Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Experienced Patients With at Least One Mutation Associated With DRV 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.

- DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.
- Pediatric dosing requires coadministration of tablets of different strengths to achieve the recommended dose for each weight band. It is important to provide careful instructions to caregivers when recommending a combination of different-strength tablets.
- Store DRV tablets and oral suspension at room temperature (25º C or 77º F). The suspension must be shaken well before dosing.
- Screen patients for hepatitis B virus (HBV) infection before using FDC tablets that contain FTC or TAF. Severe acute exacerbation of HBV infection can occur when FTC or TAF are discontinued; therefore, liver function should be monitored for several months after patients with HBV infection stop taking FTC or TAF.

Metabolism/Elimination

- Cytochrome P450 3A4 substrate and inhibitor

DRV 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.

DRV Dosing in Patients With Renal Impairment

- No DRV dose adjustment is required in patients with moderate renal impairment (creatinine clearance [CrCl] 30–60 mL/min).
- The FDC Symtuza **is not recommended** for use in patients with an estimated CrCl <30 mL/min.

Lactation

- *Milk Exposures.* Data from two mothers taking DRV 800 mg and RTV 100 mg daily found that median DRV concentration in breastmilk at 15 hours postdose was 316 mcg/L, corresponding to an infant dosage of 50 mcg/kg daily and a relative infant dose of 0.12% of the maternal weight-adjusted dosage. Another study found breastmilk concentrations all under 250 mcg/mL.

[Prezcobix] DRV/COBI **Child (Aged ≥3 Years and Weighing ≥15 kg to <25 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With No Mutations Associated With DRV Resistance** • One DRV 600-mg/COBI 90-mg tablet for oral suspension once daily with food (disperse in drinking water) **Child (Weighing ≥25 kg to <40 kg) Dose for Treatment-Naive or Treatment-Experienced Patients With No Mutations Associated With DRV Resistance** • One DRV 675 mg/COBI 150 mg tablet once daily with food **Child and Adolescent (Weighing ≥40 kg) and Adult Dose for Treatment-Naive or Treatment-Experienced Patients With No Mutations Associated With DRV Resistance** • One DRV 800-mg/COBI 150-mg tablet once daily with food **[Symtuza] DRV/COBI/Emtricitabine (FTC)/Tenofovir Alafenamide (TAF)** *Child and Adolescent (Weighing ≥40 kg) and Adult Dose* • One tablet once daily with food in antiretroviral-naive patients or in patients who have been virologically suppressed (HIV RNA <50 copies/mL) for at least 6 months with no known mutations associated with resistance to DRV or tenofovir.	• *Infant[f] Exposures.* Serum concentrations from the breastfed infant of a mother taking DRV/r 800 mg/100 mg were undetectable at 16 hours after the mother's dose. Another retrospective study found that an exclusively breastfed infant of a mother taking DRV/r 800 mg/100 mg had all serum DRV concentrations under 50 mcg/L.[g]

[a] Once-daily dosing of DRV is approved by the U.S. Food and Drug Administration (FDA), but the Panel on Antiretroviral Therapy and Medical Management of Children Living With HIV (the Panel) does not generally recommend using this dosing schedule in children (see Frequency of Administration below).

[b] RTV oral solution is no longer available. Use of DRV boosted with RTV is now limited to children weighing ≥20 kg who can receive RTV 100 mg using powder or tablets.

[c] The volumes for the 375-mg and 450-mg DRV doses are rounded for dosing convenience of suspension.

[d] Some Panel members recommend using the FDA-approved dose of once-daily DRV 675 mg (administered using a combination of tablets) plus RTV 100 mg once daily for adolescents weighing ≥30 kg to <40 kg (see Table B below).

[e] See Cobicistat for important information about toxicity, drug interactions, and monitoring in patients who receive COBI.

[f] Infant refers to a young child, from birth through one year of age.

[g] For reference, typical serum concentrations in adults taking DRV/RTV 800mg/100mg are 3,000-4,000 mcg/L.

Drug Interactions

Additional information about drug interactions is available in the Liverpool 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 suboptimal efficacy or serious and/or life-threatening events.
- Coadministration of several drugs, including other protease inhibitors (PIs) 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 aged 13 to 16 years with HIV, both TDF and DRV 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.[3] Data from the International Maternal Pediatric Adolescent AIDS Clinical Trials (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.[4] When DRV/r was coadministered with ETR twice daily in pediatric patients, target concentrations for both DRV and ETR were achieved. [5] DRV PK were not affected when DRV was coadministered with rilpivirine (RPV) in a study of adolescents and young adults.[6] DRV/r coadministration increased RPV exposure twofold to threefold; close monitoring for RPV-related adverse events is advisable.
- Coadministration of emtricitabine (FTC)/tenofovir alafenamide (TAF) plus DRV/c in children aged 2 years to <12 years weighing 14 kg to <40 kg had a favorable safety profile without any bone or renal toxicities or adverse weight effects (in an interim analysis at 24 weeks).[7]
- In a drug–drug interaction study in healthy adults without HIV, coadministration of DRV/c with bictegravir (BIC) was associated with increases in BIC exposures (74% increase in area under the concentration time curve over the dosing interval [AUC_{tau}], 52% increase in maximum plasma concentration [C_{max}], and 111% increase in trough concentration [C_{trough}]) compared with BIC administration alone, with no effect on median time to reach maximum concentration.[8]

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 levels of hepatic transaminases; lipid abnormalities; and crystalluria.
- *Rare:* New-onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of preexisting diabetes mellitus, spontaneous bleeding in people with hemophilia, and hepatic dysfunction, particularly in patients with underlying risk factors, such as hepatitis B or hepatitis C virus coinfection.
- *In utero exposure risks:* An analysis of data from the French National Health Data System from 2012 to 2022, including data on 9,035 live single-born children born to mothers with HIV who were all prenatally exposed to antiretroviral (ARV) drugs, found that the incidence[9] of neurodevelopmental disorders among exposed children was higher than in the general population, even after matching for five sociodemographic criteria (ZIP code, social vulnerability indicator, salary, maternal age, year of birth) and gestational age, (hazard ratio [HR] 1.24, 95% confidence interval [CI], 1.04–1.47). The relative contributions of maternal HIV infection as

opposed to maternal treatment could not be separated, as all children were coexposed to both HIV and its treatment. However, the combination of DRV/r/TDF/FTC was associated with a significantly higher incidence of neurodevelopmental disorders compared to other PIs with TDF/FTC (log rank, $P < 0.001$).

Resistance

The International Antiviral Society–USA maintains a list of updated HIV drug resistance mutations, and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation.

Pediatric Use

Approval

DRV/r is approved by the U.S. Food and Drug Administration (FDA) as a component of antiretroviral therapy (ART) in treatment-naive and treatment-experienced children aged ≥3 years. Because RTV oral solution is no longer commercially available, use of DRV/r is limited to children weighing ≥20 kg who can use the RTV 100-mg powder packet or 100-mg tablet.

DRV is approved by the FDA to be administered with COBI (Tybost) boosting in pediatric patients weighing ≥40 kg. The fixed-dose combination (FDC) DRV/c (Prezcobix) is approved by the FDA for use in pediatric patients aged ≥3 years weighing ≥15 kg at a dose of DRV 600 mg/COBI 90 mg, for use in pediatric patients weighing <20 kg ≥25 kg to <40 kg at a dose of DRV 675 mg/COBI 150 mg, and for use in people weighing ≥40 kg at a dose of DRV 800 mg/COBI 150 mg. DRV/c/FTC/TAF (Symtuza) is approved by the FDA for use in pediatric patients weighing ≥40 kg.

A pediatric formulation of Symtuza (DRV 675 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg) is being developed as a scored tablet (to enable splitting) for use in the European Union; this formulation **is not** approved by the FDA. In healthy adults, this FDC was found to be bioequivalent to coadministration of all of the individual formulations of each component of the FDC.[10] In another bioequivalence study, 32 healthy adult participants received either a single dose of the DRV/c 600 mg/90 mg FDC tablet dispersed in water or the separate formulations (DRV 100 mg/mL at a dose of DRV 600 mg/COBI 90 mg), after a ≥7 day washout period. The geometric mean ratios for DRV C_{max} and AUC over the dosing interval of the dispersed DRV 600-mg/ COBI 90-mg FDC tablet versus the separate formulations fell within the prespecified 80% to 125% bioequivalence limits.

The swallowability and acceptability of a placebo tablet (size 21 × 11 × 7 mm) matching this pediatric fixed-dose formulation of Symtuza has been studied in an open-label randomized crossover PK bioequivalence clinical trial in 24 virologically suppressed children with HIV aged 6 years to <12 years of age weighing 25 kg to <40 kg.[11,12]. Participants were also taking their stable ART regimen. Twenty-three of 24 (95.8%) participants were able to swallow the whole and the split tablets after one or two attempts; >70% of participants rated the tablets to be acceptable or good, and whole tablets were favored over split tablets. In a separate study[10] in children with HIV aged ≥3 years and weighing ≥15 kg to <25 kg, the acceptability of a single dose of dispersed DRV 600-mg/COBI 90-mg FDC tablet was evaluated. According to independent observers, 83% (10/12) of the children were able to swallow the dispersion completely and rated the dispersed FDC tablet as “OK” to “very easy” to swallow.

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 (81%) of 21 children who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.[13-15]

A randomized, open-label, multicenter pediatric trial[15] 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.

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.[16] 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.[17] After 48 weeks, all but one participant had viral loads <50 copies/mL.

The SMILE (Penta-17-ANRS 152) trial released results[18] showing that a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI)–sparing regimen of integrase strand transfer inhibitor (INSTI) plus boosted DRV was non-inferior to the standard of care (SOC) (i.e., two NRTIs + boosted PI/non-nucleoside reverse transcriptase inhibitor) at 48 weeks in maintaining virologic suppression among children and adolescents with HIV aged 6 to 18 years. Eight (5%) of 158 participants in the INSTI+DRV/r arm and 12 (7.5%) of 160 in the SOC arm had HIV viral loads ≥50 copies/mL at 48 weeks post-enrollment; difference of −2.5% (95% CI, −7.6% to 2.5%), meeting the non-inferiority margin of 10%. Safety was similar between the arms. There were small significant differences between the two arms in CD4 T lymphocyte (CD4) cell count mean change from baseline, high-density lipoprotein (HDL) cholesterol, weight, and body mass index (BMI): CD4 and HDL decreased more in the INSTI+DRV/r arm than in the SOC arm, and weight and BMI had greater increases in the INSTI+DRV/r arm than the SOC arm over the 48 weeks. The difference between the INSTI+DRV/r experimental arm compared to SOC in mean CD4 count change and mean HDL change from baseline were −48.3 cells/mm^3 (95% CI, −93.4 to −3.2; P = 0.036) and −4.1 mg/dL (95% CI, −6.7 to −1.4; P = 0.003), respectively. The differences in weight and BMI between the INSTI+DRV/r experimental arm and the SOC were 1.97 kg (95% CI, 1.1–2.9; P < 0.001) and 0.66 kg/m^2 (95% CI, 0.3–1.0; P < 0.001)], respectively.

Because of concerns about a potential interaction between DRV/r and dolutegravir (DTG), the SMILE trial (PENTA 17-ANRS152) also assessed the safety, efficacy, and drug interactions of once-daily dual therapy, using DTG 50 mg combined with DRV/r (100 mg/800 mg), both once daily, in virologically suppressed adolescents aged 12 years and older. Unbound DTG concentrations were measured and used in this study. There was a slight effect—DTG clearance was 12.1% lower (and corresponding DTG trough 14.3% higher) when unbound DRV AUC from time zero to 24 hours postdose ($AUC_{0–24h}$) was higher than 4.7 mg h/L. However, the key finding of this analysis was that there was a clinicially negligible impact of DRV/r on DTG concentrations at steady-state.[19] In a separate modeling paper, there was no clinically relevant interaction identified between DRV/r and the clearance of DTG at steady-state, and the influence of unbound DRV exposures on unbound DTG concentrations was quite small.

Observational Data

An observational cohort[20] of children and youth <25 years of age on DRV-based ART in nine countries in sub-Saharan Africa found that, over a median duration of follow-up of 28.3 months, 771 (87.9%) were alive at the end of follow-up for the study, 29 (3.6%) died, and 69 (8.5%) moved away or were lost to follow-up; 809 participants had final outcomes. Males were marginally less likely to be retained in care than females (adjusted HR 0.85, 95% CI, 0.72–1.0), and adolescents aged 15 to 19 years were more likely to die than children younger than 10 years (adjusted subdistribution HR 4.20, 95% CI, 1.37–12.87).

In another retrospective study[21] in India, people aged ≥13 years who experienced virological failure on first-line ART and were transitioned to second-line ART (dual NRTI + RTV-boosted PI) between September 2015 and October 2018 were followed for 5 years. Overall, 219 individuals switched to RTV-boosted PI-based second-line ART after 68 (median) months (interquartile range [IQR] 68) of first-line ART exposure and were followed up for 57 (median) months (IQR 48). The incidence of virological failure was 6.9% at 36 months and 15.9% at 60 months. Drug resistance analysis revealed 17.4% lopinavir (LPV) resistance, 34.8% atazanavir resistance, and DRV cross-resistance in only three sequences. The conclusion was that PIs are quite resilient when used as second-line ART and there was a low incidence of virologic failure that was caused by PI resistance.

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.[13,14,22] The DRV area under the curve from 0 to 12 hours ($AUC_{0–12h}$), measured as a percent of the adult AUC value,[13,14,22] was 126% overall, 143% in children weighing 10 kg to <15 kg, and 121% in children weighing 15 kg to <20 kg.

The CHAPAS-4 trial[23] examined efficacy and safety of second-line ARV treatment, including DRV/r. The study randomized African children aged 3 to 15 years who had failed first-line treatment to either TAF/FTC (dosed according to World Health Organization [WHO]–recommended weight bands) or SOC dual-NRTI treatment, in combination with DTG or a boosted PI. Out of 919 children, 232 children received DRV/r. There was favorable safety (8.6% of children experienced Grade 3 or 4 adverse events with DRV/r, as compared to 11.5% with LPV/r [*P* = 0.31]). In terms of efficacy criteria of having an HIV viral load <400 copies/mL at 96 weeks, DRV/r failed to meet the pre-specified superiority criteria for comparison to LPV/r and ATV/r (combined analysis) but had numerically higher efficacy (88.3% as compared to 82.5%, adjusted difference 5.6 percentage points; 95% CI, 0.3–11.0; *P* = 0.04 [prespecified threshold, *P* = 0.03]).

The CHAPAS-4 trial included a PK substudy[24] in a subset of 104 of children aged 3 to 15 years weighing ≥14 kg and receiving a failing first-line ART; plasma PK data were collected at steady-state. TAF was administered in combination with DTG (n = 18), DRV/r (n = 34), or LPV/r (n = 20), and the measured geometric mean (coefficient of variation [CV] %) TAF AUC from dose to the time of the last measurable concentration (AUC_{last}) for those combinations was 284.5 (79), 232.0 (61), and 210.2 (98) ng•hour/mL, respectively, similar to reference values in adults taking TAF 10 mg in conjunction with a boosted PI (adult dosing recommended by the European Medicines Agency). All of the children had TAF AUC_{last} >55 ng•hour/mL, the predefined target value associated with favorable virologic efficacy in adults. In combination with atazanavir/ritonavir (n = 32), TAF AUC_{last} was higher, at 511.4 (68) ng•hour/mL, and TAF C_{max} was 86% higher than the C_{max} in adults taking TAF 25 mg with boosted PI. In all of these combinations, tenofovir geometric mean (CV%) $AUC_{0–24h}$ and C_{max} was below the exposures observed in adults taking TAF 25 mg once daily in conjunction with boosted PI (TAF 25 mg dosing for adults is recommended by the FDA, except in the case of the FDC DRV/c/FTC/TAF, in which case the dose is 10 mg of TAF). This study provided reassurance that in children aged 3 to 15 years, TAF can achieve safe and well-tolerated exposures when used in conjunction with DRV/r.[25] See the Tenofovir Alafenamide section for more information.

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 ≥20 kg.[26] Part 1 of the trial used a weight-adjusted dose of DRV (9–15 mg/kg) and RTV (1.5–2.5 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 an $AUC_{0–24h}$ that was 81% of the $AUC_{0–24h}$ observed in adults and a predose concentration (C_{0h}) that was 91% of the C_{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 to 19 mg/kg and RTV 1.5 to 2.5 mg/kg twice daily. This dose resulted in a DRV $AUC_{0–24h}$ of 123.3 mcg•h/mL (range 71.9–201.5 mcg•h/mL) and a C_{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 below).

A small study that involved 12 treatment-experienced children aged 6 to 12 years examined the PK and efficacy of DRV/r once daily administered in combination with abacavir and lamivudine.[16] 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[27]: 600 mg/100 mg for patients weighing 15 to 30 kg, 675 mg/100 mg for patients weighing 30 to 40 kg, and 800 mg/100 mg for patients weighing >40 kg. The geometric mean $AUC_{0–24h}$ 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).[28] One child developed neuropsychiatric symptoms (anxiety and hallucinations) and was removed from study. This child did not have an excessive exposure to DRV; the $AUC_{0–24h}$ was 47.8 mg•h/L.

A population PK sub-study was done as part of the SMILE trial,[29] examining the protein binding and PK of DRV among virologically suppressed adolescents on an INSTI and DRV/r. A total of 443 plasma PK samples from 152 adolescents were incorporated. The median unbound-to–total concentration ratio was 5.4%; DRV displays a total protein binding in plasma of 94.5% (73.7% bound to alpha-1 glycoprotein and 20.8% bound to albumin). A significant impact of alpha-1 glycoprotein concentrations on DRV clearance was observed. The simulations showed that 86.8% of DRV C_{trough} were above 0.55 mg/L (10 x protein binding–adjusted EC_{50}) for wild-type HIV-1, and 86.8% of DRV *unbound* C_{trough} were above 0.0243 mg/L (10 x PA EC_{90}) for wild-type HIV-1. Overall, individual C_{trough} in adolescents given DRV/r 800 mg/100 mg daily were in line with those observed in adults given DRV/r 800/100 mg daily. This provided reassuring evidence of satisfactory exposures in adolescents given an adult dosing regimen of DRV/r.

The PK substudy of the CHAPAS-4 study also included an analysis of DRV exposures[30] in a subset of 59 CHAPAS-4 participants, with median age 10.9 (range 3.8–14.7) years and weight 26.0 (14.5–47.0) kg. The observed DRV geometric mean (%CV) $AUC_{0–24h}$ 94.3(50) mg•h/L and C_{max}, 9.1(35) mg/L were both above exposures seen in adults, but the C_{trough}, 1.5(111) mg/L, was comparable to adult exposures. Children with higher levels of alpha-1-acid glycoprotein were observed to have decreased apparent clearance of DRV, likely due to binding of DRV. Population PK methods were used to simulate the WHO-recommended 600/100 mg DRV/r dose for children in the 25 kg to 34.9 kg weight band, achieving exposures in the range of adult exposures. The conclusion of this PK substudy was that either the simulated dose (600 mg/100 mg) or the CHAPAS-4 studied dose (800 mg/100 mg) had acceptable exposures and could be used in the 25 kg to 34.9 kg weight band, depending on tablet availability.

An analysis of genotypic resistance in children in the CHAPAS-4 study was reassuring. At the 2025 Conference on Retroviruses and Opportunistic Infections (CROI), Week 96 data from this trial were presented on resistance that emerged on study and associations between baseline resistance and ultimate virological failure. Sequencing for resistance (defined using the Stanford algorithm) was performed on baseline samples and on participants who had a week 96 viral load of 400 copies/mL or greater. Intermediate or high-level resistance to the anchor drug was seen at week 96 in: 0/29 LPV/r, 1/26 (4%) ATV/r, 0/18 DRV/r and 2/9 (22%) DTG (all of whom were taking zidovudine as one of their NRTIs).

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

Population	n	Dose of DRV/r	AUC_{12h} (mcg•h/mL) Median[a]	C_{0h} (ng/mL) Median[a]
Children Weighing 10 kg to <15 kg[a]	13	20 mg/kg/3 mg/kg	66.0	3,533
Children Weighing 10 kg to <15 kg[a]	4	25 mg/kg/3 mg/kg	116.0	8,522
Children Weighing 15 kg to <20 kg[a]	11	20 mg/kg/3 mg/kg	54.2	3,387
Children Weighing 15 kg to <20 kg[a]	14	25 mg/kg/3 mg/kg	68.6	4,365
Children Aged 6 Years to <12 Years[b]	24	Determined by weight bands[b]	56.4	3,354
Adolescents Aged 12 Years to <18 Years[b]	50	Determined by weight bands[b]	66.4	4,059
Adults Aged >18 Years[c] (Three Studies)	285/278/119	600 mg/100 mg	54.7–61.7	3,197–3,539

[a] Source: U.S. Food and Drug Administration. FDA clinical pharmacologic review of darunavir. 2011. Available at: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM287674.pdf.

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

[c] Source: Darunavir [package insert]. Food and Drug Administration. 2016. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021976s043,202895s017lbledt.pdf.

Note: Ritonavir (RTV) oral solution is no longer available. Use of DRV/r is now limited to children weighing ≥20 mg who can receive 100 mg RTV using powder or tablets.

Key: AUC_{12h} = 12-hour area under the curve; C_{0h} = predose concentration; DRV/r = darunavir/ritonavir

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).[31] 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.[26,31] 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. No data are available on the safety and tolerability of using DRV with 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.[32] Data on once-daily use of the FDC tablet DRV/c 800 mg/150 mg (Prezcobix) showed bioavailability that was comparable to the bioavailability observed with the use of DRV/r 800 mg/100 mg once daily.[28]

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_{tau}) that were similar to those observed in adults, except for a lower trough concentration at the end of the dosing interval (C_{tau}). The median DRV C_{tau} (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.[33]

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 (see Table B below). 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.[14,34] Currently, limited data exist on the efficacy of once-daily DRV/r dosing in treatment-naive or treatment-experienced children aged <6 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 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.

Table B. U.S. Food and Drug Administration–Approved Once-Daily Dosing for Pediatric Patients Aged ≥3 Years and Weighing >20 kg Who Are Treatment Naive or Treatment Experienced With No Darunavir Resistance–Associated Mutations

Note: The Panel generally recommends dosing DRV plus RTV *twice daily* in children aged ≥3 to <12 years.

Weight	DRV/r Dose (Once Daily With Food)
20 kg to <30 kg	DRV 600 mg (tablet, combination of tablets, or 6 mL) plus RTV 100 mg (tablet or powder)[a]
30 kg to <40 kg	DRV 675 mg (combination of tablets or 6.8 mL)[b,c] plus RTV 100 mg (tablet or powder)[a]
≥40 kg	DRV 800 mg (tablet, combination of tablets, or 8 mL)[c] plus RTV 100 mg (tablet or powder)[a]

[a] RTV oral solution is no longer available. Use of DRV/r is now limited to children weighing ≥20 kg who can receive 100 mg RTV using powder or tablets.

[b] DRV 100 mg/mL oral suspension; the 675-mg once daily DRV dose is rounded for dosing convenience of suspension.

[c] The 6.8-mL and 8-mL DRV doses can be taken as two administrations (3.4 mL and 4 mL, respectively) once daily by refilling the oral dosing syringe supplied by the manufacturer or as one administration once daily if a larger syringe is provided by a pharmacy or provider.

Key: DRV = darunavir; DRV/r = darunavir/ritonavir; 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 DRV for 2 weeks; DRV PK 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.[28,34] The DRV/r dose for once-daily use, which was based on PK simulation and 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.[34,35] The PK data obtained from 10 children aged 3 to 6 years in this substudy (see Table C below) 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,[16] the geometric mean $AUC_{0–24h}$ 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 data set 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

PK Parameter	Children Aged 3 to 6 Years (n = 10)[a]	Adults (n = 335)
DRV $AUC_{0–24h}$ geometric mean, ng•h/mL (SD)	115 (40.6)	89.7 (27.0)
DRV C_{0h} geometric mean, ng/mL (SD)	3,029 (1,715)	2,027 (1,168)

[a] Source: Kakuda TN, Brochot A, van de Casteele T, et al. Establishing darunavir dosing recommendations in treatment-naive and treatment-experienced pediatric patients. Presented at: 14th Clinical Pharmacology Workshop on HIV. 2013. Amsterdam, Netherlands. Available at: https://www.natap.org/2013/Pharm/Pharm_19.htm.

Key: $AUC_{0–24h}$ = 24-hour area under the curve; C_{0h} = predose concentration; DRV = darunavir; PK = pharmacokinetic; SD = standard deviation

Once-Daily Administration in Adolescents Aged ≥12 Years 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 12–17 years and weighing ≥40 kg) were similar to those seen in adults treated with once-daily DRV (see Table D below).[17] After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL.[17] Interestingly, no relationship was observed between DRV $AUC_{0–24h}$ 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/r 800 mg/100 mg was administered to 24 subjects with a median age of 19.5 years (range 14–23 years).[36] 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

Population	n	Dose of DRV/r	$AUC_{0–24h}$[a] (mcg•h/L) Median	C_{0h} (ng/mL) Median
Adolescents Aged 12–17 Years (Mean Age 14.6 years)[b]	12	800 mg/100 mg	86.7	2,141
Adolescents and Adults Aged 14–23 Years (Mean Age 19.5 years)[c]	24	800 mg/100 mg	69.5	1,300
Adults Aged >18 Years (Two Studies)[a]	335/280	800 mg/100 mg	87.8–87.9	1,896–2,041

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

[a] Source: Darunavir [package insert]. Food and Drug Administration. 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021976Orig1s063lbl.pdf.

[b] Source: Kakuda TN, Brochot A, van de Casteele T, et al. Establishing darunavir dosing recommendations in treatment-naive and treatment-experienced pediatric patients. Presented at: 14th Clinical Pharmacology Workshop on HIV. 2013. Amsterdam, Netherlands. Available at: https://www.natap.org/2013/Pharm/Pharm_19.htm.

[c] Source: Flynn P, Blanche S, Giaquinto C, et al. DIONE – 24-week efficacy, safety, tolerability and pharmacokinetics of darunavir/ritonavir once daily in treatment-naive adolescents aged 12 to < 18 years. Abstract # PP_2. Presented at: 3rd International Workshop on HIV Pediatrics. 2011. Rome, Italy. Available at: https://www.natap.org/2011/IAS/IAS_40.htm.

Key: $AUC_{0–24h}$ = 24-hour area under the curve; C_{0h} = predose 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.[17,37]

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