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
- [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). 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; these events have been attributed to immaturity of the blood–brain barrier and liver metabolic pathways.

Aged ≥3 to <12 Years

- Dosing recommendations in the table below are for children aged ≥3 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%.
- DRV contains a sulfonamide moiety. Use DRV with caution in patients with known sulfonamide allergies.

Twice-Daily DRV and RTV Doses for Children Aged 3 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 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 (tablet) plus COBI[e] 150 mg (tablet) or the 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.

[Prezcobix] DRV/COBI

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

- One tablet once daily with food

[Symtuza] DRV/COBI/Emtricitabine (FTC)/ Tenofovir Alafenamide (TAF)

- 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.

Child and Adolescent (Weighing ≥40 kg) and Adult Dose • One tablet once daily with food in ARV-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.	

[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 ritonavir (DRV/r) is now limited to children weighing ≥20 kg who can receive 100 mg RTV 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 to <40 kg (see Table B below).

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

Drug Interactions

Additional information about drug interactions is available in the Adult and Adolescent Antiretroviral Guidelines and the 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 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 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 PKs 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.

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.

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 (ARV) therapy 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 combinations (FDCs) DRV/c (Prezcobix) and DRV/c/emtricitabine/tenofovir alafenamide (Symtuza) are also approved by the FDA for use in pediatric patients weighing ≥40 kg.

Efficacy in Clinical Trials

In an international, multisite clinical trial (TMC114-TiDP29-C228) that enrolled treatment-experienced children aged 3 to <6 years, 17 (81%) of 21 children who received DRV/r twice daily had viral loads <50 copies/mL at Week 48.[7-9]

A randomized, open-label, multicenter pediatric trial[9] that evaluated twice-daily DRV/r among 80 treatment-experienced children aged 6 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.[10] 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.[11] After 48 weeks, all but one participant had viral loads <50 copies/mL.

Pharmacokinetics and Dosing

Pharmacokinetics in Children Aged 3 to <6 Years

Twenty-one children aged 3 to <6 years and weighing 10 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.[7,8,12] The DRV area under the curve from 0-12 hours ($AUC_{0–12h}$), measured as a percent of the adult AUC value,[7,8,13] was 126% overall, 143% in children weighing 10 to <15 kg, and 121% in children weighing 15 to <20 kg.

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 to <18 years and weighing ≥20 kg.[14] 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 a 24-hour AUC ($AUC_{0–24h}$) 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 to <30 kg and 30 to <40 kg. The current weight-band doses of twice-daily DRV/r for treatment-experienced pediatric patients weighing >20 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.[10] 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[15]: 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).[16] 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.

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 to <12 Years[b]	24	Determined by weight bands[b]	56.4	3,354
Adolescents Aged 12 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: 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.

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 to <30 kg), 450 mg (in children weighing 30–40 kg), and 600 mg (in children weighing ≥40 kg).[17] 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.[14,17] 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.[18] 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.[16]

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 (area under the curve for the dosing interval [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 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.[19]

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 to <12 years and weighing 10 to <40 kg.[8,20] 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 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 >10 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	Dose (Once Daily with Food)
15 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 to <12 years as part of a substudy. After the conclusion of the substudy, the participants switched back to a twice-daily regimen.[16,20] 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.[20,21] 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 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,[10] 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 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).[11] After 48 weeks, 83.3% of patients had viral loads <50 copies/mL and 91.7% had viral loads <400 copies/mL.[11] 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).[22] 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

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

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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.[11,23]

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