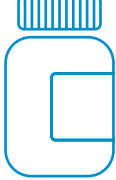



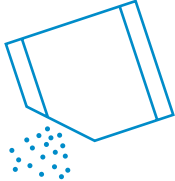




# Darunavir + ritonavir (DRV + RTV)

## Available Formulations

DRV single-drug formulations	
	
Oral suspension	Tablet
DRV 100 mg/mL	DRV 75 mg DRV 150 mg DRV 600 mg

RTV single-drug formulations		
		
Tablet	Oral suspension	Powder
RTV 25 mg RTV 50 mg	RTV 80 mg/mL	RTV 100 mg/sachet

Formulations for adults
DRV 800 mg DRV + COBI 800/150 mg DRV + COBI + FTC + TAF 800/150/200/10 mg

A fixed-dose combination for children is not available yet.

## Formulation considerations

DRV + RTV dosing with food reduces the possibility of experiencing adverse effects from DRV use and increases DRV plasma concentrations by 30%; administration together with food is therefore recommended.

The preferred formulation for DRV for children and adults is the DRV film-coated tablet. An alternative could be combining two separate liquid formulations, DRV and RTV, which are not readily available globally. The formulations have comparable bioavailability.

Under development: DRV + RTV 120/20 mg fixed-dose combination.





# Darunavir + ritonavir (DRV + RTV)

## WHO dose recommendation - age

Newborns		Infants	Children		Adolescents
Birth		4 Weeks	3 Months	2 Years	12 Years
			← Licensed and recommended from 3 years		
					18 Years

Children younger than three years should not receive DRV because the blood-brain barrier is immature and seizures have been observed in juvenile rats ([United States Food and Drug Administration label](#)).

## Current WHO/PAWG recommendations

### DRV + RTV taken once daily

Once-daily DRV + RTV can be used for children older than three years and weighing at least 14 kg without previous exposure to protease inhibitors (PIs) such as LPV/r and ATV + RTV.

Drug	Strength of paediatric tablets	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets by weight band once daily
		3 – <6kg	6 – <10kg	10 – <14kg	14 – <20 kg	20 – <25 kg		
DRV <sup>a</sup>	Tablet 600 mg	–	–	–	1	1	600 mg	1
	Tablet 150 mg	–	–	–	4	4		
RTV <sup>b</sup>	Tablet 25 mg	–	–	–	4	4	100 mg	1
	Tablet 50 mg	–	–	–	2	2		

<sup>a</sup> DRV in combination with RTV should be used for children older than three years, once daily when this is used without previous exposure to PIs. Although the approved dosing for 30–35 kg is 675 mg, preliminary data from studies of adults suggest that even lower DRV doses may be effective, and the 600-mg dose was therefore extended to the entire 25- to 35-kg weight band.

<sup>b</sup> RTV should only be used as a boosting agent in combination with ATV or DRV or to super-boost LPV/r when given with concomitant rifampicin for TB.



# Darunavir + ritonavir (DRV + RTV)

## DRV + RTV taken twice daily

Twice-daily DRV + RTV dosing is needed for those with previous PI exposure and hence should be used for children older than three years and weighing at least 14 kg with previous exposure to PIs.

Drug	Strength of paediatric tablets	Number of tablets or capsules by weight band once daily										Strength of adult tablet	Number of tablets by weight band once daily	
		3 – <6 kg		6 – <10 kg		10 – <14 kg		14 – <20 kg		20 – <25 kg			25 – <35 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
DRV <sup>a,b</sup>	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	600 mg	1	1
	100 mg/mL	–	–	–	–	2.5 mL	2.5 mL	3.5 mL	3.5 mL	–	–		–	–
RTV <sup>c</sup>	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1		–	–
	80 mg/mL	–	–	–	–	0.5 mL	0.5 mL	0.6 mL	0.6 mL	–	–		–	–

<sup>a</sup> DRV in combination with RTV should be used for children older than three years, once daily when this is used without previous exposure to PIs. Although the approved dosing for 30–35 kg is 675 mg, preliminary data from studies of adult suggest that even lower DRV doses may be effective, and the 600-mg dose was therefore extended to the entire 25- to 35-kg weight band.

<sup>b</sup> DRV for children older than three years must be administered with 0.5 mL of RTV 80 mg/mL oral suspension if they weigh less than 15 kg and with RTV 50 mg (using 25-mg or 50-mg solid formulation) for children weighing 15–30 kg. RTV 100-mg tablets can be used as a booster if lower-strength RTV tablets are not available based on limited experience suggesting good acceptability and tolerability.

<sup>c</sup> RTV should only be use as a boosting agent in combination with ATV or DRV or to super-boost LPV/r when given with concomitant rifampicin for TB.

## Rationale for WHO DRV + RTV dose selection

### Once-daily dosing

Once-daily DRV + RTV dosing for children is largely based on the data from the ARIEL study among 10 children aged 3 to <6 years old and the DIONE study among 12 adolescents aged 12 to <18 years ([Flynn et al.](#) and [Violari et al.](#)). Using these data, [Brochot et al.](#) modelled once daily DRV + RTV dosing for children aged 3 to <12 years old and provided the DRV + RTV dosing recommendations for children aged 6 to <12 years old.

The European Medicines Agency approved once-daily dosing of DRV + RTV for children aged three years and older and with weighing at least 15 kg. The label of the United States Food and Drug Administration and the guidelines of the United States National Institutes of Health do not recommend once-daily dosing of DRV + RTV for children younger than 12 years because of a scarcity of efficacy data supporting once-daily dosing of DRV + RTV in this age group. The optimal once-daily DRV + RTV dose for children weighing 30–40 kg was 675/100 mg when modelled ([Brochot et al.](#)). This dose was approved by the European Medicines Agency and was used in the DAPHNE trial ([Bastiaans et al.](#)). Preliminary data from adult studies suggest that even lower DRV doses may be effective in producing and maintaining viral suppression, and DRV 600-mg dose was therefore extended to the entire 25- to 35-kg weight band in the WHO dosing appendix for the practicality of the dose ([Lee et al.](#)).



# Darunavir + ritonavir (DRV + RTV)

## Twice-daily dosing

The European Medicines Agency approved twice-daily dosing for children aged three years or older with minimal weight of 15 kg, whereas the United States Food and Drug Administration and United States National Institutes of Health guidelines recommend twice-daily dosing of DRV + RTV for children from three years weighing at least 10 kg. The WHO-recommended DRV dose twice daily for children 10.0–14.9 kg is 250 mg DRV twice daily (25.0–16.7 mg/kg) combined with 40 mg RTV liquid or 25-mg or 50-mg RTV tablet. This dose is based on pharmacokinetic modelling ([Brochot et al.](#)). RTV 100-mg tablets can be used as a booster if lower-strength RTV tablets are not available, based on limited experience suggesting good acceptability and tolerability.

## Therapeutic drug monitoring target concentrations

DRV area under the curve or  $C_{\text{trough}}$  values have not been related to clinical effects, but an in vitro study ([Kakuda et al.](#)) showed that a protein-binding adjusted plasma DRV concentration of 0.55 mg/L produces 50% of the maximal effect ( $EC_{50}$ ) for susceptible virus. No  $EC_{90}$  or other efficacy parameters have been reported for DRV ([Kakuda et al.](#)). Mean  $C_{\text{trough}}$  for once-daily 800/100 mg DRV + RTV for adults was reported at 2.0 mg/L ([Kakuda et al.](#)).

## Current ongoing trials involving children

Clinical trials at [ClinicalTrials.gov](https://ClinicalTrials.gov)

## Knowledge gaps

Currently there are not enough data to support dosing of DRV + RTV for children weighing less than 15 kg.

DRV dosing can be boosted with COBI for adults but is not recommended for children because of lack of data.

Insufficient efficacy data have been gathered to support dosing of DRV + RTV once daily for children <12 years old.

## Drug–drug interactions

Co-administration of DRV + RTV and rifampicin is contraindicated since it may cause significant decreases in DRV blood concentrations. Moreover, increasing the DRV + RTV dose to overcome the interaction with rifampicin resulted in high rates of hepatotoxicity among adults living with HIV.