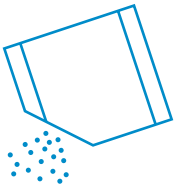
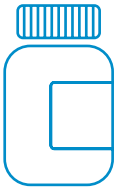
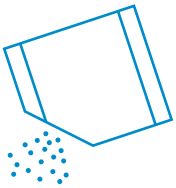
Atazanavir + ritonavir (ATV + RTV)

Available Formulations

Single-drug formulations	
	
Capsule	Powder
ATV 100 mg ATV 200 mg	ATV 50 mg/sachet

RTV		
		
Tablet	Oral suspension	Powder
RTV 25 mg RTV 50 mg	RTV 80 mg/mL	RTV 100 mg/sachet

Formulations for adults
ATV 300 mg RTV 100 mg

A fixed-dose combination is not yet available.

World Health Organization

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Formulation considerations

Administer ATV and RTV with food to enhance absorption and reduce pharmacokinetic variability.

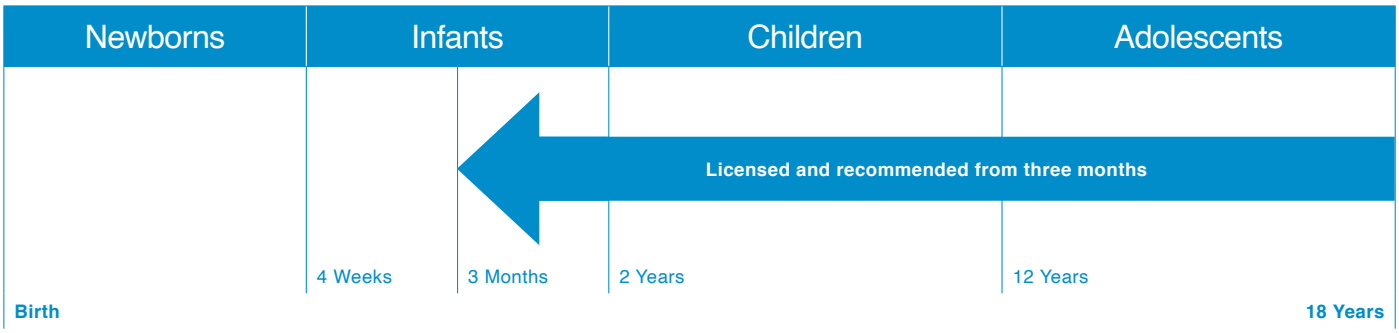
The exposure of ATV capsules and powder packets is similar (in the absence of RTV), but the doses might not be interchangeable because of the different RTV formulations and doses given (80 mg/mL RTV syrup with the ATV powder versus 100-mg RTV capsule with the ATV capsule formulation). Opened capsules have not been studied and should not be used.

Under development: ATV + RTV 300/100 mg fixed-dose combination tablet and ATV + RTV + 3TC + AZT 300/100/150/300 mg fixed-dose combination tablet.

Since the ATV powder combined with separate RTV dosing is unavailable, the preferred formulation for ATV is the ATV capsule.

ATV boosted with COBI has not been studied for children and is therefore not recommended.

WHO dose recommendation - age



Children younger than three months should not receive ATV nor should newborns because of risks associated with hyperbilirubinaemia (such as bilirubin-induced nervous system dysfunction).

Capsules can be used from 10 kg onward; for the lower weight bands ATV powder (50 mg per packet) can be used, but this is not widely available and therefore not included in the WHO recommendations.

Current WHO/PAWG recommendation:

ATV/RTV taken once daily

Once-daily ATV/RTV can be used for children older than three months and weighing at least 5 kg, but in practice the powder is not available, and dosing for the ATV capsules is recommended for children weighing 10 kg or more.

Unboosted ATV (without RTV boosting) is not recommended for children (Cressey et al.). When unboosted ATV is administered to children, therapeutic drug monitoring is recommended to ensure that adequate ATV plasma concentrations have been achieved; however, this is not feasible in many settings. A minimum target trough concentration for ATV is 150 ng/mL.

World Health Organization

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Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older

Drug	Strength of paediatric tablet	Number of tablets or capsules by weight band once daily					Strength of adult tablet	Number of tablets or capsules by weight band once daily
		3–<6 kg	6–<10 kg	10–<14 kg	14–<20 kg	20–<25 kg		25 – <35 kg
ATV[a]	Capsules 100 mg	–	–	2	2	2	300 mg	1[c]
	Capsules 200 mg	–	–	1	1	1		
RTV[b]	Tablet 25 mg	–	–	4	4	4	100 mg	1
	Tablet 50 mg	–	–	2	2	2		

[a]ATV is only approved for children three months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands 10 kg and above. ATV powder formulation has limited availability in low- and middle-income countries but enables ATV to be administered to infants and children as young as three months old; the dosing recommendation was not included in the WHO recommendations because of the very limited availability. The dosing recommendation in the label for the younger infants is: infants and children weighing 5–15 kg should be administered 200 mg of ATV powder (four packets, 50 mg/packet) with 80 mg of RTV oral solution (1 ml) once daily (United States Food and Drug Administration label).

[b]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.

[c]ATV 300 mg with RTV 100 mg for 25.0–29.9 kg is recommended based on the findings from the PRINCE-2 study (Cotton et al.).

Capsules can be used from 10 kg onward; for the lower weight bands ATV powder (50 mg per packet) can be used, but this is not widely available and therefore not included in the WHO recommendations.

World Health Organization

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Studies supporting dose in children

A study to find the dose of ATV for children (IMPAACT P1020; n = 195 children three months to 21 years of age) targeted dosing to attain ATV pharmacokinetic parameters for children similar to adults (Kiser et al.). They used a range of increasing ATV doses over an increasing range of the body surface area, both with and without RTV boosting, and attained the target pharmacokinetic parameters with ATV + RTV for children across all studied age groups, and with unboosted ATV capsules for children two to <13 years old (Kiser et al.). However, treatment with unboosted ATV powder formulation could not satisfy predetermined pharmacokinetic parameters for children aged three months to <13 years. This was likely a consequence of low ATV bioavailability, faster clearance and a wide intersubject variability in this age group (Kiser et al. and United States Food and Drug Administration label). Subsequent modelling by Hong et al. translated dosing based on the body surface area into a dosing table based on weight bands for the capsule formulations. The PRINCE-1 and PRINCE-2 trials showed that ATV powder formulation in combination with RTV liquid for children three months to <11 years old and weighing 5–34.9 kg dosed in weight bands reached the target drug exposure levels (Sevinsky et al., Cotton et al. and Strehlau et al.). The results from the PRINCE-1 and -2 trials together with IMPAACT P1020 and the modelling study by Hong et al. supported the United States Food and Drug Administration approval of ATV + RTV dosing for children. Two additional studies with ATV + RTV for children were reported: one study investigated the dosing of ATV + RTV combined with TDF among Asian children living with HIV (Bunupuradah et al.). It is hypothesized that TDF reduces ATV exposure by inducing P-glycoprotein, resulting in decreased ATV bioavailability (Taburet et al.). Higher protease inhibitor drug levels have been reported among people of Asian origin (Puthanakit et al.). Bunupuradah et al. showed that 200-mg ATV boosted with 100 mg of RTV within a regimen containing TDF was able to achieve ATV levels comparable with adult levels in Asian children aged 6–18 years. Another study investigated the possibility of using unboosted ATV in ART-experienced Thai children unable to take RTV (Cressey et al.). Doses of 400-mg and 600-mg unboosted ATV did not achieve target Ctrough levels and were highly variable.

Rationale for WHO dose selection

The United States Food and Drug Administration recommends dosing with the ATV powder boosted with RTV syrup for children weighing 5–15 kg and does not recommend dosing with the ATV capsule and RTV tablet for children weighing less than 15 kg. Since the ATV powder formulation is generally not available in low- and middle-income countries, WHO decided to recommend dosing with the capsules from 10 kg onward. In the 10- to 15-kg weight band, the WHO-suggested dose (200/100 mg ATV capsule/RTV tablet) differs slightly from the dose given in powder formulation with RTV syrup (200/80 mg ATV powder/RTV syrup) regarding the RTV dose. The reason for this choice is that, for children who are able to swallow capsules, the RTV syrup is not recommendable because of the bulky storage, taste and limited availability in low- and middle-income countries, and using RTV tablets is therefore recommended.

WHO recommends an adult 300/100 mg ATV + RTV dose for children weighing 25–35 kg based on findings from the PRINCE-2 study; this dose is higher than the United States Food and Drug Administration approved 200/100 mg dose for this weight band. In the PRINCE-2 study, 300/100 mg in the ATV powder formulation with RTV syrup or capsules was administered to children weighing at least 25 kg. This dose was safe and efficacious in children over a period of 48 weeks. The pharmacokinetic results from this study show that ATV exposure (area under the curve) in this weight band was similar to the area under the curve for adults; however, the ATV Ctrough was almost 30% lower at week 2 compared with that for adults and highly variable over time in this weight band. The modelling study by Hong et al. shows that the predicted geometric mean Ctrough on the current dose approved by the United States Food and Drug Administration (200/100 mg ATV + RTV) for children 25–35 kg is relatively low and approaches the 75% lower limit of the adult pharmacokinetic parameters, but has overall area under the curve exposure similar to that of adults.

World Health Organization

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Therapeutic drug monitoring target concentrations

ATV drug monitoring is guided by C_{trough} concentrations.

Ctrough concentrations of ATV above 0.15 mg/L are correlated with lower rates of virological failure among ART-naive adults (Goutelle et al.). People previously treated with protease inhibtor–containing ART need higher ATV trough levels for each mutation that decreases the susceptibility of HIV to ATV. A concentration of 0.23 mg/L per mutation has been correlated with higher efficacy (Cleijsen et al.). The upper limit of the treatment dose is less well defined but is determined by the rise of unconjugated bilirubin, the main adverse event caused by ATV, which is correlated with ATV Ctrough in the range of 0.50–0.76 mg/L (Ray et al. and Smith et al.). Safety data from a large cohort study of ATV + RTV among children also demonstrate increasing incidence and severity of hyperbilirubinaemia with increasing Ctrough (Sevinsky et al.). Because the increase in bilirubin is not a product of liver damage but rather because ATV interacts with bilirubin conjugation, this effect is benign.

Special attention

More common toxicity: indirect hyperbilirubinaemia that can result in jaundice or icterus but is not a marker of hepatic toxicity.

Drug-drug interactions

Drug–drug interactions with rifampicin: these drugs should not be taken together. Rifampicin reduces ATV exposure by about 75% and Ctrough by 98%. Some guidelines on drug–drug interactions advise using rifabutin as an alternative. However, a study evaluating concomitant use of rifabutin and ATV for adults was stopped because of excess toxicity (Zhang et al.).

Current ongoing trials involving children

Clinical trials on ClinicalTrials.gov

Knowledge gaps

Weight-band doses for children are derived from doses based on the body surface area in the P1020 trial and converted to weight-band dosing by modelling alone (Hong et al.). Thus, these doses need to be clinically validated, which is planned in the CHAPAS-4 trial.

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