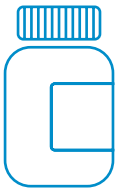
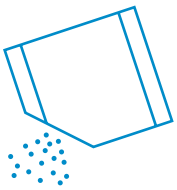
Lopinavir/ritonavir (LPV/r)

Available Formulations

Single drug formulations			
			
Liquid formulation	Granules	Pellets	Tablet (scored)
LPV/r 80/20 mg/mL	LPV/r 40/10 mg/sachet	LPV/r 40/10 mg	LPV/r 100/25 mg

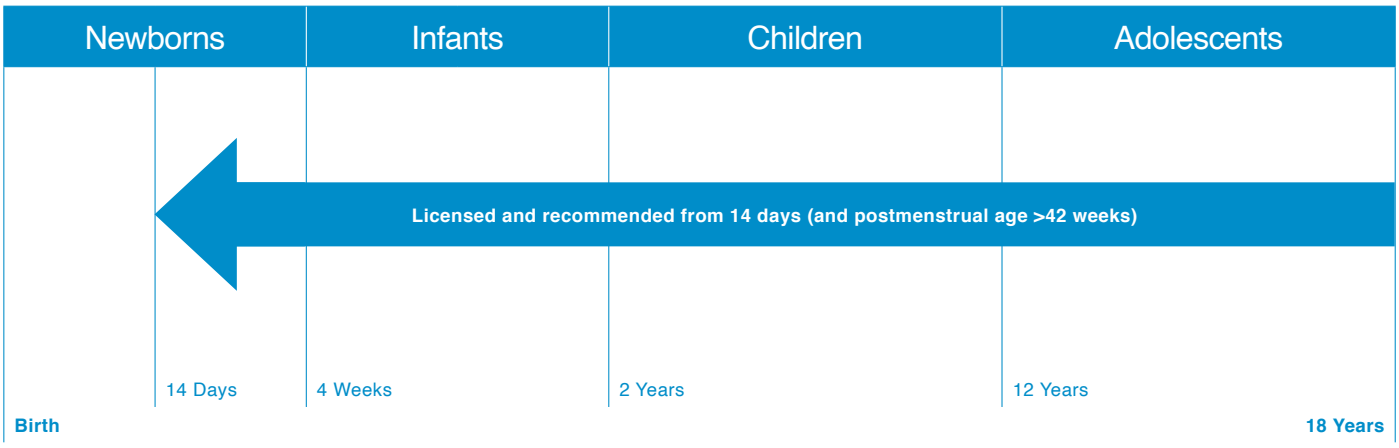
Formulations for adults
LPV/r 200/50 mg

Formulation considerations

LPV/r oral solution should be stored refrigerated and has a shelf life of one month after opening. Crushing LPV/r tablets for children results in significant reductions of LPV exposure, and they should therefore be swallowed whole.

The palatability of both LPV/r oral solution and pellets is poor, and this can be challenging in terms of treatment adherence for children (Kekitiinwa et al.). It is therefore recommended to mask its taste by administering the drug with sweet or tangy food or by using ice chips to numb the taste before administration (United States National Institutes of Health guidelines).

WHO dose recommendation - age



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WHO dose recommendation – weight bands

Oral liquid from birth to four weeks of age[a]

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening					
		2 – <3 kg		3 – <4 kg		4 – <5 kg	
		AM	PM	AM	PM	AM	PM
LPV/r[b]	80/20 mg/mL oral liquid	0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
	Granules 40 mg/10 mg sachet	–	–	2	2	2	2

[a]To avoid dose changes over a short period of time and to minimize the likelihood of errors, all ARV drugs except for RAL should be dosed based on weight when treatment starts and maintained until four weeks of age (weight gain is limited during the first four weeks of life).

[b]Do not use LPV/r solution for infants aged younger than four weeks. LPV/r pellets should not be used for infants younger than three months. More details on administering LPV/r pellets are available. Because of lack of clinical data to fully inform the use of LPV/r granules for newborns, these dosing recommendations were developed based on the current United States Food and Drug Administration approval (supporting using LPV/r granules from two weeks) and considering the substantial uncertainty, especially for newborns weighing 2–3 kg. If no other formulation exists, one sachet twice a day could be considered for newborns older than two weeks who weigh 2–3 kg to minimize the risk of potential toxicity with overdosing.

Child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children four weeks of age and older

Drug	Strength of paediatric tablets	Number of tablets by weight band morning and evening										Strength of adult tablet	Number of tablets by weight band	
		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
LPV/r[a]	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
	Pellets 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6		–	–
	Granules 40 mg/10 mg sachet	2	2	3	3	4	4	5	5	6	6		–	–
	80/20 mg/mL	1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.5 mL	2.5 mL	3 mL	3 mL	–	–	–

[a]LPV/r liquid requires a cold chain during transport and storage. The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. The 200/50 tablet for adults could be used for people weighing 14.0–24.9 kg (one morning and one evening) and for people weighing 25.0–34.9 kg (two morning and one evening). LPV/r pellets should not be used for infants younger than three months. This dosing schedule applies to equivalent solid dosage forms such as LPV/r granules, which can be used from two weeks of age. Since supply is currently constrained, both pellets and granules should be discouraged for children weighing more than 14 kg, who should receive LPV/r 100/25 mg tablets instead. Information on LPV/r formulations for children is available at: https://www.arvprocurementworkinggroup.org/lpv-r-supply.

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Rationale WHO dose selection

Dosing of LPV/r is based on weight bands or body surface area in the United States Food and Drug Administration label and only on body surface area in the European Medicines Agency label. This was converted to dosing based on weight bands to simplify dosing of ARV drugs for children for WHO recommendations. Various studies have confirmed therapeutic LPV exposure while following WHO weight-band dosing recommendations (Bastiaans et al., Pinto et al. and Nikanjam et al.)

Important information

Toxicity for newborns

Cardiac and metabolic toxicity and risk of adrenal insufficiency have been reported in children younger than 14 days or using the LPV/r liquid, and hence the LPV/r liquid formulation is not recommended for children younger than 14 days. These types of toxicity may be caused by high levels of alcohol and propylene glycol in the oral solution formulation (United States Food and Drug Administration warning in 2011). LPV/r pellets should not be used for infants younger than three months.

Once-daily dosing

Once-daily dosing of LPV/r is not recommended in the routine care of children living with HIV. LPV exposure for once-daily LPV/r was comparable to that among adults, but once-daily LPV/r dosing was inferior to the twice-daily regimen for children with suppressed viral loads. This difference was mainly attributed to treatment adherence; a once-daily dosing strategy was less forgiving than the twice-daily standard regimen for children who were nonadherent to drug administration. Once-daily dosing (total daily dose to be given for twice-daily dosing in one dose) can be considered for children with good treatment adherence or when therapeutic drug monitoring is available (PENTA).

Current ongoing trials involving children

Clinical trials at ClinicalTrials.gov

Knowledge gaps

Using solid LPV/r formulations in children younger than four weeks: currently being investigated in the PETITE study.

Research priorities according to PADO4

None

Drug–drug interactions

LPV/r reduces the enzyme activity of several metabolizing liver enzymes, resulting in higher plasma concentrations of various other drugs. Please see https://www.hiv-druginteractions.org for assessment of these drug–drug interactions.

Rifampicin is a potent inducer of liver enzymes and reduces exposure to LPV/r. The LPV/r dose should be adapted when combined with rifampicin-based TB treatment, and the RTV dose should be increased to be equivalent to the dose of LPV (LPV/r ratio 1:1 instead of 4:1). The increased LPV/r dose should be continued until two weeks after rifampicin treatment ends. This approach warrants using separate RTV dosing, which can be challenging in most countries in which HIV among children is still endemic.

Both doubling the standard LPV/r dose and using LPV/r three times daily instead of twice daily resulted in subtherapeutic LPV concentration in many children using concomitant rifampicin-based TB treatment. These approaches are therefore **not recommended** for children younger than five years.

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