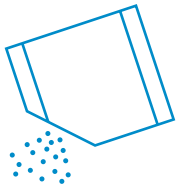
Raltegravir (RAL)

Available Formulations

Single drug formulations	
	
Chewable tablets	Oral granules for suspension
RAL 25 mg RAL 100 mg	RAL 100 mg/sachet (10 mg/mL)

Formulations for adults
RAL 400 mg

RAL oral granules for suspension are recommended for newborns who initiate therapy during the first four weeks of life. The oral granules require reconstitution with 10 mL of water to create a suspension; then a portion is measured with a syringe to accurately provide the appropriate dose. Although preparing oral granules is more complicated, with adequate training and counselling, caregivers can be successfully instructed on the procedures. After four weeks of age, WHO recommends using chewable tablets instead of oral granules for children because they are easier for caregivers to prepare. Chewable tablets can be dispersed in water, apple juice or breast-milk for administration to young children.

Of the three formulations, the oral suspension has the highest oral bioavailability followed by chewable tablets and then film-coated tablets. All formulations should be dosed according to their own specific dosing guidance (United States Food and Drug Administration RAL label).

WHO dose recommendation - age

Oral granules for suspension are approved and recommended from birth, whereas chewable tablets are recommended for children from four weeks of age.

Newborns	Infants	Children	Adolescents

Licensed and recommended from birth

4 Weeks | 2 Years | 12 Years

Birth **18 Years**

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WHO dose recommendation – weight bands

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

Drug	Strength of formulation		2 – <3 kg		3 – <4 kg		4 – <5 kg	
			AM	PM	AM	PM	AM	PM
RAL	10 mg/mL (Oral granules for suspension: 100 mg/sachet)[b]	<1 week	0.4 mL (once daily)[b]		0.5 mL (once daily)[b]		0.7 mL (once daily)[b]	
		>1 week	0.8 ml	0.8 mL	1 mL	1 mL	1.5 ml	1.5 ml

[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] RAL granules for oral suspension should be used for newborns weighing at least 2 kg and be administered once daily during the first week of life (information from Merck). and twice daily afterwards.

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

Drug	Strength of paediatric tablets	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	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
RAL[a]	Chewable tablets 25 mg	1	1	2	2	3	3	4	4	6	6	400 mg	1	1
	Chewable tablets 100 mg	–	–	–	–	–	–	1	1	1.5	1.5			
	10 mg/mL (Oral granules for suspension: 100 mg/sachet)	3 mL	3 mL	5 mL	5 mL	8 mL	8 mL	10 mL	10 mL	–	–	–	–	–

[a] RAL granules are approved from birth. The feasibility and acceptability of such formulations has not been widely investigated, and concerns have been raised regarding administration in resource-limited settings. Due to the administration challenges presented by the granule formulation, PAWG has endorsed the use of the 25-mg chewable tablets as dispersible for infants and children older than four weeks and weighing at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules and considering the limited availability of adequate alternatives for this age group. However, findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administering RAL granules in rural settings is feasible when supported with adequate training and counselling.

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Rationale WHO dose selection

RAL dosing for children four weeks to 18 years old was confirmed in a population pharmacokinetic modelling study using data from the IMPAACT P1066 trial (Rizk et al.). Children from four weeks to two years old received granules for suspension (~6 mg/kg), whereas children between two and 12 years received chewable tablets (~6 mg/kg, maximum 300 mg). Children older than 12 years and younger children weighing more than 25 kg all received 400-mg film-coated tablets. In this study, all dosing strategies met the prerequisite pharmacokinetic targets. The most recent label approved by the United States Food and Drug Administration includes the chewable tablets for children from four weeks of age weighing at least 3 kg. This corresponds with the WHO recommendations for these children, which is based on in vitro data and modelling (Teppler et al.). Although chewable tablets as dispersible tablets have not been studied for children younger than two years at the standard doses, they have been studied for children younger than two years in IMPAACT P1101 for infants and toddlers with TB and HIV coinfection who received rifampicin (a potent inducer of RAL metabolism) as part of their TB treatment. The use of RAL chewable tablets dispersed in water at a dose of RAL 12 mg/kg per dose twice daily safely achieved pharmacokinetic targets when co-administered with rifampicin (Krogstad et al.). Most other weight-band dose recommendations also correspond with the United States Food and Drug Administration label approval, except for children weighing between 3 and 10 kg receiving oral granules for suspension. The dose recommendations by WHO are simplified compared with the label approved by the United States Food and Drug Administration to ensure unified dosing strategies for all ARV drugs for children. The doses for oral granules were aligned with those for chewable tablets.

Newborns and premature infants

IMPAACT P1110 investigated RAL pharmacokinetic among full-term newborns with or without in utero RAL exposure who were exposed to HIV and at risk of acquiring HIV. They found adequate RAL exposure among full-term newborns when using the P1110 dosing regimen, which has been adopted by the WHO guidelines. Moreover, RAL was safe and well tolerated for full-term newborns. In case of in utero RAL exposure 2–24 hours before birth (mother receiving RAL-based ART), the first dose of RAL should be delayed until 24–48 hours after birth to reduce the risk of toxicity (Clarke et al.). Modelling and simulation of washout pharmacokinetic of RAL in premature infants suggest that its clearance is significantly reduced among preterm infants. RAL pharmacokinetics and safety must be studied among preterm infants before RAL can be safely used without real-time pharmacokinetic monitoring in this population (Clarke et al.).

Important information

Once-daily RAL for children

Once-daily dosing of RAL is not recommended for children weighing less than 40 kg. Although population pharmacokinetic modelling studies predict similar RAL exposure for children and adults when using RAL once daily, no clinical data are available to the confirm efficacy and safety of this strategy for children. Also, children might be susceptible to dose-related central nervous system toxicity when exposed to high concentrations of RAL (United States Food and Drug Administration clinical pharmacology review of RAL).

Current ongoing trials involving children

Clinical trials at ClinicalTrials.gov

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Knowledge gaps

Dosing of RAL for children is based on highly variable pharmacokinetic data for children. The IMPAACT P1066 trial enrolled treatment-experienced children for whom other regimens were failing and who had drug-resistance mutations. Only half the children enrolled reached viral load suppression (<50 copies/mL) after 48 weeks of therapy. This could be associated with a risk of developing RAL resistance, since RAL has a lower barrier to resistance than newer integrase inhibitors, such as DTG (Nachman et al. 2015 and Nachman et al. 2014). More pharmacokinetic data are needed for older children to ensure adequate exposure when following WHO dosing recommendations.

Research priorities according to PADO4

Dosing strategies for preterm, low-birth-weight newborns.

Drug–drug interactions

RAL is predominantly metabolized by UGT1A1, and rifampicin induces this enzyme, resulting in a reduction of RAL exposure when used concomitantly. Pharmacokinetic data for children between four weeks and 12 years old suggests that doubling the dose of RAL is sufficient to overcome the interaction with rifampicin (Krogstad et al. and Meyers et al.).

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