ANNEX 1: DOSAGES FOR ARV DRUGS

Dosages of ARV drugs for adults and adolescents

Generic name	Dose
Nucleoside reverse-transcriptase inhibitors (NRTIs)	
Abacavir (ABC)	300 mg twice daily or 600 mg once daily
Emtricitabine (FTC)	200 mg once daily
Lamivudine (3TC)	150 mg twice daily or 300 mg once daily
Zidovudine (AZT)	300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir disoproxil fumarate (TDF)	300 mg once daily[a]
Tenofovir alafenamide (TAF)	10 or 25 mg once daily[b]
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400 mg or 600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily
Protease inhibitors (PIs)	
Atazanavir/ritonavir (ATV/r)	300 mg/100 mg once daily
Darunavir + ritonavir (DRV/r)	800 mg + 100 mg once daily or 600 mg + 100 mg twice daily
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of LPV/r (double-dose LPV 800 mg + ritonavir 200 mg twice daily or super boosted with LPV 400 mg/ + ritonavir 100 mg twice daily plus additional doses of RTV 300 mg twice daily), with close monitoring. In the presence of rifabutin, no dose adjustment required. Rifapentine should not be used.
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	50 mg once daily[a]
Raltegravir (RAL)	400 mg twice daily
	Considerations for individuals receiving TB therapy In the presence of rifampicin, adjusted dose of DTG (50 mg twice daily) and RAL (800 mg twice daily), with close monitoring DTG and RAL dose should remain twice daily for additional two weeks after the last dose of rifampicin. In the presence of rifabutin or rifapentine, no dose adjustment is required.

[a] DTG 50 mg and TLD (tenofovir 300 mg, lamivudine 300 mg, dolutegravir 50 mg, fixed-dose combination) can be used once daily for adolescents living with HIV weighing at least 30 kg. DTG 50-mg film-coated tablets can be used for children and adolescents weighing at least 20 kg. TDF 300 mg can be used for adolescents weighing at least 30 kg.

[b] TAF 25 mg and TAF + FTC + DTG (TAF 25 mg, emtricitabine 200 mg, dolutegravir 50 mg, fixed-dose combination) can be used once daily for adolescents living with HIV weighing at least 25 kg. The TAF dose is reduced to 10 mg when administered in the context of boosted regimens.

Weight-based dosing for ARV drug formulations for infants and children

Prescribing information and weight-based dosing of available ARV formulations for infants and children

This annex contains information on ARV drugs for which there are paediatric indications, formulations or sufficient information and evidence to provide guidance on prescribing and dosing for infants, children and adolescents. WHO has undertaken the work to develop and update simplified guidance on ARV drugs for children through the Paediatric Antiretroviral Working Group.[1]

For simplification and ease of implementation, doses are expressed by weight band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, the expected body surface area of children from low- and middle-income countries in each weight band was carefully considered. The primary source of information for the guidance provided is the manufacturer's package insert. This was supplemented with data from other clinical studies as well as expert paediatric pharmacology consultations. For ARV drug fixed-dose combinations, a dose-modelling tool *(1)* was used to predict the dose delivered for each component drug against the recommended dosing schedule. In some cases, the dose for a component in a particular weight band may be somewhat above or below the target dose recommended by the manufacturer. This is inevitable given the limitations imposed by a fixed-dose combination, but care was taken to minimize the number of children that would receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. Pharmacokinetic efficacy and safety studies have also confirmed the overall safety of this dosing approach. For simplification, ARV drugs no longer considered preferred or alternative options for children have been removed from the dosing guidance.

In the context of increasing implementation of HIV virological testing at birth, and the shift towards treating infants earlier in an effort to reduce early mortality, these guidelines include additional weight-based dosing guidance for term infants less than four weeks old, including those weighing 2–3 kg. However, there is limited experience with initiating treatment for neonates living with HIV younger than two weeks and a paucity of pharmacokinetic data to fully inform accurate dosing for most drugs in neonates, who are undergoing rapid growth and maturation in renal and liver function. Limited pharmacokinetic data for preterm infants are available for AZT, NVP, 3TC and ABC; there is considerable uncertainty of appropriate dosing for NVP, RAL, 3TC and ABC for preterm and low-birth-weight infants. In addition, LPV/r solution should not be given to infants younger than two weeks old or to preterm infants until they have reached 42 weeks of gestational age, because of the risk of adverse effects that may occur in this population. The management of HIV treatment for preterm neonates remains challenging because of the lack of appropriate pharmacokinetic, safety and dosing information as well as suitable formulations.

[1] Paediatric Antiretroviral Working Group members: Elaine Abrams (ICAP at Columbia University, USA); Pauline Amuge (Baylor College of Medicine Children's Foundation, Uganda); Mo Archary (University of Kwazulu-Natal, South Africa); Adrie Bekker (University of Stellenbosch, South Africa); Brookie Best (University of San Diego, USA); David Burger (Radboud University Nijmegen Medical Centre, Netherlands); Esther Casas (MSF, South Africa); Luis Castaneda (Hospital de Ninos Benjamin Bloom, El Salvador); Diana Clarke (Boston Medical Center, USA); Polly Clayden (HIV i-Base, United Kingdom); Angela Colbers (Radboud University Nijmegen Medical Centre, Netherlands); Tim R. Cressey (PHPT-IRD Research Unit, Chang Mai University, Thailand); Roberto Delisa (European Medicines Agency); Paolo Denti (University of Cape Town, South Africa); Diana Gibb (MRC Clinical Trials Unit at University College London, United Kingdom); Rohan Hazra (National Institute of Child Health and Human Development, USA); Maria Kim (Baylor International Pediatric AIDS Initiative, Malawi); Shahin Lockman (Harvard T.H. Chan School of Public Health, USA); Fatima Mir (Agha Khan University, Pakistan); Mark H. Mirochnick (Boston Medical Center, USA); Elizabeth Obimbo (University of Nairobi/Kenyatta National Hospital); Thanyawee Puthanakit (Chulalongkorn University, Thailand); Natella Rakhmanina (Elizabeth Glazer Paediatric AIDS Foundation, USA); Pablo Rojo (Hospital de 12 Octubre Madrid, Spain); Vanessa Rouzier (GHESIKO); Ted Ruel (University of California, San Francisco, USA); Nadia Sam-Agudu (Institute of Human Virology, Nigeria); Mariam Sylla (EVA Network, Mali); and Anna Turkova (MRC Clinical Trials Unit at University College London, United Kingdom).
Observers: Yodit Belew (United States Food and Drug Administration, USA); Helen Bygrave (Access Campaign MSF); Shaffiq Essajee (UNICEF, USA); Stephanie Hackett (United States Centers for Dsiease Control and Prevention, USA); Marc Lallemant (PHPT Foundation, Thailand); Linda Lewis (Clinton Health Access Initiative, USA); Lynne Mofenson (Elizabeth Glaser Paediatric AIDS Foundation, USA); Irene Mukui (Drugs for Neglected Diseases initiative, Geneva, Switzerland); Sandra Nobre (Medicines Patent Pool, Switzerland); Mary Ojoo (UNICEF, Denmark); George Siberry (United States Agency for International Development, USA); Nandita Sugandhi (ICAP at Columbia University, USA); Marissa Vicari (International AIDS Society, Switzerland); Melynda Watkins (Clinton Health Access Initiative, USA); and Hilary Wolf (Office of the United States Global AIDS Coordinator, Department of State, USA).

Dosing for postnatal prophylaxis for infants exposed to HIV is also included here. These guidelines provide simplified dosing to administer enhanced or extended prophylaxis with NVP 50 mg scored dispersible tablets, which provide an alternative to NVP syrup. Finally, alternative ARV drugs were considered to address special situations in which stock-outs of NVP or AZT may affect the ability to effectively provide postnatal prophylaxis (including for enhanced and extended prophylaxis).

Since the WHO ARV drug guidelines were revised in 2018, integrase strand transfer inhibitors (INSTIs) have been included more prominently among the preferred regimens recommended by WHO, and DTG-based regimens have been recommended for all children with approved DTG dosing. At the time of this update in July 2021, the United States Food and Drug Administration and the European Medicines Agency have approved DTG for treatment-naive or treatment-experienced INSTI-naive children who are at least four weeks old and weigh at least 3 kg *(2,3)*. These approvals were granted based on data generated by the IMPAACT P1093 registration trial *(4)* as well as the multicountry Odyssey trial *(5)*, which also investigated the pharmacokinetics of DTG among children co-treated for TB.

- In November 2020, the United States Food and Drug Administration approved the first generic DTG 10 mg scored dispersible tablet. DTG dispersible tablets should be ideally dispersed in water or swallowed whole. Crushing, chewing or mixing with other foods or liquids can be considered as long as the entire tablet is ingested. DTG dispersible tablets are not bioequivalent to DTG film-coated tablets; 30 mg of DTG dispersible tablet is equivalent to 50 mg of DTG film-coated tablets *(6)*.
- For infants who received RAL-containing ART for limited duration (such as no more than three months) and without evidence or suspicion of treatment failure, the Paediatric Antiretroviral Working Group concluded that switching to standard (once-daily) weight-appropriate DTG was reasonable while encouraging the generation of direct evidence to evaluate this approach. Of note, although DTG can be dosed twice daily for treating adults with suspected INSTI resistance, this approach cannot be safely extrapolated to children given differences in pharmacokinetics. Alternative regimens should be considered and, if possible, informed by appropriate HIV drug resistance testing.
- This annex includes guidance on dose adjustment for children receiving a DTG formulation during rifampicin-based TB co-treatment. For all weights and ages with approved DTG dosing, the United States Food and Drug Administration recommended administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug–drug interaction data from adults. Direct pharmacokinetic data for children support the use of DTG twice daily for children weighing more than 25 kg *(7)*. The DTG dose will need to remain twice daily for two weeks after the last dose of rifampicin has been given since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug. The Paediatric Antiretroviral Working Group highlights the need to continue to collect confirmatory evidence in lower weight bands but, as reflected in the dosing table, endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks old and weighing at least 3 kg) and to be continued for two weeks after cessation of rifampicin-based TB treatment.

RAL granules were added in 2018 with the goal of providing a suitable formulation to deliver RAL to neonates. Because of concerns about the complexity of administering the granule formulation, the Paediatric Antiretroviral Working Group endorsed the 25-mg chewable tablets as dispersible tablets for infants and children older than four weeks and weighing at least 3 kg. This decision was largely based on in vitro data on solubility and bioequivalence between RAL chewable tablets and granules *(8)* and considering the limited availability of alternative formulations for this age group. In this update of the dosing guidance, we also recommend appropriate dose adjustment for of RAL during rifampicin-based TB treatment, to be continued for two weeks after completion of rifampicin-based TB treatment.

In this 2021 update, we confirm dosing information for children for tenofovir alafenamide (TAF), fixed-dose combinations containing TAF were included for children weighing 25 kg or more with a 25-mg dose when used with unboosted regimens. This aligns with dosing approved by United States Food and Drug Administration *(9)*. Studies to investigate dosing for children weighing less than 25 kg are ongoing, and more information will be made available as soon as approval is extended.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as additional data and new formulations become available. Updated information on ARV drug dosing in children and rationale for dose simplification is available on the newly developed paediatric ARV dosing dashboard *(10)*.

ARV drugs and formulations are available from several manufacturers, and the available dosage strengths of tablets, capsules and liquid formulations may vary from the information provided here. Several optimal dosage forms for children are currently being developed but have not yet received regulatory approval at the time these updated guidelines were published. National programme managers should ensure that products planned for use have received stringent regulatory approval and are of appropriate quality and stability. The current list of WHO prequalified drugs is available *(11)*. The United States Food and Drug Administration has a current list of approved and tentatively approved ARV drugs *(12)*. The policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance is available *(13)*.

General principles

WHO followed the following principles in developing the simplified tables.

- Using an age-appropriate fixed-dose combination is preferred for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided if possible (except for neonatal treatment and prevention). Dispersible tablets (or granules) are the preferred solid oral dosage forms, since these formulations can be made into liquid at the point of use.
- If suitable dispersible fixed-dose combinations are not available and oral liquids must be used, children should be switched to a solid oral dosage form as soon as possible.
- Although dosing newborns generally requires using oral liquid formulations for administrating precise dosing, switching to solid oral dosage form as soon as possible is recommended.
- If children have to use adult formulations, care must be taken to avoid underdosing and overdosing. Using scored tablets is preferred to ensure accurate dosing, especially if adult dosage forms are used. Splitting unscored tablets should be avoided since the uniform distribution of active drug product cannot be assured in tablet fragments.
- Some tablets such as LPV/r or ATV/r heat-stable tablets are made in a special embedded matrix formulation (a proprietary melt extrusion technology that stabilizes drug molecules that are normally heat labile) and should not be cut, split, dissolved, chewed or crushed, since bioavailability is significantly reduced when they are not swallowed whole.
- Among children for whom an LPV/r-based regimen remains the appropriate treatment choice, LPV/r is available in a 40 mg/10 mg pellet or granule formulation for infants and young children. However, children weighing 10 kg or more should be transitioned to LPV/r heat-stable tablets as soon as they are able to swallow tablets whole to ease administration and improve palatability and to reduce pill burden.
- After the first four weeks of life, at each clinic visit, infants and children should be weighed and doses should be adjusted based on observed growth and change in body weight.
- Country programmes should consider the national regulatory status and local availability status of specific dosage forms when developing national recommendations for treating children.
- Research is ongoing for several ARV medications to establish dosing guidance for neonates, infants and young children. The age indications for each drug mentioned in the drug pages are based on current evidence and will be updated as new recommendations become available.

Table A1.1 Simplified dosing of child-friendly fixed-dose solid formulations for twice-daily dosing for infants and children four weeks and older[a]

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
AZT/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg[b]	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
	Tablet (dispersible) 120 mg/60 mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600 mg/300 mg	0.5	0.5

[a] For infants younger than four weeks old, see Table A1.4 for more accurate dosing, which is reduced because of the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, the immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] This formulation will be phased out of use over time, and programmes should transition to using the 120 mg/60 mg dispersible scored tablets.

Table A1.2 Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older[a]

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
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	-	2
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	2	3	4	5	6	600 mg/300 mg	1
	Tablet (dispersible) 120 mg/60 mg	1	1.5	2	2.5	3		
TAF/FTC[c]	Tablet 25 mg/ 200 mg	–	–	–	–	–	25 mg/200 mg	1
ATV[d]	Capsules 100 mg	–	–	2	2	2	300 mg	1[e]
	Capsules 200 mg	–	–	1	1	1		
DRV[f]	Tablet 600 mg	–	–	–	1	1	600 mg	1
	Tablet 150 mg	–	–	–	4	4		
RTV[g]	Tablet 25 mg	–	–	–	4	4	100 mg	1
	Tablet 50 mg	–	–	–	2	2		

Table A1.2 Simplified dosing of child-friendly solid formulations for once-daily dosing for infants and children four weeks and older[a] (continued)

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
DTG[h]	Film-coated tablet 50 mg	–	–	–	–	1	50 mg	1
	Dispersible tablet 5 mg	1	3	4	5	6		
	Dispersible scored tablet 10 mg	0.5	1.5	2	2.5	3		

[a] See Table A1.4 for dosing recommendations for infants younger than four weeks old. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the appropriate dosing of ARV drugs for preterm and low-birth-weight infants.

[b] EFV is not recommended for children younger than three years and weighing less than 10 kg.

[c] At the time of this update, the United States Food and Drug Administration approved TAF film-coated tablets for children older than six years for use in unboosted regimens such as with DTG. The United States Food and Drug Administration tentatively approved a fixed-dose combination containing TAF/FTC/DTG (TAF 25 mg, FTC 200 mg, DTG 50 mg) that can be used once daily for children and adolescents living with HIV weighing at least 25 kg.

[d] 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. Infants and children weighing 5–<15 kg should be administered 200 mg of ATV powder (four packets, 50 mg per packet) with 80 mg of RTV oral solution (1 mL) *(14)*.

[e] ATV 300 mg with RTV 100 mg for 25–<30 kg is recommended based on the findings from the PRINCE-2 study *(15)*.

[f] 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 adult studies 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.

[g] 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 (see Table A1.5).

[h] At the time of this update, the United States Food and Drug Administration approved 5 mg dispersible tablets and tentatively approved 10-mg scored dispersible tablets for treatment-naive or treatment-experienced INSTI-naive children at least four weeks old and weighing at least 3 kg, based on data from the IMPAACT 1093 trial *(4)* and ODYSSEY *(16)*. The United States Food and Drug Administration and European Medicines Agency approved simplified dosing of the DTG 50 mg film-coated tablets for all children weighing ≥20 kg. DTG dispersible tablets and DTG film-coated tablets are not bioequivalent; 30 mg of DTG dispersible tablet corresponds to 50 mg of DTG film-coated tablets. DTG 50 mg film-coated tablets are preferred for children who have reached 20 kg (unless they cannot swallow tablets). Safety monitoring remains important given the current limited experience with this dosing. For adolescents living with HIV weighing more than 30 kg, a fixed-dose formulation of TDF 300 mg, 3TC 300 mg and DTG 50 mg (TLD) can be used and is preferred.

Table A1.3 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children four weeks of age and older[a]

Drug	Strength of paediatric tablets	Number of tablets or mL by weight-band morning (AM) and evening (PM)										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
Solid formulations														
AZT	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
ABC	Tablet (dispersible) 60 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg	1	1
LPV/r[b]	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		–	–
DRV[c]	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	400 mg	1	1
RTV[d]	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1			
RAL[e]	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			

Table A1.3 Simplified dosing of child-friendly solid and oral liquid formulations for twice-daily dosing for infants and children four weeks of age and older[a] (continued)

Drug	Strength of oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										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
Liquid formulations														
AZT	10 mg/mL	6 mL	6 mL	9 mL	9 mL	12 mL	12 mL	–	–	–	–	–	–	–
ABC[f]	20 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
3TC	10 mg/mL	3 mL	3 mL	4 mL	4 mL	6 mL	6 mL	–	–	–	–	–	–	–
LPV/r[b]	80 mg/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	–	–	–
DRV[c]	100 mg/mL	–	–	–	–	2.5 mL	2.5 mL	3.5 mL	3.5 mL	–	–	–	–	–
RTV[d]	80 mg/mL	–	–	–	–	0.5 mL	0.5 mL	0.6 mL	0.6 mL	–	–	–	–	–
RAL[e]	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] See Table A1.4 for dosing recommendations for infants younger than four weeks. Doses for this age group are reduced to account for the decreased ability to excrete and metabolize medications. For infants who are at least four weeks old but weigh less than 3 kg, immaturity of renal and hepatic pathways of elimination are less of a concern, but uncertainty still exists on the dosing of ARV drugs for preterm and low-birth-weight infants.

[b] Although ABC dose represents a significant increase compared with the neonatal dose, this dose was designed to match the recommended dose for the solid formulation above.

[c] 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. Adult 200/50 mg tablets could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children weighing 25–<35 kg (two tablets in the morning and one in the evening). The LPV/r pellet formulation should not be used for infants younger than three months. More details on the administration of LPV/r pellets are available *(17)*. This dosing schedule applies to equivalent solid dosage forms such as LPV/r granules, which can be used from two weeks of age. Since the 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 *(18)*.

[d] DRV to be used 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.

[e] RTV should only be used at this dose as a boosting agent in combination with ATV or DRV.

[f] RAL granules are approved from birth. The feasibility and acceptability of such formulations have not been widely investigated, and concerns have been raised about administration in resource-limited settings. Because of the administration challenges presented by the granule formulation, the Paediatric Antiretroviral Working Group 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 *(19)* and on considering the limited availability of adequate alternatives for this age group. However, the findings from a feasibility and acceptability assessment conducted in South Africa demonstrate that administering RAL granules in rural settings is feasible as long as it is supported by adequate training and counselling.

Table A1.4 Drug dosing of liquid formulations for infants younger than four weeks of age[a]

Drug	Strength of oral solution		2–<3 kg		3–<4 kg		4–<5 kg	
			AM	PM	AM	PM	AM	PM
AZT	10 mg/mL		1 mL	1 mL	1.5 mL	1.5 mL	2 mL	2 mL
ABC	20 mg/mL		0.4 mL	0.4 mL	0.5 mL	0.5 mL	0.6 mL	0.6 mL
NVP	10 mg/mL		1.5 mL	1.5 mL	2 mL	2 mL	3 mL	3 mL
3TC	10 mg/mL		0.5 mL	0.5 mL	0.8 mL	0.8 mL	1 mL	1 mL
LPV/r[b]	80 mg/20 mg/mL		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
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)[c]	<1 week	0.4 mL (once daily)[c]		0.5 mL (once daily)[c]		0.7 mL (once daily)[c]	
		>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 (dose change after week 1), 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). Pharmacokinetic data for preterm infants are available only for AZT; there are limited data and considerable uncertainty of appropriate dosing for NVP, RAL and 3TC for preterm and low-birth-weight infants. In addition, LPV/r solution should not be given to preterm infants until they have reached 42 weeks gestational age, because of the risk of adverse effects. This guidance will be updated when more evidence on solid LPV/r formulations is available from ongoing trials.

[b] Do not use LPV/r solution for infants aged younger than 2 weeks of age. LPV/r pellets should not be used for infants younger than three months. More details on administering LPV/r pellets is available *(17)*. 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 use of LPV/r granules from two weeks) and considering the substantial uncertainty, especially for neonates weighing 2–3 kg. If no other formulation exists, one sachet twice a day could be considered for neonates older than two weeks who weigh 2–3 kg to minimize the risk of potential toxicity with overdosing.

[c] RAL granules for oral suspension should be used for newborns weighing at least 2 kg and be administered once a day during the first week of life and twice a day afterwards *(20)*.

Table A1.5 ARV drug dose adjustment for children receiving rifampicin-containing TB treatment[a]

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										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
DTG[b]	5 mg dispersible tablets	1	1	3	3	4	4	5	5	6	6	50 mg film-coated tablets	1	1
	10 mg scored dispersible tablets	0.5	0.5	1.5	1.5	2	2	2.5	2.5	3	3			
	50 mg film-coated tablets	–	–	–	–	–	–	–	–	1	1			
RAL	10 mg/mL (Oral granules for suspension: 100 mg/ sachet)	6 mL	6 mL	10 mL	10 mL	16 mL	16 mL	20 mL	20 mL	–	–	400 mg	2	2
	Chewable tablets 25 mg	2	2	4	4	6	6	8	8	–	–			
	Chewable tablets 100 mg	–	–	–	–	–	–	2	2	3	3			
LPV/r[c] (with additional RTV)	Oral solution[d] 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	–	–	–
	Pellets[e] 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	–	–	–
	Tablet 100 mg/25 mg	–	–	–	–	2	1	2	2	2	2	100 mg/25 mg	3	3

Table A1.5 ARV drug dose adjustment for children receiving rifampicin-containing TB treatment[a] (continued)

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)										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
RTV[f]	Tablet 100 mg	–	–	–	–	1	1	1	2	1	2	100 mg	2	2
	Tablet 50 mg	–	–	–	–	2	2	3	3	3	3			
	Tablet 25 mg	–	–	–	–	4	4	6	6	6	6			
	Oral solution 80 mg/mL	0.8 mL	0.8 mL	1.2 mL	1.2 mL	1.5 mL	1.5 mL	2 mL	2 mL	2.3 mL	2.3 mL	–	–	–
	Powder 100 mg/packet	–	–	1	1	1	1	1	2	1	2	–	–	–

[a] The adapted dose of the ARV drugs needs to continue until two weeks after rifampicin treatment ends, since the enzyme-inducing effect of rifampicin slowly fades away after discontinuing the drug.

[b] The United States Food and Drug Administration recommended administering the weight-based DTG dose twice daily if taken with rifampicin based on its customary approach of extrapolating drug–drug interaction data from adults. Direct pharmacokinetic data in children support the use of DTG twice daily for children weighing more than 25 kg *(21)*. The Paediatric Antiretroviral Working Group highlights the need to continue to collect confirmatory evidence for lower weight bands but endorses immediate uptake of twice-daily dosing of DTG when taken with rifampicin for all children (at least four weeks of age and weighing at least 3 kg).

[c] The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. An adult 200/50 mg tablet could be used for children weighing 14–<25 kg (one tablet in the morning and one in the evening) and for children 25–<35 kg (two tablets in the morning and one in the evening).

[d] LPV/r liquid requires a cold chain during transport and storage.

[e] The LPV/r pellet formulation should not be used for infants younger than three months. More details on administering LPV/r pellets is available *(17)*. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPV/r granules, which the United States Food and Drug Administration has approved for from two weeks of life.

[f] Suggested RTV dose for super-boosting to achieve the same dose as LPV in mg, in a ratio equal or approaching to 1:1. This dosing approach is supported by a study that explored this approach for young children receiving LPV/r *(22)*. RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super-boosting.

Table A1.6 Simplified dosing of isoniazid and co-trimoxazole prophylaxis for infants and children at least four weeks old

Drug	Strength of paediatric tablet or oral liquid	Number of tablets or mL by weight band once daily					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
Isoniazid	100 mg	0.5	1	1.5	2	2.5	300 mg	1
Co-trimoxazole (sulfamethoxazole and trimethoprim)	Suspension 200 mg/ 40 per 5 mL	2.5 mL	5 mL	5 mL	10 mL	10 mL	–	–
	Tablets (dispersible) 100 mg/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400 mg/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800 mg/160 mg	–	–	–	0.5	0.5	800 mg/160 mg	1
Isoniazid/ (sulfamethoxazole and trimethoprim)/ B6	Tablets (scored) 300 mg/(800 mg/ 160 mg) /25 mg	–	–	–	0.5	0.5	300 mg/ (800 mg/ 160 mg)/ 25 mg	1

Table A1.7 Simplified age-based ARV drug dosing for administering enhanced and prolonged postnatal prophylaxis[a]

Drug	Strength	0–6 weeks		6–12 weeks		12 weeks to 6 months		9–24 months	
		AM	PM	AM	PM	AM	PM	AM	PM
NVP[b]	50 mg scored dispersible tablets	0.5	_	0.5	_	0.5	_	1	_
NVP	10 mg/mL	1.5 mL	_	2 mL	_	3 mL	_	4 mL	_
AZT	10 mg/mL	1.5 mL	1.5 mL	6 mL	6 mL	_	_	_	_

[a] In special circumstances with stock-out of NVP and/or AZT, alternative ARV drugs could be used: RAL with treatment dosing, 3TC or LPV/r based on evidence gathered through the PROMISE trial: 3TC was administered as follows: 7.5 mg once daily for neonates weighing 2–<4 kg, 25 mg once daily for infants weighing 4–<8 kg and 50 mg once daily for children weighing more than 8 kg; LPV/r was administered twice daily after the first week of life according to the following dosing scheme: 40/10 mg once daily for neonates weighing 2–<4 kg and 80/20 mg once daily for infants weighing more than 4 kg *(23)*.

[b] This simplified dosing was developed with a WHO generic tool based on previously established NVP prophylactic targets.

Optimal ARV drug formulary for children

In recent years, a number of improved ARV drug formulations have become available, such as dispersible, scored fixed-dose combination tablets that have replaced traditional liquid formulations. These products have greatly simplified the delivery of HIV treatment for children in low-income settings; however, the proliferation of options has resulted in a multiplicity of formulations across regimens and weight bands. Generic manufacturers use economies of scale to maintain affordable pricing, but fragmentation of demand across too many duplicative products creates instability in the reliable supply of ARV dosage forms for children and complicates procurement and supply chain management.

Partners of the ARV Procurement Working Group *(24)* and of the Global Accelerator for Paediatric Formulations Network *(16)* provide formulary guidance to programmes on selecting optimal ARV drugs for children, which have been defined using a robust set of criteria. The formulary was first developed in 2011 but is routinely revised to correspond to current WHO guidelines and available products. The current Optimal Formulary was revised in December 2020 and released in April 2021 *(25)*. It now includes seven products that deliver recommended and appropriate first and second-line regimens across all weight bands for children. Programmes are encouraged to procure dosage forms for children that are included in the Optimal ARV Formulary for Children. During periods of transition or in special circumstances (neonatal treatment, TB co-treatment and third-line ART), dosage forms included on the ARV Limited-use Formulary are sufficient to provide appropriate dosing across weight bands for children *(26)*.

The need for new formulations

As part of the Global Accelerator for Paediatric Formulations Network, the work of the Paediatric Antiretroviral Working Group and the Paediatric ARV Drug Optimization *(27,28)* groups continue to highlight the urgent need for better age-appropriate formulations for infants and children living with HIV. An additional solid fixed-dose combination formulation is under the final stage of approval (ABC/3TC/LPV/r granules). In addition, the availability of co-formulated DRV/r in a heat-stable fixed-dose combination is critical to facilitate treatment sequencing and uptake of future second- and third-line regimens for children. Several formulations containing approved ARV drugs for children have been formally given priority and are listed in Table A1.6. Finally, additional formulations containing newer drugs for which there is currently no indication for children were considered, and the central future role of DTG and TAF in optimizing dose, sequencing and harmonization across age groups was highlighted.

In moving towards promoting drug optimization for children and adolescents, WHO will continue to work to simplify prescribing, dispensing and dosing guidance and work with the pharmaceutical industry (originator and generic) and other partners to develop more practical recommendations on the range of formulations required to safely accelerate the scaling up of ART for children.

Box A1.1 Anticipated simplified dosing for formulations under development

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or mL by weight-band morning (AM) and evening (PM)											
		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
ABC/3TC/LPV/r	30 mg/15 mg/40 mg/10 mg granules	2	2	3	3	4	4	5	5	6	6	–	
DRV/r	120 mg/20 mg tablet	–	–	–	–	2	2	3	3	3	3	4	4
ABC/3TC/DTG[a]	Dispersible 60 mg/30 mg/5 mg tablet	–		3		4		5		6		–	

[a] This dosage form is the one identified by the PADO4 group *(28)* as the most likely to deliver appropriate dose based on the best available information.

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