ANNEX 3. DOSAGES OF ARV DRUGS

Dosages of ARV drugs for adults and adolescents

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)	250–300 mg twice daily
Nucleotide reverse-transcriptase inhibitors (NtRTIs)	
Tenofovir (TDF)	300 mg once daily
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	
Efavirenz (EFV)	400–600 mg once daily
Etravirine (ETV)	200 mg twice daily
Nevirapine (NVP)	200 mg once daily for 14 days followed by 200 mg twice daily (Please note that NVP based regimens are no longer recommended and should only be used in special circumstances).
Proteases 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 (LPV 800 mg + ritonavir 200 mg twice daily or LPV 400 mg + ritonavir 400 mg twice daily), with close monitoring. In the presence of rifabutin, no dose adjustment required.
Integrase strand transfer inhibitors InSTI	
Dolutegravir (DTG)	50 mg once daily*
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. In the presence of rifabutin, no dose adjustment required.

* TLD (Tenofovir 300 mg, Lamivudine 300 mg, Dolutegravir 50 mg fixed dose combination) can be used once daily in adolescents living with HIV weighting at least 30 kg.

WEIGHT-BASED DOSING FOR ARV 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 in infants, children and adolescents less than 18 years of age. The work to develop and update simplified guidance on ARV drugs for use in children has been undertaken by WHO through the Paediatric Antiretroviral Working Group.[1]

For simplification and ease of implementation, doses are expressed per weight-band rather than per kilogram or per square metre of body surface area. When this simplified weight-band dosing was developed, careful consideration was given to the expected body surface area of children from low- and middle-income countries in each weight band. 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 fixed-dose combinations, a dose-modelling tool (http://www.who.int/hiv/paediatric/generictool/en/index.html) 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 ensure that in no case would a child receive more than 25% above the maximum target dose or more than 5% below the minimum target dose. PK 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 virological testing at birth, and the shift towards treating infants earlier in an effort to reduce early mortality, these guidelines include weight-based dosing for term infants aged <4 weeks, including those weighing less than 3 kg. However, there is limited experience with initiating treatment in HIV-infected newborns aged <2 weeks, and a paucity of PK data to fully inform accurate dosing for most drugs in neonates, who are undergoing rapid growth and maturation in renal and liver function. PK data in preterm infants are available only for AZT; there is considerable uncertainty of appropriate dosing for NVP, RAL and 3TC in 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 that may occur in this population. The management of HIV treatment in preterm neonates extremely is challenging because of the lack of appropriate pharmacokinetic, safety, and dosing information as well as suitable formulations. Dosing for postnatal prophylaxis for HIV-exposed infants is not provided here but can be found at http://www.who.int/hiv/pub/arv/annexes-5Sep2016.pdf?ua=1.

In this 2018 ARV guidelines revision, integrase inhibitors have been included more prominently among the preferred regimens recommended by WHO. At the time of this guidelines update, DTG was only approved for children above 6 years and 15 kg in Europe and above 30 kg in the United States. The registration trial is anticipated to generate data for dosing DTG in children down to age 4 weeks in early 2019, with potential regulatory approval in late 2019. This dosing

annex includes approved DTG dosing as well as simplified dosing based on pk and safety data from an ongoing multicounty study, which is also investigating the pharmacokinetics of DTG in TB co-treated children. In some weight bands (14-24.9 kg) the simplified dosing is based on preliminary findings, which are expected to be confirmed in early 2019. As the introduction of paediatric DTG will take time, programmes are encouraged to begin planning for the use of DTG in paediatric populations while the simplified dosing is being confirmed.

RAL granules were also added with the goal of providing a suitable formulation to deliver RAL to neonates. Due to concerns about the complexity of administration of the granule formulation, the 25 mg chewable tablets as dispersible tablets have been endorsed by the PAWG for infants and children older than 4 weeks of age and weighting at least 3 kg. This decision was largely based on in vitro data on solubility and bioequivalence between RAL tablets and granules as well as considering the limited availability of adequate alternative formulations for this age group.

This dosing annex and the simplified dosing schedule will be regularly reviewed and updated as additional data and new formulations become available.

Antiretroviral drugs and formulations are available from several manufacturers, and available dosage strengths of tablets, capsules and liquid formulations may vary from the information provided here. Several optimal paediatric dosage forms are currently in development but have not yet received regulatory approval at the time of writing these updated guidelines. National programme managers should ensure that products planned for use have received stringent regulatory approval and of appropriate quality and stability. For guidance on the quality assurance of medicines, see the WHO medicines web site (http://www.who.int/medicines/areas/quality_safety/quality_assurance/about/en/index.html) and the Access to HIV/AIDS drugs and diagnostics of acceptable quality, which is available and updated at http://www.who.int/hiv/amds/selection/en/index.html. The current list of WHO prequalified drugs is available at http://apps.who.int/prequal. For the current list of ARV drugs approved and tentatively approved by the United States Food and Drug Administration, see https://www.fda.gov/InternationalPrograms/PEPFAR/ucm119231.htm. For the policy of the Global Fund to Fight AIDS, Tuberculosis and Malaria on procurement and quality assurance, see https://www.theglobalfund.org/en/sourcing-management/quality-assurance/medicines/.

General principles

The principles followed in developing the WHO simplified tables include the following:

- Use of 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 where possible. Dispersible tablets (or granules for oral solution) are the preferred solid oral dosage forms, since each tablet can be made into liquid at the point of use.
- If suitable dispersible FDC's are not available and oral liquids must be used, it is recommended that children be switched to a solid oral dosage form as soon as possible
- While dosing neonates generally necessitates use of oral liquid formulations for administrating precise dosing, switching to solid oral dosage form as soon as possible is recommended
- Where children have to use adult formulations, care must be taken to avoid under-dosing and overdosing. Use of scored tablets are preferred to ensure accurate dosing is provided, particularly if adult dosage forms are used. Splitting of unscored tablets should be avoided as uniform distribution of active drug product cannot be assured in tablet fragments.
- Some tablets such as LPV/r or ATV 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 seriously reduced when not swallowed whole.
- At each clinic visit, children should be weighed and doses should be adjusted based on observed growth and change in body weight.
- Country programs should consider the national regulatory status and local availability status of specific dosage forms when developing national paediatric treatment recommendations.
- Research is ongoing for several antiretroviral medications to establish dosing guidance in 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 1 Simplified dosing of child-friendly *fixed-dose solid formulations for twice-daily* dosing in infants and children 4 weeks of age 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	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 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
AZT/3TC/NVP[b]	Tablet (dispersible) 60 mg/30 mg/50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300 mg/150 mg/200 mg	1	1
ABC/3TC	Tablet (dispersible) 60 mg/30 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600 mg/300 mg	0.5	0.5
ABC/3TC	Tablet (dispersible) 120/60 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 4 weeks of age refer to table 4 for more accurate dosing which is reduced due to the decreased ability to excrete and metabolize medications. For infants who are at least 4 weeks of age but 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 ARVs in preterm and low birth weight infants.

[b] Please note that this regimen and formulation is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

Table 2 Simplified dosing of child-friendly *solid formulations for once-daily dosing* in infants and children 4 weeks of age 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
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
EFV[b]	Tablet (scored) 200 mg	–	–	1	1.5	1.5	–	2
ABC/3TC	Tablet (dispersible) 60/30 mg	2	3	4	5	6	600 mg/300 mg	1
ABC/3TC	Tablet (dispersible) 120/60 mg	1	1.5	2	2.5	3	600 mg/300 mg	1
ATV[c]	Capsules 100 mg	–	–	2	2	2	300 mg	1[d]
	Capsules 200 mg	–	–	1	1	1		
DRV[e]	Tablet 600 mg	–	–	–	1	1	600 mg	1
	Tablet 150 mg	–	–	–	4	4		
RTV[f]	Tablet 25 mg	–	–	–	4	4	100 mg	1
	Tablet 50 mg	–	–	–	2	2		
DTG[g]	Tablet 50 mg	–	–	–	–	TBC[g]	50 mg	1

[a] See table 4 for dosing recommendations for infants younger than 4 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 4 weeks of age but 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 ARVs in preterm and low birth weight infants.

[b] EFV is not recommended for children younger than 3 years and weighing less than 10 kg.

[c] ATV is only approved for use in children 3 months and older. ATV single strength capsules should be administered with RTV 100 mg for all weight bands. ATV powder formulation has limited availability in LMIC, but enables administration of ATV to infants and children as young as 3 months. Infants and children 5-15 kg should be administered 200 mg of ATV powder (4 packets, 50 mg/ packet) with 80 mg of RTV oral solution (1 ml). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021567s042,206352s007lbl.pdf

[d] A 300 mg dose for 25-29.9 kg is recommended on the basis of findings from the PRINCE-2 study[vii].

[e] DRV in combination with RTV should be used, in children older than 3 years, once daily when this is used without previous exposure to PI. While approved dosing for 30-35 kg is 675 mg, preliminary data from adult studies suggest that even lower DRV doses may be effective, therefore use of 600 mg dose was extended to the entire 25-35 kg weight band.

[f] RTV should only be use as a boosting agent in combination with ATV or DRV.

[g] At the time of this update, DTG film coated tables were approved for children above 6 years by the FDA (35mg for weight 30 to < 40 kg, 50 mg for weight ≥ 40 kg)[iii] and by the EMA (20 mg 15 to < 20, 25 mg for 20 to < 30, and 35 for 30 to < 40, 50 mg for weight ≥ 40 kg)[ii] based on data from the IMPAACT 1093 trial[iv]. Simplified weight band dosing is being investigated in the Odyssey trial which supports the use of 50 mg dose for all children ≥ 25 kg, as proposed here. An anticipated dose of 50 mg in children 20-25kg is based on predicted exposure derived from PK results on DTG 25mg (FCT) in this weight band, more data to confirm this and further inform optimal dosing in the 14 to 25 kg weight bands is expected at the beginning of 2019 and will be included in an updated version of this annex. For adolescents living with HIV weighting more than 30 Kg a fixed dose formulation of TDF 300mg/3TC 300mg/DTG 50mg (TLD) can be used and is preferred.

Table 3 Simplified dosing of child-friendly *solid and oral liquid formulations for twice-daily* dosing in infants and children 4 weeks of age and older[a]

Drug	Strength of paedaitric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening(PM)										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 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
NVP[b]	Tablet (dispersible) 50 mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200 mg	1	1
LPV/r[c]	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	–	–	–
DRV[d]	Tablet 75 mg	–	–	–	–	–	–	5	5	5	5	400 mg	1	1
RTV[e]	Tablet 25 mg	–	–	–	–	–	–	2	2	2	2	100 mg	1	1
	Tablet 50 mg	–	–	–	–	–	–	1	1	1	1			
RAL[f]	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	400 mg	1	1

Drug	Strength of paedaitric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening(PM)										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 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	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	–	–	–	–	–	–	–
NVP[b]	10 mg/ml	5 ml	5 ml	8 ml	8 ml	10 ml	10 ml	–	–	–	–	–	–	–
LPV/r[c]	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	–	–	–
DRV[d]	100 mg/ml	–	–	–	–	2.5 ml	2.5 ml	3.5 ml	3.5 ml	–	–	–	–	–
RTV	80 mg/ml	–	–	–	–	0.5 ml	0.5 ml	0.6 ml	0.6 ml	–	–	–	–	–
RAL[f]	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 4 for dosing recommendations for infants younger than 4 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 4 weeks of age but 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 ARVs in preterm and low birth weight infants.

[b] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels. However, secondary analysis from the (CHAPAS)-1 trial recently suggested that younger children have a lower risk of toxicity, and consideration can be given to starting with a full dose[ix]. More definitive evidence is expected from an ongoing trial. Please note that this regimen and formulation is no longer recommended and should only be used in special circumstances where other age appropriate formulations are not available.

[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 tablet could be used for patients 14-24.9kg (1 tab qam and 1 tab qpm) and for patients 25-34.9 kg (2 tab qam and 1 tab qpm). LPVr pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPVr pellets can be found at http://apps.who.int/iris/bitstream/handle/10665/193543/FactsheetIATT_WHO_UNICEF_lopinavir_eng.pdf?sequence=1. This dosing schedule applies to equivalent solid dosage forms that may become available in the near future (ie granules).

[d] DRV, to be used in children older than 3 years, must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if less than 15 kg and with RTV 25 or 50 mg solid formulation in children 15 to 30 kg.

[e] RTV should only be use as a boosting agent in combination with ATV or DRV.

[f] RAL granules are approved from birth. 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 the use of the 25 mg chewable tablets as dispersible has been endorsed by the PAWG for infants and children older than 4 weeks and weighting at least 3 kg. This was largely based on in vitro data on solubility and bioequivalence between tablets and granules[vi] as well as 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 administration of RAL granules in rural settings is feasible as long as supported with adequate training and counselling.

Table 4 Drug dosing of liquid formulations in *infants less than 4 weeks* of age[a]

Drug	Strength of oral liquid		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
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]	80/20 mg/mL		0.6 mL	0.6 mL	0.8 mL	0.8 mL	1 mL	1 mL
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] PK data in preterm infants are available only for AZT; there is considerable uncertainty of appropriate dosing for NVP, RAL and 3TC in 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 that may occur in this population. This guidance will be updated when more evidence is available from ongoing trials.

[b] Do not use LPV/r solution in infants aged <2 weeks of age. LPVr pellets should not be used in infants younger than 3 months. More details on the administration of LPVr pellets can be found at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf

[c] RAL granules for oral suspension should use in neonates of at least 2 kg and be administered in once a day during the first week of life (http://www.merck.com/product/usa/pi_circulars/i/isentress/isentress_pi.pdf)

Table 5 Dosing for *RTV super-boosting of LPV/r* for children receiving rifampicin-containing TB treatment[a]

Drug	Strength of paediatric tablets or oral liquid	Number of tablets or MLS by weight-band morning (AM) and evening (PM)										Strength of adult tablet	Number of tablets by weight band	
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg			25–34.9 kg	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
For children able to swallow tablets														
LPV/r[b]	Tablet 100/25 mg	–	–	–	–	2	1	2	2	2	2	–	3	3
RTV	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			
For children unable to swallow tablets														
LPV/r	Oral solution[c] 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[d] 40 mg/10 mg	2	2	3	3	4	4	5	5	6	6	-	-	-
RTV[e]	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	-	-	-
RTV	Powder 100 mg/packet	-	-	1	1	1	1	1	2	1	2	-	-	-

[a] 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 which explored this approach in young children receiving LPVr[x].

[b] The LPV/r heat-stable tablet formulation must be swallowed whole and should not be split, chewed, dissolved or crushed. Adult 200/50 tablet could be used for patients 14-24.9kg (1 tab qam and 1 tab qpm) and for patients 25-34.9kg (2 tab qam and 1 tab qpm).

[c] RTV liquid requires a cold chain during transport and storage.

[d] LPVr pellets formulation should not be used in infants younger than 3 months. More details on the administration of LPVr pellets can be found at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf. The dosing schedule provided applies to equivalent solid dosage forms that may become available such as LPVr granules.

[e] RTV oral solution dosing is based on the dosing tested in the trial that supports the use of super boosting.

Table 6 Simplified dosing of isoniazid (INH) and co-trimoxazole (CTX) prophylaxis for infants and children who are at least 4 weeks of age

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
		3–5.9 kg	6–9.9 kg	10–13.9 kg	14–19.9 kg	20–24.9 kg		25–34.9 kg
INH	100 mg	0.5	1	1.5	2	2.5	300 mg	1
CTX	Suspension 200/40 per 5 ml	2.5 ml	5 ml	5 ml	10 ml	10 ml	–	–
	Tablets (dispersible) 100/20 mg	1	2	2	4	4	–	–
	Tablets (scored) 400/80 mg	–	0.5	0.5	1	1	400 mg/80 mg	2
	Tablets (scored) 800/160 mg	–	–	–	0.5	0.5	800 mg/160 mg	1
INH/CTX/B6[a]	Tablets (scored) 300 mg/960 mg/25 mg	–	–	–	0.5	0.5	960 mg/300 mg/25 mg	1

[a] A scored tablet (480mg/150mg/12.5 mg) is under development.

Optimal Paediatric ARV Formulary

In recent years, a number of improved ARV formulations have become available, such as dispersible, scored FDC tablets in place of the traditional liquid formulations. These products have greatly simplified the delivery of paediatric HIV care in low-income settings; however, the proliferation of options, has resulted in a multiplicity of formulations across regimens and weight- bands. Economies of scale are used by generic manufacturers to maintain affordable pricing but fragmentation of demand across too many duplicative products creates instability in the reliable supply of paediatric ARV dosage forms and complicates procurement and supply chain management.

Partners of the ARV procurement working group (APWG) and of the Global Accelerator for paediatric formulations (GAP-f)[xi] provide formulary guidance to programmes on selection of optimal paediatric ARVs defined using a robust set of criteria. The Optimal formulary is currently a list of 8 products that delivery recommended and appropriate first and second line regimens across all paediatric weight bands. The formulary was first developed in 2011 but is routinely revised to correspond to current WHO guidelines and available products. Programs are encouraged to procure paediatric dosage forms that are included on the Optimal Paediatric ARV Formulary. During periods of transitions or in special circumstances (eg. Neonatal treatment, TB co treatment and third line), dosage forms included on the ARV Limited-use formulary provide appropriate coverage[xvi].

The need for new formulations

The work of the Paediatric Antiretroviral Working Group and the Paediatric ARV Drug Optimisation[xii], [xiii] groups continue to highlight the urgent need for better age appropriate formulations for infants and children living with HIV. A number of solid formulations are under final stage of development (ABC/3TC/LPVr granules as well as ABC/3TC/EFV and DTG 10 mg scored dispersible tablets). In addition, the availability of co-formulated DRV/r in heat-stable fixed-dose combination formulations is critical to facilitate treatment sequencing and uptake of future 2nd and 3rd line treatment. A number of formulations containing approved ARVs for paediatric use have been formally prioritised and are listed in table 6. Finally, additional formulations containing newer drugs for which there is currently no paediatric indication 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 optimisation 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.

Table 7 Anticipated simplified dosing for formulations under development.

Drug	Strength of dosage form (mg)	Number of tablets or sprinkle capsules or sachets by weight band											
		3–5.9 kg		6–9.9 kg		10–13.9 kg		14–19.9 kg		20–24.9 kg		25–34.9 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	2	2	3	3	4	4	5	5	6	6	–	
DRV/r	120 mg/20 mg	–	–	–	–	2	2	3	3	3	3	4	4
ABC/3TC/EFV	150 mg/75 mg/150 mg	–		–		1.5		2		2.5		3	
DTG[a]	Scored dispersible 10 mg	1		1.5		2		2.5		3		–	
ABC/3TC/DTG[b]	60 mg/30 mg/5 mg	2		3		4		5		6		–	

[a] This dosing was outlined by the PADO group in December 2017[xiv] based on best available information. However, optimal dosing of DTG in children below 25 kg is still being investigated and this proposed dosing will be revised as soon as more evidence is gathered from ongoing studies.

[b] This dosage form is the one identified by the PADO group[viii] as the most likely to deliver appropriate dose based on the best available information. However, the group strongly emphasized the importance of validating this dosing and ratio as soon as final dosing for DTG is approved down to 4 weeks of age, Scored tablets with doubled- strength of each component drug (ABC/3TC/DTG 120/60/10 mg) would enable reduction of the pill burden for children, but difficulties with assuring accuracy of dosing when scoring a triple-drug FDC will need to be addressed. Importantly, **manufacturers interested in developing ABC/3TC/DTG could start development of a prototype, but will need to delay advancing their development plans until the dosing and the ratio are confirmed** (expected in early 2019).

1 PAWG members: Elaine Abrams (ICAP at Columbia University, USA); Mo Archary (University of Kwazulu-Natal, South Africa); Yodit Belew (US Food and drug administration HHS, USA); David Burger (Radboud University Nijmegen Medical Centre, The NetherlandsEdmund Capparelli (University of California San Diego, USA); Diana Clarke (Boston Medical Center, USA); Polly Clayden (HIV i-Base, UK); Timothy R. Cressey (Program for HIV Prevention and Treatment-IRD/Harvard T.H Chan School of Public Health & Chang Mai University, Thailand); Angela Colbers (Radboud University Nijmegen Medical Centre, The Netherlands); Mutsa Dangarembizi (University of Zimbabwe, Zimbabwe); Paolo Denti (University of Cape Town, South Africa); Andrea Ecker (Eurpean Medicines Agency, The Netherlands); Shaffiq Essajee (UNICEF, USA); Carlo Giaquinto (University of Padova, Italy); Diana Gibb (MRC Clinical Trials Unit, United Kingdom); Rohan Hazra (National Institute of Child Health and Human Development, USA); Mansoor Khan (Texas A&M University Rangel College of Pharmacy, USA); Marc Lallemant (Drugs for Neglected Diseases intiative, Switzerland); Janice Lee (Drugs for Neglected Diseases intiative, Switzerland); Lana Lee (USAID, USA); Linda Lewis (Clinton Health Access Initiative, USA); Helen Mcilleron (University of Cape Town, South Africa); Anita Mesic (Medicines Sans Frontiers, France); Mark H. Mirochnick (Boston Medical Center, USA); Lynne Mofenson (Elizabeth Glaser Pediatric AIDS Foundation, USA); Victor Musiime (Joint Clinical Research Center, Uganda); Elizabeth Obimbo (University of Nairobi, Kenya); Atieno Ojoo (UNICEF, Denmark); Fernando Pascual (Medicines Patent Pool, Switzerland); Jorge Pinto (Federal University of Minas Gerais Belo Horizonte, Brazil); Nande Putta (UNICEF, USA); Natella Rakhmanina (Elizabeth Glazer Paediatric AIDS Foundation, USA); Pablo Rojo (Hospital de 12 Octubre Madrid, Spain); Ted Ruel (University of California San Francisco, USA); Saint Raymond Agnes (European Medicine Agency, UK); George Siberry (Office of the U.S. Global AIDS Coordinator U.S. Department of State, USA); Nandita Sugandhi (ICAP at Columbia University, USA); Marissa Vicari (International AIDS Society, Switzerland); Melynda Watkins (Clinton Health Access Initiative, USA); Caroline Yonaba (Resau EVA, Burkina Faso).

i http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002753/WC500160680.pdf

ii https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204790s014lbl.pdf

iii https://clinicaltrials.gov/ct2/show/NCT01302847?term=P1093&rank=2

iv Turkova et al .2018 10th International Workshop on HIV Pediatrics 20 – 21 July 2018, Amsterdam, The Netherlands.

v Teppler H, Thompson K, Chain A, Mathe M, Nachman S, Clarke D. Crushing of Raltegravir (RAL) chewable tablets for administration in infants and young children. Abstract 37. 9th International Workshop on HIV Pediatrics 21 – 22 July 2017, Paris, France

vi Cotton MF, Liberty A, Torres-Escobar I, Gonzalez-Tome MI, Lissens J, Zaru L, et al. Safety and Efficacy of Atazanavir Powder and Ritonavir in HIV-1-Infected Infants and Children From 3 Months to <11 Years of Age: The PRINCE-2 Study. Pediatr Infect Dis J. 2018 Jun;37(6):e149-e156.

vii Fillekes Q, Mulenga V, Kabamba D, Kankasa C, Thomason MJ, Cook A, et al. Pharmacokinetics of nevirapine in HIV-infected infants weighing 3 kg to less than 6 kg taking paediatric fixed dose combination tablets. AIDS. 2012 Sep 10;26(14):1795-800

viii https://www.ncbi.nlm.nih.gov/pubmed/22739394

ix Rabie H, Denti P, Lee J, Masango M, Coovadia A, Pillay S, Liberty A, McIlleron H, Cotton M, Lallemant M. Lopinavir/Ritonavir 1:1 superboosting overcomes rifampicin interactions in children. Proceedings of the Conference on Retroviruses and Opportunity Infections; 2017 Feb 13-16; Seattle, USA. This link has our abstract: https://www.dndi.org/wp-content/uploads/2018/04/Rabie_et_al_Super_Boosting_Children_Abstract_CROI2017.pdf

x APWG https://www.arvprocurementworkinggroup.org/

xi GAPf http://www.gap-f.org/

xii World Health Organization. Meeting report: Paediatric Antiretroviral Drug Optimization (PADO) Meeting 3. Geneva, Switzerland: WHO; 2016. Available at: http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en/. Accessed on November 29, 2017.

xiii World Health Organization. Meeting report: Paediatric ARV drug optimization 3 review http://www.who.int/hiv/pub/meetingreports/pado3-review/en/index1.html

xiv http://www.who.int/hiv/pub/meetingreports/paediatric-arv-optimization-pado3/en/

xvi The 2018 optimal formulary and limited-use list for paediatric ARVs. Policy brief http://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/