POLICY BRIEF — JULY 2020

CONSIDERATIONS FOR INTRODUCING NEW ANTIRETROVIRAL DRUG FORMULATIONS FOR CHILDREN

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Considerations for introducing new antiretroviral drug formulations for children: policy brief

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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
APWG	ARV Procurement Working Group
ATV/r	ritonavir-boosted atazanavir
AZT	zidovudine
DRV/r	ritonavir-boosted darunavir
DTG	dolutegravir
EFV	efavirenz
FTC	emtricitabine
LPV/r	ritonavir-boosted lopinavir
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NVP	nevirapine
RAL	raltegravir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TB	tuberculosis
VL	viral load
VS	viral suppression

1. BACKGROUND

This policy brief is for country-level programme managers, technical advisers and procurement bodies involved in the process of procuring, introducing and scaling up optimal antiretroviral therapy for infants and young children living with HIV in low and middle-income countries. With multiple new antiretroviral drug options and the availability of new evidence, antiretroviral therapy for children is a dynamic and rapidly evolving space. Although critical tools such as the antiretroviral drug optimal formulary are periodically updated to support product selection *(1)*, programmes must stay informed and up to date on availability of currently used antiretroviral drug formulations for children and anticipated new products to ensure that all children have access to the best available treatment for HIV infection. Implementing the new WHO recommendations for infants and children requires carefully considering the existing regimens in use, antiretroviral drugs for children in stock and in the pipeline and timelines for the availability of newly approved antiretroviral drug formulations for children. This publication outlines what national HIV programmes should be aware of for short- to medium-term (12–24 months) planning.

Current WHO guidelines

In 2018, WHO published up-to-date recommendations on using antiretroviral drug regimens for treating and preventing HIV infection *(2)*. These guidelines recommend a dolutegravir (DTG)-based regimen as the preferred first-line regimen for children for whom approved DTG dosing is available.

WHO also recommends DTG combined with an optimized nucleoside reverse-transcriptase inhibitor (NRTI) backbone as the preferred second-line regimen for people living with HIV, including children, for whom a non-DTG based regimen has failed.

WHO gives priority to antiretroviral drugs that have demonstrated efficacy and safety. However, data on efficacy are often limited or delayed for children. WHO therefore maintains that safety and pharmacokinetic data should remain the basis for considering any new antiretroviral drugs for infants and children living with HIV, and evidence of superior efficacy among adults is sufficient to support use among children. Evidence of the superiority of DTG compared with ritonavir-boosted lopinavir (LPV/r) from studies among adults were extrapolated in making the recommendation to include DTG as the preferred drug for infants and children *(3)*. However, in the absence of formulations and dosing for infants and young children, LPV/r-containing regimens are an acceptable alternative given their superiority over non-nucleoside reverse-transcriptase inhibitor (NNRTI)-based regimens.

Table 1. Preferred and alternative first-line antiretroviral therapy regimens

Population	Preferred first-line regimen	Alternative first-line regimen
Children	ABC + 3TC + DTG[a]	ABC + 3TC + LPV/r or RAL[b] TAF + 3TC (or FTC) + DTG[c]
Neonates	AZT + 3TC + RAL[d]	AZT + 3TC + NVP

[a] For age and weight groups with approved DTG dosing.
[b] RAL should be used as an alternative regimen only if LPV/r solid formulations are not available.
[c] For age and weight groups with approved TAF dosing.
[d] Neonates starting antiretroviral therapy with an RAL-based regimen should transition to an LPV/r solid formulation as soon as possible.

Table 2. Preferred and alternative second-line antiretroviral therapy regimens

Population	Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Children and infants	ABC + 3TC + DTG[a]	AZT+ 3TC + LPV/r (or ATV/r[b])	AZT + 3TC + DRV/r[c]
	ABC (or AZT) + 3TC + LPV/r	AZT (or ABC) + 3TC + DTG[a]	AZT (or ABC) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	AZT (or ABC) + 3TC + DTG[a]	AZT (or ABC) + 3TC + LPV/r (or ATV/r[b])
	AZT + 3TC + NVP	ABC + 3TC + DTG[a]	ABC + 3TC + LPV/r (or ATV/r[b] or DRV/r[c])

[a] For age and weight groups with approved DTG dosing.
[b] ATV/r can be used as an alternative to LPV/r for children older than three months, but the limited availability of suitable formulations for children younger than six years, the lack of a fixed-dose formulation and the need for separate administration of the ritonavir booster should be considered when choosing this regimen.
[c] DRV should not be used for children younger than three years and should be combined with appropriate dosing of ritonavir.

Optimizing antiretroviral drug regimens for children during TB co-treatment

As outlined by WHO guidelines and dosing recommendations *(4)*, children with HIV and TB coinfection require dose adjustments for the duration of TB treatment because of drug–drug interactions with rifampicin.

- Children weighing less than 20 kg and receiving an LPV/r-containing regimen: LPV should be super-boosted to achieve a 1:1 ratio between LPV and ritonavir (RTV). A heat-stable tablet of 25 mg of RTV may be used for super-boosting where available. Alternatively, children may use an efavirenz (EFV)-based regimen or triple nucleoside regimen for the duration of TB treatment and should return to using LPV/r once TB treatment has been completed. For children with HIV-associated TB infection who are being treated with a RAL-containing regimen, RAL should be given at a higher dose of 12 mg/kg twice daily as an oral chewable formulation *(5)*.

- Children weighing more than 20 kg who are receiving DTG-based regimens should continue their antiretroviral therapy regimen using an increased dose of DTG 50 mg twice daily for the duration of TB treatment, as supported by data generated by the ongoing ODYSSEY trial *(6)*. Of note, the FDA has approved the use of DTG 5 mg DT twice-daily when used in infants and children weighing 3 kg and older than 4 weeks who are being treated for TB. However, additional direct evidence to evaluate this approach is still needed.

Transition of children to more optimal regimens

Since 2013, WHO guidelines have provided considerations on how to optimize treatment regimens as children grow and as better formulations are available to them *(7)*. With increasing evidence of high rates of NNRTI resistance, it has become critical to ensure that children initiate or transition to optimal new antiretroviral drugs that are more potent to rapidly achieve and maintain viral suppression, which will prolong the duration of first- or second-line treatment and support adherence through easier administration.

Although optimal regimens provide significant individual benefits, there are also programmatic benefits to transitioning everyone to optimized regimens to simplify guidance, streamline supply chain and harmonize sequencing across populations. Until a DTG formulation for children weighing less than 20 kg is available, WHO recommends that infants and children living with HIV use LPV/r-containing regimens. For children weighing 20 kg or more, DTG-containing regimens can be delivered using available 50-mg DTG tablets. ABC + 3TC is the preferred NRTI backbone for all infants and children (older than four weeks of age) until they reach 30 kg after which TDF, 3TC (or FTC) + DTG (TLD) should be used.

Although routine viral load monitoring should be encouraged as good practice, in accordance with WHO recommendations, viral load testing is not a requirement for transitioning to any optimal regimen. With the exception of children weighing less than 20 kg who are stable on ABC + 3TC + EFV, all stable children should be transitioned to optimal regimens according to their weight. Table 3 provides guidance on appropriate transitions. Programmes should also consider transition as an opportunity to emphasize adherence counselling, identify children with suspected or confirmed treatment failure and support adherence. For children identified as having suspected treatment failure, management should follow the national treatment guidelines.

Table 3. Transitioning clinically stable children to optimal regimens *(8)*

Current regimen	Weight	Optimal regimen for transition	Considerations
AZT + 3TC + NVP **AZT + 3TC + EFV** **ABC + 3TC + NVP**	< 20 kg	ABC + 3TC + LPV/r	If stable, children can transition to DTG when they reach 20 kg
	20–30 kg	ABC + 3TC + DTG	If stable, children can transition to TDF+3TC (or FTC) + DTG when they reach 30 kg
	> 30 kg	TDF + 3TC (or FTC) + DTG	—
ABC + 3TC + EFV	< 20 kg	No change until they reach 20 kg unless treatment failure occurs	Transition to optimal regimens for these children is of value once they reach 20 kg and DTG can be used, maintaining once-daily administration
	20–30 kg	ABC + 3TC + DTG	If stable, children can be transitioned to TDF+3TC (or FTC)+DTG when they reach 30 kg
	> 30 kg	TDF + 3TC (or FTC) + DTG	—
ABC + 3TC + LPV/r **AZT + 3TC + LPV/r**	< 20 kg	No change until they reach 20 kg unless treatment failure occurs	Ensure the use of tablets as soon as possible to reduce pill burden. Transition from AZT+3TC+LPV/r can also be considered to reduce the pill burden and preserve the antiretroviral advantage of NRTI sequencing
	20–30 kg	ABC + 3TC + DTG	If stable, children can be transitioned to TDF+3TC (or FTC)+DTG when they reach 30 kg
	> 30 kg	TDF + 3TC (or FTC) + DTG	—

2. OPTIMIZING ANTIRETROVIRAL DRUG REGIMENS FOR INFANTS AND CHILDREN NOW

Implementing the new WHO recommendations will require carefully considering existing regimens and timelines for introducing and scaling up new formulations.

50 mg DTG is currently available and approved for use for children weighing ≥ 20 kg, and the adult formulation of TLD has been approved for adolescents weighing 30 kg or more. This allows for harmonization with adult treatment regimens to simplify treatment guidance and reduces the risk of inappropriate dosing and stock-outs. Country programmes are currently also in the process of introducing or scaling-up LPV/r-based regimens for infants and children weighing less than 20 kg who are not yet eligible for 50 mg DTG. The scaling up of LPV/r for children is now more feasible because of the availability of two new heat-stable solid dosage forms of LPV/r 40 mg/10 mg: oral pellets and oral granules. Both these formulations can be combined with ABC + 3TC, which is available in a 120 mg/60 mg scored dispersible tablet.

Figure 1 illustrates how preferred regimens can currently be delivered in optimal formulations. This guidance currently optimizes the use of approved and available formulations to minimize the inappropriate use of dosage forms across the age and weight spectrum.

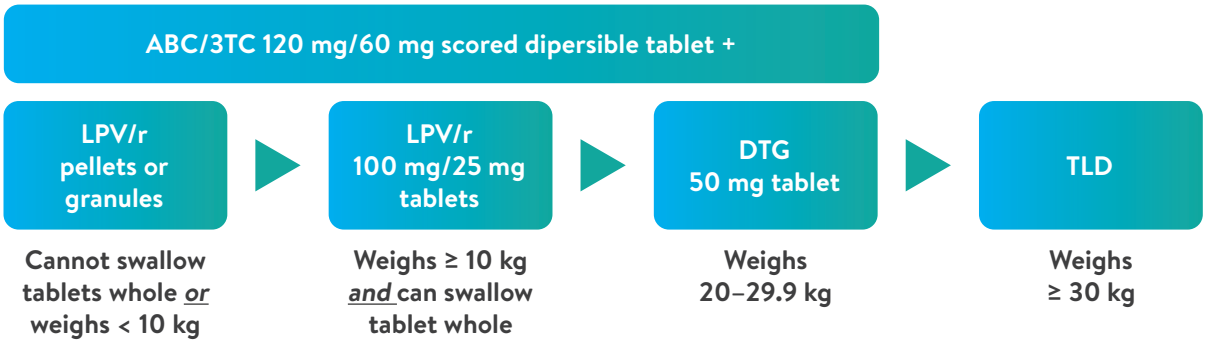

Figure 1. Optimal formulations for different weight groups

Countries have been advised to introduce and scale up either LPV/r pellets or LPV/r granules. Although they are interchangeable since they contain the same drugs at the same dosage, they require different administration instructions given differences in particle size and packaging. LPV/r pellets are contained in a capsule that must be opened and are indicated for infants and children three months and older. LPV/r granules are contained in a sachet and may be used for infants and children from two weeks onwards.

Regardless of whether LPV/r pellets or granules are being introduced, programmes should also procure LPV/r heat-stable 100 mg/25 mg tablets for children for first-line use for children weighing 10–20 kg if they can swallow the tablets whole, since these tablets cannot be broken for administration. This reduces the pill burden for older children, saves costs for the programme and reserves limited supplies of pellets and granules for younger children. Information on the availability of LPV/r formulations is available through the ARV Procurement Working Group (APWG) at: https://www.arvprocurementworkinggroup.org/?l=en.

Finally, country programmes implementing virological testing at birth and that may want to introduce RAL granules for use in the first four weeks of life are encouraged to coordinate with global stakeholders and procurement agencies to place their orders and ensure that tools are available to support adequate training and the use of this formulation.

3. OPTIMIZING ANTIRETROVIRAL DRUG REGIMENS AND FORMULATIONS FOR INFANTS AND CHILDREN OVER THE NEXT TWO YEARS

In accordance with WHO's principles for optimizing treatment for both children and adults, selection of an antiretroviral therapy regimen should account for efficacy, safety, simplification of dosing and administration, harmonization across populations and cost *(9)*. In addition, selecting the antiretroviral drugs needed for infants and young children must also consider the formulations that are appropriate for different developmental stages and timelines for their availability in country.

The end of 2020 holds potential for two improved options for infants and children living with HIV in low-and middle-income countries: a 4-in-1 fixed dose combination (FDC) of ABC+3TC+LPV/r in a granular form (4-in-1), and a DTG 10 mg scored dispersible tablet (DTG 10 mg DT). Both the 4-in-1 and DTG 10 mg DT will be made by generic manufacturers and are currently being reviewed by the United States Food and Drug Administration (FDA). Tentative approvals for both the 4-in-1 and DTG 10 mg DT are anticipated in Q4 2020 after which procurement may be initiated with in-country delivery expected in Q1 2021.

The formulations of the 4-in-1 and DTG 10 mg DT are both considered appropriate for administering to very young infants. Studies on pharmacokinetics, efficacy and safety are ongoing to inform indications for neonatal use. (See Annex: Summary of ongoing studies involving children.)

A FDC dispersible tablet of ABC + 3TC +DTG 60 mg/30 mg/5 mg is also planned but will not be available until 2022 at the earliest.

Programmes should not delay the transition to more optimal regimens for children while waiting for new products to be approved, since the timelines for procurement and distribution of new products are approximate and may change due to global or local challenges. Additionally, the rate of scale-up will vary from country to country once new products are available. **Overall, countries should focus on rapidly implementing optimal regimens according to WHO guidelines and accelerate transitions to DTG-based therapies,** including using TDF + 3TC + DTG for adolescents weighing more than 30 kg, 50-mg adult DTG tablets

DTG 5 mg dispersible tablets

The innovator product, DTG 5 mg dispersible tablets was used to investigate the most appropriate dose of DTG in children down to 4 weeks as part of the P1093 and ODYSSEY trials. This formulation was approved by the US FDA in June 2020 and will be approved in Europe by the end of 2020. However limited commercial manufacturing and cost will prohibit wide-scale use of this formulation. Also of note, the 10 and 25 mg film-coated tablets (FCT) also marketed by the innovator are not bioequivalent to dispersible tablets and cannot be used to deliver the WHO recommended dose as outlined in the WHO dosing annex *(10)*.

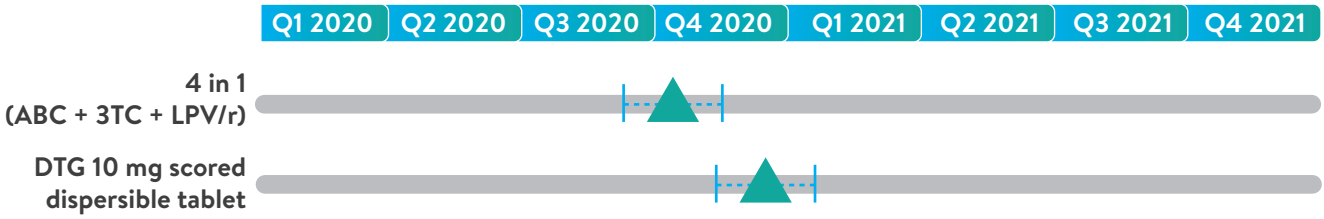

Figure 2. Estimated FDA approval dates for optimal new paediatric ARVs

for those weighing 20–30 kg and planning for transition to the 10-mg scored dispersible DTG tablet for children weighing less than 20 kg when it becomes available in the country. However, the 4-in-1 formulation will be an alternative option for national programmes, since it is an easy-to-use fixed-dose combination dosage form that delivers a full regimen to infants and younger children if DTG is not available or not tolerated.

The guiding principle for decisions about introducing these products should give priority to implementing WHO-preferred regimens.

As these products are introduced in the future, specific factors should be considered.

1. **Timelines of market entry and capacity for product transitions**
   National programmes should give priority to implementing WHO-preferred regimens and should consider what policy changes, budgetary requirements and sensitization strategies will be required for all transition processes since the 4-in-1 and DTG 10 mg are anticipated to be available on the market in close succession.

2. **Available stock in the country and orders in the pipeline**
   Countries that have significant existing stocks of antiretroviral drugs currently in use (LPV/r pellets or granules and dual-drug fixed-dose combinations of ABC + 3TC or AZT + 3TC) should consider using these stocks when planning the timing of new product introduction to enable transition to new formulations with minimal wastage, although consideration can be given if a strong rationale exists. For example, existing stocks of NVP-containing formulations that are being phased out of use are no longer indicated for treatment in children, though still should be used for infant prophylaxis. When new, more optimal antiretroviral drugs for children are available in the country, rapidly transitioning to optimal products is preferable to exhausting existing stocks of an inferior product. Programmes should plan to budget for appropriate destruction of existing formulations containing NVP, but this should only be initiated once adequate supplies of optimal replacement products are in the country.

3. **Supply availability from manufacturers**
   National programmes and procurement agencies should monitor market intelligence, such as Antiretroviral Procurement Working Group updates, for any capacity constraints related to new products. Manufacturers may not enter the market at full manufacturing capacity, and thus planning for phasing in new products and phasing out legacy products needs to be coordinated closely with supplier capacity. Supply planning should also account for lead times on orders to minimize the risk of stock-outs. Manufacturers, donors,

policy-makers, country programmes and implementers must remain coordinated to ensure that optimal antiretroviral drugs continue to be available to all children. All country programmes are encouraged to share their forecasts for children with the Antiretroviral Procurement Working Group to support coordination and ensure that manufacturers are prepared to meet demand. Up-to-date information from the Antiretroviral Procurement Working Group and contact details are available at: https://www.arvprocurementworkinggroup.org/?l=en.

4. **Transition planning**
   - Programmes should consider how to best align timelines for updating clinical and operational guidance and sensitizing health-care workers when developing a transition plan, which should include quantification, procurement timelines and strategies for distribution to the facility level.

   - New orders for paediatric ARV formulations should be quantified based on existing data on weight band distribution, also considering the timelines of future new product introduction when calculating current buffer stock needs. Stockpiling optimal formulations beyond 6 months of stock is not advised, since the timelines for rollout may be delayed for unforeseen reasons resulting in wastage and may result in shortages for other programmes.

   - For introducing all new medicinal products, ensure that plans are in place to strengthen routine toxicity monitoring and to work with global and local stakeholders to facilitate active pharmacovigilance where suitable and feasible.

   - Assess the resources available to invest in the transition process including the following.
     - The cost of new optimal antiretroviral drug formulations including 4-in-1 and DTG 10 mg scored dispersible tablets will be lower than the current cost of delivering LPV/r-containing regimens to children weighing <20 kg.
     - Operational and financial requirements for product transition, including sensitizing health-care workers and the community.
     - Aligning ordering timelines with funding cycles and guidance on management of ART programs as part of the COVID 19 response.

4. CONCLUSION

As countries move closer to achieving the UNAIDS 95–95–95 targets by 2030, it is critical that infants and children living with HIV not be left behind. At the global, national and local level, stakeholders must commit to working collaboratively to ensure that the next generation achieves the 95–95–95 targets.

Global-level stakeholders are committed to making this a reality through close coordination across the pipeline of antiretroviral drug products for children, from manufacturers to end-user.

Timelines for drug development are always uncertain, but global coordination will provide transparency and timely updates to support better antiretroviral drug products for children reaching those in most need. Information from this brief will be regularly updated and disseminated through the Antiretroviral Procurement Working Group (https://www.arvprocurementworkinggroup.org/) and the GAP-f website (http://gap-f.org).

ANNEX

Resources available

Introducing a new product is a complex process requiring guideline changes, supply planning, development of rollout plans and materials, training and monitoring. Multiple resources and support are available to support national programmes as they plan and implement transitions to optimal formulations.

The HIV New Product Introduction Toolkit (www.newhivdrugs.org) provides resources to support national programmes as they plan and implement new product transitions.

Summary of ongoing studies involving children

Drug	Study	Design	Results
4-in-1	LOLIPOP	Phase I/II, open-label, randomized crossover pharmacokinetic, safety and acceptability study of the abacavir/lamivudine/ lopinavir/ ritonavir 30/15/40/10 mg (4-in-1) fixed-dose combination versus lopinavir/ritonavir 40/10 mg pellets plus dual abacavir/lamivudine 60/30 mg tablets among HIV-infected children ClinicalTrials.gov identifier: NCT03836833	Study ongoing
	PETITE	Open-label, single-arm, two-stage trial to evaluate the single and multi-dose pharmacokinetics and safety of the abacavir/ lamivudine/lopinavir/ritonavir (30/15/40/10 mg) (4-in-1) fixed-dose granule formulation in HIV-exposed neonates	Study to start in the third quarter of 2020
DTG	P1093	The P1093 study is evaluating the pharmacokinetics, safety, tolerability and antiviral activity of DTG in combination with optimized background NRTIs in HIV-1-experienced adolescents and children as well as treatment-naive infants and toddlers ClinicalTrials.gov identifier: NCT03016533	Pharmacokinetic and 4-week safety and efficacy of dolutegravir dispersible tablets among HIV-infected children aged 4 weeks to <6 years *(9)* • Drug exposure similar to adults can be achieved with the dispersible tablet formulation of dolutegravir among children aged 4 weeks to 6 years • The dispersible tablet formulation was well tolerated and easily administered by participants and their families
	ODYSSEY	A multicentre, randomized clinical trial to assess the efficacy and toxicity of dolutegravir plus two NRTI versus standard of care among HIV-positive children and adolescents. Penta is the sponsor of this study, with 700 people to be enrolled in 30 sites in Europe, Africa and Asia	http://odysseytrial.org/publications

Dosing of optimal pediatric ARVs

Formulation	3–5.9 kg		6–9.9 kg		10–14.9 kg		15–19.9 kg		20–24.9 kg		25–29.9 kg		≥30 kg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC 120/60 mg scored dispersible tablet	1		1.5		2		2.5		3		1 adult tab (600/300 mg)		1 adult tab (600/300 mg)	
LPV/r 40/10 mg pellets (capsules)	2	2	3	3	4	4	5	5	6	6	—		—	
LPV/r 40/10 mg granules (sachets)	2	2	3	3	4	4	5	5	6	6	—		—	
LPV/r 100/25 mg tablets	—	—	—	—	2	1	2	2	2	2	3	3	3	3
4-in-1 ABC/3TC/ LPV/r 30/60/40/10 mg (capsules)	2	2	3	3	4	4	5	5	6	6	—	—	—	—
DTG 5 mg dispersible tablets[a]	2		3		4		5		—		—		—	
DTG 10 mg scored dispersible tablet	1		1.5		2		2.5		—		—		—	
DTG 50 mg tablet	—		—		—		—		1		1		1	
TDF/3TC (or FTC)/DTG 300/300 (or 200)/50 mg tablet	—		—		—		—		—		—		1	

[a] This dosing was reviewed and confirmed by the Pediatric ARV Working Group on June 19, 2020.

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