
Photo: Eric Bond/EGPAF, 2018

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Elizabeth Glaser Pediatric AIDS Foundation

Unitaid
Innovation in Global Health

Accelerating Access to Optimal Child-Friendly Antiretroviral Formulations

The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) transformed the response to pediatric HIV in nine sub-Saharan African countries by integrating innovative **point-of-care** early infant diagnosis of HIV (POC EID) technologies into national laboratory networks. The initiative, supported by Unitaid and implemented hand-in-hand with ministries of health, demonstrated that the routine use of POC technologies increases access to rapid diagnosis for HIV-exposed infants and to early treatment among HIV-positive infants. However, long-term treatment and care of HIV-infected infants will only be successful if children and health systems have immediate and sustainable access to child-friendly formulations of antiretrovirals (ARVs) that are safe, effective, affordable, and palatable.

While clinical trials have demonstrated the benefits of Dolutegravir (DTG) and Lopinavir-Ritonavir (LPV/r) over Nevirapine (NVP)-based regimens, many children are still on NVP-based regimens. Even when LPV/r syrup is available, it is poorly tolerated by children and difficult to store due to its cold chain requirement. Fortunately, several new, child-friendly ARV treatments and formulations have been approved, with more on the horizon.

World Health Organization (WHO) Recommendations: NVP is no longer recommended for first-line treatment in children due to its increased risk of drug resistance and inferior clinical outcomes. For all infants (with the exception of neonates) and children, the WHO now recommends DTG-based regimens as the preferred first-line treatment where appropriate and approved formulations exist.[1] Already, the adult 50mg formulation of DTG can be used, in combination with two other ARV drugs, to form a robust and complete regimen for children over 20kg. From two weeks of age, LPV/r can be used as a bridge until the 20kg weight band is reached. Currently approved formulations include Raltegravir (RAL) for neonates, solid LPV/r 2-in-1 pellets and granules, DTG 50mg tablets for children weighing at least 20kg (see Table 1) and the fixed-dose combination of tenofovir disoproxil fumarate (TDF) + lamivudine (3TC) (or Emtricitabine) and DTG for children over 30kg.

New Formulations: Efforts are also under way to develop and obtain regulatory approval and introduce LPV/r 4-in-1 granules, and DTG dispersible formulations (5mg and 10mg tablets) (see Figure 1).

Table 1. Child-Friendly ARV Formulations by Age Group or Weight Band as Recommended in the WHO 2019 Guidelines

	Neonates 0 to 4 weeks	Children < 20kg	Children ≥20kg
Preferred	AZT and 3TC liquids plus RAL granules[1]	ABC/3TC ^{DT} plus LPV/r solid formulations[2]	ABC/3TC$_{DT}$ plus DTG$_{AT}$
Alternatives	AZT, 3TC and NVP liquid	ABC/3TC$_{DT}$ plus RAL$_{CT}$[3]	ABC/3TC$_{DT}$ plus LPV/r^{PT} or RAL$_{CT}$ **or** TAF/FTC + DTG[4]
Special circumstances[5]	AZT, 3TC and LPV/r liquids	ABC/3TC$_{DT}$ or AZT/3TC$_{DT}$ plus EFV$_{PT}$[6] **or** ABC/3TC$_{DT}$ **or** AZT/3TC$_{DT}$ plus RAL$_{CT}$ **or** AZT/3TC/NVP$_{DT}$	ABC/3TC$_{DT}$ or AZT/3TC$_{DT}$ plus EFV$_{PT}$[6] **or** AZT/3TC$_{DT}$ plus LPV/r$_{PT}$ **or** ABC/3TC$_{DT}$ or AZT/3TC$_{DT}$ plus RAL$_{CT}$ **or** AZT/3TC/NVP$_{DT}$

DT dispersible tablets; CT chewable tablets; PT paediatric tablets; AT adult tablets; : ABC abacavir, AZT zidovudine; DTG dolutegravir; EFV efavirenz; FTC emtricitabine; LPV/r lopinavir/ritonavir; NVP nevirapine; PI/r boosted protease inhibitor; RAL raltegravir; TAF tenofovir alfenamide; TDF tenofovir; 3TC lamivudine

[1] To be used until a solid formulation of RAL, LPV/r or DTG can be used

[2] LPV/r granules are approved for use from 2 weeks. LPV/r pellets can be used from 3 months. Children should be transitioned to LPV/r tablets from 10kg as soon as able to swallow them.

[3] RAL$_{CT}$ above 4 weeks of age

[4] TAF/FTC only for use above 25kg

[5] In cases where no other alternatives are available

[6] EFV should not be used in children younger than 3 years of age

See dosing guidance at https://www.who.int/hiv/pub/guidelines/ARV2018update/en/ (Annex : Interim WHO ARV guidelines)
For guidance on formulation selection(see https://www.who.int/hiv/pub/paediatric/optimal-paediatric-arv-formulary/en/)

[1] World Health Organization (2019). Update of recommendations on first- and second-line antiretroviral regimens (https://www.who.int/hiv/pub/arv/arv-update-2019-policy/en/).

Figure 1. Timeline for the Expected Approval of Additional Child-Friendly ARVs[1]

2020				2021				2022
Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1
	LPV/r 4-in-1 granules (Cipla)	DTG 5mg dispersible (ViiV) [2]	DTG 10mg dispersible[2]		LPV/r 4-in-1 granules (Mylan)		Abacavir-lamivudine-dolutegravir (ALD) 60/30/5 dispersible	

[1] Age/weight bands and appropriate dosing still to be determined
[2] DTG 5mg and 10mg formulations must be administered together with a dispersible NRTI backbone

Supporting the Rapid Uptake of Optimal Pediatric ARVs as Recommended by WHO

As new, optimal pediatric ARV formulations become available, significant barriers to their rapid and sustainable uptake need to be removed (see Table 2). Roll-out can be complicated by delays to guideline updates, concerns about product supply and affordability, increased need for intensive health care worker training on new formulations and lack of emphasis on treatment literacy for patients and caregivers. Formulation and palatability issues also introduce patient and provider barriers to uptake. Finally, transitioning to several new formulations for a small-volume market may introduce supply-demand mismatch and result in poor delivery to peripheral sites in the context of weak supply chains.

To overcome these barriers, EGPAF will continue its work under Unitaid's POC EID grant in five implementing countries - **Côte d'Ivoire, Eswatini, Lesotho, Mozambique and Zimbabwe** - to accelerate sustainable access to optimal pediatric ARV formulations. The five countries represent diverse regional and health systems contexts; and together make up nearly one-third of the total burden of pediatric HIV in sub-Saharan Africa. The initiative will work to streamline and improve the systems needed to introduce and sustain optimal pediatric formulations in each country and, thereby, ensure that children living with HIV have access to the best available treatments.

Table 2. Common Barriers to the Roll-out of Optimal Pediatric ARV Formulations and Actions to Overcome Them

Barrier	Action
Delays in uptake and transition to newer formulations	Work with stakeholders to support implementation; ensure transition plans are in place; and build improved pharmacovigilance systems to support rapid transition with a "safety net."
Risk of unstable supply and stock-outs during the transition	Work with national programs to create transition plans; identify current stock supplies; and flag countries that may have a slower transition requiring a continued supply of older formulations until the supply of newer formulations is adequate. Work at the facility level to ensure a strong "last-mile" supply chain for pediatric ARVs.
Supply-demand mismatch: As newer formulations enter the market, supply capacity may be lower than the demand	Work as partners with national technical working groups, donors, and manufacturers to create a coordinated transition plan that recognizes supply constraints.
High prices lead to significant opportunity costs	Advocate for fair and sustainable pricing of pediatric ARVs.
The complexity of health worker and patient training	Create or adapt comprehensive tools for clinicians and patients and introduce these at the facility level with intensive training, monitoring, and mentorship.

Supporting the Achievement of Global Goals and WHO Recommendations

This initiative will greatly contribute to implementing global guidelines and achieving the UNAIDS 95-95-95 targets in the five focus countries, in close collaboration with partners. Rapid introduction of optimal pediatric ARV formulations is expected to not only produce cost savings and efficiencies in terms of decreased drug resistance and increased viral load suppression, but also improve survival among HIV-infected infants and children.

By July 2020, the initiative is expect to achieve the following:

At least five countries with approved formulations, quantification, updated treatment guidelines, revised essential medicines lists, and funding commitments to accelerate and sustain access to optimal pediatric ARVs

244 project sites in five focus countries with access to child-friendly formulations, and with at least one health care worker trained per site in the use of new formulations

At least 26,000 HIV-positive children prescribed new formulations across 244 project sites, and more than 150,000 children prescribed new formulations across the five focus countries