



## Evidence to Action: Urgent Update!

# OPTIMIZING PEDIATRIC REGIMENS

Implementation of new and improved pediatric antiretroviral formulations is required to better address the needs of children infected with HIV. Too many children are receiving nevirapine (NVP)-based antiretroviral therapy (ART), even though NVP is no longer recommended as a preferred first-line treatment for children by the World Health Organization (WHO), due to associated risk of drug resistance. EGPAF's [FAM-CARE Study in Eswatini](#) showed that, more than three years after Eswatini switched to the WHO-recommended efavirenz (EFV)-based first-line ART in children aged over 3 years, more than 43% of children were still receiving NVP-based ART, while less than one third (26%) were on EFV-based ART. FAM-CARE looked at a range of factors, including demographics; age at initiation; duration of and adherence to ART; and interruptions to care, and found that **the only factor significantly associated with lack of viral suppression in children was receiving a NVP-based regimen.**

As a leader in pediatric HIV care and treatment, EGPAF must play an important role in global efforts to optimize pediatric ART outcomes. We have demonstrated that more focus is needed in actually implementing the WHO pediatric treatment guidelines and ensuring the children we serve are promptly initiated on, and transitioned to, the most optimal ART regimens. Standardizing implementation of more efficacious ART regimens, in line with the latest 2018 WHO pediatric treatment guidelines, is a high priority for EGPAF. This document aims to help our programs better articulate why this change is urgently needed, to advocate for policy and service delivery shifts, and to overcome challenges to fully implement these guidelines in diverse settings.

### KEY FACTS ABOUT NEW GLOBALLY-RECOMMENDED TREATMENT GUIDELINES

The [2018 WHO pediatric treatment guidelines](#) recommend several key shifts, which are outlined in the [2018 Optimal Formulary and Limited-Use List for Paediatric ARVs](#):

- Due to increasing prevalence of non-nucleoside reverse transcriptase (NNRTI) resistance, transitioning from NNRTI-based ART, such as NVP or EFV, to integrase strand transfer inhibitor (INSTI)-based ART, such as dolutegravir (DTG) and raltegravir (RAL), for first-line treatment is now recommended.
- A shift from using age limits to using weight bands to determine ART formulations and dosing for children is needed.
- For children who weigh at least 25 kg, DTG-based regimens are now the preferred first-line ART, with guidelines likely to suggest use for those weighing at least 20 kg.
- For children and infants under 25 kg, lopinavir-ritonavir (LPV/r)-based ART is the recommended first-line treatment until appropriate DTG dosing is defined for young children.
- For newborns, RAL is now recommended as the preferred first-line treatment (instead of NVP-based ART) due to its ability to rapidly reduce viral load (VL). RAL is the only INSTI with approved dosing for infants and young children. However, because RAL has a lower barrier to resistance, the guidelines recommend using it for the shortest time possible.
- Infants are able to switch from RAL to LPV/r liquid or granules starting at 2 weeks of age; or infants can switch to LPV/r pellets at 3 months of age. Solid LPV/r formulations are generally preferred due to the poor taste and low tolerability of liquid LPV/r. Where solid LPV/r formulations are not available, RAL can be used in infants as an alternative regimen.

**Table 1. WHO Recommended ART Regimens for Neonates and Children**

	Neonates	Children
<b>Preferred Treatment Regimen</b>	AZT+3TC+RAL <sup>1</sup>	ABC+3TC+DTG <sup>1</sup>
<b>Alternative</b>	AZT+3TC+NVP	ABC+3TC+LPV/r <sup>2</sup> ABC+3TC+RAL <sup>1</sup>
<b>Special Circumstances (Only In Cases Where No Other Alternative Is Possible)</b>	AZT+3TC+LPV/r	ABC+3TC+EFV <sup>3</sup> AZT+3TC+EFV <sup>3</sup> AZT+3TC+LPV/r AZT+3TC+NVP AZT+3TC+RAL ABC+3TC+RAL

3TC=lamivudine; ABC=abacavir; AZT=zidovudine; DTG=dolutegravir; EFV=efavirenz; LPV/r=lopinavir/ritonavir; NVP=nevirapine; RAL=raltegravir

<sup>1</sup> Because of lower barrier to resistance than other INSTI drugs, use RAL for the shortest time possible, until a solid formulation of LPV/r or DTG can be used.

<sup>2</sup> Until DTG is approved for younger children, ABC+3TC+LPV/r is the preferred regimen for children ages 2 weeks to 6 years and <15 kg.

<sup>3</sup> EFV should only be used in children three years or older.

## STEPS TO GAIN MOMENTUM IN SWITCHING CHILDREN TO APPROPRIATE FORMULATIONS

1. Promote EGPAF leadership and Ministry of Health (MOH) awareness
2. Support MOH to revise treatment guidelines, if needed
3. Prepare for site-level implementation of the revised guidelines
4. Reevaluate forecasting to ensure adequate ARV stocks at national and sub-national levels
5. Monitor and document the transition

### 1. PROMOTE EGPAF LEADERSHIP AND MINISTRY OF HEALTH (MOH) AWARENESS

#### Talking points to use with MOH staff and other partners:

- Global targets call for 95% of HIV-positive children to be virally suppressed by 2030; current studies imply that rates for viral suppression among HIV-positive children on ART hover around 75%. We will not reach 95% viral suppression in children if they are on sub-optimal regimens.
- According to recently published EGPAF study results, the number one factor associated with low suppression rates in children is suboptimal ART regimen: NVP-based regimens are significantly less likely to produce sustained viral suppression and are also more likely to result in drug resistance with non-adherence.
- Children are the most vulnerable population and the future of our countries. We are not doing our job to provide effective care and treatment for them if we don't prioritize the implementation of currently-recommended, evidence-based HIV treatment guidelines.
- Recognizing more effective drugs are now available in appropriate formulations for newborns, infants and children, the WHO recommends all countries move to DTG-based ART for children >6 years who weigh >15 kg and to use LPV/r-based regimens for children ages 2 weeks to under <6 years who weigh <25 kg.
- Let's carefully review the revised WHO pediatric treatment guidelines (updates to these guidelines will be available in June 2019) to guide revision and inform immediate roll-out of revised national guidelines to ensure the best treatment outcomes for children.
- COP guidance states that PEPFAR will no longer purchase NVP-based regimens for use in country for any age group.
- Although many countries changed their guidelines following a WHO mandate in 2015, there is still a significant gap in site-level implementation.

## 2. SUPPORT MOH TO REVISE TREATMENT GUIDELINES, IF NEEDED

- Ensure that national ART guidelines are aligned with the 2018 WHO pediatric treatment recommendations.
- Promote change, when needed, by calling on technical working group committee involvement.
- Country programs should be familiar with and consider national regulatory and local availability status of specific dosage forms when developing national pediatric treatment guidelines.
- Guidance should address VL testing for those transitioning to a different regimen. Ideally, children should have VL test sample collected before they switch to a new regimen, without switch delay. If a child has had a VL test done within 3 to 6 months preceding the ART change, there is no need for repeat VL before the switch. Instead, VL monitoring should continue after the switch, as per the national treatment monitoring algorithm.

## 3. PREPARE FOR SITE-LEVEL IMPLEMENTATION OF THE REVISED GUIDELINES

- Determining the proportion of children receiving sub-optimal ART regimens and rapidly assessing transition needs can be done through development of a nationally adapted, pediatric treatment cohort tool (see guidance in Table 2).
- Determine which sites serve pediatric ART populations. Work with these sites to better describe their pediatric cohort, including the spectrum of the ages and weight bands, and current treatments prescribed and distributed. Support sites to assess what changes are required for transition to new regimens.
- Train health care workers on the revised ART guidelines and visit sites to provide mentorship and support. Ideally, schedule site visits with MOH and site managers.
  - Health care workers will also require support to improve routine VL testing. This is an area of weakness in pediatric populations and often prevents health care workers from ensuring all children are on optimal regimens and virally suppressed.
  - Site-level managers should also be re-trained and supported around site inventory.
- Develop appropriate job aids for health care workers on the revised ART guidelines and develop a simple algorithm for them to switch children to optimal ART regimens effectively, while also managing a shift in treatment stock supply. EGPAF's New Horizons Project has an excellent resource on this: <http://www.pedaids.org/resource/new-horizons-management-of-treatment-failure-for-pediatric-and-adolescent-patients-resource-package/>

**Table 2. Development of a Pediatric Treatment Cohort Tool**

EGPAF country programs should develop a tool that is aligned with their national guidelines. Suggested considerations are listed below.

Considerations for regimen transition	Considerations for data collection
<ul style="list-style-type: none"><li>• Which ARVs will be used for which ages/weights?</li><li>• Are improved formulations available in-country?</li><li>• Are fixed-dose combinations available?</li><li>• Do dosage forms need to be adapted?</li><li>• Current regional/site stock of ARVs including formulations</li><li>• Regional/site ARV stock needed for transition based on country guidelines.</li></ul>	<ul style="list-style-type: none"><li>• Date of ART initiation</li><li>• First ART regimen</li><li>• Weight at ART initiation</li><li>• Current age and weight (or weight band)</li><li>• Current ART regimen (including dosage and formulation)</li><li>• Date changed to current regimen</li><li>• Treatment status (active, last VL test, VL results, suppressed or not, etc.)</li><li>• History of TB</li></ul>

Contact EGPAF's TAS team (TASTeam@pedaids.org) to request assistance, if needed.

#### 4. REEVALUATE FORECASTING TO ENSURE ADEQUATE ARV STOCKS AT NATIONAL AND SUB-NATIONAL LEVELS

- Use the pediatric treatment cohort tool you have developed to improve site-level assessment of ARV stocks, including pediatric formulations.
  - Effective forecasting requires site-level identification of the numbers of children currently on ART stratified by weight and age through facility registers, while line-listing those who need to be switched to the preferred regimens.
- Support the MOH in selecting the various drugs combinations and formulations they will procure based on what is in the guidelines.
  - Forecasting should consider the estimated number of infants and children who will need to be switched to LPV/r-based regimen (from NVP) and the number of older children (>25 kg, and potentially >20kg) who will need to be switched to a DTG-based regimen.
  - Fixed-dose combination (FDC), when available, are preferable for pediatric populations. FDCs for the dual NRTI backbone are likely already in the procurement plans (e.g., ABC/3TC), so forecasting should prioritize these drugs and formulations as well as the new ones that are being rolled out.
  - The only FDC available for children is the dual formulation of ABC/3TC, because tenofovir disoproxil fumarate (TDF)/3TC is available only in adult dosing (TDF 300mg), which is too large a dose for children <30 kg
  - Sites will also need to procure single tablet DTG 50 mg, which may have occurred already in some sites as TB/HIV co infected patients should receive a double dose of DTG (50 mg twice daily) due to interactions between DTG and rifampin. The 50 mg formulation is critical for dosing children starting at 25 kg of weight (or potentially 20kg). Accurate forecasting will be essential to procure stand-alone 50 mg DTG tablets.

#### 5. MONITOR AND DOCUMENT THE TRANSITION

- Since documentation of current and changing pediatric regimens will be critical, programs should prioritize meeting with national MOH representatives to support the development and roll-out of revised clinic registers and web-based databases, where available, and build the use of the new registers into health care worker trainings.
- While it would be ideal from programs to collect baseline data on the number of children on each ART regimen for comparison (which could be done under the Patient and Program Outcomes Protocols [PPOPs], email your HQ Research Support Person for more details), it is critical for EGPAF programs to at least document how many children need to be and have transitioned to the preferred regimens. This is **NOT** currently a PEPFAR indicator, but it will be an important data point to highlight to PEPFAR and our donors in reports and presentations. This data will also be useful for monitoring the transition.
- There are many VL testing gaps across sites, programs, and countries, especially in pediatric populations. To ensure we're rolling out the new ART guidelines effectively for children, we need to improve treatment outcome (e.g., VL) monitoring. Children should not only be accessing optimal first-line regimens, but second- and third-line regimens when needed. Therefore, transition to new ART regimens should be paired with improving VL testing uptake and utilization of VL test results in practice with timely interventions.
- Since experience with DTG among children is limited, the WHO recommends that routine toxicity monitoring be ensured when this recommendation is implemented. Health care workers must also be trained on reacting to adverse events as they monitor toxicity.

## KEY CONSIDERATIONS AROUND DOSING AND COUNSELING CLIENTS ON CORRECT FORMULATIONS:

- Dispersible tablets (or granules for oral solution) are preferred formulations for children, because tablets/granules can be made into liquid at the time of administering the drug to the child. If suitable dispersible formulations are not available and oral liquids must be used, it is recommended that children be switched to a solid oral dosage form (e.g., granules, pellets, dispersible tablets), as soon as possible.
- Administration of ART to neonates generally necessitates use of oral liquid formulations, switching to solid oral dosage form as soon as possible is recommended (e.g., switch from RAL to LPV/r granules at 2 weeks of age or LPV/r pellets at 3 months of age).
- Use of scored tablets are preferred to ensure accurate dosing (splitting of unscored tablets — such as LPV/r heat-stable<sup>1</sup> tablets — should be avoided as uniform distribution of active drug product cannot be assured and bioavailability of the drug within the body may be decreased)
- Infants younger than 3 months of age should be prioritized for LPV/r oral solution.
- Infants and young children between 3 months – 3 years of age should be prioritized for starting or switching to LPV/r oral pellets or granules.
- The age at which children are able to swallow LPV/r (100 mg/25 mg) heat-stable tablets varies between 3 and 5 years. Therefore, estimate that about half (50%) of children 3 to 5 years of age will continue to use LPV/r pellets or granules and another half (50%) will be able to swallow LPV/r (100 mg/25) mg heat-stable tablets.
- Young children who weigh >25 kg should use LPV/r (100 mg/25 mg) heat-stable tablets until they can be transitioned to DTG-containing regimens at 6 years of age.
- Weight bands rather than age should guide ARV dosing. However, DTG is only approved for children >6 years who weigh at least 15 kg.
- At each clinic visit, children should be weighed and ART and other medications (such as TB drugs) doses should be adjusted based on change in body weight.

<sup>1</sup> 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.



Photo: Eric Bond/EGPAF, 2017