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POLICY BRIEF

THE 2018 OPTIMAL FORMULARY AND LIMITED-USE LIST FOR PAEDIATRIC ARVS

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1. BACKGROUND

The WHO 2018 guideline update promotes the use of optimal treatment regimens in all populations. Though new, more effective and better tolerated options with a higher genetic barrier to resistance are now available for adults, optimized treatment options for children lag significantly behind. This fifth edition of the Optimal Formulary (OF) and Limited-use List (LUL) supports the transition to optimal WHO-recommended regimens for infants and children, while giving due consideration to the rapidly evolving treatment landscape and the risks inherent in the uncertain timelines for paediatric drug development.

Publication of the OF and LUL provides guidance to country programmes, procurement entities and funding agencies on the minimum set of paediatric antiretroviral (ARV) dosage forms needed to deliver WHO-recommended ARV regimens to neonates, infants and children for all lines of treatment. Adult dosage forms that may be used in paediatric populations are not included as these are less vulnerable to supply disruption.

2. 2018 WHO GUIDELINES UPDATE

Table 1: Summary of ART regimens for first-line ART in neonates, infants and children

	Neonates	Children
Preferred	AZT+3TC+RAL[1]	ABC+3TC+DTG[2]
Alternative	AZT+3TC+NVP	ABC+3TC+LPV/r ABC+3TC+RAL[1]
Special circumstances[3]	AZT+3TC+LPV/r	ABC+3TC+EFV[4] AZT+3TC+EFV[4] AZT+3TC+LPV/r AZT+3TC+NVP AZT+3TC+RAL ABC+3TC+RAL

[1] For the shortest time possible, until a solid formulation of LPV/r or DTG can be used.
[2] As of July 2018 DTG is only approved above 6 years and 15 kg.
[3] In cases where no other alternatives are available.
[4] From 3 years of age.

Table 2: Summary of sequencing options for paediatric populations

First-line	Second-line*	Third-line
2 NRTI + LPV/r	2 NRTIs + DTG**	DRV/r + DTG**** +/- 1-2 NRTIs (where possible consider optimization using genotyping)
2 NRTI + EFV or NVP	2 NRTIs + DTG ***	
2 NRTI + DTG or RAL	2 NRTIs + ATV/r or LPV/r	

* Optimized NRTI backbone should be used: AZT following TDF or ABC failure, and vice versa.
** This applies to children for whom approved DTG dosing is available. RAL should remain the preferred second line for children for whom approved DTG is not available.
*** This applies to children for whom approved DTG dosing is available. ATV/r or LPV/r should remain the preferred second line for children for whom approved DTG is not available.
**** DTG-based third line following use of INSTI must be administered with DTG twice a day.

Major considerations for the revision of the OF and LUL include the need to support programmes in taking a pragmatic approach in the transition towards WHO-recommended regimens. However, the realities of the paediatric ARV market and the uncertainty of timelines for new paediatric drug development must be acknowledged. The OF and LUL will therefore be reviewed on a regular basis in order to take account of new developments in the paediatric market.

3. CRITERIA USED TO EVALUATE PRODUCTS FOR INCLUSION

Although drug availability is a critical consideration for implementation planning, it is not a criterion for selecting products for the OF or LUL as availability is country-specific and subject to continuous change. Funding agencies, procurement entities, manufacturers, national regulatory authorities and national governments all have a critical role in working together to ensure the availability of products on the OF and LUL, which can be achieved through fast-tracking in-country registration, support for procurement and supply-chain planning, facilitating commercialization and ensuring manufacturing capacity and filing drugs for registration. Having one or more quality-assured suppliers available is, however, a criterion for selecting products.

Table 1. 2018 criteria to define optimal paediatric ARV dosage forms

Criterion	Description
Meets WHO requirements	Included in the latest WHO guidelines for paediatric treatment
Dosing flexibility	Allows for the widest range of dosing options
Approved by SRA/WHO PQ	≥ 1 quality-assured product available
User friendly	Easy for HCWs to prescribe Easy for caregivers to administer Supports adherence in children
Optimizes supply chain	Easy to transport Easy to store Easy to distribute
Comparative cost	Cost should NOT be the deciding factor in the selection of a drug but the comparative cost of similar drugs/drug formulations should be taken into consideration

4. OPTIMAL FORMULARY

The OF is designed to include the minimum number of ARV formulations needed to deliver WHO recommended first- and second-line ARV treatment regimens for infants and children. In the 2018 WHO update, dolutegravir (DTG)-based regimens are the preferred first-line treatment for HIV-positive infants and children aged 4 weeks and above. However, it was recognized at the time of this formulary update that dosing and dosage forms to deliver DTG-based regimens are not yet available across all weight bands. In the interest of developing procurement guidance that may be acted upon immediately, a decision was made to include products needed to deliver both preferred and alternative first- and second-line regimens. Appropriate dosage forms for postnatal prophylaxis (PNP) for prevention of mother-to-child transmission of HIV (PMTCT) to HIV-exposed infants are also included in consideration of the critical need for these products.

Optimal Formulary: Minimum number of ARV formulations needed to provide all currently WHO recommended preferred and alternative first- and second-line ARV treatment options for infants and children and infant prophylaxis for PMTCT.

Drug	Formulation	Dose	Rationale for use
AZT	Oral solution*	50 mg / 5 mL, 100 mL	For PNP or neonatal treatment
NVP	Tablet (dispersible, scored)*	50 mg	PNP
NVP	Oral solution*	50 mg / 5 mL, 100 mL	For PNP or neonatal treatment
LPV/r	Tablet (heat stable)	100 mg / 25 mg	For alternative first-line or second-line for children 10 kg and above and able to swallow tablets whole
LPV/r	Solid oral dosage form	40 mg / 10 mg	For alternative first-line or second-line for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole.
AZT/3TC	Tablet (dispersible, scored)	60 mg / 30 mg	For first-line in special circumstances or second-line in infants and children 4-25 kg
ABC/3TC	Tablet (dispersible, scored)	120 mg / 60 mg	For preferred first-line or second-line in infants and children 4-25 kg
RAL	Chewable scored tablet	25 mg	To provide alternative first-line and second-line for infants and children between 3-25 kg
DTG-containing regimens are the preferred first-line treatment for infants and children age 4 weeks-10 years. At the time of this revision, 50mg adult tablets can be used for children weighing 25kg and above. When dosing is confirmed for lower weight bands, the Optimal Formulary and Limited-use List will be reviewed to include paediatric dosage forms of DTG as they are made available. Please refer to the AIDS Free Toolkit for latest Annex on Dosages of ARV Drugs.			

* For postnatal prophylaxis and/or neonatal treatment only

5. THE LIMITED-USE LIST

The LUL covers those dosage forms that may be required for limited time periods or in very low volumes. This includes dosage forms needed to provide regimens that are being phased into or out of use, regimen adjustment during TB treatment, neonatal treatment and third-line.

Limited-use List: Formulations which are included in WHO guidelines and are needed for a limited time or in low volumes.

Drug	Formulation	Dose	Rationale for use
LPV/r	Oral solution	80 mg / 20 mg/mL	For alternative first-line or second-line for infants and children below 10 kg or unable to swallow 100 mg/25 mg tablets whole, until a suitable oral solid dosage form becomes widely available
3TC	Oral solution	50 mg / 5 mL, 100 mL	For neonatal treatment only
ABC	Dispersible scored tablet	60 mg	For provision of a triple nucleoside regimen in combination with AZT/3TC dual FDC for the duration of TB treatment
DRV	Tablet	75 mg	For third-line regimens in children 3 years and above
RTV	Tablet	25 mg	For superboosting of LPV/r during TB treatment and boosting un-coformulated protease-inhibitors
RTV	Powder	100 mg	For superboosting of LPV/r during TB cotreatment and boosting non-coformulated protease-inhibitors
ATV	Capsule	200 mg	For alternative second-line in combination with RTV 100mg
AZT/3TC/ NVP	Dispersible scored tablet	60 mg / 30 mg / 50 mg	For first-line in special circumstances in children below three years until suitable bPI or INSTI dosage forms become widely available
EFV	Scored tablet	200 mg	For first-line in special circumstances in children above three years until suitable bPI or INSTI dosage forms become widely available
RAL	Granules for suspension	100 mg	For neonatal treatment only

Changes to the Optimal Formulary and Limited-use List

Drug Dosage and Form	Status
AZT oral solution 50 mg/5 mL, 100 mL	**Moved from Limited-use List to Optimal Formulary**
AZT oral solution, 100 mL bottle size, was previously included in the Limited-use List to phase in an enhanced postnatal prophylaxis regimen for infants at high risk for HIV infection. AZT oral solution 50 mg/5 mL, 100 mL was moved from the Limited-use List to the Optimal Formulary to reflect the increasing adoption of this recommendation.	
RAL 100 mg (scored chewable tablet)	**Dosing strength changed to 25 mg scored chewable tablet**
New WHO 2018 recommendations include use of RAL as an alternative first-line regimen option for children aged 4 weeks–10 years. RAL 25 mg replaces RAL 100 mg chewable scored tablets as it adds the maximum dosing flexibility to provide RAL-based regimens across all weight bands for first- and second-line treatment.	
LPV/r oral solution 80 mg/20 mg/mL	**Moved from Optimal Formulary to Limited-use List**
LPV/r solid oral dosage forms are increasingly becoming available and should be used whenever possible; however LPV/r oral liquid may still be required until a solid oral dosage form of LPV/r appropriate for infants aged 2 weeks to 3 months becomes available.	
EFV scored tablet 200 mg	**Moved from Optimal Formulary to Limited-use List**
Due to increasing resistance and reduced efficacy, NNRTI-based regimens are no longer recommended as preferred or alternative first-line regimens except in neonatal populations. However, EFV may continue to be needed until PI- or INSTI-based regimens are more widely available across all paediatric age groups.	
ABC/3TC 60 mg/30 mg scored dispersible tablet	**Removed from Optimal Formulary**
To minimize market fragmentation while decreasing pill burden for older children, ABC 120mg/60mg dispersible scored tablet has fully replaced the 60 mg/30 mg dispersible table.	
LPV/r oral pellets 40 mg/10 mg	**Dosage description changed to solid oral dosage form**
The description of the dosage form was expanded to include equivalent solid oral dosage forms that may become more widely available in the near to midterm future including pellets and granules.	
AZT 60 mg dispersible scored tablet	**Removed from Limited-use List**
AZT 60mg dispersible scored tablet was removed from the Limited-use List as the current ABC 60mg dispersible scored tablet can be used in combination with AZT/3TC dual FDCs to deliver a triple nucleoside regimen during TB treatment.	
RTV oral liquid 400 mg/5 mL	**Removed from the Limited-use List**
Challenges related to dosage form (cold chain-requiring, poor palatability and short shelf life of six months) has limited use of this product. Given available alternatives for superboosting LPV/r or providing a triple nucleoside regimen for the duration of TB treatment, RTV liquid was removed from the Limited-use List.	
RTV powder 100 mg/packet	**Added to Limited-use List**
RTV powder was included on the Limited-use List to provide an alternative dosage form for children unable to swallow RTV tablets.	
ATV 100 mg capsule	**Dosage strength changed to 200 mg**
Dosing guidance has been updated to increase dosing of ATV to 200 mg for children weighing 10 kg–35 kg.	
RAL granules for oral suspension	**Added to Limited-use List**
RAL-based regimens are now the preferred first-line for neonates. RAL granules were added to the Limited-use List for this time-limited purpose.	

6. IMPLEMENTATION

Publication of the 2018 Optimal Formulary and Limited-use List is an important tool to support programmes as they update national paediatric HIV treatment guidelines in consideration of WHO 2018 guideline updates.

It is well recognized that there are market challenges faced by countries when transitioning to new WHO guidelines. The Antiretroviral Procurement Working Group (APWG) is committed to a joint process to support countries in the transition to optimal regimens by ensuring greater availability of products included on the Optimal Formulary and Limited-use List through a process of coordinated procurement and active engagement with manufacturers.

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