POLICY BRIEF

IATT PAEDIATRIC ARV FORMULARY AND LIMITED-USE LIST: 2016 UPDATE

World Health Organization

IATT
THE INTERAGENCY TASK TEAM
The Interagency Task Team on the Prevention and Treatment of HIV Infection in Pregnant Women, Mothers and Children

unicef

BACKGROUND

Delivery of antiretroviral treatment (ART) to children living with HIV is associated with a complex set of clinical, operational and procurement challenges, particularly in resource limited settings where over 90% of these children receive care. Currently, children account for less than 5% of all people on ART,[1] and as the global community gets closer to the goal of elimination of mother-to-child transmission (eMTCT), the number of paediatric patients is expected to further decrease. This makes market coordination increasingly important to ensure pediatric products remain available and accessible in resource-limited settings.

Appropriate treatment of paediatric patients requires dosing across a range of ages and weight-bands, often using different antiretroviral (ARV) formulations. In recent years, new formulations that meet the unique administration needs of children have become available, such as dispersible fixed-dose combinations (FDCs) and the WHO provides some general principles for the dosing of available ARV formulations for infants and children (Figure 1). These products have significantly improved the quality of paediatric HIV care in resource-limited settings; however, the proliferation of these newer options, alongside the continued availability of older sub-optimal products, resulted in fragmentation of procurement orders across multiple and often duplicative products.

FIGURE 1

- It is preferable to use an age-appropriate fixed dose combination for any regimen if such a formulation is available.
- Oral liquid or syrup formulations should be avoided where possible, especially if volumes are large – such as above 10 ml.
- Dispersible tablets (or tablets for oral solution) are the preferred solid oral dosage forms, since each dispersible tablet can be made into liquid at the point of use.
- In general, young children should be switched to available solid oral dosage forms as soon as they are tolerated.
- Where children have to use adult formulations, care must be taken to avoid underdosing. Adult tablets that are scored are more easily split. For tablets that are not easily split, WHO recommends that this be done in the dispensing pharmacy using appropriate tablet cutters.
- Some tablets such as LPV/r 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 or crushed, since they lose bioavailability. Different dosing between morning and evening doses should be avoided.

[1] UNAIDS 2016 estimates

The first IATT Optimal Paediatric ARV Formulary was created in 2011 by the Child Survival Working Group (CWSG) and the Supply Chain Management Working Group (SCMWG) of the Interagency Task Team (IATT) on the Prevention and Treatment of HIV infection in Pregnant Women, Mothers and Children[2]. Since then, the group has convened in conjunction with the Antiretroviral Procurement Working Group (APWG)[3] every 6 months and following any updates from the WHO Consolidated ARV Guidelines, to update the existing Optimal Paediatric ARV Formulary. The review process is designed to ensure the Optimal Formulary remains current in order to provide the right set of formulations to cover WHO recommended paediatric ARV regimens.

This list continues to serve as guidance for national programmes, procurement agencies, funders, and manufacturers to select products that closely align to the criteria describing optimal paediatric dosage forms (Table 1).

TABLE 1 : EVALUATION CRITERIA

CRITERIA	DESCRIPTION
WHO recommended	Safety and efficacy established
Available in resource limited settings	In country registration Reliable supply
SRA/WHO PQ approved	≥ 1 quality assured product available
User friendly	Easy for HCW's to prescribe Easy for caregivers to administer Supports adherence in children
Optimizes supply chain	Easy to transport Easy to store Easy to distribute
Dosing flexibility	Allows for the widest range of dosing options
Comparative cost	Cost should NOT be the deciding factor in selection of a drug but comparative cost of similar drugs/drug formulations should be considered

[2] BIPAI, CMMB, CDC, CHAI, ICAP, EGPAF, FHI 360, Futures Group, GNP+, IAS, Intrahealth, MOH Kenya, MOH Mozambique, MOH Uganda, MOH Zimbabwe, MSH, MSI, PATA, PEPFAR, PfSCM, Save the Children, UNAIDS, UNFPA, UNICEF, USAID, WFP, WHO, World Vision
[3] Formerly known as the Paediatric ARV Procurement Working group

REVISION PROCESS AND MAJOR CONSIDERATIONS

The IATT optimal formulary subcommittee met in 2016 following the release of the WHO Policy Brief in November 2015; a precursor to the Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, released in June 2016.[4]

MAJOR CONSIDERATIONS

In 2016, for the first time, the WHO recommends all populations living with HIV be started on ART upon diagnosis, removing all prior age, immunologic and clinical thresholds for initiation. Additionally, there is now a recommendation to consider the addition of birth testing for HIV-exposed infant, which may result in the increased need for ART options in the neonatal period.

Preferred and alternative first-line ART regimens for children 0-3 years and 3-10 years have not changed from 2013 to 2016. In 2016, preferred and alternative ART regimens for adolescents are harmonized with those for adults.

For the first time, paediatric second-line recommendations now include raltegravir (RAL) for patients after first-line failure on ritonavir-boosted lopinavir (LPV/r) containing regimens, and alternative use of ritonavir-boosted atazanavir (ATV/r) after failing non- nucleoside reverse transcriptase (NNRTI) based regimens. Additional guidance has been given on third-line including use of darunavir (DRV), RAL and dolutegravir (DTG).[5] Dual drug prophylaxis containing zidovudine (AZT) and nevirapine (NVP) for infants at high risk of HIV infection is now recommended for up to 12 weeks.

Table 2: Preferred and alternative first and second-line regimens for children, according to the 2015 WHO Guidelines on the Consolidated Use of Antiretroviral Drugs for the Prevention and Treatment of HIV Infection.

	CHILDREN	FIRST-LINE ART REGIMEN	SECOND-LINE ART REGIMEN
LPV/r-based first line	Younger than 3 years	ABC + 3TC + LPV/r	AZT or ABC + 3TC + RAL
		AZT + 3TC + LPV/r	
	3 years and older	ABC + 3TC + LPV/r	AZT + 3TC + EFV or RAL
		AZT + 3TC + LPV/r	ABC or TDF + 3TC + EFV or RAL
NNRTI-based first-line regimen	All ages	ABC + 3TC + EFV (or NVP)	AZT + 3TC + ATV/r or LPV/r
		TDF + 3TC + EFV (or NVP)	
		AZT + 3TC + EFV (or NVP)	ABC or TDF + 3TC + ATV/r or LPV/r

New paediatric dosage forms have been approved by the United States Food and Drug Administration (USFDA) and WHO prequalification: LPV/r 40mg/10mg oral pellets approved by USFDA May 2015 and ritonavir (RTV) 25mg and 50mg heat stable tablets approved by USFDA in March 25 were reviewed during this revision process.

[4] WHO. Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection. WHO. Geneva. June 2016. Available at http://apps.who.int/iris/bitstream/10665/208825/1/9789241549684_eng.pdf?ua=1

[5] At the time of the revision process DTG was not yet approved for use in children <12 years and no paediatric formulations were available. However, since the finalization of the list, DTG was approved for use in children from 6 years and 30kg.

OPTIMAL PAEDIATRIC ARV FORMULARY AND LIMITED-USE LIST

In light of the 2016 WHO Consolidated Guideline revision, the IATT has updated the Paediatric ARV Optimal Formulary and Limited-use List to provide guidance for programmes in the selection of paediatric ARV dosage forms required to implement new recommendations. The definition of the Optimal Formulary has been expanded to include all preferred first and second-line paediatric ARVs and products for routine infant prophylaxis in PMTCT. Dosage forms required to deliver alternative first and second-line regimens, as well as special circumstances such as early infant treatment or third-line regimens are included on the Limited-use List.

2016 OPTIMAL PAEDIATRIC ARV FORMULARY LIST

DRUG CLASS	DRUG	FORMULATION	DOSE
NNRTI	EFV	Tablet (scored)	200 mg
NNRTI	NVP	Tablet (disp, scored)	50 mg
NNRTI	NVP	Oral liquid	50 mg/5mL, 100ml
PI	LPV/r	Tablet (heat stable)	100 mg/25mg
PI	LPV/r	Oral liquid	80 mg/20 mg/mL
PI	LPV/r	Oral pellets	40mg/10mg
FDC	AZT/3TC	Tablet (disp, scored)	60 mg/30 mg
FDC	ABC/3TC	Tablet (disp, scored)	60 mg/30 mg,120mg/60mg
INSTI	RAL	Chewable tab	100mg

CHANGES TO THE OPTIMAL PAEDIATRIC FORMULARY

In the 2016 review, two products were added to the Optimal List and one product was removed. The table below summarizes the considerations of the group.

DRUG DOSAGE AND FORM	STATUS
Lopinavir/Ritonavir 40mg/10mg (oral pellets)	**Added to Optimal List**
Comments: In resource limited settings where use of LPV/r oral liquid has precluded effective delivery of the preferred first-line regimen to infants and children less than 3 years of age, the heat-stable, coated LPV/r oral pellets offer an advantage for programmes, caregivers and young patients. Further guidance on administration and supply planning can be found on the IATT website.[6,7] At the time of this review, the first commercial batch was in production and planning for country programme introduction is underway.	
Raltegravir 100mg (scored chewable tablet)	**Added to Optimal List**
Comments: RAL- containing regimens are now included as a second-line option for patients after failure of an LPV/r - containing first-line regimen. 100mg scored chewable tablets are appropriate for use in children 14 kg and above. As the majority of children failing LPV/r - containing first-line regimens are expected to be older in age and thus above 14kg, the RAL 100mg scored chewable tablet offers a low pill burden. The 25mg chewable tablet is available for dosing in younger children (see Limited-use List below).	
Zidovudine/lamivudine/Nevirapine 60mg/30mg/50mg (scored, dispersible tablet)	**Moved from Optimal to Limited-use List**
Comments: With emphasis on inclusion of preferred first-line regimens and the availability of new formulations to provide LPV/r - containing regimens to younger children, the decision was made to remove AZT/3TC/NVP from the optimal use list. Although the product is still in widespread use, it is anticipated that with time, programmes will transition to increased use of LPV/r-based first-line regimens for younger children and use of EFV-based first-line regimens for children > 3 years.	

[6] Factsheet on Lopinavir and Ritonavir (LPV/r) Oral Pellets. IATT. New York, NY. September 2015. Available at http://www.emtct-iatt.org/wp-content/uploads/2015/09/IATT-LPVr-Factsheet-Final-30-September-2015.pdf

[7] Policy Brief on Supply Planning for New Dosage Form of Lopinavir and Ritonavir Oral Pellets: http://www.emtct-iatt.org/wp-content/uploads/2015/11/Supply-Planning-Lopinavir-Oral-Pellets-BRIEF.pdf

2016 LIMITED - USE PAEDIATRIC ARV FORMULARY LIST

DRUG CLASS	DRUG	FORMULATION	DOSE	RATIONALE FOR USE
NRTI	AZT	Oral liquid	50 mg/5mL- 100mL	For infant prophylaxis or as part of a neonatal treatment regimen
NRTI	3TC	Oral liquid	50mg/5mL- 240mL	As part of a neonatal treatment regimen
NRTI NRTI	ABC AZT	Tablet (dispersible, scored)	60mg 60mg	For children <3 years undergoing TB treatment requiring triple nucleo-side regimen
PI	DRV	Tablet	75 mg	Third line
PI	RTV	Tablet	25mg	For boosting of noncoformulated PI's (DRV and ATV)
PI	RTV	Oral liquid	400 mg/5mL, 240mL	For super boosting of LPV/r during TB treatment
PI	ATV	Solid oral dosage form	100 mg	Alternative second line
Int Inh	RAL	Chew tab (scored)	25 mg	Second line after LPV/r - containing first-line failure
FDC	AZT/ 3TC/ NVP	Tablet (dispersible, scored)	60mg/30mg/50mg	Alternative first-line

CHANGES TO THE LIMITED – USE PAEDIATRIC FORMULARY

In the 2016 review, four products were added to the Limited-use List and five products were removed. The table below summarizes the considerations of the group.

DRUG DOSAGE AND FORM	STATUS
Lamivudine 50mg/5mL (oral liquid)	**Added to Limited-use List**
Comments: With increasing availability of dispersible FDCs that can be used to dose across weight bands, programmes have been encouraged to phase out the use of oral liquids, which have challenges around cold chain requirements, toxic excipients, and foul tastes. However, with new recommendations for birth testing provision of neonatal treatment options must be considered. 3TC oral liquid may be used with AZT oral liquid to provide an NRTI backbone as part of a three drug regimen until such time as infants can be transitioned to dual dispersible FDCs.	
Raltegravir 25mg (chewable tablet)	**Added to Limited-use List**
RAL 25mg chewable tablets may be used in younger children after LPV/r failure. Note: the 25mg chewable tablet is currently approved for use in children older than 2 years and greater than 10kg. Though RAL has also been included as an option for first-line in younger infants when LPV/r is not available, the currently approved dosage form for use in children 4 weeks to 2 years, RAL granules for oral suspension, were not included at this time on the Limited-use List as the complications of dosing this form did not meet the criteria of being user-friendly.	
Ritonavir 25mg (heat stable tablet)	**Added to Limited-use List**
Comments: Both RTV 50mg and 25mg heat stable tablet formulations of ritonavir were considered during the review process. As use of the 25 mg tablet allows for flexibility in boosting of DRV across all weight bands in children 15 kg and above and can also be used for super-boosting of LPV/r during TB treatment in some weight bands, it was chosen for inclusion on the Limited-use List. As the 50mg tablet does not offer the same degree of dosing flexibility, it was not included on the list.	
Tenofovir 200mg (tablet)	**Removed from Limited-use List**
Comments: Though tenofovir (TDF) - containing regimens have been included as alternate first-line regimens for children aged 3-10 since the 2013 guidelines, use of this regimen has been challenged by the unavailability of suitable FDC's appropriate for use across paediatric weight bands. As a result, there continues to be limited use of TDF in paediatric populations. In 2014, a decision was made to limit the inclusion of paediatric TDF dosage forms on the Limited-use List to the 200mg tablet needed to dose older children weighing 20-29.9kg. However, programmatic experience with use of this product continues to be limited due to the inconvenience of needing separate 3TC or FTC to complete an NRTI backbone, as well as ongoing concerns about the long term toxicity of TDF in paediatric populations. Without the availability of a TDF - containing FDC, use of TDF in paediatric regimens adds additional cost and complexity to programmes without additional clinical benefit for the majority of paediatric patients.	
Etravirine 25mg and 100mg (tablet)	**Removed from Limited-use List**
Comments: Both etravirine (ETV) 25mg and 100mg were discussed for this revision and the decision was made to exclude them from the Limited-use List, as ETV, which is only approved for use in children 6 years and older, is not included as an option for paediatric use in the current WHO recommendations and currently there are limited indications for use of ETV in public health settings.	
Atazanavir 150mg (capsule)	**Removed from Limited-use List**
Comments: Recent WHO guidance for paediatric dosing became available which allowed for dosing of ATV across all paediatric weight bands from 10kg onwards in 100mg increments with use of a concurrent 100mg boosting dose of RTV. The ATV 100mg capsule was maintained on the Limited-use List, but this new dosing schedule now obviates the need for an additional dosage form of ATV 150mg.	

PROGRAMME IMPLEMENTATION

The IATT and the APWG have committed to a joint process to support countries in the transition to optimal products and coordinated procurement to ensure greater availability and more rational use of paediatric ARVs. The IATT recognizes there are certain programmatic challenges that countries face when transitioning to new WHO guidelines and implementing the revised IATT formulary.

- **Quantification:** The lack of programmatic data on the distribution of weight bands across paediatric populations presents a challenge in quantification for paediatric products, as different dosages are needed across various paediatric age and weight bands. The Optimal Formulary and Limited-use List aims to simplify procurement by consolidating dosage forms that offer the most flexibility in dosing. Countries are encouraged to consider the distribution of ages and weights in their paediatric treatment population and plan for regimen transitions as new guidance is implemented. Likewise, it is important to consider that as children mature into young adults, they will transition to adult dosage forms or adult regimens though still classified as paediatric patients. Programmes should consider offering clear guidance on when children should be transitioned to simplify instructions for health care workers as well as inform procurement.

- **National formulary and regimen rationalization:** As recommendations have changed over time a variety of paediatric ART regimens may be simultaneously in use by patients already on ART. Programmes are encouraged to review their consumption data as well as the distribution of different ARV regimens decide if older regimens should continue to be used or if patients should be transitioned to a new regimen. If transitioning to a new regimen is recommended, clear communication and guidance must be provided to health care workers to inform appropriate substitution strategies. Technical assistance from the IATT and APWG is available to assist countries in the formulary rationalization process.

- **New product introduction:** As new products enter the market, the IATT reviews the formulary to ensure optimization around the best available products; however, country registration and appropriate rollout planning for new products is necessary to ensure successful uptake of new products. Programmes are encouraged to consider these issues early on in the process of adopting new ARV products. Programmes should also plan for phased transition if a new product will be replacing a drug or dosage form that is to be phased out of use. However, as newly introduced products may have longer lead times, sufficient quantities of older product should be available to ensure there are no stockouts during the transition period.

Technical assistance is available via the IATT and APWG.
For further information or technical assistance please contact:

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