WHO / Christine McNab

POLICY BRIEF

THE 2021 OPTIMAL FORMULARY AND LIMITED-USE LIST FOR ANTIRETROVIRAL DRUGS FOR CHILDREN

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The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief

ISBN 978-92-4-002352-9 (electronic version)
ISBN 978-92-4-002353-6 (print version)

Suggested citation. The 2021 optimal formulary and limited-use list for antiretroviral drugs for children: policy brief. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Design and layout by 400 Communications

1. BACKGROUND

Since 2011, the publication of the Optimal Formulary and Limited-use List has provided clear guidance to country programmes, procurement entities and funding agencies on the essential antiretroviral therapy (ART) dosage forms for children needed to deliver WHO-recommended ART regimens to neonates (0- <4 weeks of age), and children for all lines of treatment. The products included on the list are regularly reviewed against a specific list of criteria (see Table 3) that considers current WHO recommendations, supply constraints and programmatic realities to support programmes in taking a pragmatic approach to implementing updated WHO-recommended regimens in a rapidly changing antiretroviral (ARV) drug landscape.

This sixth edition of the Optimal Formulary and Limited-use List is intended to support the transition and implementation of preferred and alternative ART regimens recommended for infants and children in the 2019 WHO guidelines across all lines of treatment.

WHO/Ilyas Ahmed

2. CURRENT WHO GUIDELINES

Table 1. Summary of preferred and alternative first-line ART for neonates and children

	Neonates	Children
Preferred	AZT+3TC+RAL[a]	ABC + 3TC + DTG
Alternatives	AZT+3TC+NVP	ABC + 3TC + LPVr TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + RAL[d]
Special circumstances[d]	AZT+3TC+LPVr[b]	ABC + 3TC + EFV[e] (or NVP[f]) AZT + 3TC + EFV[e] (or NVP[f]) AZT + 3TC + LPVr (or RAL)

[a] For the shortest time possible, until a solid formulation of LPVr or DTG can be safely administered.
[b] From two weeks of age if oral solution or granule formulations can be used. Although LPVr pellets cannot be used for neonates, they can be used from three months of age.
[c] For age and weight groups with approved TAF dosing (since January 2020, TAF has been approved from 25 kg).
[d] For special circumstances when preferred and alternative regimens are not available or cannot be used.
[e] From three years of age.
[f] Only in cases where no other alternatives are available.

Table 2. Summary of sequencing options for ART for children

First-line ART	Second-line ART[a]	Third-line ART
Two NRTIs + LPVr	Two NRTIs + DTG	DRV/r + DTG[b] with or without one or two NRTIs. Where possible, consider optimization using genotyping
Two NRTIs + EFV or NVP	Two NRTIs + DTG	
Two NRTIs + DTG or RAL	Two NRTIs + LPVr or ATVr	

[a] An optimized NRTI backbone should be used: AZT following TDF or ABC failure and vice versa.
[b] DTG-based third-line ART following the use of an integrase inhibitor must be administered with DTG twice daily.

In March 2021, the WHO-convened Paediatric ARV Working Group (PAWG) carefully considered the benefits and risks related to a programmatic transition to DTG-based regimens for children established on first- and second-line and encourages rapid programmatic transition to DTG-based regimens for ALL children established on first- and second-line ART irrespective of their current regimen. Transition to DTG should take into account:

- Availability and anticipated supply of DTG 10 mg score tablets and, in case of inadequate supplies to provide DTG to all children, the need to prioritize children who most need DTG beyond those starting ART:
  - Children on NNRTI-based regimens
  - Children who need to start rifampicin-based TB treatment
  - Children on LPVr liquid and solid formulations, particularly where those continue to present challenges in administration and/or challenges with attaining optimal viral load suppression

- While viral load monitoring remains a good practice to deliver appropriate care to children living with HIV, viral load (VL) should not be considered a precondition to undertaking a programmatic or individual transition and children should not have their transition to DTG delayed due to lack of documented viral load.

The group also agreed that DTG dosing recommendations during TB treatment should align with US FDA approval and support the use of DTG twice daily across age groups and weight bands (as currently recommended for adults).

Finally, the group reviewed administration guidance and agreed that DTG dispersible tablets should be ideally dispersed in water or swallowed whole. Crushing, chewing or mixing with other foods or liquids can be considered as long as the child can consume the entire amount of liquid or food.

WHO/Heehaw

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 Optimal Formulary and Limited-use List since availability is country-specific and subject to change. Funding agencies, procurement entities, manufacturers, national medicine regulatory authorities and national governments all have a critical role to play in working together to ensure the availability of products on the Optimal Formulary and Limited-use List, which can be achieved by fast-tracking in-country registration, maintaining procurement and supply-chain planning, facilitating commercialization and ensuring manufacturing capacity and filing applications for registration in other countries. Having one or more quality-assured suppliers available at the national level is, however, a criterion for selection of products.

Table 3. 2018 criteria to define optimal paediatric ARV dosage forms

Criterion	Description
Meets WHO requirements	Included in the latest WHO guidelines for treatment for children
Dosing flexibility	Allows for the widest range of dosing options
Approved by WHO Listed Authorities (WLA)	One or more quality-assured products available
User friendly	Easy for health-care workers 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 selecting a drug, but the comparative cost of similar drugs or drug formulations should be considered

4. OPTIMAL FORMULARY

The Optimal Formulary is designed to include the minimum number of ARV drug formulations needed to deliver WHO-recommended (preferred and alternative) first- and second-line ART regimens for infants and children.

Appropriate dosage forms for postnatal prophylaxis for preventing the vertical transmission of HIV to HIV-exposed infants are also included given the critical need for these products.

Optimal Formulary: Minimum number of ARV drug formulations needed to provide all currently WHO-recommended preferred and alternative first- and second-line ART options for infants and children and infant prophylaxis for preventing vertical transmission of HIV.

Drug	Dosage form	Strength	Rationale for use	Pack size
DTG[a]	Tablet (dispersible, scored)	10 mg	For first-line or second-line ART for infants and children who are ≥4 weeks of age and weighing 3-<20 kg	90 count
ABC + 3TC	Tablet (dispersible, scored)	120 mg/60 mg	For preferred first-line or second-line ART for infants and children weighting 3-25 kg	30 and 60 count packs
AZT[b]	Oral solution	50 mg/5 mL	For postnatal prophylaxis and treatment of neonates (first four weeks of life)	240 mL bottle
NVP	Oral solution	50 mg/5 mL	For postnatal prophylaxis and neonatal treatment only	100 mL bottle
LPVr	Tablet (heat stable)	100 mg/ 25 mg	For alternative first-line or second-line ART for children weighing ≥10 kg and who are able to swallow tablets whole	60 count pack
LPVr	Oral granules	40 mg/10 mg	For alternative first-line or second-line ART for infants and children weighing ≤10 kg or unable to swallow 100 mg/25 mg tablets whole	120 count pack
AZT + 3TC	Tablet (dispersible, scored)	60 mg/ 30 mg	For second-line ART for infants and children weighing 3-25 kg	60 count pack

[a] DTG 50 mg film-coated tablets is the preferred formulation for children weighing ≥20 kg (and co-formulated DTG 50 mg + TDF 300 mg + 3TC 300 mg - also known as TLD - for those weighing ≥30 kg) to reduce the pill burden, simplify supply chain processes and reduce programme costs. Programmes should ensure that the ≥20 kg population is accounted for during quantification for DTG 50 mg tablets.

[b] As of March 2021, AZT oral solution is only available in a 240 mL bottle. This formulation is only anticipated to be used for neonatal treatment or enhanced infant prophylaxis. AZT oral solution has a four-week shelf life after opening, and infants using AZT oral solution for longer than this period a new bottle should be issued after four weeks.

5. THE LIMITED-USE LIST

The Limited-use List covers the 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 tuberculosis treatment, neonatal treatment and third-line ART.

Limited-use List: ARV drug formulations that are included in the WHO guidelines and are needed for a limited time or in low volumes.

Drug	Dosage form	Strength	Rationale for use	Pack size
NVP	Tablet (scored, dispersible)	50 mg	Only for postnatal prophylaxis when NVP oral solution is not available	60 count packs
3TC	Oral solution	50 mg/5 mL	Only for treating neonates (first four weeks of life)	240 mL bottle
RAL	Granules for suspension	100 mg	Only for treating neonates (first four weeks of life)	60 count packs
LPVr	Oral pellets	40 mg/10 mg	For specific circumstances in which DTG 10 mg scored tablets or LPVr oral granules are not available or clinically indicated	120 count packs
DRV	Tablet	75 mg, 150 mg	For third-line ART regimens for children three years and older	480 and 240 count packs
RTV	Tablet	25 mg	For superboosting of LPVr with during TB treatment and required for use when administering DRV	60 count packs

6. IMPLEMENTATION

Publication of the 2020 Optimal Formulary and Limited-use List is an important tool to support programmes as they update national HIV treatment guidelines for children given updates to WHO guidelines.

Countries face market and implementation challenges when adopting new WHO guidelines. The Antiretroviral Procurement Working Group (APWG, www.arvprocurementworkinggroup.org) and the Global Accelerator for Paediatric Formulations (GAP-f, http://gap-f.org) partners are committed to supporting country programmes to successfully transition to optimal regimens by ensuring that products included on the Optimal Formulary and Limited-use List are available for procurement. The APWG and GAP-f partners are actively working to coordinate the procurement of low-volume ARV drug products by collating ARV drug forecasts, actively engaging with manufacturers and disseminating guidance and information to procurement agencies and programme managers.

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Annex 1. Modifications to the Optimal Formulary and Limited-use List

Drug Dosage and Form	Status
DTG 10 mg scored dispersible tablet	**Added to the Optimal Formulary**
The availability of the DTG 10 mg scored dispersible tablet now supports implementation of the preferred regimen for children at least 4 weeks of age and weighing at least 3 kg.	
AZT oral solution 50 mg/5 mL, 100 mL	**Bottle volume changed to 240 mL**
At the time of revision, AZT oral solution in a 100 mL bottle is available in limited supply.	
NVP 50 mg scored dispersible tablet	**Moved from Optimal Formulary to the Limited-use List**
When NVP oral solution is not available, some programmes have divided NVP tablets to provide infant prophylaxis; however, this is a less preferable option since the safety of dosing in neonates has not been adequately established.	
RAL 25 mg (scored chewable tablet)	**Removed from Optimal Formulary**
The introduction of DTG 10 mg scored dispersible tablets enables the delivery of a superior integrase inhibitor-based regimen for infants and children weighing 3-<20 kg. Raltegravir remains an alternative option when neither DTG nor LPVr solid formulations are available or indicated.	
LPVr oral solution 80 mg/20 mg/mL	**Removed from Limited-use List**
With increasing use of integrase inhibitor–based regimens and a preference for LPVr granules, LPVr oral solution should no longer be required.	
EFV scored tablet 200 mg	**Removed from the Limited-use List**
Because of increasing NNRTI resistance and suboptimal antiretroviral potency, NNRTI-based regimens are no longer recommended as preferred or alternative regimens for children. This product should be phased out.	
LPVr oral pellets 40 mg/10 mg	**Moved from Optimal Formulary to the Limited-use List**
The use of DTG for infants and young children is expected to replace the use of LPVr, and the need for LPVr is therefore anticipated to decrease. LPVr oral granules were chosen over oral pellets based on administration characteristics and age indication: LPVr oral granules can be used from two weeks (instead of three months) and are easier to administer compared to LPVr oral pellets. As a result, LPVr oral granules were retained in the optimal formulary and LPVr oral pellets were included in the Limited-use List.	
ABC 60 mg dispersible scored tablet	**Removed from the Limited-use List**
The ABC 60 mg dispersible scored tablet was removed from the Limited-use List since this was only intended to deliver a triple-nucleoside regimen during tuberculosis treatment. With increasing use of integrase inhibitor-based regimens and the commercialization of RTV 25 mg, dose adjustment (twice-daily DTG or super-boosting LPVr) is preferable to a triple-nucleoside regimen for all infants and children during tuberculosis treatment.	
RTV powder 100 mg/packet	**Removed from the Limited-use List**
RTV 25 mg is the preferred option for protease inhibitor boosting since it enables more flexible dosing for younger children.	
ATV 200 mg capsule	**Removed from the Limited-use List**
Use of ATV for children has been limited to date, better options are more widely available.	
AZT + 3TC + NVP 60/30/50 mg scored dispersible tablet	**Removed from the Limited-use List**
This regimen is no longer recommended by the WHO guidelines.	

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