Scaling up optimal antiretroviral treatment for children: A long overdue intervention

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01 Rationale

To achieve an AIDS-free generation, optimal treatment options for all infants and young children living with HIV must be available, tolerable and most importantly, **effective**. Since 2013, WHO has recommended that **all** infants and children under three years of age initiate ritonavir-boosted lopinavir (LPV/r)-based regimens.[1] However, the transition to preferred pediatric regimens has been slow, and one-third of children remain on a sub-optimal regimen of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP). Only 20% receive the WHO-preferred regimen[2] despite resistance to non-nucleoside reverse transcriptase inhibitors becoming a major concern for infants and young children.[3] While efavirenz (EFV) is increasingly used, NVP-based regimens are also very common in children older than three years. As a result, overall virological suppression reported in program settings continues to be sub-optimal and particularly poor in young children younger than five years.[4]

02 Barriers and facilitators of implementation

Barriers

Until recently, the only dosage form of LPV/r available for infants and young children was a foul-tasting liquid that requires a cold chain and contains toxic excipients. In 2015, a heat-stable pellet formulation of LPV/r received tentative approval from the United States Food and Drug Administration (U.S. FDA).[5] This new formulation initially received enthusiastic reception, but manufacturing constraints have limited its availability and uptake at country level.[6] Even where LPV/r pellets are available, administration remains a challenge because the pellets are difficult for very young infants to swallow and their taste is unpleasant.

In comparison, the fixed-dose combination (FDC) tablet of AZT/3TC/NVP can be used across all pediatric weight bands from 3kg upward. It is available as a dispersible tablet that can be administered to younger infants. Compared to preferred pediatric regimens, it is less expensive for programs. However, ongoing use of this sub-optimal option places infants and children living with HIV at substantial risk of treatment failure, disease progression and the development of additional antiretroviral (ARV) drug resistance. Convenience is no longer acceptable as a rationale to initiate or maintain children on AZT/3TC/NVP. More effective regimens must be rapidly introduced.

Facilitators

Recent years have seen greater coordination at the global level to accelerate the development of pediatric ARVs in order to ensure their availability at the country program level. The Global Accelerator for Paediatric Formulations (GAP-f) has formalized collaboration across multiple stakeholders to speed the development of new pediatric ARVs.[7] GAP-f partners work closely with the ARV Procurement Working Group (APWG), chaired by the Global Fund, which convenes the major international buyers and other stakeholders involved in procurement of pediatric ARVs to coordinate supply availability with in-country demand. This coordination has been essential to stabilize the pediatric ARV marketplace in addition to supporting the dissemination of timely information related to the supply of pediatric ARVs.[8]

03 Steps for scale-up

Drug development and global efforts to make new pediatric formulations available in lower- and middle-income countries (LMICs) are meaningless if optimized treatment options never reach those who most need them. It is essential that programs plan early to ensure that when new optimal formulations become available, they can be introduced and scaled up efficiently. Considerations for the introduction of new pediatric ARVs include:

1) Updates to national policy

National guidelines must be updated to ensure that health care workers can appropriately prescribe new pediatric ARVs. In developing new recommendations, specific considerations for infants and children include:

- Eligibility criteria for new ARVs including age and weight requirements
- Dosing guidance by weight band
- Guidance on how and when to transition from regimens used in infants and younger children to those for older children
- Administration guidance for caregivers
- How and when adolescents should be transitioned to preferred adult regimens

2) Quantification

Dosing for pediatric populations is not one-size-fits-all and quantification must account for different regimens based on age group, as well as varying numbers of packs that may be needed across different weight bands. When quantifying for pediatric ARVs, programs should examine the age and weight distribution across their pediatric population to ensure the right quantity of ARVs are procured for the right population. This is of vital importance when regimens for infants and younger children differ from those for older children, and there is limited supply of the optimal ARV formulations needed to deliver them.

3) Procurement and supply chain management

The IATT Paediatric ARV Formulary is a streamlined list of optimal products that are needed to deliver all WHO-recommended first- and second-line regimens.[9] Countries are encouraged to refer to the formulary and select only pediatric ARV products for procurement from this list, thereby reducing the use of sub-optimal options that are less effective, unnecessary and/or being phased out of use.

04 Recommendations for transitioning to new pediatric ARVs

The phasing out of sub-optimal regimens, such as the AZT/3TC/NVP FDC, requires appropriate replacement regimens, and programs should be aware of and plan to transition to new pediatric ARV products that will be available in the near future.

LPV/r formulations

Manufacturing constraints of the LPV/r formulations to date should not deter countries from planning to transition to new optimal pediatric ARVs. Ongoing demand for the LPV/r pellets has signalled to manufacturers that there is a need for increased production of this product. Additionally, by mid-2019, it is anticipated that a new taste-masked LPV/r granule formulation and a four-in-one granule formulation of ABC, 3TC and LPV/r will become available.

Integrase inhibitors

Dolutegravir (DTG) is currently recommended as an alternative first-line ARV for adolescents and adults. As a potent, well-tolerated ARV with a high genetic barrier to resistance, DTG holds significant promise for pediatric populations. Currently, DTG is approved for use in children six years and older, weighing more than 30kg (by U.S. FDA) and 15kg (by EMA). Studies are ongoing to establish dosing for infants as young as four weeks. Generic formulations of pediatric DTG are in development, but this should not preclude the use of DTG in children now. Ten and 25mg tablets are available from the originator company which, together with PEPFAR, has expressed a commitment to make these formulations accessible to LMICs at accessible prices. Acceleration of in-country registration processes will be critical to ensure rapid access to DTG for children.

Raltegravir (RAL) is another option for infants and younger children, with the added advantage that it can be used in neonates (full term and ≥ 2kg). RAL is available as a granule for oral suspension, in 25mg chewable tablets and 100mg scored chewable tablets. Like DTG, pediatric formulations of RAL are also currently only available through the originator company, but similarly, efforts are underway to ensure that these products are available in LMICs, where they are most needed.

05 Tools to support implementation

The IATT Paediatric ARV Formulary is regularly updated to reflect current WHO guidelines on pediatric ART regimens, and programs are encouraged to review its most recent version. The fourth edition is available at http://apps.who.int/medicinedocs/en/d/Js23120en/. The fifth edition is anticipated in mid-2018.

06 Conclusion

At the end of 2017, almost one million children were receiving ART.[10] However, to provide antiretroviral therapy to all infants and children living with HIV and achieve the collective goal of an AIDS-free generation and decrease pediatric AIDS-related mortality, national programs must provide the most effective treatment available for all children living with HIV. Global partners and country programs should collectively accelerate action to introduce new optimal ARV formulations for all children.

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