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Innovation Needed on Pediatric ARV Formulations

Out of the estimated 3.3 million children living with HIV, only 650,000 are currently receiving antiretroviral therapy (ART).[1] Timely initiation and retention of HIV-positive children on antiretroviral drugs (ARVs) is a matter of life and death, since without antiretroviral treatment, half of children born with HIV die by the age of two years, and 80 percent die by the age of five years.

The development of effective ARVs for the treatment of HIV was a turning point in the fight against HIV and AIDS, yet 30 years into the epidemic, there are still too few effective ARV formulations developed specifically for children living with HIV. New and improved pediatric ARV formulations must be a priority in order to better address the needs of children impacted by the HIV epidemic worldwide.

Children – especially infants and young children – have significantly fewer treatment options than adults.

Clinical studies on ARVs for use in pediatric populations often occur years after drugs are approved for adults, limiting the availability of safe and effective ARVs for children. For example, only 10 of the 29 antiretroviral medicines approved for use in adults have also been approved for use in children under two years old.[2]

Children need different drug formulations at different stages of growth and development.

How the body processes ARVs (*i.e.* absorption, distribution, and elimination from the body) changes significantly with body mass and age, which affects how much of the drug is prescribed at different times in a child's life. For example, as seen in *Table 1*, for the commonly used drug zidovudine (AZT), the World Health Organization (WHO) recommends that a child's dose change four times from infancy through childhood.

Table 1: WHO AZT Tablet Dosage for Children[3]

Weight	60 mg AZT tablet dosage
3 kg - 5.9 kg	1 tablet twice a day
6 kg - 9.9 kg	1 ½ tablets twice a day
10 kg - 13.9 kg	2 tablets twice a day
14 kg - 19.9 kg	2 ½ tablets twice a day
20 kg - 24.9 kg	3 tablets twice a day

Also, as illustrated in *Table 2,* recommended first-line regimens vary by age/weight group, based on what is known about drug safety and effectiveness for those populations. These data are difficult to obtain. A range of ARV formulations and dosing options are needed in order to effectively treat children as their bodies grow and develop while they move from infancy, through childhood and adolescence, and into adulthood.

Existing pediatric ARVs can be difficult for children to take, impacting adherence and patient outcomes.

ARV treatment for HIV-infected adults can be as simple as one pill once a day, whereas treatment for children remains significantly more complicated and often difficult for caregivers and children to administer and take. Infants and small children need oral powders/sprinkles and syrups since they cannot swallow pills. Many liquid formulations require temperature-controlled environments (which are usually not feasible in resource-limited settings). The lack of new and improved pediatric ARV formulations means that children have to swallow a bitter tasting liquid or large number of different pills throughout the day ("heavy pill burden").

Children often need second- and third-line drugs because of drug resistance and treatment failure over a lifetime of treatment.

Pediatric patients often face drug resistance due to drug tolerance challenges, difficulties with adherence, complications with drug interactions due to treatment for TB co-infection, and/or the impact of drug availability due to ARV procurement challenges. Complicating this even further is a child's exposure to maternal ARVs during pregnancy, childbirth, and breastfeeding. The full scope of ARV drug resistance and its impact on pediatric ART are not known and need to be examined in order to preserve future treatment options for adulthood.

Continued political commitment and financial investment are needed for groundbreaking initiatives designed specifically to develop new and better drug formulations that address the needs of children living with HIV.

It is imperative that every child living with HIV has access to the medicines they need to stay healthy, grow, and develop to their full potential.

Promising new efforts are emerging to develop fixed-dose combinations (FDCs) and new means of administering existing drugs. This seeks to reduce the pill burden of pediatric HIV treatment regimens, simplify dosing for caregivers and children, and improve adherence at different ages and stages of children's development.

- The recently launched Pediatric HIV Treatment Initiative will bring multiple stakeholders together to develop and increase "access to new, better-adapted pediatric ARVs and formulations to improve treatment for all children living with HIV."[4]
- The Drugs for Neglected Diseases *initiative* (DND*i*) and the pharmaceutical company Cipla have joined together to develop a 4-in-1 ARV to be used in treatment regimens for infants and young children with HIV. This development could significantly improve treatment options for children.[5]
- According to the *WHO March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection*, "non-oral routes, such as transdermal patches and long-acting ARV drugs…could play a role in improving adherence among children."[6]

Table 2: Preferred and Alternative First-Line Regimens for Children, Based on WHO 2013 Consolidated Guidelines[7]

Age Group	Preferred first-line regimens	alternative first-line regimens
Children < 3 years	ABC or AZT + 3TC + LPV/r	ABC or AZT + 3TC + NVP
Children 3-9 years and adolescents <35kg	ABC + 3TC + EFV	ABC or AZT or TDF + 3TC (or FTC) + NVP or EFV
Adolescents (10-19 years) ≥ 35kg	TDF + 3TC (or FTC) + EFV	ABC or ATZ or TDF + 3TC (or FTC) + NVP or EFV

Table 3: Disadvantages of Common Antiretroviral Drug Components Recommended for Children[8]

Drug Name	Bitter taste	Needs to be administered with food	Frequent skin rashes	Gastrointestinal intolerance (Nausea, vomiting and/or diarrhea)	Central Nervous System symptoms	Potential effect on bone and kidney development	Potential for mitochondrial toxicity
Lopinavir/ Ritonavir (LPV/r)	X	X		X			
Ritonavir Booster (RTV)	X			X			
Nevirapine (NVP)		X	X				
Efavirenz (EFV)		X	X		X		
Tenofovir Disproxil Fumarate (TDF)				X		X	
Ziduvodine (AZT)				X			X
Lamivudine (3TC)							X
Emtricitabine (FTC)							X
Abacavir (ABC)			X				X

[1] UNAIDS. Children and HIV: fact sheet. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2014/FactSheet_Children_en.pdf. Updated May 2014. Accessed June 12, 2014.
[2] UNITAID. *HIV medicines technology and market landscape*, 1st ed. UNITAID; March 2014: 70.
[3] World Health Organization. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland: World Health Organization; June 2013: 247.
[4] UNITAID. Pediatric HIV treatment initiative: closing the treatment gap through innovation. http://www.unitaid.eu/images/publications/PEDS_ARV_INITIATIVE_HR.PDF. Accessed June 13, 2014.
[5] Drugs for Neglected Diseases *Initiative*. DND*i* & Cipla advance development of paediatric 4-in-1 ARVs to fulfill new WHO guidelines. http://www.dndi.org/media-centre/press-releases/1605-dndi-cipla-advance-development-of-paediatric-4-in-1-arvs-to-fulfill-new-who-guidelines.html. Updated June 30, 2013. Accessed Jun 13, 2014.
[6] World Health Organization. *March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection*. Geneva, Switzerland: World Health Organization; March 2014: 65.
[7] World Health Organization. *March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection.* Geneva, Switzerland: World Health Organization; March 2014: 60.
[8] Panel on Antiretroviral Therapy and Medical Management of HIV Infected Children. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Available at http://www.aidsinfo.nih.gov/contentfiles/lvguidelines/pediatricguidelines.pdf. Accessed April 2014; G14-G17, O2-O94.