

TOWARDS ENDING THE NEGLECT OF PAEDIATRIC HIV?

An Update on Efforts by the Drugs for Neglected Diseases *initiative*
to Improve HIV Treatment for Children



NOVEMBER 2017

INTRODUCTION

The Drugs for Neglected Diseases *initiative* (DNDi) is developing optimal child-adapted antiretroviral (ARV) formulations for the two million children living with HIV,¹ with a special focus on infants and young children who are at the highest risk of dying if they do not have access to treatment. This patient population has been deeply neglected by pharmaceutical research and development (R&D).

Despite major efforts to increase the number of children on HIV treatment and a continuing reduction in mother-to-child transmission of HIV, children are still being left behind. In 2016, only 43% of children living with HIV received antiretroviral therapy. While this is an impressive increase from 15% in 2009, this is considerably lower than the some 54% of adults that are currently on treatment.² One major challenge that contributes to this treatment gap are suboptimal paediatric ARV formulations.

DNDi aims to replace these formulations, which are horrid-tasting, hard to administer, require refrigeration, and are difficult to give in children that have HIV and tuberculosis (TB). In particular DNDi is working with the Indian generic company Cipla Ltd. to develop a solid first-line “4-in-1” fixed-dose combination (abacavir/lamivudine/lopinavir/ritonavir) using the World Health Organization (WHO) recommended treatment regimen for infants and young children. DNDi will ensure that these easy-to-use formulations are affordable and can be rapidly introduced throughout high-burden HIV countries. At the same time, DNDi and

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“People talk about a future AIDS-free generation, but we are concerned about the present. We want a generation of children that no longer struggle to take horrid-tasting medicines. Caregivers who can simply store, dose, and administer ARVs for kids. Mothers that do not have to bury a bucket of HIV medicines in the sand to keep them cool. A world where optimal ARVs are affordable and available so children are tested and quickly put on treatment.”

its partners in South Africa have addressed the negative drug-drug interactions between WHO-recommended HIV treatments and the TB drug rifampicin through a process known as “super-boosting.”

There has been considerable progress recently. An **implementation study** is being rolled out in three countries (Kenya, Uganda and Tanzania) for an improved oral pellet formulation of the WHO-recommended treatment, an important step towards introducing the 4-in-1. At the same time, a **study in South Africa** on children co-infected with HIV and TB has finished, providing essential evidence and data in support of WHO guidelines. Finally, **formulation work on the 4-in-1**

fixed-dose combinations is being completed with promising preliminary results, meaning these treatments could be available by the end of 2018.

There have been challenges and delays, some of which are outlined below, although the programme is now on track to deliver urgently needed new ARV formulations for children living with HIV.

DNDi’s paediatric HIV programme is funded primarily by Unitaid with additional support from the UBS Optimus Foundation, the French Development Agency (AFD), and Médecins Sans Frontières/Doctors Without Borders (MSF).

(1) UNAIDS. Biomedical AIDS research: Recent and upcoming advances. 2016
http://www.unaids.org/sites/default/files/media_asset/2016reference_biomedical-aids-research_en.pdf

(2) UNAIDS. Global HIV Statistics Fact Sheet. 2017
http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

SCALING UP WITH THE RIGHT TOOLS, RIGHT NOW – THE LIVING STUDY

Although the long-term goal of DNDi's paediatric HIV programme is to develop "4-in-1" formulations, DNDi is introducing a new and better formulation of a key component of paediatric ARV regimens to improve treatment for children now and importantly, to promote in-country adoption of the 4-in-1 when it is ready.

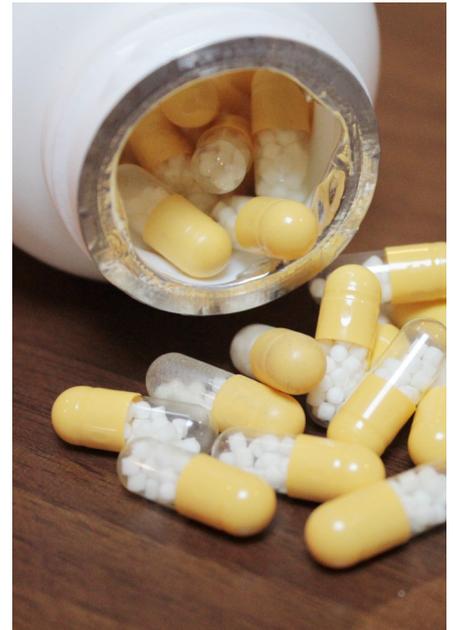
Since 2013, WHO has recommended regimens that include a class of ARVs called protease inhibitors (PIs), namely lopinavir/ritonavir (LPV/r), for infants and young children.³ Yet the only available version of LPV/r was a bitter-tasting syrup that requires refrigeration and contains 40% alcohol.⁴ In June 2015, the U.S. Food and Drug Administration (FDA) approved an oral pellet formulation of LPV/r, developed by Cipla Ltd., which can be administered to young children with food and does not require refrigeration.

In September 2015, DNDi launched the LIVING⁵ study with five sites in Kenya to provide early access to this new LPV/r

formulation, and expanded to Uganda in May 2016, and Tanzania in 2017. As of November 2017, the LIVING study has enrolled 750 patients.

Any child with a confirmed HIV-positive diagnosis, weighing from 3 kg up to 25 kg who cannot swallow pills can participate in the study. The study is intended to demonstrate the effectiveness, safety, and acceptability of LPV/r oral pellets in the field, used in association with dispersible tablets a class of ARVs known as nucleoside reverse transcriptase inhibitors (NRTIs), namely zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC).

As part of the LIVING study DNDi also evaluated the acceptance and adherence to the LPV/r pellets in a sub-study called RE-LIVING. This is the first time that these pellets are being used in real-life settings and findings from this evaluation will help programmes worldwide scale up treatment for HIV-infected children. Furthermore, an operational pilot of the use of the pellets was



launched in Zimbabwe in August 2016, in collaboration with the Clinton Health Access Initiative (CHAI), UNICEF and the Zimbabwean Ministry of Health.

Kenyan caregiver, interviewed
as part of RE-LIVING STUDY

"The pellets are easy to administer compared to the other one, the syrup. The syrup required a lot of work because you had to put it in a syringe, measure a particular quantity and give it to the child but this does not require a lot of work."

(3) World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. 30 June 2013. <http://www.who.int/hiv/pub/guidelines/arv2013/download/en/>

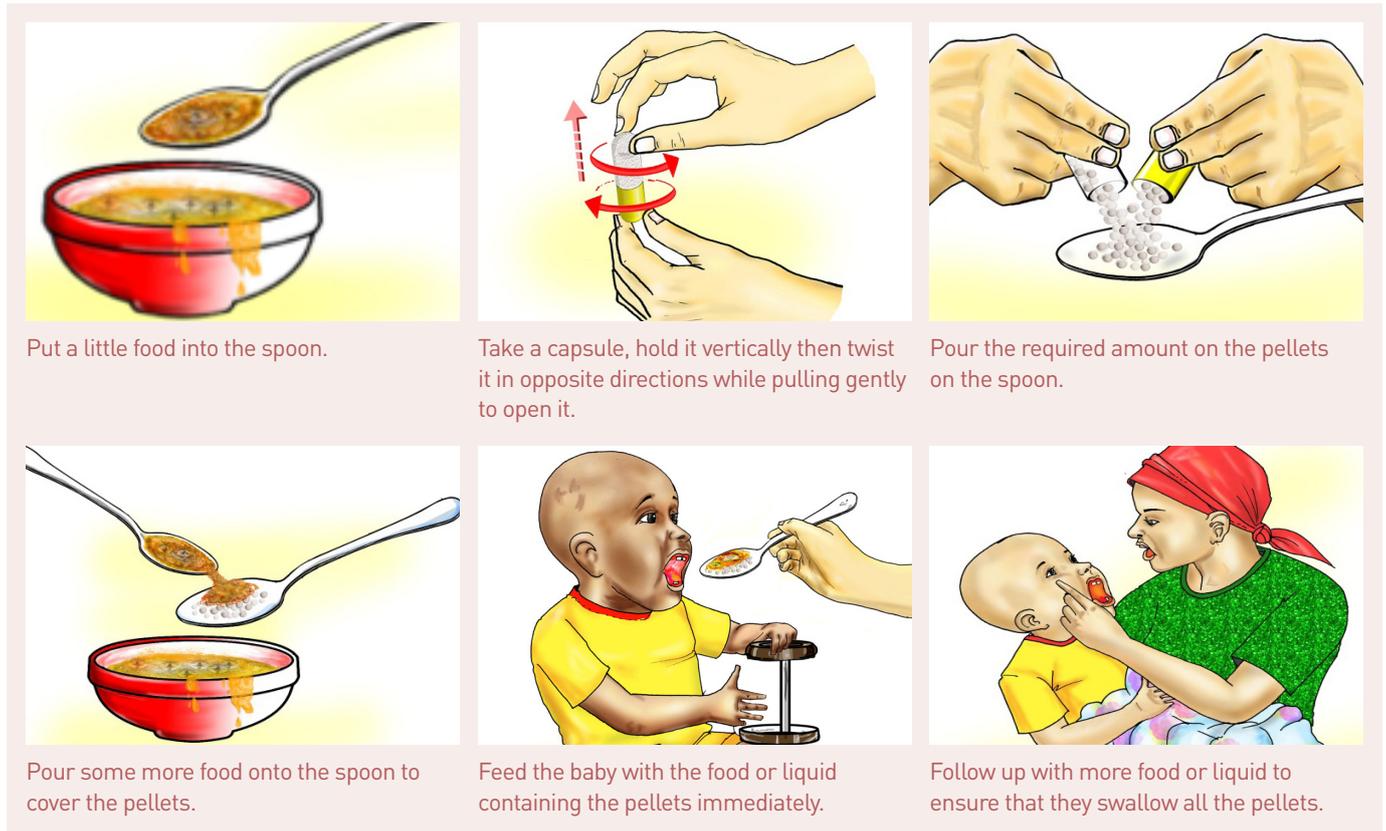
(4) For children more than 10kg, a LPV/r heat-stable tablet is available but only for children that can swallow pills.

(5) Prospective Study of Lopinavir Based ART for HIV Infected children globally." ClinicalTrials.gov Identifier: NCT02346487 <https://clinicaltrials.gov/ct2/show/NCT02346487>

HOW DO ORAL PELLETS WORK?

LPV/r pellets are stored in a capsule and can be opened and given with breastmilk or formula. The pellets can be sprinkled on a small amount of soft food and fed to the child. As part of the LIVING study, DNDi has created a set of illustrations to help health workers:⁶

LPV/r tablets are not “taste-masked,” meaning they still have a bitter taste – although they can be mixed with food. The pellets cannot be dissolved or crushed as they will develop an even more bitter taste. While refrigeration is no longer needed, pellets still can be bulky for higher weight bands. Better treatments are still needed.



(6) For more information, please consult two documents prepared by the Inter-Agency Task Team (IATT) on Children and HIV and AIDS, WHO, UNICEF and others on LPV/r oral pellets: “Supply Planning for New Dosage Form of Lopinavir and Ritonavir,”

<http://www.emtct-iatt.org/wp-content/uploads/2015/11/Supply-Planning-Lopinavir-Oral-Pellets-BRIEF.pdf> September 2015 and “On Lopinavir and Ritonavir Oral Pellets,” <http://emtct-iatt.org/wp-content/uploads/2016/04/LOPINAVIR-pellet-MEMO-English.pdf>, September 2015.

GETTING CLOSER TO OUR GOAL: PROGRESS ON THE “4-IN-1”

DNDi's long-term goal for paediatric HIV is to develop and deliver a taste-masked, heat-stable LPV/r-based fixed-dose combination for infants and young children. This treatment will combine key HIV drugs: LPV/r, which is a boosted PI, along with two NRTIs; abacavir and lamivudine.

The combination of a boosted PI such as LPV/r with two NRTIs is considered by the WHO as the most effective first-line therapy for infants and children under three years old.

When the 4-in-1 are made available, DNDi will support LIVING study sites and other programmes, as well as national governments, to transition from the interim LPV/r oral pellet to the 4-in-1.

CHALLENGES

Taste-masking has proven to be a major challenge in developing the 4-in-1 because bioavailability (i.e., the drug's ability to be absorbed by the body) can be lost when certain taste-masking agents are used. These molecules are highly insoluble and do not cross the gastro-intestinal barrier easily. They taste very bitter and cannot be made into a dispersible tablet.

An initial taste-masked formulation of LPV/r granules gave highly unpredictable LPV levels in adult volunteers and the formulation had to be abandoned. Following this, DNDi consulted various experts and worked closely with Cipla Ltd. to develop more than 30 LPV/r formulations, checking for chemical and physical stability and studying their bioavailability in animal models.

MOVING FORWARD

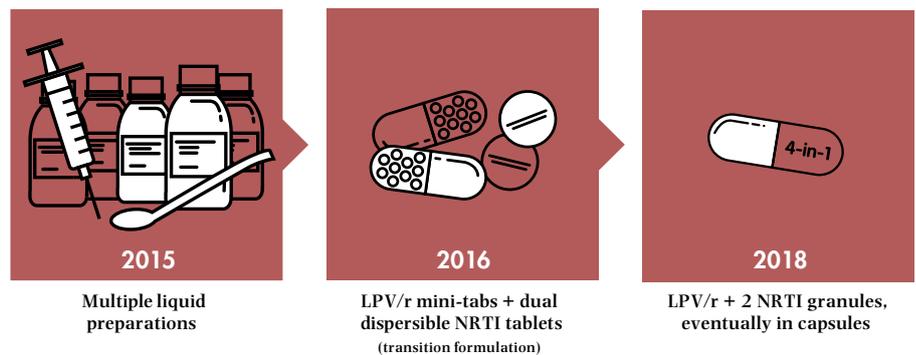
In 2015, three potential candidates were identified for further development and subsequently evaluated in phase I bioavailability studies. These studies compare the levels of a drug in the blood of two groups of adult volunteers fasted and fed, one group using the new formulation and the other using the standard formulation already on the market. All of the new formulations were taste-masked, either in the form of coated pellets, coated granules or simple granules. A new series of granules was then developed and in June 2016, two granule formulations were selected.

One of these formulations then was selected and underwent pilot studies in healthy human volunteers – results are promising for a final formulation to be submitted for registration in mid-2018. Paediatric studies are planned in Uganda and South Africa where the levels of 4-in-1 in children across a large weight range will be measured and compared to the standard treatment in these countries. Safety and efficacy data of this new formulation will also be generated to provide evidence for worldwide scale up.

HOW WILL THE 4-IN-1 WORK?

The 4-in-1 formulations will be in the form of solid granules that fit into a capsule. Caregivers will be able to open the capsules and give the granules to children with soft food or breast milk. These granules will not require refrigeration, will be taste-masked, and will be easy to dose across various weight bands.

Along with the positive results from the super-boosting studies, these 4-in-1 formulations should constitute an ideal first-line treatment for paediatric HIV: a **PI-based all-in-one ARV regimen** that is **safe and efficacious; adapted and palatable** so suitable for infants and children; **easy-to-use** as it will be a fixed-dose combination; that addresses **drug-drug interactions** with medicines for TB (see next section); and does **not require refrigeration**.



NEW HOPE FOR CHILDREN CO-INFECTED WITH HIV AND TB: “SUPER-BOOSTING” SHOWS PROMISING RESULTS

The drug rifampicin is the backbone of the regimen to treat TB in children. However, rifampicin reduces the bioavailability and hence the effectiveness of protease inhibitors such as LPV/r. This negative “drug-drug” interaction is a major challenge in treating kids that are infected with both TB and HIV – a common problem that is especially acute in southern African countries at the heart of the HIV epidemic.

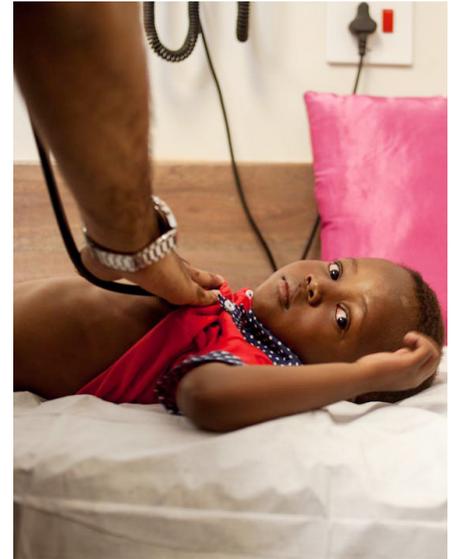
As part of its development of PI-based ARV regimens, DNDi began a pharmacokinetic (PK) study in 2013 to demonstrate the safety and effectiveness of “super-boosting,” which involves adding extra ritonavir to the LPV/r regimen.⁷ The study was initiated to collect the PK data – showing the relationship between dosing and the body’s exposure to drugs – needed to support the use of super-boosting ritonavir for TB/HIV co-infection.

This study took place at five hospitals in South Africa in infants and young-children co-infected with HIV and TB. Children were given a 1:1 ratio of lopinavir and ritonavir,

as opposed to the previously used 4:1 ratio. In May 2015, DNDi conducted an interim analysis that demonstrated excellent safety and efficacy of the super-boosting approach.⁸ The addition of ritonavir to reach a 1:1 ratio to lopinavir perfectly counteracts the negative interactions between LPV/r and rifampicin.

The results were presented to the WHO guidelines review committee and have strengthened the WHO recommendation to use super-boosting in TB/HIV co-infected children when on a LPV/r-based therapy.⁹ This study has been completed and final results were presented in 2017 showing that super-boosting is safe and effective for TB/HIV co-infected children.

DNDi would like to thank and acknowledge its South African partners who have contributed to this successful study, in particular colleagues in Cape Town, Johannesburg and Durban as well as the Department of Health.¹⁰



(7) “Pharmacokinetics of lopinavir/ritonavir superboosting in infants and young children co-infected with HIV and TB.” Pan African Clinical Trials Registry: PACTR201302000426554 <http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?dar=true&tNo=PACTR201302000426554>

(8) Rabie H, Denti P, Lee J, Kindra G, Coovadia A, Pillay S et al. Lopinavir ritonavir (1:1 ratio) in the presence of rifampicin is not inferior to lopinavir ritonavir (4:1 ratio) in the absence of rifampicin in human immune deficiency virus (HIV) children. Interim analysis of an open label sequential non-randomized pharmacokinetics study. In: 7th International Workshop on HIV Pediatrics, 2015; Vancouver, Canada, 17–18 July 2015. [LB1- Oral presentation].

(9) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016 (<http://www.who.int/hiv/pub/arv/arv-2016/en/> accessed 20 June 2016).

(10) Partners include: Stellenbosch University and Tygerberg Children’s Hospital, South Africa; Perinatal HIV Research Unit, South Africa; Shandukani Research Centre, South Africa; Empilweni Services and Research Unit, Rahima Moosa Mother and Child Hospital, South Africa; Enhancing Care Foundation, South Africa; Department of Health and Department of Science and Technology, South Africa.

BACKGROUND TO DNDi'S PAEDIATRIC HIV PROGRAMME

In 2010, DNDi was called on by various organizations, including MSE, WHO, and Unitaid, to apply its expertise to the development of paediatric HIV treatments. A paediatric HIV programme was set up at DNDi and experts were consulted to build a target product profile of the needed formulations in this population. Priority was given to the development of improved PI-based first-line ARV regimens for infants and young children with HIV.

In 2012, Unitaid awarded a significant grant to DNDi for its paediatric programme. Unitaid has been committed to paediatric HIV since its creation in 2006, and through its partnership with CHAI has significantly reduced the treatment gap between adults and children. Unitaid has enabled an increase in the number of HIV-positive children receiving treatment from 70,000 in 2006 to over 900,000 today.

THE PAEDIATRIC HIV TREATMENT INITIATIVE

The Paediatric HIV Treatment Initiative (PHTI) was set up in May 2014 to identify and overcome potential barriers to developing, producing and making available such priority medicines. This partnership - between Unitaid, WHO, the Medicines Patent Pool (MPP), the Drugs for Neglected Diseases initiative (DNDi) CHAI - focuses on intellectual property, research and development and, when needed, other market shaping interventions.

Lelio Marmora,
Executive Director
Unitaid



“Without treatment, half of all children living with HIV in Africa will die before they reach their second birthday. This is completely unacceptable and calls for a big scale-up of improved paediatric formulations for HIV. The 4-in-1 treatment adapted for infants and young children by DNDi and Cipla has the potential to have a dramatic impact on child mortality.”



Thank you to our donors:



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