TOWARDS ENDING THE NEGLECT OF PAEDIATRIC HIV?

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

JULY 2016

DNDi

Drugs for Neglected Diseases *initiative*

INTRODUCTION

The Drugs for Neglected Diseases *initiative* (DND*i*) 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 2015, only 51% 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 72% of pregnant women that are currently on treatment.[2] One major challenge that contributes to this treatment gap are suboptimal paediatric ARV formulations.

DND*i* 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, DND*i* is working with the Indian generic company Cipla Ltd. to develop two solid first-line "4-in-1" fixed-dose combinations using the World Health Organization (WHO) recommended treatment regimen for infants and young children. DND*i* will ensure that these easy-to-use formulations are affordable and can be rapidly introduced throughout high-burden HIV countries. At the same time, DND*i* and its partners in South Africa are addressing 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 several countries for an improved oral pellet formulation of the WHO-recommended treatment, an important step towards introducing the 4-in-1s. 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 the 4-in-1 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 on track to deliver urgently needed new ARV formulations for children living with HIV.

DND*i*'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).

Dr Ashraf Coovadia, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa

"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."

(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. On the Fast-Track to an AIDS-free generation. 2016 http://www.unaids.org/sites/default/files/media_asset/GlobalPlan2016_en.pdf

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

Although the long-term goal of DND*i*'s paediatric HIV programme is to develop "4-in-1" formulations, DND*i* 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-1s when they are 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 harsh-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 small children with food and does not require refrigeration, but is not "taste-masked" (see below).

In September 2015, DND*i* launched the LIVING[5] study beginning with three sites in Kenya to provide early access to this new LPV/r formulation, and expanded to Uganda in May 2016. As of June 2016, the LIVING study has enrolled nearly 150 patients. There are plans to expand to additional sites in Kenya and Uganda and to new sites in Tanzania, South Africa and Zambia before the end of 2016.

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 accessibility of LPV/r oral pellets in the field, used in association with dispersible tablets of a class of ARVs known as nucleoside reverse transcriptase inhibitors (NRTIs), namely zidovudine/lamivudine (AZT/3TC) or abacavir/lamivudine (ABC/3TC).

An acceptability study in collaboration with the Institute of Anthropology, Gender and African Studies, Nairobi (IAGAS) and the Institute of Tropical Medicine will also soon begin in Kenya to assess issues surrounding the feasibility of use of the pellets by caregivers and health workers, in particular for children three months old or younger who may have difficulties taking the pellets. Furthermore, a 6-month operational pilot of the use of the pellets will start in Zimbabwe in August 2016, in collaboration with the Clinton Health Access Initiative (CHAI), UNICEF and the Zimbabwean Ministry of Health.

Dr Stanley Ndwiga, LIVING Study Coordinator, Gertrude's Children Hospital Kenya

"Parents are finding it easier to give their children the oral pellets. One mother told me that her six year-old takes the medicine by herself under her close supervision."

(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.

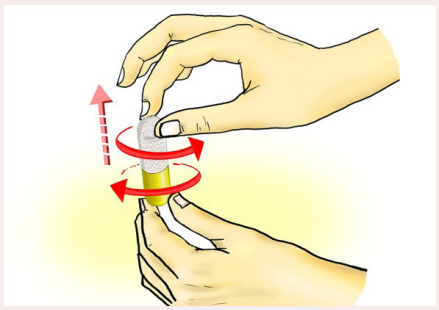
(5) Prospective Study of Lopinavir Based ART for HIV Infected children globally," ClinicalTrials.gov Identifier: NCT02346487 https://clinicaltrials.gov/ct2/show/NCT02346487

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, DND*i* 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.

Put a little food into the spoon.

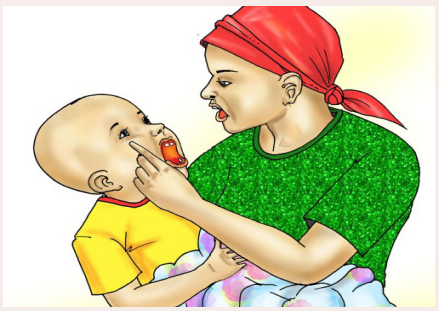


Take a capsule, hold it vertically then twist it in opposite directions while pulling gently to open it.

Pour the required amount on the pellets on the spoon.

Pour some more food onto the spoon to cover the pellets.

Feed the baby with the food or liquid containing the pellets immediately.



Follow up with more food or liquid to ensure that they swallow all the pellets.

(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.

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, DND*i* 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, DND*i* 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 analysis is expected in late 2016.

DND*i* 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]

CHALLENGES

While the PK study has already led to an important change in WHO guidelines, efforts to deliver a stand-alone solid formulation of ritonavir have been challenging. DND*i* and Cipla Ltd. evaluated several solid granule and pellet formulations of ritonavir but were not able to develop one that does not have a bitter taste and does not compromise bioavailability.

In parallel, AbbVie has developed a powder version of ritonavir that is bioequivalent to their registered liquid formulation and easier to take – but not taste-masked. DND*i* plans to test the acceptability of this formulation in association with the LIVING study.

(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.

GETTING CLOSER TO OUR GOAL: PROGRESS ON THE "4-IN-1S"

DND*i*'s long-term goal for paediatric HIV is to develop and deliver two taste-masked, heat-stable LPV/r-based fixed-dose combinations for infants and young children. These treatments will combine two sets of key HIV drugs: LPV/r, which is a boosted protease inhibitor, along with two NRTIs. The first formulation (ABC/3TC/LPV/r) combines the protease inhibitor LPV/r with the NRTIs abacavir and lamivudine (ABC/3TC) while the second formulation (AZT/3TC/LPV/r) combines LPV/r with the NRTIs zidovudine and lamivudine (AZT/3TC).

The combination of a boosted protease inhibitor 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-1s are eventually made available, DND*i* 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-1s.

CHALLENGES

Taste-masking has proven to be a major challenge in developing the 4-in-1s because bioavailability 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, DND*i* 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.

In 2015, three potential candidates were identified for further development and subsequently evaluated in phase l 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. These two granule formulations have a very low mass compared to other formulation candidates and have been selected because they have "supra-bioavailability."

Supra-bioavailability means that the dose of LPV/r can be reduced which would ultimately make the 4-in-1 less bulky, easier to administer, and more affordable due to the reduced active pharmaceutical ingredients required.

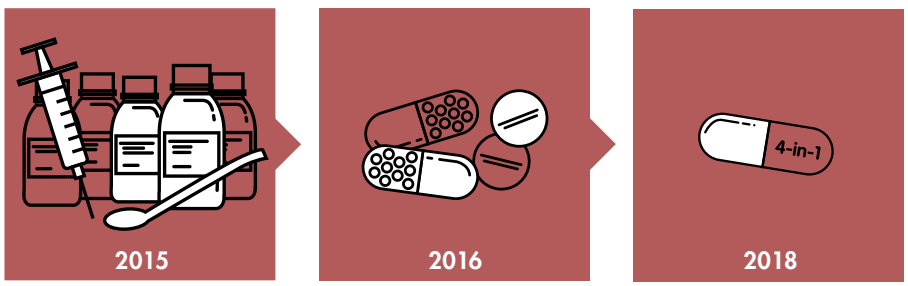
DND*i* will soon start a short phase ll dose-finding study at selected LIVING study sites to determine the dose of LPV/r granules needed for children with HIV. Once the optimal dose of LPV/r granules is determined, clinical batches of the 4-in-1s will be manufactured and DND*i* will conduct a phase II/III study in children to evaluate the efficacy, safety and PK of the 4-in-1s at select LIVING study sites. This study will support the registration dossier of the 4-in-1s, to be submitted to the U.S. Food and Drug Administration (FDA) in 2018.

HOW WILL THE 4-IN-1S 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 **protease inhibitor-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; and does **not require refrigeration.**

Thanks to the "supra-bioavailability" of new formulations described above, these 4-in-1s could have a **reduced dose,** which would lead to **reduced cost**. Finally, due to an investment in improving manufacturing capacity, Cipla Ltd. will be able to meet the increased demand for the granules and the use of oral pellets for the LIVING study.



Multiple liquid preparations

LPV/r mini-tabs + dual dispersible NRTI tablets (transition formulation)

LPV/r + 2 NRTI granules, eventually in capsules

BACKGROUND TO DND*i*'S PAEDIATRIC HIV PROGRAMME

In 2010, DND*i* was called on by various organizations, including MSF, WHO, and UNITAID, to apply its expertise to the development of paediatric HIV treatments. A paediatric HIV programme was set up at DND*i* 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 DND*i* 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 number of children HIV positive receiving treatment from 70,000 in 2006 to over 700,000 today.

THE PAEDIATRIC HIV TREATMENT INITIATIVE

In May 2014, UNITAID, DND*i*, and the Medicines Patent Pool (MPP) launched the Paediatric HIV Treatment Initiative (PHTI) to expedite the development and delivery of new ARV formulations, with a focus on overcoming the barriers to developing and delivering specific formulations and combinations appropriate for children. This partnership now includes CHAI and has a three-pronged approach to ensure appropriate HIV treatment for children: R&D for new treatments; resolving intellectual property challenges by sharing patents and knowledge; and market shaping to stabilize the small and fragmented paediatric market.

Since its launch, PHTI already has developed an operational framework and has created product specific teams to coordinate the development of priority paediatric formulations. Importantly, expressions of interest for the development of priority formulations and licensing agreements covering paediatrics have been issued and posted on the MPP website (http://www.medicinespatentpool.org/expression-of-interest-phti/).

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