

ENDING THE NEGLECT OF PAEDIATRIC HIV



Improving HIV treatment
for children: an update

DNDi
Drugs for Neglected Diseases *initiative*



Photo: Scholars and Gentlemen/DNDi.

The Drugs for Neglected Diseases *initiative* (DNDi) is developing optimal child-adapted antiretroviral (ARV) formulations for 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.

Infants and young children cannot swallow tablets intended for adults and require special dosing. Yet their needs have been neglected by pharmaceutical research and development (R&D), leading to a lack of innovation for children with HIV.

Despite major efforts to increase the number of children on HIV treatment and reduce mother-to-child transmission of HIV, many of the two million children living with HIV are still being

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left behind. In 2016, only 52% of children living with HIV received antiretroviral therapy. While this is an impressive increase from 15% in 2009, this is considerably lower than the 59% of adults that are currently on treatment.²

One major challenge that contributes to this treatment gap is the suboptimal range of paediatric ARVs available today. The treatment regimen currently recommended by the World Health Organization (WHO) for children was not designed with children's needs in mind – the medicines come in the form of syrups that are horrid-tasting, hard to administer, require refrigeration, and are difficult to give to children that have both HIV and tuberculosis (TB).

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

² UNAIDS (2018). Global HIV Statistics Fact Sheet. Available at: http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

**SUMMARY OF
DNDi'S PAEDIATRIC
HIV WORK**

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DNDi is working with the Indian generic company Cipla Ltd. to develop a solid first-line "4-in-1" fixed-dose combination of abacavir/lamivudine/ lopinavir/ritonavir for infants and young children under three years of age that meets WHO recommendations. DNDi is working to ensure that these easy-to-use formulations are affordable and can be rapidly introduced throughout high-HIV burden countries.

This collaboration has already produced concrete results: DNDi and its partners in South Africa have addressed the negative drug-drug interactions between protease inhibitor-based HIV treatments recommended by WHO and the TB drug rifampicin by providing essential evidence and data in support of a process known as "super-boosting." Meanwhile, Cipla has developed a solid "2-in-1" fixed-dose combination of lopinavir/ritonavir, a clear improvement over the current lopinavir/ritonavir syrup that is used in many countries, and an important step towards introducing the 4-in-1 once it is approved in 2019. To increase access to this interim 2-in-1 combination, DNDi has been running the LIVING implementation study in Kenya, Uganda, and Tanzania. Interim results from this study have shown very high levels of adherence and clinical improvement as well as lower HIV viral loads, showing that improved formulations can lead to better treatment outcomes.

Along with improvements in early infant diagnostic technology, these new formulations should go a long way toward ending the long-standing neglect of children living with HIV. Paediatric HIV still claims too many lives – more than 300 children die of HIV every day. Now is the time to make improved formulations available for children.

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).

**“
It's heart-breaking
to give so many
treatments to a kid
at the same time.”**

Sani Nojiyeza, mother of Mel, a two-year-old living with HIV and TB in KwaMashu township in Durban, South Africa



Photo: Scholars and Gentlemen/DNDi.

Scaling up with the right tools, right now

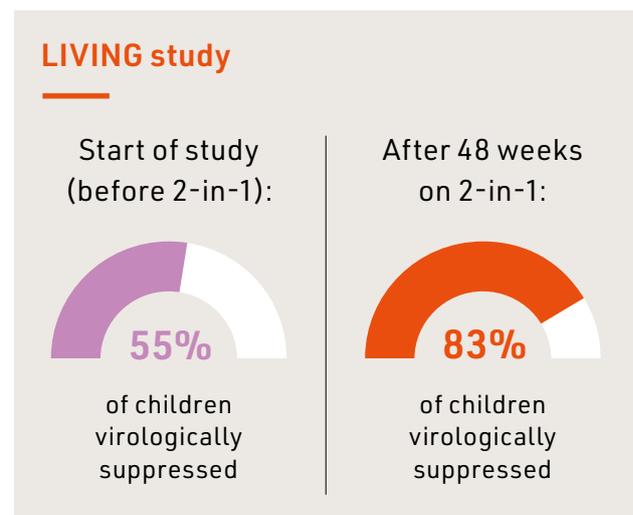
The LIVING study

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 Children struggle to take the medicine, often vomiting it back up, while caretakers in many sub-Saharan African countries are forced to store the treatments buried in sand or dirt to keep them cool.

Despite PI-based regimens being recommended by WHO, a survey in 2015 found that only 14% of children in over 60 countries received PI-based first-line regimens. Meanwhile, resistance is growing to another class of ARVs given to children known as non-nucleoside reverse transcriptase inhibitors (NNRTIs), with over 60% resistance reported in countries like South Africa.^{5,6}

The first priority of DNDi's paediatric HIV programme was therefore to introduce improved PI-based formulations as soon as possible. In June 2015, the U.S. Food and Drug Administration (FDA) approved an oral "2-in-1" formulation of LPV/r. Developed by Cipla Ltd., these formulations do not require refrigeration. The 2-in-1 oral pellets are stored in a capsule that can be opened to give with breast milk, formula or small amounts of solid food. DNDi launched the LIVING⁷ study in September 2015 with five sites in Kenya to provide early access to the 2-in-1 and facilitate in-country adoption of optimized LPV/r regimens. The study was expanded to Uganda in May 2016, and Tanzania in 2017. As of 30 April 2018, the LIVING study had enrolled 1,001 children across 12 sites in Kenya, Uganda, and Tanzania.

Any child with a confirmed HIV-positive diagnosis, weighing from 3 kg up to 25 kg and who cannot swallow pills, can participate in the study. The study is intended to demonstrate the effectiveness, safety, and acceptability of the 2-in-1, 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). The combination of a boosted PI such as LPV/r with two NRTIs is recommended by WHO as a first-line therapy for infants and children under three years old.



In February 2018, interim results of the LIVING study were released, showing that 83% of the children in the study were virologically suppressed at 48 weeks with the 2-in-1, compared to 55% at the beginning of the study. These results show that the 2-in-1 is effective and well-tolerated by children.

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

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

⁵ Internal WHO country survey.

⁶ World Health Organization (2017). WHO HIV Drug Resistance Report 2017. Available at: <http://apps.who.int/iris/bitstream/handle/10665/255896/9789241512831-eng.pdf;jsessionid=98BC8E75B95EA51AFEEF88D4EB51C7B8?sequence=1>

⁷ DNDi. Prospective Study of Lopinavir-based ART for HIV-infected Children Globally. ClinicalTrials.gov Identifier: NCT02346487. Available at: <https://clinicaltrials.gov/ct2/show/NCT02346487>

As part of the LIVING study, DNDi also evaluated the acceptability of and adherence to the 2-in-1 in a sub-study called RE-LIVING. Caregivers found the formulations to be “highly-acceptable” due to the ease of storage and packaging.

Nevertheless, the 2-in-1 pellets are not fully “taste-masked,” meaning they still have a bitter taste if not given quickly with food or drink, and are not adapted for the youngest children

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A fully taste-masked all-in-one formulation is DNDi’s ultimate goal.
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who may have difficulty swallowing the small pellets. Finally, the other two ARVs have to be given separately as dispersible tablets. A fully taste-masked all-in-one formulation is therefore DNDi’s ultimate goal.

“

The 2-in-1 pellets have improved my daughter Mary’s health and made things so much easier. Before I kept the syrups in a container of wet soil under my bed – when I travelled, I had to carry it. Now I can store the pellets on my shelf and take them with us.”

Anne Wanza, mother of Mary, living with HIV and treated at the Lea Toto Kariobangi site in Nairobi, Kenya



Photo: Paul Kamau, DonPaul Photography/DNDi.

New hope for children co-infected with HIV and TB

“Super-boosting” shows promising results

The drug rifampicin is the backbone of treatment for drug-sensitive TB. 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 have 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 child-adapted ARV formulations, DNDi began a pharmacokinetic study – which shows the relationship between dosing and the body’s exposure to drugs – in 2013 to demonstrate the safety and effectiveness of “super-boosting,” which involves adding extra ritonavir to the LPV/r regimen.⁸ 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.⁹ 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.¹⁰ This study was 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.¹¹

Final results presented in 2017 show that super-boosting is safe and effective for TB/HIV co-infected children.



Photo: Scholars and Gentlemen/DNDi.

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

9 Rabie H, Denti P, Lee J, Kindra G, Coovadia A, Pillay S et al (2015). 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. 7th International Workshop on HIV Pediatrics, 2015; Vancouver, Canada, 17-18 July 2015. [LB1- Oral presentation].

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

11 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.

The 4-in-1

A true innovation for children with HIV

DNDi's long-term goal for paediatric HIV is to develop and deliver a taste-masked, heat-stable 4-in-1 LPV/r-based fixed-dose combination for infants and young children. This 4-in-1 fixed-dose combination (ABC/3TC/LPV/r 30/15/40/10 mg) will be simple to use with water, milk, breast milk, and food. In addition to improved taste-masking, the 4-in-1 has been formulated into granules, with individual particle sizes that are nine times smaller than the 2-in-1 pellets (approximately the consistency of granulated sugar). This reduction in particle size is a key step in the development of the 4-in-1 formulation, and will facilitate swallowing by the very young infants, some of whom experience difficulties swallowing pellets.

DEVELOPING THE 4-IN-1

Taste-masking has proven to be a major challenge in developing the 4-in-1 because bioavailability can be lost when certain taste-masking agents are used. The LPV/r contained in the 4-in-1 is highly insoluble and does not cross the gastro-intestinal barrier easily. It tastes very bitter and cannot be made into a dispersible tablet.

DNDi worked closely with Cipla Ltd. to develop more than 30 LPV/r formulations, and after a series of studies, selected one formulation for testing. A bioequivalence study – comparing the reference regimen of LPV/r syrup and NRTI tablets to the 4-in-1 – is currently being run to enable regulatory submission by the end of 2018.

A PI-based, all-in-one ARV regimen that is safe and efficacious, adapted and palatable.

To provide clinical data in young HIV-infected infants and children, DNDi is preparing a study, called LOLIPOP (lopinavir/ritonavir/lamivudine/abacavir as an easy-to-use paediatric formulation in a Phase I/II study). The LOLIPOP study will begin in late 2018 in Uganda

Photo: Paul Kamau, DonPaulPhotography/DNDi.



“

I have seen that adults always had preference in getting access to [HIV] care and treatment – the children were left behind. But I'm happy now today, that new treatments are in the pipeline and are becoming a reality.”

Sister Mary Owens, Executive Director of the Children of God Relief Institute in Nairobi, Kenya

and will generate pharmacokinetic, safety, and acceptability data on the 4-in-1 to provide evidence for worldwide scale-up. Similar to what was done with the 2-in-1, DNDi is also planning a study to provide the key evidence that caregivers will need to be able to give the 4-in-1s with boosted ritonavir for children co-infected with HIV and TB.

With regulatory approval foreseen for 2019, the 4-in-1 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, suitable for infants and the youngest children; easy-to-use as it will be a fixed-dose combination; and with no requirement for refrigeration.

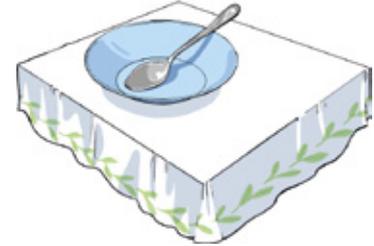
**HOW
TO USE
THE
4-IN-1**

The 4-in-1 formulation 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, breast milk, or milk/water. These granules will not require refrigeration, and will be taste-masked and easy to dose across various weight bands.

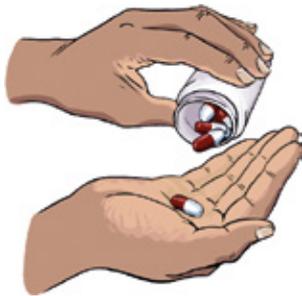
DNDi has created a set of illustrations to help caregivers and health workers understand how to open the capsules and use them with solids, semi-solids, breast milk, and other liquids. A selection is reproduced here:



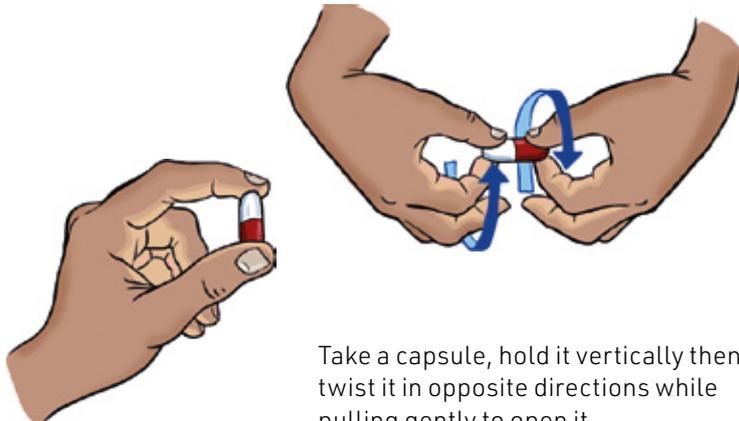
Treatment to be administered orally twice a day.



Take a clean tablespoon and set it on a plate or a dish.



Remove correct number of capsules (as prescribed by your doctor) from bottle and place on clean surface.



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



Pour the required amount of granules on the spoon. It is advisable not to pour large quantities of granules in one spoon.



Pour only one or two capsules at a time. Make sure that all granules are on the spoon and that no granules fall off.

**ENSURING ACCESS
TO OPTIMISED
FORMULATIONS – THE
NEXT PHASE OF THE
PROGRAMME**

Once the 4-in-1 receives tentative approval from the FDA and is registered and adopted in countries where it will be used, country-specific plans will have to be designed to ensure children have access to these formulations. These plans will address the three key dimensions of access: demand creation (how to inform clinicians, caregivers, programme managers, and communities of the existence of this new formulation and train relevant health personnel in its appropriate use), financing, and supply. DNDi will work on a country-by-country basis with all partners and stakeholders with a role in ensuring that the largest possible number of HIV-positive children are reached with early infant diagnosis and appropriate, optimised treatment, even in hard-to-reach areas. These plans will also need to include additional steps to reduce mother-to-child transmission of HIV.



Photo: Paul Kamau, DonPaulPhotography/DNDi

**NEW PAEDIATRIC
TREATMENTS ON THE
HORIZON?**

In 2019 and beyond, it is possible that two new HIV treatments specifically adapted for children will be developed and approved: this will represent the most significant 'treatment revolution' for children with HIV since the advent of antiretroviral therapy, a situation that was almost unimaginable just a few years ago. DNDi welcomes this positive development for children.

Efforts are underway to establish the safety, efficacy, and appropriate dosing for children of a new, promising treatment from the integrase inhibitors class of ARVs, dolutegravir (DTG).

While adults are being switched to DTG regimens as a result of a shift in WHO guidelines, it will take more time for younger children to benefit because its usage for children under six years of age has not yet been fully documented. At the same time, regimens containing NNRTIs such as efavirenz and nevirapine (with which the majority of HIV-positive children are currently being treated) will be deprioritised because viral suppression of children on NNRTI-based regimens is poor.

The 4-in-1 will therefore play a critical role in the next several years in closing the treatment gap for children with HIV.

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Background to DNDi's paediatric HIV programme

In 2010, DNDi was called upon by various organizations, including MSF, WHO, and Unitaid, to apply its expertise in neglected disease R&D to the development of paediatric HIV treatments. A paediatric HIV programme was set up at DNDi and experts were consulted to build target product profiles of needed formulations for 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 HIV programme. Unitaid remains committed to paediatric HIV care, and through its partnership with the Clinton Health Access Initiative (CHAI), has significantly reduced the treatment gap between adults and children.

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 priority paediatric HIV medicines. This partnership – between Unitaid, WHO, the Medicines Patent Pool, DNDi, and CHAI – focuses on intellectual property, research and development and, when needed, other market-shaping interventions.

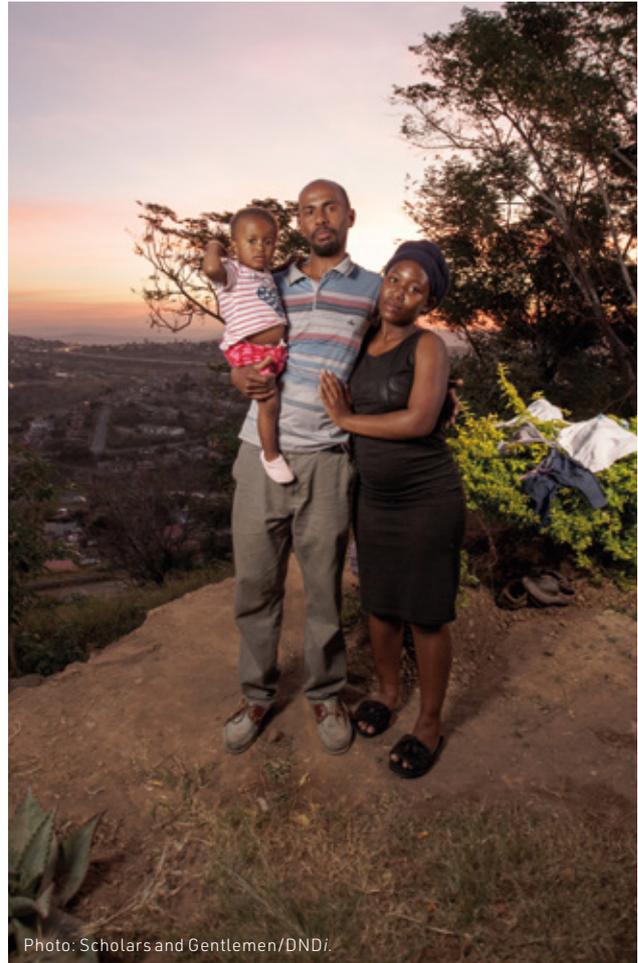


Photo: Scholars and Gentlemen/DNDi.

“

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.”

Lelio Marmora, Executive Director, Unitaid



DNDi

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A not-for-profit research and development organization, DNDi works to deliver new treatments for neglected diseases, notably leishmaniasis, human African trypanosomiasis, Chagas disease, specific filarial infections, and mycetoma, and for neglected patients, particularly those living with paediatric HIV and hepatitis C. Since its inception in 2003, DNDi has delivered seven treatments: two fixed-dose antimalarials (ASAQ and ASMQ), nifurtimox-eflornithine combination therapy (NECT) for late-stage sleeping sickness, sodium stibogluconate and paromomycin (SSG&PM) combination therapy for visceral leishmaniasis in Africa, a set of combination therapies for visceral leishmaniasis in Asia, paediatric dosage forms of benznidazole for Chagas disease, and a 'super-booster' therapy for children co-infected with HIV and TB.

By 2019, DNDi's paediatric HIV programme aims to deliver a taste-masked, fixed-dose 4-in-1 antiretroviral combination that is designed for infants and young children who cannot swallow pills.

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