PAEDIATRIC HIV

A mother of an HIV+ baby boy administering him bitter tasting ARV medication, Belville South, Cape Town, South Africa.

Developing treatments for children living with HIV/AIDS

› **HIV** continues to be a major public health problem worldwide, particularly in sub-Saharan Africa, even though international efforts to combat HIV/AIDS since the turn of the millennium have led to an overall decrease in the number of new cases diagnosed and in the number of AIDS-related deaths. Children are the worst affected, and the majority of babies born with HIV are still not diagnosed or treated. Of the approximately 2.6 million children currently living with HIV, only 32% receive treatment. Although efforts in preventing mother-to-child transmission should reduce the market size of paediatric HIV in the long term, the increased testing of pregnant women and their children is paradoxically expected to increase the paediatric market in the short to medium term, and the need for paediatric treatment will continue to increase until at least 2020. Antiretroviral therapy is not able to cure the disease and needs to be taken for life, but it can control the virus and enable the patient to live a healthy life. Early treatment is essential, as without it 50% of children infected will die before their second birthday, and 80% before their fifth. Adapted paediatric treatments are needed for infants and young children that are safe, efficacious, and easy for the child to swallow, thus ensuring their best chance of survival to adulthood. Children in Africa are frequently also co-infected with tuberculosis (TB), so HIV and TB treatments need to be compatible.

Antiretroviral treatments typically combine three or more drugs with different modes of action. The only approved protease inhibitor for young children, lopinavir boosted with ritonavir (LPV/r), comes as an unpleasant tasting oral solution with a high alcohol content. It also requires refrigeration, is difficult to store due to its large volume, and expensive, making it unsuitable for resource-poor settings. DND*i* and partners have been working on developing a taste-masked, solid LPV/r oral formulation adapted for infants and young children, which would ultimately be combined with two nucleoside reverse transcriptase inhibitors (NRTIs) into a single '4-in-1' unit or capsule. As a first step, LPV/r has been formulated into pellets by Cipla Ltd., which received the U.S. Food and Drug Administration (FDA) tentative approval for use in June 2015. These pellets can be sprinkled onto food, are alcohol-free, do not require a cold chain, and are cheaper to transport, although they still have an unpleasant taste. As such, the formulation provides a better treatment option for children and is currently undergoing evaluation in DND*i*'s LIVING study in Africa, which will give valuable information on its use under normal living conditions.

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What are the current treatments and their limitations?

The 2013 WHO guidelines recommend early diagnosis and immediate treatment of HIV-positive infants and children under the age of five, regardless of immunological status; infants under the age of three should be treated with an antiretroviral treatment (ART) combination that includes protease inhibitors, regardless of whether they have been exposed to ARVs, for the prevention of mother-to-child transmission (PMTCT).
The combination of a boosted protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs), ABC + 3TC or ZDV + 3TC, is considered by the WHO as the most effective first-line therapy for infants and children.

However, this combination therapy is not being widely used. According to a WHO survey performed in 45 countries, in 2010 only 12.2% of children with HIV were receiving a first-line treatment containing lopinavir/ritonavir (LPV/r), 97% of whom were in South Africa. The only available PI for young children, LPV/r, does not come in a child-friendly formulation: the oral solution is unpalatable, contains 42% alcohol, and is not adapted to resource-poor settings due to major logistical constraints: it requires refrigeration, has a short shelf-life when exposed to heat, is expensive, and difficult to store and transport.

In some places, the levels of co-infection with TB and HIV in infants and children are high. Drug-drug interactions between PIs in particular and rifampicin, one of the drugs used to treat TB greatly diminish the blood levels of PIs and hinder the efficacy of the antiretroviral (ARV) treatment. In order to counteract this interaction, extra ritonavir (RTV) needs to be added to the standard proportion of LPV/r. This is called 'superboosting'. The currently available ritonavir formulation suffers the same limitations as the current formulation of RTV with regard to taste, high alcohol content, and logistical constraints imposed by its short shelf-life.

2.6 million children
below the age of 5 living with HIV/AIDS

More than **86 %** of all new infections in sub-Saharan Africa

150,000 children
under 15 years of age died of AIDS-related illness in 2014 globally

WHAT IS DND*i* DOING TO ADDRESS UNMET TREATMENT NEEDS?

In 2010, DND*i* was called on by various organizations, including Médecins Sans Frontières, WHO, and UNITAID, to apply its expertise to the development of paediatric HIV treatments. DND*i*'s position, notably that paediatric HIV is a neglected disease, was published as a 'Perspective' in the New England Journal of Medicine in August 2011.

DND*i* is pursuing two objectives to address the needs of HIV-infected children:

1. Develop and register two solid first-line '4-in-1' LPV/r-based fixed-dose combinations (FDCs) with two NRTIs. All components of the combination will be developed in the form of taste-masked granules, which are stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight band dosing.
2. Evaluate the superboosting strategy: i.e. increasing the LPV:RTV ratio that can effectively and safely counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

As a short-term strategy, DND*i* will start testing the use of PI-based treatment with Cipla's LPV/r-based pellets before the '4-in-1' FDC becomes available, in order to provide better treatment for infants today and promote in-country adoption. DND*i* participated in the CHAPAS-2 trial that compared LPV/r pellets to the LPV/r liquid formulation. These pellets are being used in combination with NRTI dispersible tablets in implementation studies (LIVING study), which started in 2015. In the longer-term, DND*i* is working with Cipla, its industrial partner, on combining taste-masked LPV/r granules or pellets with two NRTIs into a single unit dose. This modular concept is flexible, so that any of the components can eventually be substituted to provide new fixed-dose combinations.

In order to address the needs of HIV/TB co-infected children, DND*i* aims to assess the addition of ritonavir for superboosting LPV/r at a 1:1 LPV:RTV ratio. DND*i* is conducting a study to establish the pharmacokinetics, efficacy, and safety of superboosted LPV/r in children in South Africa with the existing ritonavir solution. Interim results look promising for this approach and the study is being extended to include all solid formulations.

The ideal first-line treatment for paediatric HIV would be a protease inhibitor-based all-in-one antiretroviral regimen for HIV-infected children which is safe and efficacious, is an adapted formulation suitable for infants and children, is an easy-to-use fixed-dose combination, is palatable, addresses drug-drug interaction with medicines for tuberculosis, and is adapted to tropical climates (no refrigeration needed).

By 2019, DND*i* aims to deliver from its paediatric HIV portfolio:

- Two new '4-in-1' paediatric formulations containing a PI (LPV/r) and two NRTIs (ABC or AZT and 3TC)
- One new regimen recommended to treat HIV/TB coinfection

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