

## Accelerating ARV development and access for children



There have been huge increases in the number of adult patients treated for HIV infections over the last decade. Tragically, however, children have not benefited from the same level of treatment coverage. At best, only one-third of children who need paediatric antiretroviral therapy (ART) actually receive it, compared to 64% of all adults. Of the 3.4 million children currently estimated to be living with HIV, most live in sub-Saharan Africa and were infected by their HIV-positive mothers during pregnancy, childbirth, or breastfeeding. Over 700 children become newly infected every day and some 500 die each day of the disease. Without treatment, half of these children will die before their second birthday and 80% will have died before the age of five. Despite efforts to reach the goal of eliminating new paediatric HIV infections by 2015, the World Health Organization (WHO) has forecast that in 2020, 1.9 million children will be living with HIV, with an estimated 1.6 million in need of antiretroviral treatment.<sup>(1)</sup> More needs to be done to narrow, even close, the treatment gap.

For a number of years now, the WHO has recommended diagnosis and antiretroviral treatment for all children below the age of two, regardless of their clinical or immunological status. The guidelines for treating patients were consolidated and updated in June 2013, and now recommend immediate treatment of all children who are infected with HIV up to the age of five years.<sup>(2)</sup> In addition, for children with HIV who are younger than three years of age, a regimen based on lopinavir/ritonavir (LPV/r), such as those currently under development by DNDi, should now be used as first-line ART regardless of previous exposure to non-nucleoside reverse transcriptase inhibitors, which may have been used to prevent mother-to-child transmission of the virus during pregnancy and childbirth.

A further complication for many of those infected with HIV is that they are frequently,

and more easily, also infected with tuberculosis (TB), particularly in sub-Saharan Africa. These children have a particularly poor prognosis. Unfortunately, the drugs needed to combat TB have significant drug-drug interactions with those used to treat HIV. The levels of lopinavir for example, are decreased below therapeutic levels in children also treated with the anti-TB drug rifampicin. This negative interaction requires new or adapted treatments, such as ritonavir 'boosters', to increase the bioavailability of the protease-inhibitor component of the anti-HIV treatment.

A 'Paediatric HIV Roundtable with Industry' was organized by DNDi in Dakar, Senegal, in October 2013, following on from the Conference on Paediatric Antiretroviral Drug Optimisation (PADO) organized by WHO. The discussions led to a jointly endorsed call to action among participants of both meetings to donors, stakeholders, industry, national regulatory bodies, researchers and decision makers, in order to ensure funding and accelerate the development of, and access to, paediatric formulations of ARVs that can be effectively administered for newborns to up to adolescents, a truly neglected population.<sup>(3)</sup>

### Ideal Target Product Profile for Paediatric HIV

**A first-line, protease inhibitor-based all-in-one antiretroviral regimen for HIV-infected children:**

- Safe and efficacious
- Adapted formulation suitable for infants and children
- Easy-to-use fixed dose combination
- Palatable
- No drug-drug interaction with medicines for tuberculosis
- Adapted to tropical climates (no refrigeration needed)

(1) [http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement\\_march2014/en/](http://www.who.int/hiv/pub/guidelines/arv2013/arvs2013supplement_march2014/en/) (2) <http://www.who.int/hiv/pub/guidelines/arv2013/en/> (3) 'Refocusing Research and Development of Paediatric HIV Treatments on the Needs of Children in Resource-Poor Settings: A Paediatric HIV Roundtable with Industry & Joint Call to Action on Paediatric HIV'. DNDi (2013). Downloaded from [http://www.dndi.org/images/stories/diseases\\_portfolio/DNDi\\_Paediatric\\_HIV\\_roundtable.pdf](http://www.dndi.org/images/stories/diseases_portfolio/DNDi_Paediatric_HIV_roundtable.pdf)

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**WHAT IS THE IMPACT OF PAEDIATRIC HIV?**

At the end of 2012, an estimated 3.3 million children below the age of 15 were living with HIV, more than 90% of whom were in sub-Saharan Africa. An estimated 260,000 children under 15 years of age died of AIDS-related illness in 2012. In low- and middle-income countries, access to treatment has expanded to reach an estimated 647,000 HIV-infected children under the age of 15. Still, only 34% of HIV-positive children are estimated to be on antiretroviral therapy (ART), compared to 64% of all adults.<sup>(1)</sup>

**HOW IS PAEDIATRIC HIV TRANSMITTED?**

In children, HIV transmission can occur during pregnancy through the placenta, during delivery through exposure to body fluids and cervical secretions, and through breastfeeding. In the absence of antiretroviral preventive treatment, 30 to 40% of children born to an HIV-infected mother acquire infection themselves. However, with antiretroviral prophylaxis throughout pregnancy, delivery, and breastfeeding, transmission can be decreased to a few per cent.

**WHAT ARE THE SYMPTOMS?**

HIV is difficult to diagnose in children and infants: indeed, signs and symptoms are non-specific and are very common in resource-poor settings, such as chronic diarrhea, recurrent infection, and failure to thrive. However, the disease progresses rapidly and can lead to death before HIV has been diagnosed or even suspected. All children born to HIV-infected mothers carry maternal anti-HIV antibodies, and are thus seropositive. A positive serological test therefore does not necessarily indicate HIV infection. Only very expensive diagnostic tests that detect the virus itself can give an accurate diagnosis in the first months of life. New point of care tests to diagnose infants and which can give results on the same day are currently under development.

**WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?**

The 2013 WHO guidelines<sup>(2)</sup> recommend early diagnosis, and immediate treatment of HIV-positive infants and children under the age of five, regardless of CD4 count; infants, under the age of three, should be treated with an ART combination that includes protease inhibitors, regardless of whether or not they have been exposed to ARVs through prevention of mother-to-child transmission (PMTCT). The combination of a **boosted protease inhibitor with two nucleoside reverse transcriptase inhibitors (NRTIs)** is considered by many experts as the most effective first-line therapy for infants and children, regardless of prior exposure to ARVs. 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 a PI (mostly 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 formulation 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 of 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 the ARV treatment. In order to counteract this interaction, extra ritonavir needs to be added to the standard proportion of LPV/r. This is called 'superboosting', and requires the development of an infant-friendly formulation of ritonavir. The currently available ritonavir formulation suffers the same limitations as the current formulation of LPV/r with regard to taste, high alcohol content, and logistical constraints of short shelf-life.

**WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?**

In 2010, DNDi was called on by various organizations, including Médecins Sans Frontières, WHO, and UNITAID, to apply its expertise to the development of paediatric HIV treatments. DNDi'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.<sup>(3)</sup>

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

- Develop and register two solid first-line 4-in-1 LPV/r-based fixed-dose combinations (FDCs) with 2 NRTIs. All components of the combination will be developed in the form of taste-masked granules, stable with no need for refrigeration, presented in a single unit with appropriate strengths to accommodate weight-band dosing.
- Develop and register a stand-alone ritonavir booster formulation that can be added to any PI-based paediatric ARV regimen and can be used to counteract the negative drug-drug interactions between PIs and rifampicin-containing TB treatments.

As a **short-term strategy**, DNDi will start testing the use of PI-based treatment with existing LPV/r-based solid formulations before the availability of the 4-in-1 FDC, in order to provide better treatment for infants today and promote in-country adoption. DNDi participated in the CHAPAS-2 trial that compared LPV/r sprinkles (hereafter referred to as pellets) to the LPV/r liquid formulation. These pellets will be used in combination with NRTI dispersible tablets in implementation studies as part of this short-term strategy.

In the **longer-term**, DNDi is working with its industrial partner, Cipla Ltd., on combining LPV/r granules 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 addition, in order to address the needs of HIV/TB co-infected children, DNDi is developing a formulation of ritonavir for superboosting LPV/r at a 1:1 ratio. A pharmacokinetic study to establish the efficacy and safety of superboosted LPV/r is ongoing in South Africa with the existing ritonavir solution.

- By 2015-2016, DNDi aims to deliver from its paediatric HIV portfolio:**
- Two new all-in-one paediatric formulations containing a PI (LPV/r) and two NRTIs (ABC or AZT and 3TC)
  - One stand-alone paediatric booster RTV for HIV-TB co-infected children

(1) Global report: UNAIDS report on the global AIDS epidemic 2012, Geneva, 2013. (2) WHO: Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. June 2013, Geneva. (3) Lallemand M et al., (2011) Paediatric HIV - A Neglected Disease? *N Eng J Med* 365