



Urgent Need to Develop and Deliver Antiretroviral Treatment Formulations for Infants and Children with HIV/AIDS

A SITUATIONAL OVERVIEW FROM THE DRUGS FOR NEGLECTED DISEASES INITIATIVE (DNDi) AND HIV I-BASE¹

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DNDi

Drugs for Neglected Diseases *initiative*

I. THE PROBLEM:

PERSISTENT NEGLECT OF CHILDREN WITH HIV/AIDS

Despite huge progress worldwide over the past ten years in the fight for wider access to antiretroviral therapy (ART), children have often been left behind. An estimated 3.4 million children live with HIV, but only about a third of them currently have access to treatment, compared with over half of adults. Without treatment, more than half of these children will die before their second birthday and 80% will die before they turn five.

For several years now, the World Health Organization (WHO) has recommended early diagnosis and immediate treatment with antiretrovirals (ARVs) for all children under two years, whatever their CD4 count. In June 2013, the guidelines changed to recommend immediate antiretroviral therapy (ART) for all children under five years of age. This means that 2.6 million children in 2013 alone must be treated. In addition, the WHO recommends that younger kids, meaning those under three years of age, be treated with an ART combination that includes a powerful class of ARVs called protease inhibitors, regardless of CD4 count and regardless of whether or not they have been exposed to ARVs through prevention of mother-to-child transmission (PMTCT).

Early diagnosis and treatment for babies with HIV is an urgent public health priority. Far too often, young children 'fall through the cracks'. While the WHO's new guidelines propose to 'catch' these infants and children before it is too late, turning these guidelines into reality requires accelerating the policy changes needed to scale up treatment today, and the right tools to do so.

While it is vital to address poor access to ARVs for treating pregnant women and for prevention of mother-to-child transmission altogether, there are important issues to resolve, without delay, to scale up treatment for infants: overcome the technical difficulties of HIV diagnosis in infants; fight still lingering HIV stigma and denial; and have the right product in hand. In fact, with the new WHO recommendations, one of the most important problems is the lack of suitable ARV formulations adapted for children, particularly for babies and toddlers.

To treat HIV in babies, we must first diagnose it!

It is a medical emergency today to diagnose and treat babies and children living with HIV. Currently many are not being tested and treated. There are many reasons behind this, including mothers not knowing their status, stigma in the community, and failure to retain mother and child in the health system.

Current rapid tests do not detect HIV in infants and very young children. Less than one in four HIV-exposed infants benefit from early infant diagnosis, largely because the laboratory technology required is sophisticated and often only available at central laboratories, at best, and results take a very long time to be sent to clinicians and caregivers. Often, the delay in obtaining results means that mothers and caregivers do not come back and so never learn the infant's HIV status. This leads to high loss to follow-up of HIV-positive infants and children who need to be enrolled immediately into care.

We urgently need simple diagnostic tools that can be used to rapidly diagnose HIV in real time at the 'point of care', meaning at health centres at the village level.

¹ Excerpted and adapted from an article by Polly Clayden (HIV i-Base) and Rachel Cohen (DNDi) that first appeared in the November 2012 edition of the Treatment Action Campaign's newsletter *Equal Treatment*.



Traditionally, paediatric formulations of ARVs for children who are too young to swallow tablets were produced as liquids or syrups. These formulations are not ideal, particularly in resource-limited settings as they:

- **Are difficult for clinics and families to transport and store:** Because of their large volume and the need to keep these medicines cold, storage space is tricky at small health facilities. Getting the medicines there can also be difficult. For caregivers, the problems are similar. Consider the example of a child that weighs 10 kg being treated with standard triple therapy: dispensed at a clinic visit, a three-month supply of drugs for this child would involve 18 bottles of liquid weighing almost half as much as the child (4.3 kg). For a rural family who may have walked a long distance to reach the clinic, this is a significant challenge, not to mention the stigma attached to being seen carrying the medicines.
- **Have complex dosing requirements:** In high-income countries, dosing in children is usually based on either their weight or their body surface area. The WHO has developed special weight band-based dosing tables to simplify these complicated calculations for treatment at the primary healthcare level. The tables allow nurses at clinics to give out medicines. Yet even with these tables, administering the separate syrups at different dosages is impractical for caregivers, who are often grandmothers or other family members.
- **In some cases, need to be kept in the fridge:** Certain liquid formulations need to be kept at low temperatures, which of course is not possible if you don't have a fridge or a continuous supply of electricity. Many families, especially in rural areas, have to find a clay pot or dig a small hole in the dirt to keep the liquids relatively cool so that they do not become unusable.
- **Can taste horrible:** For example, because of the high alcohol content of the formulation and inherent taste of lopinavir/ritonavir (LPV/r), the only boosted protease inhibitor approved for use in infants and young children, this formulation has a very bitter taste. Some children describe LPV/r liquid as tasting like vomit, a taste which remains for hours. Naturally, this makes it very difficult for children to swallow and for caregivers to give every day.

Giving ART to children is further complicated by major co-infections, particularly tuberculosis (TB). Children receiving HIV and TB treatment at the same time must cope with taking lots of medicines. TB treatment also includes rifampicin, a drug that reduces the amount of some ARVs in the blood. This interaction between medicines makes it difficult to maintain the right drug levels in the blood when the medicines are given together.

II. WHY ARE THERE SO FEW APPROPRIATE FORMULATIONS OF ARVs FOR CHILDREN?

When it comes to research and development (R&D), it is difficult to think of HIV as a neglected disease. Since HIV was first discovered three decades ago, more than 30 single antiretroviral drugs and several ARV fixed-dose combinations (FDCs) have been approved. There is also a healthy 'pipeline' of new products in development.

However, for children – the very youngest in particular – there are far fewer options. In rich countries, the paediatric HIV market has disappeared due to the near elimination of new HIV infections in infants. As a result, there is little incentive for companies to develop formulations for children. From an R&D standpoint, children with HIV in low- and middle-income countries are neglected. Poor and voiceless, they do not represent a viable commercial market.

In addition, studies in children have not always been carried out for existing ARVs. In cases where studies are conducted, it can sometimes take years from the time when regulatory authorities approve an ARV for adults until the same drug receives approval for children of all ages. Paediatric research plans for ARVs study children in sequential age groups, all too often starting first with adolescents (12 to 18 years), then older children (6 to 12 years), followed by the younger children (2 to 6 years), and only much later, newborns and toddlers up to two years of age.

Sometimes the delay for the youngest children is because appropriate formulations are hard to develop. Safety concerns can also delay approval. Tenofovir, for example, was only recently approved by the US Food and Drug Administration (FDA) for use in children 2 to 6 years of age, ten years after the FDA had authorized the drug for adults, mainly due to difficulties with the formulation.

Regardless of the reasons for these delays, the younger the child, the longer the delay – despite the alarming death rates among babies with HIV.

Recently, things have begun to look a bit brighter. Drug regulatory authorities have introduced specific incentives and conditions for new drug approvals aimed at ensuring that companies developing new pharmaceuticals test their drugs in children. These measures seem to be having an effect. Importantly, in Europe, since 2007, it has not been possible to gain adult approval without submitting a paediatric study plan to the European Medicines Agency (EMA) early on in the development of a drug.

In addition, generic companies now play an increasingly important role in developing child-friendly formulations of ARVs.





III. POTENTIAL SOLUTIONS: PROMISING RECENT DEVELOPMENTS AND OPPORTUNITIES TO IMPROVE TREATMENT FOR CHILDREN

A few years ago, the Indian generic company Cipla developed fixed-dose combination (FDC) tablets of stavudine/lamivudine/nevirapine (d4T/3TC/NVP) that can disperse easily in liquids. These FDCs contain drug ratios that are appropriate for young children and doses suitable for WHO weight-band dosing. These new formulations made it possible to begin treating children in places where using liquids was too complicated. Since then, other formulations have also been produced, such as zidovudine/lamivudine (AZT/3TC), abacavir/lamivudine (ABC/3TC), and zidovudine/lamivudine/nevirapine (AZT/3TC/NVP) as dual and triple combination dispersible tablets. This is good news as d4T will be replaced by AZT and ABC, which are less toxic and better tolerated.

But now that WHO recommends protease inhibitor-based ART for all infants and young children with HIV/AIDS, we urgently need an appropriate combination for first-line therapy that includes this powerful class of ARVs.

Fortunately, Cipla has been developing new formulations of this boosted protease inhibitor for young children. Results from a study conducted by the Children with HIV

in Africa – Pharmacokinetics and Adherence/Acceptability of Simple Antiretroviral Regimens (CHAPAS) group of researchers from the UK and Uganda, called CHAPAS-2, were promising. Caregivers taking part in the study found the mini-tablets, formerly referred to as ‘sprinkles’, developed by Cipla to be more acceptable than liquids for infants (although older children who are able to swallow normal tablets preferred them to the mini-tablets). However, it was difficult to hide the terrible taste of the drugs, so Cipla and DNDi engaged to develop a finer ‘granule’ formulation aimed at masking the taste, one which would combine all the necessary drugs in one (see section IV).

In addition, the current drug development pipeline looks a little more hopeful for children than it has in the past. New prospects include granule formulations of the integrase inhibitors raltegravir, which was approved for adults and children from 6 years of age, and dolutegravir, which was recently approved for adults and adolescents. The originator companies for these drugs have already licensed them to two generic manufacturers in India (raltegravir) or have begun negotiations (dolutegravir).

IV. DNDi, CIPLA, UNITAID, AND OTHER PARTNERS COLLABORATE TO ACCELERATE DEVELOPMENT OF A SIMPLE 4-IN-1 LPV/R-BASED FIRST-LINE FOR INFANTS AND YOUNG CHILDREN WITH HIV/AIDS

The Drugs for Neglected Diseases initiative (DNDi), a not-for-profit R&D organization created in 2003 by Doctors Without Borders/Médecins Sans Frontières (MSF) and five public sector research institutions² – is currently working with Cipla on developing two solid 4-in-1 FDCs of these granules.

The two combinations are lopinavir/ritonavir/zidovudine/lamivudine (LPV/r/AZT/3TC) and lopinavir/ritonavir/abacavir/lamivudine (LPV/r/ABC/3TC) – and the objective is to make these FDCs available in 2015. DNDi and Cipla will also develop a stand-alone solid granule version of ritonavir to be added to paediatric treatment when children are co-infected with TB, as additional ‘boosts’ of ritonavir, to do away with the negative interaction between the TB medicine rifampicin and ARVs.

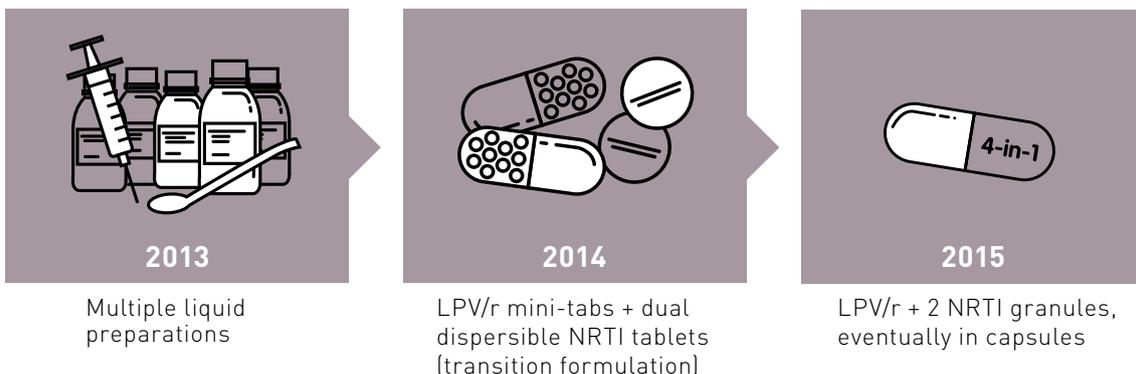
This new 4-in-1 paediatric formulation, specifically adapted for infants and young children, will be in the form of solid granules that fit into a capsule. Caregivers will be able to open the capsules and give the granules to children with soft food or breast milk. Unlike current liquid formulations, the capsules will not require refrigeration, will be ‘taste-masked’ to do away with the terrible taste, and will be easy to dose across various weight bands. That is the goal!

In order to get there, DNDi works with various programme implementers (governmental and non-governmental) and research partners, particularly in high HIV-prevalence countries, to test these products in infants and children with HIV as soon as possible.

All steps are taken to ensure that products are safe to be tested in children (for example, studies are conducted in adult healthy volunteers first). In addition, the plans for developing these products are subjected to ongoing consultations with regulatory authorities and technical agencies such as the US FDA and WHO Prequalification programme. Approvals for studies are sought from ethics committees in countries where studies are conducted as well as in Europe. All DNDi-supported studies are conducted in accordance with international standards for clinical trials to ensure patients’ safety. DNDi is firmly committed to ensuring communities are consulted before and throughout all studies.

DNDi also recognizes that, while there is a great urgency, the development of medicines takes time. For this reason, large implementation studies will be supported in order to facilitate rapid access to the LPV/r-based regimens for infants and children who need them. The information generated from these studies will be very helpful in assessing the feasibility of rolling out this regimen more widely and lessons learned will help programmes and countries to be better equipped to dramatically scale up treatment of infants and children with HIV/AIDS.

The project is made possible by major funding support from and partnership with UNITAID, in addition to funding from the French Development Agency (AFD), Médecins Sans Frontières (MSF), and the UBS Optimus Foundation.



² Brazil's Oswaldo Cruz Foundation (Fiocruz), the Indian Council of Medical Research, the Kenya Medical Research Institute (KEMRI), the Ministry of Health of Malaysia, and the Institut Pasteur of France. The WHO Special Programme for Research and Training in Tropical Diseases (TDR) serves as a permanent observer.

How can civil society groups and treatment activists support the development and delivery of urgently needed paediatric formulations?

- **Raise awareness** about the need for improved treatment options for children in national forums and urge policy-makers to adopt LPV/r-based first-line treatment for all children below three years of age in national guidelines, as recommended in WHO's 2013 guidelines. It is important to remember that many people still think that syrups are the best choice for children and infants with HIV.
- **Participate in community advisory board meetings** organized by DNDi in countries where studies of these products are being carried out and give constructive feedback on how the products can be best developed to meet the needs of children and their caregivers.
- **Be informed!** Make sure you have accurate information about when different products will be developed and available and talk to programme implementers in your country about these new formulations so that they can prepare to make use of them as soon as they are available.
- **Talk to your community** about the studies that DNDi will be carrying out and encourage participation in studies.
- **Participate in surveys** that will be conducted by DNDi to assess whether the products being developed are acceptable for children and caregivers and to make sure that large-scale use will be feasible even in very remote, rural settings.
- **When in doubt, ask tough questions** to governments, programme implementers, product developers, and others!

V. ADVOCACY PRIORITIES FOR CIVIL SOCIETY GROUPS AND TREATMENT ACTIVISTS TO IMPROVE TREATMENT OPTIONS FOR CHILDREN WITH HIV/AIDS

- **Overcome major challenges in public health programmes:** Civil society organizations and treatment activists at the community level can support programmes to improve enrollment and keep more parents and children in care. Key challenges include the low number of women attending antenatal care, the lack of access to HIV testing, poor access to good prevention of mother-to-child transmission programmes and maternal ART, and high loss to follow-up (patients not returning for further treatment). The difficulty of diagnosing infants early is a major problem, too; we need to campaign for pregnant women and babies to be tested. We urgently need a point-of-care

test for early infant diagnosis. It is also important that treatment of children not be reserved for specialists as paediatricians and specialized paediatric facilities are hard to come by in most places: nurses should be able to initiate and manage ART for children at the health centre level as they do for adults in most countries. Keeping children in treatment programmes is a further challenge, because adherence and disclosure are particularly hard for children.

- **Guarantee adoption and uptake at the national level:** As WHO now recommends protease inhibitor-based first-line therapy for infants and young children, countries must adopt this at the national

level and civil society groups and activists can push for this. Children deserve the best treatment options regardless of cost, and developers must make every effort to make their formulations as affordable as possible. In some countries, an important goal for activists will be to secure faster regulatory approval of newer formulations that are easier for children and caregivers to use. Activists may also need to campaign to overcome tricky intellectual property issues in order to secure wider access to certain child-friendly ARVs.

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- Challenge donors and governments:** Most major UN agencies and donors, as well as some national governments, today speak about 'eliminating paediatric HIV' by scaling up prevention of mother-to-child transmission. This is an important goal. However, civil society groups and treatment activists must remain vigilant so that reducing new infant infections does not happen at the expense of children who are already infected with HIV. We need to continue advocating for treatment access for all children who are in need of it. Also, nowadays very few donor agencies support procurement

of paediatric ARVs. UNITAID has played this role over the last several years, but is phasing out its project. Treatment activists need to maintain pressure on the Global Fund and PEPFAR, as well as on other key players, to secure funding for paediatric ARV procurement and paediatric HIV treatment programmes.

- Advocate to rapidly fill ongoing gaps in innovation:** Civil society groups and treatment activists need to keep visible pressure on pharmaceutical companies and other product developers to speed up the R&D process for the treatment of children with HIV and TB.



Credits: Mariella Furrer/DNDi; except: front cover, bottom photo, Raphael Bonacchi; page 3, left photo, Marc Lallemand; page 4, left photo, Julie Remy; page 5, Raphael Bonacchi; and page 8, top photo, John Morstad.

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