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Children with HIV are being left behind in the rollout of antiretroviral therapy

The challenges in providing antiretroviral care to children in resource-limited settings

WHO has made a commitment towards ensuring that children are included in national and international efforts to scale up access to treatment and reach 3 by 5 targets. But there are a number of obstacles to greater access.

Difficulty in diagnosis

A possible HIV diagnosis should be considered in any infant born to an HIV infected mother or when there are clinical signs or symptoms that suggest HIV infection. However, HIV testing in infants and children raises technical and sociological issues.

Antibody tests are unreliable in infants born to HIV positive mothers. Children may have maternal antibodies present in their blood up to the age of 18 months.

However, waiting 18 months for maternal antibodies to clear is not an option in most infected infants. The majority of infants are likely to show signs of HIV disease or AIDS within the first year of life and if left untreated, half of them will die by the end of their second year.

Clinical outcomes are even worse in some settings - in one cohort in Malawi, 89% of infected infants were dead three years after birth and only 1% remained symptom-free despite high immunisation rates.

PCR testing is an option in some settings. HIV RNA PCR testing can detect the presence of HIV's genetic material within a couple months of exposure. A second positive result on a separate sample taken on a separate occasion is considered diagnostic of HIV-infection. (False positives occasionally occur but should be viewed with scepticism if the viral load result is low (HIV RNA < than 5,000 copies/mL) since low viral loads are rare in infected infants).

Yet, even with the price reductions on PCR testing for resource-limited settings, PCR testing may be considered too costly to be used for routine diagnosis in children. Furthermore, the test must be performed by skilled technicians using expensive equipment - and is usually only available through the national reference lab. Transporting the sample thus becomes an issue.

Beyond technical considerations, testing a child for HIV can also present a dilemma for the child's family. Testing requires the permission of a parent or legal guardian. But where there is stigma against HIV, parents may not eagerly grant consent. Should the child test positive, it usually means that at least the mother, and, possibly other family members are HIV-infected, too. And the need to provide counselling and support for the family unit can serve as a disincentive to test the infant.

Difficulties in routine and accurate testing for HIV in children in turn make it difficult to say with any certainty what is the true number of children with HIV - and thus predict the need for treatment.

Lack of trained skilled health personnel or expertise in managing children with HIV

In situations where testing is not possible, healthcare workers could base treatment decisions on the basis of AIDS-defining or suggestive symptoms, the child's CD4 percentage (< 20%) and the mother's antibody status and/or clinical symptoms. But few care providers have been trained to recognise the signs of HIV infection or in the management of a child should he or she prove to be HIV infected.

While WHO has released guidelines for ART treatment in children (see pages 30-39 of WHO's 2003 Treatment Guidelines <http://scholar.google.com/url?sa=U&q=http://whqlibdoc.who.int/hq/2004/9241591552.pdf>) many experts feel that these don't reflect the reality on the ground where monitoring tests and medicines to treat HIV in children simply aren't available. Even when testing and medication is accessible, clinicians are often unsure when to start ART because clinical staging of children with HIV is non-specific (and can be significantly impacted by malnutrition) and available prognostic tests are poor in young children.

There are few suitable, affordable antiretroviral formulations for children

The form, volume and flavour of a medicine influence whether it is acceptable to a child - and whether they will be adherent to treatment. For young children, pleasant tasting liquid formulations that are low in volume are the easiest to administer - though taste varies from culture to culture. Older children often prefer simply swallowing solid formulations.

However, many antiretrovirals are only available as adult-dosed pills (see Drug Module). Many of those that have been formulated for children have significant disadvantages in different resource limited situations.

For example, the current WHO guidelines for children recommend first line therapy with 3TC plus either d4T or AZT and either nevirapine or efavirenz. While each is available in a liquid formulation, preferred for infants, each has drawbacks:

- 1 d4T's liquid formulation requires refrigeration (and thus is not appropriate in some developing world settings)
- 2 3TC is only indicated for use in children over three months of age
- 3 AZT liquid formulations have a low dose to volume ratio. This means that older children have to swallow rather large amounts of the syrup - which can pose adherence problems in growing children
- 4 Nevirapine cannot be used in children being treated with rifampicin for TB because of concerns about drug interactions
- 5 There is only limited data on the use of efavirenz (including best dose) in children younger than 3 years of age or under 12 kg in weight

Second-line regimens anchored by protease inhibitors are even more problematic. Those that are formulated for children are either unpalatable or need cold storage along the chain of distribution (or both). There are no generic formulations.

Distribution problems

Even if a paediatric formulation of an antiretroviral exists, it may not be marketed in every country - and even where the product is registered, it may not be available through the local distributor.

National programmes that have made a commitment to providing ART to children face challenges obtaining and supplying the various paediatric formulations they purchase. Health ministries must have a clear idea of need, develop supply systems to select, procure, store and distribute a steady supply of variable small volumes of ART for paediatric use.

This is a very complicated process even when procuring and distributing single FDC formulations for adults. Few countries in resource limited settings have the capacity (infrastructure, expertise) to set up, manage and monitor such supply systems.

Children's ART formulations are expensive

The costs for all paediatric formulations are currently well above the reduced prices achieved for adult antiretroviral formulations.

The cost of treatment drops markedly when switching from paediatric to solid adult formulations - particularly generic drugs. According to a presentation by Doris Messia of MSF, the cost peaks when administering liquid formulations to children of 14 kg bodyweight. Using tablets for a child of 20 kg reduces the cost per treatment per year nearly 8-fold:

For example, for d4T/3TC/NVP

Best innovator price per year \$1,706 drops to \$631

Best generic price per year \$ 566 drops to \$224

Because of difficulty in accessing paediatric ART formulations and the difference in cost, many caregivers are simply crushing up adult formulations and giving them to children. According to WHO's Dr. Charlie Gilks "Of the few children who have access to treatment, almost all rely on adult capsules or tablets broken or mixed by parents or caretakers."

Dosing issues

But there is a significant danger of over or under dosing with this practice for a number of reasons.

While children are smaller than adults and naturally need smaller volumes of drug, one cannot simply calculate the child's dose based on the adult dose/weight ratio. Drugs are processed differently in an infant's body; and as a child grows, there are changes in the way that drugs are absorbed, distributed, metabolized and excreted (pharmacokinetics/dynamics - PK/D).

But few PK/D studies have been conducted of ART in children of different ages so there is very little clinical data available on ART PK/D in children. There is even less data available from resource-limited settings where ethnicity and malnourishment could also affect PK/D and dosage.

There is greater variability in PK/D for protease inhibitors in children than in adults - which in particular raises questions about the use of nelfinavir.

Studies also suggest that the dose/weight ratio for nevirapine should be higher in younger children (7mg/kg if under 8 years of age and 4mg/kg if over the age of 8 years). Simply breaking off part of an adult FDC tablet could lead to underdosing of the nevirapine component in younger children - and the development of resistance. At the same time, when using adult FDC's, there is no guarantee that the individual drugs within the FDC tablet are evenly distributed; so accurate dosing not assured when the tablet is halved or quartered.

Also, there are no published data on the bioavailability or stability of opened capsules or crushed tablets of the adult formulations - particularly when dissolved in water, juice or mixed into food. The adult formulations were not designed with that use in mind.

For these reasons, there is little clear, practical and data based guidance on what dosage adjustments for weight and age are necessary - although several tables were presented at the November technical consultations (see the MSF presentation).

What dose guidance is available can be confusing and difficult to implement in developing world settings. Dose recommendations are usually based on either weight or body surface area (BSA).

BSA is a rough predictor of the ability of the kidney to clear certain drugs. It is derived from an equation based on height and weight measurements of the child- which are rarely if ever exact. The BSA formulae aren't simple and require a calculator. Errors are common. Even worse, BSA is based on observations in well-nourished Caucasian children. In short, BSA isn't really appropriate in resource-limited settings.

Even when dosing is based on weight bands, not all adult tablets are scored. When they are, the scoring is in halves. Small children need quarters or eighths. When using a capsule, dividing or dissolving its contents can be difficult for a professional. Measuring specific volumes of multiple drugs can be especially confusing for the child's parent or elderly caretaker who must regularly administer these drugs.

Fixed dose combinations (FDCs)

FDCs for children would be much easier to administer and could reduce the risk of over or under dosing. They would also be easier to procure and supply in national HIV treatment programmes - but at present, none have come to market.

In adults, the simplicity and ease of administration of FDCs have allowed for the standardisation of ART without compromising effectiveness. This makes widespread scale up and delivery of ART in resource constrained settings much more achievable.

Solid formulation FDCs for children would need to be produced in at least two sizes and be scored for different sized children. FDC powders for oral suspension or solutions should also be developed. Dosing should be based upon weight with clear labelling - and simple enough for an elderly caretaker to administer.

But there are variety of obstacles to the development and marketing of paediatric FDCs. The first may be the relatively small size of the market. Paediatric formulations are a niche product in low-income countries that haven't yet had the ability to accurately forecast their demand for the drugs.

"We are asking manufacturers to develop appropriate formulations (chocolate) and to register and market them at cost or low price. and there is no market!" Doris Messia of MSF noted in her presentation.

The challenges of bringing any new formulation to the market are substantial (see <http://www.who.int/3by5/en/9Parr.ppt>) and are further complicated by the lack of data on PK/D of antiretrovirals in children in general. Patents and regulatory hurdles also discourage the production and marketing of paediatric antiretroviral FDCs. WHO pre-qualification requires shelf-life studies, dissolution studies, bio-equivalence studies and PK/D studies in children. All these studies cost money and take time (For further discussions of some of these barriers see:

<http://www.who.int/3by5/en/20stahl.ppt>

<http://www.who.int/3by5/en/19lewis.ppt>

But according to WHO pharmacist János Pogány, Ph.D., "film-coated tablets and oral solutions or suspensions can be developed in about 18 months, if pre-formulation is started soon." The development can be accelerated if the paediatric FDCs have the same ratio of active pharmaceutical ingredients and compositions

are essentially similar to already existing registered or pre-qualified adult formulations.

A couple of paediatric FDC are currently in development. In Thailand, generic manufacturer GPO is developing a "mini-vir" formulation of d4t/3TC/nevirapine. At present the company is conducting studies to determine the product's shelf life. But this product is unlikely to be available globally as GPO has never applied for WHO pre-qualification status for any of its products. Cipla is also determining the stability of a paediatric FDC formulation of d4t/3TC/nevirapine, provisionally named Pedimune, which may go into clinical studies sometime this year.

Advocacy

There are only a few organisations devoted to advocacy for children with HIV and as a result paediatric AIDS has not been accorded adequate attention by multilateral health organizations, NGOs and public-private partnerships in healthcare.

Treatment advocacy is desperately needed to push for the inclusion of children in national treatment programmes, demand reductions in the cost of paediatric formulations, encourage partnerships to help develop paediatric formulations of ART FDC

and reduce unnecessary regulatory hurdles that are delaying the production and marketing of ART for children.

Final recommendations from the WHO technical consultation are still being deliberated. These are likely to include programmatic recommendations to aid countries setting up procurement, supply and delivery systems for new and existing products; ways to speed the development of paediatric FDCs and for best use guidelines using currently available products - including adult formulations.

HATIP will publish a summary of these recommendations as soon as they are released.

Some useful links to treatment advocacy oriented sites on pediatric AIDS

Elizabeth Glaser Pediatric AIDS Foundation's: <http://www.ped.aids/>
Baylor Pediatric AIDS Initiative: <http://bayloraids.org/>
MTCT+ Initiative <http://www.mtctplus.org/>

about HATiP

A regular electronic newsletter for health care workers and community-based organisations on HIV treatment in resource-limited settings.

The newsletter is edited by Theo Smart (Cape Town) and Keith Alcorn, NAM's Senior Editor (London).

For further information please visit the HATIP section of aidsmap.com