

HATIP

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Improving access to appropriate paediatric antiretroviral formulations

Final Recommendations from the UNICEF/WHO technical consultation

In the last 2 years, there has been a fundamental shift in the demand for access to antiretroviral (ARV) treatment in resource-poor settings but programmes have struggled to offer paediatric HIV/AIDS treatment to children. In the previous HATIP, we reviewed the plight of children with HIV in the developing world, referencing a number of presentations made at a joint UNICEF/WHO technical consideration held November 3-4, 2004.

The final report from that meeting is now available online at <http://www.who.int/entity/3by5/en/finalreport.pdf>.

Participants at the technical consultation identified four major barriers to scaling-up access to ARV treatment for children:

- Diagnosis of infants under 18 months is difficult
- A lack of paediatric expertise and experience (both discussed in the last HATIP)
- An (incorrect) perception that all infected children will die early in childhood. Policy makers, programmers and care providers themselves need to be convinced that ARV treatment is effective and important in the management of HIV in children.
- ARV drugs are not easily available (or not available at all) in the appropriate formulations and at affordable prices
- Programmes lack tools to accurately forecast the need for paediatric ARVs and thus generate demand. This makes supply/procurement challenging and manufacturers hesitant to invest in the development of paediatric ARVs.

In addition to describing the current dilemma in accessing appropriate care for children with HIV, participants at the technical consultation set out to make specific recommendations in several major areas:

- Principles for how best to use the currently available ARVs - including adult fixed-dose combinations - identifying preferred treatment options to develop for future use
- How UNICEF and WHO can encourage generic and originator pharmaceutical companies to prioritize the production of suitable formulations and increase access to currently available ARVs
- The tools and methods to help national HIV programmes predict their need (forecast) for paediatric ARVs, making recommendations for national HIV programmes on the package of paediatric ARVs needed and the programme indicators for monitoring and evaluating paediatric HIV care and antiretroviral therapy (ART)
- How to address the gaps, obstacles to care and priority operational research needs

Here are the abbreviated (and annotated) recommendations made in that report.

Recommendations

I. Greater advocacy is needed to include HIV-infected children in treatment initiatives

"Greater advocacy by WHO, UNICEF and other partners at Global, Regional and national levels is needed to demand the inclusion of children in treatment initiatives, for the market development of suitable paediatric ARVs, for reduction of cost of paediatric ARVs and for encouraging alternative methods for paediatric ARV development."

II. The best use of ARV formulations currently available for paediatric treatment

The currently available syrups and solutions for ARV treatment in children have a lot of shortcomings but are still the best option for treating young infants/children (usually < than 10kg).

Principles for using formulations in younger, smaller infants (<10kg) with currently available products in resource poor settings

Syrups, solutions or dissolvable formulations of the following remain the best options:

- zidovudine(AZT), abacavir (ABC), lamivudine(3TC)
- nevirapine(NVP)
- lopinavir/ritonavir (LPV/r)

Not as ideal in very young children in the developing world due to problems in dispensing, acceptability, difficulty of use or need for refrigeration

- stavudine (d4T) liquid
- didanosine(ddi) sachets
- nelfinavir powders

But the experts unanimously agreed that switching to solid formulations (usually adult) is the best available option for treating young infants/children (usually by 10-12 kg weight) until paediatric formulations are developed.

Principles for use of ARV formulations in Infants and children above 10-12 kg

- Switch to available solid formulations as soon as possible or the can tolerate them
- Use solid formulations of the same first and second line drugs as used by adults
- Tablets may be divided in half but not further for drug safety reasons
- Depending on the age/weight of the child, adult fixed dose combinations (FDCs) may result in under-dosing of individual components.
- If adult FDCs are used (crushable or solid), dual FDC may reduce chances of under-dosing NVP.

Adult FDCs can be used in combination with regular formulations either to augment one of the under-dosed components of a triple combination (example, additional NVP with a triple FDC), or to complement a dual combination (e.g., Combivir + nevirapine)

- There must be a single formulation of NVP as a single agent in addition to dual or triple NRTI FDC
- Frequent dose changes are required as children's growth, weight and development improve due to treatment

There is an urgent need for easy to follow dosing recommendations in which the dose ranges are based on weight bands. Prototype tables were drafted at the meeting and will be included in WHO guidance tools subject to further improvements and validation. See Draft Pediatric Antiretroviral Dosing Tables (can we link to the document or included it as an attachment?)

III. The long-term development of appropriate paediatric formulations

Prioritise the development of scored solid formulations for use in children of all ages (including those less than 10 kg). Improved syrups are also needed.

Characteristics of paediatric ARVs well-suited to resource poor settings

Syrups and solutions should be reserved for infants <10 -12kg. Sachets, granules, or dispersible tablets are preferable.

Liquid formulations:

- Stable at room temperature; have small dose/volume; have long shelf life at high humidity and temperatures
- In suitable dosage forms to provide appropriate dose ranges by 2-3kg weight bands for smallest infants
- Packaged to provide for 28-30 treatment days
- With masking of bad taste (e.g. AZT)

Solid formulations

- For use as soon as possible a child can swallow them (usually children >10kg weight)
- In suitable dosage forms to provide appropriate dose ranges by 2-3kg weight band for smaller infants and by 10kg weight band for larger children
- Crushable, granulate or dispersible tablets
- Stable with longer shelf life at high room temperatures and humidity
- Scored tablets
- With masking of bad taste

Single drug priorities - liquids and solids

Reduced dosage forms of adult tablets of 3TC, ZDV, ABC, NVP, EFV (note, some of these are currently available but not always licensed for paediatric use)

Pre-FDC formulation - co-packaging of e.g. ZDV/3TC/EFV: ddI/3TC/EFV

Two drug FDC priorities - solids

- d4T/3TC, ZDV/3TC, 3TC/ABC, FTC/TDF

Three drug FDC priorities - solids

Paediatric formulations of FDCs already available for adults should be produced:

- d4T/3TC/NVP, ZDV/3TC/NVP, ZDV/3TC/ABC

Any new product being developed for adults, e.g., FTC/TDF/EFV, should be concurrently investigated for children.

IV. Increasing access to appropriate paediatric ARV formulations

- WHO and UNICEF should identify originator and generic companies who might be able, and prepared, to deliver some of these products and explore with them how to expedite paediatric products for WHO pre-qualification or national registration. This

could include co-packaging as a interim step while paediatric FDCs are being developed.

- Dialogue directly with companies on a one-to-one basis as well as meeting with (selected) companies and potential funders to discuss what needs to be done in order to produce the paediatric ARV formulations and what next steps in preformulation should be undertaken.
- WHO and UNICEF should advocate for and explore with a range of partners, incentives for originator or generic manufacturers to develop paediatric formulations that can meet regulatory requirements. This may include public and intergovernmental subsidies for specified research and development, using existing public-private partnerships, tax or patent incentives or other, innovative ways, to stimulate creation of needed paediatric formulations of ARVs.
- The paediatric ARV formulations recommended by the meeting should be identified in WHO invitations for expressions of interest that are publicised as part of the prequalification programme. (The WHO prequalification project has been very important in ensuring quality drugs are available for use for the 3x5 initiative. For prequalification, WHO invites pharmaceutical manufacturers (innovator or generic) to voluntarily submit their expressions of interest (EOIs).
- Proactive efforts to encourage applications to the prequalification programme might require mobilising resources to provide WHO technical assistance (and/or other UN agencies involved) to support companies to generate product dossiers. HIV/AIDS Department could help by providing funding for expert consultants identified by EDM/UNICEF to assist the targeted companies.
- WHO and UNICEF should work to encourage other prospective purchasers of paediatric formulations to 'express their interest' to buy such drugs, in order to stimulate the market and encourage producers of the potential market.

The problem of paediatric formulations is not unique to treatment of HIV infection, but is common to other major diseases such as malaria and TB where similar initiatives for paediatric formulations could consolidate market interest. (UNICEF has recently sent out invitations for EOIs to development children's formulations of artemisia-based antimalarial drugs).

V. Programmatic issues

- UNICEF and WHO should develop and finalise the basic tools and programme indicators to monitor and plan for HIV treatment for children, including demand forecasting and using these tools assist countries to set targets for paediatric ARV coverage. This can then be used to estimate the likely market size, and possible production forecasting. Any reader interested in such tools should see the presentation at the WHO/UNICEF meeting made by Stephen W. Nicholas of the Clinton Foundation: <http://www.who.int/3by5/en/13Nicholas.ppt>
- WHO and UNICEF should identify the countries with largest expected paediatric populations to be treated with ARVs and through a quick situational analysis identify high burden countries. Then WHO/EDM, working with the regional offices, could then collaborate with relevant regional and national regulatory bodies in order to facilitate regulatory approval of new (or existing) paediatric ARV formulations including delivering regulatory advice on creating these formulations and advise on paediatric use of adult formulations. WHO and UNICEF should

assist these high burden countries to develop a mechanism to ensure a "fast track" registration process.

- As WHO and UNICEF will only promote the use of medicines which are classified as "essential medicines" the paediatric formulations should therefore be recommended in WHO treatment guidelines which can be proposed for adding to the Model List of Essential Medicines.

VI. Clinical and operational research

Further clinical research in ARVs for paediatric populations is urgently needed.

- WHO and UNICEF should explore and stimulate ways in which the clinical, pharmacokinetic (PK) and bioavailability studies can be carried out in target populations in the countries where the drugs would be used. This could be through direct dialogue or through other partners e.g. the European and Developing Countries Clinical Trial Partnership (EDCTP), Paediatric Aids Clinical Trials Group (PACTG/IMPAACT), Pediatric European Network for Treatment of AIDS (PENTA).
- More "operational research" is needed on current practices used in treating infants. For example, what is the resulting dose and bioavailability when adult formulations are crushed and/or capsules opened and mixed with different food stuffs and liquids. WHO and UNICEF should encourage partner organizations to carry out such research.

Key Research Priorities

a) Burden of disease and estimates of numbers of children requiring treatment

These data are needed for advocacy, forecasting drug needs, planning, programme monitoring and evaluation.

- Identify the countries with largest expected paediatric populations to be treated with ARVs and map the countries with significant burden of disease through a quick situational analysis. Testing and diagnosis of infants, particularly in infants >18 months should be carried out
- Improved diagnostic tools are urgently needed

b) Developing ideal paediatric dosage forms

There is a major gap in the pharmacokinetic (PK) data on antiretrovirals in children, particularly infants.

Clinical and PK evaluation in paediatric target populations and bioequivalence studies of generic drugs should be carried out. PK data is especially lacking for the dual and triple therapies.

WHO and UNICEF should explore and stimulate different ways in which these studies can be best carried out, e.g. for drugs where there is no PK data in children, registered adult formulations can be used for study purposes. This could be through direct dialogue or through other partners e.g. the European and Developing Countries Clinical Trial Partnership (EDCTP), PACTG/IMPAACT, Pediatric European Network for Treatment of AIDS (PENTA). Where pharmaceutical companies are unable or unwilling to carry out such studies, public-private partnerships could carry out such studies using crushed adult formulations and then take it forward for registration.

Current practices related to treatment of children and infants with the available (adult) formulations such as dividing tablets, opening capsules etc. raise concerns over actual dosing thus it is critical to have operational research at sentinel sites to:

- determine viral and immune response
- monitor clinical and CD4 response
- there is also a need to determine whether there is equal distribution of drug in tablets that have been split
- "Operational research" on current practices used in treating infants and what the resulting dose and bioavailability is - e.g. the crushing of adult formulations and/or opening of capsules and mixing with the drug with different foodstuffs and liquids.

- WHO and UNICEF should encourage partner organizations to carry out such research
- The prototype tables of simplified paediatric dose ranges based on weight bands should be further developed and validated in target populations.

c) Programmatic issues

Paediatric treatment programmes need to be integrated in existing PMCT interventions, maternal and newborn health programmes etc., programme evaluation, training and guidelines. Studies on longitudinal outcome cohorts in resource-constrained settings should be initiated. These model programmes should include:

- decentralised programmes
- nurse-managed programmes
- community & family based programmes with good referral network
- chronic care components

Systems for surveillance should be developed to include:

- clinical outcomes including drop out rate
- resistance
- toxicity

WHO and UNICEF should encourage partner organizations with field programmes (EGPAF, Clinton Foundation, MSF etc.) to incorporate operational research into their programmes.

Programme evaluation tools should be developed.

WHO and UNICEF should develop evaluation tools for field testing UNICEF and WHO should develop and finalize the basic tools and programme indicators to monitor and plan for HIV treatment for children, including demand forecasting and using these tools assist countries to set targets for paediatric ARV coverage. This can then be used to estimate the likely market size, and possible production forecasting.

Steps since the meeting

WHO and other partners have begun a dialogue with both originator and generic companies to stimulate production of these formulations.

According to Dr. Siobhan Crowley, WHO's next round of EOI invitations are requesting pediatric formulations, and the issue will be discussed in meetings with generic pharmaceutical manufacturers in early March.

Meanwhile, UNICEF is looking into developing an incentives fund, and to support PEPFAR purchase of ARV drugs, the FDA is reportedly developing guidance for industry on FDCs and co-packaged drug products for treatment of HIV in children.

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