



UNICEF/WHO Technical Consultation:

IMPROVING ACCESS TO APPROPRIATE PAEDIATRIC ARV FORMULATIONS

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Summary

Background

In 2003, more than 5 million people were newly infected with HIV – as many as 700,000 (13%) of them were children. Six hundred and thirty thousand (95%) of these new infections were caused through mother-to-child transmission, and 90% of the infected children live in sub-Saharan Africa. AIDS case reporting is unreliable, however it is estimated that 500,000 children are currently in need of antiretroviral therapy (ARV) world wide. In 2003 some 490,000 child deaths under age 14 were due to AIDS, and an estimated 17% of all AIDS deaths were among children. There are 7 countries where AIDS accounts for more than 10% of the under five mortality.

The best way to address paediatric HIV infection is to significantly reduce the proportion of children acquiring infection as has happened in most developed countries to date. However, in developing countries, although most governments recognize the need to integrate interventions to prevent mother-to-child transmission in antenatal care services, only 10% of pregnant HIV infected women have access to them. In addition single dose nevirapine or other anti-retroviral regimens starting late during pregnancy that are currently used in women who subsequently breastfeed, have limited efficacy, and even if the UN goal of 80% coverage of pregnant HIV-infected women receiving short course ARV was achieved today, there will still be at least 300,000 new paediatric infections occurring each year.

As ARV treatment has become available over the last decade, potentially transforming HIV disease into a chronic condition¹, the growing treatment gap between the resource-rich HIV infected populations and the bulk of those infected in resource-poor settings is unacceptable. In recognition of this there has been a fundamental shift in the last 2 years in the demand for access to ARV treatment in resource-poor settings. This is reflected in WHO 3X5 targets, the Presidents' Emergency Plan (PEPFAR), The Clinton Foundation, Mother-to-Child Transmission (MTCT) plus initiative, The Elizabeth Glaser Pediatric Aids Foundation (EGPAF) and other International NGOs². All these global efforts make clear commitments to securing equitable access for infants and children, however in reality, most HIV treatment programmes have struggled to include children and paediatric HIV/AIDS treatment has not received high priority in most settings. Even in successful ARV treatment programmes this is difficult and children are usually not included. For example, in September 2004, of 23500 patients on HAART in MSF projects only 1700 (7%) are children (< 15 years).

¹ In most resource-rich countries, HIV disease has been transformed into a chronic condition.

² including NGO driven programmes such as MSF

The ambitious target of 3 million people on ARV treatment by the end of 2005 includes children, and aims to ensure at least 10 -15 % of patients on ART are infants and children.

Countries and programmes report four major obstacles to rapidly scaling-up access to ARV treatment for children.

Firstly, there is an (incorrect) perception that all infected children will die early in childhood thus policy makers, programmers and care providers themselves remain to be convinced that ARV treatment is effective and important in the management of HIV. There is clear evidence that ARV treatment in children in resource-rich countries is very effective.

Secondly, diagnosis of infants under 18 months is difficult due to the lack of simple, affordable HIV tests; HIV antibody tests are unreliable because of the maternal antibodies. Rapid HIV tests which can indicate exposure to infection in infants <18 months, or infection in infants >18 months are becoming more widely available but are rarely used for testing children.

However, thirdly, even when HIV is suspected or diagnosed, and ART care providers recognize the need for ARV, the drugs are not easily available (or not available at all) in the appropriate formulations and at affordable prices. In addition, the lack of tools for programmes to accurately forecast the needs, and generate demand make supply and procurement challenging, and originator and generic producers hesitant to invest in the development of paediatric ARV products.

Lastly, the lack of paediatric expertise and experience is a major impediment to initiation of paediatric HIV/AIDS care and treatment. Human capacity and resources need to be addressed in parallel with other measures.

UNICEF and WHO convened a meeting of technical experts to urgently identify ways and mechanisms to overcome the key obstacles to access of appropriate, acceptable, and affordable ARV formulations for children.

Specific objectives and outcomes of the meeting

The meeting set out to;

- Review the existing realities of access to ARV for children
- Determine principles for best use of currently available ARVs, and preferred treatment options, including fixed dose combinations (FDCs) for both immediate and future use.
- Consider how UNICEF and WHO can galvanise generic and originator pharmaceutical companies to produce suitable formulations, as well as how to increase access to those ARVs that are already available.
- Review tools and methods for demand forecasting of paediatric ARV, and develop recommendations for national HIV programmes on the package of paediatric ARVs required, and the basic programming indicators required to secure suitable formulations for paediatric use within a context of family therapy.

Summary of the meeting proceedings

The following provides a brief summary of the issues considered and discussed by participants in order to develop the final recommendations on page 6.

Existing challenges to treatment for HIV infected children

There are many challenges to the treatment of paediatric populations infected with HIV, many are not exclusive to HIV infection, but are special considerations for treating infants and children with any medication. As children grow, physiological changes produce differences in absorption, distribution, metabolism and excretion of drugs which dictate the need for different dosing and treatment options. For smaller children the drugs need to be palatable, should be stable once mixed (including if mixed with a range of locally available food or drink), and should not have complex food requirements (e.g. time before or after eating, to be

taken with certain kinds of food etc.). Methods of dispensing need to be simple and practical, as they may need to be undertaken by sick parents or other elderly caregivers.

Dosage regimens must be adjusted as the child grows, and therefore, tables of standardized dose ranges by weight bands need to be developed to enable non-experts to quickly check if the child is in the appropriate dose-range. The situation is complicated by the need to use dosage regimens of more than one drug, and this in turn greatly influences adherence to treatment regimens.

Paediatric dosage regimens are usually based on either age, weight or body surface area, and can therefore be complicated to work out. For example, zidovudine (ZDV or AZT), nevirapine (NVP) and didanosine (DDI) for young infants all give dose requirements for body surface area; this is complicated in resource-poor settings where equipment, facilities and trained staff are limited. Simplified doses guidance based upon weight and/or age is urgently required.

There is still incomplete knowledge of pharmacology of ARVs in children. There is clearly marked inter-individual variability in the pharmacological and immunological responses to ARVs, and effects of nutritional status, age, and ethnicity on pharmacokinetics and pharmacodynamics is not well understood or well documented. In addition, paediatric dose ranges for children less than 3 years old have not been established for some drugs, e.g. efavirenz (EFV), tenofovir (TDF)³.

Most of the currently available paediatric ARV formulations require children to take frequent doses of unpalatable syrups, many of which need cold chain storage, have limited shelf life and stability after opening and are very costly. Once children reach 10 or more kilograms in weight, large volumes of syrups tend to be required, which is demanding for children and their care givers. There are still no pre-qualified FDCs specifically available for paediatric use (although some generic companies have produced triple FDCs and are carrying out stability studies)⁴. The few children that have access to treatment rely mainly on using adult capsules or tablets, broken or mixed by parents or carers. This can result in dangerous under- or over-dosing if providers and caregivers are not supported and guided appropriately. Importantly, many of the paediatric ARV formulations that are available are several times more expensive than the adult solid formulations.

The lack of data to guide programming and planning

There are still very little reliable data on the number of children:

- infected with HIV
- progressing to serious clinical disease (and death)
- reaching the immunological /clinical criteria for initiating ARV treatment.

This lack of data hampers the ability of planning and procurement for HIV treatment and care programmes. In addition the insufficient articulation of burden of paediatric disease has also delayed both the political and technical response, as reflected in the absence of paediatric focus in national plans, targets and care strategies.

Even where the first line and second line options have been identified, there are insufficient data about how many children will tolerate them and the proportion that will develop toxicity or resistance. Therefore programs do not have information on how long regimens can be expected to last, what second line regimens to use, and the likely longer term interactions and toxicities. However, early experience from MSF programmes in Kenya and South Africa demonstrates that children do well on treatment.

Getting new and existing products into countries for use

Regulatory, registration and intellectual property issues substantially affect pharmaceutical markets and access to medicines within resource-poor settings. These issues impact on

³ EFV dose ranges are for above 3 yrs or 10kg; TDF dose range for above 4 years

⁴ GPO and CIPLA have paediatric FDC formulations of d4T,3TC,NVP that are going into clinical trials early 2005

availability of both existing and new drugs as well as incentives that exist to invest in research and development of products. On the other hand, efforts to harmonize and standardize drug registration standards have enabled generic companies to compete nationally, regionally and internationally.

Almost all countries are obliged to follow the WTO trade agreement on TRIPS; although the least developed countries will have until 2016 to comply. For generic companies in countries like India, the transition to TRIPS compliance required from January 2005 may result in fewer drugs being produced or made available, both nationally and to other countries. The Doha Declaration and the August 30 Decision of 2003⁵, in particular, have attempted to lay out mechanisms by which countries with insufficient or no manufacturing capacity have access to affordable medicines. The August 30 decision is intended to set up a system to allow for the export and import of pharmaceutical products produced under compulsory licence, including vaccines, medical devices, diagnostics and paediatric products. However, these are not always used by countries for either adult or paediatric drugs. In the USA and Europe, regulatory authorities have been trying to encourage routine evaluation of all new products lines in pediatric patients, and in the USA this has included offering patent extension incentives.

Developing paediatric formulations

Participants were reminded that safe and effective paediatric dosage forms for many products (including FDCs) should be possible given the fact that data is available from clinical studies and available in the literature. It was suggested that film-coated tablets and oral solutions or suspensions (from existing products) could be developed in a minimum of 18 months, if the pre-formulation efforts are started promptly. Development can also be accelerated if paediatric FDCs have the same ratio of active pharmaceutical ingredients (APIs) and compositions are essentially similar to those already used and registered in the countries with stringent regulatory authorities, or already prequalified by WHO. For prequalified adult drugs where the APIs are being reduced but kept in the same ratios, additional bioequivalence data may not be required to prequalify the new pediatric product⁶.

Preferred products for treatment of paediatric populations

The clinical care experts were clear and unequivocal in stating that where possible, solid formulations, granules, chewable or crushable tablets are the preferred products for use for most children and should be used as soon as they are able to take them. In practice, given the current doses and formulations, the weight at which solid formulations should be offered will vary from around 10-12 kg depending on the ease of administration, acceptance and cost. Tables of simplified dose ranges by weight bands will also simplify use of adult formulations.

Ensuring quality formulations are available

The prequalification project has been very important in ensuring quality drugs are available for use. The process is voluntary and thus companies (innovator or generic) are required to voluntarily submit their expressions of interest (EOIs). While some companies have been able to compile good quality dossiers, others have provided insufficient information on product specifications, validation, API or bioequivalence or have not been up to the appropriate good manufacturing process (GMP) standards. Further, national drug regulatory authorities (DRAs) are frequently not applying the same standards as recommended by WHO, yet products are often registered and used in countries. However, over the past few years since the start of prequalification project an improvement in the quality of the dossiers have been noted and also an increased willingness of the manufacturers to upgrade their manufacturing sites.

To support PEPFAR purchase of ARV drugs, the FDA have also been trying to provide guidelines for rapid approval of innovator or tentative approval of non-innovator drugs for

⁵ Declaration on the Trips agreement and Public Health, WT/MIN/01/DEC/2 (2001), WT/L/540 (2003)

⁶ In some cases, it may be possible to obtain a waiver for *in vivo* bioequivalence data for BSC class 1 drugs i.e. drugs with high permeability and solubility and true solutions.

distribution outside the USA. They are also developing guidance for industry on FDCs and Co-Packaged Drug Products for treatment of HIV.

Procurement and supply

Access to paediatric ARV formulations depends on effective supply chain management. Some of the key steps in the supply chain management are poorly understood or located across different programmes. Limited demand for paediatric formulations due to either the small numbers of children under treatment, lack of national policy or treatment guidelines, lack of adequate cold storage space or difficult forecasting leave programmes hesitant to expand paediatric treatment despite national ARV PMTCT guidelines being in place. For some products, minimum order quantities make them difficult to use in start up (e.g. nelfinavir and liquid abacavir). Balancing the lead times for different products and the need for holding an emergency stock requires considerable technical expertise. WHO and UNICEF have found that many countries have little capacity to undertake effective procurement and supply management (PSM).

Service delivery models

In the majority of service delivery sites providing ARV treatment to adults and children, care is frequently delivered by nursing or other health providers under supervision of medical doctors. In resource-limited settings with severe lack of qualified staff in public health services, this approach appears to be the only realistic one for the short and medium term. Simplified, standardized guidelines are required to ensure basic standards for service delivery. Health care workers trained in the care of paediatric populations with HIV is still very limited. Capacity for paediatric care is thus limited, and counselling for the family often lacking. Disclosure of HIV infection to the child is difficult and can act as a real barrier to achieve drug adherence for older children.

Current efforts for treatment of infants and children with HIV

The diagnosis of infants under 18 months of age is often not possible in resource-poor settings due to lack of suitable diagnostic tests. The lack of equipment, reliable electricity, technical expertise, regular supplies and high cost of virological tests mean this is not likely to become available in the very near future beyond tertiary centres. Currently more than 50% of infants infected with HIV will die within their first 2 years without their clinical care providers, their mothers or parent being aware of their HIV status.

Babies born to HIV infected mothers are the most vulnerable group as serological testing can only define the exposure of the infant to HIV virus and not the infection status. Participants called for better guidance on presumptive diagnosis of HIV infection in infants. Although presumptive diagnosis may be imperfect, until the capacity to carry out diagnostic PCR tests is developed, this may be the only way forward. Where possible, early diagnosis could be centralized in regional or national facilities capable to perform PCR diagnostic (RNA or DNA PCR) on dried blood spots stored on filter papers that can be easily shipped.

Despite the considerable challenges and obstacles discussed above, participants agreed that children with HIV can, and indeed are, being treated successfully. However, far greater effort and attention need to be directed to ensure children become a priority as ARV programmes scale up. The group called for national targets for numbers of children under treatment. There are a number of success stories from Romania, Uganda, Botswana, and South Africa that could be documented and used for defining best practices. Cotrimoxazole prophylaxis for HIV exposed and HIV infected infants and children must be further promoted as it is an essential low cost intervention and appropriate and affordable formulations are already available.

Clinical and pharmacokinetic data

The urgent need for further pharmacokinetic (PK) and clinical studies in the target paediatric populations was underlined as well as the need to mobilize resources to support specific studies to advance this knowledge. Surveillance systems need to be developed and implemented in order to inform programmes about issues such as clinical outcomes, adherence rates, toxicity, resistance etc.

Working groups

The experts at this consultation worked in smaller groups to develop specific recommendations in four major areas:

1. The principles and practice to obtain best use of the ARVs currently available for paediatric treatment.
2. Principles and priorities for the design and development of modified and new appropriate paediatric ARV formulations
3. Demand forecasting and programme indicators for monitoring and evaluating paediatric HIV care and ART.
4. Gaps, obstacles and priority operational research needs.

The discussions and recommendations assumed the use of existing WHO paediatric ARV first and second line regimen choices as outlined in 'Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach are available at: http://www.who.int/3by5/publications/documents/arv_guidelines/en/

Recommendations

The following major recommendations were made by the participants to increase access to appropriate, acceptable and affordable paediatric ARV formulations, including next steps for UNICEF, WHO and key partners.

1. **Advocacy for including 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.

2. **For the short term: best use of ARV formulations currently available for paediatric treatment**

The experts agreed that the currently available syrups and solutions for ARV treatment in children have a lot of shortcomings in developing country conditions. Nevertheless, these syrups and solutions are still the main option for treating young infants/children (usually < than 10kg). However, the experts unanimously endorsed the use of solid formulations as the best available options for treating young infants/children as soon as feasible (usually by 10-12 kg weight) whilst paediatric ones are being developed. Currently, this usually means using adult formulations.

Principles for the use of solid formulations for treating infants and children with currently available products were drawn up and agreed upon. The need for dose ranges based on weight bands was recognized as urgent, and prototype tables were drafted for further development (annex 1). These should then be included in WHO guidance tools subject to further improvements and validation (in the interim, these will be put on the WHO 3X5 website

Principles for use of ARV formulations in infants and children with currently available products in resource poor settings

Younger, smaller infants (<10kg)

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 ideally recommended in the very young due to problems in dispensing, acceptability, difficulty of use or need for refrigeration

- stavudine (d4T) liquid
- didanosine(ddi) sachets
- nelfinavir powders
- Switch to available solid formulations as soon as possible or tolerated

Infants and children above 10-12 kg

- Switch to available solid formulations as soon as possible or tolerated
- Use solid formulations of the first and second line drugs used for adults
- Tablets may be divided in half but not further for drug safety reasons
- Depending on the age/weight of the child, adult FDCs may result in under-dosing of individual components and this should be checked.
- If adult FDCs are used (crushable or solid), dual FDC may reduce chances of under-dosing of 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 based combination), or to complement a dual combination (example: AZT/3TC equivalent + 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

3. For the long term: development of appropriate paediatric formulations

Criteria for optimal paediatric formulations of existing ARVs were discussed and identified, and a list of selected dual and triple FDCs, and scored single ARV drugs from originators and/or generics that would simplify treatment for all ages was developed.

The priority is development of solid formulations adapted for use in children of all ages (including those less than 10 kg). Syrups are also needed both now and for the future, and need to be improved.

It was recommended that WHO and other partners should start a dialogue with both originator and generic companies to stimulate production of these formulations (this list will be on the website until a mechanism for the dialogue has been worked out).

Recommendations for paediatric ARVs needed for resource poor settings

Syrups and solutions should be reserved for infants <10 -12kg. Where possible sachets, granules, or dispersible tablets would be preferred.

Liquid formulations:

- Should be stable at room temperature; have small dose/volume; have long shelf life at high humidity and temperatures
- Be available in suitable dosage forms to provide appropriate dose ranges by 2-3kg weight band for smallest infants,
- Be packaged to provide for 28-30 treatment days
- Have suitable masking of bad taste (e.g. AZT)

Solid formulations

- For use as soon as possible a child can swallow (usually children >10kg weight)
- Be available in suitable dosage forms to provide appropriate dose ranges by 2-3kg weight band for smaller infants and by 10kg weight band for bigger ones
- Crushable, granulate or dispersible tablets
- Stable product with longer shelf life at high room temperatures and humidity
- Scored tablets
- Have suitable 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 those FDCs already available for adults should be produced:
d4T/3TC/NVP: ZDV/3TC/NVP: ZDV/3TC/ABC

Any new product being developed for adults should be investigated for children
e.g. FTC/TDF/EFV is currently being developed for adults, paediatric formulation and established dose ranges are urgently needed.

4. 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 some of the paediatric products for WHO pre-qualification or national registration. This could include co-packaging as a short-term, 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 the product needs, 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, mechanisms and activities that might provide incentives for originator or generic manufacturers to develop paediatric formulations that can meet appropriate regulatory requirements. This may include public and intergovernmental subsidies for specified research and development including using existing public-private partnerships, tax or patent incentives or other, innovative ways, to stimulate creation of needed paediatric formulations of ARVs.
- WHO should ensure that the paediatric ARV formulations recommended by the meeting are priority products identified in the invitations to express interest that are publicized as part of the prequalification programme. This should be done through a formal memo from the HIV/AIDS department to the WHO Prequalification Programme.
- Proactive efforts to encourage applications to the prequalification programme might require mobilizing 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 /convince producers of the potential market. The problem of paediatric formulations is not unique to treatment of HIV infection, but is common to other major disease such as Malaria and TB where similar initiatives for paediatric formulations could consolidate market interest.

5. Programmatic issues

- 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.
- 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.

6. Clinical and operational research

There is an urgent need for further clinical research in ARVs for paediatric populations.

- WHO and UNICEF should explore and stimulate ways in which the clinical, pharmacokinetic (PK) and bioavailability studies in target populations and the countries where the drugs would be used can be carried out. 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).
- There is also a need for more "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 food stuffs and liquids. WHO and UNICEF should encourage partner organizations to carry out such research (annex 2).

6-10	7.5 ml	-	-	-	-	-	-	-	-
10-15	12.5 ml	1	-	-	6 ml	4	2	1	-
15-20	-	-	1	-	8.5ml	5	2.5	1.5	-
20-29	-	-	1	-	11	6	3	2.0	-

Table 3. Dual FDCs for children above 10 kg ZDV/3TC

Weight (kg)	ZDV/3TC(300mg/150mg)	With NVP 200mg tabs	Or with EFV 100mg caps
10-15	- not possible with adult FDC		
15-20	½ twice daily	-	2.5
20-29	½ twice daily	1	3 - 3 ½

Table 4. Triple FDCs for children above 10 kg d4T/3TC/NVP

Weight (kg)	d4T/3TC/NVP
10-15	30mg d4T/3TC/NVP 1/2 tab twice daily or 30mg d4T/3TC 1/2 tab + ½ NVP tab twice daily
15-20	40mg d4T/3TC/NVP ½ tab BD + NVP ½ once daily
20 -29	40mg d4T/3TC/ 172 tab twice daily + ½ NVP twice daily(AM and PM)

ANNEX 2: RESEARCH PRIORITIES IDENTIFIED

The key issues where gaps exist and operational research is needed can be broadly divided into 3 categories;

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.

- WHO and UNICEF should 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 and research and development on diagnostic in infants should be stimulated.

b) Developing ideal paediatric dosage forms

There is a need for improving the currently available paediatric dosage forms as well as developing new dosage forms. However, currently, there is a major gap in the PK data in children, particularly infants.

- Clinical and PK evaluation in paediatric target populations should be carried out as well as bioequivalence studies of generic drugs. 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, the TDR model could be used where a public-private partnership could carry out such studies using crushed adult formulation 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 food stuffs and liquids. WHO and UNICEF should encourage partner organizations to carry out such research
- The tables of simplified paediatric dose ranges based on weight bands should be further developed and validated in target populations.

c) Programmatic issues

There is a need for integration of paediatric treatment programmes 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:
 - decentralized 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.

ANNEX 3 : GLOSSARY OF ABBREVIATIONS

ABC	abacavir
APIs	active pharmaceutical ingredients
ART	antiretroviral therapy
ARV	antiretroviral
CD4	human T lymphocytes (also called helper T cells) expressing CD4 antigen
ddi	didanosine
DNA	de-oxy ribonucleic acid
DRA	drug regulatory authority
EGPAF	the Elizabeth Glaser Pediatric Aids Foundation
EFV	efavirenz
EDCTP	European and Developing Countries Clinical Trial Partnership
EDM	Essential drugs and medicines (Department within WHO of Health Technology and Pharmaceuticals Cluster)
EOI	expression of interest
FDCs	fixed dose combinations
HAART	Highly active anti-retroviral therapy
IDV	indinavir
3TC	lamivudine
LPV	lopinavir
MSF	Médecins sans Frontières
MTCT	mother-to-child transmission
NVF	nelfinavir
NVP	nevirapine
NNRTI	non-nucleoside reverse transcriptase inhibitor
NsRTI	nucleoside analogue reverse transcriptase inhibitor
NtRTI	nucleotide analogue reverse transcriptase inhibitor
PACTG	Paediatric Aids Clinical Trials Group
PENTA	Pediatric European Network for Treatment of AIDS
PEPFAR	the President's Emergency Plan for AIDS Relief (USA)
PCR	polymerase chain reaction
PK	pharmacokinetics
PMTCT	prevention of mother to child transmission
RNA	ribonucleic acid
RTV	ritonavir
/r	low dose ritonivir
SQV	saquinavir
TDR	Special Programme for Research and Training in Tropical Diseases
TRIPS	trade-related aspects of intellectual property rights
D4T	stavudine
TDF	tenofovir disoproxil fumarate
ZDV	zidovudine (AZT)