WORLD HEALTH ORGANIZATION

INTERAGENCY TASK TEAM ON PREVENTION AND TREATMENT OF HIV INFECTION IN PREGNANT WOMEN, MOTHERS AND THEIR CHILDREN

Report of the Meeting of the Paediatric Working Group

Developing an Optimized list of Paediatric ARV Formulations

Geneva, Switzerland
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Meeting Report

INTERAGENCY TASK TEAM ON PREVENTION AND TREATMENT OF HIV INFECTION IN PREGNANT WOMEN, MOTHERS AND THEIR CHILDREN

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Executive Summary

The number of paediatric options available for global programmes has increased markedly in the last 5 years with the approval of many new formulations, including child-friendly fixed dose combinations. Paradoxically, this has not increased the number of *regimen* options that can be given to children, only the number of dosage forms and strengths available to deliver any one particular regimen. For example, a provider who wishes to prescribe a combination of AZT, 3TC and NVP to her 5 year old patient has a perplexing range of options, including dual and triple fixed dose combinations and a number of single drug formulations, such as tablets, capsules, and syrup.

The global demand for paediatric antiretrovirals (ARVs) is low, as children account for only 7% of all individuals on treatment, and when this low demand is distributed over not only the large number of products available but the numerous dosage forms and strengths as well, demand for any particular product is dramatically reduced. This can result in disruptions in supply chain and threatens the sustainability of the paediatric market. Furthermore, market uncertainty serves as a disincentive to investment into future paediatric drug research and development.

In order to address this issue, the Paediatric Working Group (PWG) of the Inter-Agency Task Team on prevention and treatment of HIV infection in pregnant women, mothers and their children (IATT) met to discuss an optimal paediatric formulary to serve as guidance to national programmes, procurement agencies, funders and manufacturers. The PWG defined the criteria for optimization and then evaluated all available paediatric products against these criteria. This process resulted in three related lists: Optimal products, Limited-use products and Non-essential products.

This meeting report outlines the process of optimization and presents the product list for public comment. It is recognized that this list cannot be static over time and must evolve to incorporate new formulations when these become available. The World Health Organization (WHO) and its partners within the IATT commit to a regular re-evaluation of this list in order to ensure that the recommendations continue to offer the best treatment options for infants and children living with HIV.

Background

The IATT on Prevention of HIV Infection in Pregnant Women, Mothers and their Children was first established in 1998. The initial IATT was composed of the 5 UN agencies working in HIV and health issues: WHO, UNICEF, UNFPA, UNAIDS and the World Bank. In 2003, the IATT expanded to include key global partners involved in the prevention and treatment of HIV infection in infants and young children. The IATT supports national scale up of services for the prevention of mother-to-child transmission of HIV (PMTCT) and paediatric treatment and provides a forum for global information sharing and consensus building on issues related to PMTCT and paediatric treatment.

The IATT is currently composed of 23 agencies (Annex 1) working in the area of comprehensive PMTCT of HIV and treatment for mothers and their children. The PWG is a sub-committee of the IATT that meets on a regular basis to inform global level thinking on paediatric treatment and care. The PWG met in May 2011 in order to discuss concerns about the sustainability of the paediatric ARV market and to identify potential solutions to ensure long term access to treatment.

Access to ARV treatment for children has improved steadily since 2005, but at a much slower pace than that for adults. Currently, children account for fewer than 7% of all individuals on treatment, and as a result, the global paediatric ARV market is much smaller and more vulnerable to supply disruptions than the adult ARV market. In recent years, new formulations that meet the unique administration needs of children have become available, such as dispersible fixed-dose combinations (FDCs). These products can significantly improve the quality of HIV care in low-income settings; however, national programmes have only *partially* transitioned to the newer options, resulting in small paediatric drug volumes that are further distributed across too many products to be sustainable in the long term.

The current WHO Guidelines for Antiretroviral Therapy for HIV in Infants and Children provide clear guidance on *regimen* selection but not on what the ideal products are to deliver each regimen. At the same time, WHO strongly endorses the use of FDCs as a general principle to simplify dosing for providers and patients and to improve adherence outcomes. The recently launched WHO/UNAIDS initiative “Treatment 2.0” places further emphasis on the need to use FDCs whenever possible, as a means of simplifying treatment and decentralizing services.

In the guidance document “Adapting WHO Normative HIV Guidelines for National Programmes” WHO provides country examples of how national programmes have addressed this issue and advocates for the use of a range of paediatric FDCs to serve the first line treatment needs of children. However, there is a need for additional specific guidance on the list of optimal paediatric ARV formulations that can be used to guide national decision making around procurement and clinical use of paediatric products. A list that defines optimal formulations would also help stabilize the current market. The PWG of the IATT met to discuss the potential make-up of such a list. In order to do so, the working group defined a series of core principles for paediatric ARV product selection against which all available products were evaluated.

This meeting report details this decision making process and presents a list of “optimal”, “for limited use” and “non-essential” paediatric products as a guide for procurement managers and national programmers.

The guidance in this report is complementary to WHO recommendations, and seeks to provide the best ARV treatment options for children. At the same time the list is not intended to be definitive or all-inclusive. For example, even though many children are treated using adult products, the list does not contain any adult formulations since these are not as vulnerable to market instability as paediatric products. In addition, the list is restricted to those products that are approved and available today or anticipated soon. It does not reflect products that may be in the development pipeline. WHO and the partners within the IATT recognize that paediatric HIV is a neglected disease. There continue to be significant gaps in the repertoire of ARV drugs needed to deliver comprehensive HIV care to children – especially for infants and for those children who need second or third line therapy. It is anticipated that this list will be reviewed on a regular basis as needed to allow old formulations to be withdrawn and newly developed and approved child friendly formulations to be included[1].

Objectives

To determine the best options for a limited range of approved and available paediatric ARV formulations that offer the highest quality of care for children of all ages and can be used to deliver all required first and second line ART regimens.

Participants

The full list of participants is attached as Annex 2. All participants declared no conflict of interest.

Methodology

During the meeting, participants agreed on the principles for the selection of dosage forms and then reviewed each available formulation against these principles.

Principles of dosage form selection for paediatric ARVs

The following set of principles was used to guide the formulation selection process:

1. Products meet evaluation criteria adapted from existing WHO standards[2] for use in resource-limited settings (Note: WHO Guidelines already address issues of safety and

[1] For new formulations that meet critical unmet needs, it is strongly recommended that programmes move forward with adoption immediately on approval. This would apply to products such as LPV/r and RTV where currently available paediatric formulations are not adapted for resource limited settings and heat-stable, palatable solid forms are urgently needed

[2] http://who.int/medicinedocs/en/d/Js4882e/5.2.html
http://who.int/medicinedocs/en/d/Js2281e/4.html

efficacy in the development of paediatric ART recommendations, so these elements were not considered part of the product evaluation process).
2. Products cover WHO-recommended regimens and consider administration needs for all ages and weight-bands.
3. Products are currently available in low-income settings.
4. Products are approved by the WHO Pre-Qualification Programme (PQ) or a stringent regulatory authority such as the United States Food and Drug Administration (FDA).
5. Products are easy for patients and healthcare workers to use.

Process of drafting paediatric ARV formulation list

The IATT followed a multi-step process in drafting the Paediatric ARV Formulation List:

1. Reviewed historical global volumes.
2. Considered manufacturing capacity particularly with regard to marketplace fragmentation to ensure recommendations will allow orders to meet volume minimums for production.
3. Compared characteristics of specific drug formulations (e.g. syrup, single drug tablets, fixed-dosed combination tablet, etc.) to select best options for each regimen considering:
    - Ease and simplification of administration,
    - Ease of transport and distribution to simplify supply chain and patients taking medications home,
    - Stability and storage including cold-chain requirements and length of shelf-life
    - Comparative costs (not a primary consideration).

To the extent possible, the PWG sought to keep the list as short as possible by ensuring that only dosage forms and strengths which are necessary for the delivery of the intended dose across the different age/weight bands were chosen.

Draft Table of Optimal, For Limited Use and Non-Essential Paediatric Antiretrovirals

Item description	Dosage form
Optimal	
	Tablet (dispersible, scored): 60mg (as