WORLD HEALTH ORGANIZATION

DEVELOPING DOSING GUIDANCE FOR NEW AND UPCOMING FORMULATIONS OF PAEDIATRIC ANTIRETROVIRALS IN LINE WITH TREATMENT 2.0 PRIORITIES

Paediatric Antiretroviral Working Group

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Meeting Report

DEVELOPING DOSING GUIDANCE FOR NEW AND UPCOMING FORMULATIONS OF PAEDIATRIC ANTIRETROVIRALS IN LINE WITH TREATMENT 2.0 PRIORITIES

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Abbreviations and Acronyms

3TC	Lamivudine
API	Active Pharmaceutical Ingredients
ARV	Antiretroviral
ART	Antiretroviral Therapy
ATV	Atazanavir
AUC	Area under the plasma concentration-time curve
CHAPAS	Children with HIV in Africa - Pharmacokinetics and Adherence of Simple Antiretroviral Regimens trial
DHHS	U.S. Department of Health and Human Services
DRV	Darunavir
EFV	Efavirenz
FDA	Food and Drug Administration
FDC	Fixed-dose Combination
FTC	Emtricitabine
HIV	Human immunodeficiency virus
IMPAACT	International Maternal Paediatric Adolescent AIDS Clinical Trials Group
LPV	Lopinavir
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PAWG	Paediatric Antiretroviral Working Group
PI	Protease Inhibitor
PK	pharmacokinetics
POC	Point of Care
RTV	Ritonavir
TDF	Tenofovir disoproxil fumarate
VL	Viral Load
WHO	World Health Organization

Executive Summary

As access to paediatric antiretroviral (ARV) treatment expands worldwide, there is an increasing need to improve and simplify formulations for children. In moving towards the joint UNAIDS/ World Health Organization (WHO) Treatment 2.0 initiative, revised dosing guidance for new and current paediatric formulations will be critical to ensuring children have access to better, safer and simpler treatment.

The market for paediatric ARVs is substantially smaller and more fragmented than for adults. This is as a result of the more complicated treatment needs of children. As children grow and move through infancy, childhood and adolescence, the optimal dosing strategy changes. Infants in particular require formulations such as syrups and dispersible tablets, which are difficult to administer and pose additional supply chain challenges in resource-constrained settings. Furthermore, the development and maturation of organ systems involved in drug absorption and metabolism is influenced by age. Finally, as children are surviving longer into adolescence and adulthood, more second- and third- line regimens are needed to ensure successful and sustainable treatment throughout life.

The Paediatric Antiretroviral Working Group (PAWG) was formed in 2006 to guide the development of the WHO normative guidelines for antiretroviral therapy in infants and children. The group meets regularly to update recommendations, prioritize ARVs and review dosing guidance for new and upcoming paediatric ARV formulations. Following a recent Treatment 2.0 meeting in London on the short-term priorities for ARV drug optimization, the PAWG convened in Geneva in October 2011 to discuss and revise the dosing recommendations for priority drugs identified for children in the London meeting. Clear dosing guidance from WHO is essential for policy makers and programme implementers, as well as to inform manufacturers and drug regulatory authorities.

The PAWG meeting in Geneva focused on providing appropriate dosing of new ARVs by age group and weight-band, as well as advising on potential ratios of future paediatric fixed-dose combinations (FDCs). In addition, the group provided recommendations on the storage of LPV/r syrup and on Nevirapine (NVP) lead-in dosing.

Summary of Findings and Dosing Recommendations

ARV	Proposed Recommendation
LPV/r	• LPV/r sprinkles should replace LPV/r syrup (when this formulation is available and pending pharmacokinetics (PK) studies to support the tentative dosing schedule) • Emphasize the importance of cold chain storage of LPV/r syrup up to the point of dispensing
TDF	• Develop dual TDF/3TC FDC for paediatric use – either by scoring adult tablets if feasible or by manufacturing a child specific tablet containing TDF 75mg and 3TC 75mg (1/4 scale down of adult) • Develop triple TDF/3TC/EFV FDC for paediatric use – either by scoring adult tablets if feasible or by manufacturing a child-specific tablet containing TDF 75mg and 3TC 75mg (Efavirenz) EFV 150mg (1/4 scale down of adult) • Develop dual TDF/FTC FDC for paediatric use by manufacturing a child specific tablet containing TDF 75mg and FTC 60mg (this is not a scale down of the adult formulation) • Develop triple TDF/FTC/EFV FDC for paediatric use by manufacturing a child specific tablet containing TDF 75mg FTC 60mg and EFV 150mg (this is not a scale down of the adult formulation)
DRV/r	• For children over 10kg, the ratio of DRV (Darunavir) to RTV (Ritonavir) should be 6:1 dosed twice daily
ATV/r	• For children over 10kg, the ratio of ATV to RTV should be 3:1 dosed once daily
NVP	• Recommend full dose NVP as an alternative to lead-in dosing in children under 3 years of age starting NVP-based treatment for the first time.

* Tablets scored into two halves on one side and three thirds on the other.

Background and Context

Launched by UNAIDS and WHO in 2010, Treatment 2.0 is an initiative designed to achieve and sustain universal access to HIV treatment and care. The Treatment 2.0 initiative is supported by 5 pillars, or priority work areas, which address the need for innovation and efficiency gains, greater effectiveness, and more accessible HIV services.

Treatment 2.0 Priority Work Areas:

1. Optimize Drug Regimens
2. Provide Access to Point-of-Care (POC) Diagnostics
3. Reduce Costs
4. Adapt Delivery Systems
5. Mobilize Communities

Optimizing drug regimens is a cornerstone of Treatment 2.0. The goal is to develop and promote drug regimens that are simple, effective, low in toxicity and have high barriers to drug resistance. A key part of drug optimization involves establishing optimal dosing of ARVs for adults and children, encouraging the use of FDCs and increasing access to newer, more effective formulations.

Paediatric treatment coverage is lagging far behind that of adults and there is an urgent need to close the treatment gap. Simplifying and harmonizing paediatric regimens with adult therapies would significantly aid in the programmatic scale up of paediatric treatment coverage by making it easier for non-expert clinicians who are familiar with adult Antiretroviral Therapy (ART), to also be able to prescribe to children. The PAWG is a technical working group of the WHO that helps develop formulation and dosing guidance on ARVs for children with HIV.

The market for paediatric HIV treatment is smaller than for adults and highly fragmented due the availability of multiple formulations. Too many dosing forms of the same drug combinations cause confusion at the programmatic level, as well as difficulties for supply chain management within countries. In addition, variability and complexity of treatment recommendations for different age groups adds to the confusion and market fragmentation. These factors create a disincentive for industry to develop and produce paediatric ARVs, which is compounded by the near elimination of HIV infection in infants and young children in the United States and Europe. Consequently, there is very low demand in these markets.

This issue needs to be addressed in two ways. First, for formulations that already exist, there is a need to reduce the number of options that are available to country programmes by focusing on those products that offer ease and simplicity for paediatric dosing, without compromising quality or regimen choice. Second, for formulations that have yet to be produced, it is important to try and pinpoint the most critically needed products that align, as much as possible, with adult options in order to sustain the paediatric market.

A number of FDCs have been developed to lower the pill burden and simplify treatment in resource-constrained settings for adults and children. It is important to note that when using adult FDCs for children, the proportions required for each drug may need to be different. For these reasons, there is an urgent need for clear recommendations on the use of scored adult tablets and for the development of FDCs for children, as well as appropriate PK studies showing that paediatric FDCs deliver target drug levels.

At a recent Treatment 2.0 meeting in London, an expert panel defined a number of priority formulations that need to be developed for children. An important goal of this PAWG meeting was to develop detailed paediatric dosing and formulation guidance on the priority ARVs identified in the London meeting[1].

The 2010 WHO antiretroviral therapy guidelines for children include Annex E on dosing recommendations for each ARV based on weight-bands. With the development of new products and emerging data on the PK of ARVs in children, this annex needs to be modified and updated in the next edition of WHO's guidelines. The outcomes of the meeting described in this report will directly inform the new guidelines, as well as provide up-to-date guidance to manufacturers and policy markers.

Meeting Objectives

The key objectives of the meeting were to develop guidance on the current use of and future development of paediatric formulations in line with the principles of Treatment 2.0. Specifically, the aims of the meeting were:

A. **To provide an update on the development of a new formulation for LPV/r** and offer new guidance on **storage of LPV/r syrup**.
B. In line with the short term optimization priorities, **to determine the best TDF formulations for children**
C. **To determine the best ratio of ATV/r** to be developed into a FDC formulation for children.
D. **To determine the best ratio of DRV/r** to be developed into a FDC formulation for children.
E. **To discuss the impact of NVP lead-in dosing** for young children.
F. **To discuss discrepancies between dosing guidance from WHO and the Food and Drug Administration (FDA)**

Methodology of Meeting

The meeting was a mixture of plenary presentations and group discussions to review the results of recent studies, the analysis of unpublished data, and the outputs of dose-modeling exercises. The agenda is outlined in Annex A.