

SHORT-TERM PRIORITIES FOR ANTIRETROVIRAL  
DRUG OPTIMIZATION  
MEETING REPORT

London, UK  
18 – 19 April 2011

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**World Health  
Organization**



## INTRODUCTION

The World Health Organization (WHO), with support from the Pangaea Global AIDS Foundation and funding from the Bill & Melinda Gates Foundation, convened a meeting of experts in HIV treatment from around the world to establish short-term treatment optimization priorities for preferred first- and second-line regimens recommended in 2010 WHO guidelines for adults and paediatrics. The list of attendees is attached at Annex A.

For this meeting, short-term drug optimization was defined as a three-year window (2011-2013), and discussion focused on preferred first- and second-line regimens for adults and paediatrics recommended in the 2010 WHO Guidelines. The group prioritized fixed-dose combinations (FDCs) and other reformulations among these preferred regimens that should be advanced and made available prior to 2013 for use in global HIV treatment access programmes.

The meeting's objective was to refine the recommendations of the Conference on Anti-Retroviral Drug Optimization (CADO) held in June, 2010, and the recommendations made by the Medicines Patent Pool, UNITAID and WHO, endorsed by a number of global partners working on the Treatment 2.0 initiative, to the WHO Expert Committee on Essential Medicines in March, 2011.

The meeting was part of WHO's commitment to the broader Treatment 2.0 initiative, coordinated by the UNAIDS Secretariat and WHO, which aims to radically simplify all aspects of quality HIV treatment, including drugs, diagnostics and healthcare delivery systems, to reduce costs and to mobilize communities towards greater engagement in programme design and implementation in resource-limited settings. Treatment 2.0 focuses on short- (1-3 years), medium- (4-6 years), and long- (7-10 years) term objectives to achieve and sustain universal access to treatment for all who need it and maximize the preventive benefits of treatment.

The meeting was a key step towards guiding the field to achieve the short-term objectives of drug optimization.

The recommendations from this meeting are intended to galvanize global stakeholders towards developing and making available and affordable the recommended optimized drug regimens.

WHO is committed to working with partners to drive innovation in HIV treatment that maximizes individual and public health benefit and minimizes cost.

## OPTIMIZATION PRINCIPLES

A central, overarching recommendation of the group was to move towards increasing harmonization of adult (including for pregnant and lactating women) and paediatric ART regimens, through fixed dose combinations FDCs and other simplified formulations.

In addition, the group articulated what it considered to be the characteristics of an optimal regimen, against which it then reviewed available compounds and regimens. These characteristics are:

- **Safety/Efficacy** (optimal products must be equivalent or superior to currently available products and require minimal laboratory monitoring).
- **Tolerability** (products must have minimal side effects and toxicities to improve adherence and reduce treatment failure).
- **Durability** (products should present a high barrier to resistance and have a long half-life to allow for flexibility in the dosing schedule and minimize the likelihood of resistance developing as a result of missed doses).
- **Stability** (products should be heat-stable and simple to store over long periods of time with molecular stability).
- **Convenience** (products should be suitable for once-daily dosing in fixed dose combinations – ideally one pill per day regimens – and simplified paediatric formulations or scored fixed dose combinations – once on one side, twice on the other – with no cumbersome testing requirements and the same dosing schedule for all drugs in a regimen).
- **Special Populations** (products should be effective in all populations and in conjunction with treatment for other conditions: men and women of all ages, infants and children, people who inject drugs and patients with other co-infections, including tuberculosis, malaria and viral hepatitis).
- **Cost** (products should be available at the lowest sustainable price. Strategies to achieve this include negotiations with suppliers, interventions to influence market dynamics, use by countries as appropriate of TRIPS (Agreement on Trade-Related Aspects of Intellectual Property Rights) flexibilities and other trade agreements, as well as strategies that might include appropriate dose reduction and improvements in manufacturing and delivery processes).

## SHORT-TERM OPTIMIZATION PRIORITIES FOR FIRST-LINE THERAPY FOR ADULTS AND ADOLESCENTS

Taking account of existing data, available compounds and regimens currently recommended by WHO as preferred first-line options in 2010 ART guidelines, the group recommended the following as the short term priority:

**Tenofovir (TDF), Lamivudine (3TC) and Efavirenz (EFV) as a fixed-dose combination**

### Discussion points for optimization

*Interchangeability of 3TC and emtricitabine (FTC):* While the group noted the clinical equivalence of the two compounds, the increased cost of FTC, and broad 3TC availability made 3TC preferable as a first-line recommendation. However, the need to pool and review available data on 3TC and FTC, (including unpublished head to head studies) was recommended to further reinforce this recommendation. WHO will prepare a position statement on the interchangeability of 3TC and FTC.

*Use of EFV in pregnancy and women of reproductive age:* In the light of EFV potential toxicities (notably teratogenicity and other potential toxicities among women of childbearing age) a review of observational databases of EFV in pregnancy will be urgently conducted by WHO.

*Dose Optimization:* It was recommended that further consideration be given to dose reduction studies with efavirenz to address some of the CNS toxicities/tolerability issues. In addition, studies to evaluate lower dose-optimization strategies are either currently or may be conducted for TDF and zidovudine (AZT). The group also noted that, while no longer recommended by WHO as a component of preferred ART regimens, a dose-reduction study to evaluate the efficacy and tolerability of 20mg BID stavudine (d4T) is planned.

*Bioavailability and manufacturing process optimization:* The bioavailability and chemistry process used to manufacture some ARVs can be improved and/or simplified, increasing the efficiency with which they are produced and also reducing costs. The group recommended that process optimization or new process development for EFV and TDF should be urgently explored.

*Nevirapine (NVP)-associated skin and hepatic toxicities:* Some participants noted that experience indicated NVP was an effective component of ART regimens with minimal long-term toxicities and was suggested as a possible candidate for once-daily dose studies (including determining whether the lead-in induction phase of NVP dosing could be safely eliminated). It was noted that exposure (and development of resistant mutations) as part of either single-dose nevirapine (no longer recommended) or Option A regimens for ARV prophylaxis currently recommended in WHO PMTCT guidelines could nonetheless pose a potential barrier to its utility as a first-line regimen. The group noted that NVP should be considered a back-up drug to EFV, in case of severe adverse events, if contraindicated, or if EFV is not available in a country.

## SHORT-TERM OPTIMIZATION PRIORITIES FOR SECOND-LINE THERAPY FOR ADULTS AND ADOLESCENTS

Taking account of existing data, available compounds and regimens currently recommended by WHO as preferred second-line options in 2010 ART Guidelines, the group recommended the following as the short term priority:

**Atazanavir and low dose ritonavir (ATV/r) as a heat-stable fixed dose combination, combined with a NRTI backbone**

### Discussion points for optimization:

*ATV/r versus Darunavir/ritonavir (DRV/r):* It was noted that compelling clinical data might suggest that DRV/r dose schedule should be optimized in the short- to medium-term. However, the development of a heat-stable once daily FDC of this combination falls behind that already being developed for ATV/r. Furthermore, recently published preliminary PK data have shown that both ATV and DRV can be boosted using a lower once daily dose of ritonavir (50 mg/day) without compromising treatment efficacy. These issues fall outside the timeframe of short-term recommendations, but will likely be an important medium term recommendation for optimization. The group noted the current challenges to manufacture a full FDC with ritonavir (RTV) and other PIs, because of low solubility of RTV, but process-chemistry and dose reduction strategies over the medium-term for both regimens would be needed to explore further options for affordability and sustainability. In the meantime, co-blister packs of ATV and ritonavir could be developed and used as a short-term measure until an ATV/r FDC is approved and available for use. Establishing a fixed ratio of DRV to RTV for all indications would facilitate FDC development and should be a priority.

*Lopinavir/ritonavir (LPV/r):* The group noted that dose reduction and once-daily dosing strategies of LPV/r should be explored in the medium-term towards minimizing gastrointestinal and metabolic side-effects and pill burden.

*Protease Inhibitor Research:* The group noted that a range of studies are being undertaken which would report in the medium-term that could contribute to drug optimization, including a boosted PI induction-maintenance strategy.



# SHORT-TERM OPTIMIZATION PRIORITIES FOR FIRST-LINE THERAPY FOR CHILDREN

The market for paediatric HIV treatment is relatively small and highly fragmented due to the availability of multiple products, and the fact that treatment recommendations differ according to the age of the child. The group was unable to recommend one key short-term priority for drug optimization. Treatment options for HIV-infected children older than 3 years of age are easier to harmonize with adults and adolescents. However, HIV-infected infants and very young children urgently need better ARV options, as this group has the highest mortality and emerging evidence indicates that NVP-based therapy can be less effective in HIV+ children previously exposed to NVP containing PMTCT regimens. Furthermore, the poor palatability and cold chain dependence of LPV/r formulations for this age group is challenging. In keeping with the existing WHO ART guidelines recommendations to move away from liquid formulations towards solid and fixed dose formulations, the expert group recommended the following four short term priorities for optimization in children:

- **LPV/r reformulation (sprinkles and heat-stable solid formulations suitable for infants, with a unit dose of 40 mg LPV to 10 mg RTV)**
- **AZT/3TC dispersible formulations**
- **Paediatric heat-stable RTV formulations containing 25 mg of RTV**
- **Scored adult-strength dispersible fixed dose formulations of TDF/3TC/EFV<sup>1</sup>**

## Discussion points for optimization

*State of paediatric HIV treatment:* Current paediatric treatment regimens are not aligned with regimens for adults and adolescents. The goal of harmonisation with adult treatment in the medium- to long-term will not only help rationalize treatment provision, but help manufacturers de-prioritize those combinations and formulations which are barely used (such as stand-alone liquid formulations of d4T, 3TC, abacavir and didanosine). In addition, the promotion of scored adult-strength dispersible tablets (which will enable cutting tablets in half and in some cases thirds) will further support harmonization. One possibility for a scored adult tablet would be scored TDF/3TC/EFV. However, such a formulation should only be developed once TDF is approved for use in younger children. The group highlighted the lack of adequate safety information on TDF use in infants and young children, particularly the potential long term effects on bone growth, and the difficulties in developing a palatable TDF formulation for infants. Therefore, clinical data either supporting the use of TDF in children, particularly over

<sup>1</sup> If TDF is approved for use in younger children and appropriate dosing is established.

Therefore, clinical data either supporting the use of TDF in children, particularly over three years of age, should be submitted in a regulatory filing, or clinical data which eliminates the option to use TDF in children should be published so that it can be determined if this is a regimen appropriate for adult and paediatric guideline harmonization.

Because of the current limited number of options for paediatric treatment, AZT- and ABC- containing regimens are important options to be maintained in the short-term, particularly for young children, and d4T/3TC/NVP is still needed as a backup regimen. Despite the overall goal of harmonizing paediatric and adult regimens, the group emphasized the importance of providing HIV+ children with the best and safest regimens for their long-term health.

*Paediatric treatment post-PMTCT:* The group noted that while there is an established recommendation for the use of LPV/r in infants exposed to NNRTIs for PMTCT, there are conflicting data on treatment choices in HIV-positive infants who are not exposed to NVP and that further data are required.

*New treatment options:* While the group noted that paediatric formulations of newer compounds (both on the market and in development) are being developed, these will not be widely available during the short-term treatment optimization time period, but could be important medium-term recommendations. Such compounds and formulations include DRV/r (75mg), rilpivirine (RIL) dolutegravir (DLG) and etravirine (ETR).

## SHORT-TERM OPTIMIZATION PRIORITIES FOR SECOND-LINE THERAPY FOR CHILDREN

*Options for children failing first-line therapy using LPV/r:* The group noted that there are even fewer second-line treatment paediatric options for patients who have failed first-line LPV/r containing regimens. The group could not identify short-term priorities for optimization in this population. For the medium-term, it was considered that DRV/r as a FDC tablet for children over 3 years is a key research priority. Critical to achieving this goal is establishing a single ratio of DRV to RTV so an FDC formulation can be developed. Over the medium- to long term, a potentially feasible option could be a once-daily FDC containing abacavir (ABC), 3TC and DLG, should positive data emerge to support once daily dosing of ABC and 3TC in young children and should DLG be approved for clinical use in children.

## MEDIUM-TERM OPTIMIZATION OPPORTUNITIES: ARVS IN LATE STAGE OF DEVELOPMENT

The group noted a number of compounds in development that may be relevant to treatment optimization over the medium term. These included:

*Rilpivirine (RIL)*: While it was noted that rilpivirine was undergoing regulatory review by the FDA and EMEA [NOTE: approved by the FDA on May/2011], this compound would not be widely available during the defined short-term time frame. Data suggest it has good tolerability, low teratogenic risk and potential for use in one pill once daily FDCs. However the lower virologic efficacy of RIL when compared with EFV, particularly among patients with high viral load at baseline, and the contra-indication for use with concomitant rifampicin was also noted. Therefore, despite being initially considered a promising option for ART optimization, the group concluded that further clarity from ongoing trials would be needed before the role of RIL in global access treatment programs could be established.

*Dolutegravir (DLG)*: This compound is expected to be submitted for regulatory approval in 2013. If its preliminary clinical profile is confirmed, it has the potential to be an important medium-term recommendation for both adults and children (with the advantage of no PI boosting needed, low dose requirement, high potency (with rapid reduction of viral load) and good tolerability).

*Elvitegravir/cobicistat (EVG/COB)*: Expected to be submitted for regulatory approval in 2013. There are some concerns about high variability in blood levels, need of boosting and chemical stability of cobicistat crystals in the current formulation. Therefore it was not considered as a priority by the group, as DLG seems to be more advantageous and is expected to be available for clinical use in the same period.

In addition the group discussed the value of *rifabutin as an alternative to rifampicin for the treatment of TB in the setting of ART*. The group concluded that this is an important priority as it would enable more ARV drug options to be considered, including optimized PIs, NNRTIs and integrase inhibitors. Recent PK studies involving LPV/r and rifabutin showed that standard LPV/r dosing can be maintained if rifabutin is given in a daily dose of 150 mg/day. However, there is an urgent need to establish the ideal dose of other drugs than LPV/r in the presence of rifabutin and consider the replacement of rifampicin in current triple FDCs for TB treatment. PK studies with boosted PIs (ATV/r and DRV/r) and integrase inhibitors (DLG) with rifabutin are urgently needed.

## SHORT-TERM PRIORITIES FOR ANTIRETROVIRAL DRUG OPTIMIZATION. 18 –19 APRIL 2011, LONDON, UK

### Annex A: List of Participants

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