HIV/AIDS Programme

SHORT-TERM PRIORITIES FOR ANTIRETROVIRAL DRUG OPTIMIZATION

MEETING REPORT

London, UK
18 – 19 April 2011

World Health Organization

WHO Library Cataloguing-in-Publication Data:

Short-term priorities for antiretroviral drug optimization: meeting report.

1.HIV infections - drug therapy. 2.Acquired immunodeficiency syndrome - drug therapy. 3.Anti-retroviral agents - therapeutic use. 4.Drug therapy, Combination. 5.Anti-HIV agents - therapeutic use. I.World Health Organization.

ISBN 978 92 4 150194 1 (NLM classification: WC 503.2)

Printed by the WHO Document Production Services, Geneva, Switzerland

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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 gastro-intestinal and metabolic side-effects and pill burden.

Protease Inhibitor Research: The group noted that a range of studies are being