WHO INFORMAL CONSULTATION ON MEDIUM- AND LONG-TERM PRIORITIES FOR ARV DRUG OPTIMIZATION

MOVING TOWARDS SIMPLIFICATION, HARMONIZATION AND UNIVERSAL ACCESS

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The information provided in this report comes from an informal expert meeting ('think tank') organized by WHO with the purpose of informing the medium- and long-term future direction of antiretroviral therapy (ART). It in no way is intended to replace the normative guideline development process, for which systematic reviews, GRADE evidence profiles and programmatic risk-benefit assessments are required.

ABBREVIATIONS AND ACRONYMS

ABC	Abacavir
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
AZT	Zidovudine
bPI	Boosted protease inhibitor
CADO	Conference on antiretroviral dose optimization
COBI	Cobicistat
d4T	Stavudine
DTG	Dolutegravir
DRV	Darunavir
EFV	Efavirenz
EML	Essential Medicines List
ETR	Etravirine
FTC	Emtricitabine
FDC	Fixed-dose combination
InSTI	Integrase inhibitor
LPV/r	Lopinavir/ritonavir
MVC	Maraviroc
NVP	Nevirapine
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PMTCT	Prevention of mother-to-child transmission of HIV
PreP	Pre-exposure prophylaxis
RAL	Raltegravir
TDF	Tenofovir
3TC	Lamivudine

1. BACKGROUND AND OBJECTIVES

In July 2010, the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the *Treatment 2.0* strategy that aims to improve the efficiency and effectiveness of HIV treatment programmes. One of the major pillars of *Treatment 2.0* is the further simplification of treatment regimens to support scale up of antiretroviral therapy (ART) for treatment and prevention. This means identifying strategies that promote improvement of chemistry processes, better drug formulations, and the use of new drugs and approaches that can improve adherence, reduce pill burden, minimize side effects and reduce treatment costs.

In the two years since the launch of the *Treatment 2.0* strategy, the global ART landscape has evolved considerably. Evidence continues to be generated around the potential benefits of earlier initiation of ART for both treatment and for HIV prevention; new drugs and drug classes have been approved; and the drug development pipeline offers potential for new approaches to treatment, for example through the use of long-acting formulations.

In order to continue to develop a strategic vision for ART use in the coming years, WHO convened an informal 'think tank' meeting, bringing together a group of experts to identify and reflect on opportunities and challenges for antiretroviral (ARV) drug optimization for the next 5 years (see list of participants in annex). This report summarizes the main discussions and conclusions arising from the meeting and aims to inform potential directions on future treatment strategies. These conclusions are preliminary and are intended to inform, but not replace, the WHO normative guideline development process, for which systematic reviews, GRADE evidence profiles and programmatic risk-benefit assessments are currently underway to inform the next set of global guidelines that are planned to be released in 2013.

2. CURRENT STATUS OF HIV TREATMENT RESEARCH AND FUTURE PERSPECTIVE

While there has been considerable progress in the understanding of HIV latent infection, viral elimination from HIV-positive individuals remains an elusive goal.[1,2] Thus, control of viral replication to limit disease progression through ART will continue to be the main response to HIV in the short- and medium-term.

The progressive increase in potency, tolerability, durability, simplicity, and safety of current ARV regimens, together with a better understanding of the chronic inflammation and harm caused by uncontrolled viraemia irrespective of CD4 cell levels[3] has, in recent years, tipped the balance in favour of earlier initiation of ART. A number of studies have reported an association between CD4 cell counts and certain non-AIDS complications, including malignancies, some end organ diseases associated with aging, and death.[4 5] Inflammatory markers have been associated with mortality and some non-AIDS events,[6] although the role of chronic inflammation and HIV-associated immune activation in disease progression remains unclear. In other studies, low CD4 has also been associated with neuropsychological decline,[7] and associations have further been reported between CD4 nadir and increased rates of HIV-associated neurocognitive disorders,[8] arterial stiffness contributing to cardiovascular risk,[9] coronary heart disease,[10] and increased risk of bone fractures.[11] CD4 nadir also

predicts immune reconstitution, with suboptimal CD4 gains common among people who initiate ART late.[12] Some observational studies found an association between the impact of earlier initiation at CD4 ≥ 350 cells/mm^3 and reduced risk of death[13] and an increase in AIDS free survival,[14] although these benefits have not been consistently observed.[15] While controlled randomized trials specifically designed to assess the benefit of early initiation are expected to be completed within the coming years,[16,17] this cumulative observational data has already led several national guidelines to consider earlier ART initiation, including initiation irrespective of CD4 count.[18]

Considerations for making recommendations for earlier initiation need also to take into account potential programmatic benefits given the high rates of attrition among people not yet eligible to start treatment,[19] as well as the potential benefits of earlier ART on vertical and horizontal transmission of HIV.[20]

3. HIV TREATMENT IN THE MEDIUM TERM: OPPORTUNITIES AND CHALLENGES

At the end of 2011 ART coverage in low- and middle-income countries was estimated at approximately 54%, up from less than 20% at the end of 2005. Bold political targets aim to increase the numbers of HIV-positive individuals on treatment from 6.6 million at the end of 2010 to 15 million by 2015.[21] In order to reach this goal a number of challenges need to be overcome, including current complexities of treatment and monitoring, inefficiencies in service delivery, late presentation of patients and high rates of attrition, both prior to and following ART initiation, and threats to global financing for the HIV response. Further task shifting and integration of services, new models of community engagement, the use of point of care diagnostics, and optimization of drugs and regimens are among the strategies proposed to support continued scale up.

In terms of drug optimization, the goal is to improve currently available drugs and formulations in the short term, and stimulate the research pipeline towards development of better drugs, regimens and strategies in the medium to long term. There are now 27 United States Food and Drug Administration (FDA) approved ARVs, collectively targeting five different points in the HIV life cycle,[22] and more than 15 drugs and combinations are in the ARV pipeline.[23] In addition, ART optimization efforts are underway, with the goal of reducing toxicity and cost (through, for example, improved synthesis of active pharmaceutical ingredient), improving bioavailability, and developing additional needed fixed-dose combinations. New fixed-dose combinations (FDCs), regimens and formulations optimized for use in specific populations such as HIV-infected infants, pregnant women, tuberculosis (TB) and hepatitis B & C co-infections are urgently needed. Five considerations are particularly important: (1) better regimens are needed to prevent or reduce the risk of resistance development and maintain an effective response in patients who have failed initial therapy; (2) new paediatric formulations are needed; (3) regimens should be appropriate for specific populations (including children, pregnant women, and TB/hepatitis co-infected individuals); (4) drugs to be used for pre-exposure prophylaxis (PrEP) should not conflict with treatment; and (5) better agents are needed to prevent maternal-to-child transmission of HIV.

4. SUMMARY OF TREATMENT OPTIMIZATION ACTIVITIES TO DATE

A number of initiatives have been launched over the last two years in support of ARV drug optimization, including a Conference on Antiretroviral Drug Optimization, the WHO meeting on short-term priorities for ARV drug optimization, a meeting sponsored by Médecins Sans Frontières (MSF), Ensemble pour une Solidarité Thérapeutique Hospitalière en Reseau (ESTHER) and Solidarité thérapeutique hospitalière en réseau (SOLTHIS) on ART sequencing strategies, and two meetings convened by WHO on the Strategic use of Antiretrovirals for Treatment and Prevention.

4.1. CONFERENCE ON ANTIRETROVIRAL DOSE OPTIMIZATION[24]

The first Conference on Antiretroviral Dose Optimization (CADO) was convened in June 2010 by the Clinton Health Access Initiative (CHAI), Johns Hopkins University and the Bill and Melinda Gates Foundation (BMGF). CADO brought together technical experts to focus on opportunities to optimize existing and pipeline drugs with the aim of increasing affordability and tolerability. The meeting identified the following list of priority drugs for improvement of chemistry process and dose optimization studies: zidovudine (AZT), lamivudine (3TC), tenofovir (TDF), efavirenz (EFV), stavudine (d4T), ritonavir (/r), lopinavir/ritonavir (LPV/r), atazanavir (ATV), and darunavir (DRV). Many of these optimization studies are now underway. In addition, the following drugs were identified as having the potential to radically improve treatment approaches in the future: dolutegravir (DTG), elvucitabine (no longer in development), and CMX 157 (a long acting tenofovir prodrug). Optimized pharmacoenhancement and extend shelf life are additional strategies. The meeting highlighted a range of interventions and concluded that optimum cost savings could be achieved through combining approaches.[25] A second conference on this topic is planned to take place in 2013.

4.2. TREATMENT 2.0 MEETING ON SHORT-TERM PRIORITIES FOR ARV DRUG OPTIMIZATION[26]

Several initiatives have taken place under the umbrella of the Treatment 2.0 strategy. In April 2011, a meeting convened by WHO and supported by the Pangaea Global AIDS Foundation and funded by BMGF was held on short-term priorities for ARV drug optimization. The meeting established the characteristics of an optimal ARV regimen and identified the following three priorities: (1) moving towards one pill, once day regimens in first line therapy (short-term priority: EFV+ TDF+ 3TC or FTC as FDC) (2) increasing options for heat stable, once daily boosted protease inhibitors (PIs) in second-line therapy (short-term priority: ATV/r as a heat stable FDC) and (3) improving paediatric drug regimens, including moving from liquid to solid formulations (short term priorities: LPV/r heat stable sprinkles, AZT/3TC dispersible tablets, TDF/3TC/EFV dispersible and scored tablets for children >3 years of age).

Further outcomes of this meeting included the recommendation for the development of pharmacological dossiers on priority ARV formulations for use in adults and children to be included in the WHO Essential Medicines List (EML), and a series of technical updates on equivalence between 3TC and FTC;[27] the

safety of EFV in pregnancy;[28] and the use of TDF in children and adolescents.[29] These documents will help inform the 2013 update of the WHO EML and ARV guidelines.

A follow up meeting on medium- and long-term priorities for ARV drug optimization, building on the recommendations of the this 'think tank' meeting and bringing together the priorities of CADO and Treatment 2.0, is planned for early 2013.

4.3. ART SEQUENCING MEETING[30]

A meeting focused on ART sequencing strategies, organized by MSF, ESTHER and SOLTHIS in September 2011, aimed to define priorities for future ART regimens with a view to facilitating decentralization of services, including task shifting and community models of ART delivery.[31] Applying six key principles to guide ART choice - simplicity, tolerability and safety, durability, universal applicability, affordability, and heat stability – the meeting put forward a number of short- and medium- to long-term recommendations that are available in the meeting report.[30]

4.4. MEETINGS ON STRATEGIC USE OF ARVS FOR HIV TREATMENT AND PREVENTION [32, 33]

In order to better promote the use of ARVs for HIV treatment and for prevention, WHO convened two complementary multidisciplinary consultations on the strategic use of antiretrovirals for treatment and prevention (SUFA 1 and SUFA 2) in November 2011 and May 2012. There were four main objectives: to review new evidence and the scientific roadmap related to ARVs; to identify how to best support the translation of new evidence into policy and practice; to review parameters for prioritization and decision making; and to determine the best approach to incorporating and integrating strategic guidance into WHO's 2013 guidelines.

The first of these meetings (SUFA 1) focused mainly on clinical issues. One concrete outcome was the endorsement of a roadmap and architecture for development of 2013 global consolidated ARV guidelines, including an expansion of the scope (clinical, operational and programmatic guidance) a consolidation of guidance for different populations (infants, children, adolescents, adults, pregnant women) and interventions (treatment and prevention of HIV and major co-infections), and endorsement of the development of rapid guidance or technical update documents as needed.[32] The second meeting (SUFA 2) addressed operational and programmatic issues related to the development of consolidated ARV guidelines. Six themes were address: strategic and programmatic decision-making processes in countries; modelling of epidemiology, costs and impact; ethics, equity and human rights; health systems requirements; policy formulation and prioritization; and interventions and resources.[33]

5. WORKING GROUP ACTIVITIES

A series of working groups were held as part of the 'think tank' meeting to define short and medium term priorities for ART regimen choices for adults and adolescents, prevention of mother-to-child transmission of HIV (PMTCT), paediatrics, and specific populations.

5.1. ART FOR ADULTS AND ADOLESCENTS

Two working groups reflected on short- to medium-term preferred ART regimen choices considering different scenarios and target populations. To frame these reflections, drug and regimen choice was guided by the following major principles: minimal risk of failure: efficacy and tolerability; robustness/forgiveness (i.e. can allow for missing occasional doses); no overlapping resistance in the treatment sequencing; convenience (once daily, fixed dose, no special food/liquid requirements); affordability; and compatibility with anti-TB and anti-hepatitis treatment.

The two working groups were given a separate brief. The first group was tasked to consider "staying the course" and integrating new drugs into existing treatment strategies, while the second group was tasked to consider a "paradigm shift" and discuss novel approaches such as induction/maintenance strategies and long-acting formulations. Despite taking these different perspectives, both groups came to the same conclusion that EFV +TDF +3TC (or FTC) as a FDC was considered a very good standard of care for current first line treatment, and discussions focused on specific drug substitutions to improve this regimen in the medium-term (for example to reduce/overcome renal toxicity associated with TDF and improve tolerability of EFV).

The preferred regimens put forward by both groups were as follow:

- First-line therapy:
  - 1 non-nucleoside analogue (NNRTI) + 2 nucleoside analogues (NRTIs), eg EFV + TDF + 3TC (or FTC)[a]
- Second-line therapy:

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