WHO INFORMAL CONSULTATION ON MEDIUM- AND LONG-TERM PRIORITIES FOR ARV DRUG OPTIMIZATION
MOVING TOWARDS SIMPLIFICATION, HARMONIZATION AND UNIVERSAL ACCESS

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Disclaimer

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 levels3 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. Some observational studies found an association between the impact of earlier initiation at CD4 ≥ 350 cells/mm³ and reduced risk of death and an increase in AIDS free survival, although these benefits have not been consistently observed. While controlled randomized trials specifically designed to assess the benefit of early initiation are expected to be completed within the coming years, this cumulative observational data has already led several national guidelines to consider earlier ART initiation, including initiation irrespective of CD4 count.

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, as well as the potential benefits of earlier ART on vertical and horizontal transmission of HIV.

### 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. 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, and more than 15 drugs and combinations are in the ARV pipeline. 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 Réseau (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

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. 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

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.
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safety of EFV in pregnancy;\textsuperscript{28} and the use of TDF in children and adolescents.\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{30}

4.4. MEETINGS ON STRATEGIC USE OF ARVS FOR HIV TREATMENT AND PREVENTION\textsuperscript{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.\textsuperscript{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.\textsuperscript{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:**
  - boosted protease inhibitors (bPI)+ 2 NRTIs, eg: ATV/r or DRV/r + new NRTIs
  - bPI + integrase inhibitor (InSTI), eg: ATV/r or DRV/r + RAL or DTG or EVG.

The full range of other potential future sequencing options for adults is summarized in Table 1.

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\(^a\) A recent WHO review concluded that 3TC and FTC are interchangeable.\(^{27}\) The Think Tank participants agreed with this conclusion as long as the drugs are used in once-daily fixed-dose co-formulations.
Table 1: Potential strategies for optimization of adult ART regimens in the short- and medium-term

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Currently available or potential short-term options</th>
<th>Potential optimization strategies in medium term</th>
<th>Research agenda status</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-Line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI + 2 NRTIs</td>
<td>EFV + TDF + 3TC (or FTC) as FDC</td>
<td>New NNRTIs (eg: etravirine)</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New NRTIs (eg: GS-7340)</td>
<td>Studies underway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Potentially ABC</td>
<td>ACTG 5202 found equivalence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced doses of EFV and TDF</td>
<td>between ABC+3TC and TDF+3TC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Studies underway</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second-Line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPI + 2 NRTIs</td>
<td>ATV/r or DRV/r + AZT+ 3TC</td>
<td>Reduced doses of ATV, DRV and RTV</td>
<td>Studies underway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRV/r as heat stable FDC</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New NRTIs</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New PI boosters</td>
<td>Studies needed</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>bPI + InSTI</td>
<td>ATV/r or DRV/r or LPV/r + RAL</td>
<td>New InSTI (eg: DTG, EVG)</td>
<td>Studies underway</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRV/r as heat stable FDC</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced doses of ATV, DRV and RTV</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New PI boosters (eg: COBI)</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>bPI + NNRTI</td>
<td>ATV/r or DRV/r + EFV</td>
<td>New NNRTIs (eg: etravirine)</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DRV/r as heat stable FDC</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced doses of ATV, DRV, EFV and RTV</td>
<td>Studies needed</td>
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<tr>
<td></td>
<td></td>
<td>New PI boosters (eg: COBI)</td>
<td>Studies needed</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPI + entry blocker ± new/ recycled drugs</td>
<td>ATV/r or LPV/r + MVC</td>
<td>DRV/as heat stable FDC</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New NNRTIs (eg: etravirine)</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>New PI boosters (eg: COBI)</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reduced doses of ATV, DRV and RTV</td>
<td>Studies needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Use of MVC without HIV tropism testing</td>
<td>Studies needed</td>
</tr>
</tbody>
</table>

ABC, abacavir; ATV, atazanavir; bPI, boosted protease inhibitor; COBI, cobicistat; DTG, dolutegravir; DRV, darunavir; EFV, efavirenz; ETR, etravirine; FDC, fixed-dose combination; MVC, maraviroc; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir; TDF, tenofovir

5.2. ARVS FOR PREGNANT WOMEN

There are two reasons to provide ARVs to HIV-positive pregnant women: for their own health, and to prevent mother-to-child transmission of HIV (PMTCT). Thus, concerns about drug safety relate to the mother, the foetus, and the breastfeeding infant. Particularly in resource-limited settings, the majority of pregnant women presenting at services are newly identified as HIV-positive, and among these 25% - 40% may already be eligible to start ART for their own health. In addition, a growing proportion of women are presenting to antenatal clinics on ART (as high as 20-30%) or with a previous history of ARV use for treatment or prophylaxis. 

b Data from ICAP programmes (Elaine Abrams, personal communication, May 2012)
The 2010 WHO guidelines recommend two options for PMTCT for women who are not yet eligible for ART for their own health: Option A (antepartum AZT plus intrapartum single-dose nevirapine (NVP) and one week of AZT+3TC postpartum to the mother and daily infant NVP through 12 months of breastfeeding) and Option B (maternal triple drug regimen during pregnancy and through 12 months of breastfeeding). In addition, some countries are adopting or considering a third option called option “B+”, which means providing of ART to all pregnant women for life, irrespective of any clinical or immunologic parameter. WHO has recently provided guidance that recognizes Options B and B+ are likely to be preferable from an operational perspective.

Among these options, the working group favoured the adoption of Option B+ as the preferred approach for treatment optimization in HIV-positive pregnant women. This option provides a clear opportunity to increase access to ART, and recognizes that HIV-positive mothers are a priority in the allocation of health resources because of the direct relationship between maternal health and survival prospects of their children. A final consideration for ART regimen choices for pregnant women is the imperative to align regimens with adult regimens as far as possible, in keeping with the goals of regimen simplification. The full range of potential future sequencing options in HIV-positive pregnant women is summarized in Table 2.

Table 2: Potential strategies for optimization of ARV regimens for pregnant women in the short- and medium-term

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Currently available or potential short-term options</th>
<th>Rationale</th>
<th>Research questions</th>
</tr>
</thead>
<tbody>
<tr>
<td>First line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI + 2 NRTI</td>
<td>EFV+ TDF+ 3TC (or FTC) as FDC</td>
<td>Alignment with general adult regimens Increased confidence in safety of EFV in pregnancy Adoption of PMTCT option B+</td>
<td>Monitor maternal &amp; foetal safety of TDF in pregnancy/breast feeding; more detailed bone and renal outcomes will be data available via the PROMISE study Continue to monitor birth outcomes of EFV in pregnancy Consider potential for dose optimization (TDF, EFV) or substitution with new NRTIs (eg: GS-7340) Consider alternatives to TDF and EFV as they become available as for non-pregnant adults</td>
</tr>
<tr>
<td>Second-line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPI + 2 NRTIs</td>
<td>LPV/r or ATV/r + AZT+3TC</td>
<td>Alignment with general adult regimens Considerable experience with LPV/r</td>
<td>Safety of newer bPI regimens in pregnancy</td>
</tr>
<tr>
<td>InSTI + bPI</td>
<td>RAL+ LPV/r DTG+ATV/r or DRV/r</td>
<td>Some guidelines have begun to express an interest in InSTI use in pregnancy Need more data on pharmacokinetics and safety data on alternative bPIs (some exists for ATV/r and DRV/r) Need data on InSTIs in pregnancy Some pharmacokinetic data coming from IMPAACT 1026S trial</td>
<td></td>
</tr>
</tbody>
</table>

ATV, atazanavir; AZT, zidovudine; bPI, boosted protease inhibitor; DTG, dolutegravir; DRV, darunavir; EFV, efavirenz; InSTI, integrase inhibitor; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir; TDF, tenofovir.
5.3. ART FOR INFANTS AND CHILDREN

Antiretroviral therapy coverage among children is much lower than adults: of an estimated 2,020,000 children needing ART at the end of 2011 only 28% have access, compared to 54% for adults. The need to adjust doses as children grow, specific safety and dosing issues related to age development (e.g. bone toxicity related to TDF; proper dosing of EFV in infants), and the fragility of the paediatric ART market all contribute to complicating options for ART in children.

Nevertheless, there is potential for simplification and harmonization with adult ARV regimens. Current WHO treatment guidelines define children as aged ≤ 15 years, but within this age group there are differences in terms of disease progression, organ development and drug metabolism. Particularly for children aged ≤ 3 years, high mortality, high levels of viral replication, limited drug approvals, prior exposure to PMTCT regimens, and metabolic effects requiring careful drug dosing mean that in this age group, first line therapy may be best delivered using 2NRTIs plus a bPI; above 3 years of age, the standard of care is 2 NRTIs plus a NNRTI and there is greater potential for alignment with adult regimens. An outstanding research question relating to this alignment strategy is whether children ≤ 3 years can be switched to > 3yr old regimens once they enter this age group. A study is underway to address this issue, with data expected to be available late 2012. Other important research questions include dosing and safety of new ARV agents and formulations, particularly once-daily FDCs, the role of integrase inhibitors (InSTI) and the optimal second-line regimen for NNRTI-exposed children who fail PI-containing first-line regimens.

The full range of potential future sequencing options in HIV-positive children is summarized in Table 3 below.

Table 3: Potential strategies for ART optimization for children in the short- and medium-term

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Currently available or potential short-term options</th>
<th>Rational</th>
<th>Research questions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>≤ 3 years of age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPI + 2 NRTIs</td>
<td>LPV/r + 3TC + AZT (or ABC)</td>
<td>Experience with LPV/r</td>
<td>Definition of single boosting ratio for alternative PIs (ATV, DRV) Safety of switching regimen once children are &gt;3 years old</td>
</tr>
<tr>
<td>InSTI + 2 NRTIs or bPI</td>
<td>To be defined</td>
<td>Need for aggressive therapy to rapidly decrease VL</td>
<td>RAL now under study. DTG will be studied in the future.</td>
</tr>
<tr>
<td>Second line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>bPI + InSTI</td>
<td>To be defined</td>
<td></td>
<td>Potential to rapidly decrease viral load Potential alignment with future adult regimens Further research needed to identify specific drugs</td>
</tr>
</tbody>
</table>
### 5.4. ART FOR SPECIFIC POPULATIONS

In this working group the following co-morbidities were considered: tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), malaria, and cardiovascular disease. Finally, the ART needs for vertically-infected adolescents were briefly discussed.

**TB:** The main issue relating to ART use in patients with concomitant TB is the fact that rifampicin, an essential first-line anti-TB drug, strongly induces cytochrome P450 enzymes, leading to increased metabolism and significant plasma level reduction of many ARV drugs. Evidence to date suggests that rifabutin is a safe and effective alternative to rifampicin, although more data are needed in HIV-positive individuals. Appropriate daily dosing needs to be evaluated such that it can be incorporated into fixed-dose combinations of drugs for the treatment of TB.

**HBV:** TDF and 3TC (or FTC) both have anti-HBV activity, and have been associated with rapid and persistent suppression of HBV replication and reversion of cirrhosis. It was therefore recommended to use TDF+3TC (or FTC) based regimens in HBV+HIV-coinfected patients.

**HCV:** HCV treatment outcomes in HIV co-infected patients are poor for patients with genotypes 1 and 4. However, there are significant prospects for improved treatment, with more than 30 direct-acting antiviral drugs currently in clinical trials, offering prospects for both improving outcomes and simplifying treatment; access to these newer antivirals should be actively pursued. Interactions between new antivirals against HCV and antiretrovirals have been documented but further research is needed to understand their clinical significance. Hepatotoxic ARVs should be avoided in co-infected patients. Finally, it was noted that expanded access to HCV treatment requires expanded access to reliable HCV rapid tests and viral load testing.

**Malaria:** Interactions between antimalarial and antiretroviral drugs exist, in particular the potential interaction between artemether-lumefantrine (which is metabolized by cytochrome P450 isoenzyme CYP3A4) and NVP, EFV and other antiretrovirals. Since antimalarial drugs are administered for a limited period of time, the potential clinical significance of such drug interactions requires investigation.
Cardiovascular diseases: Antihypertensive drugs interact with several antiretroviral drugs, in particular NNRTIs and protease inhibitors PIs; interactions with statins and protease inhibitors have also been noted. Both require further investigation.

Adolescents: It was noted that an increasing number of HIV-positive adolescents will have been infected at birth, and the management of this population, that may include a mixture of long-term slow progressors and long-term ART-experienced patients, may require different approaches to ART sequencing.

6. Conclusions

- Treatment simplification is critical to further scaling up of treatment and supporting long-term retention in care. Future guidance should consider the broader benefits of earlier ART initiation beyond potential AIDS mortality reduction: mitigation of short and long term HIV-associated morbidities, reduction of HIV transmission, increased retention in care, and enhancing programme simplification.
- ARV regimen choice should be guided by the following key principles: efficacy; tolerability; robustness/forgiveness; cost-effectiveness, no overlapping resistance in treatment sequencing; convenience; and compatibility with pregnancy, and anti-TB and anti-hepatitis B & C treatments.
- There is potential for alignment and better sequencing of first- and second-line regimens for HIV-positive adults, pregnant women, TB/HIV co-infected individuals and children above 3 years of age:
  - First-line therapy: 1 non-nucleoside analogue (NNRTI) + 2 nucleoside analogues (NRTIs) eg: EFV + TDF + 3TC or FTC.
    - Potential for dose optimization (TDF, EFV) or substitution with new NRTIs (GS-7340).
  - Second-line therapy: 1 boosted-protease inhibitor (bPI) +1 integrase inhibitor (InSTI) pending further study data: eg: DRV/r or ATV/r + DTG or EVG.
- In order to move in this direction, the following research questions need to be addressed:
  - Long-term safety of TDF in pregnancy and childhood.
  - Short- and long-term safety of InSTIs in pregnancy.
  - Development of appropriate paediatric formulations, optimal dosing and safety data for new agents (new bPIs & InSTIs) for children.
- For children ≤ 3 years, bPIs will remain the preferred first-line choice for the short- and medium-term. InSTI containing regimens could be considered as safety and efficacy data becomes available as a strategy to rapidly reduce viral load, but the optimal drugs to compose these regimens need to be identified.
- The potential for daily-dosing of rifabutin should be studied as a potential for simplification of management of TB/HIV co-infection, particularly for patients using PI based regimens.
- The successful management of HCV/HIV co-infection will require access to newer HCV-antivirals without significant drug interactions with preferred ARV drugs.
- Over the longer-term (i.e. next 5-10 years and beyond), it is expected that current first- and second-line ART regimens can be further improved as new drugs and innovative strategies (e.g. induction-maintenance, long acting formulations, anti-latency drugs, gene therapy) progress through the pipeline.
7. NEXT STEPS

- WHO will, together with key partners, convene a follow up meeting to further elaborate medium- and long-term perspectives for ARV drug optimization.
- The recommendations arising from these meetings will inform the process of developing the next set of WHO consolidated ARV guidelines (to be released in 2013) and other future revisions.

ACKNOWLEDGEMENTS

Logistical and financial support for this meeting was provided by the PANGEA Global AIDS Foundation.
REFERENCES


11. Gras L, Kesselring AM, Griffith JF, van Sighem AI, Fraser C, Ghani AC, Miedema F, Reiss P, Lange JM, de Wolf F; ATHENA, Netherlands National Cohort Study. CD4 cell counts of 800 cells/mm3 or greater after 7 years of highly active antiretroviral therapy are feasible in most patients starting with 350 cells/mm3 or greater. J Acquir Immune Defic Syndr. 2007 Jun;41(2):183-92.


17. Early Antiretroviral Treatment and/or Early Isoniazid Prophylaxis Against Tuberculosis in HIV-infected Adults (ANRS 12136 TEMPRANO). ClinicalTrials.gov identifier: NCT00495651. Available at http://clinicaltrials.gov/show/NCT00495651


# APPENDIX 1: MEETING AGENDA

## Day 1: Tuesday, 29 May 2012

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:00 - 18:15</td>
<td>Welcome</td>
</tr>
<tr>
<td>18:15 - 19:00</td>
<td>Special session: “Perspectives on HIV Cure”</td>
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</tbody>
</table>

## Day 2: Wednesday, 30 May 2012

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:00 - 9:15</td>
<td>Introduction and Meeting Objectives</td>
</tr>
<tr>
<td>9:15 - 9:45</td>
<td>Plenary session: Overview of current status on HIV treatment research and future perspectives</td>
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<tr>
<td>9:45 - 10:15</td>
<td>Plenary session: The evolving scenario of global HIV treatment in medium and long term: opportunities and challenges</td>
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<tr>
<td>10:15 - 10:30</td>
<td>Break</td>
</tr>
<tr>
<td>10:30 - 11:45</td>
<td>Plenary session: What was achieved/expected in short term agenda for HIV treatment optimization? (brief reports from CADO 1, Tx 2.0, MSF ART sequencing meeting, CHAIN and Strategic Use of ARVs meetings)</td>
</tr>
<tr>
<td>11:45 - 12:00</td>
<td>Plenary discussion</td>
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<tr>
<td>12:00 - 14:00</td>
<td>Lunch</td>
</tr>
<tr>
<td>14:00 - 16:00</td>
<td>Working Group Discussions: (specific questions for the WGs to be distributed by the chairs during the meeting)</td>
</tr>
</tbody>
</table>

**WG 1: "Stay in the Course":**
Considering a hypothetical global scenario where the currently approved ARV drugs/formulations and diagnostic lab technologies are largely available for a public health approach.

**WG 2: "Paradigm Shift":**
Considering a hypothetical global scenario where new and innovative diagnostics, drugs regimens and strategies that are already in the horizon but not currently accepted as standard of practice could be made available for a public health approach in the next 3-5 years.

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>16:00 - 16:15</td>
<td>Break</td>
</tr>
<tr>
<td>16:15 - 17:00</td>
<td>Continuation working group activities and preparation of group presentations</td>
</tr>
<tr>
<td>17:00 - 18:00</td>
<td>Working group presentations and plenary discussion</td>
</tr>
<tr>
<td>18:00</td>
<td>End of activities Day 2</td>
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</table>
### Day 3: Thursday, 31 May 2012

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:00 - 9:15</td>
<td>Introduction to today's working group activities</td>
</tr>
<tr>
<td>9:00 - 11:00</td>
<td>Working Group Discussions: (specific questions for the WGs to be distributed by the chairs during the meeting)</td>
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<tr>
<td></td>
<td>&quot;What are the opportunities and challenges for treatment and care innovation in the next 10 years?&quot;</td>
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<tr>
<td>WG 3: Adults &amp; adolescents</td>
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<tr>
<td>WG 4: Infants, children &amp; pregnant women</td>
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<tr>
<td>11:00 - 11:15</td>
<td>Break</td>
</tr>
<tr>
<td>11:15 - 12:00</td>
<td>Continuation of working group activities and preparation of group presentations</td>
</tr>
<tr>
<td>12:00 - 13:00</td>
<td>Lunch</td>
</tr>
<tr>
<td>13:00 - 14:30</td>
<td>Working group presentations and plenary discussion</td>
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<tr>
<td>14:30 - 15:00</td>
<td>Conclusions and next steps</td>
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<tr>
<td>15:00</td>
<td>End of the meeting</td>
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</tbody>
</table>
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<table>
<thead>
<tr>
<th>Name</th>
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<tbody>
<tr>
<td>Gottfried Hirnschall</td>
<td>Director, HIV Department</td>
</tr>
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<td>Marco Vitoria</td>
<td>Medical Officer, HIV Treatment and Care, HIV Department</td>
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<tr>
<td>Andrew Ball</td>
<td>Coordinator a.i., HIV Treatment and Care Senior Advisor, Strategy, Policy and Equity, HIV Department</td>
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### Administrative / Logistics Support

<table>
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<tr>
<th>Name</th>
<th>Organization, Address</th>
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<tbody>
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<td>Sabine Niewiadomski</td>
<td>Pangaea Global AIDS Foundation, 472 Ninth Street, Oakland, California 94607, USA</td>
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