WHO Think Tank on HIV treatment optimization: implications for 2015 WHO ARV guidelines and future updates

Summary Meeting Report

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Westin Copley Hotel, Boston, USA

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Summary Meeting Report

Background:

In order to make progress towards reaching the new global treatment targets for 2020 (90/90/90) and end the HIV pandemic by 2030, innovation and optimization of ARV drug regimens and therapeutic strategies continue to be needed. Since 2010, WHO ARV guidelines have promoted treatment optimization through standardization and simplification of ART strategies, including pushing forward the use of one tablet a day regimens with less toxic and more efficient drugs. The emergence of new drug classes and evidence of the clinical and programmatic benefits of optimized doses of existing drugs justifies a periodic assessment to inform future WHO normative guidelines. In this context, The Department oft HIV and Global Hepatitis Programme at WHO has established technical working groups on treatment optimization for adults and children, who meet annually during the *Conference on Retroviruses and Opportunistic Infections* (CROI) to discuss the progress in HIV drug pipeline research. These "Think Tank" met in 2014 and 2015 and the respective executive summary reports of these meetings are available on the WHO website.

The 2016 Think Tank meeting was held in Boston, USA and convened approximately 50 HIV experts to evaluate research progress, emerging data of ongoing trials and the potential role of new ARVs and treatment strategies in a public health perspective. The list of participants is provided in Annex.

Meeting objectives:

1. To evaluate new data and ongoing/future research plans on ARV drugs and formulations recently included in 2015 WHO ARV consolidated guidelines (dolutegravir, low dose EFV,) and potential role of emerging new options in the HIV drug pipeline (tenofovir alfenamide, switching strategies using two drugs and use of long acting formulations) in a public health approach.

2. To promote the harmonization and integration of the adult and pediatric treatment optimization agendas.

3. To maintain an ongoing relationship with experts who would be able to advice future WHO work on ARV drug optimization for adults and children..

Meeting structure and expected outcomes:

This meeting was composed by short presentations/comments on the selected topics established in the agenda (see ANNEX 1) considering the prepared background document and a specific questionnaire to the audience, followed by plenary discussions moderated by a facilitator. At the end of the meeting the views of experts on each topic was sought in order to help WHO to develop an action plan considering the future updates of WHO ARV consolidated guidelines (what to include /when to include /what is needed to include).

Questionnaire results and comments:

The first meeting session included a review of clinical trial programs of three new treatment options: dolutegravir (DTG), low dose efavirenz (EFV 400mg) and tenofovir alafenamide (TAF). Ongoing and planned trials of these treatments in pregnant/breastfeeding women, children and in people co-infected with TB taking rifampicin-based treatment were reviewed. For each of these drugs, the main question was whether there would be sufficient information from clinical trials of these treatments to justify their recommendation in new WHO guidelines in mid-2017. These themes are covered in sessions 1a,1b and 1C, below:

Session 1a - Use of DTG, EFV 400mg and TAF in pregnant/breastfeeding women

Question: By April 2017, do you think that will be enough evidence for the safety and efficacy of dolutegravir, low dose efavirenz (400mg) and tenofovir alafenamide in pregnant/breastfeeding women to inform a recommendation about these treatments for large-scale use in treatment programs? If not, what additional studies need to be conducted?

Replies:

DTG	**Yes: 80%**	**No: 20%**
EFV 400mg	**Yes: 67%**	**No: 33%**
TAF	**Yes: 15%**	**No: 85%**

Comments:

DTG: there was general agreement that the planned program of clinical trials of DTG in pregnant women should generate enough evidence on safety and pharmacokinetics by mid-2017. Recent reports of congenital abnormalities among infants born to DTG-treated mothers, while limited and inconclusive, require further investigation.

EFV 400mg: The safety results from the original 600mg dose of EFV were generally agreed to be sufficient to cover the safety of the 400mg dose in pregnant women. However, the pharmacokinetic study of EFV 400mg in pregnancy, which is expected to be completed by mid-2017, will help establish whether pregnant women still show therapeutic levels of EFV at the lower 400mg dose. There is extensive pK data from the ENCORE-1 trial that could be used to evaluate the clinical implications of lower EFV levels during pregnancy. Some people felt that the priority would be to deliver DTG rather than continue with EFV at any dose.

TAF: The current clinical trials program for TAF in pregnant women is too small to produce sufficient information about pregnancy outcomes by mid-2017. Even though there is safety data available for the original tenofovir prodrug (TDF), the intracellular concentration of

tenofovir is 4-5 times higher for TAF. Therefore, it may not be possible for WHO to recommend TAF for pregnant women by mid-2017.

Session 1b - Use of DTG, EFV 400mg and TAF with rifampicin

Question: By April 2017, will there be enough evidence on the safety and efficacy of these three drugs with rifampicin to inform a recommendation about their combined use with rifampicin in large-scale use in treatment programs? If not, what additional studies need to be conducted?

Replies:

DTG	**Yes: 74%**	**No: 26%**
EFV 400mg	**Yes: 69%**	**No: 31%**
TAF	**Yes: 6%**	**No: 94%**

Comments:

DTG: A pK trial of DTG 50mg BID with rifampcin has already been conducted. The pharmacokinetic results need to be validated in a large randomized clinical trial, as was performed for EFV 600mg to show efficacy for this dose. The current randomized trials of DTG 50mg BID versus EFV 600mg are likely to be too small to demonstrate equivalent efficacy. In some countries with high prevalence of TB co-infection, is the complexity of double-dosing DTG going to complicate widespread use in first-line? Is it easier to stay with standard TDF/3TC/EFV as a single pill formulation with no dose adjustment until more is known about DTG and rifampicin? It may be that DTG is also highly effective when used at the standard 50mg once daily dose in combination with rifampicin, but a new pK/pD trial would be needed to establish this.

EFV 400mg: Pharmacokinetic data should be available by April 2017 to provide good evidence about the interaction between EFV 400mg and rifampicin. The drug interaction between EFV and rifampicin is known to be genotype dependent, so this needs to be accounted for in the design of new pK studies. One option is to remain with the 600mg dose of EFV for TB co-infected people, but this complicates the supply requirements. The pK studies should be validated in people with HIV and TB co-infection, not just performed in healthy volunteers.

TAF: the current contraindication of rifampicin with TAF is a major barrier to widespread introduction of TAF in settings with a high burden of HIV-TB coinfection. It may be too complex to have a single pill of TAF/3TC/DTG for people without TB co-infection, and an alternative TDF/3TC/DTG pill for people with TB co-infection. The current contraindication is based on a predicted drug interaction, but the actual pK trial needs to be conducted, and some researchers suggest that a clinical trial should be conducted afterwards to validate

the pK results in people with TB co-infection taking rifampicin. This will be a complex trials program, involving testing of tenofovir-diphosphate levels. It will be important to have these results ready by mid-2017, or widespread use of TAF may not be advisable.

Session 1c - Use of DTG and TAF in infants and children

Question: By April 2017, do you think that there will be enough evidence for the safety and efficacy of dolutegravir and TAF in infants and children to inform a recommendation about these treatments for large-scale use in treatment programs? If not, what additional studies need to be conducted?

Replies:

DTG	**Yes: 63%**	**No: 37%**
TAF	**Yes: 21%**	**No: 79%**

Comments:

DTG: The P1093 trial should be finalized by mid-2017. Data for 6 years and older is already available and submitted to FDA, but data on younger children will take longer to become available. The ODYSSEY trial which will investigate the use of DTG in first and second line will probably be still recruiting in mid-2017. It will be important to study neurotoxicity in children, given the adverse events related to DTG in adults.

TAF: There may not be sufficient data emerging on safety or efficacy of TAF in children to make a decision on recommendations by mid-2017. The consequences of higher intracellular tenofovir concentrations of TAF are unknown in children. While two trials have been planned by the company [Gilead Sciences] these don't seem to be prioritized and expected completion date is unclear. Also, results on bone toxicity could take several years to establish.

Session 2 - HIV drug resistance and transition to new regimens

Question: A nationally representative survey reports a prevalence of 15% resistance to NNRTI among patients starting ART. Do you feel this justifies moving away from an NNRTI-based first-line regimen (for example in favor of first-line integrase inhibitor-based regimen)?

Replies:

Yes: 59%	**No: 41%**

Comments:

There was a wide range of opinions on this subject. Some people felt that the improved safety profile of DTG would already provide a justification to switch away from first-line NNRTIs, even without taking drug resistance into account. Other people felt that HIVDR testing at ART initiation should be on options where resistance is starting to emerge The root causes of drug resistance would need to be investigated further – for example, assessing proportion of starters with prior ARV exposure, interruptions due to poor adherence, or lack of drug availability due to stock-outs. The differential pricing of DTG versus current NNRTIs is another factor.

Question: although not a WHO recommendation, several countries have expressed interest or are planning to introduce individual HIVDR testing for clinical care in the next five years. Some of these countries are still in early stages of scaling up VL testing. What guidance would you provide?

Replies:

1. Focus on achieving good national VL coverage (e.g. >60%) before introducing HIVDR testing	2.Focus on achieving optimal national VL coverage (e.g. >90%) before introducing HIVDR testing	3. Begin introducing HIVDR testing for priority populations, even if national VL coverage is still low	4. Other	5. No opinion
32%	**29%**	**24%**	**5%**	**9%**

Comments: The consensus was that expanding access to routine viral load monitoring was more important than evaluating drug resistance in treatment naïve patients. However, there could be special populations who should be targeted for drug resistance testing (3rd line treatment, population previously exposed to ARV including those re-initiating ART, 2nd line failures, pregnant women).

Question: For those countries planning to introduce individual HIVDR testing for clinical care in the next five years, which groups should be prioritized? [Pick three options, noting order of your preference as 1-2-3]

Replies: for each 1st preference vote, there was a score of 3 points; second preferences were given 2 points and third preference votes 1 point. The table below shows the total number of points from the overall votes.

1st line failure	2nd line failure	3rd line failure	Naïve patients	Naïve, but prior PMTCT exposure	Restarting ART after treatment interruption/default	Sero-converted while on PrEP	Other populations	HIVDR testing should not be started
9	**46**	**16**	**6**	**32**	**12**	**6**	**1**	**0**

Comments: the two highest priority population for resistance testing were for people after failure of second-line treatment (46 points) and women or children who were starting antiretroviral treatment after prior exposure as part of PMTCT (32 points). Independent from routine testing for resistance, ongoing surveillance of drug resistance in sentinel studies is important. As the risk of resistance can be considered a barrier for PrEP implementation in LMIC, resistance surveillance should be in place to inform future guidelines on HIVDR testing after PreP in LMICs. Widespread use of DTG first-line might lessen the need for drug resistance testing, but this needs careful assessment in low-income countries, where there is a greater risk of repeated stock-outs.

Session 3 - Two-drug treatments

Question: Should the following two drug-treatments be recommended for use in treatment programs, if their clinical trials, as described in this session, are successful?

Replies:

PI/r + 3TC	**Yes: 37%**	**No: 63%**
DTG + 3TC	**Yes: 53%**	**No: 47%**
DTG + RPV	**Yes: 26%**	**No: 73%**

Comments: the main problems identified with two-drug treatment in low-income countries were co-infection with Hepatitis B and underlying resistance to 3TC – both of these issues could undermine the efficacy of two-drug treatment, and baseline testing would be needed to rule out these concerns which is currently not feasible in most low- and middle-income countries. Also, the clinical trials on which the efficacy of two-drug treatments are based have mainly been carried out in people who are already virally suppressed. It would be hard to extrapolate the results of these studies to routine programme settings where viral load data may be less available, and where resistance tests may not have been conducted.

Question: Can a new combination treatments be considered for use by WHO treatment guidelines if the clinical trials program mainly includes switching studies for people with HIV RNA suppression at baseline?

Replies:

Yes: **31%**	No: **69%**

Comments: It is difficult to assume that a treatment will work in first-line if the main clinical experience is from switching studies. The example of PI monotherapy studies has shown the limitations of making this assumption. There could be drug resistance to the treatments in treatment naïve patients, which may not be evaluated routinely in low- and middle-income countries. Studies conducted in LMICs need to evaluate how well new treatment combinations perform in the type of patients who would enroll in large-scale treatment programs – for example people with very low CD4 cell counts, high baseline HIV RNA, potential baseline NRTI or NNRTI drug resistance and co-infection with TB or viral hepatitis.

Question: are there any specific considerations for two-drug treatments for infants and children?

Comments:

This area of research needs caution given the high HIV RNA levels seen in children and the need for careful evaluation of dosing by age. Induction – maintenance studies should be considered, especially with availability of VL to ensure HIV RNA suppression. This would limit the long-term risk of toxicity as well as potentially preserving NRTIs and other drugs for use in future regimens. One potential strategy suggested by some researchers is to start with TDF+3TC+DTG and then switch to DTG+3TC after one year of viral suppression. For such an approach, the potential effects of prior exposure to treatment during PMTCT and breastfeeding need to be evaluated.

Session 4 - Long-acting antivirals

Question: In situations where access to baseline resistance testing and ongoing viral load monitoring is limited, what clinical trial results would be needed to support the introduction of a long-acting antiviral treatment?

Comments: there was consensus that trials of long-acting formulations should be conducted to ensure they are applicable to large treatment programs. So if evaluation of drug resistance at baseline was not the standard of care in low- and middle-income countries, it may not be appropriate to screen out those with baseline drug resistance from these studies. Large non-inferiority trials in naïve patients comparing against a standard of care using daily oral triple combination treatment (e.g. TDF/3TC/DTG) would be the most

appropriate design.

Question: Could long-acting antiviral treatments including two antiretrovirals be sufficient for treatment programs, or should these include three antiretrovirals?

Replies:

Two ARVs sufficient: **74%**	Should include 3 ARVs: **26%**

Comments: Initial studies are suggesting that it may be possible to use long-acting antivirals as a maintenance strategy with two drug regimens. As before, large non-inferiority trials would be necessary to establish efficacy. Hepatitis B co-infection needs to be considered.

Question: Are there any specific considerations for long-acting treatments for infants and children?

Comments: Adolescents would be an important group to evaluate, given problems with adherence. There could be regulatory issues with starting paediatric studies early, given that the safety and pharmacokinetic profile of any long-acting treatment would need to be well characterised before they could be started.

Conclusions:

The following major conclusions were made during the meeting:

- **Safety and efficacy of DTG, EFV_{400} and TAF in specific populations:** The large majority of Think Tank participants are confident that the planned and ongoing trials with DTG and EFV400 mg are expected to provide sufficient data to inform a recommendation about their use in pregnant/breastfeeding women, children and PLHIV with TB co-infection by 2017/2018. However, there is concern that safety and efficacy data on TAF use in pregnant/breastfeeding women and children will not be available at that time, and there are important concerns on the impact of drug interactions with rifampicin. More studies with TAF containing regimens in these specific populations are urgently needed.

- **Impact of HIVDR in transition to new regimens:** There is some support to move away from NNRTI-based regimens in presence of 15% prevalence resistance to NNRTIs among ART starters in LMICs. The consensus was that expanding access to routine viral load monitoring is more important than evaluating drug resistance in treatment naïve patients. However, there could be special populations who should be targeted for drug resistance testing (for example in third-line treatment).

- **Two drug treatment strategies (treatment simplification & long acting ARVs):** There is a low support for treatment simplification strategies using boosted PI+3TC and DTG+RIL after viral suppression using triple drug regimens; Think Tank participants were divided about the future potential of DTG+3TC. The need of 2nd line ART studies with new combinations as DRV/r+ DTG was highlighted. There is a high expectation that long acting ARV treatments containing two drugs would to be sufficient for treatment programmes in the future.

Way forward and timelines:

This executive summary will be published in WHO/HIV website for documentation purposes. An expanded manuscript is planned for publication in a scientific journal in Q3 2016. A new Think Tank meeting is planned for February 2017, during next CROI, to be held in Seattle, USA.

ANNEX 1: MEETING AGENDA

Treatment Optimization of HIV: implications for 2015 and future updates of WHO guidelines	Time	AGENDA ITEM
	18:00-18:45	Registration and buffet dinner
	18:45-19:00	Welcome remarks, agenda overview and objectives of the meeting – 15´
	19:00-20:15	**Treatment optimization in 2015 WHO ARV guidelines... so what?** • Introduction of new ARV options (rationale) – 15´ • Updates on DTG, EFV400 and TAF studies, programmatic challenges & opportunities (new formulations, transition and procurement) - 20´ • Plenary discussion – 30´
	20:15-20:30	**BREAK – 15´**
	20:30-21:45	**WHO ARV guidelines… what's next?** • Use of HIVDR modelling and ART policy decisions – 10´ • Plenary discussion – 20´ • NRTI sparing regimens and long acting formulations – (adult and paediatric perspectives) –25´ • Plenary discussion – 20´
	21:45 -22:00	Closing remarks and next steps - 15´
	22:00	Coffee

ANNEX 2: LIST OF PARTICIPANTS

Name of participants	Major affiliation
Panel of invited experts (Adults):	
1. Andrew Hill	University of Liverpool, UK (facilitator)
2. Andrew Kambugu	Makarere University, Uganda
3. Anton Pozniak	Chelsea and Westminster Hospital, UK
4. Beatriz Grinsztejn	Oswaldo Cruz Foundation, MoH, Brazil
5. Charles Flexner	JHU, USA
6. Deenan Pillay	Africa Center for Population Health, South Africa
7. Diane Havlir	UCSF, USA
8. Elliot Raizes	CDC, USA
9. Francois Venter	Witwatersrand University, Johannesburg, South Africa
10. Jean-Michel Molina	Saint-Louis Hospital and University of Paris, France
11. Jennifer Cohn	EGPAF, Switzerland
12. Jose Gatell	Hospital Clinic-IDIBAPS, Spain
13. Kevin deCock	CDC, USA
14. Lynne Mofenson	EGPAF, USA
15. Marta Boffito	Chelsea & Westminster Hospital, UK
16. Mike Saag	University of Alabama, USA
17. N Kumarasamy	YRG Care India
18. Omar Sued	Fundacion Huesped, Argentina
19. Paul Domanico	CHAI, USA
20. Pedro Cahn	Fundación Huesped, Argentina
21. Robert Ferris	USAID, USA
22. Roy Gulick	Cornell University, USA
23. Sandeep Junjea	Medicines Patent Pool, Switzerland
24. Sean Emery	Kirby Institute, Australia
25. Serge Eholie	University of Abidjan, Cote d'Ivoire
26. Shannon Harder	CDC, USA
27. Stefano Vella	Istituto Superiore di Sanita, Italy
28. Susan Sindwells	University of Nebraska, USA
29. Yao Cheng	Medicines Patent Pool, Switzerland
Panel of invited experts (Paediatrics):	
1. Carlo Giaquinto	University of Padova, Italy
2. David Burger	UMC, The Netherlands
3. Fernando Pascual	Medicines Patent Pool, Switzerland
4. Edmund Capparelli	UCSD, USA
5. Elaine Abrams	Columbia University, USA
6. Geroge Siberry	OGAC, USA
7. Jorge Pinto	Fed Univ Minas Gerais, Brazil
8. Linda Lewis	FDA, USA
9. Marc Lallemant	DnDI, Switzerland
10. Marissa Vicari	IAS, Switzerland
11. Mark Mirochnick	Boston Medical Center, USA
12. Mirokovic Kesley	CDC, USA
13. Nandita Suhgandi	CHAI, USA
14. Natella Rakhmanina	EGPAF, USA
15. Pablo Rojo-Conejo	Hospital 12 de Octubre, Spain
16. Polly Clayden	HIV iBase, UK
17. Rohan Hazra	NIH, USA
18. Timothy Cressey	Program HIV Prev and Treatment, Thailand
19. Chewe Luo	UNICEF, USA

WHO staff:

1.	Gottfried Hirnschall	WHO/HIV/ODH, Geneva
2.	Meg Doherty	WHO/HIV/TAC, Geneva
3.	Marco Vitoria	WHO/HIV/TAC, Geneva
4.	Martina Penazzato	WHO/HIV/TAC, Geneva
5.	Silvia Bertagnolio	WHO/HIV/TCO, Geneva
6.	Cheryl Jhonson	WHO/HIV/KPP, Geneva
7.	Raleigh Watts	WHO/HIV/TAC (consultant)