Think Tank 2017: HIV treatment transition and drug sequencing in the context of new ARVs

Summary Meeting Report – 12 February 2017

Washington State Convention Center, Seattle, USA

Background and Objectives: WHO has established Adult and Paediatric Technical Working Groups, which meet annually at CROI meeting to discuss the agenda on HIV treatment optimization for adults and children, respectively. This closed meeting will provide the opportunity to discuss in more details about new data and research plans on new ARV drugs and formulations recently included in 2016 guidelines (DTG, low dose EFV) and the potential role of emerging new options in the HIV drug pipeline (TAF, long acting formulations) in a public health perspective. Furthermore, discussions on opportunities and challenges in potential scenarios for the transition to these optimal options and adequate treatment sequencing from first to second and third line regimens are needed.

Number of participants: 45 external participants, members of Adult and Paediatric Working Groups, and other ad hoc experts linked to HIV management who are planned to attend CROI 2017.

Overview of the Methodology: The agenda of this meeting will be composed by short presentations/panel comments on selected topics (considering the prepared background document and specific questions to the audience) followed by plenary discussions moderated by a facilitator. At the end of the meeting is expected to have a consensus on each topic discussed (and specific questions answered) and considerations for future technical updates of WHO ARV consolidated guidelines.

Expected outputs:

1. Meeting report including advice to the adult and paediatric working groups on what to consider for future update process of WHO normative guidance
2. List of questions related to transition and sequencing ART with priority drugs and formulations for future optimization of HIV treatment.
3. Major research gaps to inform ARV drug optimization development.

Key points discussed:

At the 2017 WHO Think Tank meeting, 53% of participants favoured a switch to first-line TDF/XTC[1]/DTG in LMICs while 47% recommended keeping country programmes using TDF/XTC/EFV.

After review of the current clinical trial data, it was agreed that the evidence base for evaluating the safety and efficacy of DTG, TAF and EFV_{400} needs to be improved to justify expanding treatment with these new drugs in millions of people in LMICs (97% of participants). Results from several key randomised clinical trials, such as NAMSAL, ADVANCE, D2EFT and VESTED, are not expected for at least another two years. Therefore, it will be important to analyse other datasets, even if non-randomised, in the interim.

As shown in Table 1, the current evidence for the safety and efficacy of DTG, TAF and EFV 400 was not considered strong enough to justify widespread introduction of these antiretrovirals in LMICs. This situation could change within the next 3 years, as results emerge from ongoing clinical trials.

By July 2017, there should be a large enough database of pregnant women treated with DTG for a first review of birth outcomes and congenital anomalies. This review could be repeated at the end of 2017, once the database has grown further. The outcomes from the pregnant mothers treated in Botswana will be of key interest in these reviews.

The reports of IRIS and CNS adverse events on DTG need to be followed up with a systematic review of clinical trials and cohort studies. The cohort studies could provide valuable information on the safety of DTG in patients typically excluded from Phase 2 and 3 studies, because of CDC C disease, low CD4 cell counts or HIV-TB co-infection. These are the patients most likely to develop IRIS.

At the meeting, the consensus was to continue using rifampicin-based treatment for HIV-TB co-infected people, despite the drug-interaction issues. The pharmacokinetic studies of DTG, TAF and EFV_{400} with rifampicin should generate results by the end of 2017. These results could allow planning of new clinical studies. For example, the pharmacokinetic interaction studies with TAF are likely to show lower concentrations of tenofovir diphosphate with rifampicin. However, if this concentration is still above the levels seen for TDF without rifampicin, this could still be therapeutic.

[1] XTC= 3TC or FTC.

There was agreement that 6-monthly reviews of safety and efficacy should be started, to be continued until the evidence is sufficient to change WHO recommendations on the use of these drugs in pregnant women, HIV-TB co-infection and people with low CD4 cell counts.

Table 1. Replies from Think-Tank questionnaire: should new antiretrovirals be recommended for use in pregnant women and with rifampicin in LMICs, based on current evidence (results from 35 questionnaires)

Antiretroviral	Percentage agreeing with mass treatment for:	
	Pregnant Women	TB with Rifampicin
Dolutegravir (DTG)	27%	38%
Tenofovir alafenamide (TAF)	6%	0%
Efavirenz (EFV)	38%	32%

Conclusions:

1. It was agreed that additional safety and efficacy data on dolutegravir, tenofovir alafenamide and efavirenz 400mg in some sub-populations are needed, particularly for pregnant women and people with HIV-TB co-infection.

2. At the meeting, there was limited support for the introduction of tenofovir alafenamide as part of first-line antiretroviral treatment in low- and middle-income settings.

3. There was an overall agreement for 6-monthly reviews of safety and efficacy data, in parallel with a phased introduction of the new antiretrovirals.

Acknowledgements: we would like to thank all of the experts who attended the WHO Think-Tank meeting in Seattle for their helpful advice and comments.

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DRAFT AGENDA

	Time	AGENDA ITEM	Speakers
Think Tank 2017: Treatment transition and sequencing in the context of new ARVs	8:30-9:00	Registration and breakfast buffet	All
	9:00–9:05	Welcome remarks (5 min)	Gottfried Hirnschall
	9:05–10:35	**How quickly new 1st line ARV options can be introduced into large-scale treatment programmes?** • **Meeting Objectives;** brief overview of previous think tanks and drug optimization work (5 min) • **Status update of clinical and pK studies** on use of new ARVs in pregnancy and TB co-infection (20 min) • **Paediatrics perspective** on new ARVs: Brief report on PADO 3 meeting (5 min) • **Panel discussion** from large-scale access ART programmes - what is their opinion in this issue, given their experience? o Is it better to (a) keep with the simple current first-line (TDF/XTC/EFV) which does not need to be modified for pregnancy or TB, but is slightly less well tolerated, or (b) switch to a more complex first-line (TDF/XTC/DTG) which needs to be dose-modified for TB, and which does not yet have full safety cover in pregnancy? Which option would work better in a setting of task-shifted care, using community workers to give out the drugs? (20 min) o Q&A (5 min) • **WHO-UNITAID Enhanced Monitoring** (5 min) • **Moderated Discussion**: o Do we need more intensive pharmacovigilance, and/or set up more studies (e.g. rifampicin & rifapentine), to answer the issues on pregnancy and TB more quickly? (20 min) o Q&A (5 min)	Marco Vitoria Andrew Hill, Marta Boffito, Anton Pozniak Martina Penazzato Francois Venter, Tendani Gaolathe .. Meg Doherty Elaine Abrams, Lynne Mofenson, Beatriz Grinsztejn, Richard Chaisson
	10:35-0:45	**BREAK** (10 min)	

	10:45-11:50	**How to plan second- line treatment, if first-line becomes based on integrase inhibitors?**
		• **General introduction** on the overview of current status and challenges to scale up 2nd line treatment in RLS (15 min)
		• **Panel discussion**:
		  ○ Should second-line treatment remain 2NRTI + PI/r, if this already works after failure of NNRTI first-line?
		  ○ What should be the preferred PI: ATV/r, LPV/r or DRV/r?
		  ○ Use of rifamycin-free treatments to avoid the issues with drug-interactions with ARVs as DTG and TAF?)
		  ○ Can DTG be used again, if there was no drug resistance at first-line failure? (20 min)
		  ○ Q&A (5 min)
		• **HIVDR considerations** for using DTG (10 min)
		  ○ Q&A (5 min)
			Andrew Hill, Marta Boffito, Lara Vojnov
			
			Charles Flexner, Carolyn Amole; Diane Havlir
			
			Michael Jordan

	11:50-12:00	**Closing remarks** and next steps (10 min)	Meg Doherty
	12:00-12:30	Lunch	All

LIST OF PARTICIPANTS

Name of participants	Major affiliation
Panel of invited experts (Adults):	
1. Adele Benzaken	MoH, Brazil
2. Aleny Couto	MoH Mozambique
3. Amandine Cournil	ANRS/IRD, France
4. Amy Lyn	USAID, USA
5. Anton Pozniak	Chelsea and Westminster Hospital, UK
6. Beatriz Grinsztejn	Oswaldo Cruz Foundation, MoH, Brazil
7. Benjamin Young	IAPAC, USA
8. Carmen Perez Casas	UNITAID, Switzerland
9. Carolyn Amole	CHAI, USA
10. Celicia Serenata	Witwatersrand University, Johannesburg, South Africa
11. Charles Flexner	Johns Hopkins University, USA
12. Danielle Ferris	UNITAID, Switzerland
13. David Cooper	Kirby Institute, Australia
14. Deenan Pillay	Africa Center for Health, South Africa
15. Diane Havlir	UCSF, USA
16. Emily Harris	USAID, USA
17. Francois Venter	Witwatersrand University, Johannesburg, South Africa
18. Kevin de Cock	CDC, Kenya
19. James Hakim	University of Zimbabwe, Zimbabwe
20. Juliana Silva	CDC, USA
21. Laura Broyles	CDC, USA
22. Lana Lee	USAID, USA
23. Lisa Nelson	OGAC, USA
24. Lynne Mofenson	EGPAF, USA
25. Marta Boffito	Chelsea & Westminster Hospital, UK
26. Melinda Watkins	CHAI, USA
27. N Kumarasamy	YRG Care, India
28. Nikos Dedes	EATG, Greece
29. Paul Domanico	CHAI, USA
30. Pedro Cahn	Fundacion Huespede, Argentina
31. Refeletswe Lebelonyane	MoH, Botswana
32. Richard Chaisson	Johns Hopkins University, USA
33. Roy Gulick	Cornell University, USA
34. Sandeep Juneja	MPP, Switzerland
35. Shannon Hader	CDC, USA
36. Stefano Vella	Istituto Superiore di Sanita, Italy
37. Tendani Gaolathe	MoH Botswana
38. Zhang Fujie	Beijing Ditan Hospital, China

Panel of invited experts (Paediatrics):

1. Diana Gibb	MRC, UK
2. David Burger	UMC, Netherlands
3. Elaine Abrams	Columbia University, USA
4. George Siberry	OGAC, USA
5. Polly Clayden	HIV i-Base, UK
6. Fernando Pascual	MPP, Switzerland
7. Tim Cressey	PHPT, Thailand

WHO staff & consultants:

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. Lara Vojnov	WHO/HIV/TAC, Geneva
6. Ying Ru Lo	WHO/WPRO, Philippines
7. Michael Jordan (consultant)	Tufts University, USA
8. Andrew Hill (consultant)	University of Liverpool, UK