2nd WHO Adult Treatment Working Group Meeting on Treatment Optimization of HIV

Executive Summary

March 3rd, 2019

Grand Hyatt Seattle, Seattle, MA

WHO has established Adult HIV Treatment Working Group, which meet annually as a proximate event associated to the Conference on Retroviruses and Opportunistic Infection (CROI) to discuss key topics of the HIV treatment optimization agenda and when and how it should feed the future global normative and policy development activities. In 2019, the meeting provided the opportunity to discuss about safety data and research plans for new ARV drugs recently included in current WHO ART guidelines, the potential role of emerging new options in the HIV drug pipeline, and the advances in co- management of some comorbidities (eg: new preventive TB treatment regimens) in a public health perspective.

The agenda of the meeting was composed by short presentations on selected topics and followed by plenary discussions moderated by a facilitator (see agenda in annex 1). A questionnaire addressing the key items discussed in each session were also distributed and filed by the participants at the end or during the sessions (see questionnaire form in annex 2). The list of participants is available in annex 3.

TAF versus TDF: Review of benefits versus risks

There was a wide range of opinions about this subject. From a programmatic point of view, TAF was the more favoured drug because of small pill size and potentially lower costs of production. However, there is still less clinical evidence to support the widespread use of TAF in low- and middle-income countries. There is still very little data available on pregnant women treated with TAF and subsequent birth outcomes. Clinical experience of using TAF with rifampicin is still very limited. There is no clear safety benefit of TAF over TDF when used without pharmacokinetic boosters (e.g. ritonavir, cobicistat).

TAF was considered to be more promising for the treatment of children, but data from clinical trials is still limited. If used with boosted protease inhibitors in second-line treatment, TAF may be preferred to TDF.

TAF is still branded in many middle-income countries. Prices of branded TAF/FTC can be significantly higher than for generic TDF/FTC, which is now widely available (except for USA).

Several attendees highlighted the need for longer-term treatment, to determine whether there are benefits of TAF over TDF for renal and bone endpoints. At the same time, TDF appears to be associated with reductions in body weight. This might make TDF the preferable NtRTI to use with DTG, which is associated with rises in body weight and clinical obesity: TDF might help to compensate for the effects of DTG on body weight.

This issue will be discussed again at the WHO Guidelines Development Group meeting in June 2019. By this time, there should be more data available from the ADVANCE trial, which compared TAF/FTC/DTG with TDF/FTC/DTG in treatment naïve patients.

Question 1: **Is there a need for TAF for treatment programmes in LMICs, or should TDF remain the standard of care?**

a. All Adults Yes:17/32 (53%)

b. All Children Yes: 17/27 (63%)

c. Subset - poor renal function / osteopenia at baseline, Yes: 23/31 (74%)

Short regimens for TB prevention: Role of 3HP

There was a wide range of opinions about this issue. Many people wanted to see clinical data on people treated with 3HP, rather than just pharmacokinetic data. It is not clear whether once daily DTG provides a high enough exposure to maintain efficacy. For the moment, twice daily dosing of DTG may be preferable. New results with 1HP would be important in the overall assessment of risk-benefit.

Question 2: Short regimens for TB prevention session. Question: "Do you agree that the new PK data provides sufficient evidence to support routine use of DTG with 3HP?"

Yes: 13/28 (46%)

Changes in body weight/BMI in PLHIV on ART: Role of DTG and TAF

Overall, there is concern about emerging reports of weight gain and clinical obesity during treatment with integrase inhibitors, particularly for DTG. However at the moment most of the results are from non-randomised cohort studies, which may be prone to bias. The ADVANCE and NAMSAL trials include body weight and DEXA measurements for over 1600 treatment naïve patients given either TAF/FTC/DTG, TDF/FTC/DTG or TDF/FTC/EFV, in sub-Saharan Africa. The results from these trials will be available for review at the WHO GDG in June 2019. Before then, there was a concern that the current results from cohort studies could be too hard to interpret when making clear recommendations about new treatment options.
We cannot assume that all weight gain will lead to adverse clinical outcomes. There is a well described gain in weight during first-line treatment which is attributed to a

"return to health". Among black women, clinical obesity does not seem to be closely correlated with falls in life expectancy in cohort studies. This is in contrast to studies of white men, where clinical obesity is highly correlated with reductions in life expectancy.

We need to see long-term data from randomised clinical trials evaluating body weight and associated issues (for example DEXA scanning, blood pressure, lipids, HbA1C). At the moment, ADVANCE and NAMSAL will only be collecting data up to Week 96. Extended follow up could improve our understanding of this situation. It is not clear whether the effects of integrase inhibitors tend to diminish over time, or if there is a continued effect on weight gain.

Also, it is rather simplistic to combine data from all Black populations, when there could be differences in body shape and propensity to gain weight between regions. Lifestyle modifications need to be considered as the first option for people who gain weight on any treatment.

It is not yet clear if there are sub-groups of people who should not be offered DTG because of a potential risk of weight gain – for example people with clinical obesity or cardiovascular disease. There was a majority of respondents in favour of stopping DTG for people who developed clinical obesity. However, this could be a complex rule to implement in low-income countries.

Question 3: Changes in body weight/BMI on ART. Questions: 1. When should people discontinue DTG for excess weight gain (assuming normal weight at baseline)?

5% increase, Yes: 1/24 (4%)

10% increase, Yes: 4/22 (18%)

Clinical obesity (BMI >30 kg/m2), Yes: 16/26 (62%)

Question 4: Are there groups of people who should not be treated with DTG, because of a high risk of developing clinical obesity (e.g. black women)?

Yes: 2/26 (8%)

TLE-TLD switching in stable patients:

There was a strong level of agreement that people should not be switched from TLE to TLD if their viral load was unknown. Some respondents predict that this could lead to the emergence of resistance to integrase inhibitors, given the uncontrolled nature of this switching. There is a large data gap here. Results from studies such as D2EFT, ARTIST, NADIA and the ACTG cohorts will not be available until 2021. Before then, results from smaller non-randomised studies such as the Botswanan BEAT study will be important. Even in the DAWNING study, where people were switched to DTG in combination with optimised NRTIs after genotypic resistance testing, there were two patients who developed resistance to DTG.

At the same time, there are countries which have very little access to viral load testing, but have already started large-scale switching from TLE to TLD.

If patients have undetectable viral load and adverse events related to efavirenz, there is a clear benefit to switching to TLD. However if people have undetectable viral load and are tolerating efavirenz, it is not clear whether a switch to TLD will cause a net benefit. These patients might start to show excess weight gain on TLD, plus new CNS side effects from DTG.

Overall, the group emphasised the need to monitor this situation carefully. Any emerging country-level results showing the outcomes of these switches to TLD should be evaluated at regular intervals. This is to ensure that viral failure and emerging resistance to integrase inhibitors is not becoming an issue.

Question 5: For mass treatment programmes in LMICs, is there enough evidence to support switching people from TLE to TLD:

a) if there are no HIV RNA results available in the past year?

Yes: 4/31 (13%)

b) if HIV RNA is known to be detectable in the past year?

Yes: 11/30 (33%)

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Results of NAMSAL study and considerations on high baseline viral load

Overall, the group has divided opinion, but most of the group has emphasized that pre-ART VL is not feasible in many settings and will make treatment algorithms more complex. Some experts suggested that the dynamics of viral load are different if baseline levels are very high and more studies are needed. Some emphasized that is important to make sure there is no selection of integrase resistance in these patients with high VL at baseline. For those that support the idea that to have a baseline VL should be helpful to make decisions on changing treatment choice, they suggested to consider a VL threshold of >200 copies/ml rather than >50 copies/ml as a basis to change treatment, for people with high baseline VL. Others suggested that these patients should be monitored more frequently (every three months). Furthermore, any VL algorithm change will require significant re-training and resources that may be diverted from other system components. The longer-term follow up for NAMSAL study was also highlighted.

Question 6: Should treatment naive people with HIV RNA >500,000 copies/mL be monitored in a different way to other patients?

Yes: 15/33 (45%)

New ARV drugs: Role of Bictegravir, Doravirine and other new options

The majority of the group agreed that there is no data available for the usual important subpopulations with these drugs, but it need to be monitored. Fostemsavir is a new mechanism of action, but there are production problems and it is not yet available or approved. Doravirine will be a niche drug for people who cannot tolerate DTG. Long-acting drugs are on the long-term horizon.

Any new drugs to be included need to be affordable. Generic formulations with accessible prices are needed to guarantee sustainability.

Fostemsavir could be an option for second-line, or third-line. CAB/RIL could be considered for young adults, given their typically poor adherence. FOS and DOR are more attractive candidates than BIC or RAL. We need to continue working on these drugs.

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Question 7: Which of these new ARVs should be considered for potential inclusion in new WHO HIV treatment guidelines in 2020:

a. Bictegravir	Yes: 2/28 (7%)
b. Doravirine	Yes: 8/28 (29%)
d. Fostemsavir	Yes: 2/26 (8%)
c. Raltegravir once-daily	Yes: 5/30 (17%)

ARV investigation and use in adolescents and pregnant women:

There was a consensus that it's imperative to accelerate access to optimal ARVs in pregnant and lactating women. Multiple agencies and actors are beginning to voice their concerns around the exclusion of pregnant women from clinical trials and associated harms and risks of this practice. Dedicated efforts ae now in place to examine existing barriers and identify targeted solutions to address these important gaps. The majority of people living with HIV in sub-Saharan Africa are young women and there is a big gap in terms of knowledge and research for these women. The group agreed that earlier completion of pre-clinical reproductive toxicity studies coupled with pre-approval conduct of pharmacokinetic studies for promising new drugs to allow enrolment of pregnant women into phase III trials of new ARVs is critical to ensure optimal treatment for women living with HIV. Real-world studies like TSEPAMO should be started in parallel to Phase 3 to prevent unnecessary delays in newer drugs getting into LMICs where needs may be critical. Earlier and better collaboration with community, industry and regulatory authorities to refine the timing and design of these studies remain critical to acceleration of this work.

Question 8: Do you agree with the proposed principles to accelerate drug investigation and use in pregnant and lactating women?"

Yes: 31/31 (100%)

Conclusions

The meeting showed that the results of ongoing and planned studies with new ARVs are needed to close some important gaps and validate the widespread use of these options in all subpopulations. Many new ARV options can bring clinical and programmatic advantages and help countries to move faster towards 90/90/90 targets. However, there are key missing evidence in safety for pregnant women, HIVTB coinfected people and for people who have not been evaluated for drug

resistance before starting their antiretroviral treatment. More studies and evidence are also needed to consider any treatment failure monitoring change, especially in the setting of optimized ARVs.

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ANNEX 1: Meeting Agenda

Time (duration)	Topic	Speaker/Moderator
7:30 - 8:15 (45´)	Registration and Coffee	
8:15 - 8:30 (15´)	Introduction - current WHO treatment guidelines, how they could change in 2019/2020	Marco Vitoria
8:30 - 8:45 (15´)	TAF versus TDF - do we need TAF? Review of benefits versus risks	Andrew Hill
8:45 - 9:00 (15´)	Changes in body weight / BMI on ART - effects of DTG, TAF, race and sex	Andrew Hill
9:00 - 9:15 (15´)	What is new in short regimens for TB prevention?	Susan Swindells
9:15 -9:45 (30´)	Discussion	
9:45 -10:00 (15´)	Coffee break	
10:00 - 10:15 (15´)	NAMSAL - is high baseline viral load a risk factor for treatment failure?	Andrew Hill
10:15 - 10:30 (15´)	Switching from TLE to TLD with unknown viral load - what do we know so far?	Charles Flexner
10:30 - 11:00 (30´)	Discussion	
11:00– 11:15 (15´)	Which new drugs do we need? Role of doravirine, eFDA, bictegravir. New treatment strategies	Anton Pozniak
11:15 - 11:30 (15´)	How to optimize investigation of new ARVs in adolescents and pregnant women?	Elaine Abrams
11:30 - 11:50 (20´)	Discussion	
11:50 - 12:00 (10´)	Conclusions & next steps	Meg Doherty

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ANNEX 2: Questionnaire

Name: _____

Institution: _____

TAF vs TDF session:

1. Is there a need for TAF for treatment programmes in LMICs, or should TDF remain the standard of care?

a. All Adults

Yes____ No____

b. All Children

Yes____ No____

c. Subset - poor renal function / ostepenia at baseline

Yes____ No____

Comments: _____

Short regimens for TB prevention session:

2."Do you agree that the new PK data provides sufficient evidence to support routine use of DTG with 3HP?"

Yes____ No____

Comments: _____

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Changes in body weight/BMI on ART session:

3.When should people discontinue DTG for excess weight gain (assuming normal weight at baseline)?

5% increase Yes____ No____

10% increase Yes____ No____

Clinical obesity (BMI >kg/m2)

Yes____ No____

4.Are there groups of people who should not be treated with DTG, because of a high risk of developing clinical obesity (e.g. black women)?

Yes____ No____

Comments: _____

TLE-TLD switching session:

5.For mass treatment programmes in LMICs, is there enough evidence to support switching people from TLE to TLD:

a) if there are no HIV RNA results available in the past year?

Yes____ No____

b) if HIV RNA is known to be detectable in the past year?

Yes____ No____

Comments: _____

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NAMSAL & high baseline viral load session:

6. Should treatment naive people with HIV RNA >500,000 copies/mL be monitored in a different way to other patients?

Yes____ No____

Comments: _____

New ARV drugs session:

7. Which of these new ARVs should be considered for potential inclusion in new WHO HIV treatment guidelines in 2020:

a. Bictegravir Yes____ No____

b. Doravirine Yes____ No____

d. Fostemsavir Yes____ No____

c. Raltegravir once-daily Yes____ No____

Other drugs? _____

Comments: _____

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ARV investigation and use in adolescents and pregnant women session:

8. Do you agree with the proposed principles to accelerate drug investigation and use in pregnant and lactating women?"

Yes____ No____

Comments: _____

_____

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Annex 3: List of participants

Expert members

Name	Country	Affiliation	Email contact
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