World Health Organization

UPDATE ON THE TRANSITION TO DOLUTEGRAVIR-BASED ANTIRETROVIRAL THERAPY: REPORT OF A WHO MEETING

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Update on the transition to dolutegravir-based antiretroviral therapy: report of a WHO meeting, 29–30 March 2022

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CONTENTS

ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
AIDS	Acquired Immunodeficiency Syndrome
ARV	anritetroviral
ART	antiretroviral therapy
AZT	zidovudine
BMI	body mass index
DTG	dolutegravir
DRV/r	darunavir/ritonavir
EFV	efavirenz
EVG/c	elvitegravir/cobicistat
FTC	emtricitabine
HbA1C	glycated hemoglobin
HIV	human immunodeficiency virus
HIV ResNET	WHO HIV Drug Resistance Netwrok
IeDEA	International Epidemiology Databases to Evaluate AIDS
INSTI	integrase strand-transfer inhibitor
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
PEPFAR	United States President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PrEP	pre-exposure prophylaxis
RCT	randomized clinical trial
TAF	tenofovir alafenamide fumarate
TAF-ED	tenofovir alafenamide fumarate + emtricitabine+ dolutegravir
TB	tuberculosis
TDF	tenofovir disoproxil fumarate
TLD	tenofovir disoproxil fumarate + lamivudine + dolutegravir
TLE	tenofovir disoproxil fumarate + lamivudine + efavirenz
TEE	tenofovir disoproxil fumarate+ emtricitabine+ efavirenz
WHO	World Health Organization

1. INTRODUCTION

Since 2018, WHO HIV treatment guidelines have recommended the combination of tenofovir disoproxil fumarate (TDF), lamivudine and dolutegravir (TLD) as the preferred first-line regimen for initiating antiretroviral therapy (ART) among adults and adolescents living with HIV (1). Dolutegravir (DTG) is also recommended as a preferred choice in second-line regimens for treating individuals for whom a non-nucleoside reverse-transcriptase inhibitor (NNRTI)–based first-line regimen has failed. In July 2021, WHO released updated the consolidated HIV guidelines, providing further support on adopting DTG as a preferred option in first- and second-line ART for all populations because of reassuring safety data, including for women and adolescent girls using it during the peri-conception period (2). As of June 2021, 110 low- and middle-income countries had transitioned to DTG and an estimated 22 million people living with HIV were receiving DTG-based ART. However, emerging evidence shows that body weight gain is associated with using DTG-containing regimens (3,4), and concerns about the long-term implications of this adverse event and the risk of DTG resistance development with TLD use in situations of poor adherence or use of suboptimal DTG regimens are emerging topics that need more information for guidance.

1.1 Approach

The treatment working group was convened virtually, and the agenda was composed by short presentations on selected topics followed by plenary discussions moderated by a facilitator (see agenda in Annex 1). Resource materials were made available before the meeting, including recent systematic reviews, programmatic data and the list of major clinical and observational studies on the topics of the meeting. An online survey was also conducted with the participants, and the results are included in this report.

1.2 Overview of sessions

This meeting reviewed the status of TLD transition in low- and middle-income countries, addressing the best practices and major challenges in various countries. The data on safety and efficacy of DTG-containing regimens were also reviewed, addressing key considerations associated with newer antiretroviral (ARV) drugs – including body weight gain and other cardiometabolic risks, tolerability of regimens, safety in pregnancy and HIV drug resistance. The meeting participants reviewed data sources, including clinical trials, observational studies and programmatic data in the context of digitalization, that can inform future reviews for updating HIV treatment policies. Finally, the technical working group identified the critical gaps in knowledge, research, monitoring and surveillance on DTG and TLD transition and listed the future priorities.

1.3 Participants

The technical working group comprised 40 external participants, including academic experts, clinicians, civil society representatives, nongovernmental organizations, national HIV programme managers and regulatory agencies. Observers from funders and partners including the United States Centers for Disease Control and Prevention, Clinton Health Access Initiative, United States President's Emergency Plan for AIDS Relief (PEPFAR), Global Fund to Fight AIDS, Tuberculosis and Malaria, Medicines Patent Pool, United States Agency for International Development and Unitaid (see list of meeting participants in Annex 2).

WHO was represented by staff members from the Department of Global HIV, Hepatitis and Sexually Transmitted Infection Programmes and from regional and country offices.

1.4 Expected outcomes

The key expected outcomes of the meeting were:

- a summary of status of TLD programmatic transition in countries;
- a summary of recent data on toxicity, safety and drug resistance of DTG-containing regimens and associations with other newer ARV drugs used in special circumstances;
- a list of questions, gaps and priority areas for new research, monitoring and surveillance on TLD and DTG transition; and
- an updated list of ongoing and planned clinical trials and observational studies addressing priority research questions and timeline for new evidence (see Annex 3).

2. SUMMARY OF PLENARY PRESENTATIONS

2.1 Programmatic transition to TLD in PEPFAR-supported countries

The United States Agency for International Development presented the status of TLD transition in the 40 countries supported by PEPFAR. By September 2021, 78% of the people receiving ART were receiving TLD (50% in September 2020). In most PEPFAR-supported countries, more than 80% of the people living with HIV receiving ART were receiving TLD, with all countries demonstrating progress in scale-up albeit with different adoption trends. This rapid scale-up was accompanied by nearly universal improvement in viral suppression at the population level, regardless of the country adoption trends. Some potential factors that could affect the various adoption rates were the health-care provider or patient opinions on switching treatment, complexity of the procurement process, specific policy choices (such as consent for women of childbearing age) and simultaneous programmatic policies implemented (such as multimonth dispensing medicines). Disaggregating the TLD transition data by sex and age showed lower rates of TLD uptake among women of childbearing age compared with men, despite some additional training being provided. Most countries are transitioning to electronic medical records and digitalized patient monitoring systems that strengthen person-centred patient monitoring, with the potential to assess some of the critical knowledge gaps in treatment outcomes.

2.2 Update on safety and efficacy studies

The treatment working group reviewed the latest data from the ongoing clinical trials (ADVANCE, ARTIST, d2EFT, NADIA, NAMSAL, VISEND and VESTED) and observational studies (ACTG 5381, AFRICOS, DO REAL, DISCO, EMEDT and Tsepamo) evaluating the safety of DTG and tenofovir alafenamide (TAF) in various populations and clinical situations, including in switching people established on ART, with the following conclusions.

- Using DTG is non-inferior to a protease inhibitor with a ritonavir boost (PI/r) in second-line therapy, with trends for superiority in some trials.
- Clinical and observational data from these studies support switching from TDF, lamivudine and efavirenz (TLE) to TLD without viral load testing or regardless of the viral load. The key questions are to identify what and how to monitor in transitioned people in different situations (naive, stable on ART, treatment is failing, already on first- or second-line regiment and high viral load).
- Continued TDF containing a nucleoside reverse-transcriptase inhibitor (NRTI) backbone was shown to be non-inferior to switching to NRTIs in second-line regimens.
- Benefits of TAF over TDF were found in some subgroups, but the comparative clinical and programmatic advantages for switching TDF to TAF for all people living with HIV require more analysis.

As an example of safety on the TLE-to-TLD transition, MSF Malawi presented the latest results of the EMEDT study in detail. They found good clinical tolerability and monitored TLD safety during one year after transitioning. After this period, only 2.2% (41 of 1893) of the cohort had at least one adverse drug reaction, including 21 hospitalizations, 18 deaths and two TLD discontinuations because of adverse drug reactions (acute psychosis with symptoms that subsided once treatment was switched). No indication of significant weight gain during one year of follow-up (based on routine data). Among 746 (78%) of women assessed after 12 months, the median weight difference was 1 kg [interquartile range: −0.5, 3.0]. Among 720 men (76%) assessed at the same time, the median weight difference was 0 kg [interquartile range: −1.5, 2.0].

Annex 3 presents a summary table of status of ongoing clinical trials and observational studies and when the next results are expected to be published.

2.3 Community perspectives on TLD transition

The community panel highlighted that more emphasis should be given to quality-of-life aspects and the indicators of adverse drug reactions. Greater involvement of people living with HIV is needed in the TLD transition plan at the country level. The need to simplify and improve communication on the risks of potential toxicity and focus on the tangible immediate needs and well-being of people living with HIV receiving ART were also emphasized.

2.4 Systematic review and network meta-analysis on body weight gain among people living with HIV on ART

The systematic review was conducted in September 2021 and recently published (3). The treatment working group presented and discussed the results, with the following conclusions.

- DTG-containing regimens lead to larger weight gain than EFV400-, EFV600- and EVG/c-containing regimens (moderate-certainty evidence).
- DTG- and TAF-containing regimens lead to larger weight gain than DTG combined with other NRTI backbones (moderate-certainty evidence).
- Larger weight gain was observed in TAF-containing regimens compared with TDF- or other NRTI-containing regimens (moderate-certainty evidence).
- No significant risk of hyperglycaemia or diabetes was detected with DTG- or TAF-containing regimens but data were limited.
- Among predicting factors, the presence of low CD4 cell count and high HIV viral load highly indicate larger weight gain, and the effects of sex differences on weight gain appear to be associated with African origin.
- Several other new studies published after the systematic review on this subject were presented at the 2022 Conference on Retroviruses and Opportunistic Infections and further support the association of the use of DTG and TAF with larger weight gain (see Annex 4).

2.5 Considerations of management of body weight gain and ART

body weight gain has been documented with the use of new ARV drugs, especially integrase inhibitors. This metabolic event seems to be multifactorial (potential risk factors include race, sex, advance disease, CD4 cell count, HIV viral load, previous weight loss and switching), and a multidisciplinary approach is suggested for proper management. There are several important knowledge gaps, and current studies have shown heterogeneous results. More studies are needed. Regarding other cardiometabolic events, several cohorts indicate minimal impact on glucose, lipids and blood pressure levels. More data are required on which switch strategies should be adopted. Some implications and questions for WHO guidelines were highlighted:

- What to advise people? More data are needed on people with normal BMI.
- Observational studies frequently exclude people using obesogenic agents.
- When receiving DTG- based regimen from ART initiation, weight gain could be higher and the risk of metabolic consequence increase on the longer term.

Data from electronic medical records and sentinel surveillance represent important data sources that may help address these questions.

2.6 Updates on new ARV drug safety use during pregnancy

New data on ARV drug safety pregnancy registry and recent published studies were presented. Several birth defect surveillance studies are planned: (1) the Mango Study in Kenya (part of the IeDEA project) will collect routine data on all deliveries; (2) Western Cape Pregnancy exposure registry, in South Africa, will use electronic medical records to assess pregnancy outcomes; and (3) Elizabeth Glaser Pediatric AIDS Foundation one-year study in five sentinel sites in Eswatini. This last study started in October 2021, and as of February 2022, had enrolled more than 11 000 women, of which about 3500 are living with HIV and >60% of whom were using DTG during the preconception period.

2.7 Updates on risk of neural tube defects and use of DTG in the preconception period (Tsepamo study)

The investigators of the Tsepamo study presented the latest report on the prevalence of neural tube defects among women with preconception DTG exposure, with cumulative data from April 2018 to September 2021. The total prevalence of neural tube defects among babies born to mothers exposed to DTG during the conception period declined further and is in the same range observed among women using non-DTG regimens at conception (0.13% versus 0.10%).

These data continue to support WHO guidelines on the use of DTG as a preferred first-line option for pregnant women and for women of reproductive potential and women trying to conceive. The next report of the study was expected in May 2022. Future directions of the Tsepamo study are on monitoring birth outcomes with new ARV drugs as they are introduced (TAF and pre-exposure prophylaxis (PrEP)).

2.8 VESTED study analysis on pregnancy outcomes using TAF

VESTED is one of the major clinical trials evaluating several pregnancy and birth outcomes associated with using TAF and DTG during pregnancy. Recent data from the VESTED study were presented at the 2022 Conference on Retroviruses and Opportunistic Infections (5) and further discussed by the treatment working group.

- Abstract 30 (6): improved infant growth in DTG arms compared with EFV at birth and persisted at 50-week analysis.
- Abstract 509 (7): treatment failure and HIV drug resistance at 50 weeks were assessed for pregnant women by treatment arm. Higher rates of treatment failure with EFV (10.4%) than DTG (4.1–5.1%); more HIV drug resistance at treatment failure with EFV (6.2%) versus DTG (0.9–1.9%) and no differences observed in the TAF/FTC + DTG versus TDF/FTC + DTG arms.
- Abstract 679 (8): in terms of pregnancy and infant adverse events, TAF/FTC+DTG had the best risk–benefit trade-offs compared with TDF/FTC+DTG (odds ratio (OR) = 0.64, 95% confidence interval (CI): 0.5–0.8) and TDF/FTC + EFV (OR = 0.28, 95% CI: 0.2–0.4). TDF/FTC + DTG had a better risk–benefit trade-off than TDF/FTC + EFV (OR = 0.41, 95% CI: 0.3–0.5).
- Abstract 680 (9): adverse birth outcomes were assessed among 19 women with subsequent pregnancies (n = 20). Adverse birth outcomes in 11 of 20 (58%) with 7 of 20 (35%) spontaneous abortion or stillbirth. More than one adverse birth outcome in 8 of 12 (67%) taking EFV and 1 of 4 (25%) taking DTG at conception. No birth defects were found.
- Abstract 687 (10): no differences were found in glycated haemoglobin (HbA1c) levels, and no clinically meaningful differences in maternal or infant glucose levels were detected between arms in a subset of 348 mothers and 65 infants at 12 weeks antepartum and at delivery periods.

2.9 Update on DTG resistance

WHO presented key data on DTG acquired resistance from clinical trials and available limited survey data from countries that indicated overall low levels of DTG resistance outweighed by improvements in viral load suppression observed across several countries. However, among those failing treatment, DTG resistance was higher (ranging from 8% to 30% in country survey data presented at the meeting). Data on recycling TDF with DTG in second-line ART from three clinical trials and two observational cohorts were also presented, and research questions compiled by HIVResNet. Important questions on previous ART resistance in viral suppression and resuppression were raised. Important to expand and strengthen the surveillance through HIV drug resistance national surveys. Considering the huge gap in HIV drug resistance testing capacity in sub-Saharan Africa, the treatment working group raised how to balance using empirical ART sequencing versus using HIV drug resistance testing among people with treatment failure receiving DTG-based regimens. The EMEDT cohort evaluated the prevalence of acquired DTG resistance and failure to suppress viral loads. Data presented 12 months following TLD switch indicate overall very low rates of DTG resistance (0.1%, 2 of 1836) in a population with high rates of viral suppression before (94.7%) and after TLD transition (97.9%), but among those with failure to suppress viral loads, DTG resistance was 15% (2 of 14).

2.10 Community perspectives on DTG drug resistance

The community panel highlighted the importance of viral load monitoring to ensure the longest benefits of DTG-containing regimens, especially considering adherence challenges and the potential role of new toxicity and adverse drug reactions that can compromise adherence and drug tolerability, causing drug resistance. Support for communities should address these issues. The panel also called for promoting the use of robust second-line regimens for individuals for whom DTG is failing and ensuring options to transition quickly. Monitoring children on using DTG-containing regimens and how this might affect their care over their life-course were also noted to be important.

3. SUMMARY OF DISCUSSION POINTS

3.1 Body weight gain and new ARV drugs

- The treatment working group presented diverging views on body weight gain associated with new ARV drugs. The group agreed to recommend caution in associating DTG and TAF as the primary cause of body weight gain observed. To some experts, this effect could appear to be what is expected compared with those who "return to health". Further, some data suggest that TDF and efavirenz (EFV) are "body weight suppressive" agents. The overall analysis could be viewed as DTG and TAF acting as neutral agents and EFV and TDF suppress body weight.
- The treatment working group also noted that most studies do not differentiate between people with and without body weight gain, return to health and becoming overweight, and/or normal versus abnormal weight gain, which make the analysis more difficult.
- "Return to health" needs to be defined. This concept should not be limited to return to a healthy body weight but the return to the weight one would have if never infected with HIV; this should consider the high rates of obesity observed in many populations.
- Management of clinical obesity – need to review traditional diet and exercise advice in accordance with the WHO obesity guidelines given challenges in managing obesity among people switching ARV drugs with this approach.
- Need to acknowledge that there is substantial variance of appreciation of body weight gain based on the country context – and that ARV drug regimens might be used for purposes beyond just viral load suppression, such as retaining weight by using an EFV-containing regimen – that is, a refined approach to assessing the issue of body weight gain.
- Does body weight gain compromise treatment adherence among people using DTG or TAF?
- Patient values and preferences on ARV drug toxicity and how they affect treatment decisions and quality of life.
- Effects of long-term ART and body weight gain among women on TAF + FTC + DTG, including at conception and on adverse birth outcomes.
- Are there any data on weight gain and metabolic consequences among people 50 years and older?

3.2 TAF versus TDF

- There is a growing consensus that TDF and TAF are pharmaceutically equivalent. Recent data from the VESTED trial and some other small studies on pregnant women are also reassuring on TAF pregnancy safety and suggest that its use can be expanded to this group. However, the benefits of a full replacement or transition from TDF to TAF among all people living with HIV are still not very clear in a public health approach.
- How to manage clinical obesity on TAF users, versus renal issues with TDF use among adults and adolescents: the treatment working group agreed that neither is ideal, but in modelling studies the long-term clinical obesity associated with TAF predicted excess myocardial infarction, diabetes and adverse birth outcomes among pregnant women.
- Can TAF be considered for children? There are no large clinical trials comparing TAF versus TDF among older children, and TDF is not used for young children because of potential bone toxicity. So reliable comparative data are not available.
- TAF versus TDF by population – concerns that recommendations for TAF by population are unlikely to be feasible from a supply chain perspective and will be programmatically challenging to implement for non-pregnant women.

3.3 Programme monitoring

- Leveraging data from electronic medical records (and hence looking at large numbers of clients at higher age ranges) and assessing whether weight gain patterns are similar to those observed in clinical trials with smaller sample sizes. In addition, assessing whether there are more concerns about noncommunicable diseases, although these may not routinely be captured in electronic medical records.
- What proportion of recipients of care are crossing into overweight (BMI > 25) or obese (BMI > 30) categories after transitioning to DTG? Are there predictors of risk?
- Are age and sex patterns in excessive weight gain consistent with ADVANCE and AFRICOS? What do they tell us about equity in access and outcomes?
- What are real-world rates of changes from DTG-based regimens to another regimen because of toxicity or failure?
- What are rates of subsequent viral load suppression among recipients of care transitioned from protease inhibitors to DTG?
- Does DTG-related excessive weight gain result in greater interruptions in treatment over time?

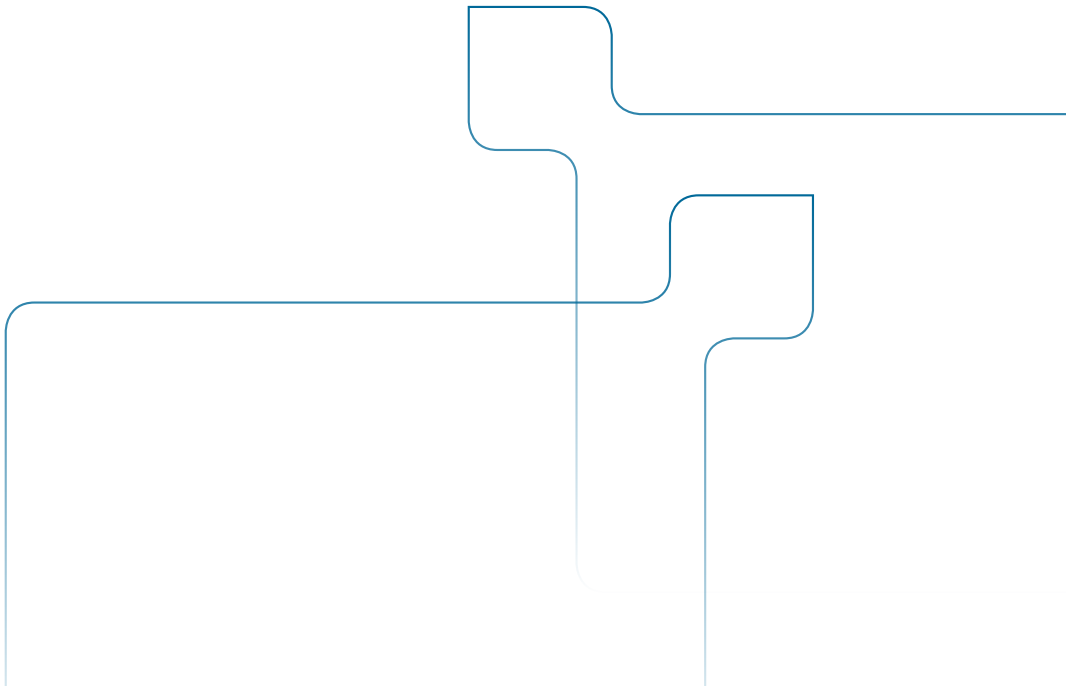
3.4 Switching NRTI backbone in second-line treatment

- When DTG is used in second-line ART, can the NRTI component be recycled when switching from first- to second-line ART among people with treatment failure?
- How to manage individuals who meet viral load criteria for treatment failure on using TLD in terms of changing or maintaining their regimen? Switch to a protease inhibitor–based regimen in accordance with current WHO guidelines?
- Switching for viraemia with DTG questioned, since no evidence indicates it will benefit patients and may mean switching to less tolerable protease inhibitor regimens and a higher pill burden. On a public health level, the trade-off is switching people unnecessarily where the problem is adherence versus not switching when there is resistance. Evolving data from sentinel resistance testing will help inform this decision. In South Africa, people living with HIV are kept on DTG for a minimum of two years before switching is considered.
- Issues of stigma and relevance or utility of differentiating between first-, second- and third-line ART sequencing in the context of DTG raised by civil society organization representatives. Possibility of options rather than first-, second- and third-line sequencing was raised.

4. CONCLUSIONS

4.1 Key messages

- **What and how to monitor TLE to TLD transition:** new evidence from clinical trials (ARTIST, NADIA and VISEND), observational studies (ACTG 5381, AFRICOS and EMEDT) and the PEPFAR programmatic data support a switch from TLE to TLD without or regardless of viral load. The risk of integrase strand-transfer inhibitor (INSTI) resistance has been low and is outweighed by improvements in viral load suppression across several countries. The uptake and speed of the transition has been variable. The key question is to identify what and how to monitor the transitioned people in different situations (naive, established on ART, ART is failing, already on first- or second-line regimens and high viral load). Differentiated adherence support strategies and enhanced use of electronic medical records data need to be explored.
- **Monitoring body weight gain and metabolic events associated with use of dolutegravir and TAF:** seems to be a multifactorial phenomenon that needs a multidisciplinary approach for proper management. Several important questions need to be answered, and study results have shown heterogeneous results. More research is needed.
- **Identifying risk factors, switching criteria for DTG in the context of clinical obesity:** a definition of return to health (beyond the return to adequate body-mass index (BMI) or body weight) is needed, and the impact in various populations (adolescents, children, pregnant women and older people) and outside the WHO African Region seems to be a priority. Data from electronic medical records and sentinel sites can be very important data sources to address these issues.
- **TAF versus TDF:** VESTED data and some other small studies on pregnant women are reassuring about TAF safety in pregnancy and suggest that its use could be expanded to this group. However, the benefits of a full programmatic transition from TDF to TAF to all people living with HIV is still not clear in a public health approach, and there are questions and trade-offs to be balanced, including how to manage the potential excess of clinical obesity among people using TAF versus renal toxicity with TDF. Recent modelling studies show that the long-term excess clinical obesity from TAF predicted excess myocardial infarction, diabetes and adverse birth outcomes.
- **Enhance DTG resistance monitoring in low- and middle-income countries:** the prevalence of DTG resistance among people for whom treatment has failed (ranging from 8% to 30% according to survey data). Important questions on previous ART resistance in viral suppression or resuppression. Importance of expanding and strengthening the surveillance through HIV drug resistance national surveys. Considering the huge gap in HIV drug resistance testing capacity in sub–Saharan Africa, how to balance the use of empirical regimen sequencing versus HIV drug resistance testing for people with treatment failure on DTG-based regimens.



4.2 Priority areas for new research, monitoring and surveillance

Managing ARV drug treatment failure and adherence approaches

- What is the most appropriate monitoring approach for people receiving TLD with treatment failure?
- When should there be a regimen change, and how long can a client with treatment failure be kept on DTG before switching? Is the threshold of two consecutive unsuppressed viral loads with adherence counselling in between in accordance with current WHO guidelines too low? Especially since data indicate that individuals with treatment failure go on to resuppress following adherence counselling. Clinical trials to assess this were proposed in addition to observational studies.
- Can higher doses of DTG be used to address treatment failure among those already using DTG?
- Can a new drug be added to the TLD regimen in treatment failure instead of switching (intensification)?
- Assessment of clinical outcomes and programmatic data of people living with HIV on failing DTG-containing regimens who are not switched in long-term clinical trials (such as ADVANCE and NADIA).
- What should be used for second-line ART when DTG is used in first-line ART?
- Feasibility and cost of point-of-care urine tests as an indicator of adherence in low- and middle-income countries.
- Counselling and differentiated adherence approaches for different populations, especially adolescents, young adults and migrants: groups with frequent treatment interruptions and retention challenges (and hence adherence challenges) that affect decisions on what regimens should be restarted or when switch timing might be ideal.

Body weight gain, cardiometabolic events and new ARV drugs

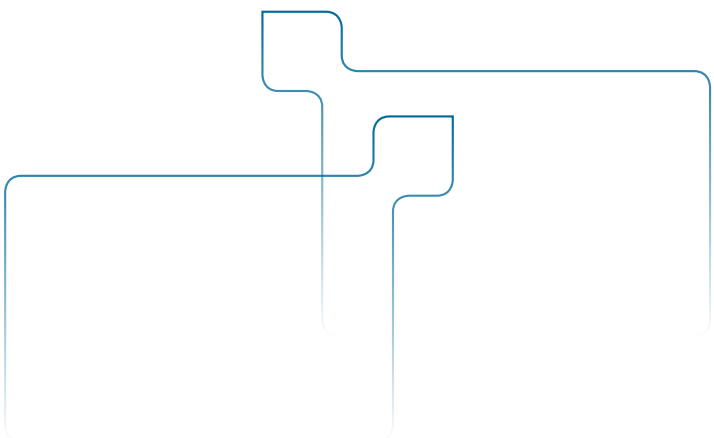
- Values and preferences on toxicity, especially weight gain, from qualitative patient-focused studies.
- Qualitative research to understand the risks of poor adherence and better management.
- Is there a role for TAF for people with the lowest body weight at baseline who could then benefit from the return to the health effects of higher weight? For people with normal or overweight BMI, is TDF more appropriate?
- More data on switching people with poorly controlled diabetes or with high BMI.
- Is DTG or TAF associated with increased cardiometabolic risk among people with BMI 25–30?

HIV drug resistance and adherence

- Data on DTG resistance in high-income countries
- Model the predicted attributable fraction of circulating INSTI resistance likely to relate to ART versus PrEP use in different scenarios to consider the effect of cabotegravir use in PrEP.

Pregnant women

- Pharmacokinetic data on TAF in pregnant women with TB and HIV.
- Data on TAF among breastfeeding women.



REFERENCES

1. Policy brief: update of recommendations on first- and second-line antiretroviral regimens. Geneva: World Health Organization; 2019 (https://apps.who.int/iris/handle/10665/325892, accessed 8 July 2022).

2. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach, 2021 update. Geneva: World Health Organization; 2021 (https://apps.who.int/iris/handle/10665/342899, accessed 8 July 2022).

3. Kanters S, Renaud F, Rangaraj A, Zhang K, Limbrick-Oldfield E, Hughes M et al. Evidence synthesis evaluating body weight gain among people treating HIV with antiretroviral therapy – a systematic literature review and network meta-analysis. EClinicalMedicine. 2022;48:101412.

4. WHO think-tank meeting on optimizing antiretroviral therapy: meeting report, 12 March 2020. Geneva: World Health Organization; 2020 (https://apps.who.int/iris/handle/10665/338735, accessed 8 July 2022).

5. Conference on Retroviruses and Opportunistic Infections [website]. International AIDS Society USA; 2022 (https://www.croiconference.org, accessed 8 July 2022).

6. Stranix-Chibanda L, Ziemba L, Brummel S, Johnston B, Mbengeranwa TG, Cassim H et al. Growth of infants with perinatal exposure to maternal DTG vs EFV and TDF vs TAF. Conference on Retroviruses and Opportunistic Infections, 12–16 February 2022, virtual (Abstract 30; (https://www.croiconference.org/abstract/growth-of-infants-with-perinatal-exposure-to-maternal-dtg-vs-efv-and-tdf-vs-taf, accessed 8 July 2022).

7. Boyce CL, Brummel S, Ziemba L, McCarthy K, Knowles K, Styrchak S et al. HIV drug resistance in women randomized to DTG vs EFV or TDF vs TAF in pregnancy. Conference on Retroviruses and Opportunistic Infections, 12–16 February 2022, virtual (Abstract 509; https://www.croiconference.org/abstract/hiv-drug-resistance-in-women-randomized-to-dtg-vs-efv-or-tdf-vs-taf-in-pregnancy, accessed 8 July 2022).

8. Brummel S, Ziemba L, Coletti A, Chinula L, Krotje C, Browning R et al. Risk–benefit trade-off for pregnancy and infant outcomes: DTG, EFV, TAF and TDF. Conference on Retroviruses and Opportunistic Infections, 12–16 February 2022, virtual (Abstract 679; https://www.croiconference.org/abstract/risk-benefit-trade-off-for-pregnancy-and-infant-outcomes-dtg-efv-taf-and-tdf, accessed 8 July 2022).

9. Fairlie L, Brummel S, Ziemba L, Coletti A, Chinula L, Shapiro RL et al. Adverse outcomes in subsequent pregnancies in the IMPAACT 2010 trial. Conference on Retroviruses and Opportunistic Infections, 12–16 February 2022, virtual (Abstract 680; (https://www.croiconference.org/abstract/adverse-outcomes-in-subsequent-pregnancies-in-the-impaact-2010-trial, accessed 8 July 2022).

10. Chinula L, Goldberg E, Ziemba L, McCarthy K, Krotje C, Knowles K et al. Pregnancy hemoglobin A1c and glucose with DTG vs EFV, TDF vs TAF: IMPAACT 2010. Conference on Retroviruses and Opportunistic Infections, 12–16 February 2022, virtual (Abstract 687; (https://www.croiconference.org/abstract/pregnancy-hemoglobin-a1c-and-glucose-with-dtg-vs-efv-tdf-vs-taf-impaact-2010, accessed 8 July 2022).

ANNEX 1. MEETING AGENDA

Meeting agenda

Day 1: Tuesday, 29 March, 14:00–16:40 CET		
Session 1: Update on transition status to TLD		
14:00–14:05	Welcome remarks	Moderator: Morkor Newman
14:05–14:10	Objectives and expected outcomes	Marco Vitoria, WHO
14:10–14:30	Key considerations: • Status of major RCTs and observational studies • Transition from TLE to TLD: uptake and health outcomes (efficacy and safety) • Inequalities in access across populations • Responses to obstacles	Moderator: Morkor Newman Speakers: • Marco Vitoria, mapping the status of major studies • Lana Lee and Tom Minior, TLD transition in real life – PEPFAR data • Andrew Hill, switching TLD to protease inhibitor second-line ART (pooled analysis)
14:30–14:40	Patient perspectives	Community representatives: Florence Anam and Martin Choo
14:40–15:05	Discussion	Moderators: Morkor Newman and Marco Vitoria, WHO
15:05–15:10	Break	
Session 2: Update on antiretroviral drug–related toxicity and pregnancy safety		
15:10–15:35	Update on body weight gain, diabetes and cardiometabolic risks with INSTIs and TAF: • BMI changes • Metabolic consequences • Risk factors • Co-administration with TAF • Monitoring and clinical considerations	Moderator: Ajay Rangaraj, WHO Speakers: • Steve Kanters, Evidence Synthesis • Birgit Schramm, EMEDT data • François Venter, clinical considerations on body weight gain and cardiometabolic effects of ARV drugs
15:35–15:55	Update on pregnancy safety of new antiretroviral drugs – maternal, pregnancy and birth outcomes (including neural tube defects) • Tsepamo • Vested study • Update on safety in pregnancy	Moderator: Françoise Renaud, WHO Speakers: • Rebecca Zash, Tsepamo study • Shahin Lockman, Vested study • Lynne Mofenson, what is new (including Conference on Retroviruses and Opportunistic Infections 2022)
15:55–16:05	Patient perspectives	Community representatives: Imelda Mahaka and Polly Clayden
16:05–16:25	Discussion	Moderator: Françoise Renaud
16:25–16:35	Pulse survey (day 1)	Ajay Rangaraj
16:35–16:40	Wrap-up of day 1	Marco Vitoria

Day 2 – Wednesday, 30 March, 14:00–16:00 CET		
Session 3: Update on DTG resistance		
14:00–14:20	Drug resistance • Current programmatic evidence and new WHO monitoring framework on HIV drug resistance (focus on DTG)	Moderator: Marco Vitoria Speakers: • Michael Jordan • Daniel Kuritzkies, clinical considerations
14:30–14:35	Patient perspectives	Community representative: Kenly Sikwese
14:35–14:55	Discussion	Moderator: Michael Jordan
14:55–15:00	Pulse survey (day 2)	Ajay Rangaraj
15:00–15:05	Break	

Day 2 Continued		
Session 4: Priority areas for research, monitoring and surveillance		
15:05–15:45	List questions, gaps and priority areas for research, surveillance and monitoring • Clinical trials, observational studies, implementation studies, eHealth data • Populations • ARV drugs and ART Contributions from the pulse survey (day 2)	Moderators: Elaine Abrams and Yazdan Yazdanpanah Discussion
15:45–15:55	Wrap up of day 2 and next steps	Marco Vitoria
15:55–16:00	Closing remarks	Meg Doherty

ANNEX 2. TREATMENT WORKING GROUP MEETING PARTICIPANTS

Elaine Abrams (United States of America (USA)), Florence Anam (Kenya), Pedro Cahn (Argentina), Alexandra Calmy (Switzerland), Maria Ruano Campos (Mozambique), Mohamed Chakroun (Tunisia), Martin Choo (Malaysia), Polly Clayden (United Kingdom of Great Britain and Northern Ireland), Aleny Couto (Mozambique), Judith Currier (USA), Meg Doherty (WHO), Serge Eholie (Côte d'Ivoire), Tom Ellman (South Africa), Charles Flexner (USA), Tendani Gaolathe (Botswana), Beatriz Grinsztejn (Brazil), Hiwot Haile-Selassie (WHO consultant, Ethiopia), Andrew Hill (United Kingdom), Daine Havlir (USA), Seth Inzaule (WHO consultant, Kenya), Andreas Jahn (Malawi), Michael Jordan (WHO consultant, USA), Steve Kanters (Canada), Cordelia Katurebbe (Uganda), Nagalineswaran Kumarasamy (India), Daniel Kuritzkies (USA), Mohamed Lamorde (Uganda), Thuy Le (Viet Nam), Lana Lee (USA), Shahim Lockman (USA), Frank Lule (WHO Regional Office for Africa), Valerie Makori (Kenya), Catia Marzolini (United Kingdom), Gail Mathwes (Australia), Graeme Meintjes (South Africa), Fabio Mesquita (WHO Country Office for Myanmar), Tom Minior (USA), Lynne Mofenson (USA), Lloyd Mulenga (Zambia), Pamela Nawaggi (Unitaid), Morkor Newman (WHO), Frederic Ello Nogbou (Côte d'Ivoire), Clara Nyapokoto (Eswatini), Anton Pozniak (United Kingdom), Elliot Raizes (USA), Ajay Rangaraj (WHO), Françoise Renaud (WHO), Bharat Rewari (WHO Regional Office for South-East Asia), Birgit Schramm (France), Kenly Sikwese (Kenya), Vindi Singh (Global Fund to Fight AIDS, Tuberculosis and Malaria), Omar Sued (WHO Regional Office for the Americas), Simeon Tuyishime (Rwanda), François Venter (South Africa), Marco Vitoria (WHO), Elena Vovc (WHO Regional Office for Europe), Yazdan Yazdapanah (France), and Rebecca Zash (USA).

ANNEX 3. LIST OF CLINICAL TRIALS AND OBSERVATIONAL STUDIES ADDRESSING PRIORITY RESEARCH QUESTIONS AND TIMELINE FOR NEW EVIDENCE

Clinical trials

Research priority and topic	ADVANCE*	ARTIST	D2EFT	DOlPHIN2*	NADIA	NAMSAL*	VESTED	VISEND
Safety of DTG and/or TAF in periconception and pregnancy				●			●	●
Changes in body weight and cardiometabolic risk with DTG combined with TAF or TDF	●	●	●	●	●	●	●	●
Outcomes from switching from TLE to TLD without viral load testing		●	●		●			●
Recycling TDF with TLD in the presence of TDF resistance		●	●		●			●
Viral outcomes for people retained on DTG despite unsuppressed viral loads	●							
Safety and efficacy of DTG and/or TAF among adolescents	●		●		●	●		●
Post hoc analysis and substudies				●	●	●	●	

* ADVANCE, DOlPHIN2 and NAMSAL, were extended until 2022 to investigate how DTG and TAF affect weight gain and cardiometabolic parameters and were collectively renamed as the TRIO study.

Clinical trials

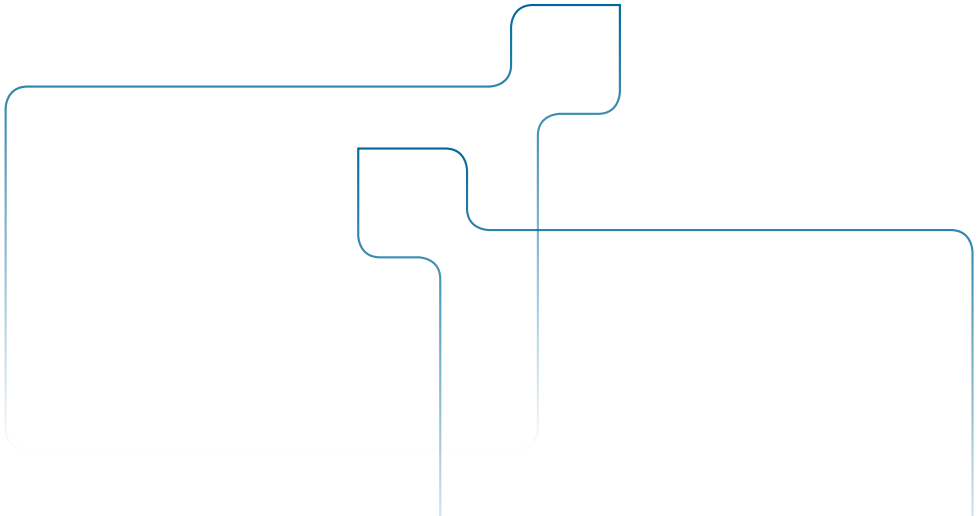
Study	Study design	Current status (Q1 2022)	Major outcomes	Sub studies or post hoc analysis
ADVANCE *	South Africa TEE versus TLD versus TAF, TAF-ED (TAF, emtricitabine and dolutegravir) efficacy and safety among people living with HIV initiating treatment (RCT)	96 weeks	TAF-ED Viral load suppression 79% TED Viral load suppression 78% TEE: 74% Body weight gain >TAF regimens (women > men)	Effect of weight gain and cardiometabolic parameters Resistance and viral load resuppressing rates
ARTIST	South Africa TLD efficacy in second line (single-arm study)	72 weeks	Viral load suppression: 75.4%	
D2EFT	Multicountry (14 countries in Africa, Asia and the Americas) DTG + DRV/r versus TLD versus DRV/r + two NRTIs in second line (RCT)	No data published yet	Recruitment complete	Effects on weight gain, COVID-19 impact, pregnancy outcomes, pharmacokinetics and HIVDR
DOlPHIN2*	DTG versus EFV: efficacy and safety among pregnant and breastfeeding women initiating ART during third trimester (open label)	96 weeks	Viral load suppression DTG : 74% Viral load suppression EFV: 50%	Effect of weight gain and cardiometabolic parameters
NADIA	Multicountry (Kenya, Uganda and Zimbabwe) DTG versus DRV/r and TDF versus AZT in second-line treatment (non-inferiority)	96 weeks	Viral load suppression: DTG: 89.9% Viral load suppression DRV/r: 86.9% Viral load suppression TDF: 91.8% Viral load suppression AZT: 84.8%	
NAMSAL*	Cameroon DTG versus EFV 400 mg: efficacy and safety among people living with HIV initiating ART (RCT)	144 weeks	DTG Viral load suppression 69% EFV400 Viral load suppression 62% Body weight gain or obesity women > men	Effect of weight gain and cardiometabolic parameters Resistance and viral load resuppressing rates
VESTED	Multicountry (nine countries in Africa, Asia and the Americas) TEE versus TED versus TAF-ED: efficacy and safety among pregnant women initiating ART at 14–28 weeks of gestation (open label)	50 weeks (postpartum)	Viral failure EFV (10.4%) Viral failure DTG (4.1–5.1%) Adverse event risk benefit (trade-offs) TAF-ED versus TED (0.64) TAF-ED versus TLE (0.28) TLD versus EFV (0.41)	Effect of weight gain and cardiometabolic parameters RBC folate
VISEND	Zambia TAF-ED or TLD efficacy among people living with HIV with viral load <1000 copies/ml TLD versus TAF-ED versus AZT/3TC-PI: efficacy among people living with HIV for whom NNRTIs are failing with viral load >1000 copies/ml (RCT)	96 weeks	Viral load suppression TAF-ED: 88% Viral load suppression TLD: 82% Viral load suppression PI: 76% Weight gain among women on TAF-ED	Effect of weight gain and cardiometabolic parameters Resistance and viral load resuppressing rates Pregnancy outcomes and safety

* ADVANCE, DOLPHIN-2and NAMSAL were extended until 2022 to investigate how DTG and TAF affect weight gain and cardiometabolic parameters and were collectively renamed as the TRIO study.

Observational studies

Research priority and topic	ACTG-5381* (Hakim study)	AFRICOS	DISCO	DO REAL	EMEDT	Tsepamo
Safety of DTG and/or TAF periconception and pregnancy						●
Changes in body weight and cardiometabolic risk with DTG combined with TAF or TDF	●	●	●	●		
Outcomes from switching from TLE to TLD without viral load	●	●	●	●	●	
Recycling TDF with TLD in the presence of TDF resistance	●	●	●	●	●	
Viral outcomes for people retained on DTG despite unsuppressed viral loads						
Safety and efficacy of DTG and/or TAF among adolescents	●					
Post hoc analysis and substudies	●	●	●		●	

* ACTG5381 (Hakim study) is a multi-arm study. The evaluated arms include the participants switching to TLD from a virally suppressive first-line NNRTI-based regimen (group 1b) and for those initiating ART with TLD (group 4).



Observational studies

Study	Study design	Current status (Q1 2022)	Major outcomes	Sub studies or post hoc analysis
ACTG 5381* **(Hakim study)**	Multicountry (Haiti, Kenya, Malawi, South Africa, Uganda and Zimbabwe) TLD transition efficacy and safety in first and second line (multiarm – prospective cohort)	24 weeks (NNRTI viral load suppressed and ART initiators arms)	Viral load suppression 99% (NNRTI viral load suppressed arm) Viral load suppression 90% (ART initiators arm)	DTG mutations Drug interactions with TB medications
AFRICOS	Multicountry (Kenya, Nigeria, Uganda and United Republic of Tanzania) TLD transition efficacy in first and second line (prospective cohort)	96 weeks	Viral load suppression 94% TLD transition slower among women 1.77 times increased risk weight gain No impact on hyperglycaemia	TLD uptake by gender Weight gain and hyperglycaemia
EMEDT	Malawi TLD transition efficacy (blind transitioning) (prospective cohort with retrospective viral load assessment)	72 weeks	Viral load suppression 93%	Long-term efficacy if elevated viral load ± TDF/3TC resistance
DISCO	Uganda and South Africa TLD transition efficacy in first line (NNRTI users) (prospective cohort)	48 weeks (Uganda sites)	Viral load suppression 92% 2% TLD discontinuation rate	Weight gain/BMI
DO REAL	Lesotho TLD efficacy with viral load <1000 copies/ml transitioning to TLD DTG optimized background as second line with viral load >1000 copies/ml (prospective cohort)	16 weeks	Viral load suppression 98%	Impact of transitioning to DTG on self-reported mental and physical health
Tsepamo	Botswana DTG versus non-DTG birth outcome surveillance (neural tube defects and birth outcomes)	144 weeks (September 2021)	DTG neural tube defect risk rate: 0.13% Prevalence difference (DTG versus non-DTG regimens): 0.04%	

* ACTG5381 (Hakim study) is a multi-arm study. The evaluated arms include those participants switching to TLD from a virally suppressive first-line NNRTI-based regimen (group 1b) and for those initiating ART with TLD (group 4).

Clinical trials (timeline for new evidence)

Study	Q1 2022	Q2 2022	Q3 2022	Q4 2022
ADVANCE * (192 weeks)		●		
ARTIST (96 weeks)				●
D2EFT (24 weeks)			●	
DOlPHIN2* (96 weeks)			●	
NADIA (96 weeks)	●	Completed		
NAMSAL* (192 weeks)		●		
VESTED (50 weeks)	●	Completed		
VISEND (96 weeks)		●		

*ADVANCE, DOlPHIN2 and NAMSAL were extended until 2022 to investigate how DTG and TAF affect weight gain and cardiometabolic parameters and were collectively renamed as the TRIO study.

Observational studies (timeline for new evidence)

Study	Q1 2022	Q2 2022	Q3 2022	Q4 2022
ACTG-5381* (Hakim study) (96 weeks)				●
AFRICOS (144 weeks)	●			
DISCO (96 weeks)			●	
DO REAL (96 weeks)				●
EMEDT (72 weeks)	●			
Tsepamo (192 weeks)		●		

*ADVANCE, DOlPHIN2 and NAMSAL were extended until 2022 to investigate how DTG and TAF affect weight gain and cardiometabolic parameters and were collectively renamed as the TRIO study.

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