World Health Organization

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

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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).

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.