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Tenofovir, Lamivudine, and Dolutegravir (TLD) Transition

General Information for Clients, Clinicians, Counselors, and other Service Providers

BACKGROUND

The backbone for HIV treatment has been the combination of at least two nucleoside (and nucleotide) reverse transcriptase inhibitors (NRTIs) such as tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and emtricitabine (FTC) and a third drug from any of the following medication groups:

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs)
  - nevirapine and efavirenz (EFV)
- Protease inhibitors (PIs)
  - lopinavir/ritonavir (LPV/r)
  - atazanavir
- Integrase strand transfer inhibitors (INSTIs)
  - dolutegravir (DTG)
  - raltegravir (RAL)

This combination has been the source of success of antiretroviral treatment, because the combination of three drugs allows three options for attacking and defeating the virus.

CURRENT FIRST-LINE REGIMENS IN MOST COUNTRIES

The current first-line regimen for HIV treatment in many countries is the combination of TDF, 3TC, and EFV; that is, two NRTIs and one NNRTI. This regimen is generally referred to as **TLE** because it has **T** (TDF), **L** (lamivudine, also known as 3TC) and **E** (efavirenz).

WHAT IS TLD TRANSITION?

The World Health Organization (WHO) has recommended that all countries using **TLE** as a first-line regimen should transition all eligible clients to a different combination, which contains dolutegravir (DTG) in place of efavirenz—that is, TLD, with the "D" standing for dolutegravir. This recommended regimen is a combination of two NRTIs and one INSTI. **TLD** is a fixed-dose combination of TDF 300 mg, 3TC 300 mg, and DTG 50 mg. TLD is also recommended for use as a second-line regimen for patients failing on efavirenz- or nevirapine-containing regimens or for those failing a non-DTG-containing first-line regimen.

WHY TRANSITION FROM TLE TO TLD?

TLD is superior to TLE in several ways:

- TLD is more potent, suppressing viral load more quickly compared to EFV-based regimens. Eighty-one percent of individuals who started with a DTG-based regimen presented a viral load below 50 copies/ml after 3 months of treatment, compared to 61% for those on an EFV-based regimen.[1]
- TLD is more durable, featuring a higher drug-resistance barrier compared to NNRTIs and older integrase inhibitors. Therefore, the risk of drug resistance and the need for early switch to the costlier and more complicated second-line regimens are much lower than with TLE.
- TLD is more convenient to take. It is a smaller tablet that is taken once per day.
- TLD is better tolerated with fewer side effects and lower overall incidence of adverse events (<5%) compared to EFV.[2]
- TLD is associated with fewer drug interactions. This means that compared to other regimens, it is easier to administer TLD with most commonly used medications.

Because TLD is better tolerated and has fewer side effects than TLE, treatment adherence and retention should be higher, especially if patients are properly educated and prepared. As a result, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), is supporting countries to accelerate their transition to TLD in the form of an affordable fixed-dose combination tablet.

[1]WHO. Dolutegravir (DTG) and the fixed dose combination of tenofovir/lamivudine/dolutegravir (TLD). Briefing Note, April 2018

[2]Fettiplace A, Stainsby C, Winston A, Givens N, Puccini S, Vannappagari V, et al. Psychiatric Symptoms in Patients Receiving Dolutegravir. J Acquir Immune Defic Syndr. 2017;74(4):423-431

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WHO IS ELIGIBLE FOR TLD TRANSITION?

Populations (both general and key populations) that are recommended to transition to TLD include:

- All newly diagnosed adults who need to be started on a first-line regimen and all adults currently on other first-line regimens* (e.g., patients on TLE as a first-line regimen).
- All newly diagnosed adolescents (≥10 years and ≥30 kg) who need to be started on a first-line regimen and all adolescents currently on other first-line regimens* (e.g., patients on TLE as a first-line regimen).
- Patients with treatment failure on first-line who need to be switched to second-line (since TLD is also recommended as a second-line regimen).
- Patients currently failing on an NNRTI-based first-line regimen or who have failed on an NNRTI-containing regimen in the past and are currently on a PI-based second-line regimen in programs that can confirm virologic suppression 3-6 months after transition to TLD.
- New WHO recommendations state that DTG is now the preferred first-line and second-line treatment for all populations, including pregnant women and women of child-bearing age. (See Special Considerations, below.)

HOW TO EDUCATE PATIENTS ABOUT TLD

- Take one pill, once a day, around the same time every day.
- The TLD tablet can be taken with or without food.
- After initiating TLD, patients should return to the clinic for a follow-up visit in two weeks, but they may return before then if they have any problems.

POTENTIAL SIDE EFFECTS OF TLD

- Insomnia
- Headache
- Agitation
- Nausea
- Diarrhea
- Skin rash (patients should contact their health care provider immediately if they develop a rash)

VIRAL LOAD MONITORING AND TLD TRANSITION

Viral load monitoring is an important component of TLD transition. Because access to viral load testing remains limited in many settings, programs must intensify efforts to improve access among all eligible clients. Some country programs may recommend ensuring that patients are virally suppressed on the current regimen before transitioning them to TLD, but the limited availability of viral load testing should not be a barrier in transitioning patients to TLD. There is evidence that even in the presence of multiple drug resistance mutations after the use of an NRTI, a DTG-containing regimen may still be able to effectively suppress the virus.

**Patients on other first-line regimens such as the following should also be transitioned to TLD: (ABC/3TC/NVP), (AZT/3TC/NVP), (AZT/3TC + EFV), (TDF/3TC/EFV), and (TDF/3TC + NVP).*

SPECIAL CONSIDERATIONS

1. Use of TLD by women of child-bearing age	In July 2019, WHO announced that DTG is safe for women of child-bearing age. Therefore, TLD is now the preferred first-line and second-line regimen for all populations, including pregnant women and those of child-bearing age.
	The recommendation also stresses the importance of providing information and options to help women make an informed choice, irrespective of the treatment regimen.
	Exposure to DTG around the time of conception and during the first 8 weeks of pregnancy was previously thought to be associated with an increased risk of neural tube defects in the fetus. This was based on initial reports from a study in Botswana. However, new data from two large clinical trials comparing the efficacy and safety of DTG and EFV in Africa have now expanded the evidence base. The risks of neural tube defects are significantly lower than what the initial studies may have suggested.
2. Patients with HIV/tuberculosis (TB) coinfection	One of the anti-TB medications, rifampicin, lowers the level of DTG when both are taken together.
	Therefore, patients who have diagnosed TB will need to modify their DTG dose while they are taking rifampicin-containing anti-TB treatment.
	Patients with HIV/TB may take their usual dose of TLD (one tablet, once daily), but they need to add an additional dose of DTG 50 mg 12 hours after taking their TLD.
	It is important to tell patients that the additional dose of DTG must be taken 12 hours ***after*** their TLD, not at the same time (for example, take the TLD tablet in the morning and the DTG single tablet in the evening).
3. Warnings and Precautions	Previous hypersensitivity reaction to DTG
	Uncontrolled diabetes
	Renal impairment creatinine clearance <50 ml/min
	Liver impairment: ascites; albumin <2.8 g/dL; total bilirubin >50 mmol/L; encephalopathy

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LINKAGES is the largest global project dedicated to key populations—sex workers, men who have sex with men, people who inject drugs, and transgender people. The project is led by FHI 360 in partnership with IntraHealth International, Pact, and the University of North Carolina at Chapel Hill.