


Optimize

Considerations for the Introduction of TLD in National Programs: PEPFAR Guidance on Developing Clinical and Programmatic Recommendations

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ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ADR	Adverse Drug Reaction
AE	Adverse Event
APR	Antiretroviral Pregnancy Register
ART	Antiretroviral Therapy
ARV	Antiretroviral Drug
AZT	Zidovudine
bPI	Boosted Protease Inhibitor
DNA	Deoxyribonucleic Acid
DSDM	Differentiated Service Delivery Model
DTG	Dolutegravir
EFV	Efavirenz
FDC	Fixed-Dose Combination
FP	Family Planning
FTC	Emtricitabine
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
IAS	International AIDS Society
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MMP	Multi-month Prescribing
MTCT	Mother to Child Transmission
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NTP	National Tuberculosis Program
NVP	Nevirapine
PEPFAR	U.S. President's Emergency Plan for AIDS Relief
PI	Protease Inhibitor
PLHIV	People Living with HIV
Q&A	Question and Answer
RTV	Ritonavir
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TLD	Tenofovir Disoproxil Fumarate, Lamivudine and Dolutegravir
TLE	Tenofovir Disoproxil Fumarate, Lamivudine and Efavirenz
USAID	United States Agency for International Development
VL	Viral Load
WHO	World Health Organization

INTRODUCTION

This document is intended to support country programs to develop clinical guidance and implementation plans for the introduction of the fixed-dose combination (FDC) tablet of tenofovir (TDF), lamivudine (3TC) and dolutegravir (DTG), (TLD). The primary audiences for this document are HIV program managers, technical working group members, national HIV guideline committees and other stakeholders contributing to the development of national normative guidance for HIV treatment and planning for the rollout of TLD.

DTG-based regimens have demonstrated superiority over both efavirenz (EFV) and protease inhibitor (PI) based regimens^{i, ii} with better tolerability and fewer discontinuations, rapid suppression of viral load (VL), and a high genetic barrier to resistance. This clinical evidence combined with the availability of a convenient and cost-saving FDC tablet that can be used in adolescent and adult populations makes it an optimal regimen for patients on first-line antiretroviral therapy (ART).

Recommendations on the use of TLD are available from the World Health Organization (WHO) and President's Emergency Plan for AIDS Relief (PEPFAR). However, planning for the rollout of TLD includes several decisions at the country level, taking into consideration clinical risks and benefits as well as practical programmatic issues. Many of these decisions will be country-specific and some may change over time as new evidence becomes available. In the interim, this document is intended to inform some of the practical decisions that countries should consider when rolling out TLD under PEPFAR guidance.

NORMATIVE GUIDANCE

WHO Guidance

In the WHO 2016 Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection, the combination of TDF + 3TC (or emtricitabine (FTC)) + DTG was introduced as an alternative first-line ART regimen for adults, and TDF or abacavir (ABC) + 3TC (or FTC) + DTG as an alternative first-line for adolescents. The WHO guidelines acknowledged the clinical and programmatic advantages of DTG including: improved tolerability, lower potential for drug interactions, shorter median time to viral suppression and a higher genetic barrier to resistanceⁱⁱⁱ. At the time of publication however, the safety and efficacy of DTG during pregnancy and among tuberculosis (TB)/HIV co-infected patients using rifampicin had not yet been established. Since then, additional evidence to support the use of DTG in pregnancy and in patients on rifampicin-containing TB treatment has become available^{iv,v,vi}.

In July 2017, the WHO published a technical update on the Transition to New Antiretroviral Drugs in HIV Programmes: Clinical and Programmatic Considerations^{vii}, providing advice on a phased approach to transitioning to new HIV treatment regimens and noted that DTG in particular is a strategically preferred choice for drug optimization in the longer term. Following the announcement of the FDC, TLD, at a price of US \$75 per patient, per year in September 2017^{viii}, the WHO published a Questions and Answers (Q&A) on Transition to the Use of DTG with a summary of current WHO guidance as well as additional information about new evidence on the safety and pharmacokinetics of DTG during pregnancy^{ix}.

In July 2018, the WHO released updated interim guidance on first- and second-line ARV regimens including DTG-based regimens as a preferred first-line ARV for adults, adolescents and all infants and children with approved DTG dosing. However, given concern about the potential increased risk of birth defects, the WHO included a note of caution around the use of DTG during the periconception period in adolescent girls and women of childbearing potential who are not using reliable and consistent contraception. WHO also recommends that programs adopt a woman-centred approach that enables women to make an informed choice after all risks have been explained. (Box 1) (See next section August 2018 Update on the Potential Risk of Increased Birth Defects with Use of DTG Prior to Conception).

Box 1: A Woman-Centred Approach

Woman-centred health services involve an approach to health care that consciously adopts the perspectives of women and their families and communities. This means that health services see women as active participants in and beneficiaries of trusted health systems that respond to women's needs, rights and preferences in humane and holistic ways. Care is provided in ways that respect women's autonomy in decision-making about their health, and services must provide information and options to enable women to make informed choices. The needs and perspectives of women, their families and communities are central to providing care and to designing and implementing programmes and services. A woman-centred approach is underpinned by two guiding principles: promoting human rights and promoting gender equality.

Additionally, the 2018 WHO update includes a recommendation to use DTG in combination with an optimized nucleoside reverse transcriptase inhibitor (NRTI) backbone as a preferred second-line option if failing a non-DTG containing first-line. Lastly, TDF and 3TC (FTC) continues to be recommended as a preferred NRTI backbone for HIV post-exposure prophylaxis (PEP) with DTG recommended as a preferred third drug. Therefore, TLD may be used for PEP in adolescents and adults. The note of caution for using DTG in women and adolescent girls of childbearing potential extends to the use of DTG in second-line and as PEP^x.

PEPFAR Recommendations

PEPFAR now recommends DTG-containing regimens as the preferred first-line antiretroviral therapy due to its superior efficacy, tolerability and higher threshold for resistance compared to EFV-containing regimens. The fixed-dose combination tablet of TLD is now available at a cost affordable to low- and middle-income countries; prices are expected to further decrease as generic manufacturers increase production.

PEPFAR recommends that programs rapidly transition to the use of TLD as the preferred option for ART. However, PEPFAR also advises that transition planning should consider existing antiretroviral (ARV) stocks and minimize wastage of legacy first-line ART regimens. Populations that are recommended to transition to TLD include:

- All new adolescent (≥ 10 years and ≥ 30 kg) and adult first-line populations.
- All existing adolescent (≥ 10 years and ≥ 30 kg) and adult first-line populations.
- Patients currently failing a non-nucleoside reverse transcriptase (NNRTI)-based first-line regimen, or have failed an NNRTI-containing regimen in the past and are currently on a protease-inhibitor (PI)-based second-line regimen in programs that can confirm virologic suppression 3-6 months after transition to TLD.

Additionally, programs should also plan to include:

- Adults and adolescents receiving treatment for tuberculosis with rifampicin-containing regimens, with an additional 50 mg dose of DTG added 12 hours after TLD is taken, for the duration of TB treatment.

PEPFAR also recommends that pregnant and breastfeeding women should be included in plans to transition to TLD. Given the potential risk of increased birth defects that was reported in May 2018, PEPFAR recommends that TLD counseling on the potential benefits and risks of the drug, including non-nucleoside (NNRTI) resistance, drug availability, and maternal and infant toxicity profile be provided, along with access to voluntary family planning (FP) services, to women of reproductive potential to help them make informed decisions about their ARV regimen and preferences for FP.

Pediatric patients (< 30kg) are not expected to be included in the initial rollout of TLD. However, WHO recommends DTG as part of preferred regimens for children < 30kg as approved dosing and formulations become available. WHO guidance permits use of DTG 50mg in children down to 25kg body weight and anticipates being able to use DTG 50mg in children down to 20kg.

AUGUST 2018 UPDATE ON POTENTIAL RISK OF INCREASED BIRTH DEFECTS WITH USE OF DTG IN THE PERICONCEPTION PERIOD

In May 2018, a potential safety issue affecting women living with HIV using DTG at the time of conception was identified from an ongoing observational study in Botswana; additional data became available in July 2018. Four cases of neural tube defects (NTDs) were reported in infants born to 596 (0.67%) women who started DTG around the time of conception. In comparison, 86 NTDs were identified among 89,064 (0.1%) deliveries in women taking other antiretroviral regimens (not containing DTG) at the time of conception.

At this time, it is unknown if these findings from Botswana indicate a true increased risk of NTDs with periconception exposure to DTG. Given the low incidence of NTDs, a larger number of exposures is needed to definitively determine the level of risk.

On May 18, 2018, WHO released a statement advising that ART for women of childbearing potential, including pregnant women, should be based on drugs with adequate efficacy and safety data. For example, EFV-based regimens are safe and effective first-line regimens that may be provided to women of childbearing potential, once the risks and benefits of different ARV options have been explained and understood. Programs should also strengthen the integration of FP services within ART programs for women and adolescent girls of childbearing potential and adopt a “woman-centred approach” that provides information and options to women to make informed decisions about their health.^{xi}

Over one thousand ongoing pregnancies among women in the Botswana study who initiated DTG before conception continue to be monitored, and data on these additional birth outcomes will become

available by March 2019. Additional data from other countries using DTG-based regimens in clinical trials or observational studies is also anticipated to contribute to the understanding of the potential risk of DTG-use among women of childbearing potential. These data will provide more conclusive evidence to update global recommendations on how DTG should be used in women of childbearing potential. In the meantime, as evidence emerges, decision-making about the choice of ART regimen for women of childbearing potential will need to balance the potential risks against the potential benefits.

COUNTRY IMPLEMENTATION PLANNING

When planning for the rollout of TLD, four key issues that programs should take into consideration are: the specific recommendations for use of TLD in women of childbearing potential; laboratory capacity for VL monitoring; service delivery models in use, and; supply planning during the transition to TLD. Consideration of these crosscutting issues will support the development of a comprehensive implementation plan and inform the development of guidance for health care workers.

Women of childbearing potential

As of July 2018, four infants with NTDs were identified among 596 births to women initiated on DTG-containing regimens around the time of conception. This represents an incidence of 0.67% compared to a background rate of 0.1% in women who were taking ARV regimens that did not include DTG. As the neural tube forms and closes within the first month of pregnancy, data from the Botswana study suggests that the risk of neural tube defect is limited to women who begin TLD before conception or shortly after; often before a woman is aware of pregnancy and usually well before she presents for antenatal care.

It is important to note that there have been no other signals of increased risk of NTDs or other adverse birth outcomes with exposure to DTG in early animal studies, clinical trials or birth registries such as the Antiretroviral Pregnancy Registry (APR) though there have been relatively few reported exposures to date. No increased risks of adverse birth outcomes have been identified in over 1729 women in Botswana who started on DTG-containing regimens when already pregnant^{xii}. Additional data from over 1000 birth outcomes with preconception exposure to DTG should become available from Botswana by mid-2019. This will enable further clarification on the level of increased risk of adverse birth outcomes with preconception or early exposure to DTG in pregnancy.

When making a decision about the use of TLD in women of childbearing potential, the overall approach should respond to women's needs, rights and preferences. Community perspectives in particular should be included in the decision-making process and clear information about the known risk and benefits of DTG should be communicated to enable informed choice with the understanding that as new data become available about preconception exposure to DTG, recommendations on the use of TLD in women of childbearing potential may change. Regardless of the initial approach adopted to introduce TLD, messaging to the community and health care workers should convey that there is currently uncertainty on the degree of risk and that there may be future changes in guidance. Counseling messages for patients will also need to be carefully communicated to avoid misconceptions about toxicity related to TLD or ARVs in general which may result in undue apprehension about initiating or remaining on treatment.

When rolling out TLD, PEPFAR recommends transition for adolescents and adults using a woman-centred approach. This includes providing counseling for women about potential risks and benefits of

available ARV regimen options and support for informed decision-making. Additionally, access to family planning services, including access to or referrals for contraception should be made available for women who do not desire pregnancy and wish to use FP. Women of reproductive potential who are considering TLD/DTG use and do not currently want to be pregnant should be asked about their fertility intentions and counseled on FP options, including voluntary contraception. Women of reproductive potential who choose to use TLD/DTG without concurrent use of contraception should be allowed to do so, if they have been appropriately counseled and understand the possible risks associated with periconceptual exposure to DTG. In order to balance the safety concerns regarding TLD and ensure that women's rights to voluntary FP are respected, countries may consider requiring women of reproductive potential who wish to use TLD and are not using contraception to sign consent forms that acknowledge that they have been counseled on possible side effects of TLD and understand the risks.^{xiii}

TLD roll out efforts need to be responsive to potential challenges associated with the provision of high quality integrated FP services; including tailored interpersonal counseling; capacity to provide, refill and/or remove contraceptive methods; implement appropriate quality assurance monitoring; program documentation and contraceptive stock management. (Box 2) For additional considerations regarding the rollout of TLD and women of child bearing potential, please see the International AIDS Society's 2018 brief, "Dolutegravir & Women of Childbearing Potential".^{xiv}

Box 2: Key programming considerations for introduction or scale-up of FP services in ART settings

- ART providers should be trained on FP service provision and receive supportive supervision on activities including client-centered counseling, data collection and reporting, stock management and provision (and removal) of short- and long-acting contraceptive methods.
 - ART settings should be equipped to offer appropriate FP services, including private spaces for counseling, screening and method provision as well as having necessary instruments and medical equipment.
 - If ART providers are not able to offer high-quality family planning services on demand, they should consider other options to support their clients such as; routinely using the services of a dedicated FP provider to offer FP on site or providing referrals to sites that offer comprehensive FP services.
 - Providers should have capacity to track essential FP indicators and contraceptive stock information for national and sub-national data collection.
 - Contraceptive commodity needs of PLHIV in ART sites should be quantified in national FP forecasting efforts to ensure appropriate ordering and distribution of commodities.
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Laboratory capacity: Viral load monitoring

Countries are in different stages of scaling up access to routine VL monitoring. Access to VL testing varies between countries and even within programs. Some programs may recommend ensuring viral suppression prior to substitution. However, limited availability of VL should not be a barrier in transitioning patients to TLD.

The rationale for use of VL to ensure viral suppression prior to substitution is that patients with viral suppression are less likely to have ARV drug resistance mutations, which has been a growing concern in countries where NNRTI-based first-line regimens are widely used^{xv}. The substitution of DTG for EFV in the context of viral suppression reduces the concern about the new regimen being fully active when maintaining the same NRTI backbone (e.g. substituting TLE for TLD).

However, patients on TLE who have ongoing viral replication (i.e. not virally suppressed) are likely to have the M184 and K103N mutations conferring resistance to 3TC (and FTC) and NNRTIs respectively. This would leave TDF as the only fully active drug. With prolonged viremia on TLE, K65R, which confers four-fold resistance to TDF, may also emerge. In these cases, transitioning from TLE to TLD in effect may result in transitioning to a regimen where DTG is the only fully active drug and the efficacy of the new regimen could potentially be compromised.

The risk in taking this approach is the emergence of further drug resistance. Although DTG has a higher genetic barrier to resistance, our current understanding of DTG remains limited and resistance to DTG has been identified in only a few cases thus far^{xvi-xvii}.

The rationale for not requiring VL prior to substitution is that there is evidence that even in the presence of multiple drug resistance mutations, NRTIs may maintain some antiviral ability^{xviii,xix}. In combination with a potent drug such as DTG, patients may still be able to effectively suppress the virus, even if they may have developed high levels of NRTI resistance. The DAWNING^{xx,xxi} study demonstrated the superiority of DTG-based regimens compared to LPV-based regimens in patients failing an NNRTI-containing first-line, though genotyping was used to ensure that at least one active NRTI was included in the new second-line regimen. However, given this evidence, it has been suggested that in patients failing first-line with TLE, both TDF and 3TC may be maintained with the addition of DTG.

Additional evidence is needed to determine whether the same NRTI backbone can be maintained if switching from TLE to TLD in viremic patients. In settings where patients may be transitioned to TLD without demonstrating evidence of VL suppression (if VL prior to substitution was not available, or the patient was viremic), PEPFAR recommends that these patients should be prioritized for VL three to six months after making the switch.

Service delivery: Differentiated models of care

Historically, the majority of ART services including testing, initiation, follow-up and dispensing have been delivered at health facilities. However, differentiated service delivery models (DSDMs) are now

being introduced as a client-centered approach to adapt HIV services across the cascade of ART care and treatment to both better serve the needs of people living with HIV (PLHIV) as well as reduce burden on overstretched health systems. DSDMs now include a variety of services such as decreased frequency of clinical visits, provision of multi-month prescribing (MMP), and non-facility-based provision of HIV testing, ART initiation and ART distribution for stable patients.

The introduction of TLD should not be a barrier or delay the scale-up of DSDM. If differentiated ART delivery models are in use for stable clients, additional guidance may be needed to ensure appropriate clinical management following drug substitution as well as to support supply chain management to ensure that adequate stocks of new ARVs are available to provide MMP. Consideration should also be given to the use of different pack sizes, which may be used to support MMP including 30, 90 or 180-tablet pack sizes.

When making changes to a treatment regimen, more frequent clinical follow-up may be considered so patients are not experiencing challenges such as new adverse drug reactions that may compromise adherence. Additionally, the introduction of new ARVs have historically encountered supply chain challenges including stock-outs^{xxii}, and pharmacy managers should determine if stocks are sufficient to dispense MMP to the number of patients anticipated to be transitioned to TLD.

A requirement for more frequent clinical follow-up or dispensing of limited supplies of ARVs may discourage patients from transitioning to TLD, overload already congested health facilities, or delay the scale-up of TLD. If this is a concern, alternative guidance could be considered such as advising patients that they should return to the clinic sooner only if they have trouble, or planning for follow-up by phone, text message or home visits.

Increasingly, HIV care and treatment is being delivered outside of facility settings, and it is essential that any regimen changes be communicated at all points where ART care and delivery are provided. This should be done through sensitization of lay counselors, community health workers and other non-facility-based health workers.

Phase-in and supply planning

At the program level, there are scenarios where multiple implementation options may be acceptable. In rolling out TLD, countries are advised to take a phased approach to ensure supplies are available and to avoid wastage of existing stocks. Programs developing a transition plan may choose to phase-in TLD geographically, by sub-population, or a mixture of both, based on what is most appropriate for the country, including decisions around the use of TLD in adolescents and women of childbearing potential.

In programs where the majority of first-line patients will be transitioned to TLD, the decision to continue patients who are currently stable on a first-line regimen of TDF/3TC/EFV (TLE), or transition them to TLD are both clinically acceptable options. While both are clinically acceptable, PEPFAR recommends transition to TLD for the advantages listed earlier in the document. However, in programs that have large stocks of TLE, a practical decision may be to delay transition of stable patients on TLE to avoid wasting stock and previous investment; prioritizing specific sub-populations

for transition to TLD until existing stocks of TLE are consumed. Larger TLE stocks will also need to be maintained in programs if adolescents and women of childbearing potential will not be eligible for TLD.

If prioritizing sub-populations for the rollout of TLD, it is important that clear and quantifiable definitions to inform forecasting, quantification and procurement be established. Clear and quantifiable definitions are also important to enable health care workers to easily determine eligibility for TLD in different patient populations. This includes identification of women of childbearing potential who will need to be appropriately counseled on risks and benefits of TLD- or other DTG containing regimens in order to make an informed choice about ART and FP use.

HEALTHCARE WORKER GUIDANCE

In public health settings where decentralization and task shifting are key to scaling up ART, simple and clear guidance is required for health care workers to provide appropriate care to different categories of patients that are also aligned with laboratory capacity, DSDM and supply planning during the transition period.

The subsequent sections in this document include specific considerations to support country implementation planning and the development of clinical guidance for various patient groups. These groups are organized in the following categories: 1) Patients starting TLD for first-line, 2) Patients starting TLD for second-line, 3) Managing patients on TLD, and 4) Special populations. As resources, recommendations and phase-in plans may vary across countries, users of this document are encouraged to refer to those sections that are most applicable.

PATIENTS STARTING TLD FOR FIRST-LINE

- Initiating patients
- Patients on TLE and doing well
- Patients experiencing EFV-related ADRs on TLE
- Patients on legacy regimens

STARTING PATIENTS ON TLD FOR SECOND-LINE

- Patients failing first-line and needing to switch to second-line
- Patients already on second-line with a boosted PI

MANAGEMENT OF PATIENTS ON TLD

- Patients with TB-HIV co-infection
- Patients needing alternative regimens
- Patients with treatment failure on TLD

CONSIDERATIONS FOR SPECIAL POPULATIONS

- Pregnant women
- Breastfeeding women
- Adolescents
- Migrants

1. Considerations and Clinical Guidance for Patients Starting TLD For First-Line

A. Initiating Patients

With the introduction of Treat All, many patients may be started that were previously not eligible for ART. Patients who are feeling well may be less tolerant of drug-related side effects so the tolerability and convenience of TLD may be more acceptable compared to other regimens if use of DTG is not contraindicated. In settings where Treat All is also being introduced, quantification for TLD should account for the anticipated influx of previously “Pre-ART” patients that may increase the number of patients that are initiating ART.

When patients have had prior ART exposure and are returning to care, there may be concerns about the development of NNRTI HIV drug resistance (HIVDR) and, in some settings, a non-NNRTI-containing first-line may be recommended for this group of patients. TLD provides an advantage in that it will still likely be an active regimen even if a patient has had prior exposure to ARVs and NNRTI HIVDR.

- No change in laboratory monitoring or follow-up schedule is required for patients initiated on TLD. In some settings, it may be recommended that patients starting a TDF-based regimen have a baseline creatinine test and for patients at risk of renal disease a baseline and follow-up creatinine monitoring.
- Patients initiating first-line may be started on TLD regardless of prior ARV exposure.

B. Patients on TLE and Doing Well

The majority of adolescents and adults are currently on TLE for first-line due to its affordability and availability in a convenient once-daily FDC. With the demonstrated superiority of DTG-containing regimens, including improved tolerability and higher genetic barrier to resistance, as well as the programmatic advantages of supply chain simplification and cost savings of TLD, patients who are currently stable on TLE and have no contraindication to use of DTG may also be transitioned to TLD. PEPFAR notes that those doing well on TLE should be switched to TLD without need for VL or other pre-conditions. At a country level, the clinical and program context should be taken into consideration when making recommendations about substitution with TLD in patients who are currently stable on TLE including:

- Recommendation for use of VL before substitution;
- Implementation of differentiated service delivery models

Clinical guidance for health care workers:

- If evidence of VL suppression is a prerequisite for transition to TLD, guidance should be provided regarding:
 - The VL threshold at which substitution may be made.

- The acceptable duration of time since the last suppressed VL prior to substitution with TLD.
- Management of patients who do not have a VL below the threshold for substitution should be developed. This may include determining if patients should still be transitioned to TLD, or if patients should follow the current algorithm for management of patients with VL > 1,000 cop/ml.
- If VL testing to confirm suppression is not feasible prior to transition to TLD, guidance should be provided regarding:
 - If patients should be assessed for stability using clinical and immunologic criteria prior to substitution or if patients may be transitioned without such an assessment.
 - How and when patients should be monitored following transition if VL was unknown or not suppressed prior to transition.
- In settings where spacing of clinical follow-up and/or MMP is being implemented, guidance should be provided on:
 - How and when patients should be followed-up after transitioning to TLD.
 - The number of months of supply of TLD that may be provided to stable patients.

C. Patients experiencing EFV-related Adverse Drug Reactions (ADRs) on TLE

In programs where patients with EFV-related ADRs are initially prioritized for transition to TLD, it may be necessary to establish clear criteria to define which patients are eligible for transition. Over 50% of patients report EFV-related ADRs, particularly neuropsychiatric side effects, when starting EFV-containing regimens^{xxiii}. Alternatives for patients intolerant to EFV previously included substitution with nevirapine (NVP) or a boosted protease inhibitor (bPI) which add the inconvenience of twice-daily dosing and/or increased pill burden; and evidence demonstrates that substitution for EFV intolerance occurs infrequently^{xxiv}. As the introduction of TLD offers a convenient and well-tolerated alternative, substitution with TLD for EFV-related ADRs may be seen as more acceptable for both health care workers and patients, lowering the threshold of severity that is deemed appropriate for drug substitution. As TLD may be a more acceptable option for patients experiencing EFV-related ADRs, when quantifying the need for this sub-population historical rates of drug substitution for EFV-related may underestimate rates of substitution with TLD. (For patients with contraindication to TDF, see section below on Management of Patients on TLD, Patients needing alternative regimens.)

Clinical guidance for health care workers:

- Programs choosing to prioritize patients experiencing EFV-related ADRs for TLD should define types of drug reactions and the severity at which TLD should be substituted for TLE.

D. Patients on legacy regimens

While most programs have transitioned the majority of first-line adolescent and adult patient populations to TLE, there may still be significant numbers remaining on legacy regimens such as zidovudine (AZT), 3TC and nevirapine (NVP) (ZLN), or on alternative regimens such as TDF/3TC and NVP. For patients on legacy regimens with no contraindication to TDF or DTG, transitioning to TLD supports the simplification of supply chain with the phase-out of less optimal drugs such as NVP.

Programs with patients on alternative ARVs such as AZT and NVP should be transitioned to TLD as rapidly as programmatically feasible. For patients with contraindication to TDF, see section below on Management of Patients on TLD, Patients needing alternative regimens.

Clinical guidance for health care workers:

- Programs recommending transition to TLD for patients on legacy or alternative regimens should provide guidance on whether VL is needed prior to regimen substitution following the same principles as outlined in the considerations section for patients on TLE and doing well.
- Guidance should also be provided on when and how a change to NRTI backbone should be made (in patients using either AZT or abacavir (ABC)).

2.Considerations and Clinical Guidance for Starting Patients on TLD for Second-Line

The following section includes considerations for programs that recommend the use of TLD for second-line ART. PEPFAR encourages the use of TLD for second-line in patients failing an NNRTI-containing first-line regimen as well as those already receiving a bPI-containing second-line regimen in programs that can confirm viral suppression within three to six months following transition. However, there is currently limited evidence to support the approach of maintaining TDF/3TC (or FTC) for second-line after failure on a TDF-containing first-line regimen.

A. Patients failing first-line needing switch to second-line

The use of TLD in second-line would reduce the need for expensive bPIs as well as streamline the supply chain for programs. Additionally, available evidence demonstrates that non-adherence is a significant contributor to poor rates of viral suppression on bPI-based second-line^{xxv} and substitution of a more convenient and better-tolerated regimen may increase rates of second-line treatment success.

However, current evidence only demonstrates the effectiveness of TLD as second-line only after failure on an AZT-containing first-line or with the use of genotyping that can allow for the selection of at least one active NRTI. Thus, the benefits of recycling a TDF/3TC backbone with DTG for second-line after failure on TLE must be weighed against the risks of further selection of drug resistance, including emerging DTG resistance. In settings where confirmation of VL suppression is not readily accessible, this approach may not be advisable until additional evidence is available. Additionally, in programs where reporting differs for first- and second-line patients, consideration should be given on how patients on TLD for first-line will be distinguished from those on TLD for second-line.

Clinical guidance for health care workers:

- Guidance should be provided on whether TLD should be used for second-line ART after first-line failure using a TDF-containing NRTI backbone and/or after failure on first-line using an alternative NRTI backbone (e.g. AZT) and if monitoring approaches (i.e. requirement for viral suppression) are different between these groups.
- Guidance should be provided for patients who are switched to TLD for second-line on the frequency of VL monitoring, use of MMP as well as management for patients who do not achieve VL suppression on TLD after switch.

B. Patients already on second-line with a boosted PI

For patients with prior failure who have already been switched to a standard second-line regimen (generally with a bPI) consideration may also be given to substitution of TLD. As TLD is also better tolerated than a standard bPI-based regimen, patients may have better adherence and higher likelihood of achieving viral suppression on TLD as second-line, particularly after failure on an AZT-containing first-line

Clinical guidance for health care workers:

- If evidence of VL suppression is a prerequisite to transition patients currently on a PI-based regimen, guidance should be provided regarding:
 - The VL threshold at which substitution may be made with TLD; and
 - The acceptable duration of time since the last suppressed VL prior to substitution with TLD.
- Guidance should be provided on when patients on second-line who have been transitioned to TLD should receive their next VL as well as guidance on management if patients are not able to achieve or maintain viral suppression.

3. Considerations and Clinical Guidance for Management of Patients currently taking TLD

A. Patients with TB-HIV co-infection

Rifampicin is a potent inducer of cytochrome P450, which significantly decreases DTG levels. An effective strategy to overcome this interaction includes adding an additional dose of DTG 50 mg 12 hours following a patient's once-daily dose of TLD^{xxvi}. DTG 50 mg tablets must be available in the program to allow for this dose adjustment for the duration of TB treatment. PEPFAR recommends that the additional dose of DTG 50 mg be started early during TB treatment and end with the cessation of TB treatment for simplicity. However, the induction effect of rifampicin may continue even after stopping and programs may consider continuing DTG dose adjustment for up to two weeks after completion of TB treatment.

In settings where treatment for HIV-TB co-infection is not fully integrated, programs should ensure the national TB program (NTP) is aware of the dose adjustment required during TB treatment and that this recommendation is integrated into NTP protocols and guidance. Additionally, the need for DTG 50 mg tabs should be quantified and procured based on the number of patients on TLD that are anticipated to be diagnosed and started on TB treatment.

Additionally, concurrent use of hormonal contraceptives may interact with some TB drugs resulting in contraceptive failure. Further information may be found at:

<https://www.fhi360.org/sites/default/files/media/documents/resource-art-provider-reference-tool.pdf>

Women of childbearing potential who are using hormonal contraception and require TB treatment should be counseled about the potential risk of drug interaction and the use alternate forms of contraception for the duration of TB treatment if they do not desire pregnancy.

Clinical guidance for health care workers:

- Guidance should be provided to health care workers on prescribing additional DTG 50 mg to patients on TLD who are starting TB treatment and reinforce that the additional DTG 50 mg should be taken 12 hours after the dose of TLD. Emphasize that doubling the dose to DTG 100 mg once daily is not sufficient to overcome the interaction and the additional dose of DTG 50 mg must be given 12 hours after TLD is taken.
- Guidance should also be provided on alternative regimens for use during TB treatment if DTG 50mg tablets are not available.
- Health care workers should be reminded that women using hormonal contraception should be counseled about potential drug interactions with some TB drugs and supported to make an informed decision about the use of alternate methods of contraception if they do not desire pregnancy.

B. Patients needing alternative regimens

Though TLD is a well-tolerated regimen, observational studies in the US and Europe demonstrated a rate of up to 13% drug substitution due to DTG intolerance, though this was observed to be more common in patients on an ABC-containing NRTI backbone, in women and elderly patients^{xxvii, xxviii}. Observational studies from sub-Saharan Africa, though limited at present, have demonstrated a far lower rate of drug substitution due to DTG intolerance as compared with the 13% in the US and Europe^{xxix}. Given the relative lack of experience with the use of DTG in resource-limited settings, rates of treatment-limiting DTG-related ADRs are unknown in all populations. Programs may consider additional toxicity monitoring for treatment-limiting adverse events (AEs) when introducing TLD utilizing existing pharmacovigilance programs or developing new systems to enable reporting on ADRs.

Patients with contraindication to TDF will also require a regimen with an alternative NRTI-backbone. The WHO currently recommends AZT as an alternative for patients unable to tolerate TDF. While evidence is limited on the use of an AZT-containing NRTI backbone with DTG 50mg, this may be considered as an option though this would require the use of DTG 50 mg once daily with a twice-daily NRTI backbone. It should be noted that DTG is available as a fixed-dose combination tablet with ABC and 3TC (Triumeq™) and generic versions of ABC/3TC/DTG may become available in the future. However, they are anticipated to be significantly more expensive compared to TLD and there is concern about the risk of ABC hypersensitivity in programs where screening for HLA B*5701 is not available.

Though TLD is anticipated to be appropriate for the majority of adolescents and adults, alternative ARV regimens will continue to be needed. When choosing alternative regimens, programs should consider maintaining simplicity by opting for fewer choices to cover all clinical scenarios, which would allow for the complete phase-out of suboptimal drugs such as NVP. The anticipated demand for alternative ARVs should be communicated to clinicians, pharmacy staff and logistics departments to ensure alignment with available stock and ongoing procurement of alternative options

Clinical guidance for health care workers:

- Guidance should be provided on regimens for patients with intolerance to DTG and/or contraindications to TDF.
- If alternative ARVs (including single drugs) are to be phased out of use, guidance should be provided on how and what alternative regimen patients should be transitioned to if they are unable to take one or more of the components of TLD.

C. Patients with treatment failure on TLD

The current recommendation for the diagnosis of treatment failure was developed based on the assumption that patients have been on an NNRTI-based regimen and resistance may rapidly develop during ongoing replication in the presence of ARVs.

However, TLD is a more durable regimen and patients on TLD meeting the current criteria for defining treatment failure are more likely to have adherence challenges than resistance compared to those failing on NNRTI-containing regimens. Therefore, use of the current criteria for diagnosis of treatment failure requiring a switch to second-line with a bPI and at least one new NRTI may result in unnecessarily switching patients to a less tolerable and more expensive regimen with a higher pill burden. Programs should consider developing an alternative algorithm for the management of patients with viral failure on TLD taking into consideration the lower risk of emergent drug resistance on DTG-containing regimens.

Clinical guidance for health care workers:

- Guidance should be provided on the management of patients on TLD that do not achieve or maintain viral suppression including frequency of repeat VLs or use of other diagnostics.
- Criteria to define treatment failure requiring switch to second-line should be defined if different from criteria to define treatment failure on NNRTI-based regimens.

- Guidance should be provided on sequencing and the selection of the next regimen after a diagnosis of treatment failure on TLD is made.

4. Considerations and Clinical Guidance for Special Populations

A. Pregnant and breastfeeding women

Though there is concern about the potential increased risk of birth defects, specifically neural tube defects, with periconceptional exposure to DTG, there has thus far been no evidence of safety issues for women who are already pregnant and started on DTG-based regimens. The increasing evidence of the effectiveness and safety of DTG for maintaining maternal VL suppression and preventing mother to child transmission, as well as its improved tolerability, potency and ability to rapidly decrease VL offers additional advantages to decrease the risk of mother-to-child transmission (MTCT) of HIV.

Available data suggests there is no increased risk of adverse pregnancy or birth outcomes in pregnant women starting DTG-containing regimens compared to TLE. Therefore, for women who are already pregnant and initiated on a DTG-containing regimen, they may be maintained on their ART regimen with no change during pregnancy until delivery. In the postpartum period, DTG may need to be substituted with an alternative ARV according to national policy on use of TLD in women of childbearing potential.

However, though evidence on the use of DTG in women who are pregnant has thus far been reassuring, additional pregnancy surveillance is still warranted since evidence to date is still quite limited. Programs are encouraged to report data on pregnancy and birth outcomes for women on TLD or other ARV regimens to the Antiretroviral Pregnancy Registry (APR), a prospective, voluntary, ARV exposure study that requires registering patients exposed to ARVs and reporting data on fetal and neonatal outcomes^{xxx}.

Drug interactions should also be considered as many pregnant women are prescribed prenatal vitamins containing calcium (Ca) and iron (Fe), or medications that contain other polyvalent cations such as magnesium (Mg), or aluminum (Al) which can interact with DTG. TLD or other DTG-containing regimens can be administered simultaneously with supplements containing Ca and/or Fe if taken with food, however should otherwise be administered at least two hours before or six hours after any supplement. If other medications containing polyvalent cations such as Mg, Al or Zinc (Zn) are prescribed, TLD or other DTG-containing regimens should be given at least two hours before or six hours regardless of food intake.

Lastly, in pregnant women who are stable and have VL suppression on either TLE or TLD, the risks of disrupting adherence during the breastfeeding period due to a change in regimen must be considered.

Clinical guidance for health care workers:

- Programs should provide clear guidance on counseling women about the potential risk for NTDs if TLD was started prior to conception or early in pregnancy.

- Health care workers should be reminded to counsel women about managing potential drug interactions.

B. Adolescents

The improved tolerability, potency, convenience and high genetic barrier to resistance that is associated with TLD may also be an advantage for adolescents as this population remains one of the most challenged in achieving viral suppression. However, as interpretation of “adolescent” may vary, when specifying recommendations and quantifying for this population, providing an objective, age- and weight-based definition will support health care workers to identify eligible adolescent patients for TLD.

Clear and quantifiable definitions based on both age and weight of adolescent patients should be established to ensure accurate quantification and procurement of both TLD for adolescents ≥ 10 years and ≥ 30 kg, as well as the ongoing need for pediatric regimens.

Lastly, adolescents living with HIV (ALHIV) face significant barriers in accessing sexual reproductive health services. Therefore, they either may not disclose sexual activity, or may not be offered contraception, resulting in unintended pregnancies. Integration of FP services into ART programs offers an opportunity to increase access to contraception for all populations, including adolescents.

Clinical guidance for health care workers:

- Guidance should be provided on the age and weight at which adolescents should be initiated or transitioned to TLD.
- Guidance should also be provided on how and when patients on pediatric regimens should be transitioned to TLD, including patients on both ABC and AZT-containing regimens.
- Guidance should be provided on the use of TLD in adolescent girls post menarche in accordance with national recommendations on use of TLD in women of childbearing potential.
- Health care workers should be reminded to maintain a non-judgmental approach when offering SRH services to all adolescents

C. Migrants

In planning for the introduction of TLD, programs should address the impact of migration in developing both clinical guidance and programmatic decisions. Programs may also take into consideration the practice of MMP to ensure temporary migrants have access to a consistent regimen. However, in settings where MMP is not in practice or sufficient stocks of ARVs are not available, the program should decide on an alternative approach.

General guidance on provision of ART to migrant populations is available for further reference^{xxxi}. However, it is important that health care workers should understand that migration should not be used as a reason to deny treatment and be provided with guidance necessary to ensure the management of migrating patients is aligned to country supply planning. Health care workers should be encouraged to discuss intentions for migration with patients, including planning and scheduling for refill

appointments as well as preparation for scenarios when regimen substitution may be necessary. To support migrants' access to TLD, voluntary FP services should also be available to them, to ensure that women of reproductive potential have access to contraception if they chose to use it.

If MMP is provided for migrant populations, sufficient stocks of TLD will be required and guidance on the number of months of TLD that may be dispensed to migrant populations should be determined. When ongoing migration is anticipated in settings where TLD has been rolled out but adequate stocks for MMP prescribing are not available, programs may consider recommending that facilities maintain adequate stocks of TLE to dispense to migrant populations to avoid frequent shifts in regimen changes.

Clinical guidance for health care workers:

- Guidance should be provided to health care workers on the management of patients who may transfer to new facilities or migrate between regions that are in different stages of TLD introduction.
- Patients require counseling about the change in regimen and the likelihood of EFV-related side effects should they migrate to regions where TLD is not yet available and need to substitute their current regimen with TLE.

CONCLUSION

Though normative guidance is available for the rollout of TLD, at the implementation level practical decisions must be made for scenarios where multiple options exist or when sufficient evidence is not yet available to make a strong recommendation.

There are a number of considerations that decision-makers must take into account when developing national guidance that include both clinical evidence as well as practical programmatic realities. This includes:

- Balancing the timing of the rollout of TLD with the need to use existing stocks of legacy ARVs; however, PEPFAR recommends that patients on the suboptimal regimen of ZLN should be transitioned to TLD or another optimal regimen as soon as programmatically feasible.
- Women of reproductive potential who are considering TLD use require counseling on the potential benefits and risks of the drug, including non-nucleoside (NNRTI) resistance, drug availability, and maternal and infant toxicity profile to help them make informed decisions about their ARV regimen.
- Women of reproductive potential should be counseled about family planning options including voluntary use of contraception if they do not desire pregnancy.
- Developing a phase-in plan that may include geographic or regional rollout, rollout by sub-population, or a combination of both.
- If rolling out TLD by sub-population, using clear and quantifiable definitions to enable health care workers to easily identify patients eligible for TLD.
- Ensuring health care workers have guidance to appropriately manage different patient populations and clinical scenarios
- Providing sensitization on the transition to TLD throughout the health system and planning for TLD to be available at all points where ART delivery occurs.
- Updating or strengthening documentation systems to monitor transition to TLD and patient outcomes.

Careful planning at the country level is essential in realizing the clinical, programmatic and economic benefits of transitioning the majority of adolescent and adults living with HIV to TLD. Additional support for planning and implementation may be found online at the following sites:

- The USAID-funded OPTIMIZE website: <https://optimize.icap.columbia.edu>
- The Unitaid-funded CHAI website: <https://www.newhivdrugs.org/>

END NOTES

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