

Nevirapine Explainer May 2018

Background on nevirapine and HIV drug regimens

Note: This document refers to the HIV antiretroviral treatment of adults and adolescents living with HIV. Pediatric formulations and antiretroviral treatment regimens for infants and children are not discussed at length, due to the unique circumstances and considerations for the treatment of infants and children such as the use and availability of different antiretroviral drugs, doses, administration, and formulations (e.g. liquids, powders, and granules), and other factors as children grow older.

Nevirapine (NVP)-containing regimens have been on the list of recommended first-line antiretroviral treatment (ART) regimens¹ for adult patients living with HIV since the World Health Organization (WHO) began publishing HIV treatment guidelines in 2002. Prior to 2013, both NVP- and Efavirenz (EFV)-containing regimens were recommended as first-line treatment regimens for patients starting treatment; no regimen was identified as being preferred.

In 2013, the fixed-dose combination of Tenofovir-Lamivudine (or Emtricitabine, a structurally similar drug to lamivudine and used interchangeably)-Efavirenz (TLE or TEE) achieved status as a “preferred” first-line regimen, less on the basis of overall superior efficacy compared to NVP as on the convenience of once daily dosing in a fixed dose combination with Tenofovir. Regimens containing NVP and other EFV-containing regimens were recommended as an “alternative” first-line therapy if TLE/TEE could not be used. Patients unable to use an EFV-based regimen due to side effects or because of a contraindication such as severe mental illness were switched to a NVP-containing regimen. From a clinical perspective, individuals on a recommended preferred or alternative treatment regimen, including those containing NVP, who achieve viral load suppression, are not failing treatment and are considered stable on an effective regimen.

The WHO treatment recommendations for first-line treatment regimens are for patients newly starting treatment. For patients who started on NVP-containing regimens following global or country treatment guidelines (most before 2013) and who are doing well on treatment, there has been no global guidance to actively switch stable patients on NVP-containing regimens to TLE. In some countries, patients who were stable on NVP-containing regimens have continued their regimen and not switched to TLE. Some stable patients have also opted to stay on their NVP-containing regimens based on personal preference. Patients found to be failing NVP-containing

¹ A combination of HIV antiretroviral drugs are required for the treatment of HIV. These combination regimens typically consist of three drugs from at least two active antiretroviral drug classes that form the basis of antiretroviral therapy (ART) for effective HIV treatment. While NVP, EFV, and DTG have been the focus of current discussions, the two other recommended antiretroviral drugs used in combination with NVP, EFV, or DTG to complete the HIV treatment regimen have also changed through the years.

regimens as determined through viral load testing and clinical assessment² should be switched to a second-line treatment regimen, not an EFV-containing regimen. EFV would not be appropriate in these situations since there is broad cross-resistance between NVP and EFV, such that resistance to one drug often produces drug resistance to the other even without prior exposure.

In the most recent WHO treatment guidelines updates released in 2016, TLE remains the preferred first-line regimen for patients starting HIV treatment and NVP- and other EFV-containing regimens remain alternative first-line regimens. New regimens containing dolutegravir (DTG) and a lower dose of efavirenz (EFV400) were introduced as additional alternative first-line treatments in the 2016 WHO guidelines as well. However, the WHO advised countries that there was insufficient data related to the safety and efficacy of using DTG or EFV400 among pregnant and breastfeeding women as well as individuals receiving concurrent treatment for tuberculosis and HIV.

NVP has also been an important drug used in the prevention of maternal-to-child-transmission (PMTCT) algorithms. Early in the HIV response, a single dose of NVP (sd-NVP) was used for pregnant women in labor in combination with time-limited courses of other antiretroviral drugs during pregnancy. However, the use of sd-NVP in these algorithms is now obsolete as treatment priorities have shifted to treating all people living with HIV with lifelong antiretroviral therapy (ART). Importantly, however, the use of NVP syrup for infants born to HIV+ mothers continues to be strongly recommended to prevent the transmission of HIV from mother to child.

Since the release of the 2013 WHO Treatment guidelines, TLE and TEE have become the most commonly used fixed-dose combination tablets currently in use for first-line treatment regimens, with 78 percent of patients on first-line ART in low- and middle-income countries currently taking TLE or TEE. The current national HIV treatment guidelines for 23 PEPFAR countries³, published between 2015-2017, have adopted the use of TLE/TEE as a preferred first-line regimen. The use of NVP-containing regimens has decreased and is reflected in the sharp declines in PEPFAR procurement for NVP-containing formulations, which has now been halted per the COP 2018 guidance issued in January 2018. However, until other alternatives such as DTG becomes widely available in countries, a small amount of NVP-containing regimens will be needed as an alternative first-line option to prevent disruption or delay of treatment for the small numbers of patients who are unable to take TLE/TEE in accordance with the 2016 WHO treatment guidelines.

² Viral load testing measures the amount of HIV virus in the blood. It is the standard of care to measure response to HIV treatment and is being scaled up in PEPFAR countries. Prior to the availability of viral load testing, other measures such as CD4 count, which indicates the degree of immunodeficiency, and clinical outcomes were used to assess response to HIV treatment.

³ Country guidelines reviewed for: Angola, Botswana, Burundi, Cameroon, Côte d'Ivoire, Democratic Republic of the Congo, Ethiopia, Ghana, Haiti, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, Rwanda, South Africa, South Sudan, Swaziland, Tanzania, Uganda, Zambia and Zimbabwe.

Transition to dolutegravir

Since 2016, and further with the transition to Tenofovir-Lamivudine-Dolutegravir (TLD) at the end of 2017, USAID's procurement of nevirapine has drastically decreased and been halted following the FY18 COP guidance and due to additional manufacturing capacity of TLE and due to the introduction of DTG and EFV400 as first line alternative options for the anchor drug. We recognize the benefits of TLD and are starting to transition countries to this regimen so that newly diagnosed patients and existing patients on nevirapine can be safely shifted to TLD, **as appropriate.**

We continue to have a small quantities of legacy nevirapine order scheduled for delivery for patients who are stable and have responded favorably to the regimen, as well as for those who may not be able to tolerate the current preferred first-line treatment regimen. The introduction of DTG has been highly anticipated due to its multiple benefits for patients, programs, and the impact on the HIV epidemic. It is recognized for being more effective at rapidly decreasing the amount of virus in the blood, better tolerated and easier to adhere to, more robust against developing resistance, and less expensive. These benefits, along with the potential to harmonize treatment using a DTG-containing regimen across multiple populations, are among the many reasons why DTG is viewed as an important drug in the HIV treatment toolbox.

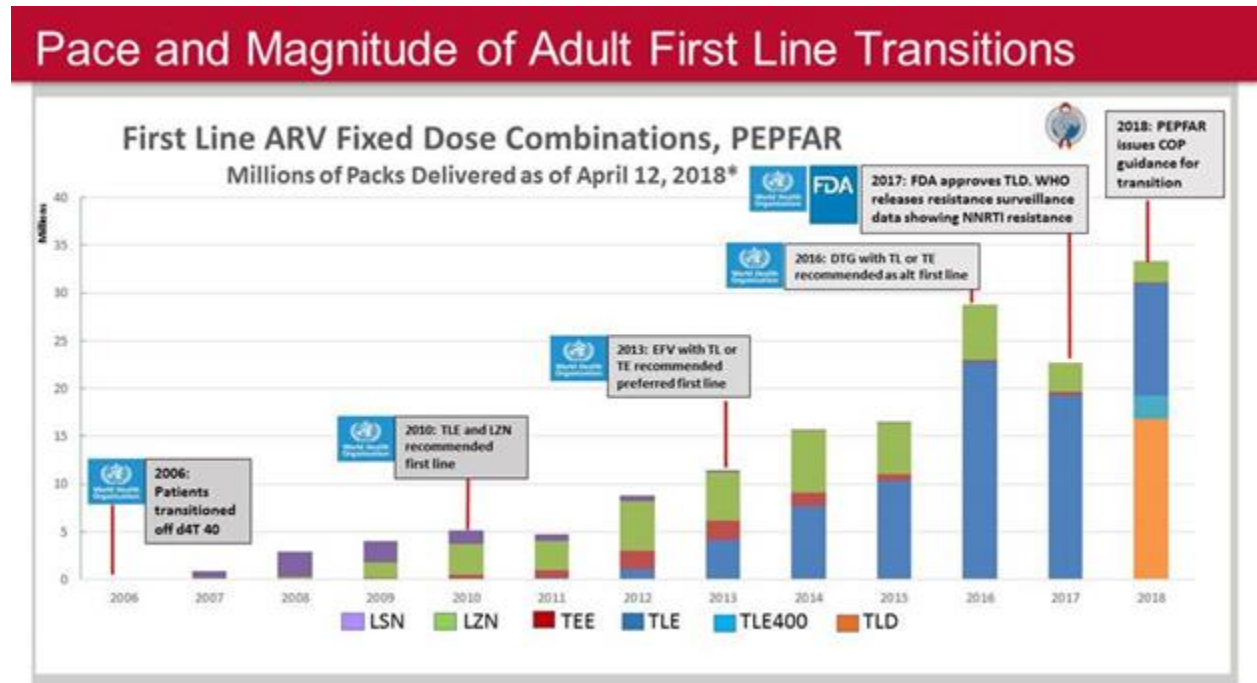
However, at the time of the 2016 WHO guidelines development, safety and efficacy data were not available for pregnant and breastfeeding women and individuals on concurrent treatment for tuberculosis and HIV. Up until last week, studies among pregnant and breastfeeding women appeared to be reassuring. However, on Friday, July 18, 2018, the FDA announced a new potential safety issue among women living with HIV using DTG at the time of conception (<https://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm608168.htm>). A preliminary unscheduled analysis of an ongoing observational study in Botswana reported four neural tube defects (birth defects of the brain, spine, or spinal cord) among 426 women who conceived while on DTG. This rate of approximately 0.9% compares to a 0.1% risk of neural tube defects in infants born to women taking other antiretroviral medicines at the time of conception.

From the same study, there is currently no evidence of any infant born with a neural tube defect to a woman who started DTG during her pregnancy. According to the manufacturer, prior studies which included embryofetal development studies in animals did not show evidence of adverse developmental outcomes. This finding is significant and serious, however additional data are necessary to further understand the safety of DTG use among women of childbearing age. USAID remains fully supportive of a safe and efficient transition to TLD for the appropriate patients and remains actively engaged in working with the Office of the Global AIDS Coordinator (SGAC) Short Term Task Team (ST3). This interagency working group is a group

of clinicians and supply chain experts from USAID, CDC and SGAC, mandated to rapidly facilitate transition to TLD effectively and efficiently, with the goal of ensuring the best outcomes for all patients PEPFAR supports.

We are working with countries to remove bottlenecks, train healthcare workers, and monitor the effects of the new medicines to identify and evaluate previously unreported adverse reactions.

Below is a graphic of the progress of guidance and purchasing of antiretrovirals.



**APPENDIX I: TIMELINE OF NEVIRAPINE USE AS RECOMMENDED
BY WHO HIV TREATMENT GUIDELINES AND PEPFAR COUNTRY
OPERATIONAL PLAN (COP) GUIDANCE AND TECHNICAL
CONSIDERATIONS DOCUMENTS**

(see Appendix 2 for full text excerpts from COP Guidances)

2010 (July 15 and 19) WHO 2010 HIV treatment guidelines released.

Summary

- Adults and adolescents
 - Recommended 1st line regimens: EFV- or NVP-containing regimen (with 2 other antiretroviral drugs)
 - No preferred 1st line regimen
- Pregnant women initiating lifelong ART (based on severity of immunodeficiency)
 - NVP- or EFV-based regimen, similar to other adults/adolescents
 - However, due to concerns on safety concerns of EFV in pregnant women, use of EFV during 1st trimester of pregnancy was not recommended

WHO 2010 First Line HIV Treatment Regimens for Patients Starting ART

Adults & Adolescents	Pregnant Women starting lifelong ART (based on severity of immunodeficiency)	Children and Infants
AZT or TDF <i>plus</i> 3TC (or FTC) <i>plus</i> EFV or NVP	AZT preferred but TDF acceptable <i>plus</i> 3TC (or FTC) <i>plus</i> NVP or EFV but do not initiate EFV during first trimester of pregnancy	Infant or child <24 months not exposed to ARVs: NVP + 2 NRTI Infant or child <24 months exposed to NNRTI: LPV/r + 2 NRTI Infant or child <24 months with unknown ARV exposure: NVP + 2 NRTI Children 24 months to 3 years: NVP + 2 NRTI Children >3 years: NVP or EFV + 2 NRTI

Abbreviations: 3TC=Lamvidine; AZT=Zidovudine; EFV=Efavirenz; FTC =Emtricitabine; NRTI=Nucleoside Reverse Transcriptase Inhibitors; NVP=Nevirapine; LPV/r=Lopinavir/ritonavir; TDF=Tenofovir disoproxil fumarate

2011 (August 2) PEPFAR FY 2012 COP Guidance published (FY 2013 implementation). See Appendix 2, section on FY 2012 COP Guidance for full excerpt of references

- Specific references to “NVP” or “nevirapine” are in the context of Prevention of Mother-to-Child Transmission (PMTCT) programs and includes language to shift away from the use of sd-NVP to triple therapy regimens recommended by WHO in 2010.
- NVP specifically mentioned in the context of infant prophylaxis for HIV-exposed infants.

2012 (October 1) PEPFAR FY 2013 COP Guidance published (FY2014 implementation). See Appendix 2, section on FY 2013 COP Guidance for full excerpt of references

- Specific references to “NVP” or “nevirapine” are in the context of infant prophylaxis for HIV-exposed infants.
- Guidance on PMTCT strategies focused on shifting away from Option A (ie, sd-NVP) to Option B or B+ (lifelong triple therapy)

2013 (June 30) WHO 2013 HIV treatment guidelines released.

Summary

Adults & adolescents:

- Tenofovir-Lamivudine-Efavirenz (TLE) or Tenofovir-Emtricitabine-Efavirenz (TEE) as a fixed-dose combination single tablet recommended as the ‘preferred’ 1st line regimen
- NVP-containing regimens and EFV in combination with other NRTIs become ‘alternative’ first line.
- Pregnant women:
 - TLE or TEE as a fixed dose combination
 - NVP-containing regimens and EFV in combination with other NRTIs become alternative.
 - Recommendation to initiate all pregnant and breastfeeding women with HIV on treatment. Option A no longer recommended.

WHO 2013 First Line HIV Treatment Regimens for Patients Starting ART

Adults & Adolescents	Pregnant Women	Children and Infants
<p>Preferred: TDF + 3TC (or FTC) + EFV as a fixed dose combination</p> <p>Alternatives: AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP</p>	<p>Preferred: TDF + 3TC (or FTC) + EFV as a fixed dose combination</p> <p>Alternatives: AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP</p>	<p>Preferred: 3 yrs to < 10 yrs, and adolescents < 35 kg: ABC + 3TC + EFV</p> <p>< 3 yrs ABC or AZT + 3TC + LPV/r</p> <p>Alternatives: 3 yrs to < 10 yrs, and adolescents < 35 kg: ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP</p> <p>< 3 yrs ABC + 3TC + NVP AZT + 3TC + NVP</p>

Abbreviations: 3TC=Lamivudine; ABC=Abacavir; AZT=Zidovudine; EFV=Efavirenz; FTC =Emtricitabine; NVP=Nevirapine; LPV/r=Lopinavir/ritonavir; TDF=Tenofovir disoproxil fumarate

2013 (October 31) PEPFAR FY 2014 COP Guidance published (FY2015 implementation). See Appendix 2, section on FY 2012 COP Guidance for full excerpt of references

- Specific references to “NVP” or “nevirapine” are in the context implementing key WHO treatment recommendations (phasing out sd-NVP)
- References to “EFV” or “efavirenz” are noted in the context of the use of TLE in accordance with the WHO 2013 HIV treatment guidelines
- Other references to ARVs, specifically with regards to phasing out d4T (antiretroviral drug no longer recommended for use), and transition from AZT to tenofovir disoproxil fumarate (TDF) for first-line treatment, including discussions of renal toxicity associated with TDF and pharmacovigilance

2015 (January 9) PEPFAR FY2015/COP15 Guidance published (FY 2016 implementation). See Appendix 2, section on FY 2015 COP Guidance for full excerpt of references

- Specific references to “NVP” or “nevirapine” are in the context of phasing out Option A (ie, sd-NVP) . Commodities considerations include procuring only ART (ie, triple therapy), and maternal AZT or sd-NVP no longer being approved options.

2015 (December) PEPFAR FY2016/COP16 Guidance published (FY2017 implementation). See Appendix 2, section on FY 2016 COP Guidance for full excerpt of references

- No specific references to “NVP” or “nevirapine”

2016 (June 9) WHO 2016 HIV Treatment Guidelines released.

Summary

- TLE/TEE fixed dose combinations remain as preferred 1st line regimens
- NVP-containing regimens remain as alternative 1st line regimen options
- DTG-containing regimens added as alternative 1st line regimen option
- A regimen containing a lower dose of EFV (EFV400) also added as an alternative 1st line regimen option
- At the time of guidelines review, safety and efficacy data on the use of DTG and EFV400 in pregnant women, people with HIV/TB co-infection, and adolescents younger than 12 years of age were not yet available

WHO 2016 First Line HIV Treatment Regimens for Patients Starting ART

Adults & Adolescents	Pregnant Women	Children and Infants
<p>Preferred: TDF + 3TC (or FTC) + EFV as a fixed dose combination</p> <p>Alternatives: AZT + 3TC + EFV (or NVP) TDF* + 3TC (or FTC) + DTG TDF* + 3TC (or FTC) + EFV400 TDF* + 3TC (or FTC) + NVP</p> <p>“Safety and efficacy data on the use of DTG and EFV400 in pregnant women, people with HIV/TB coinfection and</p>	<p>Preferred: TDF + 3TC (or FTC) + EFV as a fixed dose combination</p> <p>Alternatives: AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP</p>	<p>Preferred: 3 yrs to < 10 yrs, and adolescents < 35 kg: ABC + 3TC + EFV</p> <p>< 3 yrs ABC or AZT + 3TC + LPV/r</p> <p>Alternatives: 3 yrs to < 10 yrs, and adolescents < 35 kg: ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP</p>

<p>adolescents younger than 12 years of age are not yet available”</p> <p>*Adolescents may use ABC instead of TDF</p>		<p>TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP</p> <p>< 3 yrs ABC + 3TC + NVP AZT + 3TC + NVP</p>
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Abbreviations: 3TC=Lamivudine; ABC=Abacavir; AZT=Zidovudine; DTG=Dolutegravir; EFV=Efavirenz; EFV400=low-dose efavirenz; FTC=Emtricitabine; NVP=Nevirapine; TDF=Tenofovir disoproxil fumarate

2017 (January 18) PEPFAR FY2017/COP17 Guidance published (FY2018 implementation). See Appendix 2, section on FY 2017 COP Guidance for full excerpt of references

- Specific reference to “NVP” or “nevirapine” is in the context of continued use of NVP in infants and young children < 3 years, and poor viral load suppression and uptake of lopinavir/ritonavir-containing regimens in this population.

2018 (January 18) PEPFAR FY2018/COP18 Guidance published (FY2019 implementation). See Appendix 2, section on FY 2018 COP Guidance for full excerpt of references

- Specific reference to “NVP” or “nevirapine” are in the context of the TLD transition approach outlining the following:
 - Populations to transition
 - All adults and adolescents ≥ 10 years old and body weight ≥ 30 kg, including pregnant and breastfeeding women and those receiving concurrent treatment for TB and HIV
 - Use of TLD in the algorithm
 - First-line treatment
 - Second-line treatment, in programs that can confirm virologic suppression within 3-6 months of transition to TLD

- Which antiretroviral regimens to transition away from for those already on treatment
 - TLE/TEE
 - LZN
 - Role of viral load testing
 - No specific guidance for patients on first-line treatment (countries to follow country guidelines)
 - Patients requiring second-line treatment can switch in programs that can confirm virologic suppression within 3-6 months
 - Dosing adjustments for patients receiving treatment for TB infection
 - **Procurement restriction on NVP-containing regimens**
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APPENDIX II: EXCERPTS FROM COP GUIDANCE REFERENCING NEVIRAPINE (NVP), EFAVIRENZ (EFV), OR DOLUTEGRAVIR (DTG)

FY2012 COP (released Aug 2, 2011)

- *Page 8, “C. Adaptation and Implementation of 2010 World Health Organization (WHO) Guidelines ARVs for PMTCT”*

“The PMTCT landscape changed significantly in 2010 with the release of new WHO PMTCT ARV recommendations (preceded by —rapid advice in 2009). <http://www.who.int/hiv/pub/mtct/advice/en/index.html>. In last year’s technical considerations, the PMTCT/Peds TWG encouraged countries to assist with adapting the guidelines and highlighted the following important changes, including:

- Initiating antiretrovirals (ARV) earlier in pregnancy,
- Continuing ARVs throughout breastfeeding,
- Replacing single dose nevirapine with more efficacious regimens (Option A or B) , and
- Prescribing ARVs for the pregnant woman’s own health if her CD4 count is less than 350/mm³, taking into account risks of specific drugs and regimens.

This year, countries are encouraged to focus and share experience with implementation of the new guidelines, in particular to:

- Prioritize pregnant HIV positive women for ARVs, especially women who are eligible for treatment (Clinical Stage III/IV or CD4 \leq 350), as they constitute >70% of total MTCT and >80% of postnatal MTCT. This may require discussion with broader ART working groups to ensure that ARV drugs for pregnant women are prioritized and made available.
- Transition to more efficacious regimens for PMTCT. This should be documented by counting number of women receiving ARVs for PMTCT, disaggregated by type of regimen as required in the next generation indicators.
- Developing strategies to promote follow up in post-natal follow-up and adherence of mother and baby, particularly at Primary Health Care settings, to ensure a high level of adherence for ARV prophylaxis throughout the breastfeeding period.

II. Infant Feeding and Nutrition

In 2010 WHO also issued new infant feeding guidelines which recommend that ARV prophylaxis be administered for the duration of breastfeeding. This prophylaxis can be in the form of:

- Mothers receiving HAART for their own health,
- Mothers receiving triple ARV prophylaxis as per option B of the PMTCT guidelines, or
- Infants receiving daily **NVP** prophylaxis as per option A of the PMTCT guidelines.”

- *Page 15, Excerpt from section on “ARV prophylaxis for women not eligible for treatment (CD4+ > 350 cells/mm³)”*

“Countries are strongly encouraged to shift to the regimens recommended by WHO in 2010 and only use **SD-NVP** when other regimens are not available or feasible (e.g., woman presenting at L&D without antenatal care, or in settings with extremely limited resources but with a plan to transition all facilities to using the new WHO guidelines).”

- *Page 15, Excerpt from section on “Essential care for Women and Children Identified in PMTCT Programs”*

“All HIV-exposed children are highly vulnerable children who should receive interventions included in the PEPFAR basic preventive care package for children. HIV exposed infants receiving long-term **NVP** prophylaxis require systematic long-term follow up and programs may have to improve how they provide follow up to these babies. HIV-infected infants identified through PMTCT programs need to be started on appropriate treatment early in life to prevent high mortality in infants (see Care and Support section of Technical Considerations).”

- *Page 125, Excerpt from section on Pediatric Treatment*

“Recommended first-line regimen for HIV-infected infants (age <12 months) exposed to nevirapine (**NVP**). 2010 WHO guidance on optimal first-line ART regimens for HIV-infected infants exposed to single dose **NVP** (or other non-nucleoside reverse transcriptase inhibitor-containing maternal antiretroviral therapy regimens) states that a protease inhibitor-based triple antiretroviral therapy

regimen should be used as part of a three drug combination regimen. However, it is recognized that in many resource-constrained settings, lopinavir/ritonavir is not available, affordable, or feasible for use. In these situations, whatever regimen is available should be used and initiation of treatment should not be delayed.”

- *Other references to ARVs:*

Page 25, Table 1a. Reference to EFV

ARV Prophylaxis for pregnant women who do not need treatment for their own health		
Key Issue	2009 ART guidelines	2006 ART guidelines
When to start ARV prophylaxis	<ul style="list-style-type: none"> ● As early as 14 weeks of pregnancy 	<ul style="list-style-type: none"> ● Starting at 28 weeks of pregnancy
Recommended prophylaxis regimens for the mother	<p>Option A: maternal AZT</p> <ul style="list-style-type: none"> ● AZT during pregnancy plus ● sd-NVP + AZT/3TC during labour and delivery plus ● AZT/3TC x 7days postpartum* <p>Option B: triple ARV prophylaxis</p> <p>Provided to pregnant women until one week after all exposure to breast milk has ended:</p> <ul style="list-style-type: none"> ● AZT + 3TC + LPV/r or ● AZT + 3TC + ABC or ● AZT + 3TC + EFV ● TDF + 3TC (or FTC) + EFV 	<ul style="list-style-type: none"> ● AZT during pregnancy plus ● sd-NVP + AZT/3TC during labor and delivery plus ● AZT/3TC x 7days postpartum
Recommended prophylaxis regimens for exposed infants	<p>Option A: maternal AZT</p> <p>Breastfeeding infants</p> <ul style="list-style-type: none"> ● sd-NVP at birth, then daily NVP until one week after all exposure to breastfeeding <p>Infants receiving only replacement feeding</p> <ul style="list-style-type: none"> ● sd-NVP at birth, then daily NVP or AZT x 4 to 6 weeks <p>Option B: triple ARV prophylaxis</p> <ul style="list-style-type: none"> ● NVP or AZT x 4 to 6 weeks 	<ul style="list-style-type: none"> ● sd-NVP + AZT x 7 days

FY2013/COP 13 (released Oct 1, 2012)

- *Page 14, Section on “Increase PMTCT Coverage, Effectiveness and Retention”*

“Consider Option B or B+ where appropriate: The WHO recommends that HIV-positive pregnant women in low and middle-income countries receive one of two prophylaxis options (Options A and B) for the prevention of mother-to-child transmission (PMTCT). Both WHO Options A and B provide eligible pregnant

women with life saving triple ARVs as soon as diagnosed and continues for life for those with CD4 <350 . For women with CD4+ >350, Option A provides intermittent ARV regimens at key points during the pregnancy intrapartum and postpartum/breast feeding period, while Option B recommends starting triple ARVs as early as 14 weeks gestation and continued through the intrapartum and childbirth (if not breast feeding) or after cessation of breast feeding. All Options provide daily nevirapine (**NVP**) for infants from birth but with Option A the meds are given daily through completion of breastfeeding (or up to 4-6 weeks if not breast fed); with Option B, daily **NVP** or AZT is given through 4-6 weeks regardless of feeding method.

While Option A and Option B are considered equally effective at preventing MTCT when implemented properly, many PEPFAR-supported countries initially began to implement Option A due to cost considerations. However, recent data indicate that an Option B approach, which involves the provision of a full antiretroviral regimen throughout pregnancy and breastfeeding, will reduce horizontal transmission while also potentially benefiting the health of the mother. As CD4 testing is not required before starting antiretrovirals under this approach, Option B also avoids delays in the initiation of antiretrovirals for PMTCT prophylaxis. In addition, over the past year newly released WHO Guidelines offer the Option B+ approach, which involves starting pregnant, HIV+ women on antiretroviral therapy (ART) for life regardless of CD4 count. Given the potential benefits of Option B and B+ in reducing HIV-transmission to serodiscordant partners and in decreasing barriers to PMTCT and HIV treatment, all PEPFAR programs providing PMTCT should conduct an analysis to determine the incremental cost of transitioning to Option B in countries currently implementing Option A, and to estimate incremental cost of B vs. B+. Countries must assume that 40 percent of HIV-infected pregnant women are eligible for ART prior to the post-partum period, and therefore provision of ART for life to these patients should be considered in the costing analysis regardless of which Option is used.”

FY2014/COP 14 (released Oct 31, 2013)

NVP-specific references

- *Page 139, Box 1 “Factors to consider when deciding to implement the new WHO Guidelines”*

“Implementation status of other key recommendations (i.e., phase-out of d4T and single dose **nevirapine (sdNVP)**)”

References to multiple ARVs (NVP references bolded)

- *Page 5-6, “3.1 Anti-retroviral Drug Treatment (ART) for Pregnant, Postpartum and Breastfeeding Women and Infant Prophylaxis (Prong 3)”*

“Key recommendations relevant to PMTCT are summarized below:

- All pregnant, postpartum and breastfeeding women with HIV should initiate ART;
 - In countries with generalized epidemics, for programmatic and operational reasons, all pregnant and breastfeeding women should initiate ART as lifelong treatment (Option B+); and
 - In countries with concentrated epidemics that have high access to CD4 testing, adequate capacity to provide ART to the pregnant and breastfeeding women eligible for treatment, low fertility rates and/or where breastfeeding for mothers with HIV is not recommended, consideration can be given to stopping the ARVs in women not eligible for ART after breastfeeding is discontinued (Option B).
- Use of the preferred first-line ART regimen harmonized for adults, pregnant women and older children: a once-daily, fixed-dose combination (FDC) pill containing tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC), and efavirenz (EFV);
- Option A should be phased out;
- Use of viral load testing is preferred for clinical monitoring;
- Decentralizing delivery of ART to peripheral health facilities;
- Integrating ART services within maternal and child health clinical sites with arrangements for ongoing HIV care and treatment in a delivery model that provides high-quality HIV services, including excellent retention and ART adherence as well as excellent MNCH services;
- Task sharing to allow nurses and midwives to initiate and maintain ART within the national regulatory framework; and

- Task sharing to allow community health workers to dispense ARVs and/or deliver ART between regular clinic visits within the national regulatory framework”

- *Page 9, “3.1 Anti-retroviral Drug Treatment (ART) for Pregnant, Postpartum and Breastfeeding Women and Infant Prophylaxis (Prong 3)”*

“14. Pharmacovigilance: The new WHO 2013 Consolidated ARV guidelines recommend TDF-based regimens for first line therapy in pregnant women and other adults. There are many advantages to using a TDF-based regimen, including the ease of administration as a once-daily regimen and overall simplification of regimens. Many studies highlighting the efficacy of TDF have been performed in settings where screening for kidney dysfunction (usually through a blood test for creatinine and/or creatinine clearance calculation) is possible, and in some of these studies TDF has been associated with the development of renal toxicity, as well as changes in bone density (19)(20). HIV infection itself has been clearly identified as a risk factor for kidney dysfunction, and TDF-containing ARVs effectively treat HIV-related kidney disease (21)(22)(23)(24). On balance, given the low risk of TDF-associated renal dysfunction and demonstrated benefits of ART for HIV-associated renal disease, TDF-based regimens can be used as first-line ART in patients with low-risk of renal disease. Further discussion of HIV and TDF-associated renal dysfunction can be found in Section 2.2 of the Technical Considerations (Adult Treatment).

15. Birth Defects Surveillance: Any drug has the potential for risk in pregnancy. Current data do not indicate an increased risk of birth defects with use of any ARV in the first trimester of human pregnancy. Given currently available information on serious side effects of some drugs, costs, dosing, potential drug interactions, and antiretroviral efficacy, the regimen of TDF/FTC or 3TC/EFV appears to be the best choice for first line treatment for pregnant women. The benefits of early initiation of ART (reduced MTCT, improved maternal health) using this simple, once-daily fixed drug combination likely outweighs any potential risk in pregnant women. Countries implementing B+ as recommended in the consolidated 2013 WHO guidelines are not required to have a birth defects surveillance program. PEPFAR is funding birth defects surveillance programs in selected countries to provide birth defects information to the global community. If any PEPFAR team would like to implement a birth defects surveillance program or requires further information

about birth defects risks, please request support from the PMTCT-Pediatric TWG, via your CSTL. Inappropriately designed and implemented birth defects surveillance programs are not only ineffective but may create unnecessary anxiety and apprehension over using ART in women of reproductive age.

- *Page 135, “1.1.2 WHO 2013 Consolidated Antiretroviral Guidelines”*

Highlights of the WHO 2013 Consolidated ARV Guidelines: Related to Treatment
1) ART should be initiated in all individuals with HIV with CD4 count ≤ 500 cells/mm ³ regardless of WHO clinical stage, as well as in HIV+ partners (at any CD4 count) in a serodiscordant partnership. However, ART should be prioritized for all individuals with advanced HIV clinical disease (WHO clinical stage 3 or 4) and individuals with CD4 count ≤ 350 cells/mm ³ .
2) TDF/XTC/EFV (tenofovir, emtricitabine or lamivudine, and efavirenz) as a fixed-dose combination is recommended as the preferred option for initiation of ART.
3) ART should be initiated in all HIV-infected children below five years of age, regardless of WHO clinical stage or CD4 count.
4) All pregnant and breastfeeding women with HIV should initiate triple ARVs. ART should be maintained for the duration of mother-to-child transmission risk at minimum. Women meeting treatment eligibility criteria should continue lifelong ART. For programmatic and operational reasons, particularly in generalized epidemics, all pregnant and breastfeeding women with HIV should initiate ART as lifelong treatment [“Option B+”].
5) Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure.

- *Page 141, “2.2.2 ARV Regimen Schedule”*

“The WHO 2013 Consolidated ARV Guidelines recommend TDF/XTC/EFV (tenofovir, emtricitabine or lamivudine, and efavirenz) as a fixed-dose combination (FDC) regimen for most patients. This regimen is recommended as first-line therapy unless it is not available in-country or is contraindicated for an individual patient. Although this approach simplifies treatment and regimen choice, there are several important issues to consider:

- While adoption of a TDF/XTC/EFV fixed-drug combination as the preferred national first-line regimen is recommended, a gradual transition scheme is absolutely essential given the significant existing supply constraints for TDF- and EFV- containing regimens;
- When possible, PEPFAR-supported programs should use existing stocks of ARVs already purchased and available in country. This will ease the transition to TDF regimens, avoid waste of valuable resources, and eliminate the need for destruction of existing stocks;

- Reducing the number of ARV regimens in-country will simplify ARV options and reduce the complexity of procurement and supply chain logistics;
- Supply planning must incorporate anticipated increases in procurement lead times for FDC treatment regimens. Orders should be placed as far in advance as possible (at least 8 months);
- While country-specific stock, consumption, and forecasting data (taking into account expected lead-times for TDF/XTC/EFV procurements) may impact the transition scheme, consider the following phased approach:
 - Place patients newly initiating ART on a TDF-based regimen;
 - When beginning transition of patients already on ART, switch those patients currently receiving stavudine (d4T)-based regimens first; and
 - Phase in the transition of AZT and **NVP-containing** regimens to TDF-based regimens to mitigate potential stock-outs or shortages. Based on current projections, a phase in time frame from mid-2013 through mid-2015 will allow the market to “catch-up” with the increased demand. A phase-in approach, that transitions more patients later in 2014, will best support a smooth transition.
- Timelines and details of the phase-in plan can be determined based on country-specific data. It will be important not to modify existing procurement orders for ARVs (e.g., switching AZT orders to TDF), as this may lead to delays in receiving orders in country.”

- *Page 152, “3.2.4 Pharmacovigilance”*

“Standardized laboratory monitoring guidelines for ART toxicity should be developed that are evidence-based and balance maximum utility of scarce laboratory resources and quality of patient care (e.g., serum creatinine monitoring with tenofovir (TDF) use, hemoglobin measurement with AZT use).

The new WHO 2013 Consolidated ARV guidelines recommend TDF-based regimens for first line therapy in adults and pregnant women. There are many advantages to using a TDF-based regimen, including the ease of administration as a once-daily regimen and overall simplification of regimens. However, TDF has also been associated with the development of renal toxicity (19) and changes in bone density (20), and many studies highlighting the efficacy of TDF have been

performed in settings where screening for kidney dysfunction (usually through a blood test for creatinine and/or creatinine clearance calculation) is possible. HIV infection itself has been identified as a risk factor for kidney dysfunction, and in some cases ARVs, including TDF, can help treat HIV-related kidney disease.

3.2.4.1 Risk of renal disease in persons living with HIV (PLHIV)

- PLHIV have an increased risk of renal disease when compared to HIV-uninfected individuals. Based on a recent meta-analysis, the relative risk of renal disease is 3.87 times greater than in HIV-uninfected people. PLHIV with more advanced immunosuppression are 3.32 times more likely than patients with earlier stages of infection to have renal disease (21). Older age and other underlying conditions, including diabetes and hypertension, also increase the risk of developing renal disease.
- Chronic kidney disease is relatively common in PLHIV. In patients of African descent, this is predominantly caused by HIV-associated nephropathy (HIVAN). (22)
- However, the relative risk of renal disease among PLHIV on ART is 46% lower than treatment-naïve PLHIV, which is due, in part, to reduction in the direct damage to the kidney from the HIV(22).

3.2.4.2 Risk of TDF-associated Nephrotoxicity in PLHIV:

- Use of TDF has been associated with renal dysfunction when compared to other antiretroviral medications, though it remains a relatively uncommon side effect (20) (22)(309);
- Several risk factors have been shown to increase the risk of TDF-associated nephrotoxicity, including: (a) age over 50 years, (b) low body weight, (c) concomitant use of nephrotoxic drugs, (d) pre-existing kidney dysfunction, (e) low CD4 count and advanced immunosuppression, and (f) hepatitis C co-infection (310) (311) (20); and
- Post-marketing surveillance studies conducted by pharmaceutical companies have demonstrated a < 0.2% risk of severe renal failure over an estimated 400,000 person-years of TDF exposure (312); however, a retrospective cohort study of over 1,000 HIV-infected individuals receiving TDF-containing ART suggested a risk closer to 1% (313). A meta-analysis of 17 studies published in 2010 found a slightly (0.7%) higher risk of acute renal

failure with TDF, but no significant differences in rates of chronic kidney failure or end-stage kidney failure (314) (315).

Given the low risk of TDF-associated renal dysfunction and demonstrated benefits of ART for HIV-associated renal disease, TDF can be used as first-line ART in patients with low-risk of renal disease. Furthermore, current data do not show a risk of teratogenicity from any ARV. The benefits of early initiation of ART (reduced MTCT, improved maternal health), using a simple, once-daily TDF-based FDC likely outweigh any potential risk in pregnant women. Additional information about the risk of TDF, EFV and other ARVs is discussed in Section 1.1 of the Technical Considerations (Prevention of Mother to Child Transmission).

Birth defect surveillance is expensive and must be done correctly to yield useful data, so it should not be implemented everywhere routinely. TDF/XTC/EFV regimens can be implemented (e.g. PMTCT Option B or B+) without birth defect surveillance, as the risk of birth defects is far outweighed by benefits to maternal health with ART. Birth defect surveillance could be considered in a country, if all births (livebirths and stillbirths) at selected sites can be examined and outcomes can be linked to drug exposures in early pregnancy, and if numbers are adequate to provide meaningful estimates of birth defect rates. If a country is interested in developing a birth defects surveillance program, PEPFAR Headquarters staff can assist with development of an appropriate program.”

- *Page 347, “3.4 Supply Chain considerations for Care and Treatment”*
“The WHO 2013 Consolidated ARV Guidelines recommend TDF/XTC/EFV (tenofovir, emtricitabine or lamivudine, and efavirenz) as a fixed-dose combination (FDC) regimen for most patients. This regimen is recommended as first-line therapy unless it is not available in-country or is contraindicated for an individual patient. As Tenofovir (TDF)-based regimens and/or FDC regimens is phased in as a preferred first-line treatment, countries will need to develop responsible, globally-aware procurement plans for these commodities. This includes:
 - Development of a gradual transition scheme given the significant existing supply constraints for TDF- and EFV- containing regimens;
 - Supply planning for anticipated increases in procurement lead times for FDC treatment regimens. Orders should be placed as far in advance as possible;

- When possible, programs should use existing stocks of ARVs already purchased and available in country. This will ease the transition to TDF regimens, avoid waste of valuable resources, and eliminate the need for destruction of existing stocks. Further guidance on d4T phase-out and use of AZT-based regimens during this transition can be found in Section 2.2 of the Technical Considerations (Adult Treatment);
- Reducing the number of ARV regimens in-country will simplify ARV options and reduce the complexity of procurement and supply chain logistics; and
- Priority should be given for transition of patients currently on d4T-based regimens to a TDF-based regimen, as this is no longer a recommended regimen based on WHO guidelines (406).”

FY2015/COP 15 (released Jan 9, 2015)

- *Page 44, “1.2 Option A Phase Out- Anti-retroviral Drug Treatment (ART) and Lifelong Care for Pregnant, Postpartum and Breastfeeding Women HIV Exposed Infants, and their Families”*

“ The 2013 WHO Consolidated Guidelines on the use of Antiretroviral Drugs for Treating and Preventing HIV Infection (<http://www.who.int/hiv/pub/guidelines/arv2013/en/>) recommend ART for all HIV-positive pregnant and breastfeeding women to protect a women’s own health and prevent HIV transmission to her infant and sexual partner. These guidelines were in large part based on the “treatment as prevention” benefits demonstrated in the HPTN 052 study and Malawi’s early success in implementing their innovative Option B+ approach for PMTCT (Cohen, et al., 2011) (Schouten, Jahn, Midian, Makombe, & Mnthambala, 2011). Implicit in these guidelines is that pregnant and breastfeeding women should also receive the same quality of HIV care as other individuals on ART. In addition, the recently released PROMISE study results demonstrated significantly lower transmission rates with triple therapy regimens

compared to Option A of zidovudine (AZT) or nevirapine (**NVP**) monotherapy with additional peripartum drugs. The link to the press release can be found here <http://www.nih.gov/news/health/nov2014/niaid-17.htm>

Key priorities include:

- Training and Commodity considerations:
 - Commodities: only ART should be procured for PMTCT; maternal AZT or **NVP** alone are no longer approved options
 - Training should be aligned with Option B/B+ and HIV exposed infant (HEI) testing and care
 - Targets should not include Option A or **SD-NVP**
- All pregnant postpartum and breastfeeding women with HIV should be encouraged to initiate ART after a thorough discussion of benefits and risks;
 - In countries with generalized epidemics, for programmatic and operational reasons, all pregnant and breastfeeding women should be encouraged to initiate ART as lifelong treatment (Option B+); and
 - In countries with concentrated epidemics that have high access to CD4 testing, adequate capacity to provide ART to the pregnant and breastfeeding women eligible for treatment, low fertility rates and/or where breastfeeding for mothers with HIV is not recommended, consideration can be given to stopping the ARVs in women not eligible for ART after breastfeeding is discontinued (Option B);
 - Starting lifelong ART is a major decision and is ultimately the woman's choice to accept treatment or not.
- Use of the preferred first-line ART regimen harmonized for adults, pregnant women and older children: a once-daily, fixed-dose combination (FDC) pill containing tenofovir (TDF), lamivudine (3TC) or emtricitabine (FTC), and efavirenz (EFV)."

- *Other References to **NVP** and EFV (No reference to DTG)*

Page 107- 108, section on Adult Treatment, "Introduction and "Technical Considerations for Priority Areas":

Technical Priorities:

1. Support adoption and phased roll-out of 2013 WHO Guidelines for expanded treatment eligibility.
2. Focus treatment scale-up to high burden geographic areas and high-risk populations (TB/HIV co-infection, pregnant and breastfeeding women, pediatric patients, key populations), as a part of combination prevention efforts, to maximize impact on the HIV epidemic.
3. Support ART service quality for adherence, retention, and viral suppression, using quality management and quality improvement (QM/QI) processes.
4. Support adoption of VL monitoring through development of country-specific viral load strategies.
5. Support implementation of HIV drug resistance surveillance in settings of ongoing ART scale-up.
6. Identify strategies to assess readiness for transition, to develop country and context-specific transition plans (approach and timeline), and monitor the quality of services during transition.

- *Page 116, Section on Adult Treatment, “Other Technical Background”*

“3.2 ARV Regimen Selection

Once-daily and fixed-dose combinations (FDCs) have been associated with improved adherence, reduced side effects, and fewer regimen substitutions (Parienti, Bangsberg, Verdon, & Gardner, 2009) (Dejesus, Young, Morales-Ramirez, & et al., 2009) The WHO 2013 Consolidated ARV Guidelines recommend TDF/XTC/EFV (tenofovir, emtricitabine or lamivudine, and efavirenz) as a FDC regimen for most patients. This regimen is recommended as first-line therapy unless it is not available in-country or is contraindicated for an individual patient. Although this approach simplifies treatment and regimen choice, there are several important issues to consider:

- While adoption of a TDF/XTC/EFV fixed-drug combination as the preferred national first-line regimen is recommended, a gradual transition scheme is absolutely essential given the significant existing supply constraints for TDF- and EFV- containing regimens;
- When possible, PEPFAR-supported programs should use existing stocks of ARVs already purchased and available in country. This will ease the

transition to TDF regimens, avoid waste of valuable resources, and eliminate the need for destruction of existing stocks;

- Critical to ART scale-up is simplifying prescribing practices and supply chain management (Vitoria, Ford, & Doherty, 2014). Reducing the number of ARV regimens in-country will simplify ARV options and reduce the complexity of procurement and supply chain logistics; reducing the risk of stock outs and supporting task shifting and decentralization (Ramjan, et al., 2014). Supply planning must incorporate anticipated increases in procurement lead times for FDC treatment regimens. Orders should be placed as far in advance as possible (at least 8 months);
 - While country-specific stock, consumption, and forecasting data (taking into account expected lead-times for TDF/XTC/EFV procurements) may impact the transition scheme, consider the following phased approach:
 - Place patients newly initiating ART on a TDF-based regimen;
 - When beginning transition of patients already on ART, switch those patients currently receiving stavudine (d4T)-based regimens first; and
 - Phase in the transition of AZT and **NVP-containing** regimens to TDF-based regimens to mitigate potential stock-outs or shortages.
- Timelines and details of the phase-in plan can be determined based on country-specific data. It will be important not to modify existing procurement orders for ARVs (e.g., switching AZT orders to TDF), as this may lead to delays in receiving orders in country.”

COP 16 (released Dec, 2015)

- No reference to EFV, **NVP** or DTG in COP guidance/technical considerations documents

COP 17 (released Jan 18, 2017):

- *Page 159, Excerpt from section on “Population Specific Approaches to Improving Retention and Viral Load Suppression”*

“Virologic suppression remains a particular challenge among children (Figure C.5.2.1)⁴⁸ who have unique adherence challenges and an increased risk for resistance. Effective ART regimens are essential to achieving VL suppression and persistently poor uptake of recommended first-line lopinavir/ritonavir-based regimens (and continued use of inferior **nevirapine-based** regimens) in infants and young children remains a major factor contributing to poor suppression rates in these children. For children, caregiver engagement is key: WHO recommends supporting caregivers to attend regular clinic visits all while reinforcing the importance of age-appropriate disclosure to children. The OVC platform can be leveraged to contribute support to retention of children, adolescents, and their caregivers on treatment, as well as viral load uptake. Community-based OVC workers and volunteers should be utilized to provide case management services that support access to comprehensive services and to provide regular follow up and monitoring at the household level.”

COP18 (released Jan 18, 2018)

- *Page 241-2, Appendix 9.1.2 “Transition to TLD as Preferred ART for Adults & Adolescents (>= 10 years old and body weight >= 30 kg.)*

“Dolutegravir (DTG)-containing regimens are the preferred first-line antiretroviral therapies (ART) due to superior efficacy, tolerability and higher threshold for resistance compared to efavirenz (EFV)-containing regimens. The fixed dose combination (FDC) of tenofovir disoproxil fumarate/lamivudine/dolutegravir (TLD) is currently priced as the least expensive FDC, and it is expected that prices will go down as generic manufacturing scales up. For these reasons, PEPFAR now recommends TLD as the preferred option for ART, and further recommends that countries switch over to TLD as soon as possible in a coordinated fashion as supply becomes available.

S/GAC and the agency headquarters will work with country governments and multilateral partners to support rapid adoption of TLD for adults and adolescents (≥ 10 years old and body weight ≥ 30 kg.) currently receiving legacy first-line ARVs, including tenofovir/efavirenz/ emtricitabine (TLE), tenofovir/efavirenz/emtricitabine (TEE), lamivudine/zidovudine/ **nevirapine** (LZN) or ready to start ART. TLD is also encouraged for use as second-line (for patients failing an EFV- or **nevirapine** (NVP)-based first-line regimen as well as those already receiving a protease inhibitor [PI]-based second-line regimen) in programs that can confirm virologic suppression within 3-6 months of transition. Evidence is reassuring for the use of DTG at standard dosages for pregnant women and is recommended as an alternative first-line ARV for pregnant women in the United States¹⁹. Country teams should therefore plan to include pregnant and breastfeeding women in their transition planning. Programs are encouraged to follow program data closely, and report ARV exposures during pregnancy to The Antiretroviral Pregnancy Registry²⁰. Available evidence also indicates that patients receiving treatment for tuberculosis (with rifampin-containing regimens) require an additional DTG 50mg when taking TLD; therefore TLD planning should include planning for procurement of adequate DTG 50mg tablets for management of patients with TB coinfection. We recommend including the additional 50 mg DTG as part of early TB therapy so it starts and stops with the TB treatment.

Children (< 30 kg) are not expected to be included in the initial roll-out of TLD. Development of pediatric DTG formulations and evaluation of appropriate DTG dosing in infants and children are underway.

Given the critical need for detailed planning to allow for global coordination and to ensure that supply chain lead times are met, all country teams should initiate transition planning as soon as possible (if they haven't already done so). These plans should detail a seamless transition to the new regimen, while minimizing challenges and wastage of legacy first-line ART stock. No countries should be using **NVP-based** regimens and PEPFAR will not fund **NVP-based** regimens.

Before TLD is received in-country, the following activities should be completed. Be prepared to articulate these plans during the COP 18 Regional Planning

Meeting to be held from February 19-23, 2018 and February 25, 2018 through March 1, 2018.

- National guidelines are adjusted to include TLD.
- Establish a clinical and health care providers plan for training on TLD; this training should include an understanding of the benefits TLD will provide. Additionally, training planning should include educational materials for patients transitioning to TLD.
- Provide TLD transition plan and supply plan using the provided templates (see below) or a similar tool that provides all of the information requested. The transition plan must identify which patients (naïve, which legacy ARVs, and current patients) will transition and a timeline when the transition will occur.
- Ensure that supply chain systems are adjusted to integrate TLD.
- Supply plans and supply chain managers must assure that the TLD transition coincides with patients and stock levels decreasing for various legacy ARVs, to minimize wastage, and advance ARV optimization in-country.

Countries can utilize this checklist to ensure that all of the elements of its transition plan are complete.

- TLD Transition Strategy and Budget
- National Guideline Updates
- Product Registration
- Stakeholder Engagement
- Supply Plan (Quantification and Forecasting)
- Facility Level Implementation, Monitoring, and Uptake

PEPFAR recommends that the draft TLD transition plan for each country be led by the country government with input from the USG team, other donors such as Global Fund, implementing partners, and other local stakeholders that address policy, regulatory and operational issues of transition. These should address the total volume of TLD to be purchased (not just that procured by PEPFAR) and include these additional planning factors:

- Timing of anticipated country-led adoption of TLD, including estimates for stock build-up deliveries and timing of when first patients will be started on TLD.

- Roll-out approach, including plans to transition adults and adolescents starting ART as well as legacy adults and adolescents. PEPFAR recommends a regional or geographic roll-out (i.e., use of TLD for all patients in a given geographical unit) rather than roll-out by sub-population (in which TLD is used first for those starting ART followed by switching those already on legacy first-line ART regimens).
- Explicit description of plans for patients on second-line therapy, pregnant and breast-feeding women and patients with tuberculosis.
- Assessment and documentation of viral load capacity, with a plan to prioritize patients who are transitioning to TLD as second-line therapy.
- Status and planned timelines for any needed National Guideline Updates and status of drug regulatory authority approval (and/or plans to use waiver).
- Plans for HCW training and engagement of patient advocacy groups.
- Plans to minimize risk of and expenses associated with wastage of legacy LZN, TLE, and TEE stock.
- Detailed budgeting (in many cases the transition will require a timing shift of planned spending to accumulate the required buffer stocks).
- Include funding for observational monitoring for TLD transition (this should be included within OU COP planning).

The recommended PEPFAR Transition and Supply plan templates can be found on the PEPFAR Sharepoint COP 18 folder under the guidance, tools and resources folder. Each of these template tools are provided for countries to utilize and bring to the Regional Planning meeting. Within this folder, PEPFAR teams can find Transition Plan instructions, the interactive TLD Forecasting/Supply Plan tool, and the TLD Transition template tool. All country teams and PEPFAR Coordinators should share these tools with their respective Ministry of Health commodities planners.”