Implementation manual for DTG rollout and ART optimization in Ethiopia

Federal Democratic Republic of Ethiopia
Ministry of Health

Addis Ababa, Ethiopia

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List of Acronyms and Abbreviations

Acronym / Abbreviation	Description
3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
ATV/r	Atazanavir combined with ritonavir
AZT	Zidovudine
DRV	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
FDC	Fixed dose combination
FMOH	Federal Ministry of Health
HIV	Human Immunodeficieny Virus
HIVDR	HIV drug resistance
LPV/r	Lopinavir combined with ritonavir
NVP	Nevirapine
RAL	Raltegravir
RTV or /r	Ritonavir
TB	Tuberclosis
TDF	tenofovir disoproxil fumarate
TLD	Combination of Tonofovir, lamivudine and dolutegravir
WHO	World Health Organization

1. Introduction

There are ongoing advances in the selection and optimization of HIV drugs and regimens. The World Health Organization (WHO) has recommended drug regimens with high potency, lower toxicity, high genetic barriers to resistance, and usefulness across different populations, and lower cost. The use of optimized drug regimens can improve the durability of the treatment and quality of care of people living with HIV. Adopting optimized antiretroviral (ARV) drug regimens can also significantly affect the speed at which the 90–90–90 targets are achieved, enhancing access to treatment and improving treatment outcomes with impact on treatment adherence, viral suppression, and the quality of life of people living with HIV, reducing pressures on health systems, and the risk of HIV transmission.

Although there are no adequate data about the Ethiopian national pre-treatment HIV drug resistance (HIVDR) to Efavirenz (EFV) or Nevirapine (NVP) among people naïve for ARVs, the studies in other African countries indicate increasing trend. For example, the WHO guidance issued in July 2017 shows that pretreatment HIVDR in Uganda, Kenya, Namibia and Zimbabwe exceeded 10%. When there are countries with $\geq$ 10% national prevalence of pretreatment HIVDR to EFV or NVP among people initiating first-line ART, WHO recommends using other alternative ARVs.

Besides, reports in Ethiopia show that utilization of pediatric ARVs is not in line with the recommendations of national and WHO guidelines. While the preferred ARVs for pediatrics are boosted-lopinavir (LPV/r) and EFV for children younger than 3 years and 3 to 10 years, respectively, the actual practice shows that 78% of children younger than 10 years are being treated with NVP, which is non-optimal and not recommended as preferred ARV in the guidelines.

Furthermore, there is increasing trend of enrolling clients to second line regimens in Ethiopia due to increasing access to ART and routine viral load monitoring. Similarly, program data on viral load monitoring revealed increased number of clients on second line ART with unsuppressed viral load. The WHO also recommends third-line ART for patients with failure of their second-line ART. Although there were few studies with newer agents, cohort data showed high mortality

among people for whom second-line ART had failed. Salvage regimens were recommended with or without previously used ARVs that potentially maintained residual antiviral activity.

As part of its continued efforts to prevent further spread of HIV and to improve the quality of HIV care and treatment service, the government of Ethiopia is:

- Adopting and introducing new antiretroviral medicines (ARVs) with proven safety and efficacy. Accordingly, Dolutegravir (DTG) is one of those ARVs included into the 2018 edition of the national comprehensive HIV prevention, care and treatment guidelines of Ethiopia.
- Working to optimize pediatric ART by introducing preferred and optimal ARVs.
- Adopting and introducing third line ART service.

However, transitioning to new ARV drugs requires careful clinical and programmatic considerations. Evidence for the safety and efficacy of these new options is still needed for some important subpopulations, and programmatic experience with these drugs is still very limited in low and middle-income countries. Further, the longer-term complications of ART can be underestimated because most clinical trials enroll selected group of people based on highly specific inclusion criteria, and the duration of participant follow-up is relatively short, which requires that programs closely monitor the introduction of these new ARV drugs.

The Federal Ministry of Health (FMOH) has undertaken various actions to avail new ARV drugs to optimize first line ART regimens and for third line considerations. This manual is therefore developed to serve as a guide for all stakeholders involved in the national rollout of DTG and TLD, pediatric ART optimization, implementation of third line ART, and Nevirapine phase out.

2. Objectives

This implementation manual serves as an addendum reference material to **the 2018** national comprehensive HIV prevention, care and treatment guideline regarding:

- Rollout of DTG and TLD
- Optimization of adult and pediatric ART
- Rollout of third line ART
- Phasing out of Nevirapine

3. Target Audiences

The target audiences of this implementation manual are:

- Health care workers (physicians, health officers, nurses, pharmacy personnel, laboratory personnel) and case managers/adherence supporters/mother support groups
- HIV program managers, health planners, and researchers
- Organizations involved in antiretroviral drug procurement, supply management, and ART service delivery
- Community and faith-based organizations working on HIV programs including PLHIV

4. Basics on DTG and TLD

a. Summary of first line ART regimens

This section, **as an addendum to the 2018 national HIV treatment guidelines**, summarizes the revised list of ARV regimens in Table 1 below. Hence, **the regimen list** in this table has to be taken as the substitute for the regimens in the 2018 national HIV guideline.

Table 1: Updated summary of first-line ART regimens.

Population	Preferred first-line regimens	Alternative first-line regimens	Special circumstances [c]
Adults (including those with TB/ HIV[b]- co infection)	TDF+ 3TC+ DTG (FDC)	TDF + 3TC + EFV* AZT + 3TC + DTG AZT + 3TC + EFV	AZT+ 3TC + ATV/r** TDF+ 3TC+ ATV/r
Adolescent girls and women of childbearing potential who are on consistent & reliable contraception	TDF+3TC+DTG (FDC)	TDF + 3TC + EFV* AZT + 3TC + DTG AZT + 3TC + EFV	AZT+3TC+ATV/r TDF+3TC+ATV/r
Women & adolescent girls who have desire for pregnancy or are pregnant	TDF+3TC+ EFV* (FDC)	AZT + 3TC + EFV	TDF+3TC+ ATV/r AZT+3TC + ATV/r
Adolescents (10 to 19 years OR weight ≥30 kg) (*Including those with TB/HIV[b]- co infection*.)	TDF+3TC+DTG (FDC)	TDF+3TC+EFV * AZT + 3TC + EFV ABC + 3TC + EFV	TDF+3TC + ATV/r AZT+3TC + ATV/r
Children less than 10 years or weight. ≥ 20kg)	ABC + 3TC + DTG	ABC+ 3TC+EFV AZT+3TC+DTG AZT+3TC+EFV ABC+ 3TC+LPV/r	ABC+3TC+NVP AZT+3TC+NVP
Children between 4 weeks and 10 years and body weight <20kg	ABC+3TC+LPV/r	No alternative first line regimen for this group.	ABC+3TC+EFV*** AZT + 3TC +EFV (or NVP) AZT + 3TC +LPV/r

[a] ABC or boosted PIs (ATV/r, LPV/r) can be used in special circumstances. For those clients who could take neither DTG nor EFV due to contraindication and/or side effects.

[b] In case of TB-HIV co-infection, the dose of DTG should be 50mg **BID**.*TDF+3TC+EFV400 (FDC) and TDF+3TC+EFV600 (FDC) can be used interchangeably based on stock availability.

** WHO recommends ATV/r as alternative first-line when DTG or EFV can't fit. Besides, LPV/r has more side effects and drug interactions. LPV/r has also pill burden impact. The only concern when using ATV/r as first- line is transmitted resistance that would affect its use as second line ARV.

*** **Caution**: co-administration of ABC with NVP in pediatric patients will increase the risk of hypersensitivity reaction and requires extreme precaution.

**** EFV is for children 3 years and older.

b. What is DTG?

Dolutegravir (DTG) is an antiretroviral (ARV) drug that belongs to the class of Integrase Inhibitors. DTG acts by impairing the function of HIV integrase and preventing integration (insertion) of HIV DNA into the host cell DNA. DTG is included in the 2018 edition of the comprehensive HIV prevention, care and treatment guidelines of Ethiopia as a preferred first line ARV (Refer Table 1 above).

Advantages of using DTG as preferred first line ARV:

As stated in the World Health Organization (WHO) 2018 interim guideline, using DTG as preferred first line ARV has the following benefits.

- More rapid and higher viral suppression
- Higher CD4 cell count recovery rates
- Higher genetic barrier against ARV drug resistance.
- Lower risk of treatment discontinuation and
- Lower potential for drug–drug interactions

DTG is currently available in the market as a generic FDC combined with TDF and 3TC (TDF300mg+3TC300mg+DTG50mg) as a once daily dose. It is also available as a single 50mg tablet for convenience of users who need to take a separate DTG tablet. Its availability as a generic formulation at a price cheaper or comparable to other currently existing ARVs in most low- and middle-income countries also supports the use of DTG as a better option.

c. What is TLD?

TLD is a new fixed-dose combination (FDC) tablet consisting of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and dolutegravir (DTG) (TDF300mg+3TC300mg+DTG50mg). The national comprehensive guideline recommends TLD as a preferred first-line regimen for adults and adolescents (age ≥10; or weight ≥30 kg) as a once-daily dose.

d. Dosage of TLD and DTG

One tablet of TLD (TDF300mg+3TC300mg+DTG50mg) (FDC) should be taken orally the same time every day for adults and adolescents starting from the age of 10 or body weight of ≥30 kg. In case of TB-HIV coinfection, 1 tablet of TLD should be taken in the morning and 1 tablet of lose DTG 50mg alone in the evening or vice versa (i.e. take loose DTG 50mg 12 hours after taking TLD tablet). This tablet can be taken with or without food.

DTG 50mg as a single tablet can also be administered with AZT/3TC or ABC/3TC when clients are not eligible for TLD FDC because of tenofovir (TDF) associated contraindications.

e. Potential side effects

Although TLD is proved to be safe and effective regimen to most clients, there are concerns about using DTG during the first eight weeks of pregnancy. Besides, the three components of TLD may cause the following side effects:

Side effects associated with TDF: kidney failure, bone problems, lactic acidosis and liver problems.

Side effects associated with 3TC: Headache, nausea, diarrhea and abdominal pain.

Side effects associated with DTG: Mild or moderate nausea, headache and diarrhea; abnormal liver function, particularly in patients with HBV and HCV coinfection; potentially serious hypersensitivity reactions; and insomnia. Most side effects of DTG are limited to toxicity level Grade-1 or Grade-2 that doesn't prevent the use of DTG. However if there is grade-3 or Grade-4 toxicity, manage the patient as per the recommendation in the national HIV guideline. When there is a need to change DTG, consider from the replacement of alternative and special circumstance regimens.

f. DTG drug interactions

- Food doesn't affect DTG hence it can be taken with or without food.
- Rifampicin lowers DTG levels and co-administration is not recommended at standard doses.
- DTG increases metformin levels, which may lead to hypoglycemia. Close monitoring of blood sugars is recommended when initiating DTG in patients taking metformin.
- DTG interacts with aluminum, magnesium, calcium, and iron-containing medicines.

- Anticonvulsants interact with DTG. Co-administration with anticonvulsants is not recommended at standard doses of DTG. Consult expert opinion or consider substituting DTG with EFV as an alternative. For more information on drug interactions, please see Table 2 below and the 2018 National Guidelines.

Table 2: Key DTG drug interactions and suggested management

Key interactions	**Effects**	**Suggested management**
Carbamazepine, Phenobarbital and phenytoin	Decreases effectiveness of DTG	Use alternative anticonvulsant agent such as valproic acid or gabapentin. OR use EFV in place of DTG.
Polyvalent Cation products containing Mg, Al, Fe, Ca, and Zn.	Reduces absorption of DTG	Use DTG at least 2 hours before or at least 6 hours after supplements containing polyvalent cations, including but not limited to – Fe, Ca, Mg, or Zn multivitamin supplements; mineral supplements, cation containing laxatives and Al, Ca or Mg containing antacids. Monitor for virological efficacy.
Rifampicin	Increases metabolism of DTG, and hence reduces concentration of DTG in the blood.	Increase the dose of DTG to 50mg BID.
Metformin	DTG increases metformin levels, which may lead to hypoglycemia.	Close monitoring of blood sugar.

5. Eligibility for DTG

a. Eligibility criteria

Dolutegravir will be introduced in a phase based approach for the different target groups. According to the 2018 national consolidated guideline, initiation and transition to DTG-based first line regimen is indicated as preferred option for the following new and existing recipients of care:

- Adults and adolescent male (≥10 years old OR >30kg in weight)
- Adolescent girls (≥10 years old OR ≥30kg in weight) and women of reproductive age group with consistent and reliable contraceptive use
- Women without pregnancy potential (>49 years)
- Children (<10 years old and ≥20kg in weight)

Table 3: Eligibility criteria to shift patients from **existing regimens** to DTG

Existing ART patient group	**Eligibility criteria to shift patients from existing regimens to DTG**	**Exclusion criteria**
Male	• **Body weight**: ≥ 20KG • **Virally suppressed:** recent (within 12 months) viral load ≤1,000 copies/ml.	Adolescent girls and women of childbearing potential who do not currently use reliable contraception.
Female	• **Body weight**: ≥ 20KG • **Virally suppressed:** recent (within 12 months) viral load ≤1,000 copies/ml. • Adolescent girls and women of childbearing age who are not pregnant and are currently use reliable and consistent contraception.	

b. Contraindications for DTG

The following are contraindications for initiation and/or transition to TLD:

i. **Renal failure**: Because of TDF, TLD is not recommended for people with renal failure. Hence, renal function test has to be done before prescribing TLD
ii. Adolescent girls and women of childbearing potential who do not currently use reliable contraception and/or have desire for pregnancy
iii. Treatment failure suspects until it is ruled out

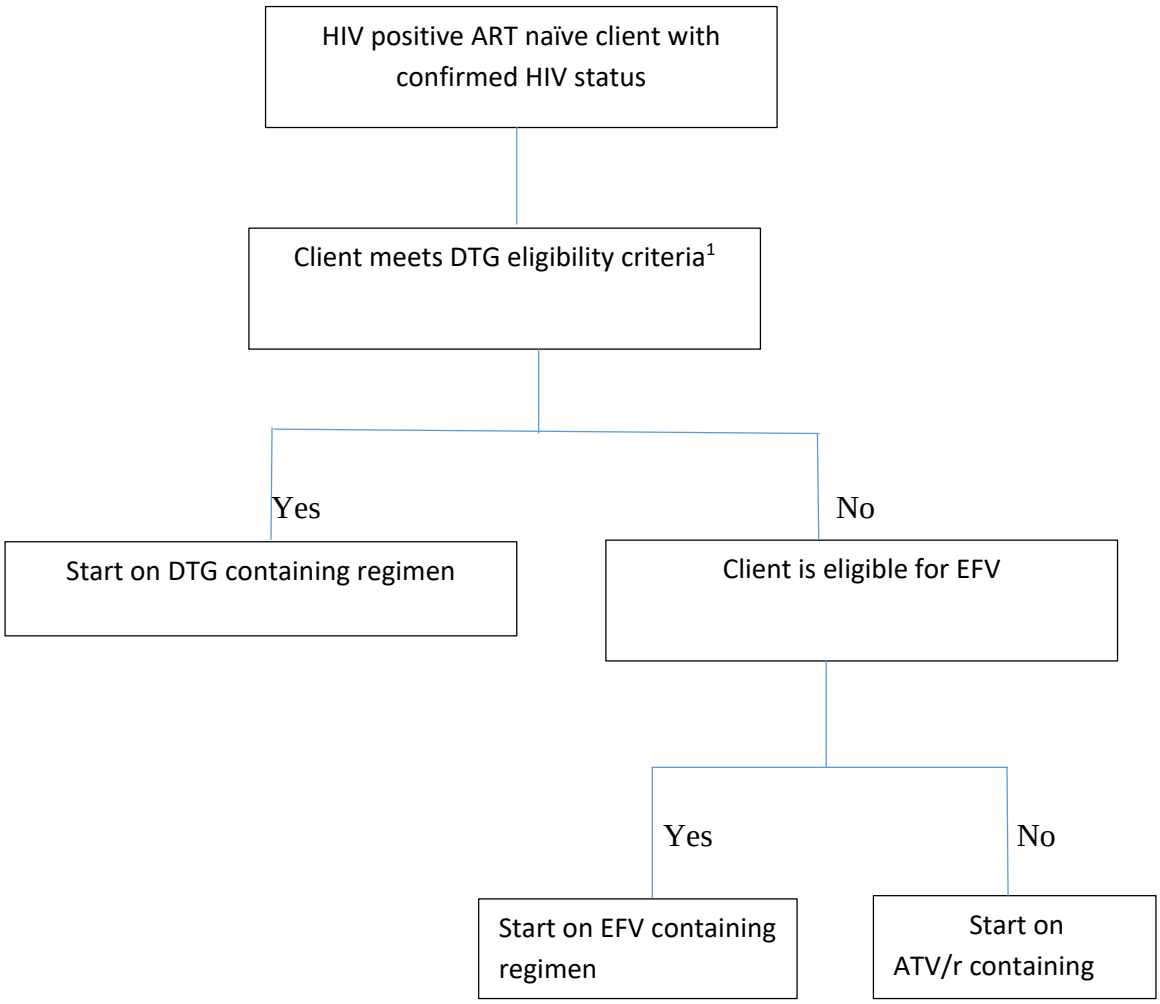
c. Special precautions for DTG use

i. For women on DTG and identified as pregnant immediately after conception, DTG should be substituted with efavirenz during the first trimester of pregnancy. But if the pregnancy is identified after the first trimester, they can remain on DTG based regimen with close follow up of the pregnancy outcome.
ii. Provide close monitoring for individuals with hepatitis B or C co-infection or other liver diseases.
iii. Dose adjustment is required for TB co-infected individuals.

d. DTG prescribing algorithm for first line ART

DTG-containing regimens will be offered **for eligible treatment naïve clients starting from April 2019**. Then **all eligible existing** first-line clients will be shifted to DTG containing regimens starting from June 2019 thereby completing the transition by June 2020. The shift to DTG for existing clients will be implemented based on their appointment schedule and individualized assessment and clinical evaluation.

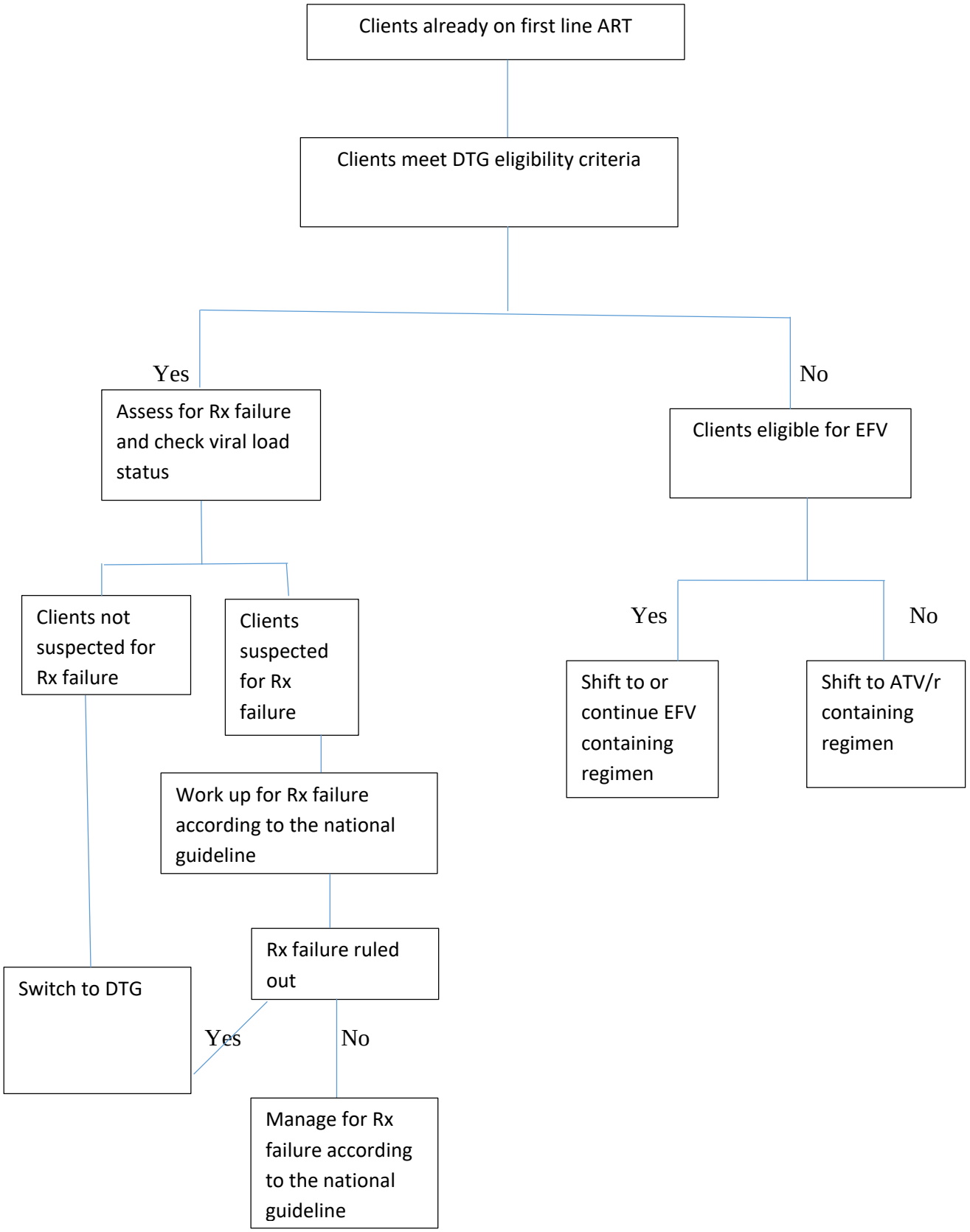
Algorithm for initiating DTG in treatment naïve clients



[1] **The following are DTG eligibility criteria for ART naïve clients**.

- *Adults and adolescent male (≥10 years old OR >30kg in weight)*
- *Adolescent girls (≥10 years old OR ≥30kg in weight) and women of reproductive age group with consistent and reliable contraceptive use*
- *Women without pregnancy potential (>49 years)*
- *Children (≥20kg in weight)*

Algorithm for shifting existing first line clients to DTG-containing regimens



e. List of existing regimens to be shifted to DTG-containing regimens

Please shift clients from existing regimens to DTG-containing regimens based on the guidance with the table below.

Table 4: Existing regimens to be shifted to DTG-containing options

Age group	**Existing Regimens**	**Preferred regimen**	**Alternative Regimens [a]**	**Special circumstance [b]**	**Remark**
Adults & adolescents (≥ 10 years)	TDF+3TC+EFV TDF+3TC+NVP	TDF+3TC+DTG	TDF+3TC+EFV	TDF/3TC/ATV/r	
	ABC+3TC+EFV ABC+3TC+NVP	TDF+3TC+DTG	ABC+3TC+DTG	ABC/3TC/EFV ABC/3TC/ATV/r	If TDF is contraindicated, the ABC+3TC back bone will be maintained.
	AZT+3TC+EFV AZT+3TC+NVP	TDF+3TC+DTG	AZT+3TC+DTG	AZT/3TC/DTG AZT/3TC/EFV AZT/3TC/ATV/r	If TDF is contraindicated, AZT+3TC back bone will be maintained.
<10 years (Wt ≥20kg)	AZT+3TC+NVP or EFV ABC+3TC+NVP or EFV	ABC+3TC+DTG	ABC+ 3TC+LPV/r or AZT+3TC+DTG	AZT+3TC+EFV ABC+3TC+EFV ABC + 3TC +EFV* (or NVP) AZT + 3TC +LPV/r	AB is the preferred back bone for children.
4weeks-10 years (Wt <20kg)	AZT+3TC+NVP or EFV*	ABC+3TC+LPV/r	AZT+3TC+LPV/r	**For > 3 yrs**. :- AZT+3TC+EFV ABC+3TC+EFV **For < 3 yrs**.:- Consider maintaining LPV/r containing regimens	
	ABC+3TC+NVP				
	ABC+3TC+ EFV*	No change until reach 20 kg unless treatment failure occurs			

Note: [a] alternative regimens are used when preferred regimens are contraindicated

[b] special circumstances are when both preferred and alternative regimens are contraindicated

f. Laboratory Monitoring of patients on DTG

- Viral load test is required to identify treatment failure and to determine whether the client is eligible for transition to DTG

- Pregnancy test is required for women of child bearing age before initiation or transition to DTG. We also should ask all our patients of childbearing potential if they are sexually active, are using contraception or desire pregnancy. If a woman is already beyond the first trimester of pregnancy TLD may be safely used.

- Laboratory tests may be done at baseline to assess for the presence of liver or kidney disease, anemia and immune status.
- In general, for patients on TLD, we monitor them the same way we monitor patients on other regimens. No different laboratory tests are needed to monitor patients on TLD.
- If we do measure creatinine, we should remember that DTG might also increase levels of serum creatinine a little bit, but by no more than 10%. This is not due to toxicity. In cases where we may be monitoring creatinine in patients on TLD, if we see an increase after starting TLD we need to differentiate whether this is due to DTG and when it may be a sign of TDF-related renal toxicity.
- Provide close monitoring of liver function tests for individuals with hepatitis B or C co-infection or other liver diseases.

6. Pediatrics ART optimization

i. Background

The national HIV guidelines since 2014 recommend ABC+3TC+EFV (or AZT+3TC+EFV) as preferred first line regimen for children 3 to 10 years, and ABC+3TC+LPV/r (or AZT+3TC+LPV/r) as preferred first line regimens for children younger than 3 years. However, the actual practice in Ethiopia shows 78% of children younger than 10 years are being treated with NVP, which is non-optimal and not preferred ARV for first line ART.

Optimizing ART is very critical to achieve **rapid** and **sustained viral suppression** in children. Optimal ARVs are efficacious, well tolerated, have high genetic barrier to resistance, and less toxic.

As presented with Table 5 below, Ethiopia adopted **ABC+3TC+DTG** as preferred regimen for children between 6weeks and 10yrs starting from body weight of **≥ 20 kg**, for whom DTG 50mg tablet can be taken daily, same time every day. For children younger than 10 years and body weight <20kg, the preferred regimen is **ABC+3TC+LPV/r**. This manual is therefore prepared to improve prescribing and dispensing of pediatric preferred regimens and ARV formulations as per the latest WHO recommendations, and to ensure proper quantification and procurement of optimal pediatric ARVs.

ii. Optimal regimens for ART naïve children

ART naïve children less than 10years of age and body weight of < 20kg

For all newly identified HIV positive children less than 10 years and body weight less than 20kg, the preferred first line regimen is **ABC+3TC+LPV/r**. For those who are not eligible for the preferred first line option, it is also important to consider **AZT+3TC+LPV/r, ABC or AZT+3TC+EFV** or **ABC or AZT+3TC+NVP** as special circumstances when preferred and the alternative option cannot be used.(Refer Table 5)

ART naïve children less than 10 years of age and body weight ≥20kg

For all newly identified HIV positive children **less than 10 years of age and body weight ≥20kg**, the preferred first line regimen is **ABC+3TC+DTG**. The dose for children with body weight of **≥ 20 kg** is DTG 50mg tablet once daily, same time every day. For those who are not eligible for **ABC+3TC+DTG**, the alternative first line regimen is **ABC+ 3TC+LPV/r**. For special circumstances when both the preferred and the alternative options cannot be used. (Refer Table 5).

ART naïve children greater than 10 years of age

For all newly HIV identified children greater than 10 years of age or ≥30 kg body weight, the preferred first line regimen is **TDF+3TC+DTG (TLD)**. For those who are not eligible for the preferred first line regimen, consider TDF or AZT or ABC+3TC+**EFV**. It is also important to

consider TDF or AZT+3TC+**ATV/r** for special circumstances when both the preferred and the alternative options cannot be used. For further information, please refer Table 5 below.

Table 5: Pediatric First line regimens

Regimens	**Children (>4weeks -10 years)**		**≥10 years of age or ≥30kg body weight**
	<20kg	**≥ 20kg**	
Preferred regimens	ABC + 3TC + LPV/r	ABC + 3TC + DTG	TDF+3TC+DTG(FDC)
Alternative regimens	No alternative first line regimen for this group.	ABC+ 3TC+LPV/r	TDF+3TC+EFV **(FDC) AZT + 3TC + EFV ABC + 3TC + EFV
special circumstance regimens	ABC + 3TC +EFV* (or NVP) AZT + 3TC +EFV (or NVP) AZT + 3TC +LPV/r	ABC + 3TC +EFV* (or NVP) AZT + 3TC +EFV (or NVP) AZT + 3TC +LPV/r	TDF+3TC+ATV/r AZT+3TC+ATV/r ABC+3TC+ATV/r

* EFV400 will replace EFV600 up on availability.

** EFV is for children 3 years and older.

iii. Optimal regimens for existing (ART experienced) children

Children between 4weeks and 10 years of age and body weight <20kg

Existing (ART experienced) children between 4weeks and 10 years of age and body weight less than 20kg should be shifted to **ABC+3TC+LPV/r.** For special circumstance regimen and additional information, please refer Table 5 above.

Children less than 10 years of age and body weight of ≥ 20kg

Existing (ART experienced) children less than 10 years of age and body weight of **≥ 20kg** should be shifted to **ABC+3TC+DTG.** For alternative options and additional information, please refer Table 5 above.

Children on ART greater than ten years of age or body weight of ≥ 30kg

Existing children greater than 10 years of age or body weight of ≥ 30kg should be shifted to **TDF/3TC/DTG**, which is preferred first line regimen for this group of children. For alternative options and additional information, please refer Table 5 above.

iv. Progressive ARVs dosage adjustment in children

Progressive assessment of body weight and ARVs dose adjustment for children is very essential component of pediatric ART. As children growths fast and continuously, there must be progressive adjustment of ARVs dose. If dose is not adjusted when weight increases, the concentration of the drug will be suboptimal and unable to control viral replication in the child body, which will lead to resistance development and treatment failure. When there is weight loss, dose must be adjusted accordingly to avoid toxicity due to overconcentration of the drug in the body.

v. Optimal ARV formulations for children

Pediatric ARV formulations should be simple and convenient for use with minimal pill burden. Such formulations can improve adherence. Besides, their convenience for transportation and handling both in the health facilities and at the client house has to be considered while selecting such formulations. For example:

- Administering many tablets (e.g. 4 tablets) as one time dose will lead to pill burden and may affect adherence.
- Unpalatable formulations (products) such as LPV/r syrup may affect adherence due to their bitter taste.
- Products that need cold storage temperature are difficult for clients who don't have refrigerator.

Newly introduced pediatrics ARV formulations

1. ABC+3TC (120+60mg) tablet

ABC+3TC (120+60mg) tablet is fixed-dose combination (FDCs) that will replace **ABC/3TC** (60mg/ 30mg) tablet **because ABC/3TC** (120mg/60mg) reduces pill burden for older/heavier children and less expensive compared to ABC 60mg/3TC 30mg.

Administration

ABC+3TC (120+60mg) tablet can be given with food. For those who can't swallow whole tablet, **dispersible tablets** can be dissolved with 2 teaspoons (10ml) water in a small and clean container and taken immediately. **Scored tablets** can be broken to administer lower doses for younger children as per the dosing chart indicated with the table below (Table 6).

Table 6: Dosing chart for ABC+3TC formulations (Dual FDCs)

Formulation	Dose by weight band									
	3 - 5.9kg		6 - 9.9kg		10 - 13.9kg		14- 19.9kg		20 - 24.9kg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
ABC/3TC 120/60mg	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5
ABC/3TC 60/30mg	1	1	1.5	1.5	2	2	2.5	2.5	3	3

2. Lopinavir /LPV/r/ (40/10mg) pellet

This formulation is composed of LPV 40mg and Ritonavir 10mg in pellet form. The pellets are filled and presented in capsules. LPV/r (40/10mg) oral pellet is being introduced to replace LPV/r 80mg/20mg/ml oral solution in the long run. Unlike the oral solution (syrup), the pellet form does not require refrigeration, has no unpleasant taste and is easy to calculate and administer dose. LPV/r 100mg/25mg Tablets can be considered for children weighing greater than 10kg and who are trained and are able to swallow whole tablets. The dosing chart for the LPV/r oral pellet and tablet are depicted below with Table 7.

Administration

- Should be taken with food.
- LPV/r oral pellets are administered twice daily (every 12 hours).
- Open the capsules and then add the pellets from the capsule onto small soft food or milk (not more than 2ml);
- It is important to make sure the child has taken the entire dose of pellets by limiting the food used to an amount the child is able to easily consume in one swallow
- The pellets **MUST NOT** be stirred, crushed, dissolved/dispersed in food or liquid, or not to be chewed.
- No mixture of the pellets and food is to be stored for later use.

Table 7: Dosing chart of LPV/r for children

	3 - 5.9kg		6 - 9.9kg		10 - 13.9kg		14 - 19.9kg		20 - 24.9kg		25 - 34.9kg	
	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM	AM	PM
LPV/r 40mg/10mg, Pellet in capsule	2	2	3	3	4	4	5	5	6	6		
LPV/r 100mg/25mg, Tablets	-	-	-	-	2	1	2	2	2	2	3	3

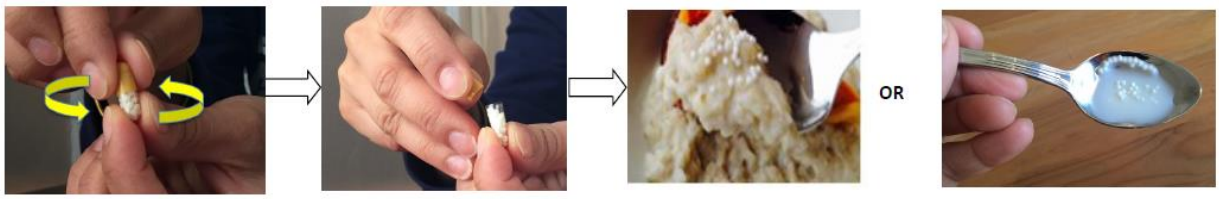
Considerations while prescribing and dispensing pediatric ARVs:

- Due to the variety of pediatric formulations of LPV/r, healthcare workers should support caregivers to ensure they are administering the medication properly to their children.
- Since many healthcare providers and caregivers have not had experience with medications in pellet form, caregivers of children on this formulation will need additional counseling and monitoring to ensure appropriate administration.
- It may be helpful to follow up with the child in the home soon after initiating LPV/r pellets to ensure proper administration and address any challenges the caregiver may be having.

- Improper administration of the medication, challenges with the child spitting out the medication, or poor adherence compromises treatment outcomes. Pre-ART counseling and early follow-up should assess for these challenges.
- Children with elevated VL should have a thorough review of how the caregiver is administering the medication, with demonstration if possible.
- It may be helpful to group appointments of children on LPV/r regimens on the same day to allow for group counseling and education of the caregivers, as well as sharing experiences among caregivers.

Instructions for counseling caregivers on LPV/r pellet administration:

1. LPV/r pellets are to be given twice daily (every 12 hrs.), in addition to their other ARV medications (ABC/3TC or AZT/3TC). The number of capsules to be given at each time should be determined by the child's current weight. *Please note that the dose is referencing the number of capsules, NOT the number of pellets contained within the capsule*.
   The LPV/r capsule **should not be** swallowed by the child. The capsule should be opened by *holding the ends of the capsule with both hands and twisting the capsule in opposite directions*. The pellets contained inside the capsule should be given with food (breast milk, porridge, yogurt, or other age-appropriate soft food). See the figure below to demonstrate proper administration.



2. Give the pellets with breastmilk or food to infant/child as soon as possible, as the medication will become bitter if left to dissolve in food, which may result in children spitting out or vomiting the pellets. Do not crush, dissolve, or stir contents of pellets as this may increase the bitter taste. The caregiver may need to divide giving the pellets over several spoonful.

3. For small infants who may not yet be able to swallow solids, monitor for any choking or gagging during administration.
4. Be sure to use all pellets in the required number of capsules for the medication dose. The capsules should be empty after the medication has been given. *Empty capsules should be disposed/ thrown away*.
5. Ensure guardians have time to ask clarifying questions on proper administration. For the first dose of LPV/r pellets, it is preferable to observe the caregiver administering the pellets to ensure given correctly and that the infant/child is able to swallow without difficulty.

DTG

- DTG 50 mg tablet can be used with ABC/3TC for children 20-30kg of body weight as a once daily dose. If they are stable on this regimen, they can be switched to the fixed dose combination TLD when they reach 30kg or 10 years.
- Adolescents who weigh ≥30kg should be transitioned to TLD.

3. Other formulations dose

Please refer Annex 1 and Annex 2 for dosage of other pediatric ARV formulations.

7. Third line ART

World Health Organization (WHO) recommends national programs should develop policies for third-line ART including new drugs with minimal risk of cross-resistance to previously used regimens, such as INSTIs and PIs. Therapy with newer third line agents is associated with a reduction in clinical progression and immunological deterioration. DRV/r has a higher genetic barrier to resistance compared to early-generation PIs and is active against multidrug-resistant HIV isolates and it has been demonstrated to be cost-effective compared to other boosted PIs.

In Ethiopia there is increasing trend of enrolling clients to second line regimens due to increasing access to ART and routine viral load monitoring. Similarly, program data on viral load monitoring revealed increased number of clients on second line ART with unsuppressed viral load. Due to this Federal Ministry of Health adopted and introduced third line ART service in August 2018.As of September 2018, DHIS2 report clients on second line regimen were 13,507

which accounts 3.2% of total clients active on ART of which 1414 were children under 15 years. Even though there is limited data regarding second line treatment failure, the national routine viral load program data from EPHI showed that 40 out of 198 (20%) patients on second-line had virology failure for second line regimens. i.e. viral load of >1000copies/ml.

Identification of second-line treatment failure in adults and pediatrics

Patients who are on second-line regimen and have high viral load level(>1000copies/ml) after 6 months of treatment need to go through the algorithm similar to first line treatment failure with enhanced adherence support and repeat test after three months to decide second line treatment failure. Once patients are confirmed to have second line failure they should be referred to hospital with experienced physicians for initiation of third line regimens. (Refer annex for algorithm of diagnosis and management of treatment failure and enhanced adherence support sessions).

Management of second-line treatment failure in adults and pediatrics

Treatment failure is indicated by virological non-suppression with or without immunologic and/or clinical deterioration. Before switching to third-line regimen, the issue should be discussed with experienced physician in HIV care and treatment. Treatment failure while on a second line PI regimen is often due to non-adherence. Doctors and nurses should participate directly in the adherence assessments, and do not delegate the assessment to the adherence counselor alone (see enhanced adherence counseling section for detailed steps of adherence counseling for patients with adherence problems). Before switching to third line regimen, health care providers should ensure the following.

- Two consecutive viral load measurements > 1000 copies/ml at least 3 months apart.
- First viral load measurement done at least 6 months after switching to second-line regimen.
- The repeat viral load test should be done after 3 months of enhanced adherence support.

The approach in switching to third-line should follow the guiding principles listed out for switching to second line drugs.

  - Ensure diagnosis of treatment failure to avoid premature switching.
  - Assess adherence and address barriers.
  - Assess for and Address drug interaction issues.

- Do not add one drug to a failing regimen.
- Consider resistance and cross resistance patterns.
- Get advice from experienced clinicians.
- At least two new drugs, preferably one new drug class.

Table 8: Summary of sequencing options for preferred first, second and third-line ART regimens in adults, adolescents, pregnant women and children

Population	**weight**	**1st line regimens**	**2nd line regimens**	**3rd line regimens**
Adults, and adolescents (including pregnant, breast feeding & child bearing women)	≥30kg	AZT+3TC+ EFV/NVP	TDF+3TC+ATV/r or LPV/r	DRV/r [a] +DTG+AZT+3TC
		TDF+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r	DRV/r+DTG+TDF+3TC
		ABC+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r	DRV/r+DTG+TDF+3TC
Adults and adolescents 10 years & older	≥30kg	TDF + 3TC + DTG[f]	AZT+3TC+ATV/r or LPV/r	DRV/r+ABC+3TC+EFV or NVP
Children 4weeks to 10 years	≤ 20kg	ABC+3TC+LPV/r	RAL [b] +AZT+3TC	Maintain second line regimens until they became become 20kg or approved DTG dosing become available.
		AZT+3TC+LPV/r	RAL+ABC+3TC	
	≥20kg	AZT+3TC+EFV	ABC+3TC+DTG	DRV/r+DTG[g]+ABC+3TC
		ABC/TDF[c] +3TC+EFV	AZT+3TC+DTG	DRV/r[h]+DTG+AZT+3TC

- *[a] In PI-experienced patients, the recommended DRV/r dose should be 600mg/100 mg twice daily.*
- *[b] If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r.*

- [c] *TDF may only be given to children >2 years.*
- [d] *ATV/r can be used as an alternative to LPV/r in children older than three months of age, however the limited availability of suitable formulations for children younger than six years of age, the lack of a fixed-dose formulation and the need for separate administration of RTV booster should be considered when choosing this regimen.*
- [e] *DRV/r should not be used in children younger than three years of age.*
- [f] *RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently only approved for children 6 years and older, however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future. DTG containing regimens are not approved for pregnant and breast feeding mothers. For HIV/TB co-infected adults & adolescents, the recommended dose of DTG is 50 mg twice daily.*
- [g] *DTG based 3rd line following use of INSTI must be administered with DTG BD.*
- [h] *Children younger than three years should not use DRV/r*

Table 9: Recommended dose of third line ARV drugs for adults and adolescents

Generic Name	Dose
Proteases inhibitors (PIs)	
Darunavir+ritonavir (DRV/r)	800mg + 100mg once daily [a] or 600mg + 100mg twice daily [b]
Integrase strand transfer inhibitors (INSTIs)	
Dolutegravir (DTG)	Dolutegravir (DTG) 50mg once daily
Raltegravir (RAL)	Raltegravir (RAL) 400mg twice daily

- [a] For individuals with no previous use of protease inhibitors.
- [b] For individuals with previous use of protease inhibitors.

Table 10: Recommended strength of Third line ARV drugs for children

Drugs	Strength of tablets (mg) or oral liquid (mg/ml)
DRV[a]	Tablet 150 mg or Tablet 75mg
DRV[a]	Solution 100mg/ml

DRV/r	120mg/20mg
RAL	Chewable tablets 25 mg
	Chewable tablets 100 mg
	Granules [b] (100 mg/sachet)

- Note: Doses for children based on their weight and age. See Annex 1 and Annex 2 for details.

Monitoring response to third line ART

- Clients after starting third line ARVs shall be appointed within two weeks of initiation for close follow up.
- Monthly clinical and laboratory Screening for opportunistic infections and drug side effects in the first six months
- The client should receive enhanced adherence support for the first six months
- Senior physicians and nurses should directly do adherence support to clients on third line ART; they should not leave to case managers/ adherence supporters alone.
- First viral load measurement should be done at least 6 months after switching to third-line regimen.
- Routine viral load monitoring should be carried out at six months, at 12 month and then every 12 months thereafter.

Eligible hospitals to provide third line ART service

- **Selected General Hospitals and Referral Hospitals**
- **Client load (number of clients on second line ART $\geq$ 20)**
- Availability of experienced and senior Physicians, (internist, pediatrician and General practitioners) that have worked at ART service and managed HIV/ART patients for at least two years and above.
- Routine Viral Load monitoring is well implemented
- Availability of enhanced Adherence support service for high Viral Load (Structured and documented)
- Availability of Laboratory services (Organ function tests like creatinine, liver enzymes, CBC)
- Availability of functional appointment system and lost to follow up tracking system,

- Service Integration (FP/ART, MHI, Good Referral system for non-clinical complimentary services).
- Strong clinical and laboratory monitoring for OI screening (X – Ray and others)

1.1. **Follow-up schedule for patients on third line ART at selected hospitals**

- Client first visit after switched to 3rd line ART will be at two weeks and then every month.
- VL monitoring is at six month ,at 12 month after put on 3rd Line ART services and followed by every 12 months
- Enhanced adherence support at each visit for the first six months.
- Followed by experienced and senior physician for the first six months (internist, pediatrician and General practitioners that have worked at ART service and managed HIV/ART patients for at least two years and above.)
- Monthly clinical and laboratory Screening for OI management in the first six months should be provided.
- Ensure appropriate recording and reporting of the third line ART service
- Patients who are switched to third line ART in General and referral Hospitals will be referred to district/ primary hospitals for follow up after six month of third line ART initiation and achieved viral load suppression.

1.2. Monitoring and evaluation of Third Line ART services

Antiretroviral provision boosts quality of life for people living with HIV. Patients on third line ART benefit largely from monitoring and evaluation. As part of services monitoring the following activities need to be performed:

Follow-up and support system for Hospitals providing third line ART

- Clinical Mentorship (Internal and External Mentorship)
- Focused coaching visit, and onsite support
- Provide Supportive supervision to care providers
- Review of the services on monthly basis

1.3. Third Line starter stock and resupply management

Medicines for Adult on Third line ARV regimen will be supplied to selected hospitals with the starter stock determined using assumption of 3.5 % of clients on second line treatment be switched to third Line Regimen. Among those patient 70 % will be put on DRV/r+DTG+AZT/3TC (600+100+50+300+150) and the rest will be taking DRV/r+DTG+TDF/3TC (600+100+50+300+300). The maximum starter issued for fourth month.

Table on how to determine starter stock for Adult

a. Total patient number on second Line
b. Eligible for third line will be 3.5% on second Line

No. of clients on second line ART	proportion of clients with 2L ART failure	3L regimens	Proportion of 3L clinets eligible for this regimen	Formulations that constitute the regimen	proption of the formulation from this regimen	Starter quantity
	3.50%	DRV/r+DTG+AZT+3TC	70%	DRV 600mg tablet	100%	
				RTV (ritonavir) 100mg tablet	100%	
				DTG 50mg tablet	100%	
				AZT/3TC (300/150mg) tablet	100%	
		DRV/r+DTG+TDF+3TC	30%	DRV 600mg tablet	100%	
				RTV (ritonavir) 100mg tablet	100%	
				TDF+3TC+DTG - TLD (300+300+50mg) FDC tablet	100%	

For children

S.N	Regimen with formulations	Remark
1	AZT+3TC+RAl	
	AZT/3TC (60+30)mg	
	RAL 100mg	
2	ABC+3TC+RAL	
	ABC/3TC (120/60)	
	RAL 100 mg	
3	AZT+3TC+RAl+DRV/r	
	AZT/3TC (60+30)mg	

	RAL 100mg	
	DRV 75 mg	
	DRV 150mg	
4	ABC+3TC+RAL+DRV/r	
	ABC/3TC(120/60)mg	
	RAL 100 mg	
	DRV 150mg tablet	
	DRV 75 mg tab	
	Ritonavir 25 mg tab	

Pediatric 3rd Line medicines for starter stock determination

a. Total pediatrics on second line
b. 3.5 % of pediatrics on second line will be eligible for third Line regimen

List of Medicine	Proportion
AZT/3TC (60+30)mg	42%
ABC/3TC (120/60)	16%
AZT/3TC (60+30)mg	42%
DRV 75 mg or DRV 150mg	54%
RAL 100 mg	100%
Ritonavir 25 mg tab	54%

Recording and reporting

To monitor the status of the services provided the health facilities have to:-

- Ensure proper Documentation and reporting for third Line ART services
- Properly document client on third Line ART on standardized patient follow up and ART register.
- Review performance and challenges of the services on monthly bases
- Ensure proper monthly reporting by DHIS-2.

8. Nevirapine Phase out

According to the recent WHO interim recommendation, for countries with national pretreatment resistance at or above 10%, alternative options to NNRTIs needs to be made by weighing ARV drug availability and the toxicity profile. In this case, DTG and PIs are suitable ARV drug options to be considered. For adults and adolescents, TLD is the preferred first line regimen and TLE is considered as alternative first line ART for those who are not eligible to DTG based regimen.

Accordingly, adults and adolescents taking Nevirapine containing regimens will be shifted to DTG based regimen as preferred option. Those clients who are not eligible to take DTG will be shifted to EFV containing regimens. Those clients who are not eligible to take either DTG or EFV containing regimen will be shifted to ATV/r containing regimen.

ABC+3TC+DTG is preferred regimen for children starting from body weight of $\geq$ 20 kg, for whom DTG 50mg tablet can be taken daily, same time every day. For children less than 20kg body weight, the preferred regimen is ABC+3TC+LPV/r. (Refer Table 11 below).

The shift from all NVP-containing regimens will start in June 1, 2019 and completes in September 2019. The preferred regimen for the shift is TDF/3TC/DTG. However, those clients on Nevirapine who are child bearing age and who are not receiving consistent and reliable contraception will be switched to EFV based regimen. Most of the clients on AZT/3TC backbone can be shifted to TDF/3TC backbone while some clients who can't tolerate or are contraindicated to TDF will remain on AZT based regimens. Clients on ABC/3TC/NVP will be transitioned to DTG containing regimen as preferred option; those who can't be transitioned to TLD will be shifted to either ABC/3TC/DTG or ABC/3TC/EFV or ABC/3TC/ATV/r. (Refer Table 11 below).

Table 11: Regimens to be used in the transition of clinically stable clients to optimal regimens

Age group	Weight	Existing Regimen	Preferred regimen	Alternative Regimen	Special circumstance*	Timeline to start the shift
Adults &		TDF/3TC/NVP	TLD	TLE	TDF/3TC/ATV/r	June , 2019

<table>
<tr><td rowspan="4">adolescents (≥ 10 years)</td><td rowspan="4">≥30kg</td><td>ABC/3TC/NVP</td><td>TLD</td><td>TLE or ABC/3TC/DTG</td><td>ABC/3TC/EFV
ABC/3TC/ATV/r</td><td>June, 2019</td></tr>
<tr><td>TDF/3TC/EFV</td><td>TLD</td><td></td><td></td><td>June, 2019</td></tr>
<tr><td>AZT/3TC/NVP(FDC)</td><td>TLD</td><td>TLE</td><td></td><td>June, 2019</td></tr>
<tr><td>ABC+3TC+EFV</td><td>TLD</td><td>TLE</td><td>AZT/3TC/DTG
AZT/3TC/EFV
AZT/3TC/ATV/r</td><td>June, 2019</td></tr>
<tr><td rowspan="5">4weeks to 10 years</td><td rowspan="2">≥20kg</td><td>AZT/3TC/NVP (FDC)
ABC/3TC/NVP</td><td rowspan="2">ABC+3TC+DTG</td><td rowspan="2">ABC+3TC+LPV/r</td><td rowspan="4">ABC + 3TC +EFV* (or NVP)
AZT + 3TC +EFV (or NVP)
AZT + 3TC +LPV/r</td><td rowspan="4">June, 2019</td></tr>
<tr><td>ABC+3TC+EFV</td></tr>
<tr><td rowspan="3"><20kg</td><td>AZT/3TC/NVP (FDC)
ABC/3TC/NVP</td><td>ABC+3TC+LPV/r</td><td>AZT+3TC+LPV/r</td></tr>
<tr><td>ABC+3TC+EFV</td><td colspan="2">No change until reach 20 kg unless treatment failure occurs</td></tr>
</table>

* For those clients who could take neither DTG nor EFV due to contraindication and/or side effects.

** EFV is for children 3 years and older.

Product allocation and distribution during nevirapine phase out

- Lose NVP 200mg tab and AZT/3TC/NVP triple FDC tablets will be shifted staring June 1, 2019. Adequate quantity of other products such as TLD and DTG has to be distributed to health facilities before the end of May 2019.
- Expired lose NVP 200mg tab and AZT/3TC/NVP triple FDC tablets have to be properly disposed.

- There will be a national regimen data collection in September/October 2019 to analyze and standardize the regimen proportions of all clients on ARV. This assessment will help the program to see whether the shift is going as planed and guide the logistics system in the measures to be taken, if necessary.
- There should be stringent stock status monitoring for all ARVs at hub and facility level to ensure smooth implementation of the shifts
- There will be pipeline monitoring to adjust supply planning and procurement
- Strong collaboration between ART clinic and pharmacy staffs is necessary to ensure the phase-in phase-out process is as smooth as anticipated.

9. Operational considerations for national DTG rollout and ART regimen optimization

a. Supply and distribution plan for DTG containing regimens

DTG containing products allocation and distribution for ART naïve clients

DTG-containing regimens will be offered for eligible treatment naïve adults, adolescents and children starting from April 2019. Based on this:

- EPSA hubs, in collaboration with near-by RHBs or ZHDs, will calculate and distribute starter stock of TLD to every ART facility before the end of March 2019.
- The TLD starter stock for new clients will be calculated based on the number of adults, adolescents, and children enrolled every month (based on average enrollment data).

Note: -

- Starter stock of loose DTG 50mg tablet will be calculated and distributed for 7% of new clients of every ART facilities.
- All other ARV products will be refilled based on RRF submitted by ART facilities.
- After a starter stock is distributed, the routine refill of TLD will be managed based on the RRF reporting system.

DTG containing products allocation and distribution for existing ART clients

The shift of existing clients to DTG containing regimens will begin in June 2019. The table (template) below will be used to calculate TLD starter stock to be allocated for existing ART clients that would be shifted from existing regimens to DTG containing regimens.

Table 12: TLD **starter stock allocation** template for existing ART clients

		A	B	C	D	E	F	G
Existing regimen	**Unit**	**Facility SOH**	**Number of clients on the Regimen**	**Proportion to be shifted to TDF/3TC/DTG**	**Proportion that require additional DTG 50mg single tab**	**Quantity of TDF/3TC/DTG to be distributed to**	**Quantity of DTG 50mg single tablet (F=D*E)**	**Quantity of existing regimens to be refilled (G=B-E-**

						facilities (E=B*C)		**A)**
TDF/3TC/EFV*				70%	10%			
TDF/3TC/NVP				70%	10%			
AZT/3TC/EFV				70%	10%			
AZT/3TC/NVP				70%	10%			
ABC/3TC/EFV**				0%				
Total quantity								

* Refill TLE to the maximum quantity

** All clients on ABC+3TC+EFV regimen will remain on the same backbone (ABC/3TC). However, its end locks will be refilled with 70% DTG and 30% EFV

- The EPSA hub will distribute a starter stock of TLD and lose DTG for existing ART clients based on the proportion of first line clients for DTG containing regimens before the end of May 2019.
- Then, the routine refill will be based on the standard procedure using RRF.

b. Training/Orientation plan on DTG rollout ART regimen optimization

The topics to be covered by this training/orientation include:

- ❖ DTG rollout;
- ❖ pediatrics ART optimization
- ❖ Third line ART introduction
- ❖ NVP phase out;

Note: - Circular letters will be issued as follows.

a. The FMoH will issue a circular letter not later than March 1, 2019 to RHBs mentioning about rollout of DTG, TLD, TLE400, ABC/3TC (120/60mg), & LPV/r pellets starting from April 2019 at facility level. The letter will also mention about NVP phase out.

b. RHBs will send the circular to their respective zones, woredas, and health facilities.

c. EPSA central will issue circular to its branches mentioning about distribution schedule and rollout of DTG, TLD, TLE400, ABC/3TC (120/60mg), & LPV/r pellets.

d. The circular letter about NVP phase out must be issued again to facilities by July 2019. The circular letter will mention that loose NVP use will be phased out starting from September while phase out of AZT/3TC/NVP FDC starting from January 2020.

Length of time required for the training/orientation to cover the topics: A total of **1 to 2 days** is required to cover all the following topics included under this orientation.

- DTG rollout: **2.5 to 4.5 hrs.**
- NVP phase out: **0.5 to 1 hrs**.
- Pediatrics ART: **2 to 3.5 hrs.**
- Third line ART introduction: **0.5 to 1 hr.**

Training Approaches:

National (Central) Level and **Regional Level** Orientation/Training will be conducted **off-site**. Then those who received Orientation/Training at central and regional level will cascade the orientation using both **off-site** and **onsite** methods to health facilities under the catchment area of each hospital/mentors who received the central and regional level Orientation/Training.

The cascading method (i.e. onsite vs offsite) for the training/orientation will be decided by RHBs or other sub-regional responsible body based on availability of trainers (who received the central &/or regional level training) and financial resources. Regional level training and cascading can be conducted in parallel sessions based on availability of adequate number of qualified trainers that received central &/or regional level training.

During the central level training, RHBs will be given a template to prepare and submit their detailed plan for regional level training; cascading to health facilities; and monitoring of DTG rollout. Their planning exercise will also identify/indicate the required and available resources and partners to support cascading activities in their specific region, setting target number for ART naïve clients who can start with DTG and/or existing clients who can be shifted to DTG.

Participants of the Orientation/Training:

National (Central) Level: FMOH; central EPSA; FHAPCO; EPHI; Partners; RHB HIV program managers; EPSA branches; and selected mentors from lead hospitals.

Regional Level: It will be implemented based on the detail plan to be prepared by the RHBs during the central level training. Participants will include ART clinical mentors from selected hospitals; ZHD HIV program focal/managers; and RHB and EPSA staffs working on HIV program and logistics.

Timeline for the trainings

Session	Timeline		venue	Responsible body
Central level training	February 5, 2019	February 8, 2019	Addis Ababa	FMOH, EPSA, Partners
Regional level training	February 13, 2019	February 20, 2019	Regions	RHBs & EPSA hubs
Cascading of the training	February 21, 2019	March 20, 2019	Zonal/woreda level **OR** on-site	RHBs and mentor hospitals/mentors

c. Implementation timeline for DTG rollout and ART regimen optimization

S.N	List of Activities	Time line																		
		2018			2019												2020			
		Oct	Nov	Dec	Jan	Feb	Mar	April	May	June	July	Aug	Sep	Oct	Nov	Dec	Q1	Q2	Q3	Q4
1.	Organize task force																			
2.	Amend Quantification																			
3.	Prepare DTG rollout and ART regimen optimization implementation manual																			
4.	Amend DTG Procurement																			
5.	Suppliers deliver DTG, ABC/3TC (120/60mg) and LPV/r pellet (40/10mg)and LPV/r 100/25mg tablet and third line ARV shipment to EPSA central warehouse																			
6.	Prepare detailed distribution plan by EPSA																			
7.	Issue circular to RHBs (from FMOH) and EPSA hubs (from																			

	EPSA central)																			
8.	RHBs issue letters to their health facilities																			
9.	Distribute DTG, ABC/3TC (120/60mg) and LPV/r pellet (40/10mg)and LPV/r 100/25mg tablet and third line ARV to EPSA hubs																			
10.	Distribute DTG and third line ARV starter stock to HFs for naïve clients																			
11.	Distribute ABC/3TC (120/60mg) and LPV/r (40/10mg) pellet and LPV/r (100/25mg) tablet to HFs																			
12.	Distribute DTG and third line ARV starter stock to HFs for existing clients																			
13.	Organize national level orientation workshop for all stakeholders																			
14.	Cascade the orientation to HFs																			

15.	Prescribe and dispense DTG for treatment naïve clients																			
16.	Provide third Line ART services for eligible clients in the selected Hospitals																			
17.	Prescribe and dispense ABC/3TC (120/60mg) and LPV/r (40/10mg) pellet and LPV/r (100/25mg) tablets for eligible CLHIV																			
18.	Conduct supportive supervision & review meetings																			
19.	Monitor stock status stringently																			
20.	Collect regimen data for stock distribution planning																			
21.	Prescribe and dispense DTG for existing (ART experienced) clients																			
22.	Start NVP phase out																			

	implementation																			
23.	Conduct program review on performance and progress																			
24.	Integrate with the routine implementation																			

d. Monitoring of DTG rollout

- Harmonize appointment of contraception and DTG refill. Those clients enrolled for Appointment Spacing Model (ASM) may need readjustment of their follow up as per the type of contraception.
- There will be a parallel monthly reporting of the roll out at health facility using a DTG roll out monitoring tool until fully integrated into the HMIS system,
- FMOH will undertake supportive supervision biannually until the completion of the transition
- FMOH will conduct review meetings involving relevant stakeholders
- EPSA will collect regimen data immediately after introduction of DTG and at middle of transition period
- RHBs will conduct supportive supervision every quarter until the end of the transition
- RHBs and EPSA hubs will have a joint taskforce to further smoothen the DTG transition and ART optimization process
- ZHD/sub cities/WoHO will ensure DTG rollout and ART regimen optimization is a standing agenda during the catchment area meetings until the end of the transition period
- Health facilities make TLD transition a standing agenda during the MDT meeting

e. Roles and responsibilities

FMoH:

- Endorse the global recommendation on DTG rollout, ART regimen optimization and define policy direction on third line ART service
- Revise the national GL incorporating the globally recommended DTG/TLD as FDC and loose combination,
- Lead the task force in the harmonization of the DTG roll out in line with logistic preparation,
- Harmonize the participation of different stake holders for smooth implementation of the DTG roll out,
- Conduct site readiness assessment and site selection for the implementation of third line ART service
- Write a circular letter to RHBs & facilities mentioning about rollout of DTG, TLD, TLE400, ABC/3TC (120/60mg), & LPV/r pellets not later than March 1, 2019.
- Develop a detailed transition plan
- Prepare orientation materials and job aids
- Organize national launching/orientation workshop on DTG rollout and ART regimen optimization for RHBs and stakeholders
- Develop monitoring tool and Monitor the implementation

FHAPCO

- Endorsing the global recommendation into the national program,
- Advocacy and coordination of stake holders on incorporating DTG as First line regimen,
- In collaboration with FMOH, organize press conference to create awareness on the roll out of DTG and ART optimization,
- Closely monitor the progress of the implementation,
- Incorporate the implementation of DTG roll out in its regular supportive supervision and monitoring scheme,

EPSA

- Write a circular letter to its branches mentioning about rollout of and distribution plan for TLD, TLE400, ABC/3TC(120/60mg), & LPV/r pellets not later than March 1, 2019.
- Plan and execute the forecasting and procurement in line with the direction given by the FMoH about the new products rollout.
- Organize and lead the logistics side of the transition including training/orientation.
- Determine quantity to be supplied and distributed as a starter stock of all newly introduced products.
- Strictly monitor the stock in order to minimize/avoid stock out and wastage of ARVs.
- Avail logistics data timely to stakeholders for decision making.
- Support facilities for appropriate inventory management, reporting and requisition, and storage.
- Handle emergency orders properly (if any).
- Ensure continuous availability of ARVs for the smooth implementation of the shifts.

Ethiopian Public Health Institute (EPHI)

- Closely follow up and make sure that those facilities have uninterrupted testing services with shorter TAT
- Ensure early High viral load result delivery to hospitals
- Generate viral load related report to inform the health program

PLHIV Associations/ NNPWE/ NEP+

- Be actively involved in the endorsement of the DTG global recommendation,
- Advocacy on the new changes to PLHIV and make aware the phased based implementation,
- Develop document on new regimen and drug for its members, ,
- Demand creation from national through health facility level to enhance the national roll out,
- Advocate and support adherence support to clients
- Write a circular letter to all PLHIV associations and case managers on the TLD/DTG50, TLE400, ABC/3TC (120/60), and LPV/r pellets,
- Create awareness about the benefits and roll out of DTG to its members PLHIV,
- Sensitize PLHIV and the general community on the cascaded implementation of the DTG roll out,

RHBs/ZHDs/WoHO

- Write a circular letter to facilities mentioning about rollout of TLD, TLE400, ABC/3TC (120/60mg), & LPV/r pellets not later than March 15, 2019.
- Cascade regional and sub-regional level training/orientation
- Participate in hospital readiness assessment and site determination.
- Monitor the overall rollout of TLD, TLE400, ABC/3TC (120/60), and LPV/r pellets.
- Coordinate with EPSA to ensure continuous availability of ARV products, starter and refill.
- Support facilities for the smooth implementation of the transition.
- Ensure the availability and utilization of ARV drugs dispensing register and patient information sheet.
- Monitor the facility level Implementation of the roll out collecting monthly report using the prepared format,

Health Facilities

- Ensure ART providers received orientation/training on rollout of DTG, third line ART, TLE400, ABC/3TC (120/60), and LPV/r pellets.
- If there is a gap, coordinate with WoHO/ZHDs/ RHBs/any available stakeholder to arrange trainings/orientations.
- Ensure regular stock status monitoring for all ARVs considering the rollout.
- Make sure that clients are properly informed about TLD and other new products by engaging health care providers.
- Ensure adequate availability of TLD, DTG, third line ART, TLE400, ABC/3TC (120/60), and LPV/r pellets.
- Ensure the third line ARV services are provided in compliance to the national standard
- Close follow up of VL and support for third Line ART services and EAS
- Keeping appropriate medication records on patient information sheet (yellow sheet).
- Compile and report on regimen breakdown to RHB/ZHD and EPSA.
- Make rollout of TLD and other new products an agenda on their MDT and other plat forms.
- Ensure patient and regimen records properly filled and complete.
- Request supports from RHBs if there is any need.

- Engaging PLHIV associations and volunteers while implementing DTG rollout and optimized regimen as per the national guidance.

Partners

- Provide technical and financial resources to support DTG rollout and ART regimen optimization at all levels from design to the implementation, Monitoring and evaluation phases

Annexes

Annex 1: Simplified dosing of solid and oral liquid formulations for twice-daily dosing for infants and children 4 weeks of age and older

Drug	Formulations (tablet, capsule or oral liquid) and strength (mg/tab. or mg/ml for liquids)	Dose as number of tablets or ml by weight band, morning(AM) and evening (PM)										Adult tablets and their strength in mg	Dose as number of tablets by weight band			
		3 – 5.9Kg		6-9.9kg		10-13.9kg		14-19.9kg		20-24.9kg			25-29.9		30-34.9	
		AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM	AM	PM
Solid formulations																
ABC/3TC	120mg/60mg (scored,	0.5	0.5	0.5	1	1	1	1	1.5	1.5	1.5	600mg/300mg tab	0.5	0.5	0.5	0.5
ABC/3TC	60mg/30mg (scored,	1	1	1.5	1.5	2	2	2.5	2.5	3	3	600mg/300mg tab	0.5	0.5	0.5	0.5
ABC	60mg(dispersible	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg tab	1	1	1	1
AZT/3TC	60mg/30mg (scored,	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg tab	1	1	1	1
AZT/3TC/NVP	60mg/30mg/50mg (scored,	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg/150mg/200mg tab	1	1	1	1
AZT	60mg (dispersible	1	1	1.5	1.5	2	2	2.5	2.5	3	3	300mg tab	1	1	1	1
DRV [a]	75mg tablet	-	-	-	-	3	3	5	5	5	5	600mg tab	1	1	1	1
DRV [a]	150mg tablet	-	-	-	-	One 150mg + one 75mg	One 150mg + one 75mg	Two 150mg + one 75mg	Two 150mg + one 75mg	Two 150mg + one 75mg	Two 150mg + one 75mg					
LPV/r [b, c]	40mg/10mg oral pellets per capsule	2	2	3	3	4	4	5	5	6	6	200mg/50mg tab	2	1	2	1
	100mg/25mg tablet	-	-	-	-	2	1	2	2	2	2		2	1	2	1

NVP [d]	50mg (scored,	1	1	1.5	1.5	2	2	2.5	2.5	3	3	200mg tab	1	1	1	1
RAL	100 mg, chewable	-	-	-	-	-	-	1	1	1.5	1.5	400mg tab	1	1	1	1
	25mg, chewable	-	-	-	-	3	3	4	4	6	6		1	1	1	1
	100 mg granules per sachet	0.25	0.25	0.5	0.5	-	-	-	-	-	-		1	1	1	1
Liquid formulations																
ABC	20mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-		-	-	-	-
AZT	10mg/ml	6ml	6ml	9ml	9ml	12ml	12ml	-	-	-	-		-	-	-	-
3TC	10mg/ml	3ml	3ml	4ml	4ml	6ml	6ml	-	-	-	-		-	-	-	-
NVP [d]	10mg/ml	5ml	5ml	8ml	8ml	10ml	10ml	-	-	-	-		-	-	-	-
LPV/r [e]	80mg/20mg/ml	1ml	1ml	1.5ml	1.5ml	2ml	2ml	2.5ml	2.5ml	3ml	3ml		-	-	-	-
DRV [a]	100mg/ml	-	-	-	-	2.5ml	2.5ml	3.5ml	3.5ml	-	-		-	-	-	-
RTV [f]	25mg tablet	-	-	-	-	2	2	2	2	2	2		2	2	2	2
	80mg/ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	0.5ml	-	-	-	-		-	-	-	-

[a] DRV must be administered with 0.5ml of RTV 80mg/mL oral suspension if the child weighs less than 15kg and with RTV 50mg solid formulation for children weighing 15–30kg. DRV/r should not be used in children younger than 3 years of age.
[b] LPV/r heat-stable oral pellets (presented in a capsule) must be administered by **opening the capsule and pouring the pellets over a small soft food** at room temperature and swallowed without chewing. The pellets **MUST NOT** be stirred, crushed, dissolved/dispersed in food. The capsules containing LPV/r oral pellets **must not** be swallowed whole.
[c] The LPV/r heat-stable tablet must be swallowed whole and should not be split, chewed, dissolved or crushed.
[d] NVP dose escalation with half dose for 2 weeks when initiating ART is still recommended to avoid toxicity from high initial NVP levels.
[e] LPV/r liquid requires a cold chain during transport and storage.
[f] RTV is a booster for other protease inhibitors such as LPV, ATV and DRV.

ABC=Abacavir; AZT=Zidovudine; 3TC= Lamivudine; DRV=Darunavir; LPV/r= Lopinavir combined with ritonavir; NVP=Nevirapine; RAL=Raltegravir; RTV=Ritonavir; ATV=Atazanavir.

Annex 2: Simplified dosing of solid and oral liquid formulations for once-daily dosing for infants and children 4 weeks of age and older

Drug	Formulations (tablet, capsule or oral liquid) and strength (mg/tab. or mg/ml for liquids)	Dose as number of tablets or ml by weight band					Adult tablets and their strength in mg	Dose as number of tablets by weight band	
		3 – 5.9Kg	6-9.9kg	10-13.9kg	14-19.9kg	20-24.9kg		25-29.9kg	30-34.9kg
EFV [a]	200mg tablet	-	-	1	1.5	1.5	200 tab	2	2
	50mg capsule	-	-	4	6	6	600mg		
ABC/3TC	120mg/60mg (scored, dispersible tablet)	1	1.5	2	2.5	3	600mg/300mg	1	1
	60mg/30mg (scored, dispersible tablet)	2	3	4	5	6		1	1
ATV [b]	100mg capsule	-	-	1	2	2		2 capsules of 100mg	1 tablet of 300mg
TDF [c]	Oral powder (40mg TDF per scoop of powder)	-	-	3	-	-		1 tablet of 200mg	1 tablet of 300mg
	150mg tablet	-	-	-	1	-			
	200mg tablet	-	-	-	-	1			
TDF/3TC	75mg/75mg tablet	-	-	1.5	2	2.5		3	3.5
TDF/3TC	300mg/300mg tablet	-	-	One	One half	Two		1	1
TDF/3TC/EFV	300mg/300mg/600mg tablet	-	-	One third	One half	Two		1	1

[a] Two EFV 50mg capsules is administered in combination with EFV 200mg tablet for children weighing 14-24.9KG.

b ATV is only approved for use for children 3 months and older. ATV single-strength capsules should be administered with RTV 100 mg for all weight bands. The ATV powder formulation enables administration of ATV to infants and children as young as 3 months. Infants and children weighing 5–10 kg should be administered 200 mg of ATV with 80 mg of RTV oral solution (5 ml).

c TDF is only approved for use for children 2 years and older. Target dose: 8 mg/kg or 200mg/m^2 (maximum 300mg). A child would not receive more than 25% above the maximum target dose or more than 5% below the minimum target dose.

EFV=Efavirenz; TDF=Tenofovir disoproxil fumarate

Annex 3: Sequencing Options for first second and third line ART for adults and pediatrics.

Population	weight	1st line regimens	2nd line regimens	3rd line regimens
Adults, and adolescents (including pregnant, breast feeding & child bearing women)	≥30kg	AZT+3TC+ EFV/NVP	TDF+3TC+ATV/r or LPV/r	DRV/r [a] +DTG+AZT+3TC
		TDF+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r	DRV/r+DTG+TDF+3TC
		ABC+3TC+EFV/NVP	AZT+3TC+ATV/r or LPV/r	DRV/r+DTG+TDF+3TC
Adults and adolescents 10 years & older	≥30kg	TDF + 3TC + DTG[f]	AZT+3TC+ATV/r or LPV/r	DRV/r+ABC+3TC+EFV or NVP
Children 4weeks to 10 years	≤ 20kg	ABC+3TC+LPV/r	RAL [b] +AZT+3TC	Maintain second line regimens until they became become 20kg or approved DTG dosing become available.
		AZT+3TC+LPV/r	RAL+ABC+3TC	
	≥20kg	AZT+3TC+EFV	ABC+3TC+DTG	DRV/r+DTG[g]+ABC+3TC
		ABC/TDF[c] +3TC+EFV	AZT+3TC+DTG	DRV/r[h]+DTG+AZT+3TC

- [a] *In PI-experienced patients, the recommended DRV/r dose should be 600mg/100 mg twice daily.*
- [b] *If RAL is not available, no change is recommended unless in the presence of advanced clinical disease progression or lack of adherence specifically because of poor palatability of LPV/r.*

- *[c] TDF may only be given to children >2 years.*
- *[d] ATV/r can be used as an alternative to LPV/r in children older than three months of age, however the limited availability of suitable formulations for children younger than six years of age, the lack of a fixed-dose formulation and the need for separate administration of RTV booster should be considered when choosing this regimen.*
- *[e] DRV/r should not be used in children younger than three years of age.*
- *[f] RAL can be used in children failing PI-based second-line treatment when DTG is not available and when RAL has not been not used in a previous regimen. DTG is currently only approved for children 6 years and older, however studies are ongoing to determine dosing in younger children and approval to lower age groups is expected in the near future. DTG containing regimens are not approved for pregnant and breast feeding mothers. For HIV/TB co-infected adults & adolescents, the recommended dose of DTG is 50 mg twice daily.*
- *[g] DTG based 3rd line following use of INSTI must be administered with DTG BD.*
- *[h] Children younger than three years should not use DRV/r*

Annex 4: Recommended doses of third line ARV drugs for children.

Drugs	Strength of tablets (mg) or oral liquid (mg/ml)		Number of tablets or ml by weight-band morning (AM) and evening (PM)										Strength of adult tablet (mg)	Number of tablets by weight band	
			3.0–5.9 kg		6.0–9.9kg		10.0–13.9kg		14.0–19.9kg		20.0–24.9 kg			25.0–34.9 kg	
			AM	PM	AM	PM	AM	PM	AM	PM	AM	PM		AM	PM
Solid formulations:															
DRV[a]	75 mg		-	-	-	-	3	3	5	5	5	5			
DRV/r	120mg/20mg		-	-	-	-	2	2	3	3	3	3		4	4
RAL	Chewable tablets 25 mg		-	-	-	-	3	3	4	4	4	6	400	1	1
	Chewable tablets 100 mg		-	-	-	-	-	-	1	1	1.5	1.5	400	1	1
	Granules[b] (100 mg/sachet)		0.25	0.25	5	5		-	-	-	-	-		-	-
Liquid formulations															
DRV[a]		100mg/ml	-	-	-	-	2.5ml	2.5ml	3.5ml	23.5ml	-	-			

[a] *DRV must be administered with 0.5 ml of RTV 80 mg/mL oral suspension if the child weighs less than 15 kg and with RTV 50 mg solid formulation for children weighing 13-30 kg*

[b] *RAL granules are approved for use for children as young as 4 weeks, but the feasibility and acceptability of such formulations has not been widely investigated, andconcerns have been raised regarding administration in resource-limited settings. The bioequivalence of RAL chewable tablets dispersed in liquid is currently being explored, and more guidance will be provided as soon as additional evidence becomes available*

Annex 5: Algorithm for diagnosis and management of treatment failure