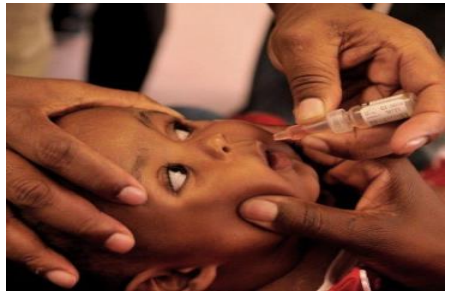
National Department of Health, South Africa



Paediatric Dolutegravir 10mg Dispersible, Scored Tablets Training Slides

Information for healthcare workers

February 2023

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REPUBLIC OF SOUTH AFRICA

2030 NDP

The Goal of Antiretroviral Therapy (ART)

Achieve and Maintain
Viral suppression

- Decrease opportunistic infections and other HIV-related conditions
- Minimise the development of treatment resistance
- Decrease the morbidity and mortality from HIV/AIDS
- Improve quality and length of life

Minimise Treatment side-effects and toxicity

Poll Question 1 (Single Selection)

ABC + 3TC + DTG is a preferred regimen for a 3 year old child with weight of 15Kgs

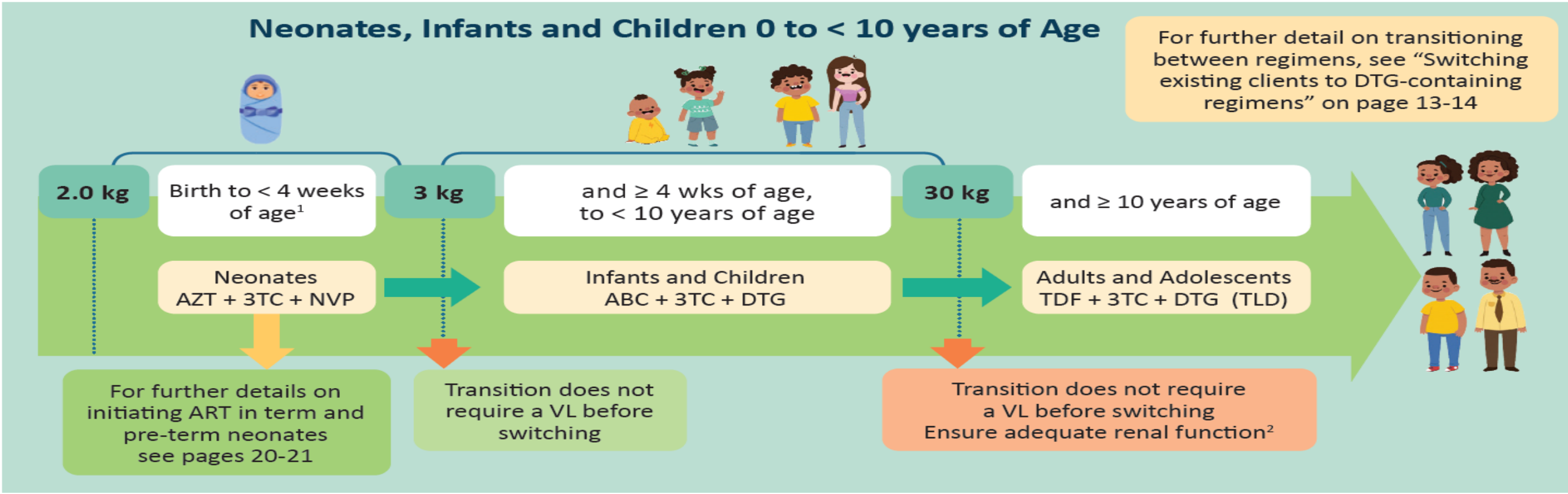
a) True

b) False

c) Not Sure

NDoH recommended 1st line regimens for Neonates, Infants and Children

All children should be to be switched to optimal formulations to enhance adherence, clinical efficacy, administration, palatability and to reduce side effects.



Source : Draft Abridged HIV guidelines

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Changes to the 1st ART regimens

Changes in the 2023 ART guidance for CLHIV

Age & Weight	Current Regimen	New Regimen
Birth to 4 weeks and up to 2.9kg	AZT + 3TC + NVP	AZT + 3TC + NVP
Over 4 weeks and 3 kg to 19.9kg	ABC + 3TC + LPV/r	ABC + 3TC + DTG
20 to 29.9kg	ABC + 3TC + DTG	ABC + 3TC + DTG
30 to 34.9kg	ABC + 3TC + DTG	TDF + 3TC + DTG
Over 35kg	TDF + 3TC + DTG	TDF + 3TC + DTG

DTG should be part of the preferred first-line ART regimen for **all adults, adolescents, children and infants living with HIV**, including women of child-bearing potential but excluding neonates.

Introducing Paediatric Dolutegravir (pDTG) 10mg dispersible, scored tablets:

A new and optimal product that is more effective, more palatable and easier to administer

WHAT IS pDTG?

- Since 2019, Dolutegravir (DTG) has been the preferred first-line (1L) regimen for adults, adolescents, and children living with HIV ≥20 kg.
- Following registration with the South African Health Products Regulatory Authority (SAHPRA), Paediatric Dolutegravir (pDTG) 10mg dispersible, scored tablets are now recommended by the National Department of Health as part of the standard first-line antiretroviral regimen for children (≥ 4 weeks to <10 years of age) in the weight band 3 – 20kg, in combination with 2 NRTIs, ABC (abacavir) and 3TC (lamivudine)
- pDTG is an INSTI (integrase strand transfer inhibitor) that prevents HIV replication by inhibiting catalytic activity for HIV-1 integrase, an HIV encoded enzyme that is required for viral replication.

pDTG is the preferred first line antiretroviral over lopinavir/ritonavir (LPV/r) formulations for paediatric patients who weigh **3 – 20kg**

NOTE: Paediatric Dolutegravir 10mg dispersible, scored tablets can be prescribed by a doctor or a professional nurse.

Poll Question 2 (Multi Selection)

Which of the following are advantages of Dispensable pDTG?

a) High genetic barrier to resistance

b) Better taste

c) Less tolerable

d) DTG is taken once daily

e) Superior clinical efficacy

Advantages of pDTG dispersible, scored tablets

Paediatric dolutegravir 10mg dispersible, scored tablets (pDTG) is a new generic formulation of DTG that allows antiretroviral treatment (ART) for children living with HIV (CLHIV) who are at least 4 weeks of age and weigh 3 to 20kg.

Clinically Superior:

- ✓ Demonstrated superior clinical efficacy
- ✓ DTG's high genetic barrier to resistance
- ✓ Increasing NNRTI resistance necessitates a transition away from EFV- and NVP-based regimens

Bolsters Adherence:

- ✓ DTG is taken once daily
- ✓ Better side effect profile
- ✓ DTG dispersible tablet is easily dissolved in **water, juice, milk, breast milk, yoghurt and porridge** and allows easier administration as a solution or can be swallowed whole.
- ✓ DTG dispersible tablet has a strawberry taste and is more palatable

Paediatric ARV Product Optimisation:

All children should be switched to optimal formulations to enhance adherence, clinical efficacy, administration, palatability and to reduce side effects.

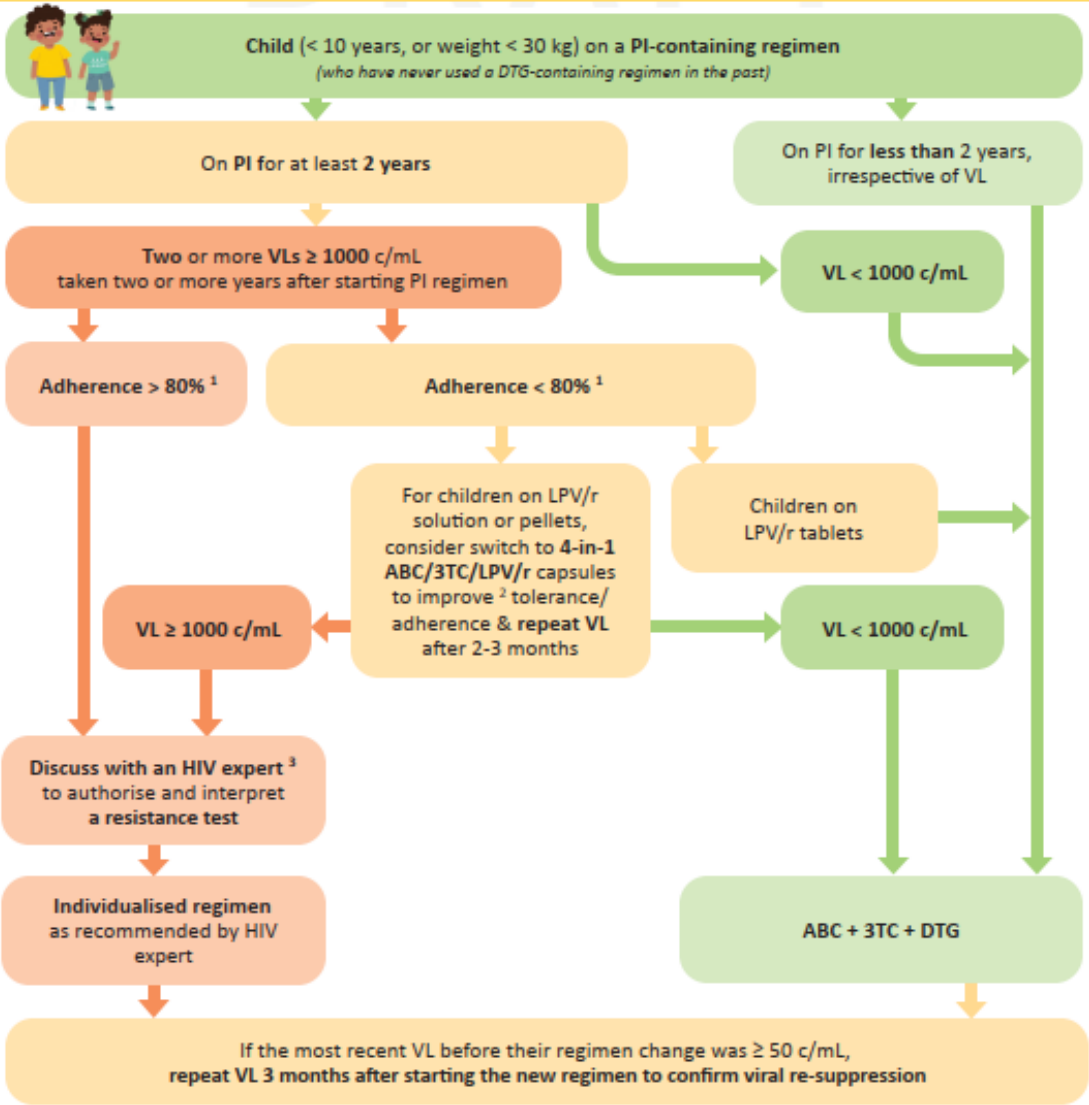
PRODUCT	OPTIMAL PRODUCT	ELIGIBILITY
Abacavir 20mg/ml oral solution	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Abacavir 60mg dispersible/crushable tablet	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Lamivudine 10mg/ml oral solution	Abacavir 120mg, Lamivudine 60mg dispersible tablet	Weight 3 -24.9kg
Abacavir 600mg and Lamivudine 300mg tablet	Abacavir 600mg, Lamivudine 300mg, Dolutegravir 50mg tablet	If on Dolutegravir 50mg tablet
Lopinavir 40mg, Ritonavir 10mg capsule	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 80mg, Ritonavir 20mg/ml oral solution	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 100mg and Ritonavir 25mg film coated	Dolutegravir 10mg dispersible tablet	Weight 3 -19.9kg
Lopinavir 200mg, Ritonavir 50mg film coated tablet	Dolutegravir 10mg dispersible tablet	Weight 14-19.9kg
Lopinavir 200mg, Ritonavir 50mg film coated tablet	Dolutegravir 50mg tablet	Weight >=20kg

Initiate the process of switching

All children above the age of 10 years and over 30kgs should be switched if eligible to TLD: Tenofovir 300mg, Lamivudine 300mg, Dolutegravir 50mg tablet

The NDoH recommends all children ≥4 weeks and ≥3 kg be transitioned to a DTG containing regimen

All children should be initiated on a DTG-based regimen



Source : 2023 ART Clinical Guidelines Draft 3

1. Although objective measures of poor adherence include pharmacy refills or attendance of scheduled clinic visits in the previous 6-12 months of <80%, adherence difficulties in young children are often linked to poor tolerability of unpalatable formulations, particularly LPV/r solution. It is important to ask the caregiver about how the child tolerates the medication e.g., does the child refuse to swallow the medicine or spit out or vomit the medicine, and whether the caregiver has been able to overcome this. Considering these limitations, objective measures of good adherence could include one of the following:
    a) Pharmacy refills > 80% in the last 6-12 months (if this is known)
    b) Attendance of > 80% of scheduled clinic visits in the last 6-12 months (if this is known)
    c) Detection of current antiretroviral drug/s in the client's blood or urine, if available
2. If a switch to the 4-in1 capsules does not improve adherence, or is not available, continue to switch to ABC + 3TC + DTG as for non-adherent children on LPV/r tablets
3. The following would qualify as HIV experts: the HIV Helplines, a paediatric infectious disease specialist or the paediatric Third line ART committee

NDoH recommended daily dosing for ABC/3TC & DTG-based formulations

NDoH Recommended Daily Dosing							
Formulation	**3 – 5.9 kg**	**6 – 9.9 kg**	**10 – 13.9 kg**	**14 – 19.9 kg**	**20 – 24.9 kg**	**25 – 29.9 kg**	**≥ 30 kg**
ABC/3TC 120/60mg dispersible, scored tablet [1]	1	1.5	2	2.5	3	*[transition to ABC/3TC 600/300mg][3]*	–
DTG 10mg dispersible, scored tablet [1 & 2]	0.5	1.5	2	2.5	*[transition to DTG 50mg][3]*	–	–
ABC/3TC 600/300 mg tablet [4]	–	–	–	–	–	1	–
DTG 50 mg tablet [2 & 5]	–	–	–	–	1	1	1
ABC/3TC/DTG 600/300/50 mg tablet	–	–	–	–	–	1	1
TDF/3TC/DTG 300/300/50 mg tablet	–	–	–	–	–	–	1

1. Can be dissolved in the same solution

2. Twice daily with concomitant use of rifampicin

3. If able to swallow whole tablets

4. Transition to ABC/3TC/DTG if eligible

5. Transition to ABC/3TC/DTG or TDF/3TC/DTG if eligible

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Demonstration on the use of pDTG dispersible, scored tablets

pDTG is a scored, dispersible tablet (DT). The dispersible formulation allows **pDTG to be easily administered to children by dispersing and drinking the medicine in a small amount of water**, rather than having to swallow multiple pills, pellets, or granule formulations.

Administration Instructions

Caregivers should be guided to **add the appropriate dose for weight of pDTG to clean water**, **stir until the tablet(s) dissolves**, and **administer to the child**.

- *The child should drink all of the water straight away or within no more than 30 mins.*
- *If dispersing between 0.5 or 1.5 DTG 10 mg tablets, 5 mL (1 teaspoon) of clean water should be used. When dispersing 2 or more tablets, 10 mL (2 teaspoons) of water should be used.*
- *If any medicine remains in the cup, add a small amount of additional water to the cup, swirl, and give to the child. Repeat as necessary.*

Co-administration with ABC/3TC 120/60 mg DT: pDTG can be **dispersed and administered in the same solution of clean water as ABC/3TC 120/60 mg DT.** When dispersing both products together, use 10-20 mL (2-4 teaspoons) of clean water and **ensure both medicines are properly dissolved** before administering. If not dissolved (i.e., lumping occurs), stir and slowly add water until all DTs are dissolved.

Other liquids/foods (e.g., juice, milk, breast milk, yoghurt, porridge): If a child is unable to use water, other age-appropriate liquids or foods may be used. Follow the above volume recommendations to ensure the child takes the full dose. If mixing with foods, the tablets can be crushed to aid in dissolution.

The dispersible tablets can be swallowed whole; however, the tablets should not be chewed.

How to administer pDTG in combination with ABC/3TC dispersible, scored tablets with water or other liquids

- pDTG & ABC/3TC dispersible, scored tablets can be dissolved and mixed in a small amount of water, breastmilk or other liquids prior to administration.
- pDTG & ABC/3TC dispersible, scored tablets can also be split/crushed before mixing them with water or other liquids.
- The tablets can be swallowed whole and HCWs and caregivers should, when appropriate, start teaching the child how to swallow whole tablets to enable an easier transition to non-dispersible formulations when the child reaches the appropriate weight band.

STEP 1: DETERMINE THE DOSE

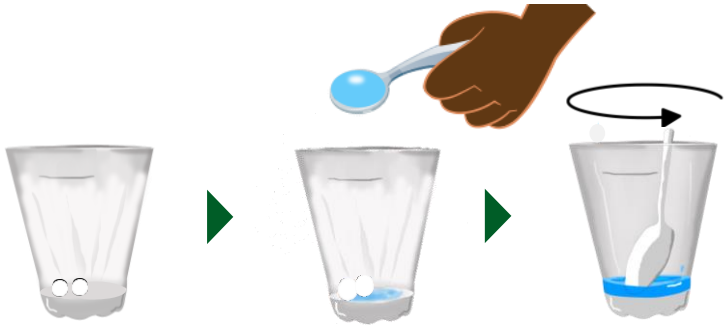
Add the correct number of pDTG & ABC/3TC tablets to a clean, empty glass or cup based on the child's weight. (See Dosing Table)

Weight	No. of pDTG (10 mg) Daily Tablets	No. of ABC/3TC (120/60 mg) Daily Tablets
3 – 5.9kg	0.5	1
6 – 9.9kg	1.5	1.5
10 – 13.9kg	2	2
14 – 19.9kg	2.5	2.5
20 – 24.9kg	-	3

TIP: If you are administering 0.5, 1.5 or 2.5 tablets, you can easily split the tablets down the middle on the solid line.

STEP 2: PREPARE THE pDTG & ABC/3TC MIXTURE

Add 10 -20mL (2-4 teaspoons) of clean water into the glass or cup and stir until the tablets dissolve.



TIP: If the tablets do not dissolve completely (i.e., they lump together), stir and slowly add another 10ml (2 teaspoons) of extra water until the tablets fully dissolve.

STEP 3: GIVE THE MIXTURE TO THE CHILD

Give the medicine to the child to drink. Make sure they drink all the medicine right away or within a maximum of 30 minutes.

OPTION 1: The child can drink the mixture directly from the glass.

OR

OPTION 2: Feed the mixture to the child using a spoon.

TIP: If any medicine remains in the glass, add a little more water to the glass and give it to the child. Repeat until no medicine remains in the glass.

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Note: Addition information on the ABC/3TC (120/60 mg) dispersible, scored tablets can be found on the NDoH Knowledge Hub eLibrary
A demo video on the use of the product can be found here

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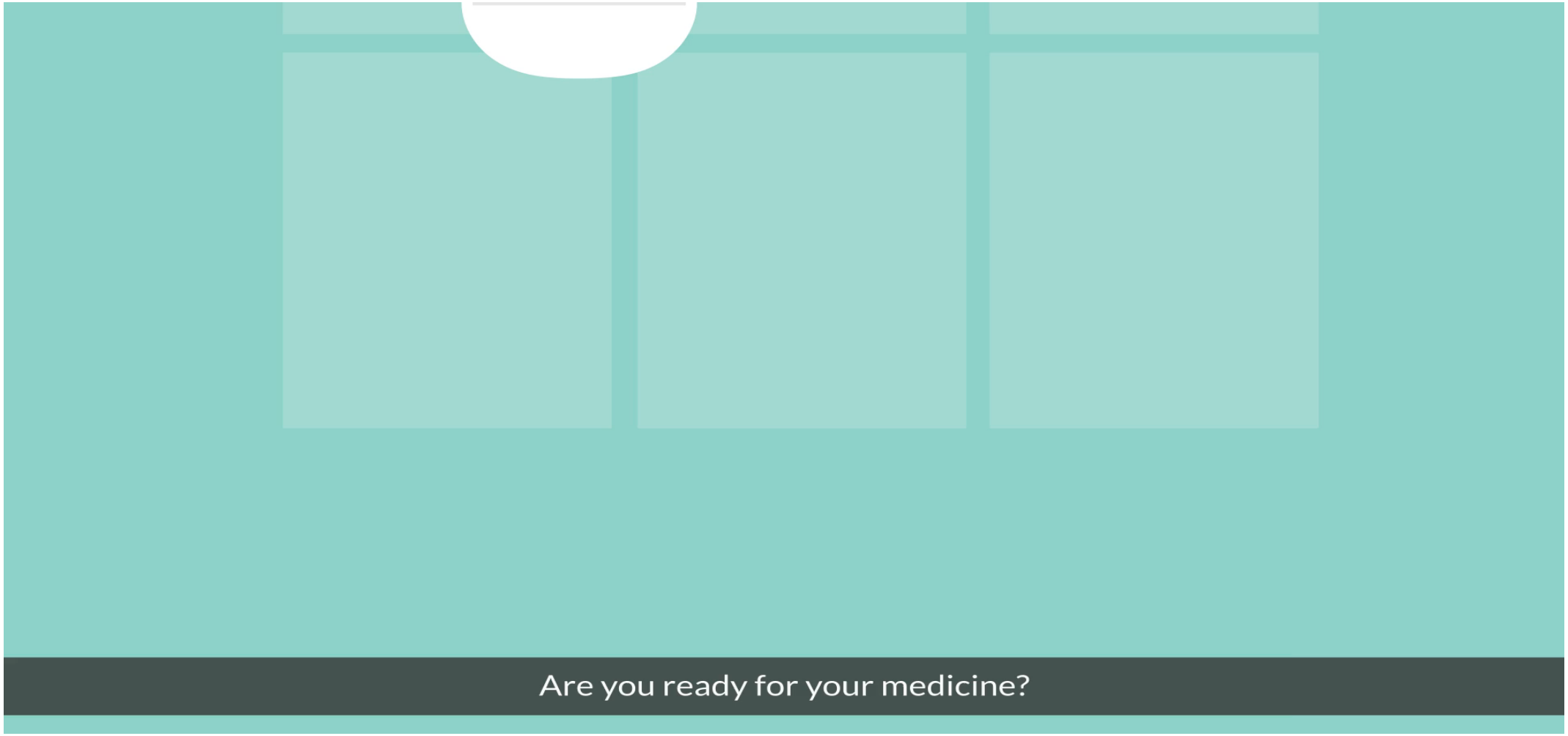
Demo video on how to administer pDTG in combination with ABC/3TC dispersible, scored tablets with water or other liquids



There are some considerations for pDTG when used to treat CHLIV with TB, as well as other drug-drug interactions

Administration Instructions

- DTG interacts with the TB medicine rifampicin (RIF). Children receiving TB treatment containing RIF should have **their standard daily dose according to weight given both in the morning and in the evening** for the duration of the TB treatment.
- Continue the dosing pDTG twice daily for two weeks after the completion of the RIF-containing TB treatment and then go back to dosing once daily after the two weeks.

Additional Drug-Drug Interactions

- **Iron, aluminium, magnesium, and calcium-containing medicines bind with and reduce absorption of DTG. If co-administered,** DTG should be **taken with food** to enhance DTG absorption **or taken at alternate times (6 hours apart)**.

- Drugs that **are metabolic inducers may decrease the plasma concentrations** of DTG. This includes some anticonvulsants such as phenobarbital. **Co-administration with these anticonvulsants is not recommended with DTG**. Consult expert opinion for further guidance on this.

- For more information on drug interactions, please see the latest national guidelines.

Dosing differences between the DTG 50 mg film-coated tablets and DTG 10 mg dispersible tablets

DTG 50 mg Film-Coated Tablets

- **Administration:** The 50 mg tablet is a small, film coated tablet (FCT) that should be swallowed whole
- While 50 mg is the adult dose, it can also be used for children who weigh 20kg or more

DTG 10 mg Dispersible Tablets

- **Administration:** The DTG 10 mg scored, dispersible tablet (DT) can be swallowed whole, but is meant to be dissolved in water

Dosing Differences Between 50 mg DTG FCT and 10 mg DTG DT

- DTG dispersible tablets are much **better absorbed** than DTG film coated tablets. As a result, when switching between products, **the product dosing is not 1:1** (i.e. 5 x 10 mg DT is *not* equivalent to 1 x 50 mg FCT). In the event there is a need to transition between the two formulations:
- **DTG dose of 50 mg FCT is approximately equal to 30 mg of DT (i.e. 3 x 10 mg DTs).**

1 x 50 mg DTG FCT = *3 x 10 mg paediatric DTG DT*

Note: The pDTG tablets replace Lopinavir/ritonavir and children should be switched to the DTG 50mg formulation after 20kg unless there are challenges swallowing whole tablets.

While usually well tolerated, pDTG is associated with some infrequent side effects in children

Side Effects

- As with all ARVs, it is possible to have side effects when taking pDTG. However, **in clinical studies, no participants permanently discontinued DTG due to adverse events from pDTG.** Possible side effects include:
  - **Insomnia**
  - **Fatigue**
  - **Headache**
- Incidence of high blood sugar and possible weight gain following DTG has also been reported in ART experienced adults. Related symptoms such as polyuria, polydipsia should also be monitored routinely.

Discuss possible side effects with patients and care givers to enhance adherence.

Report any persistent Adverse Drug Reactions to SAHPRA on the SAHPRA MedSafety App.

Poll Question 3 (Multi Selection)

A 2 year-old boy, Bongani, was started on Abacavir (ABC), Lamivudine (3TC) and Lopinavir/Ritonavir (LPV/r) 15 months ago. At the time, the child had a history of oral candidiasis and recurrent bacterial pneumonia.

Vitals: Temperature: 37ºC, Pulse: 80, Respiratory Rate: 20, Weight 10.4 kg

6 month VL: 60,899 copies/mL
12 month CD4/VL: 14%, 35,679 copies/mL

The patient presents with a history of recurrent diarrhoea, and his grand mother complaints that giving him his medicines is challenging because he spews his medicines.

1. What do you suspect is occurring?

a) Virological treatment failure

b) Poor adherence

c) Opportunistic infection

d) None of the above

Poll Question 4 (Single Selection)

A 2 year-old boy, Bongani, was started on Abacavir (ABC), Lamivudine (3TC) and Lopinavir/Ritonavir (LPV/r) 15 months ago. At the time, the child had a history of oral candidiasis and recurrent bacterial pneumonia.

Vitals: Temperature: 37ºC, Pulse: 80, Respiratory Rate: 20, Weight 10.4 kg

6 month VL: 60,899 copies/mL
12 month CD4/VL: 14%, 35,679 copies/mL

The patient presents with a history of recurrent diarrhoea, and his grand mother complaints that giving him his medicines is challenging because he spews his medicines.

2. Is there an indication for switching or stopping a regimen?

a) Yes switch regimen, the viral load is too high.

b) Yes switch, LPV/rt is a weak ARV drug.

c) No need to switch or stop, high viral loads are acceptable in children.

d) No need to with switch or stop, repeat viral load in 6 months time.

Poll Question 5 (Single Selection)

A 2 year-old boy, Bongani, was started on Abacavir (ABC), Lamivudine (3TC) and Lopinavir/Ritonavir (LPV/r) 15 months ago. At the time, the child had a history of oral candidiasis and recurrent bacterial pneumonia.

Vitals: Temperature: 37ºC, Pulse: 80, Respiratory Rate: 20, Weight 10.4 kg

6 month VL: 60,899 copies/mL
12 month CD4/VL: 14%, 35,679 copies/mL

The patient presents with a history of recurrent diarrhoea, and his grand mother complaints that giving him his medicines is challenging because he spews his medicines.

3. Is an HIV resistance test indicated?

a) Yes

b) No

c) Not Sure

Poll Question 6 (Multi Selection)

A 2 year-old boy, Bongani, was started on Abacavir (ABC), Lamivudine (3TC) and Lopinavir/Ritonavir (LPV/r) 15 months ago. At the time, the child had a history of oral candidiasis and recurrent bacterial pneumonia.

Vitals: Temperature: 37ºC, Pulse: 80, Respiratory Rate: 20, Weight 10.4 kg

6 month VL: 60,899 copies/mL
12 month CD4/VL: 14%, 35,679 copies/mL

The patient presents with a history of recurrent diarrhoea, and his grand mother complaints that giving him his medicines is challenging because he spews his medicines.

3. So, what's your plan (s)?

a) Switch ABC + 3TC + DTG and repeat VL in 3 months time

b) Stop current regimen, and give: AZT + 3TC + EFV

c) Enhanced Adherence Counselling

d) Continue current ART regimen and repeat VL in 3 months

For further assistance on how and when to use this formulation please contact the following:

National HIV and TB Care Worker Hotline:

- This helpline can be contacted by calling 0800 212 506 or 021 406 6782
- This helpline can be contacted via SMS / Please Call Me / WhatsApp on 071 840 157

Right To Care Paediatric, Adolescent and Adult HIV Helpline:

- This helpline can be contacted via SMS / Please Call Me / WhatsApp/Missed Call on 082 352 6642

KZN Paediatric Hotline:

- This helpline can be contacted by calling 0800 006 603

Weight based dosing for all other paediatric formulations are available on KnowledgeHub in the 2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates, October 2019

Poll Question 7 (Single Selection)

ABC + 3TC + DTG is a preferred regimen for a 3 year old child with weight of 15Kgs

a) True

b) False

c) Not Sure